This Agreement (‘the Agreement’) is between the following parties:

on the one part,

the European Union (‘the EU’), represented by the European Commission (‘the Commission’), represented for the purposes of signature of this Agreement by the Head of Unit, Directorate-General for Research and Innovation, Innovative Administration, Financial Management & Program Support II, Mila BAS SANCHEZ,

and

on the other part,

1. ‘the coordinator’:

   NEDERLANDSE ORGANISATIE VOOR TOEGEPAST NATUURWETENSCHAPPELIJK ONDERZOEK TNO (TNO), established in ANNA VAN BUERENPLEIN 1, DEN HAAG 2595 DA, Netherlands, VAT number: NL002875718B01, represented for the purposes of signing the Agreement by Managing Director HL, Peter VAN DIJKEN

   and the following other beneficiaries, if they sign their ‘Accession Form’ (see Annex 3 and Article 56):

2. FUNDACION PRIVADA INSTITUTO DE SALUD GLOBAL BARCELONA (ISGLOBAL), established in C ROSSELLO 132 PLANTA 05, BARCELONA 08036, Spain, VAT number: ESG65341695,

3. INSTITUTE OF OCCUPATIONAL MEDICINE (IOM), established in Research Avenue North, Riccarton 45, EDINBURGH EH14 4AP, United Kingdom,

4. AARHUS UNIVERSITET (AU), established in NORDRE RINGGADE 1, AARHUS C 8000, Denmark, VAT number: DK31119103,

5. KAROLINSKA INSTITUTET (KI), established in Nobels Väg 5, STOCKHOLM 17177, Sweden, VAT number: SE202100297301,

6. KATHOLIEKE UNIVERSITEIT LEUVEN (KUL), established in OUDE MARKT 13, LEUVEN 3000, Belgium, VAT number: BE0419052173,
7. STATENS ARBEIDSMILJOINSTITUTT (STAMI), established in GYDAS VEI 8, OSLO 0363, Norway,

8. THE UNIVERSITY OF MANCHESTER (UNIMAN), established in OXFORD ROAD, MANCHESTER M13 9PL, United Kingdom, VAT number: GB849738956,

9. UNIVERSITEIT UTRECHT (UU), established in HEIDELBERGLAAN 8, UTRECHT 3584 CS, Netherlands, VAT number: NL001798650B01,

10. INSTITUT NATIONAL DE LA SANTE ET DE LA RECHERCHE MEDICALE (INSERM), established in RUE DE TOLBIAC 101, PARIS 75654, France, VAT number: FR31180036048,

11. TYOTERVEYLAITOS (FIOH), established in TOPELIUKSENKATU 41 B, HELSINKI 00250, Finland, VAT number: FI02202669,

12. PANEPISTIMIO DYTIKIS ATTIKIS (PDA), established in PETROU RALLI KAI THIVON, AIGALEO 122 44, Greece, VAT number: EL997018536,

13. VTEC ENGINEERING BV (VTEC), established in KASTANJELAAN 400, EINDHOVEN 5616 LZ, Netherlands, VAT number: NL853153449B01,

14. UNIVERSITEIT I BERGEN (UiB), established in MUSEPLASSEN 1, BERGEN 5020, Norway, VAT number: NO874789542MVA,

15. LIFEGLIMMER GMBH (LIFE), established in MARKELSTRASSE 38, BERLIN 12163, Germany, VAT number: DE282940451,

16. OWLSTONE MEDICAL LIMITED (OWL), established in 183 CAMBRIDGE SCIENCE PARK, MILTON ROAD, CAMBRIDGE CB4 0GA, United Kingdom, VAT number: GB260449214,

17. INTERAKTIV GMBH (INTER), established in MAX PLANCK STR 6-8, KOLN 50858, Germany, VAT number: DE210904165,

18. TECHNOLOGIKO PANEPISTIMIO KYPROU (CUT), established in ARCHBISHOP KYPRIANOS 31 SAVINGS COOPERATIVE BANK BUILDING 3RD FLOOR, LEMESOS 3036, Cyprus, VAT number: CY90002687H,

19. STOCKHOLMS LANS LANDSTING (SLL), established in HANTVERKARGATAN 45, STOCKHOLM 104 22, Sweden, VAT number: SE232100001601,

Unless otherwise specified, references to ‘beneficiary’ or ‘beneficiaries’ include the coordinator.

The parties referred to above have agreed to enter into the Agreement under the terms and conditions below.

By signing the Agreement or the Accession Form, the beneficiaries accept the grant and agree to implement it under their own responsibility and in accordance with the Agreement, with all the obligations and conditions it sets out.
The Agreement is composed of:

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Annex 2 Estimated budget for the action
  2a Additional information on the estimated budget
Annex 3 Accession Forms
Annex 4 Model for the financial statements
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CHAPTER 1 GENERAL

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This Agreement sets out the rights and obligations and the terms and conditions applicable to the grant awarded to the beneficiaries for implementing the action set out in Chapter 2.

CHAPTER 2 ACTION

ARTICLE 2 — ACTION TO BE IMPLEMENTED — COMPLEMENTARY GRANT

The grant is awarded for the action entitled ‘Exposome project for health and occupational research’ — ‘EPHOR’ (‘action’), as described in Annex 1.

The grant is a ‘complementary grant’ to the following complementary grant agreement(s) No(s):


ARTICLE 3 — DURATION AND STARTING DATE OF THE ACTION

The duration of the action will be 60 months as of 1 January 2020 (‘starting date of the action’).

ARTICLE 4 — ESTIMATED BUDGET AND BUDGET TRANSFERS

4.1 Estimated budget

The ‘estimated budget’ for the action is set out in Annex 2.

It contains the estimated eligible costs and the forms of costs, broken down by beneficiary and budget category (see Articles 5, 6).

4.2 Budget transfers

The estimated budget breakdown indicated in Annex 2 may be adjusted — without an amendment (see Article 55) — by transfers of amounts between beneficiaries, budget categories and/or forms of costs set out in Annex 2, if the action is implemented as described in Annex 1.

However, the beneficiaries may not add costs relating to subcontracts not provided for in Annex 1, unless such additional subcontracts are approved by an amendment or in accordance with Article 13.

CHAPTER 3 GRANT

ARTICLE 5 — GRANT AMOUNT, FORM OF GRANT, REIMBURSEMENT RATES AND FORMS OF COSTS

5.1 Maximum grant amount
The ‘maximum grant amount’ is EUR 11 981 851.64 (eleven million nine hundred and eighty one thousand eight hundred and fifty one EURO and sixty four eurocents).

5.2 Form of grant, reimbursement rates and forms of costs

The grant reimburses 100% of the action's eligible costs (see Article 6) (‘reimbursement of eligible costs grant’) (see Annex 2).

The estimated eligible costs of the action are EUR 11 981 851.64 (eleven million nine hundred and eighty one thousand eight hundred and fifty one EURO and sixty four eurocents).

Eligible costs (see Article 6) must be declared under the following forms (‘forms of costs’):

(a) for direct personnel costs:
   - as actually incurred costs (‘actual costs’) or
   - on the basis of an amount per unit calculated by the beneficiary in accordance with its usual cost accounting practices (‘unit costs’).

   Personnel costs for SME owners or beneficiaries that are natural persons not receiving a salary (see Article 6.2, Points A.4 and A.5) must be declared on the basis of the amount per unit set out in Annex 2a (unit costs);

(b) for direct costs for subcontracting: as actually incurred costs (actual costs);

(c) for direct costs of providing financial support to third parties: not applicable;

(d) for other direct costs:
   - for costs of internally invoiced goods and services: on the basis of an amount per unit calculated by the beneficiary in accordance with its usual cost accounting practices (‘unit costs’);
   - for all other costs: as actually incurred costs (actual costs);

(e) for indirect costs: on the basis of a flat-rate applied as set out in Article 6.2, Point E (‘flat-rate costs’);

(f) specific cost category(ies): not applicable.

5.3 Final grant amount — Calculation

The ‘final grant amount’ depends on the actual extent to which the action is implemented in accordance with the Agreement’s terms and conditions.

This amount is calculated by the Commission — when the payment of the balance is made (see Article 21.4) — in the following steps:

   Step 1 — Application of the reimbursement rates to the eligible costs
   Step 2 — Limit to the maximum grant amount
Step 3 — Reduction due to the no-profit rule

Step 4 — Reduction due to substantial errors, irregularities or fraud or serious breach of obligations

5.3.1 Step 1 — Application of the reimbursement rates to the eligible costs

The reimbursement rate(s) (see Article 5.2) are applied to the eligible costs (actual costs, unit costs and flat-rate costs; see Article 6) declared by the beneficiaries (see Article 20) and approved by the Commission (see Article 21).

5.3.2 Step 2 — Limit to the maximum grant amount

If the amount obtained following Step 1 is higher than the maximum grant amount set out in Article 5.1, it will be limited to the latter.

5.3.3 Step 3 — Reduction due to the no-profit rule

The grant must not produce a profit.

‘Profit’ means the surplus of the amount obtained following Steps 1 and 2 plus the action’s total receipts, over the action’s total eligible costs.

The ‘action’s total eligible costs’ are the consolidated total eligible costs approved by the Commission.

The ‘action’s total receipts’ are the consolidated total receipts generated during its duration (see Article 3).

The following are considered receipts:

(a) income generated by the action; if the income is generated from selling equipment or other assets purchased under the Agreement, the receipt is up to the amount declared as eligible under the Agreement;

(b) financial contributions given by third parties to the beneficiary specifically to be used for the action, and

(c) in-kind contributions provided by third parties free of charge and specifically to be used for the action, if they have been declared as eligible costs.

The following are however not considered receipts:

(a) income generated by exploiting the action’s results (see Article 28);

(b) financial contributions by third parties, if they may be used to cover costs other than the eligible costs (see Article 6);

(c) financial contributions by third parties with no obligation to repay any amount unused at the end of the period set out in Article 3.

If there is a profit, it will be deducted from the amount obtained following Steps 1 and 2.
5.3.4 Step 4 — Reduction due to substantial errors, irregularities or fraud or serious breach of obligations — Reduced grant amount — Calculation

If the grant is reduced (see Article 43), the Commission will calculate the reduced grant amount by deducting the amount of the reduction (calculated in proportion to the seriousness of the errors, irregularities or fraud or breach of obligations, in accordance with Article 43.2) from the maximum grant amount set out in Article 5.1.

The final grant amount will be the lower of the following two:

- the amount obtained following Steps 1 to 3 or
- the reduced grant amount following Step 4.

5.4 Revised final grant amount — Calculation

If — after the payment of the balance (in particular, after checks, reviews, audits or investigations; see Article 22) — the Commission rejects costs (see Article 42) or reduces the grant (see Article 43), it will calculate the ‘revised final grant amount’ for the beneficiary concerned by the findings.

This amount is calculated by the Commission on the basis of the findings, as follows:

- in case of rejection of costs: by applying the reimbursement rate to the revised eligible costs approved by the Commission for the beneficiary concerned;
- in case of reduction of the grant: by calculating the concerned beneficiary’s share in the grant amount reduced in proportion to the seriousness of the errors, irregularities or fraud or breach of obligations (see Article 43.2).

In case of rejection of costs and reduction of the grant, the revised final grant amount for the beneficiary concerned will be the lower of the two amounts above.

ARTICLE 6 — ELIGIBLE AND INELIGIBLE COSTS

6.1 General conditions for costs to be eligible

‘Eligible costs’ are costs that meet the following criteria:

(a) for actual costs:

(i) they must be actually incurred by the beneficiary;
(ii) they must be incurred in the period set out in Article 3, with the exception of costs relating to the submission of the periodic report for the last reporting period and the final report (see Article 20);
(iii) they must be indicated in the estimated budget set out in Annex 2;
(iv) they must be incurred in connection with the action as described in Annex 1 and necessary for its implementation;
(v) they must be identifiable and verifiable, in particular recorded in the beneficiary’s accounts.
in accordance with the accounting standards applicable in the country where the beneficiary is established and with the beneficiary’s usual cost accounting practices;

(vi) they must comply with the applicable national law on taxes, labour and social security, and

(vii) they must be reasonable, justified and must comply with the principle of sound financial management, in particular regarding economy and efficiency;

(b) for **unit costs**:

(i) they must be calculated as follows:

{amounts per unit set out in Annex 2a or calculated by the beneficiary in accordance with its usual cost accounting practices (see Article 6.2, Point A and Article 6.2.D.5) multiplied by

the number of actual units};

(ii) the number of actual units must comply with the following conditions:

- the units must be actually used or produced in the period set out in Article 3;
- the units must be necessary for implementing the action or produced by it, and
- the number of units must be identifiable and verifiable, in particular supported by records and documentation (see Article 18);

(c) for **flat-rate costs**:

(i) they must be calculated by applying the flat-rate set out in Annex 2, and

(ii) the costs (actual costs or unit costs) to which the flat-rate is applied must comply with the conditions for eligibility set out in this Article.

6.2 Specific conditions for costs to be eligible

Costs are eligible if they comply with the general conditions (see above) and the specific conditions set out below for each of the following budget categories:

A. direct personnel costs;
B. direct costs of subcontracting;
C. not applicable;
D. other direct costs;
E. indirect costs;
F. not applicable.

‘Direct costs’ are costs that are directly linked to the action implementation and can therefore be attributed to it directly. They must not include any indirect costs (see Point E below).

‘Indirect costs’ are costs that are not directly linked to the action implementation and therefore cannot be attributed directly to it.

A. **Direct personnel costs**
Types of eligible personnel costs

A.1 Personnel costs are eligible, if they are related to personnel working for the beneficiary under an employment contract (or equivalent appointing act) and assigned to the action (‘costs for employees (or equivalent)’). They must be limited to salaries (including during parental leave), social security contributions, taxes and other costs included in the remuneration, if they arise from national law or the employment contract (or equivalent appointing act).

Beneficiaries that are non-profit legal entities\(^1\) may also declare as personnel costs additional remuneration for personnel assigned to the action (including payments on the basis of supplementary contracts regardless of their nature), if:

(a) it is part of the beneficiary’s usual remuneration practices and is paid in a consistent manner whenever the same kind of work or expertise is required;

(b) the criteria used to calculate the supplementary payments are objective and generally applied by the beneficiary, regardless of the source of funding used.

‘Additional remuneration’ means any part of the remuneration which exceeds what the person would be paid for time worked in projects funded by national schemes.

Additional remuneration for personnel assigned to the action is eligible up to the following amount:

(a) if the person works full time and exclusively on the action during the full year: up to EUR 8 000;

(b) if the person works exclusively on the action but not full-time or not for the full year: up to the corresponding pro-rata amount of EUR 8 000, or

(c) if the person does not work exclusively on the action: up to a pro-rata amount calculated as follows:

\[
\{\text{EUR 8 000 divided by the number of annual productive hours (see below)}, \text{ multiplied by the number of hours that the person has worked on the action during the year}\}
\]

A.2 The costs for natural persons working under a direct contract with the beneficiary other than an employment contract are eligible personnel costs, if:

(a) the person works under conditions similar to those of an employee (in particular regarding the way the work is organised, the tasks that are performed and the premises where they are performed);

(b) the result of the work carried out belongs to the beneficiary (unless exceptionally agreed otherwise), and

\(^1\) For the definition, see Article 2.1(14) of the Rules for Participation Regulation No 1290/2013: ‘non-profit legal entity’ means a legal entity which by its legal form is non-profit-making or which has a legal or statutory obligation not to distribute profits to its shareholders or individual members.
(c) the costs are not significantly different from those for personnel performing similar tasks under an employment contract with the beneficiary.

A.3 The **costs of personnel seconded by a third party against payment** are eligible personnel costs, if the conditions in Article 11.1 are met.

A.4 **Costs of owners** of beneficiaries that are small and medium-sized enterprises (‘SME owners’) who are working on the action and who do not receive a salary are eligible personnel costs, if they correspond to the amount per unit set out in Annex 2a multiplied by the number of actual hours worked on the action.

A.5 **Costs of ‘beneficiaries that are natural persons’** not receiving a salary are eligible personnel costs, if they correspond to the amount per unit set out in Annex 2a multiplied by the number of actual hours worked on the action.

**Calculation**

Personnel costs must be calculated by the beneficiaries as follows:

\[
\text{hourly rate} \times \text{the number of actual hours worked on the action},
\]

plus

for non-profit legal entities: additional remuneration to personnel assigned to the action under the conditions set out above (Point A.1).

The number of actual hours declared for a person must be identifiable and verifiable (see Article 18).

The total number of hours declared in EU or Euratom grants, for a person for a year, cannot be higher than the annual productive hours used for the calculations of the hourly rate. Therefore, the maximum number of hours that can be declared for the grant are:

\[
\text{number of annual productive hours for the year (see below)} - \text{total number of hours declared by the beneficiary, for that person in that year, for other EU or Euratom grants}.
\]

The ‘**hourly rate**’ is one of the following:

(a) for personnel costs declared as **actual costs** (i.e. budget categories A.1, A.2, A.3): the hourly rate is calculated per full financial year, as follows:

\[
\text{actual annual personnel costs (excluding additional remuneration) for the person} \div \text{number of annual productive hours}.
\]
reporting period, the beneficiaries must use the hourly rate of the last closed financial year available.

For the ‘number of annual productive hours’, the beneficiaries may choose one of the following:

(i) ‘fixed number of hours’: 1 720 hours for persons working full time (or corresponding pro-rata for persons not working full time);

(ii) ‘individual annual productive hours’: the total number of hours worked by the person in the year for the beneficiary, calculated as follows:

\[
\text{annual workable hours of the person (according to the employment contract, applicable collective labour agreement or national law)} \\
\text{plus} \\
\text{overtime worked} \\
\text{minus} \\
\text{absences (such as sick leave and special leave)}. \\
\]

‘Annual workable hours’ means the period during which the personnel must be working, at the employer’s disposal and carrying out his/her activity or duties under the employment contract, applicable collective labour agreement or national working time legislation.

If the contract (or applicable collective labour agreement or national working time legislation) does not allow to determine the annual workable hours, this option cannot be used;

(iii) ‘standard annual productive hours’: the ‘standard number of annual hours’ generally applied by the beneficiary for its personnel in accordance with its usual cost accounting practices. This number must be at least 90% of the ‘standard annual workable hours’.

If there is no applicable reference for the standard annual workable hours, this option cannot be used.

For all options, the actual time spent on parental leave by a person assigned to the action may be deducted from the number of annual productive hours.

As an alternative, beneficiaries may calculate the hourly rate per month, as follows:

\[
\frac{\text{actual monthly personnel cost (excluding additional remuneration) for the person}}{\text{number of annual productive hours / 12}}
\]

using the personnel costs for each month and (one twelfth of) the annual productive hours calculated according to either option (i) or (iii) above, i.e.:

- fixed number of hours or
- standard annual productive hours.
Time spent on parental leave may not be deducted when calculating the hourly rate per month. However, beneficiaries may declare personnel costs incurred in periods of parental leave in proportion to the time the person worked on the action in that financial year.

If parts of a basic remuneration are generated over a period longer than a month, the beneficiaries may include only the share which is generated in the month (irrespective of the amount actually paid for that month).

Each beneficiary must use only one option (per full financial year or per month) for each full financial year;

(b) for personnel costs declared on the basis of unit costs (i.e. budget categories A.1, A.2, A.4, A.5):
the hourly rate is one of the following:

(i) for SME owners or beneficiaries that are natural persons: the hourly rate set out in Annex 2a (see Points A.4 and A.5 above), or

(ii) for personnel costs declared on the basis of the beneficiary’s usual cost accounting practices: the hourly rate calculated by the beneficiary in accordance with its usual cost accounting practices, if:

- the cost accounting practices used are applied in a consistent manner, based on objective criteria, regardless of the source of funding;

- the hourly rate is calculated using the actual personnel costs recorded in the beneficiary’s accounts, excluding any ineligible cost or costs included in other budget categories.

The actual personnel costs may be adjusted by the beneficiary on the basis of budgeted or estimated elements. Those elements must be relevant for calculating the personnel costs, reasonable and correspond to objective and verifiable information;

and

- the hourly rate is calculated using the number of annual productive hours (see above).

B. Direct costs of subcontracting (including related duties, taxes and charges such as non-deductible value added tax (VAT) paid by the beneficiary) are eligible if the conditions in Article 13.1.1 are met.

C. Direct costs of providing financial support to third parties

Not applicable

D. Other direct costs

D.1 Travel costs and related subsistence allowances (including related duties, taxes and charges such as non-deductible value added tax (VAT) paid by the beneficiary) are eligible if they are in line with the beneficiary’s usual practices on travel.

D.2 The depreciation costs of equipment, infrastructure or other assets (new or second-hand) as recorded in the beneficiary’s accounts are eligible, if they were purchased in accordance with
Article 10.1.1 and written off in accordance with international accounting standards and the beneficiary’s usual accounting practices.

The **costs of renting or leasing** equipment, infrastructure or other assets (including related duties, taxes and charges such as non-deductible value added tax (VAT) paid by the beneficiary) are also eligible, if they do not exceed the depreciation costs of similar equipment, infrastructure or assets and do not include any financing fees.

The costs of equipment, infrastructure or other assets **contributed in-kind against payment** are eligible, if they do not exceed the depreciation costs of similar equipment, infrastructure or assets, do not include any financing fees and if the conditions in Article 11.1 are met.

The only portion of the costs that will be taken into account is that which corresponds to the duration of the action and rate of actual use for the purposes of the action.

D.3 **Costs of other goods and services** (including related duties, taxes and charges such as non-deductible value added tax (VAT) paid by the beneficiary) are eligible, if they are:

(a) purchased specifically for the action and in accordance with Article 10.1.1 or

(b) contributed in kind against payment and in accordance with Article 11.1.

Such goods and services include, for instance, consumables and supplies, dissemination (including open access), protection of results, certificates on the financial statements (if they are required by the Agreement), certificates on the methodology, translations and publications.

D.4 **Capitalised and operating costs of ‘large research infrastructure’**

2 directly used for the action are eligible, if:

(a) the value of the large research infrastructure represents at least 75% of the total fixed assets (at historical value in its last closed balance sheet before the date of the signature of the Agreement or as determined on the basis of the rental and leasing costs of the research infrastructure);

(b) the beneficiary’s methodology for declaring the costs for large research infrastructure has been positively assessed by the Commission (**ex-ante assessment**);

(c) the beneficiary declares as direct eligible costs only the portion which corresponds to the duration of the action and the rate of actual use for the purposes of the action, and

(d) they comply with the conditions as further detailed in the annotations to the H2020 grant agreements.

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2 **‘Large research infrastructure’** means research infrastructure of a total value of at least EUR 20 million, for a beneficiary, calculated as the sum of historical asset values of each individual research infrastructure of that beneficiary, as they appear in its last closed balance sheet before the date of the signature of the Agreement or as determined on the basis of the rental and leasing costs of the research infrastructure.

3 For the definition, see Article 2(6) of the H2020 Framework Programme Regulation No 1291/2013: **‘Research infrastructure’** are facilities, resources and services that are used by the research communities to conduct research and foster innovation in their fields. Where relevant, they may be used beyond research, e.g. for education or public services. They include: major scientific equipment (or sets of instruments); knowledge-based resources such as collections, archives or scientific data; e-infrastructures such as data and computing systems and communication networks; and any other infrastructure of a unique nature essential to achieve excellence in research and innovation. Such infrastructures may be ‘single-sited’, ‘virtual’ or ‘distributed’.

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D.5 Costs of internally invoiced goods and services directly used for the action are eligible, if:

(a) they are declared on the basis of a unit cost calculated in accordance with the beneficiary’s usual cost accounting practices;

(b) the cost accounting practices used are applied in a consistent manner, based on objective criteria, regardless of the source of funding;

(c) the unit cost is calculated using the actual costs for the good or service recorded in the beneficiary’s accounts, excluding any ineligible cost or costs included in other budget categories.

The actual costs may be adjusted by the beneficiary on the basis of budgeted or estimated elements. Those elements must be relevant for calculating the costs, reasonable and correspond to objective and verifiable information;

(d) the unit cost excludes any costs of items which are not directly linked to the production of the invoiced goods or service.

‘Internally invoiced goods and services’ means goods or services which are provided by the beneficiary directly for the action and which the beneficiary values on the basis of its usual cost accounting practices.

E. Indirect costs

Indirect costs are eligible if they are declared on the basis of the flat-rate of 25% of the eligible direct costs (see Article 5.2 and Points A to D above), from which are excluded:

(a) costs of subcontracting and

(b) costs of in-kind contributions provided by third parties which are not used on the beneficiary’s premises;

(c) not applicable;

(d) not applicable.

Beneficiaries receiving an operating grant\(^4\) financed by the EU or Euratom budget cannot declare indirect costs for the period covered by the operating grant, unless they can demonstrate that the operating grant does not cover any costs of the action.

F. Specific cost category(ies)

Not applicable

6.3 Conditions for costs of linked third parties to be eligible

Not applicable

6.4 Conditions for in-kind contributions provided by third parties free of charge to be eligible

In-kind contributions provided free of charge are eligible direct costs (for the beneficiary), if the costs incurred by the third party fulfil — mutatis mutandis — the general and specific conditions for eligibility set out in this Article (Article 6.1 and 6.2) and Article 12.1.

6.5 Ineligible costs

‘Ineligible costs’ are:

(a) costs that do not comply with the conditions set out above (Article 6.1 to 6.4), in particular:

(i) costs related to return on capital;
(ii) debt and debt service charges;
(iii) provisions for future losses or debts;
(iv) interest owed;
(v) doubtful debts;
(vi) currency exchange losses;
(vii) bank costs charged by the beneficiary’s bank for transfers from the Commission;
(viii) excessive or reckless expenditure;
(ix) deductible VAT;
(x) costs incurred during suspension of the implementation of the action (see Article 49);

(b) costs declared under another EU or Euratom grant (including grants awarded by a Member State and financed by the EU or Euratom budget and grants awarded by bodies other than the Commission for the purpose of implementing the EU or Euratom budget); in particular, indirect costs if the beneficiary is already receiving an operating grant financed by the EU or Euratom budget in the same period, unless it can demonstrate that the operating grant does not cover any costs of the action.

6.6 Consequences of declaration of ineligible costs

Declared costs that are ineligible will be rejected (see Article 42).

This may also lead to any of the other measures described in Chapter 6.

CHAPTER 4 RIGHTS AND OBLIGATIONS OF THE PARTIES
SECTION 1  RIGHTS AND OBLIGATIONS RELATED TO IMPLEMENTING THE ACTION

ARTICLE 7 — GENERAL OBLIGATION TO PROPERLY IMPLEMENT THE ACTION

7.1  General obligation to properly implement the action

The beneficiaries must implement the action as described in Annex 1 and in compliance with the provisions of the Agreement and all legal obligations under applicable EU, international and national law.

7.2  Consequences of non-compliance

If a beneficiary breaches any of its obligations under this Article, the grant may be reduced (see Article 43).

Such breaches may also lead to any of the other measures described in Chapter 6.

ARTICLE 8 — RESOURCES TO IMPLEMENT THE ACTION — THIRD PARTIES INVOLVED IN THE ACTION

The beneficiaries must have the appropriate resources to implement the action.

If it is necessary to implement the action, the beneficiaries may:

- purchase goods, works and services (see Article 10);
- use in-kind contributions provided by third parties against payment (see Article 11);
- use in-kind contributions provided by third parties free of charge (see Article 12);
- call upon subcontractors to implement action tasks described in Annex 1 (see Article 13);
- call upon linked third parties to implement action tasks described in Annex 1 (see Article 14);
- call upon international partners to implement action tasks described in Annex 1 (see Article 14a).

In these cases, the beneficiaries retain sole responsibility towards the Commission and the other beneficiaries for implementing the action.

ARTICLE 9 — IMPLEMENTATION OF ACTION TASKS BY BENEFICIARIES NOT RECEIVING EU FUNDING

Not applicable

ARTICLE 10 — PURCHASE OF GOODS, WORKS OR SERVICES

10.1  Rules for purchasing goods, works or services

10.1.1  If necessary to implement the action, the beneficiaries may purchase goods, works or services.
The beneficiaries must make such purchases ensuring the best value for money or, if appropriate, the lowest price. In doing so, they must avoid any conflict of interests (see Article 35).

The beneficiaries must ensure that the Commission, the European Court of Auditors (ECA) and the European Anti-Fraud Office (OLAF) can exercise their rights under Articles 22 and 23 also towards their contractors.

10.1.2 Beneficiaries that are ‘contracting authorities’ within the meaning of Directive 2004/18/EC⁵ (or 2014/24/EU⁶) or ‘contracting entities’ within the meaning of Directive 2004/17/EC⁷ (or 2014/25/EU⁸) must comply with the applicable national law on public procurement.

10.2 Consequences of non-compliance

If a beneficiary breaches any of its obligations under Article 10.1.1, the costs related to the contract concerned will be ineligible (see Article 6) and will be rejected (see Article 42).

If a beneficiary breaches any of its obligations under Article 10.1.2, the grant may be reduced (see Article 43).

Such breaches may also lead to any of the other measures described in Chapter 6.

ARTICLE 11 — USE OF IN-KIND CONTRIBUTIONS PROVIDED BY THIRD PARTIES AGAINST PAYMENT

11.1 Rules for the use of in-kind contributions against payment

If necessary to implement the action, the beneficiaries may use in-kind contributions provided by third parties against payment.

The beneficiaries may declare costs related to the payment of in-kind contributions as eligible (see Article 6.1 and 6.2), up to the third parties’ costs for the seconded persons, contributed equipment, infrastructure or other assets or other contributed goods and services.

The third parties and their contributions must be set out in Annex 1. The Commission may however approve in-kind contributions not set out in Annex 1 without amendment (see Article 55), if:

- they are specifically justified in the periodic technical report and

- their use does not entail changes to the Agreement which would call into question the decision awarding the grant or breach the principle of equal treatment of applicants.

The beneficiaries must ensure that the Commission, the European Court of Auditors (ECA) and the

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European Anti-Fraud Office (OLAF) can exercise their rights under Articles 22 and 23 also towards the third parties.

11.2 Consequences of non-compliance

If a beneficiary breaches any of its obligations under this Article, the costs related to the payment of the in-kind contribution will be ineligible (see Article 6) and will be rejected (see Article 42).

Such breaches may also lead to any of the other measures described in Chapter 6.

ARTICLE 12 — USE OF IN-KIND CONTRIBUTIONS PROVIDED BY THIRD PARTIES FREE OF CHARGE

12.1 Rules for the use of in-kind contributions free of charge

If necessary to implement the action, the beneficiaries may use in-kind contributions provided by third parties free of charge.

The beneficiaries may declare costs incurred by the third parties for the seconded persons, contributed equipment, infrastructure or other assets or other contributed goods and services as eligible in accordance with Article 6.4.

The third parties and their contributions must be set out in Annex 1. The Commission may however approve in-kind contributions not set out in Annex 1 without amendment (see Article 55), if:

- they are specifically justified in the periodic technical report and
- their use does not entail changes to the Agreement which would call into question the decision awarding the grant or breach the principle of equal treatment of applicants.

The beneficiaries must ensure that the Commission, the European Court of Auditors (ECA) and the European Anti-Fraud Office (OLAF) can exercise their rights under Articles 22 and 23 also towards the third parties.

12.2 Consequences of non-compliance

If a beneficiary breaches any of its obligations under this Article, the costs incurred by the third parties related to the in-kind contribution will be ineligible (see Article 6) and will be rejected (see Article 42).

Such breaches may also lead to any of the other measures described in Chapter 6.

ARTICLE 13 — IMPLEMENTATION OF ACTION TASKS BY SUBCONTRACTORS

13.1 Rules for subcontracting action tasks

13.1.1 If necessary to implement the action, the beneficiaries may award subcontracts covering the implementation of certain action tasks described in Annex 1.

Subcontracting may cover only a limited part of the action.

The beneficiaries must award the subcontracts ensuring the best value for money or, if appropriate, the lowest price. In doing so, they must avoid any conflict of interests (see Article 35).
The tasks to be implemented and the estimated cost for each subcontract must be set out in Annex 1 and the total estimated costs of subcontracting per beneficiary must be set out in Annex 2. The Commission may however approve subcontracts not set out in Annex 1 and 2 without amendment (see Article 55), if:

- they are specifically justified in the periodic technical report and
- they do not entail changes to the Agreement which would call into question the decision awarding the grant or breach the principle of equal treatment of applicants.

The beneficiaries must ensure that the Commission, the European Court of Auditors (ECA) and the European Anti-Fraud Office (OLAF) can exercise their rights under Articles 22 and 23 also towards their subcontractors.

13.1.2 The beneficiaries must ensure that their obligations under Articles 35, 36, 38 and 46 also apply to the subcontractors.

Beneficiaries that are ‘contracting authorities’ within the meaning of Directive 2004/18/EC (or 2014/24/EU) or ‘contracting entities’ within the meaning of Directive 2004/17/EC (or 2014/25/EU) must comply with the applicable national law on public procurement.

13.2 Consequences of non-compliance

If a beneficiary breaches any of its obligations under Article 13.1.1, the costs related to the subcontract concerned will be ineligible (see Article 6) and will be rejected (see Article 42).

If a beneficiary breaches any of its obligations under Article 13.1.2, the grant may be reduced (see Article 43).

Such breaches may also lead to any of the other measures described in Chapter 6.

ARTICLE 14 — IMPLEMENTATION OF ACTION TASKS BY LINKED THIRD PARTIES

Not applicable

ARTICLE 14a — IMPLEMENTATION OF ACTION TASKS BY INTERNATIONAL PARTNERS

Not applicable

ARTICLE 15 — FINANCIAL SUPPORT TO THIRD PARTIES

15.1 Rules for providing financial support to third parties

Not applicable

15.2 Financial support in the form of prizes

Not applicable

15.3 Consequences of non-compliance
ARTICLE 16 — PROVISION OF TRANS-NATIONAL OR VIRTUAL ACCESS TO RESEARCH INFRASTRUCTURE

16.1 Rules for providing trans-national access to research infrastructure

Not applicable

16.2 Rules for providing virtual access to research infrastructure

Not applicable

16.3 Consequences of non-compliance

Not applicable

SECTION 2 RIGHTS AND OBLIGATIONS RELATED TO THE GRANT ADMINISTRATION

ARTICLE 17 — GENERAL OBLIGATION TO INFORM

17.1 General obligation to provide information upon request

The beneficiaries must provide — during implementation of the action or afterwards and in accordance with Article 41.2 — any information requested in order to verify eligibility of the costs, proper implementation of the action and compliance with any other obligation under the Agreement.

17.2 Obligation to keep information up to date and to inform about events and circumstances likely to affect the Agreement

Each beneficiary must keep information stored in the Participant Portal Beneficiary Register (via the electronic exchange system; see Article 52) up to date, in particular, its name, address, legal representatives, legal form and organisation type.

Each beneficiary must immediately inform the coordinator — which must immediately inform the Commission and the other beneficiaries — of any of the following:

(a) events which are likely to affect significantly or delay the implementation of the action or the EU's financial interests, in particular:
   (i) changes in its legal, financial, technical, organisational or ownership situation

(b) circumstances affecting:
   (i) the decision to award the grant or
   (ii) compliance with requirements under the Agreement.

17.3 Consequences of non-compliance
If a beneficiary breaches any of its obligations under this Article, the grant may be reduced (see Article 43).

Such breaches may also lead to any of the other measures described in Chapter 6.

**ARTICLE 18 — KEEPING RECORDS — SUPPORTING DOCUMENTATION**

18.1 **Obligation to keep records and other supporting documentation**

The beneficiaries must — for a period of five years after the payment of the balance — keep records and other supporting documentation in order to prove the proper implementation of the action and the costs they declare as eligible.

They must make them available upon request (see Article 17) or in the context of checks, reviews, audits or investigations (see Article 22).

If there are on-going checks, reviews, audits, investigations, litigation or other pursuits of claims under the Agreement (including the extension of findings; see Article 22), the beneficiaries must keep the records and other supporting documentation until the end of these procedures.

The beneficiaries must keep the original documents. Digital and digitalised documents are considered originals if they are authorised by the applicable national law. The Commission may accept non-original documents if it considers that they offer a comparable level of assurance.

18.1.1 **Records and other supporting documentation on the scientific and technical implementation**

The beneficiaries must keep records and other supporting documentation on scientific and technical implementation of the action in line with the accepted standards in the respective field.

18.1.2 **Records and other documentation to support the costs declared**

The beneficiaries must keep the records and documentation supporting the costs declared, in particular the following:

(a) for **actual costs**: adequate records and other supporting documentation to prove the costs declared, such as contracts, subcontracts, invoices and accounting records. In addition, the beneficiaries’ usual cost accounting practices and internal control procedures must enable direct reconciliation between the amounts declared, the amounts recorded in their accounts and the amounts stated in the supporting documentation;

(b) for **unit costs**: adequate records and other supporting documentation to prove the number of units declared. Beneficiaries do not need to identify the actual eligible costs covered or to keep or provide supporting documentation (such as accounting statements) to prove the amount per unit.

In addition, **for unit costs calculated in accordance with the beneficiary's usual cost accounting practices**, the beneficiaries must keep adequate records and documentation to prove that the cost accounting practices used comply with the conditions set out in Article 6.2.

The beneficiaries may submit to the Commission, for approval, a certificate (drawn up in accordance with Annex 6) stating that their usual cost accounting practices comply with these
conditions (‘certificate on the methodology’). If the certificate is approved, costs declared in line with this methodology will not be challenged subsequently, unless the beneficiaries have concealed information for the purpose of the approval.

(c) for flat-rate costs: adequate records and other supporting documentation to prove the eligibility of the costs to which the flat-rate is applied. The beneficiaries do not need to identify the costs covered or provide supporting documentation (such as accounting statements) to prove the amount declared at a flat-rate.

In addition, for personnel costs (declared as actual costs or on the basis of unit costs), the beneficiaries must keep time records for the number of hours declared. The time records must be in writing and approved by the persons working on the action and their supervisors, at least monthly. In the absence of reliable time records of the hours worked on the action, the Commission may accept alternative evidence supporting the number of hours declared, if it considers that it offers an adequate level of assurance.

As an exception, for persons working exclusively on the action, there is no need to keep time records, if the beneficiary signs a declaration confirming that the persons concerned have worked exclusively on the action.

18.2 Consequences of non-compliance

If a beneficiary breaches any of its obligations under this Article, costs insufficiently substantiated will be ineligible (see Article 6) and will be rejected (see Article 42), and the grant may be reduced (see Article 43).

Such breaches may also lead to any of the other measures described in Chapter 6.

ARTICLE 19 — SUBMISSION OF DELIVERABLES

19.1 Obligation to submit deliverables

The coordinator must submit the ‘deliverables’ identified in Annex 1, in accordance with the timing and conditions set out in it.

19.2 Consequences of non-compliance

If the coordinator breaches any of its obligations under this Article, the Commission may apply any of the measures described in Chapter 6.

ARTICLE 20 — REPORTING — PAYMENT REQUESTS

20.1 Obligation to submit reports

The coordinator must submit to the Commission (see Article 52) the technical and financial reports set out in this Article. These reports include requests for payment and must be drawn up using the forms and templates provided in the electronic exchange system (see Article 52).

20.2 Reporting periods

The action is divided into the following ‘reporting periods’:
20.3 Periodic reports — Requests for interim payments

The coordinator must submit a periodic report within 60 days following the end of each reporting period.

The periodic report must include the following:

(a) a ‘periodic technical report’ containing:
   (i) an explanation of the work carried out by the beneficiaries;
   (ii) an overview of the progress towards the objectives of the action, including milestones and deliverables identified in Annex 1.

   This report must include explanations justifying the differences between work expected to be carried out in accordance with Annex 1 and that actually carried out.

   The report must detail the exploitation and dissemination of the results and — if required in Annex 1 — an updated ‘plan for the exploitation and dissemination of the results’.

   The report must indicate the communication activities;

   (iii) a summary for publication by the Commission;

   (iv) the answers to the ‘questionnaire’, covering issues related to the action implementation and the economic and societal impact, notably in the context of the Horizon 2020 key performance indicators and the Horizon 2020 monitoring requirements;

(b) a ‘periodic financial report’ containing:
   (i) an ‘individual financial statement’ (see Annex 4) from each beneficiary, for the reporting period concerned.

   The individual financial statement must detail the eligible costs (actual costs, unit costs and flat-rate costs; see Article 6) for each budget category (see Annex 2).

   The beneficiaries must declare all eligible costs, even if — for actual costs, unit costs and flat-rate costs — they exceed the amounts indicated in the estimated budget (see Annex 2). Amounts which are not declared in the individual financial statement will not be taken into account by the Commission.

   If an individual financial statement is not submitted for a reporting period, it may be included in the periodic financial report for the next reporting period.

   The individual financial statements of the last reporting period must also detail the receipts of the action (see Article 5.3.3).

   Each beneficiary must certify that:
- the information provided is full, reliable and true;
- the costs declared are eligible (see Article 6);
- the costs can be substantiated by adequate records and supporting documentation (see Article 18) that will be produced upon request (see Article 17) or in the context of checks, reviews, audits and investigations (see Article 22), and
- for the last reporting period: that all the receipts have been declared (see Article 5.3.3);

(ii) an explanation of the use of resources and the information on subcontracting (see Article 13) and in-kind contributions provided by third parties (see Articles 11 and 12) from each beneficiary, for the reporting period concerned;

(iii) not applicable;

(iv) a ‘periodic summary financial statement’, created automatically by the electronic exchange system, consolidating the individual financial statements for the reporting period concerned and including — except for the last reporting period — the request for interim payment.

20.4 Final report — Request for payment of the balance

In addition to the periodic report for the last reporting period, the coordinator must submit the final report within 60 days following the end of the last reporting period.

The final report must include the following:

(a) a ‘final technical report’ with a summary for publication containing:

   (i) an overview of the results and their exploitation and dissemination;

   (ii) the conclusions on the action, and

   (iii) the socio-economic impact of the action;

(b) a ‘final financial report’ containing:

   (i) a ‘final summary financial statement’, created automatically by the electronic exchange system, consolidating the individual financial statements for all reporting periods and including the request for payment of the balance and

   (ii) a ‘certificate on the financial statements’ (drawn up in accordance with Annex 5) for each beneficiary, if it requests a total contribution of EUR 325 000 or more, as reimbursement of actual costs and unit costs calculated on the basis of its usual cost accounting practices (see Article 5.2 and Article 6.2).

20.5 Information on cumulative expenditure incurred

Not applicable
20.6 Currency for financial statements and conversion into euro

Financial statements must be drafted in euro.

Beneficiaries with accounting established in a currency other than the euro must convert the costs recorded in their accounts into euro, at the average of the daily exchange rates published in the C series of the Official Journal of the European Union, calculated over the corresponding reporting period.

If no daily euro exchange rate is published in the Official Journal of the European Union for the currency in question, they must be converted at the average of the monthly accounting rates published on the Commission’s website, calculated over the corresponding reporting period.

Beneficiaries with accounting established in euro must convert costs incurred in another currency into euro according to their usual accounting practices.

20.7 Language of reports

All reports (technical and financial reports, including financial statements) must be submitted in the language of the Agreement.

20.8 Consequences of non-compliance

If the reports submitted do not comply with this Article, the Commission may suspend the payment deadline (see Article 47) and apply any of the other measures described in Chapter 6.

If the coordinator breaches its obligation to submit the reports and if it fails to comply with this obligation within 30 days following a written reminder, the Commission may terminate the Agreement (see Article 50) or apply any of the other measures described in Chapter 6.

ARTICLE 21 — PAYMENTS AND PAYMENT ARRANGEMENTS

21.1 Payments to be made

The following payments will be made to the coordinator:

- one pre-financing payment;
- one or more interim payments, on the basis of the request(s) for interim payment (see Article 20), and
- one payment of the balance, on the basis of the request for payment of the balance (see Article 20).

21.2 Pre-financing payment — Amount — Amount retained for the Guarantee Fund

The aim of the pre-financing is to provide the beneficiaries with a float.

It remains the property of the EU until the payment of the balance.

The amount of the pre-financing payment will be EUR 4 792 740.66 (four million seven hundred and ninety two thousand seven hundred and forty EURO and sixty six eurocents).
The Commission will — except if Article 48 applies — make the pre-financing payment to the coordinator within 30 days, either from the entry into force of the Agreement (see Article 58) or from 10 days before the starting date of the action (see Article 3), whichever is the latest.

An amount of EUR **599 092.58** (five hundred and ninety nine thousand ninety two EURO and fifty eight eurocents), corresponding to 5% of the maximum grant amount (see Article 5.1), is retained by the Commission from the pre-financing payment and transferred into the ‘Guarantee Fund’.

### 21.3 Interim payments — Amount — Calculation

Interim payments reimburse the eligible costs incurred for the implementation of the action during the corresponding reporting periods.

The Commission will pay to the coordinator the amount due as interim payment within 90 days from receiving the periodic report (see Article 20.3), except if Articles 47 or 48 apply.

Payment is subject to the approval of the periodic report. Its approval does not imply recognition of the compliance, authenticity, completeness or correctness of its content.

The **amount due as interim payment** is calculated by the Commission in the following steps:

1. **Step 1 — Application of the reimbursement rates**
2. **Step 2 — Limit to 90% of the maximum grant amount**

#### 21.3.1 Step 1 — Application of the reimbursement rates

The reimbursement rate(s) (see Article 5.2) are applied to the eligible costs (actual costs, unit costs and flat-rate costs; see Article 6) declared by the beneficiaries (see Article 20) and approved by the Commission (see above) for the concerned reporting period.

#### 21.3.2 Step 2 — Limit to 90% of the maximum grant amount

The total amount of pre-financing and interim payments must not exceed 90% of the maximum grant amount set out in Article 5.1. The maximum amount for the interim payment will be calculated as follows:

\[
\{90\% \text{ of the maximum grant amount (see Article 5.1)} \}
\]

\[
\text{minus}
\]

\[
\{\text{pre-financing and previous interim payments}\}
\].

### 21.4 Payment of the balance — Amount — Calculation — Release of the amount retained for the Guarantee Fund

The payment of the balance reimburses the remaining part of the eligible costs incurred by the beneficiaries for the implementation of the action.

If the total amount of earlier payments is greater than the final grant amount (see Article 5.3), the payment of the balance takes the form of a recovery (see Article 44).

If the total amount of earlier payments is lower than the final grant amount, the Commission will
pay the balance within 90 days from receiving the final report (see Article 20.4), except if Articles 47 or 48 apply.

Payment is subject to the approval of the final report. Its approval does not imply recognition of the compliance, authenticity, completeness or correctness of its content.

The amount due as the balance is calculated by the Commission by deducting the total amount of pre-financing and interim payments (if any) already made, from the final grant amount determined in accordance with Article 5.3:

\[
\text{final grant amount (see Article 5.3)} - \text{pre-financing and interim payments (if any) made}
\]

At the payment of the balance, the amount retained for the Guarantee Fund (see above) will be released and:

- if the balance is positive: the amount released will be paid in full to the coordinator together with the amount due as the balance;

- if the balance is negative (payment of the balance taking the form of recovery): it will be deducted from the amount released (see Article 44.1.2). If the resulting amount:
  - is positive, it will be paid to the coordinator
  - is negative, it will be recovered.

The amount to be paid may however be offset — without the beneficiaries' consent — against any other amount owed by a beneficiary to the Commission or an executive agency (under the EU or Euratom budget), up to the maximum EU contribution indicated, for that beneficiary, in the estimated budget (see Annex 2).

21.5 Notification of amounts due

When making payments, the Commission will formally notify to the coordinator the amount due, specifying whether it concerns an interim payment or the payment of the balance.

For the payment of the balance, the notification will also specify the final grant amount.

In the case of reduction of the grant or recovery of undue amounts, the notification will be preceded by the contradictory procedure set out in Articles 43 and 44.

21.6 Currency for payments

The Commission will make all payments in euro.

21.7 Payments to the coordinator — Distribution to the beneficiaries

Payments will be made to the coordinator.

Payments to the coordinator will discharge the Commission from its payment obligation.
The coordinator must distribute the payments between the beneficiaries without unjustified delay.

Pre-financing may however be distributed only:

(a) if the minimum number of beneficiaries set out in the call for proposals has acceded to the Agreement (see Article 56) and

(b) to beneficiaries that have acceded to the Agreement (see Article 56).

21.8 Bank account for payments

All payments will be made to the following bank account:

- Name of bank: ING BANK N.V.
- Full name of the account holder: TNO EC GELDEN
- IBAN code: NL30INGB0651227798

21.9 Costs of payment transfers

The cost of the payment transfers is borne as follows:

- the Commission bears the cost of transfers charged by its bank;
- the beneficiary bears the cost of transfers charged by its bank;
- the party causing a repetition of a transfer bears all costs of the repeated transfer.

21.10 Date of payment

Payments by the Commission are considered to have been carried out on the date when they are debited to its account.

21.11 Consequences of non-compliance

21.11.1 If the Commission does not pay within the payment deadlines (see above), the beneficiaries are entitled to late-payment interest at the rate applied by the European Central Bank (ECB) for its main refinancing operations in euros (‘reference rate’), plus three and a half points. The reference rate is the rate in force on the first day of the month in which the payment deadline expires, as published in the C series of the Official Journal of the European Union.

If the late-payment interest is lower than or equal to EUR 200, it will be paid to the coordinator only upon request submitted within two months of receiving the late payment.

Late-payment interest is not due if all beneficiaries are EU Member States (including regional and local government authorities or other public bodies acting on behalf of a Member State for the purpose of this Agreement).

Suspension of the payment deadline or payments (see Articles 47 and 48) will not be considered as late payment.

Late-payment interest covers the period running from the day following the due date for payment (see above), up to and including the date of payment.
Late-payment interest is not considered for the purposes of calculating the final grant amount.

21.11.2 If the coordinator breaches any of its obligations under this Article, the grant may be reduced (see Article 43) and the Agreement or the participation of the coordinator may be terminated (see Article 50).

Such breaches may also lead to any of the other measures described in Chapter 6.

ARTICLE 22 — CHECKS, REVIEWS, AUDITS AND INVESTIGATIONS — EXTENSION OF FINDINGS

22.1 Checks, reviews and audits by the Commission

22.1.1 Right to carry out checks

The Commission will — during the implementation of the action or afterwards — check the proper implementation of the action and compliance with the obligations under the Agreement, including assessing deliverables and reports.

For this purpose the Commission may be assisted by external persons or bodies.

The Commission may also request additional information in accordance with Article 17. The Commission may request beneficiaries to provide such information to it directly.

Information provided must be accurate, precise and complete and in the format requested, including electronic format.

22.1.2 Right to carry out reviews

The Commission may — during the implementation of the action or afterwards — carry out reviews on the proper implementation of the action (including assessment of deliverables and reports), compliance with the obligations under the Agreement and continued scientific or technological relevance of the action.

Reviews may be started up to two years after the payment of the balance. They will be formally notified to the coordinator or beneficiary concerned and will be considered to have started on the date of the formal notification.

If the review is carried out on a third party (see Articles 10 to 16), the beneficiary concerned must inform the third party.

The Commission may carry out reviews directly (using its own staff) or indirectly (using external persons or bodies appointed to do so). It will inform the coordinator or beneficiary concerned of the identity of the external persons or bodies. They have the right to object to the appointment on grounds of commercial confidentiality.

The coordinator or beneficiary concerned must provide — within the deadline requested — any information and data in addition to deliverables and reports already submitted (including information on the use of resources). The Commission may request beneficiaries to provide such information to it directly.
The coordinator or beneficiary concerned may be requested to participate in meetings, including with external experts.

For on-the-spot reviews, the beneficiaries must allow access to their sites and premises, including to external persons or bodies, and must ensure that information requested is readily available.

Information provided must be accurate, precise and complete and in the format requested, including electronic format.

On the basis of the review findings, a ‘review report’ will be drawn up.

The Commission will formally notify the review report to the coordinator or beneficiary concerned, which has 30 days to formally notify observations (‘contradictory review procedure’).

Reviews (including review reports) are in the language of the Agreement.

22.1.3 Right to carry out audits

The Commission may — during the implementation of the action or afterwards — carry out audits on the proper implementation of the action and compliance with the obligations under the Agreement.

Audits may be started up to two years after the payment of the balance. They will be formally notified to the coordinator or beneficiary concerned and will be considered to have started on the date of the formal notification.

If the audit is carried out on a third party (see Articles 10 to 16), the beneficiary concerned must inform the third party.

The Commission may carry out audits directly (using its own staff) or indirectly (using external persons or bodies appointed to do so). It will inform the coordinator or beneficiary concerned of the identity of the external persons or bodies. They have the right to object to the appointment on grounds of commercial confidentiality.

The coordinator or beneficiary concerned must provide — within the deadline requested — any information (including complete accounts, individual salary statements or other personal data) to verify compliance with the Agreement. The Commission may request beneficiaries to provide such information to it directly.

For on-the-spot audits, the beneficiaries must allow access to their sites and premises, including to external persons or bodies, and must ensure that information requested is readily available.

Information provided must be accurate, precise and complete and in the format requested, including electronic format.

On the basis of the audit findings, a ‘draft audit report’ will be drawn up.

The Commission will formally notify the draft audit report to the coordinator or beneficiary concerned, which has 30 days to formally notify observations (‘contradictory audit procedure’). This period may be extended by the Commission in justified cases.

The ‘final audit report’ will take into account observations by the coordinator or beneficiary concerned. The report will be formally notified to it.
Audits (including audit reports) are in the language of the Agreement.

The Commission may also access the beneficiaries’ statutory records for the periodical assessment of unit costs or flat-rate amounts.

22.2 Investigations by the European Anti-Fraud Office (OLAF)

Under Regulations No 883/2013\(^\text{16}\) and No 2185/96\(^\text{17}\) (and in accordance with their provisions and procedures), the European Anti-Fraud Office (OLAF) may — at any moment during implementation of the action or afterwards — carry out investigations, including on-the-spot checks and inspections, to establish whether there has been fraud, corruption or any other illegal activity affecting the financial interests of the EU.

22.3 Checks and audits by the European Court of Auditors (ECA)

Under Article 287 of the Treaty on the Functioning of the European Union (TFEU) and Article 161 of the Financial Regulation No 966/2012\(^\text{18}\), the European Court of Auditors (ECA) may — at any moment during implementation of the action or afterwards — carry out audits.

The ECA has the right of access for the purpose of checks and audits.

22.4 Checks, reviews, audits and investigations for international organisations

Not applicable

22.5 Consequences of findings in checks, reviews, audits and investigations — Extension of findings

22.5.1 Findings in this grant

Findings in checks, reviews, audits or investigations carried out in the context of this grant may lead to the rejection of ineligible costs (see Article 42), reduction of the grant (see Article 43), recovery of undue amounts (see Article 44) or to any of the other measures described in Chapter 6.

Rejection of costs or reduction of the grant after the payment of the balance will lead to a revised final grant amount (see Article 5.4).

Findings in checks, reviews, audits or investigations may lead to a request for amendment for the modification of Annex 1 (see Article 55).

Checks, reviews, audits or investigations that find systemic or recurrent errors, irregularities, fraud or


\(^{17}\) Council Regulation (Euratom, EC) No 2185/1996 of 11 November 1996 concerning on-the-spot checks and inspections carried out by the Commission in order to protect the European Communities' financial interests against fraud and other irregularities (OJ L 292, 15.11.1996, p. 2).

breach of obligations may also lead to consequences in other EU or Euratom grants awarded under similar conditions (‘extension of findings from this grant to other grants’).

Moreover, findings arising from an OLAF investigation may lead to criminal prosecution under national law.

### 22.5.2 Findings in other grants

The Commission may extend findings from other grants to this grant (‘extension of findings from other grants to this grant’), if:

(a) the beneficiary concerned is found, in other EU or Euratom grants awarded under similar conditions, to have committed systemic or recurrent errors, irregularities, fraud or breach of obligations that have a material impact on this grant and

(b) those findings are formally notified to the beneficiary concerned — together with the list of grants affected by the findings — no later than two years after the payment of the balance of this grant.

The extension of findings may lead to the rejection of costs (see Article 42), reduction of the grant (see Article 43), recovery of undue amounts (see Article 44), suspension of payments (see Article 48), suspension of the action implementation (see Article 49) or termination (see Article 50).

### 22.5.3 Procedure

The Commission will formally notify the beneficiary concerned the systemic or recurrent errors and its intention to extend these audit findings, together with the list of grants affected.

#### 22.5.3.1 If the findings concern eligibility of costs: the formal notification will include:

(a) an invitation to submit observations on the list of grants affected by the findings;

(b) the request to submit revised financial statements for all grants affected;

(c) the correction rate for extrapolation established by the Commission on the basis of the systemic or recurrent errors, to calculate the amounts to be rejected if the beneficiary concerned:

- considers that the submission of revised financial statements is not possible or practicable or
- does not submit revised financial statements.

The beneficiary concerned has 90 days from receiving notification to submit observations, revised financial statements or to propose a duly substantiated alternative correction method. This period may be extended by the Commission in justified cases.

The Commission may then start a rejection procedure in accordance with Article 42, on the basis of:

- the revised financial statements, if approved;
- the proposed alternative correction method, if accepted

or
- the initially notified correction rate for extrapolation, if it does not receive any observations or revised financial statements, does not accept the observations or the proposed alternative correction method or does not approve the revised financial statements.

22.5.3.2 If the findings concern **substantial errors, irregularities or fraud** or **serious breach of obligations**: the formal notification will include:

(a) an invitation to submit observations on the list of grants affected by the findings and

(b) the flat-rate the Commission intends to apply according to the principle of proportionality.

The beneficiary concerned has 90 days from receiving notification to submit observations or to propose a duly substantiated alternative flat-rate.

The Commission may then start a reduction procedure in accordance with Article 43, on the basis of:

- the proposed alternative flat-rate, if accepted

or

- the initially notified flat-rate, if it does not receive any observations or does not accept the observations or the proposed alternative flat-rate.

### 22.6 Consequences of non-compliance

If a beneficiary breaches any of its obligations under this Article, any insufficiently substantiated costs will be ineligible (see Article 6) and will be rejected (see Article 42).

Such breaches may also lead to any of the other measures described in Chapter 6.

**ARTICLE 23 — EVALUATION OF THE IMPACT OF THE ACTION**

#### 23.1 Right to evaluate the impact of the action

The Commission may carry out interim and final evaluations of the impact of the action measured against the objective of the EU programme.

Evaluations may be started during implementation of the action and up to five years after the payment of the balance. The evaluation is considered to start on the date of the formal notification to the coordinator or beneficiaries.

The Commission may make these evaluations directly (using its own staff) or indirectly (using external bodies or persons it has authorised to do so).

The coordinator or beneficiaries must provide any information relevant to evaluate the impact of the action, including information in electronic format.

#### 23.2 Consequences of non-compliance

If a beneficiary breaches any of its obligations under this Article, the Commission may apply the measures described in Chapter 6.
SECTION 3  RIGHTS AND OBLIGATIONS RELATED TO BACKGROUND AND RESULTS

SUBSECTION 1  GENERAL

ARTICLE 23a — MANAGEMENT OF INTELLECTUAL PROPERTY

23a.1  Obligation to take measures to implement the Commission Recommendation on the management of intellectual property in knowledge transfer activities

Beneficiaries that are universities or other public research organisations must take measures to implement the principles set out in Points 1 and 2 of the Code of Practice annexed to the Commission Recommendation on the management of intellectual property in knowledge transfer activities 19.

This does not change the obligations set out in Subsections 2 and 3 of this Section.

The beneficiaries must ensure that researchers and third parties involved in the action are aware of them.

23a.2  Consequences of non-compliance

If a beneficiary breaches its obligations under this Article, the Commission may apply any of the measures described in Chapter 6.

SUBSECTION 2  RIGHTS AND OBLIGATIONS RELATED TO BACKGROUND

ARTICLE 24 — AGREEMENT ON BACKGROUND

24.1  Agreement on background

The beneficiaries must identify and agree (in writing) on the background for the action (‘agreement on background’).

‘Background’ means any data, know-how or information — whatever its form or nature (tangible or intangible), including any rights such as intellectual property rights — that:

(a) is held by the beneficiaries before they acceded to the Agreement, and

(b) is needed to implement the action or exploit the results.

24.2  Consequences of non-compliance

If a beneficiary breaches any of its obligations under this Article, the grant may be reduced (see Article 43).

Such breaches may also lead to any of the other measures described in Chapter 6.

19 Commission Recommendation C(2008) 1329 of 10.4.2008 on the management of intellectual property in knowledge transfer activities and the Code of Practice for universities and other public research institutions attached to this recommendation.
ARTICLE 25 — ACCESS RIGHTS TO BACKGROUND

25.1 Exercise of access rights — Waiving of access rights — No sub-licensing

To exercise access rights, this must first be requested in writing (‘request for access’).

‘Access rights’ means rights to use results or background under the terms and conditions laid down in this Agreement.

Waivers of access rights are not valid unless in writing.

Unless agreed otherwise, access rights do not include the right to sub-license.

25.2 Access rights for other beneficiaries, for implementing their own tasks under the action

The beneficiaries must give each other access — on a royalty-free basis — to background needed to implement their own tasks under the action, unless the beneficiary that holds the background has — before acceding to the Agreement —:

(a) informed the other beneficiaries that access to its background is subject to legal restrictions or limits, including those imposed by the rights of third parties (including personnel), or

(b) agreed with the other beneficiaries that access would not be on a royalty-free basis.

25.3 Access rights for other beneficiaries, for exploiting their own results

The beneficiaries must give each other access — under fair and reasonable conditions — to background needed for exploiting their own results, unless the beneficiary that holds the background has — before acceding to the Agreement — informed the other beneficiaries that access to its background is subject to legal restrictions or limits, including those imposed by the rights of third parties (including personnel).

‘Fair and reasonable conditions’ means appropriate conditions, including possible financial terms or royalty-free conditions, taking into account the specific circumstances of the request for access, for example the actual or potential value of the results or background to which access is requested and/or the scope, duration or other characteristics of the exploitation envisaged.

Requests for access may be made — unless agreed otherwise — up to one year after the period set out in Article 3.

25.4 Access rights for affiliated entities

Unless otherwise agreed in the consortium agreement, access to background must also be given — under fair and reasonable conditions (see above; Article 25.3) and unless it is subject to legal restrictions or limits, including those imposed by the rights of third parties (including personnel) — to affiliated entities established in an EU Member State or ‘associated country’, if this is needed to exploit the results generated by the beneficiaries to which they are affiliated.

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20 For the definition see Article 2.1(2) Rules for Participation Regulation No 1290/2013: ‘affiliated entity’ means any legal entity that is:
- under the direct or indirect control of a participant, or
- under the same direct or indirect control as the participant, or
Unless agreed otherwise (see above; Article 25.1), the affiliated entity concerned must make the request directly to the beneficiary that holds the background.

Requests for access may be made — unless agreed otherwise — up to one year after the period set out in Article 3.

**25.5 Access rights for third parties**

Not applicable

**25.6 Consequences of non-compliance**

If a beneficiary breaches any of its obligations under this Article, the grant may be reduced (see Article 43).

Such breaches may also lead to any of the other measures described in Chapter 6.

**SUBSECTION 3 RIGHTS AND OBLIGATIONS RELATED TO RESULTS**

**ARTICLE 26 — OWNERSHIP OF RESULTS**

**26.1 Ownership by the beneficiary that generates the results**

Results are owned by the beneficiary that generates them.

‘Results’ means any (tangible or intangible) output of the action such as data, knowledge or information — whatever its form or nature, whether it can be protected or not — that is generated in the action, as well as any rights attached to it, including intellectual property rights.

**26.2 Joint ownership by several beneficiaries**

Two or more beneficiaries own results jointly if:

(a) they have jointly generated them and

(b) it is not possible to:

- directly or indirectly controlling a participant.

‘Control’ may take any of the following forms:

(a) the direct or indirect holding of more than 50% of the nominal value of the issued share capital in the legal entity concerned, or of a majority of the voting rights of the shareholders or associates of that entity;

(b) the direct or indirect holding, in fact or in law, of decision-making powers in the legal entity concerned.

However the following relationships between legal entities shall not in themselves be deemed to constitute controlling relationships:

(a) the same public investment corporation, institutional investor or venture-capital company has a direct or indirect holding of more than 50% of the nominal value of the issued share capital or a majority of voting rights of the shareholders or associates;

(b) the legal entities concerned are owned or supervised by the same public body.

21 For the definition, see Article 2.1(3) of the Rules for Participation Regulation No 1290/2013: ‘associated country’ means a third country which is party to an international agreement with the Union, as identified in Article 7 of Horizon 2020 Framework Programme Regulation No 1291/2013. Article 7 sets out the conditions for association of non-EU countries to Horizon 2020.
(i) establish the respective contribution of each beneficiary, or

(ii) separate them for the purpose of applying for, obtaining or maintaining their protection (see Article 27).

The joint owners must agree (in writing) on the allocation and terms of exercise of their joint ownership (‘joint ownership agreement’), to ensure compliance with their obligations under this Agreement.

Unless otherwise agreed in the joint ownership agreement, each joint owner may grant non-exclusive licences to third parties to exploit jointly-owned results (without any right to sub-license), if the other joint owners are given:

(a) at least 45 days advance notice and

(b) fair and reasonable compensation.

Once the results have been generated, joint owners may agree (in writing) to apply another regime than joint ownership (such as, for instance, transfer to a single owner (see Article 30) with access rights for the others).

26.3 Rights of third parties (including personnel)

If third parties (including personnel) may claim rights to the results, the beneficiary concerned must ensure that it complies with its obligations under the Agreement.

If a third party generates results, the beneficiary concerned must obtain all necessary rights (transfer, licences or other) from the third party, in order to be able to respect its obligations as if those results were generated by the beneficiary itself.

If obtaining the rights is impossible, the beneficiary must refrain from using the third party to generate the results.

26.4 EU ownership, to protect results

26.4.1 The EU may — with the consent of the beneficiary concerned — assume ownership of results to protect them, if a beneficiary intends — up to four years after the period set out in Article 3 — to disseminate its results without protecting them, except in any of the following cases:

(a) the lack of protection is because protecting the results is not possible, reasonable or justified (given the circumstances);

(b) the lack of protection is because there is a lack of potential for commercial or industrial exploitation, or

(c) the beneficiary intends to transfer the results to another beneficiary or third party established in an EU Member State or associated country, which will protect them.

Before the results are disseminated and unless any of the cases above under Points (a), (b) or (c) applies, the beneficiary must formally notify the Commission and at the same time inform it of any reasons for refusing consent. The beneficiary may refuse consent only if it can show that its legitimate interests would suffer significant harm.
If the Commission decides to assume ownership, it will formally notify the beneficiary concerned within 45 days of receiving notification.

No dissemination relating to these results may take place before the end of this period or, if the Commission takes a positive decision, until it has taken the necessary steps to protect the results.

26.4.2 The EU may — with the consent of the beneficiary concerned — assume ownership of results to protect them, if a beneficiary intends — up to four years after the period set out in Article 3 — to stop protecting them or not to seek an extension of protection, except in any of the following cases:

(a) the protection is stopped because of a lack of potential for commercial or industrial exploitation;

(b) an extension would not be justified given the circumstances.

A beneficiary that intends to stop protecting results or not seek an extension must — unless any of the cases above under Points (a) or (b) applies — formally notify the Commission at least 60 days before the protection lapses or its extension is no longer possible and at the same time inform it of any reasons for refusing consent. The beneficiary may refuse consent only if it can show that its legitimate interests would suffer significant harm.

If the Commission decides to assume ownership, it will formally notify the beneficiary concerned within 45 days of receiving notification.

26.5 Consequences of non-compliance

If a beneficiary breaches any of its obligations under this Article, the grant may be reduced (see Article 43).

Such breaches may also lead to the any of the other measures described in Chapter 6.

ARTICLE 27 — PROTECTION OF RESULTS — VISIBILITY OF EU FUNDING

27.1 Obligation to protect the results

Each beneficiary must examine the possibility of protecting its results and must adequately protect them — for an appropriate period and with appropriate territorial coverage — if:

(a) the results can reasonably be expected to be commercially or industrially exploited and

(b) protecting them is possible, reasonable and justified (given the circumstances).

When deciding on protection, the beneficiary must consider its own legitimate interests and the legitimate interests (especially commercial) of the other beneficiaries.

27.2 EU ownership, to protect the results

If a beneficiary intends not to protect its results, to stop protecting them or not seek an extension of protection, the EU may — under certain conditions (see Article 26.4) — assume ownership to ensure their (continued) protection.

27.3 Information on EU funding
Applications for protection of results (including patent applications) filed by or on behalf of a beneficiary must — unless the Commission requests or agrees otherwise or unless it is impossible — include the following:

“The project leading to this application has received funding from the European Union’s Horizon 2020 research and innovation programme under grant agreement No 874703”.

27.4 Consequences of non-compliance

If a beneficiary breaches any of its obligations under this Article, the grant may be reduced (see Article 43).

Such a breach may also lead to any of the other measures described in Chapter 6.

ARTICLE 28 — EXPLOITATION OF RESULTS

28.1 Obligation to exploit the results

Each beneficiary must — up to four years after the period set out in Article 3 — take measures aiming to ensure ‘exploitation’ of its results (either directly or indirectly, in particular through transfer or licensing; see Article 30) by:

(a) using them in further research activities (outside the action);

(b) developing, creating or marketing a product or process;

(c) creating and providing a service, or

(d) using them in standardisation activities.

This does not change the security obligations in Article 37, which still apply.

28.2 Results that could contribute to European or international standards — Information on EU funding

If results are incorporated in a standard, the beneficiary concerned must — unless the Commission requests or agrees otherwise or unless it is impossible — ask the standardisation body to include the following statement in (information related to) the standard:

“Results incorporated in this standard received funding from the European Union’s Horizon 2020 research and innovation programme under grant agreement No 874703”.

28.3 Consequences of non-compliance

If a beneficiary breaches any of its obligations under this Article, the grant may be reduced in accordance with Article 43.

Such a breach may also lead to any of the other measures described in Chapter 6.

ARTICLE 29 — DISSEMINATION OF RESULTS — OPEN ACCESS — VISIBILITY OF EU FUNDING

29.1 Obligation to disseminate results
Unless it goes against their legitimate interests, each beneficiary must — as soon as possible — *disseminate* its results by disclosing them to the public by appropriate means (other than those resulting from protecting or exploiting the results), including in scientific publications (in any medium).

This does not change the obligation to protect results in Article 27, the confidentiality obligations in Article 36, the security obligations in Article 37 or the obligations to protect personal data in Article 39, all of which still apply.

A beneficiary that intends to disseminate its results must give advance notice to the other beneficiaries of — unless agreed otherwise — at least 45 days, together with sufficient information on the results it will disseminate.

Any other beneficiary may object within — unless agreed otherwise — 30 days of receiving notification, if it can show that its legitimate interests in relation to the results or background would be significantly harmed. In such cases, the dissemination may not take place unless appropriate steps are taken to safeguard these legitimate interests.

If a beneficiary intends not to protect its results, it may — under certain conditions (see Article 26.4.1) — need to formally notify the Commission before dissemination takes place.

## 29.2 Open access to scientific publications

Each beneficiary must ensure open access (free of charge online access for any user) to all peer-reviewed scientific publications relating to its results.

In particular, it must:

(a) as soon as possible and at the latest on publication, deposit a machine-readable electronic copy of the published version or final peer-reviewed manuscript accepted for publication in a repository for scientific publications;

Moreover, the beneficiary must aim to deposit at the same time the research data needed to validate the results presented in the deposited scientific publications.

(b) ensure open access to the deposited publication — via the repository — at the latest:

(i) on publication, if an electronic version is available for free via the publisher, or

(ii) within six months of publication (twelve months for publications in the social sciences and humanities) in any other case.

(c) ensure open access — via the repository — to the bibliographic metadata that identify the deposited publication.

The bibliographic metadata must be in a standard format and must include all of the following:

- the terms “European Union (EU)” and “Horizon 2020”;

- the name of the action, acronym and grant number;

- the publication date, and length of embargo period if applicable, and
29.3 Open access to research data
Not applicable;

29.4 Information on EU funding — Obligation and right to use the EU emblem
Unless the Commission requests or agrees otherwise or unless it is impossible, any dissemination of results (in any form, including electronic) must:

(a) display the EU emblem and

(b) include the following text:

“This project has received funding from the European Union’s Horizon 2020 research and innovation programme under grant agreement No 874703”.

When displayed together with another logo, the EU emblem must have appropriate prominence.

For the purposes of their obligations under this Article, the beneficiaries may use the EU emblem without first obtaining approval from the Commission.

This does not however give them the right to exclusive use.

Moreover, they may not appropriate the EU emblem or any similar trademark or logo, either by registration or by any other means.

29.5 Disclaimer excluding Commission responsibility
Any dissemination of results must indicate that it reflects only the author's view and that the Commission is not responsible for any use that may be made of the information it contains.

29.6 Consequences of non-compliance
If a beneficiary breaches any of its obligations under this Article, the grant may be reduced (see Article 43).

Such a breach may also lead to any of the other measures described in Chapter 6.

ARTICLE 30 — TRANSFER AND LICENSING OF RESULTS

30.1 Transfer of ownership
Each beneficiary may transfer ownership of its results.

It must however ensure that its obligations under Articles 26.2, 26.4, 27, 28, 29, 30 and 31 also apply to the new owner and that this owner has the obligation to pass them on in any subsequent transfer.

This does not change the security obligations in Article 37, which still apply.

Unless agreed otherwise (in writing) for specifically-identified third parties or unless impossible under
applicable EU and national laws on mergers and acquisitions, a beneficiary that intends to transfer ownership of results must give at least 45 days advance notice (or less if agreed in writing) to the other beneficiaries that still have (or still may request) access rights to the results. This notification must include sufficient information on the new owner to enable any beneficiary concerned to assess the effects on its access rights.

Unless agreed otherwise (in writing) for specifically-identified third parties, any other beneficiary may object within 30 days of receiving notification (or less if agreed in writing), if it can show that the transfer would adversely affect its access rights. In this case, the transfer may not take place until agreement has been reached between the beneficiaries concerned.

30.2 Granting licenses

Each beneficiary may grant licences to its results (or otherwise give the right to exploit them), if:

(a) this does not impede the access rights under Article 31 and

(b) not applicable.

In addition to Points (a) and (b), exclusive licences for results may be granted only if all the other beneficiaries concerned have waived their access rights (see Article 31.1).

This does not change the dissemination obligations in Article 29 or security obligations in Article 37, which still apply.

30.3 Commission right to object to transfers or licensing

Not applicable

30.4 Consequences of non-compliance

If a beneficiary breaches any of its obligations under this Article, the grant may be reduced (see Article 43).

Such a breach may also lead to any of the other measures described in Chapter 6.

ARTICLE 31 — ACCESS RIGHTS TO RESULTS

31.1 Exercise of access rights — Waiving of access rights — No sub-licensing

The conditions set out in Article 25.1 apply.

The obligations set out in this Article do not change the security obligations in Article 37, which still apply.

31.2 Access rights for other beneficiaries, for implementing their own tasks under the action

The beneficiaries must give each other access — on a royalty-free basis — to results needed for implementing their own tasks under the action.

31.3 Access rights for other beneficiaries, for exploiting their own results
The beneficiaries must give each other — under fair and reasonable conditions (see Article 25.3) — access to results needed for exploiting their own results.

Requests for access may be made — unless agreed otherwise — up to one year after the period set out in Article 3.

31.4 Access rights of affiliated entities

Unless agreed otherwise in the consortium agreement, access to results must also be given — under fair and reasonable conditions (Article 25.3) — to affiliated entities established in an EU Member State or associated country, if this is needed for those entities to exploit the results generated by the beneficiaries to which they are affiliated.

Unless agreed otherwise (see above; Article 31.1), the affiliated entity concerned must make any such request directly to the beneficiary that owns the results.

Requests for access may be made — unless agreed otherwise — up to one year after the period set out in Article 3.

31.5 Access rights for the EU institutions, bodies, offices or agencies and EU Member States

The beneficiaries must give access to their results — on a royalty-free basis — to EU institutions, bodies, offices or agencies, for developing, implementing or monitoring EU policies or programmes.

Such access rights are limited to non-commercial and non-competitive use.

This does not change the right to use any material, document or information received from the beneficiaries for communication and publicising activities (see Article 38.2).

31.6 Access rights for third parties

The beneficiaries must give — under the conditions set out in Article 31.2 and 31.3 — access to their results to complementary beneficiaries\(^{22}\), for the purposes of the complementary grant agreement(s) (see Article 2).

31.7 Consequences of non-compliance

If a beneficiary breaches any of its obligations under this Article, the grant may be reduced (see Article 43).

Such breaches may also lead to any of the other measures described in Chapter 6.

SECTION 4 OTHER RIGHTS AND OBLIGATIONS

ARTICLE 32 — RECRUITMENT AND WORKING CONDITIONS FOR RESEARCHERS

32.1 Obligation to take measures to implement the European Charter for Researchers and Code of Conduct for the Recruitment of Researchers

\(^{22}\) ‘Complementary beneficiary’ means a beneficiary of a complementary grant agreement.
The beneficiaries must take all measures to implement the principles set out in the Commission Recommendation on the European Charter for Researchers and the Code of Conduct for the Recruitment of Researchers\textsuperscript{23}, in particular regarding:

- working conditions;
- transparent recruitment processes based on merit, and
- career development.

The beneficiaries must ensure that researchers and third parties involved in the action are aware of them.

32.2 Consequences of non-compliance

If a beneficiary breaches its obligations under this Article, the Commission may apply any of the measures described in Chapter 6.

ARTICLE 33 — GENDER EQUALITY

33.1 Obligation to aim for gender equality

The beneficiaries must take all measures to promote equal opportunities between men and women in the implementation of the action. They must aim, to the extent possible, for a gender balance at all levels of personnel assigned to the action, including at supervisory and managerial level.

33.2 Consequences of non-compliance

If a beneficiary breaches its obligations under this Article, the Commission may apply any of the measures described in Chapter 6.

ARTICLE 34 — ETHICS AND RESEARCH INTEGRITY

34.1 Obligation to comply with ethical and research integrity principles

The beneficiaries must carry out the action in compliance with:

(a) ethical principles (including the highest standards of research integrity)

and

(b) applicable international, EU and national law.

Funding will not be granted for activities carried out outside the EU if they are prohibited in all Member States or for activities which destroy human embryos (for example, for obtaining stem cells).

The beneficiaries must ensure that the activities under the action have an exclusive focus on civil applications.

The beneficiaries must ensure that the activities under the action do not:

(a) aim at human cloning for reproductive purposes;

(b) intend to modify the genetic heritage of human beings which could make such changes heritable (with the exception of research relating to cancer treatment of the gonads, which may be financed), or

(c) intend to create human embryos solely for the purpose of research or for the purpose of stem cell procurement, including by means of somatic cell nuclear transfer.

In addition, the beneficiaries must respect the fundamental principle of research integrity — as set out, for instance, in the European Code of Conduct for Research Integrity24.

This implies compliance with the following fundamental principles:

- **reliability** in ensuring the quality of research reflected in the design, the methodology, the analysis and the use of resources;

- **honesty** in developing, undertaking, reviewing, reporting and communicating research in a transparent, fair and unbiased way;

- **respect** for colleagues, research participants, society, ecosystems, cultural heritage and the environment;

- **accountability** for the research from idea to publication, for its management and organisation, for training, supervision and mentoring, and for its wider impacts

and means that beneficiaries must ensure that persons carrying out research tasks follow the good research practices and refrain from the research integrity violations described in this Code.

This does not change the other obligations under this Agreement or obligations under applicable international, EU or national law, all of which still apply.

34.2 Activities raising ethical issues

Activities raising ethical issues must comply with the ‘ethics requirements’ set out as deliverables in Annex 1.

Before the beginning of an activity raising an ethical issue, each beneficiary must have obtained:

(a) any ethics committee opinion required under national law and

(b) any notification or authorisation for activities raising ethical issues required under national and/or European law

needed for implementing the action tasks in question.

The documents must be kept on file and be submitted upon request by the coordinator to the Commission (see Article 52). If they are not in English, they must be submitted together with

24 European Code of Conduct for Research Integrity of ALLEA (All European Academies)
an English summary, which shows that the action tasks in question are covered and includes the conclusions of the committee or authority concerned (if available).

34.3 Activities involving human embryos or human embryonic stem cells

Activities involving research on human embryos or human embryonic stem cells may be carried out, in addition to Article 34.1, only if:

- they are set out in Annex 1 or
- the coordinator has obtained explicit approval (in writing) from the Commission (see Article 52).

34.4 Consequences of non-compliance

If a beneficiary breaches any of its obligations under this Article, the grant may be reduced (see Article 43) and the Agreement or participation of the beneficiary may be terminated (see Article 50).

Such breaches may also lead to any of the other measures described in Chapter 6.

ARTICLE 35 — CONFLICT OF INTERESTS

35.1 Obligation to avoid a conflict of interests

The beneficiaries must take all measures to prevent any situation where the impartial and objective implementation of the action is compromised for reasons involving economic interest, political or national affinity, family or emotional ties or any other shared interest (‘conflict of interests’).

They must formally notify to the Commission without delay any situation constituting or likely to lead to a conflict of interests and immediately take all the necessary steps to rectify this situation.

The Commission may verify that the measures taken are appropriate and may require additional measures to be taken by a specified deadline.

35.2 Consequences of non-compliance

If a beneficiary breaches any of its obligations under this Article, the grant may be reduced (see Article 43) and the Agreement or participation of the beneficiary may be terminated (see Article 50).

Such breaches may also lead to any of the other measures described in Chapter 6.

ARTICLE 36 — CONFIDENTIALITY

36.1 General obligation to maintain confidentiality

During implementation of the action and for four years after the period set out in Article 3, the parties must keep confidential any data, documents or other material (in any form) that is identified as confidential at the time it is disclosed (‘confidential information’).

If a beneficiary requests, the Commission may agree to keep such information confidential for an additional period beyond the initial four years.
If information has been identified as confidential only orally, it will be considered to be confidential only if this is confirmed in writing within 15 days of the oral disclosure.

Unless otherwise agreed between the parties, they may use confidential information only to implement the Agreement.

The beneficiaries may disclose confidential information to their personnel or third parties involved in the action only if they:

(a) need to know to implement the Agreement and

(b) are bound by an obligation of confidentiality.

This does not change the security obligations in Article 37, which still apply.

The Commission may disclose confidential information to its staff, other EU institutions and bodies. It may disclose confidential information to third parties, if:

(a) this is necessary to implement the Agreement or safeguard the EU’s financial interests and

(b) the recipients of the information are bound by an obligation of confidentiality.

Under the conditions set out in Article 4 of the Rules for Participation Regulation No 1290/2013, the Commission must moreover make available information on the results to other EU institutions, bodies, offices or agencies as well as Member States or associated countries.

The confidentiality obligations no longer apply if:

(a) the disclosing party agrees to release the other party;

(b) the information was already known by the recipient or is given to him without obligation of confidentiality by a third party that was not bound by any obligation of confidentiality;

(c) the recipient proves that the information was developed without the use of confidential information;

(d) the information becomes generally and publicly available, without breaching any confidentiality obligation, or

(e) the disclosure of the information is required by EU or national law.

36.2 Consequences of non-compliance

If a beneficiary breaches any of its obligations under this Article, the grant may be reduced (see Article 43).

Such breaches may also lead to any of the other measures described in Chapter 6.

ARTICLE 37 — SECURITY-RELATED OBLIGATIONS

37.1 Results with a security recommendation

Not applicable

37.2 Classified information

Not applicable

37.3 Activities involving dual-use goods or dangerous materials and substances

Not applicable

37.4 Consequences of non-compliance

Not applicable

ARTICLE 38 — PROMOTING THE ACTION — VISIBILITY OF EU FUNDING

38.1 Communication activities by beneficiaries

38.1.1 Obligation to promote the action and its results

The beneficiaries must promote the action and its results, by providing targeted information to multiple audiences (including the media and the public) in a strategic and effective manner.

This does not change the dissemination obligations in Article 29, the confidentiality obligations in Article 36 or the security obligations in Article 37, all of which still apply.

Before engaging in a communication activity expected to have a major media impact, the beneficiaries must inform the Commission (see Article 52).

38.1.2 Information on EU funding — Obligation and right to use the EU emblem

Unless the Commission requests or agrees otherwise or unless it is impossible, any communication activity related to the action (including in electronic form, via social media, etc.) and any infrastructure, equipment and major results funded by the grant must:

(a) display the EU emblem and

(b) include the following text:

For communication activities:

“This project has received funding from the European Union’s Horizon 2020 research and innovation programme under grant agreement No 874703”.

For infrastructure, equipment and major results:

“This [infrastructure]/[equipment]/[insert type of result] is part of a project that has received funding from the European Union’s Horizon 2020 research and innovation programme under grant agreement No 874703”.

When displayed together with another logo, the EU emblem must have appropriate prominence.
For the purposes of their obligations under this Article, the beneficiaries may use the EU emblem without first obtaining approval from the Commission.

This does not, however, give them the right to exclusive use.

Moreover, they may not appropriate the EU emblem or any similar trademark or logo, either by registration or by any other means.

38.1.3 Disclaimer excluding Commission responsibility

Any communication activity related to the action must indicate that it reflects only the author’s view and that the Commission is not responsible for any use that may be made of the information it contains.

38.2 Communication activities by the Commission

38.2.1 Right to use beneficiaries’ materials, documents or information

The Commission may use, for its communication and publicising activities, information relating to the action, documents notably summaries for publication and public deliverables as well as any other material, such as pictures or audio-visual material received from any beneficiary (including in electronic form).

This does not change the confidentiality obligations in Article 36 and the security obligations in Article 37, all of which still apply.

If the Commission’s use of these materials, documents or information would risk compromising legitimate interests, the beneficiary concerned may request the Commission not to use it (see Article 52).

The right to use a beneficiary’s materials, documents and information includes:

(a) use for its own purposes (in particular, making them available to persons working for the Commission or any other EU institution, body, office or agency or body or institutions in EU Member States; and copying or reproducing them in whole or in part, in unlimited numbers);

(b) distribution to the public (in particular, publication as hard copies and in electronic or digital format, publication on the internet, as a downloadable or non-downloadable file, broadcasting by any channel, public display or presentation, communicating through press information services, or inclusion in widely accessible databases or indexes);

(c) editing or redrafting for communication and publicising activities (including shortening, summarising, inserting other elements (such as meta-data, legends, other graphic, visual, audio or text elements), extracting parts (e.g. audio or video files), dividing into parts, use in a compilation);

(d) translation;

(e) giving access in response to individual requests under Regulation No 1049/200127, without the right to reproduce or exploit;

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(f) **storage** in paper, electronic or other form;

(g) **archiving**, in line with applicable document-management rules, and

(h) the right to authorise **third parties** to act on its behalf or sub-license the modes of use set out in Points (b), (c), (d) and (f) to third parties if needed for the communication and publicising activities of the Commission.

If the right of use is subject to rights of a third party (including personnel of the beneficiary), the beneficiary must ensure that it complies with its obligations under this Agreement (in particular, by obtaining the necessary approval from the third parties concerned).

Where applicable (and if provided by the beneficiaries), the Commission will insert the following information:

“© [year] – [name of the copyright owner]. All rights reserved. Licensed to the European Union (EU) under conditions.”

### 38.3 Consequences of non-compliance

If a beneficiary breaches any of its obligations under this Article, the grant may be reduced (see Article 43).

Such breaches may also lead to any of the other measures described in Chapter 6.

**ARTICLE 39 — PROCESSING OF PERSONAL DATA**

#### 39.1 Processing of personal data by the Commission

Any personal data under the Agreement will be processed by the Commission under Regulation No 45/2001 and according to the ‘notifications of the processing operations’ to the Data Protection Officer (DPO) of the Commission (publicly accessible in the DPO register).

Such data will be processed by the ‘**data controller**’ of the Commission for the purposes of implementing, managing and monitoring the Agreement or protecting the financial interests of the EU or Euratom (including checks, reviews, audits and investigations; see Article 22).

The persons whose personal data are processed have the right to access and correct their own personal data. For this purpose, they must send any queries about the processing of their personal data to the data controller, via the contact point indicated in the privacy statement(s) that are published on the Commission websites.

They also have the right to have recourse at any time to the European Data Protection Supervisor (EDPS).

#### 39.2 Processing of personal data by the beneficiaries

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The beneficiaries must process personal data under the Agreement in compliance with applicable EU and national law on data protection (including authorisations or notification requirements).

The beneficiaries may grant their personnel access only to data that is strictly necessary for implementing, managing and monitoring the Agreement.

The beneficiaries must inform the personnel whose personal data are collected and processed by the Commission. For this purpose, they must provide them with the privacy statement(s) (see above), before transmitting their data to the Commission.

39.3 Consequences of non-compliance

If a beneficiary breaches any of its obligations under Article 39.2, the Commission may apply any of the measures described in Chapter 6.

ARTICLE 40 — ASSIGNMENTS OF CLAIMS FOR PAYMENT AGAINST THE COMMISSION

The beneficiaries may not assign any of their claims for payment against the Commission to any third party, except if approved by the Commission on the basis of a reasoned, written request by the coordinator (on behalf of the beneficiary concerned).

If the Commission has not accepted the assignment or the terms of it are not observed, the assignment will have no effect on it.

In no circumstances will an assignment release the beneficiaries from their obligations towards the Commission.

CHAPTER 5 DIVISION OF BENEFICIARIES’ ROLES AND RESPONSIBILITIES — RELATIONSHIP WITH COMPLEMENTARY BENEFICIARIES — RELATIONSHIP WITH PARTNERS OF A JOINT ACTION

ARTICLE 41 — DIVISION OF BENEFICIARIES’ ROLES AND RESPONSIBILITIES — RELATIONSHIP WITH COMPLEMENTARY BENEFICIARIES — RELATIONSHIP WITH PARTNERS OF A JOINT ACTION

41.1 Roles and responsibility towards the Commission

The beneficiaries have full responsibility for implementing the action and complying with the Agreement.

The beneficiaries are jointly and severally liable for the technical implementation of the action as described in Annex 1. If a beneficiary fails to implement its part of the action, the other beneficiaries become responsible for implementing this part (without being entitled to any additional EU funding for doing so), unless the Commission expressly relieves them of this obligation.

The financial responsibility of each beneficiary is governed by Article 44.

41.2 Internal division of roles and responsibilities
The internal roles and responsibilities of the beneficiaries are divided as follows:

(a) Each **beneficiary** must:

   (i) keep information stored in the Participant Portal Beneficiary Register (via the electronic exchange system) up to date (see Article 17);

   (ii) inform the coordinator immediately of any events or circumstances likely to affect significantly or delay the implementation of the action (see Article 17);

   (iii) submit to the coordinator in good time:

       - individual financial statements for itself and, if required, certificates on the financial statements (see Article 20);

       - the data needed to draw up the technical reports (see Article 20);

       - ethics committee opinions and notifications or authorisations for activities raising ethical issues (see Article 34);

       - any other documents or information required by the Commission under the Agreement, unless the Agreement requires the beneficiary to submit this information directly to the Commission.

(b) The **coordinator** must:

   (i) monitor that the action is implemented properly (see Article 7);

   (ii) act as the intermediary for all communications between the beneficiaries and the Commission (in particular, providing the Commission with the information described in Article 17), unless the Agreement specifies otherwise;

   (iii) request and review any documents or information required by the Commission and verify their completeness and correctness before passing them on to the Commission;

   (iv) submit the deliverables and reports to the Commission (see Articles 19 and 20);

   (v) ensure that all payments are made to the other beneficiaries without unjustified delay (see Article 21);

   (vi) inform the Commission of the amounts paid to each beneficiary, when required under the Agreement (see Articles 44 and 50) or requested by the Commission.

   The coordinator may not delegate or subcontract the above-mentioned tasks to any other beneficiary or third party (including linked third parties).

### 41.3 Internal arrangements between beneficiaries — Consortium agreement

The beneficiaries must have internal arrangements regarding their operation and co-ordination to ensure that the action is implemented properly. These internal arrangements must be set out in a written ‘**consortium agreement**’ between the beneficiaries, which may cover:

- internal organisation of the consortium;
- management of access to the electronic exchange system;

- distribution of EU funding;

- additional rules on rights and obligations related to background and results (including whether access rights remain or not, if a beneficiary is in breach of its obligations) (see Section 3 of Chapter 4);

- settlement of internal disputes;

- liability, indemnification and confidentiality arrangements between the beneficiaries.

The consortium agreement must not contain any provision contrary to the Agreement.

### 41.4 Relationship with complementary beneficiaries — Collaboration agreement

The beneficiaries must conclude a written ‘collaboration agreement’ with the complementary beneficiaries to coordinate the work under the Agreement and the complementary grant agreement(s) (see Article 2), covering for instance:

- efficient decision making processes and

- settlement of disputes.

The collaboration agreement must not contain any provision contrary to the Agreement.

The beneficiaries and complementary beneficiaries must create and participate in common boards and advisory structures to decide on collaboration and synchronisation of activities, including on management of outcomes, common approaches towards standardisation, SME involvement, links with regulatory and policy activities, and commonly shared dissemination and awareness raising activities.

The beneficiaries must give access to their results to the complementary beneficiaries, for the purposes of the complementary grant agreement(s) (see Article 31.6).

The beneficiaries must share the technical reports (see Article 20.3 and 20.4). The confidentiality obligations in Article 36 apply.

### 41.5 Relationship with partners of a joint action — Coordination agreement

Not applicable
42.1 Conditions

The Commission will — after termination of the participation of a beneficiary, at the time of an interim payment, at the payment of the balance or afterwards — reject any costs which are ineligible (see Article 6), in particular following checks, reviews, audits or investigations (see Article 22).

The rejection may also be based on the extension of findings from other grants to this grant (see Article 22.5.2).

42.2 Ineligible costs to be rejected — Calculation — Procedure

Ineligible costs will be rejected in full.

If the rejection of costs does not lead to a recovery (see Article 44), the Commission will formally notify the coordinator or beneficiary concerned of the rejection of costs, the amounts and the reasons why (if applicable, together with the notification of amounts due; see Article 21.5). The coordinator or beneficiary concerned may — within 30 days of receiving notification — formally notify the Commission of its disagreement and the reasons why.

If the rejection of costs leads to a recovery, the Commission will follow the contradictory procedure with pre-information letter set out in Article 44.

42.3 Effects

If the Commission rejects costs at the time of an interim payment or the payment of the balance, it will deduct them from the total eligible costs declared, for the action, in the periodic or final summary financial statement (see Articles 20.3 and 20.4). It will then calculate the interim payment or payment of the balance as set out in Articles 21.3 or 21.4.

If the Commission rejects costs after termination of the participation of a beneficiary, it will deduct them from the costs declared by the beneficiary in the termination report and include the rejection in the calculation after termination (see Article 50.2 and 50.3).

If the Commission — after an interim payment but before the payment of the balance — rejects costs declared in a periodic summary financial statement, it will deduct them from the total eligible costs declared, for the action, in the next periodic summary financial statement or in the final summary financial statement. It will then calculate the interim payment or payment of the balance as set out in Articles 21.3 or 21.4.

If the Commission rejects costs after the payment of the balance, it will deduct the amount rejected from the total eligible costs declared, by the beneficiary, in the final summary financial statement. It will then calculate the revised final grant amount as set out in Article 5.4.

ARTICLE 43 — REDUCTION OF THE GRANT

43.1 Conditions

The Commission may — after termination of the participation of a beneficiary, at the payment of the balance or afterwards — reduce the grant amount (see Article 5.1), if:
(a) a beneficiary (or a natural person who has the power to represent or take decisions on its behalf) has committed:

(i) substantial errors, irregularities or fraud or

(ii) serious breach of obligations under the Agreement or during the award procedure (including improper implementation of the action, submission of false information, failure to provide required information, breach of ethical principles) or

(b) a beneficiary (or a natural person who has the power to represent or take decision on its behalf) has committed — in other EU or Euratom grants awarded to it under similar conditions — systemic or recurrent errors, irregularities, fraud or serious breach of obligations that have a material impact on this grant (extension of findings from other grants to this grant; see Article 22.5.2).

43.2 Amount to be reduced — Calculation — Procedure

The amount of the reduction will be proportionate to the seriousness of the errors, irregularities or fraud or breach of obligations.

Before reduction of the grant, the Commission will formally notify a ‘pre-information letter’ to the coordinator or beneficiary concerned:

- informing it of its intention to reduce the grant, the amount it intends to reduce and the reasons why and
- inviting it to submit observations within 30 days of receiving notification.

If the Commission does not receive any observations or decides to pursue reduction despite the observations it has received, it will formally notify confirmation of the reduction (if applicable, together with the notification of amounts due; see Article 21).

43.3 Effects

If the Commission reduces the grant after termination of the participation of a beneficiary, it will calculate the reduced grant amount for that beneficiary and then determine the amount due to that beneficiary (see Article 50.2 and 50.3).

If the Commission reduces the grant at the payment of the balance, it will calculate the reduced grant amount for the action and then determine the amount due as payment of the balance (see Articles 5.3.4 and 21.4).

If the Commission reduces the grant after the payment of the balance, it will calculate the revised final grant amount for the beneficiary concerned (see Article 5.4). If the revised final grant amount for the beneficiary concerned is lower than its share of the final grant amount, the Commission will recover the difference (see Article 44).

ARTICLE 44 — RECOVERY OF UNDUE AMOUNTS

44.1 Amount to be recovered — Calculation — Procedure

The Commission will — after termination of the participation of a beneficiary, at the payment
of the balance or afterwards — claim back any amount that was paid, but is not due under the Agreement.

Each beneficiary’s financial responsibility in case of recovery is limited to its own debt, except for the amount retained for the Guarantee Fund (see Article 21.4).

44.1.1 Recovery after termination of a beneficiary’s participation

If recovery takes place after termination of a beneficiary’s participation (including the coordinator), the Commission will claim back the undue amount from the beneficiary concerned, by formally notifying it a debit note (see Article 50.2 and 50.3). This note will specify the amount to be recovered, the terms and the date for payment.

If payment is not made by the date specified in the debit note, the Commission will recover the amount:

(a) by ‘offsetting’ it — without the beneficiary’s consent — against any amounts owed to the beneficiary concerned by the Commission or an executive agency (from the EU or Euratom budget).

In exceptional circumstances, to safeguard the EU’s financial interests, the Commission may offset before the payment date specified in the debit note;

(b) not applicable;

(c) by taking legal action (see Article 57) or by adopting an enforceable decision under Article 299 of the Treaty on the Functioning of the EU (TFEU) and Article 79(2) of the Financial Regulation No 966/2012.

If payment is not made by the date specified in the debit note, the amount to be recovered (see above) will be increased by late-payment interest at the rate set out in Article 21.11, from the day following the payment date in the debit note, up to and including the date the Commission receives full payment of the amount.

Partial payments will be first credited against expenses, charges and late-payment interest and then against the principal.

Bank charges incurred in the recovery process will be borne by the beneficiary, unless Directive 2007/64/EC applies.

44.1.2 Recovery at payment of the balance

If the payment of the balance takes the form of a recovery (see Article 21.4), the Commission will formally notify a ‘pre-information letter’ to the coordinator:

- informing it of its intention to recover, the amount due as the balance and the reasons why;
- specifying that it intends to deduct the amount to be recovered from the amount retained for the Guarantee Fund;

- requesting the coordinator to submit a report on the distribution of payments to the beneficiaries within 30 days of receiving notification, and

- inviting the coordinator to submit observations within 30 days of receiving notification.

If no observations are submitted or the Commission decides to pursue recovery despite the observations it has received, it will confirm recovery (together with the notification of amounts due; see Article 21.5) and:

- pay the difference between the amount to be recovered and the amount retained for the Guarantee Fund, if the difference is positive or

- formally notify to the coordinator a debit note for the difference between the amount to be recovered and the amount retained for the Guarantee Fund, if the difference is negative. This note will also specify the terms and the date for payment.

If the coordinator does not repay the Commission by the date in the debit note and has not submitted the report on the distribution of payments: the Commission will recover the amount set out in the debit note from the coordinator (see below).

If the coordinator does not repay the Commission by the date in the debit note, but has submitted the report on the distribution of payments: the Commission will:

(a) identify the beneficiaries for which the amount calculated as follows is negative:

\[
\frac{\{\text{beneficiary’s costs declared in the final summary financial statement and approved by the Commission multiplied by the reimbursement rate set out in Article 5.2 for the beneficiary concerned}\}}{\text{the EU contribution for the action calculated according to Article 5.3.1}} \times \text{the final grant amount (see Article 5.3)}
\]

minus

\{\text{pre-financing and interim payments received by the beneficiary}\}.

(b) formally notify to each beneficiary identified according to point (a) a debit note specifying the terms and date for payment. The amount of the debit note is calculated as follows:

\[
\frac{\text{amount calculated according to point (a) for the beneficiary concerned}}{\text{the sum of the amounts calculated according to point (a) for all the beneficiaries identified according to point (a)}} \times \text{the amount set out in the debit note formally notified to the coordinator}.
\]

If payment is not made by the date specified in the debit note, the Commission will recover the amount:
(a) by **offsetting** it — without the beneficiary’s consent — against any amounts owed to the beneficiary concerned by the Commission or an executive agency (from the EU or Euratom budget).

In exceptional circumstances, to safeguard the EU’s financial interests, the Commission may offset before the payment date specified in the debit note;

(b) by **drawing on the Guarantee Fund**. The Commission will formally notify the beneficiary concerned the debit note on behalf of the Guarantee Fund and recover the amount:

(i) not applicable;

(ii) by **taking legal action** (see Article 57) or by **adopting an enforceable decision** under Article 299 of the Treaty on the Functioning of the EU (TFEU) and Article 79(2) of the Financial Regulation No 966/2012.

If payment is not made by the date in the debit note, the amount to be recovered (see above) will be increased by **late-payment interest** at the rate set out in Article 21.11, from the day following the payment date in the debit note, up to and including the date the Commission receives full payment of the amount.

Partial payments will be first credited against expenses, charges and late-payment interest and then against the principal.

Bank charges incurred in the recovery process will be borne by the beneficiary, unless Directive 2007/64/EC applies.

**44.1.3 Recovery of amounts after payment of the balance**

If, for a beneficiary, the revised final grant amount (see Article 5.4) is lower than its share of the final grant amount, it must repay the difference to the Commission.

The beneficiary’s share of the final grant amount is calculated as follows:

\[
\left\{ \left( \left\{ \frac{\text{beneficiary’s costs declared in the final summary financial statement and approved by the Commission multiplied by the reimbursement rate set out in Article 5.2 for the beneficiary concerned}}{\text{the EU contribution for the action calculated according to Article 5.3.1}} \right\} \times \text{the final grant amount (see Article 5.3)} \right\} \right.
\]

If the coordinator has not distributed amounts received (see Article 21.7), the Commission will also recover these amounts.

The Commission will formally notify a **pre-information letter** to the beneficiary concerned:

- informing it of its intention to recover, the due amount and the reasons why and
- inviting it to submit observations within 30 days of receiving notification.
If no observations are submitted or the Commission decides to pursue recovery despite the observations it has received, it will confirm the amount to be recovered and formally notify to the beneficiary concerned a debit note. This note will also specify the terms and the date for payment.

If payment is not made by the date specified in the debit note, the Commission will recover the amount:

(a) by offsetting it — without the beneficiary’s consent — against any amounts owed to the beneficiary concerned by the Commission or an executive agency (from the EU or Euratom budget).

In exceptional circumstances, to safeguard the EU’s financial interests, the Commission may offset before the payment date specified in the debit note;

(b) by drawing on the Guarantee Fund. The Commission will formally notify the beneficiary concerned the debit note on behalf of the Guarantee Fund and recover the amount:

(i) not applicable;

(ii) by taking legal action (see Article 57) or by adopting an enforceable decision under Article 299 of the Treaty on the Functioning of the EU (TFEU) and Article 79(2) of the Financial Regulation No 966/2012.

If payment is not made by the date in the debit note, the amount to be recovered (see above) will be increased by late-payment interest at the rate set out in Article 21.11, from the day following the date for payment in the debit note, up to and including the date the Commission receives full payment of the amount.

Partial payments will be first credited against expenses, charges and late-payment interest and then against the principal.

Bank charges incurred in the recovery process will be borne by the beneficiary, unless Directive 2007/64/EC applies.

ARTICLE 45 — ADMINISTRATIVE SANCTIONS

In addition to contractual measures, the Commission may also adopt administrative sanctions under Articles 106 and 131(4) of the Financial Regulation No 966/2012 (i.e. exclusion from future procurement contracts, grants, prizes and expert contracts and/or financial penalties).

SECTION 2 LIABILITY FOR DAMAGES

ARTICLE 46 — LIABILITY FOR DAMAGES

46.1 Liability of the Commission

The Commission cannot be held liable for any damage caused to the beneficiaries or to third parties as a consequence of implementing the Agreement, including for gross negligence.

The Commission cannot be held liable for any damage caused by any of the beneficiaries or third parties involved in the action, as a consequence of implementing the Agreement.
46.2 Liability of the beneficiaries

Except in case of force majeure (see Article 51), the beneficiaries must compensate the Commission for any damage it sustains as a result of the implementation of the action or because the action was not implemented in full compliance with the Agreement.

SECTION 3 SUSPENSION AND TERMINATION

ARTICLE 47 — SUSPENSION OF PAYMENT DEADLINE

47.1 Conditions

The Commission may — at any moment — suspend the payment deadline (see Article 21.2 to 21.4) if a request for payment (see Article 20) cannot be approved because:

(a) it does not comply with the provisions of the Agreement (see Article 20);

(b) the technical or financial reports have not been submitted or are not complete or additional information is needed, or

(c) there is doubt about the eligibility of the costs declared in the financial statements and additional checks, reviews, audits or investigations are necessary.

47.2 Procedure

The Commission will formally notify the coordinator of the suspension and the reasons why.

The suspension will take effect the day notification is sent by the Commission (see Article 52).

If the conditions for suspending the payment deadline are no longer met, the suspension will be lifted — and the remaining period will resume.

If the suspension exceeds two months, the coordinator may request the Commission if the suspension will continue.

If the payment deadline has been suspended due to the non-compliance of the technical or financial reports (see Article 20) and the revised report or statement is not submitted or was submitted but is also rejected, the Commission may also terminate the Agreement or the participation of the beneficiary (see Article 50.3.1(l)).

ARTICLE 48 — SUSPENSION OF PAYMENTS

48.1 Conditions

The Commission may — at any moment — suspend payments, in whole or in part and interim payments or the payment of the balance for one or more beneficiaries, if:

(a) a beneficiary (or a natural person who has the power to represent or take decision on its behalf) has committed or is suspected of having committed:

   (i) substantial errors, irregularities or fraud or
(ii) serious breach of obligations under the Agreement or during the award procedure (including improper implementation of the action, submission of false information, failure to provide required information, breach of ethical principles) or

(b) a beneficiary (or a natural person who has the power to represent or take decision on its behalf) has committed — in other EU or Euratom grants awarded to it under similar conditions — systemic or recurrent errors, irregularities, fraud or serious breach of obligations that have a material impact on this grant (extension of findings from other grants to this grant; see Article 22.5.2).

If payments are suspended for one or more beneficiaries, the Commission will make partial payment(s) for the part(s) not suspended. If suspension concerns the payment of the balance, — once suspension is lifted — the payment or the recovery of the amount(s) concerned will be considered the payment of the balance that closes the action.

48.2 Procedure

Before suspending payments, the Commission will formally notify the coordinator or beneficiary concerned:

- informing it of its intention to suspend payments and the reasons why and
- inviting it to submit observations within 30 days of receiving notification.

If the Commission does not receive observations or decides to pursue the procedure despite the observations it has received, it will formally notify confirmation of the suspension. Otherwise, it will formally notify that the suspension procedure is not continued.

The suspension will take effect the day the confirmation notification is sent by the Commission.

If the conditions for resuming payments are met, the suspension will be lifted. The Commission will formally notify the coordinator or beneficiary concerned.

During the suspension, the periodic report(s) for all reporting periods except the last one (see Article 20.3), must not contain any individual financial statements from the beneficiary concerned. The coordinator must include them in the next periodic report after the suspension is lifted or — if suspension is not lifted before the end of the action — in the last periodic report.

The beneficiaries may suspend implementation of the action (see Article 49.1) or terminate the Agreement or the participation of the beneficiary concerned (see Article 50.1 and 50.2).

ARTICLE 49 — SUSPENSION OF THE ACTION IMPLEMENTATION

49.1 Suspension of the action implementation, by the beneficiaries

49.1.1 Conditions

The beneficiaries may suspend implementation of the action or any part of it, if exceptional circumstances — in particular force majeure (see Article 51) — make implementation impossible or excessively difficult.
49.1.2 Procedure

The coordinator must immediately formally notify to the Commission the suspension (see Article 52), stating:

- the reasons why and
- the expected date of resumption.

The suspension will take effect the day this notification is received by the Commission.

Once circumstances allow for implementation to resume, the coordinator must immediately formally notify the Commission and request an amendment of the Agreement to set the date on which the action will be resumed, extend the duration of the action and make other changes necessary to adapt the action to the new situation (see Article 55) — unless the Agreement or the participation of a beneficiary has been terminated (see Article 50).

The suspension will be lifted with effect from the resumption date set out in the amendment. This date may be before the date on which the amendment enters into force.

Costs incurred during suspension of the action implementation are not eligible (see Article 6).

49.2 Suspension of the action implementation, by the Commission

49.2.1 Conditions

The Commission may suspend implementation of the action or any part of it, if:

(a) a beneficiary (or a natural person who has the power to represent or take decisions on its behalf) has committed or is suspected of having committed:

   (i) substantial errors, irregularities or fraud or

   (ii) serious breach of obligations under the Agreement or during the award procedure (including improper implementation of the action, submission of false information, failure to provide required information, breach of ethical principles);

(b) a beneficiary (or a natural person who has the power to represent or take decisions on its behalf) has committed — in other EU or Euratom grants awarded to it under similar conditions — systemic or recurrent errors, irregularities, fraud or serious breach of obligations that have a material impact on this grant (extension of findings from other grants to this grant; see Article 22.5.2), or

(c) the action is suspected of having lost its scientific or technological relevance.

49.2.2 Procedure

Before suspending implementation of the action, the Commission will formally notify the coordinator or beneficiary concerned:

- informing it of its intention to suspend the implementation and the reasons why and
- inviting it to submit observations within 30 days of receiving notification.
If the Commission does not receive observations or decides to pursue the procedure despite the observations it has received, it will formally notify confirmation of the suspension. Otherwise, it will formally notify that the procedure is not continued.

The suspension will take effect five days after confirmation notification is received (or on a later date specified in the notification).

It will be lifted if the conditions for resuming implementation of the action are met.

The coordinator or beneficiary concerned will be formally notified of the lifting and the Agreement will be amended to set the date on which the action will be resumed, extend the duration of the action and make other changes necessary to adapt the action to the new situation (see Article 55) — unless the Agreement has already been terminated (see Article 50).

The suspension will be lifted with effect from the resumption date set out in the amendment. This date may be before the date on which the amendment enters into force.

Costs incurred during suspension are not eligible (see Article 6).

The beneficiaries may not claim damages due to suspension by the Commission (see Article 46).

Suspension of the action implementation does not affect the Commission’s right to terminate the Agreement or participation of a beneficiary (see Article 50), reduce the grant or recover amounts unduly paid (see Articles 43 and 44).

**ARTICLE 50 — TERMINATION OF THE AGREEMENT OR OF THE PARTICIPATION OF ONE OR MORE BENEFICIARIES**

**50.1 Termination of the Agreement, by the beneficiaries**

**50.1.1 Conditions and procedure**

The beneficiaries may terminate the Agreement.

The coordinator must formally notify termination to the Commission (see Article 52), stating:

- the reasons why and
- the date the termination will take effect. This date must be after the notification.

If no reasons are given or if the Commission considers the reasons do not justify termination, the Agreement will be considered to have been ‘terminated improperly’.

The termination will take effect on the day specified in the notification.

**50.1.2 Effects**

The coordinator must — within 60 days from when termination takes effect — submit:

(i) a periodic report (for the open reporting period until termination; see Article 20.3) and

(ii) the final report (see Article 20.4).
If the Commission does not receive the reports within the deadline (see above), only costs which are included in an approved periodic report will be taken into account.

The Commission will calculate the final grant amount (see Article 5.3) and the balance (see Article 21.4) on the basis of the reports submitted. Only costs incurred until termination are eligible (see Article 6). Costs relating to contracts due for execution only after termination are not eligible.

Improper termination may lead to a reduction of the grant (see Article 43).

After termination, the beneficiaries’ obligations (in particular Articles 20, 22, 23, Section 3 of Chapter 4, 36, 37, 38, 40, 42, 43 and 44) continue to apply.

50.2 Termination of the participation of one or more beneficiaries, by the beneficiaries

50.2.1 Conditions and procedure

The participation of one or more beneficiaries may be terminated by the coordinator, on request of the beneficiary concerned or on behalf of the other beneficiaries.

The coordinator must formally notify termination to the Commission (see Article 52) and inform the beneficiary concerned.

If the coordinator’s participation is terminated without its agreement, the formal notification must be done by another beneficiary (acting on behalf of the other beneficiaries).

The notification must include:

- the reasons why;
- the opinion of the beneficiary concerned (or proof that this opinion has been requested in writing);
- the date the termination takes effect. This date must be after the notification, and
- a request for amendment (see Article 55), with a proposal for reallocation of the tasks and the estimated budget of the beneficiary concerned (see Annexes 1 and 2) and, if necessary, the addition of one or more new beneficiaries (see Article 56). If termination takes effect after the period set out in Article 3, no request for amendment must be included unless the beneficiary concerned is the coordinator. In this case, the request for amendment must propose a new coordinator.

If this information is not given or if the Commission considers that the reasons do not justify termination, the participation will be considered to have been terminated improperly.

The termination will take effect on the day specified in the notification.

50.2.2 Effects

The coordinator must — within 30 days from when termination takes effect — submit:

(i) a report on the distribution of payments to the beneficiary concerned and

(ii) if termination takes effect during the period set out in Article 3, a ‘termination report’
from the beneficiary concerned, for the open reporting period until termination, containing an overview of the progress of the work, an overview of the use of resources, the individual financial statement and, if applicable, the certificate on the financial statement (see Articles 20.3 and 20.4).

The information in the termination report must also be included in the periodic report for the next reporting period (see Article 20.3).

If the request for amendment is rejected by the Commission (because it calls into question the decision awarding the grant or breaches the principle of equal treatment of applicants), the Agreement may be terminated according to Article 50.3.1(c).

If the request for amendment is accepted by the Commission, the Agreement is amended to introduce the necessary changes (see Article 55).

The Commission will — on the basis of the periodic reports, the termination report and the report on the distribution of payments — calculate the amount which is due to the beneficiary and if the (pre-financing and interim) payments received by the beneficiary exceed this amount.

The amount which is due is calculated in the following steps:

Step 1 — Application of the reimbursement rate to the eligible costs

The grant amount for the beneficiary is calculated by applying the reimbursement rate(s) to the total eligible costs declared by the beneficiary in the termination report and approved by the Commission.

Only costs incurred by the beneficiary concerned until termination takes effect are eligible (see Article 6). Costs relating to contracts due for execution only after termination are not eligible.

Step 2 — Reduction due to substantial errors, irregularities or fraud or serious breach of obligations

In case of a reduction (see Article 43), the Commission will calculate the reduced grant amount for the beneficiary by deducting the amount of the reduction (calculated in proportion to the seriousness of the errors, irregularities or fraud or breach of obligations, in accordance with Article 43.2) from the grant amount for the beneficiary.

If the payments received exceed the amounts due:

- if termination takes effect during the period set out in Article 3 and the request for amendment is accepted, the beneficiary concerned must repay to the coordinator the amount unduly received. The Commission will formally notify the amount unduly received and request the beneficiary concerned to repay it to the coordinator within 30 days of receiving notification. If it does not repay the coordinator, the Commission will draw upon the Guarantee Fund to pay the coordinator and then notify a debit note on behalf of the Guarantee Fund to the beneficiary concerned (see Article 44);

- in all other cases, in particular if termination takes effect after the period set out in Article 3, the Commission will formally notify a debit note to the beneficiary concerned. If payment...
is not made by the date in the debit note, the Guarantee Fund will pay to the Commission the amount due and the Commission will notify a debit note on behalf of the Guarantee Fund to the beneficiary concerned (see Article 44);

- if the beneficiary concerned is the former coordinator, it must repay the new coordinator according to the procedure above, unless:
  
  - termination takes effect after an interim payment and
  
  - the former coordinator has not distributed amounts received as pre-financing or interim payments (see Article 21.7).

In this case, the Commission will formally notify a debit note to the former coordinator. If payment is not made by the date in the debit note, the Guarantee Fund will pay to the Commission the amount due. The Commission will then pay the new coordinator and notify a debit note on behalf of the Guarantee Fund to the former coordinator (see Article 44).

If the payments received do not exceed the amounts due: amounts owed to the beneficiary concerned will be included in the next interim or final payment.

If the Commission does not receive the termination report within the deadline (see above), only costs included in an approved periodic report will be taken into account.

If the Commission does not receive the report on the distribution of payments within the deadline (see above), it will consider that:

- the coordinator did not distribute any payment to the beneficiary concerned and that

- the beneficiary concerned must not repay any amount to the coordinator.

Improper termination may lead to a reduction of the grant (see Article 43) or termination of the Agreement (see Article 50).

After termination, the concerned beneficiary’s obligations (in particular Articles 20, 22, 23, Section 3 of Chapter 4, 36, 37, 38, 40, 42, 43 and 44) continue to apply.

50.3 Termination of the Agreement or the participation of one or more beneficiaries, by the Commission

50.3.1 Conditions

The Commission may terminate the Agreement or the participation of one or more beneficiaries, if:

(a) one or more beneficiaries do not accede to the Agreement (see Article 56);

(b) a change to their legal, financial, technical, organisational or ownership situation is likely to substantially affect or delay the implementation of the action or calls into question the decision to award the grant;

(c) following termination of participation for one or more beneficiaries (see above), the necessary changes to the Agreement would call into question the decision awarding the grant or breach the principle of equal treatment of applicants (see Article 55);
(d) implementation of the action is prevented by force majeure (see Article 51) or suspended by the coordinator (see Article 49.1) and either:

(i) resumption is impossible, or

(ii) the necessary changes to the Agreement would call into question the decision awarding the grant or breach the principle of equal treatment of applicants;

(e) a beneficiary is declared bankrupt, being wound up, having its affairs administered by the courts, has entered into an arrangement with creditors, has suspended business activities, or is subject to any other similar proceedings or procedures under national law;

(f) a beneficiary (or a natural person who has the power to represent or take decisions on its behalf) has been found guilty of professional misconduct, proven by any means;

(g) a beneficiary does not comply with the applicable national law on taxes and social security;

(h) the action has lost scientific or technological relevance;

(i) not applicable;

(j) not applicable;

(k) a beneficiary (or a natural person who has the power to represent or take decisions on its behalf) has committed fraud, corruption, or is involved in a criminal organisation, money laundering or any other illegal activity;

(l) a beneficiary (or a natural person who has the power to represent or take decisions on its behalf) has committed:

(i) substantial errors, irregularities or fraud or

(ii) serious breach of obligations under the Agreement or during the award procedure (including improper implementation of the action, submission of false information, failure to provide required information, breach of ethical principles);

(m) a beneficiary (or a natural person who has the power to represent or take decisions on its behalf) has committed — in other EU or Euratom grants awarded to it under similar conditions — systemic or recurrent errors, irregularities, fraud or serious breach of obligations that have a material impact on this grant (extension of findings from other grants to this grant; see Article 22.5.2);

(n) not applicable.

50.3.2 Procedure

Before terminating the Agreement or participation of one or more beneficiaries, the Commission will formally notify the coordinator or beneficiary concerned:

- informing it of its intention to terminate and the reasons why and

- inviting it, within 30 days of receiving notification, to submit observations and — in case of
Point (l.ii) above — to inform the Commission of the measures to ensure compliance with the obligations under the Agreement.

If the Commission does not receive observations or decides to pursue the procedure despite the observations it has received, it will formally notify to the coordinator or beneficiary concerned confirmation of the termination and the date it will take effect. Otherwise, it will formally notify that the procedure is not continued.

The termination will take effect:

- for terminations under Points (b), (c), (e), (g), (h), (j), (l.ii) and (n) above: on the day specified in the notification of the confirmation (see above);

- for terminations under Points (a), (d), (f), (i), (k), (l.i) and (m) above: on the day after the notification of the confirmation is received.

50.3.3 Effects

(a) for termination of the Agreement:

The coordinator must — within 60 days from when termination takes effect — submit:

(i) a periodic report (for the last open reporting period until termination; see Article 20.3) and

(ii) a final report (see Article 20.4).

If the Agreement is terminated for breach of the obligation to submit reports (see Articles 20.8 and 50.3.1(l)), the coordinator may not submit any reports after termination.

If the Commission does not receive the reports within the deadline (see above), only costs which are included in an approved periodic report will be taken into account.

The Commission will calculate the final grant amount (see Article 5.3) and the balance (see Article 21.4) on the basis of the reports submitted. Only costs incurred until termination takes effect are eligible (see Article 6). Costs relating to contracts due for execution only after termination are not eligible.

This does not affect the Commission’s right to reduce the grant (see Article 43) or to impose administrative sanctions (Article 45).

The beneficiaries may not claim damages due to termination by the Commission (see Article 46).

After termination, the beneficiaries’ obligations (in particular Articles 20, 22, 23, Section 3 of Chapter 4, 36, 37, 38, 40, 42, 43 and 44) continue to apply.

(b) for termination of the participation of one or more beneficiaries:

The coordinator must — within 60 days from when termination takes effect — submit:

(i) a report on the distribution of payments to the beneficiary concerned;
(ii) a request for amendment (see Article 55), with a proposal for reallocation of the tasks and estimated budget of the beneficiary concerned (see Annexes 1 and 2) and, if necessary, the addition of one or more new beneficiaries (see Article 56). If termination is notified after the period set out in Article 3, no request for amendment must be submitted unless the beneficiary concerned is the coordinator. In this case the request for amendment must propose a new coordinator, and

(iii) if termination takes effect during the period set out in Article 3, a termination report from the beneficiary concerned, for the open reporting period until termination, containing an overview of the progress of the work, an overview of the use of resources, the individual financial statement and, if applicable, the certificate on the financial statement (see Article 20).

The information in the termination report must also be included in the periodic report for the next reporting period (see Article 20.3).

If the request for amendment is rejected by the Commission (because it calls into question the decision awarding the grant or breaches the principle of equal treatment of applicants), the Agreement may be terminated according to Article 50.3.1(c).

If the request for amendment is accepted by the Commission, the Agreement is amended to introduce the necessary changes (see Article 55).

The Commission will — on the basis of the periodic reports, the termination report and the report on the distribution of payments — calculate the amount which is due to the beneficiary and if the (pre-financing and interim) payments received by the beneficiary exceed this amount.

The amount which is due is calculated in the following steps:

Step 1 — Application of the reimbursement rate to the eligible costs

The grant amount for the beneficiary is calculated by applying the reimbursement rate(s) to the total eligible costs declared by the beneficiary in the termination report and approved by the Commission.

Only costs incurred by the beneficiary concerned until termination takes effect are eligible (see Article 6). Costs relating to contracts due for execution only after termination are not eligible.

Step 2 — Reduction due to substantial errors, irregularities or fraud or serious breach of obligations

In case of a reduction (see Article 43), the Commission will calculate the reduced grant amount for the beneficiary by deducting the amount of the reduction (calculated in proportion to the seriousness of the errors, irregularities or fraud or breach of obligations, in accordance with Article 43.2) from the grant amount for the beneficiary.

If the payments received exceed the amounts due:

- if termination takes effect during the period set out in Article 3 and the request for
amendment is accepted, the beneficiary concerned must repay to the coordinator the amount unduly received. The Commission will formally notify the amount unduly received and request the beneficiary concerned to repay it to the coordinator within 30 days of receiving notification. If it does not repay the coordinator, the Commission will draw upon the Guarantee Fund to pay the coordinator and then notify a debit note on behalf of the Guarantee Fund to the beneficiary concerned (see Article 44);

- in all other cases, in particular if termination takes effect after the period set out in Article 3, the Commission will formally notify a debit note to the beneficiary concerned. If payment is not made by the date in the debit note, the Guarantee Fund will pay to the Commission the amount due and the Commission will notify a debit note on behalf of the Guarantee Fund to the beneficiary concerned (see Article 44);

- if the beneficiary concerned is the former coordinator, it must repay the new coordinator according to the procedure above, unless:
  - termination takes effect after an interim payment and
  - the former coordinator has not distributed amounts received as pre-financing or interim payments (see Article 21.7).

In this case, the Commission will formally notify a debit note to the former coordinator. If payment is not made by the date in the debit note, the Guarantee Fund will pay to the Commission the amount due. The Commission will then pay the new coordinator and notify a debit note on behalf of the Guarantee Fund to the former coordinator (see Article 44).

If the payments received do not exceed the amounts due: amounts owed to the beneficiary concerned will be included in the next interim or final payment.

If the Commission does not receive the termination report within the deadline (see above), only costs included in an approved periodic report will be taken into account.

If the Commission does not receive the report on the distribution of payments within the deadline (see above), it will consider that:

- the coordinator did not distribute any payment to the beneficiary concerned and that
- the beneficiary concerned must not repay any amount to the coordinator.

After termination, the concerned beneficiary’s obligations (in particular Articles 20, 22, 23, Section 3 of Chapter 4, 36, 37, 38, 40, 42, 43 and 44) continue to apply.

SECTION 4　FORCE MAJEURE

ARTICLE 51 — FORCE MAJEURE

‘Force majeure’ means any situation or event that:

- prevents either party from fulfilling their obligations under the Agreement,
- was unforeseeable, exceptional situation and beyond the parties’ control,
- was not due to error or negligence on their part (or on the part of third parties involved in the action), and
- proves to be inevitable in spite of exercising all due diligence.

The following cannot be invoked as force majeure:
- any default of a service, defect in equipment or material or delays in making them available, unless they stem directly from a relevant case of force majeure,
- labour disputes or strikes, or
- financial difficulties.

Any situation constituting force majeure must be formally notified to the other party without delay, stating the nature, likely duration and foreseeable effects.

The parties must immediately take all the necessary steps to limit any damage due to force majeure and do their best to resume implementation of the action as soon as possible.

The party prevented by force majeure from fulfilling its obligations under the Agreement cannot be considered in breach of them.

CHAPTER 7 FINAL PROVISIONS

ARTICLE 52 — COMMUNICATION BETWEEN THE PARTIES

52.1 Form and means of communication

Communication under the Agreement (information, requests, submissions, ‘formal notifications’, etc.) must:
- be made in writing and
- bear the number of the Agreement.

All communication must be made through the Participant Portal electronic exchange system and using the forms and templates provided there.

If — after the payment of the balance — the Commission finds that a formal notification was not accessed, a second formal notification will be made by registered post with proof of delivery (‘formal notification on paper’). Deadlines will be calculated from the moment of the second notification.

Communications in the electronic exchange system must be made by persons authorised according to the Participant Portal Terms & Conditions. For naming the authorised persons, each beneficiary must have designated — before the signature of this Agreement — a ‘legal entity appointed representative (LEAR)’. The role and tasks of the LEAR are stipulated in his/her appointment letter (see Participant Portal Terms & Conditions).
If the electronic exchange system is temporarily unavailable, instructions will be given on the Commission website.

52.2 Date of communication

Communications are considered to have been made when they are sent by the sending party (i.e. on the date and time they are sent through the electronic exchange system).

Formal notifications through the electronic exchange system are considered to have been made when they are received by the receiving party (i.e. on the date and time of acceptance by the receiving party, as indicated by the time stamp). A formal notification that has not been accepted within 10 days after sending is considered to have been accepted.

Formal notifications on paper sent by registered post with proof of delivery (only after the payment of the balance) are considered to have been made on either:

- the delivery date registered by the postal service or
- the deadline for collection at the post office.

If the electronic exchange system is temporarily unavailable, the sending party cannot be considered in breach of its obligation to send a communication within a specified deadline.

52.3 Addresses for communication

The electronic exchange system must be accessed via the following URL:

https://ec.europa.eu/info/funding-tenders/opportunities/portal/screen/myarea/projects

The Commission will formally notify the coordinator and beneficiaries in advance any changes to this URL.

Formal notifications on paper (only after the payment of the balance) addressed to the Commission must be sent to the official mailing address indicated on the Commission’s website.

Formal notifications on paper (only after the payment of the balance) addressed to the beneficiaries must be sent to their legal address as specified in the Participant Portal Beneficiary Register.

ARTICLE 53 — INTERPRETATION OF THE AGREEMENT

53.1 Precedence of the Terms and Conditions over the Annexes

The provisions in the Terms and Conditions of the Agreement take precedence over its Annexes.

Annex 2 takes precedence over Annex 1.

53.2 Privileges and immunities

Not applicable

ARTICLE 54 — CALCULATION OF PERIODS, DATES AND DEADLINES
In accordance with Regulation No 1182/71\(^{30}\), periods expressed in days, months or years are calculated from the moment the triggering event occurs.

The day during which that event occurs is not considered as falling within the period.

**ARTICLE 55 — AMENDMENTS TO THE AGREEMENT**

**55.1 Conditions**

The Agreement may be amended, unless the amendment entails changes to the Agreement which would call into question the decision awarding the grant or breach the principle of equal treatment of applicants.

Amendments may be requested by any of the parties.

**55.2 Procedure**

The party requesting an amendment must submit a request for amendment signed in the electronic exchange system (see Article 52).

The coordinator submits and receives requests for amendment on behalf of the beneficiaries (see Annex 3).

If a change of coordinator is requested without its agreement, the submission must be done by another beneficiary (acting on behalf of the other beneficiaries).

The request for amendment must include:

- the reasons why;
- the appropriate supporting documents, and
- for a change of coordinator without its agreement: the opinion of the coordinator (or proof that this opinion has been requested in writing).

The Commission may request additional information.

If the party receiving the request agrees, it must sign the amendment in the electronic exchange system within 45 days of receiving notification (or any additional information the Commission has requested). If it does not agree, it must formally notify its disagreement within the same deadline. The deadline may be extended, if necessary for the assessment of the request. If no notification is received within the deadline, the request is considered to have been rejected.

An amendment **enters into force** on the day of the signature of the receiving party.

An amendment **takes effect** on the date agreed by the parties or, in the absence of such an agreement, on the date on which the amendment enters into force.

**ARTICLE 56 — ACCESSION TO THE AGREEMENT**

56.1 Accession of the beneficiaries mentioned in the Preamble

The other beneficiaries must accede to the Agreement by signing the Accession Form (see Annex 3) in the electronic exchange system (see Article 52) within 30 days after its entry into force (see Article 58).

They will assume the rights and obligations under the Agreement with effect from the date of its entry into force (see Article 58).

If a beneficiary does not accede to the Agreement within the above deadline, the coordinator must — within 30 days — request an amendment to make any changes necessary to ensure proper implementation of the action. This does not affect the Commission’s right to terminate the Agreement (see Article 50).

56.2 Addition of new beneficiaries

In justified cases, the beneficiaries may request the addition of a new beneficiary.

For this purpose, the coordinator must submit a request for amendment in accordance with Article 55. It must include an Accession Form (see Annex 3) signed by the new beneficiary in the electronic exchange system (see Article 52).

New beneficiaries must assume the rights and obligations under the Agreement with effect from the date of their accession specified in the Accession Form (see Annex 3).

ARTICLE 57 — APPLICABLE LAW AND SETTLEMENT OF DISPUTES

57.1 Applicable law

The Agreement is governed by the applicable EU law, supplemented if necessary by the law of Belgium.

57.2 Dispute settlement

If a dispute concerning the interpretation, application or validity of the Agreement cannot be settled amicably, the General Court — or, on appeal, the Court of Justice of the European Union — has sole jurisdiction. Such actions must be brought under Article 272 of the Treaty on the Functioning of the EU (TFEU).

As an exception, if such a dispute is between the Commission and STATENS ARBEIDSMILOJNSTITUTT, UNIVERSITETET I BERGEN, the competent Belgian courts have sole jurisdiction.

If a dispute concerns administrative sanctions, offsetting or an enforceable decision under Article 299 TFEU (see Articles 44, 45 and 46), the beneficiaries must bring action before the General Court — or, on appeal, the Court of Justice of the European Union — under Article 263 TFEU.
ARTICLE 58 — ENTRY INTO FORCE OF THE AGREEMENT

The Agreement will enter into force on the day of signature by the Commission or the coordinator, depending on which is later.

SIGNATURES

For the coordinator

Peter VAN DUKEN with ECAS id ndijkenp signed in the Participant Portal on 10/12/2019 at 13:11:21 (transaction id SigId-116833-SdJKudif3SBNdKRFJULh6deiyvbqgDwibKqilFhtH1t66Q4dag xMtkvGS2JcZidmnPE6gAgvVIGYSvdfxEdhSHm-jpJZsgsw0KqgsaRezgPjqG-JojyILREE3cbqRCVbhLGmaCnf7WzQb4n1fNwTJRqrF).

Timestamp by third party at
Tue Dec 10 13:11:27 CET 2019

For the Commission

Signed by Milagros BAS SANCHEZ with ECAS id bassami as an authorised representative on 06-12-2019 20:48:47 (transaction id SigId-78201-WNMKnVtahg9OR8Je7VKDSVeuFljgEyT1U2VLgzmTp pTlovhQ3RCWcogqYXRzR2FfREEmKU60Kt5kJEEeqzggs-jpJZsgsw0KqgsaRezgPjqG-D2kgP0GWsnMaZvFevTYczMfMzUIo0TqbxRolsUnTxi)

Fri Dec 06 20:48:51 CET 2019
EUROPEAN COMMISSION
Directorate-General for Research and Innovation
Healthy Lives

ANNEX 1 (part A)
Research and Innovation action
NUMBER — 874703 — EPHOR
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1.1. The project summary

<table>
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One form per project

General information

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<td>Call (part) identifier</td>
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| Topic | SC1-BHC-28-2019 
The Human Exposome Project: a toolbox for assessing and addressing the impact of environment on health |
| Fixed EC Keywords | Public and environmental health, Epigenetics and gene regulation, Environmental stressors |
| Free keywords | working life exposome, occupational exposure, cohort studies, sensors, job exposure matrix, omics, pathways, non-communicable diseases, shift work, respiratory health, health & economic impact. |

Abstract

Exposures at the workplace contribute to many non-communicable diseases (NCDs) with a similar magnitude as urban air pollution or obesity. Given the associated societal and economic (2-6% GDP) pressure, ensuring a healthy work environment is a strategic goal for the European Commission. Demographic changes (aging workforce, female workers) and the rapidly changing nature of work with respect to secure employment and migration, are posing additional challenges. We define the working-life exposome as all occupational and related non-occupational factors (general and socio-economic environment, lifestyle, behaviour). Taking a working-life exposome approach will help address these challenges by providing better insights in how complex working-life exposures are related to NCDs, for vulnerable groups (female, migrant, insecure job workers) or life stages. The working-life exposome is in its infancy and new approaches and methods are needed. In EPHOR a consortium of exposure, health and data scientists and technology developers will develop a working-life exposome toolbox, with stakeholder involvement. The toolbox will make available to scientists, policy makers and occupational health practitioners: 1) innovative methods for collection, storage, and interpretation of more complete and individual level working life exposome data; 2) better knowledge on how the working life exposome relates to NCDs, including complex interactions, vulnerability, biological pathways and early signs of health damage, by uniquely combining large-scale pooling of existing cohorts with focused case studies; 3) models for assessing the economic and societal impact of working life exposures. EPHOR will lay the groundwork for evidence-based and cost-effective preventive actions to reduce the burden of NCDs as a result of the working-life exposome. Thereby, health, wellbeing and productivity of the EU population will be improved and the burden on the EU health care systems reduced. EPHOR is part of the European Human Exposome Network comprised of 9 projects selected from this same call.
## List of Beneficiaries

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### 1.3. Workplan Tables - Detailed implementation

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<td>WP8</td>
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<td>WP8</td>
<td>8 - UNIMAN</td>
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<td>WP12</td>
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<td>Due Date (in months)</td>
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1.3.3. WT3 Work package descriptions

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<tr>
<td>Start month</td>
<td>1</td>
<td>End month</td>
<td>58</td>
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Objectives

The objective is to develop methodology for collecting and analysing individual level external exposome assessment including a wearable sensor system, wearable passive sampling of chemical and biological exposures and digital questionnaires to be applied in the case studies (WP6,7) and made available in the working-life exposome toolbox (WP9). Specific objectives are:

- Development of a wearable sensor system consisting of at least one light, dust, noise, sleep, physical activity level, heart rate and location including a protocol for deployment (T1.1)
- Protocol development for passive sampling and laboratory chemical and biological analyses (T1.2)
- Development of a protocol for external exposome assessment in the case studies (T1.3)
- Processing of sensor data into several exposure metrics (T1.4)

Description of work and role of partners

WP1 - New technologies for external exposome and health [Months: 1-58]

IOM, TNO, ISGLOBAL, AU, UNIMAN, UU, VTEC

Description of work

Task 1.1 Development of wearable sensor system (VTEC, TNO, IOM, UNIMAN, ISGLOBAL, AU) (M1-24)

A literature review will be done for relevant sensor technologies. At a minimum sensors for light, dust, noise, sleep, physical activity, heart rate and location will be selected. In WP10, a stakeholder consultation will be held to understand acceptability and perceptions of sensor use by employees, employers and occupational health practitioners, both for work and lifestyle. This consultation involves issues on usability (operating and interaction with sensors) and privacy and user interfaces/tools for sensor data collection and readout.

Based on identified sensors, a wearable sensor system will be developed that can be modified for implementation in a variety of research and user needs. The system will allow for integration of different types of sensors. For the case studies 50 systems will be produced. Only sensors that have already been developed for market will be included, to ensure that the sensor system can be finished and implemented within the project timeframe.

The system will allow for data to be gathered in a secure online data portal and transferred to the Yoda system (with WP4). A protocol for use of the wearable sensor system will be developed which will form the basis for Task 1.4 and for further development of the protocol for different stakeholders in the working-life exposome toolbox (WP9).

Task 1.2 Passive sampling: Protocol development and laboratory analyses (TNO, AU) (M1-48)

Existing protocols will be adapted for applying and analysing passive sampling wristbands for chemical analyses and passive dust collection for biological analyses. Analyses of samples collected in the case studies (WP6 & 7) will take place: 400 wristbands on 90 chemicals in the following compound groups: polychlorinated biphenyls, polycyclic aromatic hydrocarbons, methylated naphthalene’s, musk compounds, organochlorine pesticides, organophosphate esters and 400 passive dust samples on endotoxins, aeroallergens and other biological exposures. This protocol will form the basis for Task 1.3 and will be made available in the working life exposome toolbox (WP9).

Task 1.3 External exposome protocol development for the case studies, including a feasibility study (IOM, UNIMAN, TNO, ISGLOBAL, AU, VTEC) (M1-M24)

Development of a full external exposome protocol for in the case studies that will bring together the protocols on the wearable sensor system and passive sampling (see Figure for overview of all components of the external exposome protocol, dots are sensors). A protocol for field implementation, informed consent forms, data collection, QA/QC, data management, and data analysis will be developed with the case studies. The protocol will also encompass a digital questionnaire on working time, sleep, specific chemical and physical exposures, diet, lifestyle, workplace organisation, psychosocial factors and job-records. A first protocol for obtaining ethical approval for the feasibility study and case studies will be prepared by M9. A feasibility study will be conducted to test the exposure protocol, including the wearable sensor system in the field.

The study will be performed in at least two countries, with at least 12 participants. Participant feedback will be obtained regarding the implementation of the protocol, and revisions to the protocol will be made as necessary based on the
experience and results of the feasibility study. Ethical approval will be obtained if necessary. Based on the feasibility study the protocol will be filled in with further details by M18. The protocol will then be implemented in the field studies in WP6&7.

Task 1.4 Processing of sensor data (TNO, IOM, UU) (M36-58)
Methods will be developed for processing high resolution sensor data into usable exposure metrics for the case study data (to be incorporated in Yoda, WP4) and for future use by occupational health practitioners to be further developed into a tool for automated report generation based on sensor data (in WP9). Analyses on the case study data (WP6,7) will include both within-type analyses (e.g. exploring variability in a particular type of exposure data, such as chemical exposures, lifestyle exposures) and exposure profiling (e.g. determining combinations of exposure types and profiles over a day).

Participation per Partner

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List of deliverables

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<td>D1.3</td>
<td>Protocol for feasibility study</td>
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Description of deliverables
D1.1 Report on the development of a wearable sensor system (T1.1) (M24)
D1.2 Report on methods and results passive sampling method (T1.2) (M48)
D1.3 Protocol for feasibility study (T1.3) (M12)
D1.4 Report on the external exposome protocol development for the case studies (T1.3) (M24)
D1.5 Report on method development for processing of sensor data (T1.4) (M58)

Development of a wearable sensor system consisting of at a minimum light, dust, noise, sleep, physical activity level, heart rate and location. In addition a protocol for deployment in the case studies will be developed.

D1.2 : Report on methods and results passive sampling method [48]
Protocol development for applying and analyzing passive sampling wristbands for chemical analyses and passive dust collection for biological analyses. Analyses and reporting on passive samples collected in the case studies.

D1.3 : Protocol for feasibility study [12]
Protocol for the feasibility study, that will be conducted in at least two countries with at least 12 participants, to test the exposure protocol including the wearable sensor system in the field. The exposure protocol will ultimately be applied in the case studies.

D1.4 : Report on the external exposome protocol development for the case studies [24]
Development of a full external exposome protocol for in the case studies that will bring together the protocols on the wearable sensor system and passive sampling. A protocol for field implementation, informed consent forms, data collection, QA/QC, data management, and data analysis will be developed with the case studies. The protocol will also encompass a digital questionnaire on working time, sleep, specific chemical and physical exposures, diet, lifestyle, workplace organisation, psychosocial factors and job-records.

D1.5 : Report on method development for processing of sensor data [58]
Methods will be developed for processing high resolution sensor data into usable exposure metrics for the case study data (to be incorporated in Yoda, WP4) and for future use by occupational health practitioners to be further developed into a tool for automated report generation based on sensor data (in WP9).

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**Schedule of relevant Milestones**

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<td>3 - IOM</td>
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<td>Start of feasibility study on external exposome protocol</td>
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<td>MS6</td>
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<td>Feasibility study on external exposome protocol completed</td>
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<td>MS7</td>
<td>WP 1: deliver tools to toolbox</td>
<td>1 - TNO</td>
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<td>Deliver of tools to toolbox regarding wearable sensor system and passive sampling</td>
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<td>Work package title</td>
<td>Standardized assessment of multiple exposures in large populations</td>
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### Objectives

The objective is to develop a dynamic EuroJEM permitting standardized assessment of multiple exposures in large populations across Europe. Specific objectives are:

- Harmonize existing JEMs into a comprehensive set (EuroJEM) for retrospective exposure assessment in the EPHOR mega cohort (WP5) and in the case studies (WP6,7) (T2.1, T2.2)
- Develop and apply protocols for validation of the EuroJEM and for inclusion of new data (T2.3)
- Develop new and more specific JEM modules for selected exposures (T2.4)
- Provide data input for the interactive tool for exploration of exposure prevalence and exposure levels in European populations (WP9) and for health impact assessment (WP8) (T2.5)
- Provide a validated and standardized dynamic tool for state-of-the-art exposure assessment in future European studies (outside EPHOR) (WP9) (T2.5)

### Description of work and role of partners

**WP2 - Standardized assessment of multiple exposures in large populations** [Months: 1-58]

**KI, TNO, ISGLOBAL, AU, STAMI, UNIMAN, UU, INSERM, FIOH, SLL**

Task 2.1 Collecting and defining existing JEMs (FIOH, KI, SLL, STAMI, ISGLOBAL, AU, UU) (M1-M26).

For each JEM, information will be collected on coding systems of occupation and industry, time-periods covered and time intervals, exposure indices and data sources. For each exposure, definitions of exposed/non-exposed will be suggested based on an agreed European background level of exposure, and the unit of exposure to be used.

Task 2.2 Harmonizing existing JEMs (KI, SLL, UU, STAMI, INSERM, AU, FIOH) (M6-M30)

Occupational codes will be harmonized. Inconsistencies and gaps between different JEMs will be resolved by expert judgement, leaving the possibility to keep between-country differences when factually motivated. Imputation will be applied to cover missing values (occupations/countries), resulting in a first version of EuroJEM. This version will be shared with WP5 and 6 for retrospective exposure assessment in the EPHOR mega cohort and the case-study in WP6, with WP8 for input into development of impact assessment methods and with WP9 as a first basis for the development of the interactive tool.

Task 2.3 Protocol for including new data in EuroJEM (UNIMAN, TNO, FIOH, UU, STAMI, KI, SLL) (M1-M30)

To ensure that the dynamic EuroJEM includes the latest available information of highest quality possible, a protocol will be developed for including new data into EuroJEM.

The protocol will include methods for searching and collecting new data from literature (assisted by text mining WP4), exposure databases (e.g. ECHA REACH database, reports) and (Bayesian) decision criteria to determine if and how to revise exposure estimates in the JEM. This task will also investigate the use of optimized and dynamic coding systems. For example, depending on the exposure of interest, job categories can be merged or separated to reduce exposure variability within occupational job categories to improve the performance of the JEMs. Developed protocols will feed into task 2.5 and will be made available to the toolbox (WP9).

Task 2.4 Development of new and more specific JEMs (AU, FIOH, KI, SLL, STAMI, UU) (M1-M30)

New parts/dimensions for the EuroJEM will be developed to cover:

1. selected exposures which for the same occupational code vary largely by industry (e.g. mechanic, maintenance or assembly worker) or by gender (e.g. job control, physical work load);
2. key emerging risks (e.g. threats and violence at work);
3. new concepts (e.g. societal status of the work);
4. employment conditions (e.g. non-standard , temporarily in another country, “precarious”); and
5. key non-occupational exposures (life-style, socioeconomic conditions) will be addressed when country-specific data are available by occupational code.

Further needs may be identified during the collection and harmonization of existing JEMs (T2.1, T2.2) and will be taken into account as much as possible in this task.

Task 2.5 Evaluation and transition into dynamic EuroJEM (UU, STAMI, FIOH, UNIMAN, TNO, INSERM, KI, SLL, ISGLOBAL) (M26-M58)
We will evaluate EuroJEM, using the most efficient approach for each selected exposure, including measurement databases as well as the use of text-mining techniques on studies with expert case-by-case exposure assessment. In the absence of expert assessment, self-reported exposures in population health surveys, and positive predictive value for expected outcome may also be used. The evaluation will be used to revise EuroJEM (T2.2) into the dynamic EuroJEM based on the protocol developed in Task 2.3. The dynamic EuroJEM will be made available to the toolbox (WP9).

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<tbody>
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**Description of deliverables**

- D2.1 Report on collection and defining JEMs (T2.1) (M24)
- D2.2 Report on harmonizing existing JEMs (T2.2) (M30)
- D2.3 Report on protocol for including new data in EuroJEM (T2.3) (M30)
- D2.4 Report on development of new and more specific JEMs (T2.4) (M30)
D2.5 Report on evaluation and transition into dynamic EuroJEM (T2.5) (M58)

D2.1 : Report on collection and defining JEMs [24]
For each JEM, information will be collected on coding systems of occupation and industry, time-periods covered and time intervals, exposure indices and data sources. For each exposure, definitions of exposed/non-exposed will be suggested based on an agreed European background level of exposure, and the unit of exposure to be used.

D2.2 : Report on harmonizing existing JEMs [30]
Occupational codes will be harmonized. Inconsistencies and gaps between different JEMs will be resolved by expert judgement, leaving the possibility to keep between-country differences when factually motivated. Imputation will be applied to cover missing values (occupations/countries), resulting in a first version of EuroJEM.

D2.3 : Report on protocol for including new data in EuroJEM [30]
To ensure that the dynamic EuroJEM includes the latest available information of highest quality possible, a protocol will be developed for including new data into EuroJEM. The protocol will include methods for searching and collecting new data from literature (assisted by text mining WP4), exposure databases (e.g. ECHA REACH database, reports) and (Bayesian) decision criteria to determine if and how to revise exposure estimates in the JEM. This task will also investigate the use of optimized and dynamic coding systems.

D2.4 : Report on development of new and more specific JEMs [30]
New parts/dimensions for the EuroJEM will be developed to cover: 1) selected exposures which for the same occupational code vary largely by industry (e.g. mechanic, maintenance or assembly worker) or by gender (e.g. job control, physical work load); 2) key emerging risks (e.g. threats and violence at work); 3) new concepts (e.g. societal status of the work); 4) employment conditions (e.g. non-standard, temporarily in another country, “precarious”); and 5) key non-occupational exposures (life-style, socioeconomic conditions) will be addressed when country-specific data are available by occupational code.

D2.5 : Report on evaluation and transition into dynamic EuroJEM [58]
EuroJEM will be evaluated using the most efficient approach for each selected exposure, including measurement databases as well as the use of text-mining techniques on studies with expert case-by-case exposure assessment. The evaluation will be used to revise EuroJEM (T2.2) into the dynamic EuroJEM based on the protocol developed in Task 2.3.

### Schedule of relevant Milestones

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<tr>
<td>MS8</td>
<td>EuroJEM first version</td>
<td>5 - KI</td>
<td>24</td>
<td>EuroJEM first version and input data for the working-life exposome exploration tool ready for toolbox and for HIA</td>
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<tr>
<td>MS12</td>
<td>Final version Dynamic EuroJEM</td>
<td>5 - KI</td>
<td>48</td>
<td>Dynamic EuroJEM final version ready for toolbox</td>
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The objective is to develop (non-invasive) methodology for characterising the internal exposome in case studies (WP6,7), comprising the identification of biological pathways and early markers of exposure and effect. Specific objectives are:

- To provide protocols on sample collection compatible with omics and bioanalyses to WP6,7 (T3.1)
- To provide data for mechanistic modelling in WP4 by performing targeted and agnostic biomonitoring, omics and bioassays on traditional biological matrices (T3.2)
- To develop new methods for non-invasive monitoring of the internal exposome by applying targeted and untargeted analyses to assess occupational exposure and effect in exhaled breath (EB) (T3.3)

**WP3 - Internal exposure and effect assessment using biomonitoring, omics and minimally invasive biomarker development**  
[Months: 1-60]  
KUL, TNO, ISGLOBAL, AU, KI, STAMI, UU, LIFE, OWL, CUT

**Task 3.1 Protocol development**  
(KUL, ISGLOBAL, AU, OWL) (M1-6)
Protocols will be developed for the collection, pre-processing and storage of blood, urine, exhaled breath and exhaled breath condensate samples to be incorporated in WP6 and 7 study protocols.

**Task 3.2 Targeted and agnostic common biomonitoring, omics and bioassays on traditional biological matrices obtained from subjects in WP6 and 7**  
(KUL, CUT, ISGLOBAL, KI, STAMI) (M6-44)
Targeted and agnostic biomonitoring, omics and bioassays will be performed in a tiered approach following a logical biological sequence.

Internal exposures are first verified via

1. conventional biomonitoring for known exposures, followed by the
2. agnostic identification of novel internal exposures, in relation to
3. relatively stable epigenetic changes and
4. downstream gene/protein expression changes, all in relation to (5) more established biomarkers of effect (clinical chemistry, hormones, immune responses, allostatic load/aging)

**Task 3.2.1 Internal exposome characterisation using conventional biomonitoring**  
(KUL, CUT) (M6-44)
Internal exposure assessment will be done using biomonitoring approaches in blood/plasma for metals, cotinine (smoking behaviour) and PAHs (1-hydroxypyrene, hydroxybenzo(a)pyrene). This will be done in up to 400 subjects from WP6 and up to 800 subjects from WP7. In addition, to monitor exposure to shift work, the cortisol-awakening response will be determined in saliva samples obtained from WP7.

**Task 3.2.2 Exposure and effect assessment using targeted bioassays and omics in blood and urine**  
(KUL, ISGLOBAL, KI, STAMI) (M6-44)
To verify exposures in relation to effects, omics analyses will be performed in a tiered approach in peripheral blood mononuclear cells of up to 400 (WP6, 2 time points) and up to 800 (WP7, single time point) individuals. Epigenomics will be performed by means of Infinium Methylation EPIC Bead Chip microarray, and confirmatory Targeted Deep Bisulfate pyrosequencing, in up to 400 and 200 samples, respectively (combined for WP6 and WP7, either subjects or time points). Transcriptomics will be performed subsequently, using RNAseq and/or qPCR. Analyses also involve targeted bioassays: inflammatory biomarkers YKL40 and CC16 (ELISA); Luminex for cytokines/chemokines/growth factors; oxidative stress markers, 8-OHdG; mtDNA copy number and telomere length; clinical chemistry to monitor organ function/metabolism (ALT, cholesterol, glucose, urinary creatinine). In addition, analysis of melatonin (by means of RIA), cortisol and corticosteroids, androgens, progestogens and oestrogens (by means of metabolomics) will be performed for WP7.

**Task 3.3 Method development for non-invasive monitoring**  
(KUL, OWL) (M30-58)
Task 3.3.1. Epigenetic and proteome markers in EBC (KUL) (M30-58)
Cell free DNA (cfDNA) from EBC (exhaled breath condensate) and blood will also be studied in a subset of the subjects from WP6 and 7 case studies. Methylation analysis will be performed in cfDNA, as described in task 3.2.2 and compared to methylation patterns in blood. The methylome data will be supplemented with EBC proteome analysis (Orbitrap Mass Spectrometry) for a more robust functional interpretation of cfDNA data in biological pathway context. These analyses will be performed in the subset of up to 400 subjects or time points from WP6 and 7 combined. A report on the use of omics in EBC for non-invasive monitoring will be written and made available to the toolbox (WP9).

Task 3.3.2 VOC analysis of markers in non-invasive samples (OWL, KUL) (M30-58)
Breath samples will be analysed for VOCs using TD-GC mass spectrometry. VOC profiles will be correlated to the external and internal exposome (blood and saliva data described above) and health data (Task 3.2; Task 3.3.1 and WP6 and 7) to identify markers related to exposure or early health effect. A report on the use of VOCs in exhaled breath for non-invasive monitoring will be written and made available to the toolbox (WP9).

Task 3.4 Bioinformatics analysis of omics data and stratification of exposomes (KUL, TNO, ISGLOBAL, KI, STAMI, UU, OWL, CUT, LIFE) (M24-48)
All data will be made available to Yoda (WP4) to facilitate bioinformatics analysis involving pathway and stratification analysis of exposomes. First, after omics data pre-processing, large-scale enrichment of gene ontology and pathways will be conducted using tools (e.g. GSEA, Cytoscape, GrandForest and EnrichmentMap). Second, small-scale enrichment will be performed on the level of pathway modules (using e.g. BioNet, ConsensusPathDB). The data will be integrated to generate signatures or “fingerprints” of particular exposomes, on individual and group levels. Processed omics and biomonitoring data will further feed into task 4.2.6 and Task 6.3 and 7.3 towards quantitative mechanism-based exposure effect relationships.

Participation per Partner

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List of deliverables

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## List of deliverables

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<td>Report on the validated breathomics techniques; including cfDNA/proteomics and VOCs, respectively, to assess exposure and early health effects within the working-life exposome</td>
<td>16 - OWL</td>
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<td>Confidential, only for members of the consortium (including the Commission Services)</td>
<td>58</td>
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<tr>
<td>D3.4</td>
<td>Report describing the outcome of bioinformatics analysis on omics data (pathway and exposome stratification)</td>
<td>6 - KUL</td>
<td>Report</td>
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## Description of deliverables

D3.1: Protocol for the collection, pre-processing and storage of biological samples in WP6, WP7 (T3.1) (M6)

D3.2: Report describing the biomonitoring, omics and bioassays methods on traditional biological matrices including quality control (T3.2) (M60)

D3.3: Report on the validated breathomics techniques, including cfDNA/proteomics and VOCs, respectively, to assess exposure and early health effects within the working-life exposome (T3.3) (M58)

D3.4: Report describing the outcome of bioinformatics analysis on omics data (pathway and exposome stratification) (T3.4) (M48)

D3.1: Protocol for the collection, pre-processing and storage of biological samples in WP6, WP7 [6]

Protocols will be developed for the collection, pre-processing and storage of blood, urine, exhaled breath and exhaked breath condensate samples to be incorporated in WP6 and 7 study protocols.

D3.2: Report describing the biomonitoring, omics and bioassays methods on traditional biological matrices including quality control [50]

Targeted and agnostic biomonitoring, omics and bioassays will be performed in a tiered approach following a logical biological sequence. The report will describe both conventional biomonitoring and targeted bioassays and omics.

D3.3: Report on the validated breathomics techniques; including cfDNA/proteomics and VOCs, respectively, to assess exposure and early health effects within the working-life exposome [58]

Report on the validated breathomics techniques. The use of epigenetic and proteome markers in EBC (exhaled breath condensate) by investigating cell free DNA (cfDNA) from EBC and blood will be described. In addition, the use of VOC profiles will be described by correlating them to the external and internal exposome and health data to identify markers related to exposure or early health effect.

D3.4: Report describing the outcome of bioinformatics analysis on omics data (pathway and exposome stratification) [48]

All data will be made available to Yoda (WP4) to facilitate bioinformatics analysis involving pathway and stratification analysis of exposomes. First, after omics data pre-processing, large-scale enrichment of gene ontology and pathways will be conducted using tools (e.g. GSEA, Cytoscape, GrandForest and EnrichmentMap). Second, small-scale enrichment will be performed on the level of pathway modules (using e.g. BioNet, ConsensusPathDB).
These processed omics and biomonitoring data will further feed into task 4.2.6 and Task 6.3 and 7.3 towards quantitative mechanism-based exposure effect relationships.

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<tr>
<td><strong>Milestone number</strong></td>
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Objective

The objective is to develop a data management and analytics platform capable of storing, bringing together and analysing data from multiple locations/countries and exposome technology platforms, in accordance with the FAIR guidelines (findable, accessible, interoperable and reusable). Specific objectives are:

- To adopt a data management platform, provide data management and ensure compliance with the EU General Data Protection Regulation for bringing together and storing existing and new data (T4.1).
- To adopt, develop and apply new data interpretation methods, specifically for multiple exposure and outcome modelling (T4.2.1), exposure time response models (T4.2.2), hierarchical analyses (T4.2.3), automated job coding (T4.2.4), dynamic coding of jobs into codes that are more meaningful for exposure assessment (T4.2.5) and quantification of internal mechanisms (T4.2.6).

Description of work and role of partners

WP4 - Working-life exposome data management and analytics platform

Task 4.1 Data management platform (UU, ESDY) (M1-60)

The Yoda platform is a generic, flexible and scalable solution that will be used for reliable, long-term storing and archiving large amounts of research data during all stages of a study. The existing Yoda platform will be customized to the needs and requirements of the EPHOR project. The variety of data types, as collected within EPHOR, can be stored in Yoda. A framework using DataSHIELD for joint analyses across cohorts either through meta-analysis or pooling of the individual cohorts in WP5 will be developed.

Task 4.2 Development of new data interpretation methods (UU, ISGLOBAL, STAMI, AU, KI, LIFE, TNO) (M1-58)

Task 4.2.1 Multiple-exposure and outcome modelling using advanced statistical tools (UU, ISGLOBAL, STAMI, AU) (M1-24)

Methods capable of handling multiple exposures in exposure-response analyses will be developed. This includes the conventional approach of analysing all exposure-response associations in parallel, while adjusting for multiple comparisons and novel methods based on machine learning approaches that account for the correlations between exposures. These methods will allow for mutual adjustment of the exposure-response relations under investigation. These methods will also include relevant exposure-exposure and gene, gene transcript or protein exposure interactions in a principled and comprehensive way. These models will be applied within WP5-7, and a tutorial will be provided to WP9.

Task 4.2.2 Exposure-time-response (ETR) models (UU, TNO, ISGLOBAL, STAMI, AU) (M1-36)

An inventory will be compiled of all Compartmental (multi-state) models, (two-stage) clonal expansion models, and exposure rate models for ETR analyses that have been published to date. This inventory will document what the underlying assumptions of these models are, what inference they provide, and to what extent they overlap. From this overview we will select a suite of ETR models that will be applied within WP5 and 6, and made available as tutorial in WP9. In parallel we will investigate to what extent existing ETR models can be modified to allow for multiple exposures (strongly linked with task 4.2.1) and nonlinear exposure-response relations, and to incorporate biological data to strengthen these models.

Task 4.2.3 Hierarchical analyses (UU, KI, STAMI) (M1-24)

Hierarchical regression methods will be further developed and applied this to the EPHOR mega cohort (WP5) to identify new exposure-disease associations (in the agnostic analyses) and use the outcomes within WP2 to evaluate and improve EuroJEM. A tutorial will be provided to WP9.

Task 4.2.4 Automated job coding (UU, UNIMAN, STAMI, KI, INSERM) (M1-18)

Improved methods for automated coding of free text fields in occupational histories into job coding will be developed based on artificial intelligence (AI) mimicking human experts for coding of occupational histories, to be used in WP5. Based on human knowledge, AI rules will be formed. Free text analysis will be based on natural language processing. The system will result in a decision support tool (WP9), where codes with low reliability will be flagged by the expert.
system and highlighted to assure a final check of a human coder. This method will be used in WP5 to code free text job histories in cohorts where occupational data has been collected, but not yet coded.

Task 4.2.5 Dynamic coding into new codes for more meaningful categories for exposure assessment (UNIMAN, TNO, UU, KI) (M1-42)
Improved coding systems will be developed and used in by WP2 for more flexible coding that allows for different coding structures depending on the risk factor.
We will expand on existing descriptive clustering approaches to map job descriptions and estimated exposures using previous expert assessments of exposure and develop candidate cluster labels into a common semantic vector space by using context-sensitive embeddings. The number of labels (keywords) used for each cluster can subsequently be used for automated coding (see Task 4.2.4).

Task 4.2.6 Quantification of internal biological pathways in relation to external exposome (TNO, LIFE, KUL, UM, UU, ISGLOBAL, AU) (M1-58)
External exposure, biological pathways, health outcome and impaired body functions, derived from sensor, biomarkers, omics and case study data (from WP3, 6 and 7) will be integrated with AOPs.
Data on molecular initiating events (MIEs) of AOPs, and AOPs themselves, will be collected from e.g. OECD AOP knowledge base, comparative toxicogenomics database, public omics datasets and (text-based) knowledge mining. Information from gene, chemicals, diseases will be integrated with relevant tools towards qualitative AOP’s for EPHOR. These will be used for subsequent quantitative modelling:
1) PBTK modelling to link external exposure and biomonitoring/omics levels (WP3,6,7) to target organ concentrations, in particular at the site of the MIE;
2) quantitative description of MIEs in relation to predicted target organ concentrations to propose a likelihood of MIE/AOP activation within the cases from WP6 and WP7 (via Reverse Causal Reasoning); and
3) use of predefined AOP/toxicological networks to aid in the analysis of omics data to infer quantitative exposure-response relationships.
Task 4.2.6 is performed in collaboration with WP6 and 7 and will result in knowledge on exposure, early biological pathway changes and disease mechanisms, including quantitative biomarkers for these. A report on the methodology will be delivered for the toolbox (WP9).

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Participation per Partner
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Description of deliverables

D4.1 Report on tutorial for the application of a suite of ‘multiple exposure methods’ (T4.2.1) (M24)

Methods capable of handling multiple exposures in exposure-response analyses will be developed. This includes the conventional approach of analysing all exposure-response associations in parallel, while adjusting for multiple comparisons and novel methods based on machine learning approaches that account for the correlations between exposures.

D4.2 Report on inventory of ETR models relevant for EPHOR (T4.2.2) (M36)

An inventory will be compiled of all Compartmental (multi-state) models, (two-stage) clonal expansion models, and exposure rate models for ETR analyses that have been published to date. This inventory will document what the underlying assumptions of these models are, what inference they provide, and to what extent they overlap.

D4.3 Report on tutorial on the use of hierarchical models in working-life exposome research (T4.2.3) (M24)

Hierarchical regression methods will be further developed and applied to the EPHOR mega cohort (WP5) to identify new exposure-disease associations (in the agnostic analyses) and use the outcomes within WP2 to evaluate and improve EuroJEM.

D4.4 Report on automated job coding (T2.4.4) (M18)

Improved methods for automated coding of free text fields in occupational histories into job coding will be developed based on artificial intelligence (AI) mimicking human experts for coding of occupational histories, to be used in WP5.

D4.5 Report on dynamic coding for more meaningful categories for exposure assessment (T4.2.5) (M42)

D4.6 Report on quantification of internal biological pathways in relation to external exposome (T4.2.6) (M58)
D4.5 : Report on dynamic coding for more meaningful categories for exposure assessment [42]
Improved coding systems will be developed and used in by WP2 for more flexible coding that allows for different coding structures depending on the risk factor.

D4.6 : Report on quantification of internal biological pathways in relation to external exposome [58]
External exposure, biological pathways, health outcome and impaired body functions, derived from sensor, biomarkers, omics and case study data (from WP3, 6 and 7) will be integrated with AOPs. This will result in knowledge on exposure, early biological pathway changes and disease mechanisms, including quantitative biomarkers for these.

<table>
<thead>
<tr>
<th>Milestone number</th>
<th>Milestone title</th>
<th>Lead beneficiary</th>
<th>Due Date (in months)</th>
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<td>MS1</td>
<td>Data management platform</td>
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<td>MS2</td>
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<td>MS13</td>
<td>description to the Yoda system to toolbox</td>
<td>9 - UU</td>
<td>46</td>
<td>Provide description and link to the Yoda system to toolbox, incl. protocol for gaining access to the data and for making use of Yoda (including new data)</td>
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The objective is to provide new evidence of the impact of occupational exposures on the risk of major non-communicable diseases (NCDs), through both systematic and agnostic analyses of occupational exposures and risk factors across the life-course. Specific objectives are:

- To create EPHOR mega cohort, based on large-scale pooling of existing European cohorts with data on occupational exposures that will be registered in an inventory (T5.1 and 5.2).
- To evaluate occupational risk factors for the incidence of major NCDs over the life course within the EPHOR mega cohort, Large-scaled pooled- analyses (T5.3) will include:
  - Known/suspected occupational risk factors to advance knowledge on rare health effects, interactions between occupational exposures and with general life exposures, critical exposure time periods/ temporal variations, identify vulnerable subpopulations, multimorbidity and transgenerational effects
  - previously unknown or unrecognised occupational exposure and health outcome relationships through a complementary agnostic, and hierarchical analysis approach.
  - To provide additional data supporting the case studies using cohorts with existing data collected to directly measure or monitor specific exposures of interest (T5.3.4).

**Description of work and role of partners**

**WP5 - EPHOR mega cohort [Months: 1-58]**

**STAMI, TNO, ISGLOBAL, IOM, AU, KI, KUL, UU, INSERM, FIOH, SLL**

Task 5.1 Extension and further development of a searchable web-based database of occupational cohorts (ISGLOBAL, AU, STAMI, FIOH) (M1-18)

This task will extend and further develop the work of the ongoing COST Action OMEGA-NET to extend and refine a searchable web-based database inventory of occupational cohorts.

The database will become publicly available through the toolbox (WP9) and will be continually updated, including both European and other international cohorts. Systematic literature searches and contact with relevant cohort PIs will foster the inclusion of new and ongoing cohort studies together with updated cohort information.

Task 5.2 Creation of EPHOR mega cohort (ISGLOBAL, UU, STAMI, KI, SLL, AU, KUL, INSERM) (M9-30)

Based upon the cohorts contained in Task 5.1 that have already provided agreement to participate and provide access to cohort data, the EPHOR mega cohort will be created, including cohorts with data on occupational histories which can be linked with EuroJEM (WP2), using the Yoda data management platform (WP4).

A meeting of all cohort PIs will be held in the first year of EPHOR (M12) to facilitate cohort creation and discuss and finalize the data sharing procedure and analytic strategy. Occupations will be coded, including using automated free text mining (developed in WP4), crosswalks between different coding systems will be developed and used to harmonize data across different occupational coding systems and versions (together with WP4), and the newly developed EuroJEM (WP2) will be applied to occupational histories over the life-course of included participants.

A framework for de-centralized large-scale pooling of data for epidemiological analyses will be implemented with WP4, taking into account relevant privacy and ethical issues (WP11), and ethics approval will be obtained from all relevant local/regional/national ethics boards. Outcome follow-up will be based on both registry and specific cohort approaches.

Task 5.3 Systematic and agnostic epidemiological analyses to investigate known or suspected, and unknown or unrecognized occupational risk factors in relation to multiple associated health outcomes (STAMI, ISGLOBAL, AU, UU, KI, SLL, FIOH, TNO, IOM, KUL, INSERM) (M30-58)

Through systematic pooled analyses of the EPHOR mega cohort, using DataSHIELD technology (WP4), we will investigate the influence of working life exposures for the risk of major specific NCDs, including cancers, respiratory, cardiovascular, and metabolic, musculoskeletal, mental, and neurodegenerative disorders, including multimorbidity and transgenerational effects.

Health outcomes will be determined based on the data available from the cohorts. In addition to the evaluation of exposures which have been previously defined as known or suspected in relation to health, an hierarchical approach will be taken to identify potential additional previously unknown or non-suspected exposures. All analyses will include multiple-exposure and outcome modelling using advanced statistical tools capable of handling groups or clusters of
exposures in relation to multiple outcomes, modified exposure-time-response models to investigate the effect of timing of exposure, hierarchical regression, and other techniques (WP4). Results will feed into health impact assessment (WP8) and the toolbox (WP9). Specific subtasks include:

Task 5.3.1 Analyses by job title (STAMI, FIOH, ISGLOBAL, AU, UU, KI, SLL) (M30-52)
Systematic and agnostic analyses of associations of job title and industry with multiple health outcomes will be conducted to provide understanding of associations at the job level, and will be the basis for the hierarchical analyses with also EuroJEM defined occupational exposure (T5.3.3).

Task 5.3.2 Analyses by EuroJEM defined exposure (STAMI, KI, SLL, ISGLOBAL, AU, UU, FIOH, KUL, IOM, TNO, INSERM) (M30-52)
Systematic and agnostic analyses of associations of EuroJEM defined occupational exposure with multiple health outcomes will be conducted to provide understanding of associations at the exposure level, both qualitatively and quantitatively, informing the identification of new associations. Analyses will advance knowledge on rare health effects, interactions of occupational exposures, interactions of occupational and general life exposures, critical exposure time periods and temporal variation of exposure, as well as identification of vulnerable subpopulations.

Task 5.3.3 Hierarchical approach combining analyses by job title and EuroJEM (UU, FIOH, KI, SLL, TNO, ISGLOBAL) (M30-52)
A hierarchical approach will be taken to compare associations observed in the job-based approach with those based on the EuroJEM will be conducted. Analysis will determine which proportion of associations observed in the job-based approach can be explained by specific EuroJEM exposures; the remaining unknown proportion of associations observed can be determined and provides hypotheses for previously unknown or unrecognised exposures for future research.

Task 5.3.4 Agnostic analyses of associations of measured/monitored occupational exposures with health outcomes (ISGLOBAL, AU; UU, STAMI, KI, SLL, INSERM, TNO)(M30-M58). Agnostic analyses of associations of directly measured occupational exposures with health outcomes will be conducted with a particular focus on 1) associations of multiple occupational exposures with respiratory outcomes (decline in lung function, asthma, COPD) allowing for the provision of complementary evidence and comparisons with findings in WG6; and 2) associations of night shift work exposure and multiple health outcomes allowing for the provision of complementary evidence and comparisons with findings on clinical outcomes in WP7. Results of these analyses will also be compared with results of analyses based on EuroJEM defined exposure. Protocols for future work based on the combined results of this task and of those of WP6 and WP7 will be jointly prepared.

### Participation per Partner

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## List of deliverables

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<td>2 - ISGLOBAL</td>
<td>Report</td>
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<tr>
<td>D5.2</td>
<td>Report on the establishment of the EPHOR mega cohort</td>
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<td>D5.3</td>
<td>Report on results of systematic and agnostic epidemiological analyses to investigate known and suspected occupational risk factors and multiple associated health outcomes</td>
<td>7 - STAMI</td>
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<tr>
<td>D5.4</td>
<td>Report on results of systematic and agnostic epidemiological analyses to investigate unknown and unrecognised occupational risk factors and multiple associated health outcomes</td>
<td>9 - UU</td>
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<td>D5.5</td>
<td>Protocol (including results of analyses) for future studies on respiratory health based on combining the EPHOR mega cohort approach with the detailed case study approach (shared deliverable with WP 6)</td>
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<td>58</td>
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<tr>
<td>D5.6</td>
<td>Protocol (including results of analyses) for future studies on shift work based on combining the EPHOR mega cohort approach with the detailed case study approach (Shared deliverable with WP 7)</td>
<td>2 - ISGLOBAL</td>
<td>Report</td>
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<td>58</td>
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## Description of deliverables

D5.1 Inventory of European cohorts with extensive information on occupational exposures (T5.1) (M18)
D5.2 Report on the establishment of the EPHOR mega cohort including ethics approval (T5.2) (M30)
D5.3 Report on results of systematic and agnostic epidemiological analyses to investigate known and suspected occupational risk factors and multiple associated health outcomes (T5.3.2) (M52)
D5.4 Report on results of systematic and agnostic epidemiological analyses to investigate unknown and unrecognised occupational risk factors and multiple associated health outcomes (T5.3.1 & 5.3.3) (M52)

D5.5 Protocol (including results of analyses) for future studies on respiratory health based on combining the EPHOR mega cohort approach with the detailed case study approach (T5.3.4 and T6.3.3) (M58) (shared deliverable)

D5.6 Protocol (including results of analyses) for future studies on shift work based on combining the EPHOR mega cohort approach with the detailed case study approach (T5.3.4 and T7.4) (M58) (Shared deliverable)

D5.1 : Inventory of European cohorts with extensive information on occupational exposures [18]

Extension and refinement of a searchable web-based database inventory of occupational cohorts based on the ongoing COST Action OMEGA-NET.

D5.2 : Report on the establishment of the EPHOR mega cohort [30]

The EPHOR mega cohort will be created, including cohorts with data on occupational histories. Occupations will be coded, including using automated free text mining (developed in WP4), crosswalks between different coding systems will be developed and used to harmonize data across different occupational coding systems and versions (together with WP4), and the newly developed EuroJEM (WP2) will be applied to occupational histories over the life-course of included participants. A framework for de-centralized large-scale pooling of data for epidemiological analyses will be implemented with WP4.

D5.3 : Report on results of systematic and agnostic epidemiological analyses to investigate known and suspected occupational risk factors and multiple associated health outcomes [52]

Systematic and agnostic analyses of associations of EuroJEM defined occupational exposure with multiple health outcomes will be conducted to provide understanding of associations at the exposure level, both qualitatively and quantitatively, informing the identification of new associations.

D5.4 : Report on results of systematic and agnostic epidemiological analyses to investigate unknown and unrecognised occupational risk factors and multiple associated health outcomes [52]

Systematic and agnostic analyses of associations of job title and industry with multiple health outcomes will be conducted to provide understanding of associations at the job level. A hierarchical approach will be taken to compare these associations with those based on the EuroJEM to determine which proportion of associations observed in the job-based approach can be explained by specific EuroJEM exposures

D5.5 : Protocol (including results of analyses) for future studies on respiratory health based on combining the EPHOR mega cohort approach with the detailed case study approach (shared deliverable with WP 6) [58]

Agnostic analyses of associations of directly measured occupational exposures with health outcomes will be conducted with a particular focus on associations of multiple occupational exposures with respiratory outcomes (decline in lung function, asthma, COPD) allowing for the provision of complementary evidence and comparisons with findings in WP6. Protocols for future work based on these combined results will be prepared in collaboration with WP 6.

D5.6 : Protocol (including results of analyses) for future studies on shift work based on combining the EPHOR mega cohort approach with the detailed case study approach (Shared deliverable with WP 7) [58]

Agnostic analyses of associations of directly measured occupational exposures with health outcomes will be conducted with a particular focus on associations of night shift work exposure and multiple health outcomes allowing for the provision of complementary evidence and comparisons with findings in WP6. Protocols for future work based on these results will be prepared.

Schedule of relevant Milestones

<table>
<thead>
<tr>
<th>Milestone number</th>
<th>Milestone title</th>
<th>Lead beneficiary</th>
<th>Due Date (in months)</th>
<th>Means of verification</th>
</tr>
</thead>
</table>

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Work package number 9 WP6  Lead beneficiary 18 4 - AU

Work package title Working-life exposome, lung function, and obstructive lung disease among men and women

Start month 1  End month 60

Objectives

The objective is to evaluate the impact of working-life exposome on respiratory health. Specific objectives are:

• To apply new targeted and agnostic exposome methods (developed in WP1-3) to collect individual level data on the external and internal exposome in selected existing cohorts with extensive respiratory outcome data (T6.1, 6.2);
• To examine how the long-term and short-term external working-life exposome affects lung function, asthma and COPD and investigate if this is influenced by gender and age (T6.3);
• To identify key biological pathways and markers for exposure and respiratory health effects associated with the working-life exposome, using biomonitoring, targeted biomarker assays and agnostic genetics, epigenetics, transcriptomics and proteomics (T6.3).

Description of work and role of partners

WP6 - Working-life exposome, lung function, and obstructive lung disease among men and women [Months: 1-60]

AU, TNO, ISGLOBAL, IOM, KI, KUL, STAMI, UNIMAN, UU, INSERM, PDA, UiB, OWL

Task 6.1 Protocol development, ethical approval and coordination of field work (UiB, AU, INSERM, ISGLOBAL, TNO, ESDY) (M1-48)

A protocol will be developed for new data collection in 12 study centres from 7 European countries (Spain, France, Sweden, Norway, Estonia, Iceland, Denmark) and Australia.

Ten of the centres are part of the European Community Respiratory Health Survey (ECRHS), and two French centres are part of the French Constances population-based cohort. Protocol development involves collaboration with WP1 and 3 for external and internal exposome data collection. Protocols will also describe the follow-up of the work done in WP1, 3, and 4. The development of ethics protocol, approval from corresponding committees and follow-up of good practices will be ensured.

Task 6.2 Conduct of the field studies: exposome and health data collection (AU, INSERM, KI, UiB, KUL, IOM, ISGLOBAL, OWL) (M18-40)

Task 6.2.1 Collection of data on long-term external exposome, respiratory health and biomaterials among 3000 subjects (AU, INSERM, KI, UiB, KUL) (M18-40)

Blood samples as well as lung function and questionnaire data (working time, sleep, specific chemical and physical exposures, diet, lifestyle, workplace organisation, psychosocial factors and job-records) will be collected for 3000 individuals from 12 centres from the ECRHS and Constances cohorts based on the protocol developed in Task 6.1.

In WP5, as part of the EPHOR mega cohort, information of occupation and industry from the 3000 individuals will be coded and combined with EuroJEM (WP2), providing multiple occupational exposures over the course of the lifetime, including, chemical, biological, physical, psychosocial and ergonomic exposures, as well as non-occupational exposures.

Task 6.2.2 Collection of data on short-term external exposome, respiratory health and biomaterials among 400 subjects (AU, INSERM, KI, UiB, KUL) (M18-40)

Based on the exposure assessment, lung function and questionnaire data during the clinical investigations in Task 6.2.1, 400 subjects will be selected for more detailed exposome characterisation: 100 COPD patients, 100 asthma patients, 150 matched healthy controls from occupations with high particulate exposure (i.e. construction) and 50 healthy controls from low exposed occupations.

Lung function and blood samples will be collected twice in one week (e.g. Monday morning and Friday afternoon) in 400 subjects. Exhaled breath and exhaled breath condensate will be collected in 200 subjects.

In addition, external exposure assessment with passive sampling and wearable sensor systems for personal light, dust, noise, sleep, physical activity, heart rate and location will be performed during the same week. Passive dust and wristband samples will be analysed for biological exposures (400 samples) and chemical exposures (200 samples) in Task 1.2.

Task 6.2.3 Internal exposome assessment (KUL, AU, UiB, AU, ISGLOBAL) (M24-40)

For the subset of 400 subjects blood samples will be used for an agnostic as well as a targeted internal exposome analyses.
This will include classic biomonitoring for metals, PAHs and cotinine (400 samples), biological effect monitoring: clinical chemistry and proteomics for immune factors (including YKL40 and CC16) and 8-OHdG (800 samples) and (other) omics: genotype, mtDNA/telomere length, epigenomics, cfDNA methylation and pyrosequencing (in 150-400 samples). For these analyses, blood samples will be available from Task 6.2.1/6.2.2 as well as from an existing biobank with ECRHSIII (2010-12).

Samples for biomarker and omics analyses will be selected to optimally support the exposure-response analyses described below. Blood samples will be provided for analysis in WP3. In addition, 200 exhaled breath condensate and exhaled breath samples will be provided to WP3 for development of non-invasive markers.

Task 6.3 Statistical analyses for exposure-response associations and disease mechanisms (AU, STAMI, KUL, TNO, UiB, ISGLOBAL, INSERM, UU, UNIMAN) (M40-58)
Exposure and response data will be stored in the Yoda system and exposure-response analyses, including mechanistic modelling, will be performed in collaboration with WP4.

Task 6.3.1 Association between long-term exposome and respiratory health (AU, STAMI, KUL, TNO ) (M40-58)
Analyses of long-term external exposome and lung function decline (EPHOR data vs previous cohort sampling wave), asthma and COPD, both direct (n = 3000) and via stable biological markers (within the subset of 400 selected subjects), will be performed. A key analysis will be to assess the interaction between long-term occupational exposure and YKL40 and CC16 on lung function decline. The interaction by sex and age (above and below 55 years at last follow-up) as well as the impact of lifestyle factors (smoking patterns, physical activity) will be systematically assessed by interview data and by biological markers. These analyses will be assisted using the data management and analytical platform from WP4. The results will also feed into Task 6.3.3.

Task 6.3.2 Associations between short-term exposome, acute biological markers and cross-week change in lung function (AU, TNO, KUL). (M40-58)
Analyses of short-term external exposome and acute decline in lung function (cross week changes) directly or indirectly (via biological markers) will be determined. Biomarkers will include both targeted and non-targeted markers from urine, exhaled breath condensate and exhaled air. Interaction by sex and age (above and below 55 years at last follow-up) as well as the impact of lifestyle factors (smoking patterns, physical activity) will be assessed by interview data as well as cotinine (WP3) and activity sensors (WP1), respectively. These analyses will be assisted using the data management and analytical platform from WP4. Results will feed into task 6.3.3.

Task 6.3.3 Integrated statistical analysis, development of predictive models and reporting of results (AU, TNO, UiB, ISGLOBAL, INSERM, UU, KUL, STAMI, UNIMAN) (M40-58)
The overall associations between short- and long-term external occupational exposome and health including biomarkers/biological pathways of exposure and effect will be compared and investigated, in collaboration with WP4. From this, mechanistic pathways and novel and existing stable biological markers for both the short- and long-term working-life exposure, lung function decline and asthma/COPD status will be identified. Agnostic analyses of a wide range of exposures in relation to respiratory health in the EPHOR mega cohort performed in Task 6.3.4 will be compared with the data from the more focussed approach in this task. This will provide complementary evidence which will be translated into a protocol for future work which will be provided to the toolbox (WP9). The results will also feed into WP8 (Impact Assessment).

<table>
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<tr>
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<td>Partner number and short name</td>
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### List of deliverables

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<td>Report</td>
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<td>D6.2</td>
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<td>D6.4</td>
<td>Protocol (including results of analyses) for future studies on respiratory health based on combining the EPHOR mega cohort approach with the detailed case study approach (shared deliverable WP5)</td>
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### Description of deliverables

D6.1 Protocol (T6.1) (M18)
D6.2 Midterm recruitment report according to template for clinical studies (T6.2) (M32)
D6.3 Report containing results of long-term and short-term exposome in relation to respiratory health, including report on status of posting results according to template for clinical studies (T6.3) (M58)
D6.4 Protocol (including results of analyses) for future studies on respiratory health based on combining the EPHOR mega cohort approach with the detailed case study approach (T6.3.3 and T5.3.4) (M58) (shared deliverable)

D6.1 : Protocol of study on working life exposome and respiratory health [18]
A protocol will be developed for new data collection on respiratory health and working life exposome in 12 study centres from 7 European countries (Spain, France, Sweden, Norway, Estonia, Iceland, Denmark) and Australia.
D6.2 : Recruitment report midterm according to template for clinical studies [32]
Progress on collection of data on short-term and long-term external exposome, respiratory health and biomaterials in the 12 study centers. In addition progress on the assessment of the internal exposome markers in the collected biomaterials.

D6.3 : Report containing results of long-term and short-term exposome in relation to respiratory health [58]
Results on analyses of long-term external exposome and lung function decline (EPHOR data vs previous cohort sampling wave), asthma and COPD, both direct (n = 3000) and via stable biological markers (within the subset of 400 selected subjects).

D6.4 : Protocol (including results of analyses) for future studies on respiratory health based on combining the EPHOR mega cohort approach with the detailed case study approach (shared deliverable WP5) [58]
The associations between the external occupational exposome and health including biomarkers/biological pathways of exposure and effect will be compared with the results of WP 5. A protocol for future work based on the combined findings of WP5 and 6 will be delivered with WP 5.

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Objectives

The objective is to evaluate how unusual working hours, including night work and extended working hours impact health. Specific objectives are:

- To apply new targeted and agnostic exposome methods to collect individual level data on the external and internal exposome (developed in WP1&3) among shift workers in both existing cohorts and a new to establish cohort (T7.1, 7.2);
- To examine how the long- and short-term external working-life exposome among shift workers affects key body functions and ageing in relation to the development of NCDs and mortality and investigate if this is influenced by gender or age (T7.3, 7.4);
- To identify key biological pathways for health effects associated with night shift, conducting biomarker analyses using biomonitoring, targeted assays and agnostic genetics, proteomics, epigenetics and transcriptomics (T7.3, 7.4).

Description of work and role of partners

WP7 - Exposome case studies on night shift work and health [Months: 1-60]

ISGLOBAL, TNO, IOM, KI, KUL, STAMI, UU, PDA, OWL, SLL

Task 7.1 Development of protocols, ethical approval and coordination for shift studies (ISGLOBAL, UU, KI, SLL, IOM, KUL, ESDY, TNO) (M1-40)

Protocols will be prepared (M1-12) for collection of external and internal exposome data among 800 shift workers. Protocol development involves collaboration with WP1 and 3 to include the protocols developed for external and internal exposome data collection and WP4 for data handling and analyses. Protocols will also describe the follow-up of the work done in these WPs: laboratory analyses and data processing. The development of an ethics protocol, approval from corresponding committees and follow-up of good practices will be ensured. A meeting to discuss the planning of case study fieldwork will be held in M8.

Task 7.2 Conduct of field studies: exposome and health data collection (ISGLOBAL, UU, KI, SLL, KUL, IOM) (M18-40)

Task 7.2.1 Collection of the study population (ISGLOBAL, UU, KI, SLL ) (M18-30)

In the Spanish study, 400 subjects involved in shift work will be newly recruited from a car factory. In the Netherlands, 200 subjects will be sampled from the Nightingale nurses cohort which is focused on shift work. And in Sweden, 200 subjects will be sampled from a large administrative cohort of municipal workers, selected based on available administrative job and time shift records.

Task 7.2.2 Collection of external working-life exposome data (ISGLOBAL, UU, KI, SLL, IOM ) (M18-40)

In 800 subjects a wide range of occupational and non-occupational exposures will be measured using external exposure assessment with passive sampling, the wearable sensor systems for personal airborne particulate matter, sleep quality, physical activity, light and psychosocial stress and a questionnaire on working time, sleep, specific chemical and physical exposures, diet, lifestyle, workplace organisation, psychosocial factors and job-records.

Passive wristband samples will be analysed for chemical exposures (200 samples) in Task 1.2. For the two existing studies in Sweden and the Netherlands, all available exposure data will be additionally retrieved and harmonised based on expert judgment. Long-term occupational exposure in previous jobs will be determined by applying EuroJEM to the occupational histories.

Task 7.2.3 Collection of internal exposome data (ISGLOBAL, UU, KI, SLL, KUL, OWL) (M18-40)

Blood samples and 24 hour urine (all voids separately) will be collected for 800 subjects. Breath samples (both for VOCs and omics analysis) will be collected for 400 subjects in Spain only. Blood samples will be collected in two occasions for a selection of the workers. Samples will be analysed within WP3 for agnostic as well as targeted internal exposome analyses.

This will include classic biomonitoring for metals, PAHs and cotinine (800 samples), biological effect monitoring: clinical chemistry, cortisol awakening response, melatonin, sex steroid hormones and proteomics for immune factors and 8-OHdG (800 samples) and (other) omics: genotype, mtDNA/telomere length, epigenomics, c/dNA methylation and pyrosequencing (in 150-400 samples). Multiple samples may be analysed from the same subjects.
Samples for biomarker and omics analyses will be selected for optimal support of the exposure-response analyses described below. In addition, 200 exhaled breath condensate and exhaled breath samples will be provided to WP3 for development of non-invasive markers.

**Task 7.2.4 Measurement of key body functions and ageing (ISGLOBAL, KUL, UU, KI, SLL) (M18-40)**
Analyses will be conducted to evaluate key body functions and ageing closely related to the development of NCDs and mortality through a combination of biomarkers, clinical chemistry and biochemical analyses (WP3), harmonized tests, clinical evaluations (in 400 subjects) and questionnaires. These will include cognitive development and mental health determination and assessment of neurodegenerative status, lung function assessment, anthropometry to define obesity, cardiometabolic parameters and metabolic syndrome. Hallmarks of ageing will also be included.

**Task 7.3 Harmonization and incorporation of exposure, omics and agnostic data from existing studies and replication (STAMI, UU, ISGLOBAL) (M30-38)**
Retrieval and harmonisation of existing data from additional small scale studies with existing internal exposome data among shift workers (Norwegian Nurses cohort, Hormonit and Klokwerk) for replication of exposure-response results in Task 7.4.

**Task 7.4 Integrated statistical analysis, development of predictive models and reporting of results (ISGLOBAL, UU, TNO, KUL, IOM) (M40-58)**
Exposure and response data will be stored in the Yoda system and exposure-response analyses, including mechanistic modelling, will be performed in collaboration with WP4.
Information on long- and short-term exposure, mechanistic and outcome data will be combined to develop complex models integrating exposure, to biological pathways, to impaired body functions and ageing in collaboration with WP4. Biomarkers will include both targeted and non-targeted markers from urine, exhaled breath, and exhaled breath condensate. Besides classic shift work metrics, other occupational exposures and wider workplace organizational and social context and interactions with lifestyle factors will be incorporated in these models.
This will provide insights on the how working-life exposome is related to health including mechanistic insights and biomarkers of exposure and disease which will provide the basis for future personalized and workplace preventive actions. Agnostic analyses of a wide range of NCDs in relation to shift work in the EPHOR mega cohort performed in Task 5.3.4 will be compared with the data from the more focussed approach in this task. This will provide complementary evidence which will be translated into a protocol for future work which will be provided to the toolbox (WP9). The results will also feed into WP8 (Impact Assessment).

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<td>Protocol of exposome shift study</td>
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## Description of deliverables

D7.1 Protocol of exposome shift study (T8.1) (M18)
D7.2 Midterm recruitment report according to template for clinical studies (T8.2) (M32)
D7.3 Report containing results of night shift exposome and replication using existing studies, including report on status of posting results according to template for clinical studies (T8.4) (M60)
D7.4 Protocol (including results of analyses) for future studies on respiratory health based on combining the EPHOR mega cohort approach with the detailed case study approach (T7.4 and T5.3.5) (M58) (shared deliverable)

D7.1 : Protocol of exposome shift study [18]
Protocols will be prepared for collection of external and internal exposome data among 800 shift workers.

D7.2 : Midterm recruitment report according to template for clinical studies [32]
Progress on collection of data on external exposome, internal exposome and key functions of aging among 400 study subjects in Spain, 200 study subjects in the Netherlands and 200 study subjects in Sweden.

D7.3 : Report containing results of night shift exposome and replication using existing studies, including report on status of posting results according to template for clinical studies [60]
Report on the following analyses: Information on long- and short-term exposure, mechanistic and outcome data will be combined to develop complex models integrating exposure, to biological pathways, to impaired body functions and ageing. Biomarkers will include both targeted and non-targeted markers from urine, exhaled breath, and exhaled breath condensate. Besides classic shift work metrics, other occupational exposures and wider workplace organizational and social context and interactions with lifestyle factors will be incorporated in these models.
D7.4 : Protocol for future studies on shift work based on combining the EPHOR mega cohort approach with the detailed case study approach including replica [58]

The associations between the external occupational exposome and health including biomarkers/biological pathways of exposure and effect will be compared with the results of WP 5. A protocol for future work based on the combined findings of WP5 and 7 will be delivered with WP 5.

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<td>MS10</td>
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<td>Data collection completed for the study on respiratory health</td>
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The objective is to bring the exposome concept to health impact assessment by developing methods to incorporate life course and co-exposures to multiple risks. Specific objectives are:

- Incorporate the exposome concept (complex exposure scenarios with increased multiple exposures, internal as well as external, and early markers of effects along mechanistic biological pathways) and working-life (working-life specific health metrics) into the models currently used to determine health impact (T 8.1, 8.2)
- Incorporate new knowledge obtained during the EPHOR project to estimate health impact for several hypothetical health-based interventions in the workplace (T8.3)
- Develop guidelines for health impact assessment to be included in the toolbox (T8.4)

**Description of work and role of partners**

**WP8 - Impact Assessment** [Months: 1-58]

**UNIMAN, TNO, ISGLOBAL, IOM, KI, STAMI, UU, FIOH**

Task 8.1 Exposome burden of disease model (UU, UNIMAN, TNO, IOM, FIOH) (M1-24)

Conceptual models will be developed for exposome burden of disease for several health outcomes that are of relevance for working-life health (and based on studies included in WP5) describing the interlinkages between the various internal and external exposures and confounding factors and with health outcomes, including markers along the AOPs. The conceptual model will be visualised highlighting the relative importance of exposure metrics and exposure-response pathways based on existing evidence from the peer-reviewed literature. The conceptual model will be used to develop the complex modelling of interacting risk factors and interventions in Task 8.3.

Task 8.2 Working-life specific health metrics for impact assessment (FIOH, UNIMAN, IOM) (M1-12)

A detailed and systematic literature review will be carried out to establish current knowledge on the link between exposures, socioeconomic indicators (e.g. educational level, social class, income) and working-life expectancy. Working-life specific health metrics will subsequently be used within Task 8.3 to estimate health impact.

Task 8.3 Exposome health impact assessment (UNIMAN, UU, IOM, FIOH, TNO, STAMI, KI) (M12-56)

A simulated longitudinal population cohort will be developed based on empirical data from WP2 and 5 to estimate the impact of workplace interventions.

The exposure, demographic and socioeconomic profiles of the simulated datasets will be based on data from WP2 and 5 and information obtained from the literature.

The conceptual model(s) developed in Task 8.1 will be used to implement initially relatively simple exposure scenarios and risk functions, evolving into more complex exposome profiles with various correlation structures and risk functions, involving multiple exposures and confounders, such as socioeconomic status as well as interactions between the risk factors. In particular, correlations between exposures and socioeconomic factors in relation to disease outcomes will be studied. A set of intervention scenarios will be developed, aimed to reduce future health burden and calculate the expected health impacts over a 20-60 year time period, accounting for regional and population differences.

Scenarios will be developed with the benefit of stakeholder consultations organised in collaboration with WP10. Such scenarios would also look at changing exposures and risks over the life course, extending the working age, precarious work (e.g. people who do multiple temporary jobs), migratory work, etc. In addition to estimating the impact of interventions on clinical health outcomes, models will be developed for impact assessment using intermediate markers of exposure and incorporating concepts from the adverse outcome pathways. Such approaches would enable combination of health impact modelling with quantitative or qualitative evaluations of interventions, in relation to external exposures. This work will build on the mechanistic biological pathway modelling developed in T6.3 and T7.4. Task 8.3 will inform the development of guidelines in Task 8.4, in particular providing guidance on when the inclusion of complex exposure scenarios will result in more accurate estimates of burden of disease/health impact (and when conventional impact assessment models suffice).

Task 8.4 Tools and guidance for impact assessment (UNIMAN, UU, IOM, FIOH, TNO) (M36-56)

Guidance and tools will be developed (feed into toolbox WP9) to incorporate exposome complexity in health impact assessment and determine criteria to assess conditions when taking account of whether exposome complexity is of
benefit and efficient in estimating the health impact of interventions. Guidelines and criteria will be developed based on the purpose of the health impact assessment, knowledge available on risk functions and complexity of the exposure scenario, to determine the method most appropriate for the health impact assessment required.

### Participation per Partner

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<td>D8.2</td>
<td>Report on the development of an exposome health impact model for working-life health, including specific health metrics, and application to intervention scenarios</td>
<td>8 - UNIMAN</td>
<td>Report</td>
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<td>D8.3</td>
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<td>Report</td>
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### Description of deliverables

D8.1 Report on a conceptual model of exposome health impact assessment (M24) (T8.1)
D8.2 Report on the development of an exposome health impact model for working-life health, including specific health metrics, and application to intervention scenarios (M56) (T8.2, T8.3)
D8.3 Tools and guidance on exposome health impact assessment to feed into WP9 (M56) (T8.4)
Conceptual models will be developed for exposome burden of disease for several health outcomes that are of relevance for working-life health (and based on studies included in WP5) describing the interlinkages between the various internal and external exposures and confounding factors and with health outcomes, including markers along the AOPs.

D8.2 : Report on the development of an exposome health impact model for working-life health, including specific health metrics, and application to intervention scenarios [56]

The conceptual model(s) developed in Task 8.1 will be used with simulated populations to implement initially relatively simple exposure scenarios and risk functions, evolving into more complex exposome profiles with various correlation structures and risk functions, involving multiple exposures and confounders, such as socioeconomic status as well as interactions between the risk factors.

D8.3 : Tools and guidance on exposome health impact assessment to feed into WP9 [56]

Guidance and tools will be developed (feed into toolbox WP9) to incorporate exposome complexity in health impact assessment and determine criteria to assess conditions when taking account of whether exposome complexity is of benefit and efficient in estimating the health impact of interventions.

**Schedule of relevant Milestones**

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<td>MS8</td>
<td>EuroJEM first version</td>
<td>5 - KI</td>
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<td>EuroJEM first version and input data for the working-life exposome exploration tool ready for toolbox and for HIA</td>
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<td>MS14</td>
<td>First version of Guideline and criteria for future impact assessment</td>
<td>8 - UNIMAN</td>
<td>46</td>
<td>First version of Guideline and criteria for future impact assessment based on exposome studies delivered to the toolbox</td>
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Objectives

The objective is to develop a toolbox that can be used by health scientists, policy makers, and occupational health practitioners (from in SMEs and large industries) to better understand and manage the working-life exposome. This working-life exposome toolbox will provide tools such as interactive web tools, software tools, searchable databases, protocols and guidance documents that can be used for new research, impact assessment, work (and related lifestyle) exposure management and development of interventions. Specific objectives are:

- To provide health scientists with a) an interactive visualisation tool for exploring the working-life exposome and exposure-response associations, and b) tools for exposome data collection, storage and interpretation. These tools will enable scientists to further investigate the working-life exposome in future exposome studies (T9.1, 8.2).
- To provide occupational health practitioners with a) an interactive visualisation tool for exploring the working-life exposome and exposure-response associations, and b) practical tools for external and internal exposome data collection and interpretation. This will enable them to develop effective and data-driven workplace interventions and exposure management strategies at the individual, group or population level (T9.1, 9.3).
- To provide policy makers with a) an interactive visualisation tool for exploring the working-life exposome and exposure-response associations, and b) methods and guidance documents for health impact assessment. This will enable them to develop new effective policies at the individual, group or population level (T10.1, 10.4).

Description of work and role of partners

WP9 - EPHOR Working-life Exposome Toolbox [Months: 1-60]

TNO, ISGLOBAL, IOM, AU, KI, KUL, STAMI, UNIMAN, UU, FIOH, LIFE, INTER

Task 9.1 Interactive visualisation tool for exploring the current working-life external exposome and exposure-response associations (KI, STAMI, FIOH, AU, TNO, ISGLOBAL) (M1-58)

Task 9.1.1 Tool for exploring the current working-life external exposome (KI, FIOH, STAMI, TNO) (M1-30)

An online and interactive tool will be developed designed for policy makers, occupational health practitioners and health scientists seeking information about current working-life exposures (including chemicals, light, work shifts, sleep, lifestyle, physical, emerging risks and new employment conditions) by job, but also at a higher granulation by industry, gender, region. The tool aims to make available the developed knowledge on current exposure by job in a comprehensive way. EuroJEM (developed in WP2) will be the basis for the development of this tool.

Task 9.1.2 Extension of the tool: exposome-response associations (STAMI, KI, AU, ISGLOBAL, FIOH, TNO) (M30-58)

The online and interactive tool (task 10.1.1) will be extended with EPHOR data on the association between the current working-life external exposome and exposure-response associations (based on WP5, 6 and 7).

Task 9.2: Tools for working-life exposome data collection, storage and interpretation for health scientists (FIOH, TNO, IOM, KUL, UU, LIFE) (M1-58)

Task 9.2.1 Protocols (FIOH, TNO, IOM, KUL, UU) (M1-24)

The following tools will be made available:

- Tool for exposure methods:
  - Protocols on the application of wearable sensor systems and passive sampling for new collection of external working-life exposome data in epidemiological studies (based on results WP1).
- Tools for data mining:
  - A proof of concept of exposure assessment based on big data in cohort studies using artificial intelligence (based on results WP2 and 4).
  - A decision support tool for automated job coding based on artificial intelligence (based on results WP4).
  - Tool for access to data collected in EPHOR:
  - A description and link to Yoda, including protocols for gaining access to the publicly available EPHOR data and for making use of the database (based on results WP4).

Tools for exposure-response analyses:
- Descriptions on study design (WP5,6,7)
• Tutorials on a suite of models for multiple exposure-response, exposure-time-response, and hierarchical analyses (based on results WP4).
• Protocols for future working-life exposome studies and data analyses based on WP5, 6 and 7 including a protocol for confirmation of biological pathway analyses and biomarker identification in new studies.
• A protocol describing a tiered-approach in the application of omics technologies to unravel exposure health relations and obtain mechanistic insights (based on results WP3 and 4).

Task 9.2.2 Searchable databases: EuroJEM and occupational cohorts (STAMI, KI, TNO) (M1-30)
Two searchable databases will be developed and made available: 1) EuroJEM including a guidance document (based on results WP2); and 2) Inventory of occupational cohorts for studying working-life exposome (based on WP5).

Task 9.2.3 Visualisation: Adverse Outcome Pathways (LIFE, TNO) (M30-58)
Visualisations will be developed for in silico adverse outcome pathways (biological pathways) for application in the quantitative analysis of (individualized) working-life exposome data.

Task 9.3 Tools for external and internal exposome data collection and interpretation for OSH practitioners (IOM, FIOH, KUL, TNO, UU) (M1-58)
Task 9.3.1 Protocols (IOM, FIOH, KUL, TNO) (M1-24)
The following protocols will be developed and made available: 1) A protocol and demonstration video for data collection and interpretation of personal external exposome using a flexible wearable sensor system (based on WP1 and 4); 2) A protocol for omics/bioassays analysis using exhaled breath, to support biomonitoring and health effect monitoring (based on WP3); and 3) A protocol for biomonitoring and biomarkers approaches to monitor health effects from shift work and respiratory exposures.

Task 9.3.2 Software (TNO, UU, KUL) (M25-58)
A software tool will be developed for (temporary) storage and (online or offline) automated report generation of sensor data including a guidance document. Organisations that already have collected data will be able to analyse their data in a harmonised way. To be used in conjunction with the protocol described under 9.3.1.

Task 9.4 Tools for health impact assessment for policy makers (UNIMAN, IOM, TNO) (M25-58)
Guidelines and criteria for estimating health impact from interventions in complex exposome-relevant scenarios will be made available, being a basis for developing effective data driven prevention strategies. These documents will include guidance on the ‘next generation’ health impact assessment, including some aspect of exposome, e.g. longitudinal assessment, greater consideration of differences in population groups and consideration of non-occupational factors. In addition, a demonstrator of the developed simulation technology will be published.

Task 9.5 Toolbox website development and coordination of the toolbox (TNO, IOM, FIOH, KI, UNIMAN, INTER) (M1-58)
A toolbox webpage will be developed on the EPHOR project website (WP10). Results from task 9.1 – 9.4 will be placed on this toolbox webpage. The toolbox will be tailored to health scientists, occupational health practitioners and policy makers based on their needs obtained during the stakeholder workshops (activity in WP10). During the project a strategy will be developed for making the toolbox a sustainable and well-maintained resource after the course of the project (activity in WP10).

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<td>Websites, patents filling, etc.</td>
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### Description of deliverables

D9.1: Web-based toolbox version 1.0 including results from task 9.1.1, 9.2.1, 9.2.2 and 9.3.1 (M30)
D9.2: Web-based toolbox version 2.0 including results from task 9.1.2, 9.2.3, 9.3.2 and 9.4 (M58)

**D9.1 : Part 1: Web-based toolbox version 1.0 [30]**
Web-based toolbox version 1.0 including an interactive visualization tool, several protocols for external and internal exposome assessment, searchable databases of JEMs and populations.

**D9.2 : Part 2: Web-based toolbox version 2.0 [58]**
Extension on version 1.0 with visualization of exposure response associations, visualization of AOPs, software for internal exposome and tools for HIA

### Schedule of relevant Milestones

<table>
<thead>
<tr>
<th>Milestone number¹⁸</th>
<th>Milestone title</th>
<th>Lead beneficiary</th>
<th>Due Date (in months)</th>
<th>Means of verification</th>
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<tr>
<td>MS3</td>
<td>Report on non-invasive monitoring of internal exposome</td>
<td>6 - KUL</td>
<td>12</td>
<td>Report on non-invasive monitoring of internal exposome ready as input for the toolbox</td>
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<tr>
<td>MS7</td>
<td>WP 1: deliver tools to toolbox</td>
<td>1 - TNO</td>
<td>24</td>
<td>Deliver of tools to toolbox regarding wearable sensor system and passive sampling</td>
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<tr>
<td>MS8</td>
<td>EuroJEM first version</td>
<td>5 - KI</td>
<td>24</td>
<td>EuroJEM first version and input data for the working-life exposome exploration tool ready for toolbox and for HIA</td>
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<td>Dynamic EuroJEM final version ready for toolbox</td>
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<td>MS14</td>
<td>First version of Guideline and criteria for future impact assessment</td>
<td>8 - UNIMAN</td>
<td>46</td>
<td>First version of Guideline and criteria for future impact assessment based on exposome studies delivered to the toolbox</td>
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### Work package number

**WP10**

### Lead beneficiary

1 - TNO

### Work package title

Dissemination, Communication and Exploitation

### Start month

1

### End month

60

---

### Objectives

The objective is to disseminate key information on the project, associated activities and outcomes to an international audience. Specific objectives are:

- Coordination of project dissemination and communication activities to/with stakeholders (T10.1);
- Identification of business and market opportunities, and providing exploitation plans (T10.2);
- Ensure that project results are of relevance to stakeholders and sustainable into the future by organising stakeholder consultation workshops and a final stakeholder workshop to disseminate the results of the project with stakeholders (T10.3).

---

### Description of work and role of partners

**WP10 - Dissemination, Communication and Exploitation [Months: 1-60]**

TNO, ISGLOBAL, IOM, AU, KI, KUL, STAMI, UNIMAN, UU, VTEC, LIFE, OWL, INTER

**Task 10.1 Communication and Dissemination Plan (TNO, ISGLOBAL, IOM, AU, KI, KUL, STAMI, UNIMAN, UU, INTER) (M1-60)**

A plan will be developed on actions regarding communication, dissemination and exploitation to various stakeholders, including:

- **Identification of relevant stakeholders:**
  - a stakeholder mapping exercise which will be conducted to identify the key stakeholders within the stakeholder groups identified for the EPHOR project.
  - A stakeholder databases with contact details will be created for proactive targeted communication. The stakeholders will be asked for permission to be included in this database.

- **Communication:**
  - main messages the project would like to communicate will be identified. Those may include project announcements/calls for participation, latest highlights, and news from related projects, success stories and lessons learned.
  - Tools and channels to be used to communicate with stakeholders will be identified. This will include a public website, a project brochure, the toolbox (WP9) and other channels described in chapter 2.3.

- **Dissemination:**
  - a procedure on reviewing manuscripts within the consortium including author guidelines.
  - All papers will be published in open-access journals.
  - The concept and results of EPHOR will be presented at relevant conferences and symposia.
  - Also, workshops will be organized for various stakeholders (see task 10.3).

- **Engagement:**
  - workshops for various stakeholder groups (see task 10.3).
  - Continued engagement with stakeholders and project partners for the duration of the project (sharing results, news items).

The first version of the plan will be described in M3. An update will be given in M36. The update will also describe the results regarding communication and dissemination. In M60 a final report describing the results regarding communication and dissemination will be presented.

**Task 10.2 Exploitation and IP management (TNO, ISGLOBAL, IOM, AU, KI, KUL, STAMI, UNIMAN, UU, VTEC, LIFE, OWL) (M1-60)**

During the project, each EPHOR partner will prepare exploitation plans, indicating in detail what market and business opportunities will be favoured by the development of the new technologies produced in the EPHOR Project. IP management will be part of the exploitation plan. For IP management, an initial list of reusable and non-reusable pre-existing know-how (background knowledge) will be made available at the beginning.

This list will be a dynamic IP management database. This will make exploitation of the results convenient, such as technology transfer, spin-off creation and publication strategy.

The final report will incorporate all results and recommendations. It will form the basis for maintenance and further development of the outputs (including the toolbox) and will include measures to ensure that the benefits of the project...
will endure beyond the lifetime of the project. As part of the exploitation activities, project partners will also consult with stakeholders, to extend the impact of the projects, circulate the knowledge and scale-up the solutions developed. A consortium agreement will fix the rules of knowledge sharing between academics partners and companies, regarding the IPR, rules of publications, commercial activities, spin-off or entrepreneurship.

The first version of the plan will be described in M3. An update will be given in M36. The update will also describe the results regarding exploitation. In M60 a final report describing the results regarding communication, dissemination and exploitation will be presented.

Task 10.3 Workshops with stakeholders (IOM, TNO, UNIMAN) (M1-60)
We will organize stakeholder workshops during the project to ensure engagement with the stakeholders in the overarching aims of the project, to obtain end-user input on the practical use of wearable sensor systems (WP1), to obtain stakeholder input on hypothetical intervention scenarios (WP8) and to obtain stakeholder input on needs and criteria regarding the Toolbox (WP9). The following workshops are planned:
• M3: a stakeholder consultation will be held to understand acceptability and perceptions of sensor use from employees and employers, both for work and lifestyle (in collaboration with WP1).
• M24: Stakeholder workshop with representatives from policy makers, scientists, occupational health practitioners, industry to present and discuss the plans for the toolbox version 1 (in collaboration with WP9).
  The outcome of the workshop will be used to improve the toolbox and make the toolbox better ‘fit for purpose’ for the stakeholders.
• M42: Stakeholder workshop for demonstrating the applicability of the impact assessment models to policy makers and occupational health practitioners, a set of hypothetical intervention scenarios will be developed (in collaboration with WP8).
• M54: Stakeholder workshop with representatives from policy makers, researchers, occupational health and safety professionals and industry to present and discuss the plans for the toolbox version 2 (in collaboration with WP9).
  The outcome of the workshops will be used to further improve the toolbox and make the toolbox better ‘fit for purpose’ for the stakeholders.
• Final workshop with stakeholders to widely disseminate the results of EPHOR, including policy makers, scientists, occupational health practitioners, industry, technology developers, at M60 to disseminate the results of the project.

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<th>Partner number and short name</th>
<th>WP10 effort</th>
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# List of deliverables

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<th>Type</th>
<th>Dissemination level</th>
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<tbody>
<tr>
<td>D10.1</td>
<td>Communication, dissemination and exploitation plans</td>
<td>1 - TNO</td>
<td>Report</td>
<td>Confidential, only for members of the consortium (including the Commission Services)</td>
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<tr>
<td>D10.2</td>
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<td>D10.4</td>
<td>Updated communication, dissemination and exploitation plans, including a report of the activities to date</td>
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<td>D10.5</td>
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<td>D10.7</td>
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# Description of deliverables

- D10.1 Communication, dissemination and exploitation plans (T10.1, 10.2) (M3)
- D10.2 Minutes of stakeholders consultation together with WP1 (T10.3) (M5)
- D10.3 Minutes of first stakeholders workshop together with WP9 (T10.3) (M28)
- D10.4 Updated communication, dissemination and exploitation plans, including a report of the activities to date (T10.1, 10.2) (M36)
- D10.5 Minutes of stakeholders workshop together with WP8 (T10.3) (M54)
- D10.6 Minutes of second stakeholders workshop together with WP9 (T10.3) (M54)
- D10.7 Final report on communication, dissemination and exploitation activities (T10.1, 10.2) (M60)

D10.1: Communication, dissemination and exploitation plans [3]
This deliverable will contain two plans: - communicaion and dissemination plan (related to task 10.1) - Exploitaion and IP management plan (related to task 10.2) If needed a link will be made to the plans formed by the European Human Exposome Network

D10.2 : Minutes of stakeholders consultation together with WP1 [5]
Minutes of stakeholders consultation to understand acceptability and perceptions of sensor use from employees and employers, both for work and lifestyle

D10.3 : Minutes of first stakeholders workshop together with WP9 [28]
Minutes of first stakeholders workshop with representatives from policy makers, scientists, occupational health practitioners, industry to present and discuss the plans for the toolbox version 1

D10.4 : Updated communication, dissemination and exploitation plans, including a report of the activities to date [36]
This deliverable will contain two updated plans - communicaion and dissemination plan (related to task 10.1) - Exploitaion and IP management plan (related to task 10.2) These updated plans will also include a report of the activities performed. If needed a link will be made to the plans/activities formed by the European Human Exposome Network

D10.5 : Minutes of stakeholders workshop together with WP8 [46]
Minutes of stakeholders workshop for demonstrating the applicability of the impact assessment models to policy makers and occupational health practitioners, a set of hypothetical intervention scenarios will be developed

D10.6 : Minutes of second stakeholders workshop together with WP9 [54]
Minutes of second stakeholders workshop with representatives from policy makers, researchers, occupational health and safety professionals and industry to present and discuss the plans for the toolbox version 2

D10.7 : Final report on communication, dissemination and exploitation activities [60]
This deliverable will contain two reports - communicaion and dissemination report (related to task 10.1) - Exploitaion and IP management report (related to task 10.2) If needed a link will be made to the activities performed by the European Human Exposome Network

<table>
<thead>
<tr>
<th>Schedule of relevant Milestones</th>
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<tbody>
<tr>
<td><strong>Milestone number</strong></td>
</tr>
<tr>
<td>MS15</td>
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The objective is to ensure achievement of the objectives of the project through effective and efficient management, financial control and administrative work of the project.

Specific objectives are:

- To perform scientific, financial and contractual management (T11.1)
- To develop and update a Data Management Plan (DMP), including data quality (T11.2)
- To collaborate with exposome cluster partners (T11.3)

**WP11 - Project management** [Months: 1-60]

TNO, ISGLOBAL, IOM, AU, KI, KUL, STAMI, UNIMAN, UU, PDA

**Task 11.1 Scientific, financial and contractual management (TNO, ISGLOBAL, IOM, AU, KI, KUL, STAMI, UNIMAN, UU) (M1-60)**

- **Scientific management**
  - Timely delivery of all deliverables, periodic and final progress reports
  - Organize consortium meetings: twice a year, 8 meetings in total

- **Financial management and periodic reporting**
  - Management of budgets to ensure activity and budgets are appropriate to deliver the project within the EC contribution granted.
  - Monitoring of project spent versus budget; provision of budget reports to the
  - Distribution and follow-up of EC payments
  - Timely delivery of periodic reports and financial statements, and certificates on the financial statements to the commission

- **Legal and contracting management**
  - Manage and implement the contract with the European Commission
  - Information exchanges with the Commission within the scope of the grant agreement, including amendments and clarifications
  - Execution of the Consortium Agreement
  - Management of possible conflicts by application of the foreseen procedures and constantly cooperating with the project’s scientific and technical management.

**Task 11.2 Data Management Plan (DMP) (TNO, ISGLOBAL, IOM, AU, KI, KUL, STAMI, UNIMAN, UU) (M1-60)**

Develop a Data Management Plan that covers the following topics:

- Details what data the project will generate
- How the quality of the data will be managed
- How the data/database will be exploited and made accessible for verification and re-use, under the FAIR principles
- How the data will be curated and preserved
- Open access of the data
- How privacy and ethical issues will be dealt with

The first version of the DMP will be drafted at M6, updates will be provided at M36 and M60.

**Task 11.3 Collaboration with exposome cluster partners (TNO) (M1-60)**

At the beginning of the action a cluster contact person will be appointed in UOULU to implement the overarching European Exposome Network cluster foreseen by the European Commission i.e. the respective options of Article 2, Article 31.6 and Article 41.4 of the Model Grant Agreement will be applied. The Cluster contact person will also be responsible for the management of the different technical issues related to the creation and participation in the European Exposome Network (name to be agreed on) working groups and advisory structures to decide on collaboration and synchronization of activities, as described in WP12.
## Participation per Partner

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## Description of deliverables

- **D11.1 Minutes of consortium meetings year 1 (T11.1) (M12)**
  This deliverable will contain the minutes of the stakeholder meetings in year 1. The plan is to have two meetings in year 1.

- **D11.2 Minutes of consortium meetings year 2 (T11.1) (M24)**
  This deliverable will contain the minutes of the stakeholder meetings in year 2. The plan is to have one meetings in year 2.

- **D11.3 Minutes of consortium meetings year 3 (T11.1) (M36)**
  This deliverable will contain the minutes of the stakeholder meetings in year 3. The plan is to have one meetings in year 3.

- **D11.4 Minutes of consortium meetings year 4 (T11.1) (M48)**
  This deliverable will contain the minutes of the stakeholder meetings in year 4. The plan is to have two meetings in year 4.

- **D11.5 Minutes of consortium meetings year 5 (T11.1) (M60)**
  This deliverable will contain the minutes of the stakeholder meetings in year 5. The plan is to have two meetings in year 5.

- **D11.6 Data Management Plan (T11.2) (M6)**
  Data Management Plan describing, amongst others: data generated in the project, datamangement, privact/ethical issues (related to task 11.2).

- **D11.7 Updated Data Management Plan (T11.2) (M36)**
  Updated Data Management Plan describing, amongst others: data generated in the project, datamangement, privact/ethical issues (related to task 11.2).

- **D11.8 Final Data Management Plan (T11.2) (M60)**
Final Data Management Plan describing, amongst others: data generated in the project, data management, privacy/ethical issues (related to task 11.2).

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<th>Milestone title</th>
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<th>Due Date (in months)</th>
<th>Means of verification</th>
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</table>
Objectives

- Establish a European Human Exposome Network comprising all projects funded from the call ‘SC1-BHC-28-2019: The Human Exposome Project: a toolbox for assessing and addressing the impact of environment on health’ and implement joint actions
- Set up an external Network Advisory Board (NAB), providing strategic advice to the network.
- Develop and implement a common communication and dissemination strategy for the European Human Exposome Network.
- Develop and implement a joint strategy on how scientific evidence can be translated to policy.
- Organise periodic meetings (‘conferences’) of the European Human Exposome Network.
- Establish joint working groups on topics of interest.

Description of work and role of partners

WP12 - European Human Exposome Network Activities [Months: 1-60]

TNO

Task 12.1: Governance of the Network (All) (M1-45)

Participants: All

The collaboration within the European Human Exposome Network will be governed by a Collaboration Agreement. A 15-month rotating leadership of teams of project coordinators (‘network coordinating team’) will be implemented, as follows: (M1-M15: EXPANSE and HEAP, M16-M30: ATHLETE and EQUAL-LIFE, M31-M45: LONGITOOLS and EXIMIOUS, M46-M60: EPHOR, REMEDIA and HEDIMED). DG RTD will act as the overall facilitator, ensuring continuity between teams and smooth running of the network. The network coordinating team will be responsible for:
1) Managing the network, including teleconferences and ad hoc meetings, if needed;
2) Co-organising the European Human Exposome Network launch event together with the European Commission (M2);
3) Organising the periodic network meetings (‘conferences’) (M15, 30, 45);
4) Co-organising the European Human Exposome Network final event, together with the European Commission (M60);
5) Overseeing the network communication and dissemination strategy;
6) Overseeing the network strategy on linking science to policy;
7) Interacting with the Network Advisory Board;
8) Overseeing the joint working groups.

Each leadership team will ensure a written handover to the next team at the end of their mandate (Report 1, EXPANSE/HEAP [M15], Report 2, ATHLETE/EQUAL-LIFE [M30], Report 3, LONGITOOLS/EXIMIOUS [M45].

Task 12.2: Set up an external Network Advisory Board (NAB), (All)

Participants: All

An external Network Advisory Board (NAB) will be set up to oversee the activities of the European Human Exposome Network and facilitate links to international activities, relevant stakeholder communities, infrastructures and dissemination channels. The NAB will advise on
1) the network strategy on linking research results to policy;
2) the network communication and dissemination strategy;
3) linking to international activities and initiatives; and
4) the joint working groups.

The NAB will not advise on the scientific quality of individual exposome network projects, which is covered by the project-specific Scientific Advisory Boards (SABs). Members of the NAB will not be part of any individual project SAB as to avoid conflict of interests. Secretarial support of the NAB is provided by the network coordinating team at the time of the meeting. Commission services, as relevant, will have an observer role in the NAB. A NAB meeting will be held annually.

The mandate of the NAB and a list of proposed members will be developed and finalised by M3 by project EPHOR/REMEDIA/HEDIMED (Report 4).
Task 12.3: Periodic Human Exposome Network meetings (All)
Participants: All

The network coordinating team will organise meetings which will be attended by the 9 project coordinators, invited WP, work group leaders and the NAB. The purpose of these meetings is to exchange information between the projects, to evaluate the network performance, and to identify new areas for shared work and working groups. Face-to-face network meetings will be organised in Months 15, 30 and 45 so that each network coordinating team will organise one meeting at the end of their coordinating period. Network meetings will be streamed live (including interactive Q&A sessions) to allow all project participants to participate. Periodic web-meetings will be organised every 6 months between the project coordinators to monitor progress, identify collaborative opportunities and exchange experiences.

In addition, network events will be co-organized in Brussels with DG RTD in M2 (launch event) and M60 (final event). The primary purpose of these meetings is to promote and raise awareness of the European Human Exposome Network and, in M60, to present the main results of the Network.

Task 12.4: Joint strategy for communication and dissemination and linking to policy (All)
Participants: All

An overarching joint Communication and Dissemination Strategy (CDS) will be set-up to streamline the project specific CDS (ATHELETE/EQUAL-LIFE, report 5).

The main aim of the network CDS is to ensure project specific communication and dissemination can be identified as originating from the network. This will be ensured by 1) the development of a European Human Exposome Network website (HEAP, report 6) that links to the project specific websites and can be used as point of reference for the entire network, and 2) the development of a virtual exposome toolbox with an inventory of all tools developed in the projects and which can be accessed via the network website (i.e. cohorts, exposure assessment tools and resources, data-analytical tools), facilitated by the network coordinating team with input from all projects. A visual identity and a logo will be created to represent the European Human Exposome Network and will be used in all communication and dissemination activities (Report 6, HEAP, M6).

The joint CDS will be updated (LONGITOOLS and EXIMIOUS, report 7), to explore possibilities for further integration of the project specific CDS.

A joint strategy for science to policy translation of the scientific evidence generated by the projects in the Network will be developed in M18 (EPHOR/REMEDIA/HEDIMED, report 8), and updated in M54 (ATHLETE/EQUAL-LIFE, report 9).

Task 12.5: Joint working groups (All)
Participants: all

Joint working groups will be the fora where projects collaborate on common topics of interest. A first set of working groups will be established by M3 of the project (EXPANSE/HEAP, report 10). The Term of Reference (ToR) for the WGs will be agreed including the selection of work group leaders, co-leads and members. The list of working groups will be updated at each periodic network meeting where amendments to existing working groups can be proposed and where new working groups can be suggested. Working groups will meet virtually and, if needed, through face-to-face meetings. It can also be envisaged that one or several consortia will organize joint workshops where all network partners are invited to attend.

Examples of possible Working Groups are:

• Stakeholder engagement

Although partners in the network may diverge in terms of content, design, and potential stakeholders, much can be learned by exchanging information on how to interact with stakeholders. Furthermore, mapping the stakeholders across the network projects will allow a more efficient approach. This working group will have a representative from each project who will exchange experiences from his or her project, with the ultimate aim of establishing similar practices across projects.

• Metadata and sustainability

In this working group existent metadata infrastructures (cohorts, biobanks, exposure databases, …) are inventoried to map where existent catalogues suffice, where synergies can be obtained and where gaps can be identified. The working group will also make recommendations on sustainability and legacy and how existing infrastructures can be linked and where developments are needed to reach this goal, including potential standardisation efforts. A possible output of this working group could be a proposal for a joint sustainable metadata infrastructure.

• Bioinformatics/biostatistics/data science

This working group will discuss challenges in bioinformatics/biostatistics/data science in the exposome projects, identify overlapping issues, and, where appropriate, collaborate to develop solutions.

• Interventions and impact assessment

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Many of the projects have envisioned interventions and impact assessments (health and economics). To allow more comparability between interventions evaluated in different projects, the use of similar methodologies may help. This working group will focus on best practices of interventions and impact assessment.

- **Ethical and legal issues surrounding personal data**
  Ethics and legal issues regarding handling of personal data in the European Human Exposome Network are foreseen. A working group will define the best-practice of data handling and invite all partners, including the DPO officers in the network, to a joint working group.

- **Modelling of the external exposome**
  This working group will work on inventorying of tools and methods that are available to assess the external exposome (e.g. exposure surfaces, Job Exposure Matrices) and discuss avenues to improve methods.

- **OMICS to study the internal exposome**
  OMICS technologies are used in many of the projects to study the internal exposome. This working group will exchange views of best-practices in acquiring OMICS data and advise on data harmonisation procedures that would enable a better exchange of information between projects in the network.

- **Sensors**
  Sensor systems are used in multiple projects. The working group will exchange views on best practices in sensor application, including sensor selection and approaches for validation and calibration of sensors and for sensor data infrastructure and analyses.

**Common reports for the Network**

These reports will be submitted as deliverables by the projects in charge of the deliverable.

- **Report 1**: Handover document to next coordinating team – EXPANSE/HEAP (M15)
  Document summarising network activities and ongoing activities to facilitate a smooth transition to the next team. This document will include concise reports from working groups.

- **Report 2**: Handover document to next coordinating team – ATHLETE/EQUAL-LIFE (M30)
  Document summarising network activities and ongoing activities to facilitate a smooth transition to the next team.

- **Report 3**: Handover document to next coordinating team – LONGITOOLS/EXIMIOUS (M45)
  Document summarising network activities and ongoing activities to facilitate a smooth transition to the next team.

- **Report 4**: Joint Network Advisory Board – EPHOR/REMEDIA/HEDIMED (M3)
  Identify the members, mandate as well rules and work plan for NAB.

- **Report 5**: Dissemination and Communication strategy (M3) - ATHLETE/EQUAL-LIFE (M3)
  Joint dissemination and communication activities for the network.

- **Report 6**: Network website – HEAP (M6)
  Website with network activities and links to all individual network websites. Includes network logo and visual identity.

- **Report 7**: Updated Dissemination and Communication strategy - LONGITOOLS/EXIMIOUS (M36)
  Joint dissemination and communication activities for the network.

- **Report 8**: Policy Strategy - EPHOR/REMEDIA/HEDIMED (M18)
  Joint strategy for science to policy translation of the scientific evidence generated by the network.

- **Report 9**: Updated policy Strategy – ATHLETE/EQUAL-LIFE (M54)
  Joint strategy for science to policy translation of the scientific evidence generated by the network.

- **Report 10**: List of Working Groups and ToR for the WGs (M3) - EXPANSE/HEAP (M3)
  A first set of working groups will be made and Term of Reference for the WGs will be specified including the selection of work group leaders, co-leads and members.

**Participation per Partner**

<table>
<thead>
<tr>
<th>Partner number and short name</th>
<th>WP12 effort</th>
</tr>
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<tbody>
<tr>
<td>1 - TNO</td>
<td>5.00</td>
</tr>
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<td>5.00</td>
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### List of deliverables

<table>
<thead>
<tr>
<th>Deliverable Number</th>
<th>Deliverable Title</th>
<th>Lead beneficiary</th>
<th>Type</th>
<th>Dissemination level</th>
<th>Due Date (in months)</th>
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<tbody>
<tr>
<td>D12.1</td>
<td>Report 4 Joint Network Advisory Board</td>
<td>1 - TNO</td>
<td>Report</td>
<td>Confidential, only for members of the consortium (including the Commission Services)</td>
<td>3</td>
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<tr>
<td>D12.2</td>
<td>Report 8 Policy Strategy</td>
<td>1 - TNO</td>
<td>Report</td>
<td>Confidential, only for members of the consortium (including the Commission Services)</td>
<td>18</td>
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</tbody>
</table>

### Description of deliverables

- **D12.1 Report 4 Joint Network Advisory Board (M3)**
  Identify the members, mandate as well rules and work plan for NAB. This is a joined effort of EPHOR/REMEDIA/HEDIMED.

- **D12.2 Report 8 Policy Strategy [18]**
  Joint strategy for science to policy translation of the scientific evidence generated by the network. Joined effort of EPHOR/REMEDIA/HEDIMED

### Schedule of relevant Milestones

<table>
<thead>
<tr>
<th>Milestone number</th>
<th>Milestone title</th>
<th>Lead beneficiary</th>
<th>Due Date (in months)</th>
<th>Means of verification</th>
</tr>
</thead>
<tbody>
<tr>
<td>MS16</td>
<td>Final cluster meeting</td>
<td>1 - TNO</td>
<td>60</td>
<td>Final meeting with open registration will be co-organized with DG R&amp;I in Brussels in M60 to present the main results of the European Human Exposome Network projects to relevant stakeholders.</td>
</tr>
</tbody>
</table>
**Work package number**  WP13

**Lead beneficiary**  1 - TNO

**Work package title**  Ethics requirements

**Start month**  1  **End month**  60

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### Objectives

The objective is to ensure compliance with the 'ethics requirements' set out in this work package.

---

### Description of work and role of partners

**WP13 - Ethics requirements**  [Months: 1-60]

**TNO**

This work package sets out the 'ethics requirements' that the project must comply with.

---

### List of deliverables

<table>
<thead>
<tr>
<th>Deliverable Number</th>
<th>Deliverable Title</th>
<th>Lead beneficiary</th>
<th>Type</th>
<th>Dissemination level</th>
<th>Due Date (in months)</th>
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List of deliverables

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<th>Dissemination level</th>
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<td>D13.8</td>
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<td>H - Requirement No. 13</td>
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<td>Ethics</td>
<td>Confidential, only for members of the consortium (including the Commission Services)</td>
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</tbody>
</table>

Description of deliverables

The 'ethics requirements' that the project must comply with are included as deliverables in this work package.

D13.1 : H - Requirement No. 1 [18]
This deliverable will address the following requirements related to WP1: 1. The informed consent procedures that will be implemented for the participation of humans 2. Copies of opinions/approvals by ethics committees and/ or competent authorities for the research with humans 3. Details on incidental findings policy 4. Templates of the informed consent/assent forms and information sheets (in language and terms intelligible to the participants) must be kept on file and submitted upon request. Lead beneficiary: IOM

D13.2 : HCT - Requirement No. 2 [18]
This deliverable will address the following requirements: 1. A detailed table describing the biological sources to be used in this project (retrospectively and prospectively) 2. Details on the cell/tissue types and on the biobank and access to in case human cells/tissues are obtained from a biobank, 3. A clear procedure on the procurement, storage and use of the biological collection to be set up in the course of the project 4. Copies of relevant documents for using, producing or collecting human cells or tissues (e.g., ethics approval, import licence, accreditation/designation/licensing) must be kept on file and submitted upon request. Lead beneficiary: KUL

D13.3 : POPD - Requirement No. 3 [12]
This deliverable will address the following requirements: 1. The beneficiary must check if special derogations pertaining to the rights of data subjects or the processing of genetic, biometric and/or health data have been established under the national legislation of the country where the research takes place and submit a declaration of compliance with respective national legal framework(s). 2. The host institution must confirm that it has appointed a Data Protection Officer (DPO) and the contact details of the DPO are made available to all data subjects involved in
the research. For host institutions not required to appoint a DPO under the GDPR a detailed data protection policy for the project must be submitted. 3. In case of further processing of previously collected personal data, an explicit confirmation that the beneficiary has lawful basis for the data processing and that the appropriate technical and organisational measures are in place to safeguard the rights of the data subjects must be submitted. 4. The beneficiary must evaluate the ethics risks related to the data processing activities of the project. This includes also an opinion if data protection impact assessment should be conducted under art.35 General Data Protection Regulation 2016/679. The risk evaluation and the opinion must be submitted. 5. In case personal data are transferred from the EU to a non-EU country or international organisation, confirmation that such transfers are in accordance with Chapter V of the General Data Protection Regulation 2016/679, must be submitted. 6. A description of the technical and organisational measures that will be implemented to safeguard the rights and freedoms of the data subjects/research participants must be submitted. 7. A description of the security measures that will be implemented to prevent unauthorised access to personal data or the equipment used for processing must be submitted. Lead beneficiary: PDA

D13.4 : NEC - Requirement No. 4 [12]

This deliverable will address the following requirements: 1. Details on the materials which will be imported to/ exported from the EU. 2. Copies of import/export authorisations, as required by national/EU legislation. 3. In case activities undertaken in non-EU countries raise ethics issues, the applicants must ensure that the research conducted outside the EU is legal in at least one EU Member State and submit a confirmation. Lead beneficiary: PDA

D13.5 : GEN - Requirement No. 8 [12]
Minutes of Privacy and Ethics Committee report of preceding year

D13.6 : GEN - Requirement No. 9 [36]
Minutes of Privacy and Ethics Committee report of preceding year

D13.7 : GEN - Requirement No. 10 [48]
Minutes of Privacy and Ethics Committee report of preceding year

D13.8 : H - GEN - Requirement No. 11 [60]
Minutes of Privacy and Ethics Committee report of preceding year

D13.9 : H - Requirement No. 13 [18]

This deliverable will address the following requirements related to WP6: 1. The informed consent procedures that will be implemented for the participation of humans. 2. Copies of opinions/approvals by ethics committees and/ or competent authorities for the research with humans. 3. Details on incidental findings policy. 4. Templates of the informed consent/assent forms and information sheets (in language and terms intelligible to the participants) must be kept on file and submitted upon request. Lead beneficiary: UiB

D13.10 : H - Requirement No. 14 [18]

This deliverable will address the following requirements related to WP7: 1. The informed consent procedures that will be implemented for the participation of humans. 2. Copies of opinions/approvals by ethics committees and/ or competent authorities for the research with humans. 3. Details on incidental findings policy. 4. Templates of the informed consent/assent forms and information sheets (in language and terms intelligible to the participants) must be kept on file and submitted upon request. Lead beneficiary: ISGlobal

D13.11 : GEN - Requirement No. 15 [24]
Minutes of Privacy and Ethics Committee of preceding year

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<th>Milestone number</th>
<th>Milestone title</th>
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<th>Due Date (in months)</th>
<th>Means of verification</th>
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### 1.3.4. WT4 List of milestones

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<th>WP number</th>
<th>Lead beneficiary</th>
<th>Due Date (in months)</th>
<th>Means of verification</th>
</tr>
</thead>
<tbody>
<tr>
<td>MS1</td>
<td>Data management platform</td>
<td>WP4</td>
<td>9 - UU</td>
<td>6</td>
<td>Data management platform ready to use: data generated by relevant WPs can be stored.</td>
</tr>
<tr>
<td>MS2</td>
<td>Analytics platform</td>
<td>WP4</td>
<td>9 - UU</td>
<td>12</td>
<td>Analytics platform ready to use: first data can be analyzed in the data platform</td>
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<tr>
<td>MS3</td>
<td>Report on non-invasive monitoring of internal exposome</td>
<td>WP3, WP9</td>
<td>6 - KUL</td>
<td>12</td>
<td>Report on non-invasive monitoring of internal exposome ready as input for the toolbox</td>
</tr>
<tr>
<td>MS4</td>
<td>WP 7-first subject included</td>
<td>WP7</td>
<td>2 - ISGLOBAL</td>
<td>24</td>
<td>Inclusion of first subject in the shift work study</td>
</tr>
<tr>
<td>MS5</td>
<td>Start of feasibility study WP1</td>
<td>WP1</td>
<td>3 - IOM</td>
<td>12</td>
<td>Start of feasibility study on external exposome protocol</td>
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<tr>
<td>MS6</td>
<td>Feasibility study WP1 completed</td>
<td>WP1</td>
<td>3 - IOM</td>
<td>14</td>
<td>Feasibility study on external exposome protocol completed</td>
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<tr>
<td>MS7</td>
<td>WP 1: deliver tools to toolbox</td>
<td>WP1, WP9</td>
<td>1 - TNO</td>
<td>24</td>
<td>Deliver of tools to toolbox regarding wearable sensor system and passive sampling</td>
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<tr>
<td>MS8</td>
<td>EuroJEM first version</td>
<td>WP2, WP8, WP9</td>
<td>5 - KI</td>
<td>24</td>
<td>EuroJEM first version and input data for the working-life exposome exploration tool ready for toolbox and for HIA</td>
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<tr>
<td>MS9</td>
<td>WP 6 - inclusion first subject</td>
<td>WP6</td>
<td>4 - AU</td>
<td>24</td>
<td>Inclusion of first subject in the study on respiratory health</td>
</tr>
<tr>
<td>MS10</td>
<td>WP 6 data collection completed</td>
<td>WP7</td>
<td>4 - AU</td>
<td>40</td>
<td>Data collection completed for the study on respiratory health</td>
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<tr>
<td>MS11</td>
<td>WP 7 data collection completed</td>
<td>WP6</td>
<td>4 - AU</td>
<td>40</td>
<td>Data collection completed for the study on shift work</td>
</tr>
<tr>
<td>MS12</td>
<td>Final version Dynamic EuroJEM</td>
<td>WP2, WP9</td>
<td>5 - KI</td>
<td>48</td>
<td>Dynamic EuroJEM final version ready for toolbox</td>
</tr>
<tr>
<td>MS13</td>
<td>description to the Yoda system to toolbox</td>
<td>WP4</td>
<td>9 - UU</td>
<td>46</td>
<td>Provide description and link to the Yoda system to toolbox, incl. protocol for gaining access to the data and for making use of Yoda (including new data)</td>
</tr>
<tr>
<td>MS14</td>
<td>First version of Guideline and criteria for future impact assessment</td>
<td>WP8, WP9</td>
<td>8 - UNIMAN</td>
<td>46</td>
<td>First version of Guideline and criteria for future impact assessment based on exposome studies delivered to the toolbox</td>
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<tr>
<td>Milestone number</td>
<td>Milestone title</td>
<td>WP number</td>
<td>Lead beneficiary</td>
<td>Due Date (in months)</td>
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<tr>
<td>MS15</td>
<td>Scientific dissemination meeting</td>
<td>WP10</td>
<td>1 - TNO</td>
<td>60</td>
<td>Scientific dissemination meeting for stakeholders presenting the results of EPHOR held</td>
</tr>
<tr>
<td>MS16</td>
<td>Final cluster meeting</td>
<td>WP12</td>
<td>1 - TNO</td>
<td>60</td>
<td>Final meeting with open registration will be co-organized with DG R&amp;I in Brussels in M60 to present the main results of the European Human Exposome Network projects to relevant stakeholders.</td>
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</table>
### 1.3.5. WT5 Critical Implementation risks and mitigation actions

<table>
<thead>
<tr>
<th>Risk number</th>
<th>Description of risk</th>
<th>WP Number</th>
<th>Proposed risk-mitigation measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Brexit Level of likelihood: High</td>
<td>WP1, WP10, WP11, WP13, WP2, WP3, WP4, WP5, WP6, WP7, WP8, WP9</td>
<td>Follow discussions on Brexit Discuss impact on funding with all and more specifically the UK partners and take measures accordingly. For now it is assumed that the UK government will fund the UK partners based on the following information <a href="https://www.gov.uk/government/publications/horizon-2020-funding-if-theres-no-brexit-deal/horizon-2020-funding-if-theres-no-brexit-deal--2">https://www.gov.uk/government/publications/horizon-2020-funding-if-theres-no-brexit-deal/horizon-2020-funding-if-theres-no-brexit-deal--2</a> Review the impact on exchange of personal data and task measures (additional contracts might be needed, an example is given in: <a href="https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2001:181:0019:0031:EN:PDF">https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2001:181:0019:0031:EN:PDF</a>)</td>
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<tr>
<td>2</td>
<td>Interdependencies within the WP Level of likelihood: Medium</td>
<td>WP1, WP10, WP11, WP13, WP2, WP3, WP4, WP5, WP6, WP7, WP8, WP9</td>
<td>In the proposal phase we have dealt with these interdependencies by assuring representation of WP leaders in linked WPs and assigning WP linking milestones. Discussion of progress of these milestones in the PMT and EB. During consortium meetings there will be sessions with multiple WP’s to assure the interlinking in practice</td>
</tr>
<tr>
<td>3</td>
<td>Recruitment of participants to studies Level of likelihood: low</td>
<td>WP1, WP6, WP7</td>
<td>Participants in WP6 and 7 will be recruited mostly from large existing cohorts in which previous follow ups have been performed. The participation rates are based on these previous studies. If the participation rates are less than expected, more participants are available in the cohorts and will be invited. In WP1 only a small number of participants will be recruited. Which are readily available.</td>
</tr>
<tr>
<td>4</td>
<td>Delay in ethical approval Level of likelihood: Low</td>
<td>WP1, WP5, WP6, WP7</td>
<td>Partner performing the studies have a great experience with ethical approvals. Furthermore, we have an ethical committee within EPHOR to discuss potential issues beforehand and limit the risk of a delay due to ethical approval.</td>
</tr>
<tr>
<td>5</td>
<td>A partner leaves consortium and/or disagreement among consortium partners Likelihood: Low</td>
<td>WP1, WP10, WP11, WP13, WP2, WP3, WP4, WP5, WP6, WP7, WP8, WP9</td>
<td>The procedures for this event are settled in the consortium agreement.</td>
</tr>
<tr>
<td>6</td>
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<td>Absence of the project coordinator (PC) is arranged by the assignment of a supportive scientific coordinator (SSC) in the PMT in the project who will be closely involved in the project and can replace the project coordinator. The project manager (PM) in the PMT can be replaced by another project manager within TNO experienced in EU projects to assure a smooth transition. Absence of the supporting scientific</td>
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<tr>
<td>Risk number</td>
<td>Description of risk</td>
<td>WP Number</td>
<td>Proposed risk-mitigation measures</td>
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<td>------------</td>
<td>---------------------------------------------------------------</td>
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<td></td>
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<td>WP12</td>
<td>Describe the governance in the collaboration agreement Good communication Active involvement</td>
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<td></td>
<td>Sensor development is more difficult / takes longer then planned Low/Intermediate risk</td>
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<td>Monitor progress Consider back up plans (like commercially available sensors) in time to not delay the work in WP 6 and WP 7</td>
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<tr>
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<th>WP2</th>
<th>WP3</th>
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<th>WP5</th>
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<th>WP12</th>
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### 1.3.7. WT7 Tentative schedule of project reviews

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<th>Planned venue of review</th>
<th>Comments, if any</th>
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<td>RV1</td>
<td>30</td>
<td>Tbd</td>
<td>Common midterm review of European Human Exposome Network</td>
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</table>
1. Project number
The project number has been assigned by the Commission as the unique identifier for your project. It cannot be changed. The project number should appear on each page of the grant agreement preparation documents (part A and part B) to prevent errors during its handling.

2. Project acronym
Use the project acronym as given in the submitted proposal. It can generally not be changed. The same acronym should appear on each page of the grant agreement preparation documents (part A and part B) to prevent errors during its handling.

3. Project title
Use the title (preferably no longer than 200 characters) as indicated in the submitted proposal. Minor corrections are possible if agreed during the preparation of the grant agreement.

4. Starting date
Unless a specific (fixed) starting date is duly justified and agreed upon during the preparation of the Grant Agreement, the project will start on the first day of the month following the entry into force of the Grant Agreement (NB: entry into force = signature by the Commission). Please note that if a fixed starting date is used, you will be required to provide a written justification.

5. Duration
Insert the duration of the project in full months.

6. Call (part) identifier
The Call (part) identifier is the reference number given in the call or part of the call you were addressing, as indicated in the publication of the call in the Official Journal of the European Union. You have to use the identifier given by the Commission in the letter inviting to prepare the grant agreement.

7. Abstract

8. Project Entry Month
The month at which the participant joined the consortium, month 1 marking the start date of the project, and all other start dates being relative to this start date.

9. Work Package number
Work package number: WP1, WP2, WP3, ..., WPN

10. Lead beneficiary
This must be one of the beneficiaries in the grant (not a third party) - Number of the beneficiary leading the work in this work package

11. Person-months per work package
The total number of person-months allocated to each work package.

12. Start month
Relative start date for the work in the specific work packages, month 1 marking the start date of the project, and all other start dates being relative to this start date.

13. End month
Relative end date, month 1 marking the start date of the project, and all end dates being relative to this start date.

14. Deliverable number
Deliverable numbers: D1 - Dn

15. Type
Please indicate the type of the deliverable using one of the following codes:
R Document, report
DEM Demonstrator, pilot, prototype
DEC Websites, patent filings, videos, etc.
OTHER
ETHICS Ethics requirement
ORDP Open Research Data Pilot
DATA data sets, microdata, etc.
16. Dissemination level

Please indicate the dissemination level using one of the following codes:

- **PU** Public
- **CO** Confidential, only for members of the consortium (including the Commission Services)
- **EU-RES** Classified Information: RESTREINT UE (Commission Decision 2005/444/EC)
- **EU-CON** Classified Information: CONFIDENTIEL UE (Commission Decision 2005/444/EC)
- **EU-SEC** Classified Information: SECRET UE (Commission Decision 2005/444/EC)

17. Delivery date for Deliverable

Month in which the deliverables will be available, month 1 marking the start date of the project, and all delivery dates being relative to this start date.

18. Milestone number

Milestone number: MS1, MS2, ..., MSn

19. Review number

Review number: RV1, RV2, ..., RVn

20. Installation Number

Number progressively the installations of a same infrastructure. An installation is a part of an infrastructure that could be used independently from the rest.

21. Installation country

Code of the country where the installation is located or IO if the access provider (the beneficiary or linked third party) is an international organization, an ERIC or a similar legal entity.

22. Type of access

- **VA** if virtual access,
- **TA-uc** if trans-national access with access costs declared on the basis of unit cost,
- **TA-ac** if trans-national access with access costs declared as actual costs, and
- **TA-cb** if trans-national access with access costs declared as a combination of actual costs and costs on the basis of unit cost.

23. Access costs

Cost of the access provided under the project. For virtual access fill only the second column. For trans-national access fill one of the two columns or both according to the way access costs are declared. Trans-national access costs on the basis of unit cost will result from the unit cost by the quantity of access to be provided.
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<td>September 2019</td>
<td>- (Part B of original proposal) &lt;br&gt; - Removed table 3.1.2.1 and tables 3.1.2.2, table 3.1.2.3, table 3.2.3, table 3.2.4</td>
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<td>October 2019</td>
<td>- Included European Human Exposome Network activities in abstract, chapter 1 (objective, section 1.3.1, figure 1.3.5, section 1.3.9), chapter 2 (section 2.1.2 and section 2.3.1.2), chapter 3 (figure 3.2.1, section 3.1.1., section 3.2.7, table 3.2.1) &lt;br&gt; - Included text based on ethics review (table 3.2.1, section 5.1.) &lt;br&gt; - Changed time line of the project (4 to 5 years) (section 3.2.8 and gantt chart) &lt;br&gt; - Inclusion of new partner (partner 19; SSL) (section 3.3, 4.1.5, 4.1.19 and 4.2) &lt;br&gt; - Included information of subcontracting done by partner 4 (AU) in 4.2 &lt;br&gt; - Included external independent ethics advisor to table 3.2.2 &lt;br&gt; - Table 3.2.1: added WP 12 and WP 13, change in WP leader of WP 9 &lt;br&gt; - Table 3.4.1: remove audit costs from direct costs for OWL &lt;br&gt; - Adjusted text in 4.2 regarding subcontracting of AU &lt;br&gt; - Budget change between UU and TNO related to WP 4 activities &lt;br&gt; - Budget change between all partners related to 50 keuro direct costs for WP 12 (network activities) &lt;br&gt; - Change of legal name partner 12 (ESDY to PDA)</td>
</tr>
</tbody>
</table>
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Abstract

Exposures at the workplace contribute to many non-communicable diseases (NCDs) with a similar magnitude as urban air pollution or obesity. Given the associated societal and economic (2-6% GDP) pressure, ensuring a healthy work environment is a strategic goal for the European Commission. Demographic changes (aging workforce, female workers) and the rapidly changing nature of work with respect to secure employment and migration, are posing additional challenges. We define the working-life exposome as all occupational and related non-occupational factors (general and socio-economic environment, lifestyle, behaviour). Taking a working-life exposome approach will help address these challenges by providing better insights in how complex working-life exposures are related to NCDs, for vulnerable groups (female, migrant, insecure job workers) or life stages. The working-life exposome is in its infancy and new approaches and methods are needed. In EPHOR a consortium of exposure, health and data scientists and technology developers will develop a working-life exposome toolbox, with stakeholder involvement. The toolbox will make available to scientists, policy makers and occupational health practitioners: 1) innovative methods for collection, storage, and interpretation of more complete and individual level working life exposome data; 2) better knowledge on how the working life exposome relates to NCDs, including complex interactions, vulnerability, biological pathways and early signs of health damage, by uniquely combining large-scale pooling of existing cohorts with focused case studies; 3) models for assessing the economic and societal impact of working life exposures. EPHOR will lay the groundwork for evidence-based and cost-effective preventive actions to reduce the burden of NCDs because of the working-life exposome. Thereby, health, wellbeing and productivity of the EU population will be improved and the burden on the EU health care systems reduced. EPHOR is part of the European Human Exposome Network comprised of 9 projects selected from this same call.

Glossary

AOP  Adverse outcome pathway
cfDNA  cell free DNA
COPD  Chronic obstructive pulmonary disease
EB  exhaled breath
EBC  exhaled breath condensate
ECH A  European Chemicals Agency
ECRHS  European Community Respiratory Health Survey
EPHOR  Exposome Project for Health and Occupational Research
ETR  exposure-time-response relationship
EuroJEM  harmonised and enhanced job-exposure matrices developed in EPHOR
FAIR  findable, accessible, interoperable, reusable
GDPR  General Data Protection Regulation
JEM  Job Exposure Matrix
NCDs  non-communicable diseases
OMEGA-NET Network on the Coordination and Harmonisation of European Occupational Cohorts
OSH  occupational safety and health
REACH  Registration, Evaluation, Authorisation and Restriction of Chemicals
SES  socioeconomic status
VOC  Volatile organic compound
Yoda  Your Data platform
1. Excellence

1.1 Objectives

In industrialised countries nearly, all occupational diseases are non-communicable diseases (NCDs), especially cancers, cardiovascular, respiratory, neurodegenerative and musculoskeletal diseases\(^1\text{-}^3\). It is well-known that external factors play an important role in the causation or exacerbation of NCDs and various occupational exposures have been traditionally studied in relation to NCDs. Examples are dust and chemical exposures linked to respiratory disease and cancer, noise linked to hearing loss and heavy lifting and vibrations linked to musculoskeletal disorders\(^4\). Estimates of the global burden of occupational disease based on these studies vary between 5-7% of global mortality, translating to 2.3 million deaths each year\(^5\). The contribution of these occupational exposures to several of these NCDs is of a similar magnitude to general environmental risk factors such as urban air pollution and obesity\(^4,^6\). The exposome is a promising concept for elucidating the complex relationships between environment and disease\(^7\).

 Until now, work-related exposures have been largely neglected in exposome studies, despite the fact that the working-life covers the major part of our total life span (\(-16\) to \(-67\) years old), work-related exposures can be relatively high and frequent, and their effects may be modified by interactions with non-occupational exposures.

The ultimate aim of the Exposome Project for Health and Occupational Research (EPHOR) is to develop the working-life exposome, defined as all occupational and related non-occupational (i.e. general environment, lifestyle, behavioural and socio-economic) exposure factors, to lay the groundwork for evidence-based and cost-effective preventive actions to improve working life health and reduce the burden of NCDs.

Associated economic costs of NCDs caused by occupational exposures vary between 2-6% of a country’s GDP in the EU\(^2\). Therefore, ensuring a safe and healthy work environment is a strategic goal for the European Commission. Current risk reduction policies and strategies are informed by the existing scientific evidence and estimates of the burden of occupational NCDs. However, these are limited by several factors: 1) today’s insights are predominantly based on a “one exposure, one disease” approach in the occupational health domain while exposure-disease associations are really multifactorial and interactions between exposures both inside and outside the workplace should be taken into account; 2) these insights are limited to a specific set of risk factors and do not include currently unknown or suspected risk factors; 3) insights regarding vulnerable life stages and sub-populations are very limited; and 4) insights in biological pathways and early markers of disease are mostly lacking.

Applying the exposome concept to improve working-life health means a fundamental shift in approach and methods (Figure 1.1.1). Characterising the working-life exposome is in its infancy. New methods are required for the collection, storage and analyses of more complete and accurate individual level data on external and internal working-life exposures.

![Figure 1.1.1: Taking an exposome approach to the working-life: a fundamental shift from studying one occupational exposure in relation to one defined health effect (left), to mapping the complex picture of interrelated exposures in relation to inherent biological pathways, key body functions and health, identifying also vulnerable individuals, groups or life stages (right).](image)

The EPHOR objective is a working-life exposome toolbox making available:

- Better and more complete knowledge on how multiple exposures within the working-life exposome are related to the occurrence of cancers, cardiovascular, respiratory, musculoskeletal, mental, metabolic and neurodegenerative diseases, including complex interactions of exposures, biological pathways and early signs of health damages, and vulnerability at different life-stages;
- Innovative methods for collection, storage, and interpretation of working-life exposome data, including its economic and societal impact:
  - Tools for scientists to expand the current knowledge base on the exposome in relation to health;
  - Tools for policy makers and occupational health practitioners to obtain data and information for developing evidence-based and cost-effective preventive actions and policies.
  - Setting up of a European Human Exposome Network together with network project partners.
Subobjective 1: Methods for collection, storage and interpretation of working-life exposome data (WP1-4)

EPHOR will innovate the field of environmental health science by developing methods and tools for the collection of more complete and individual level external working-life exposome data using a wearable sensor system including sensors for light, dust, noise, sleep, physical activity, heart rate and location, and a new way of environmental exposure data collection based on passive sampling (WP1); 2) assessment of the external working-life exposome in large-scale (pooled) cohort studies, based on job title and existing exposure data through the development of harmonised and enhanced job-exposure matrices (JEMs): EuroJEM (WP2); 3) assessment of internal exposome data based on non-invasive breath analyses techniques and collecting cross-omics and biological pathway data (WP3); and 4) data management and analytics for (decentralised) analyses of complex and high throughput working-life exposome data, ensuring data privacy and security. New data analyses methods will be developed, including modelling of complex interactions, data mining techniques for better exposure assessment and interpretation of biological pathways making use of omics data and text-mining (WP3-4).

Subobjective 2: Better and more complete knowledge on the working-life exposome in relation to NCDs (WP5-7)

EPHOR will uniquely obtain better and more complete knowledge by combining two study approaches:
1) Large-scale pooling of at least 40 existing European cohorts with data on working-life amounting to nearly 21 million study subjects (WP5). Known, suspected and unknown occupational risk factors will be systematically linked to cancers, cardiovascular, respiratory, musculoskeletal, mental, metabolic and neurodegenerative diseases. This will advance knowledge on interactions (both occupational and general life exposures), vulnerable life stages and subpopulations within the EPHOR mega cohort. In addition, we have access to 6 mother child cohorts with occupational data during pregnancy and health data of 2 million children.
2) Two focused case studies will investigate short-term exposures in relation to biological pathways, early markers of disease and key body functions by collecting new external and internal exposome data in selected cohort studies within the EPHOR mega cohort. These case studies will investigate the effects of working-life exposures on respiratory health in the general population (WP6) and on several health end-points in night shift workers (WP7).

Subobjective 3: Methods for impact assessment of the exposome (WP8)

EPHOR will develop models and guidance for health scientists and policy makers to estimate the impact of the working-life on health, including complex interactions, insights in biological pathways and early markers of disease and vulnerable groups (e.g. gender or socioeconomic parameters) (WP8).

Subobjective 4: EPHOR project outcomes (WP9-10)

The project data, methods and models will be made available in the EPHOR working-life exposome toolbox (WP9) to health scientists, policy makers and occupational health practitioners. Stakeholders will be engaged in project activities. The data, methods and models developed in the project will also be commercially exploited (WP10).

Based on the EPHOR outcomes, scientists will be enabled to use and enhance the data, methods and models in exposome research, rapidly increasing the knowledge base on the working-life exposome (Figure 1.1.2). Policy makers and occupational health practitioners will use the toolbox for the development of evidence-based and cost-effective preventive policies and actions. Furthermore, the outcomes will generate a wealth of opportunities for innovation by EU industries developing sensors, apps, or non-invasive biomarker tests for early signs of disease.

Ultimately, EPHOR will contribute to reducing the burden of NCDs on the EU health care systems, improving the health and wellbeing of the EU population, improving the productivity of the EU workforce and increasing the competitiveness of EU industry.

Figure 1.1.2: EPHOR: Developments and output, intermediate outcomes and impact
1.2 Connection to the working programme

EPHOR addresses 3 out of 4 main challenges within Work Programme 2018-2020 Health, demographic change and wellbeing:

- ‘Rising health and care costs,... due to... increasing prevalence of... diseases... ageing population requiring... care... increasing societal demands’. EPHOR delivers knowledge and methods to characterize the working-life exposome. This facilitates the development of disease prevention measures, resulting in a more resilient population at higher age, reducing ‘health and care costs’.
- ‘The influence on health of external environmental factors’. The exposome is concerned with the very study of environmental factors in relation to health, and de facto addresses this challenge.
- ‘...health inequalities...access to health and care’. EPHOR contributes to alleviating health inequalities by enabling the assessment of individualized or vulnerable group specific exposure-related health effects, and providing a basis for specific risk mitigation and health advice systems for vulnerable individuals or subgroups.

EPHOR contribution to SC1-BHC-28-2019 Challenge:

- ‘...uncertainty as to the global burden of disease attributable to environmental ...factors, including healthcare costs ...negative economic impact’. EPHOR addresses the contribution of the working-life exposome to health and NCDs. Previously unknown exposures or interactions will be identified. This will feed into health/economic impact assessment modelling to improve estimates of ‘healthcare costs and negative economic impact’.
- ‘... require improved knowledge of health risks,...combinations of several risk factors ...mechanisms by which they affect health at different stages throughout ...life ...including exposures in foetal life’. EPHOR will study how ‘combinations of several risk factors’ affect health, at ‘different life stages’. EPHOR addresses how combinations of occupational and related non-occupational exposures during the working-life period spanning different life stages (adolescence, reproductive age, elderly) affect NCDs by combining large epidemiological analyses based on data of over nearly 21 million employed persons across Europe who have been followed-up for multiple health outcomes. These analyses will be combined with two targeted exposome case studies focusing on short-term exposures and acute effects, biological pathways and markers of (early) disease. The effect of working-life exposures in foetal life is also studied through the use of mother-child cohorts.
- ‘...Human Exposome Project ...presents a fundamental shift in looking at health ...moving ...away from ‘one exposure, one disease’ understanding to a more complex picture’. EPHOR will create understanding of multiple (combined) working-life exposures, in relation to multiple health endpoints, both for long-term exposures as addressed in the EPHOR mega cohort and for short-term exposures as addressed in the case studies.
- ‘... need for ... individual-level exposure data ...estimate the ...environmental component of NCDs’. EPHOR will adopt wearable sensor systems, personal passive sampling and (non-invasive) biomonitoring and omics to obtain ‘individual-level exposure data’ in the case studies.

EPHOR contribution to SC1-BHC-28-2019 Scope:

EPHOR will ‘collect, combine, analyse large data sets’ to ‘understand ...contribution of environmental factors to... burden of ...diseases’. EPHOR will develop the EPHOR mega cohort involving ‘well-designed retrospective epidemiological studies’, specifically to estimate the past working-life exposome in relation to NCDs retrieved partly from clinical records. EPHOR will perform new case studies in population-, occupation- and industry-based cohorts, with an emphasis on working-life interactions (occupational, lifestyle/behavioural, socioeconomic factors) in exposures. These case studies will generate large amounts of data. These two research approaches address all ‘components’ as defined in the call:

- ‘agnostic evaluation of the role of multiple and unknown exposures’: agnostic evaluation of multiple exposures in the EPHOR mega cohort and case studies; a hierarchical approach combining job-based with exposure-based exposure-response analyses in the EPHOR mega cohort to provide hypotheses for unknown exposures; (un)targeted omics analyses (incl. DNA methylation, transcriptomics, proteomics) to discover novel markers of exposure/effect.
- ‘assessment of individual exposure to multiple stressors’: a wearable sensor system including sensors for light, dust, noise, sleep, physical activity, heart rate and location, and passive sampling for offline laboratory analyses of biological (e.g. endotoxins) and chemical exposures (incl. volatile organic compounds, polychlorinated biphenyls, polycyclic aromatic hydrocarbons) in the case studies.
- ‘sensors that combine external exposure and health data measurements’: personal sensors as mentioned above.
- ‘integration of external exposome data with cross-omics responses and (epi)genetic data’: case studies involve sensor, passive sampling and JEM-based exposure data, integrated with biomonitoring, targeted bioassays and (minimally-invasive) cross-omics.
• 'systematic evaluation and simulations of the health impacts': methods for simulating and evaluating the impact of the working-life exposome on health and working-life. Economic parameters will be developed.

• 'better data mining tools, ...advanced statistical analysis of complex data and high-performance/high throughput computing and storage; a long-term host ...single shared data infrastructure, taking ...existing structures ...ensuring open access to data.' The analyses within EPHOR of ‘complex data and high-performance/high throughput computing and storage’, includes existing cohort data, sensor data, biomarkers and omics data and other relevant (exposure) data. The analyses will involve: data mining for improved job coding and exposure assessment in large retrospective cohort studies; statistical methods for multiple exposure-response relationships in relation to timing of exposure; biological pathway discovery resulting from bioinformatics on omics data; quantitative adverse outcome pathway (AOP-)based modelling to support exposure-response relations.

• Yoda, an (‘…existing, ...’) FAIR (Findable, Accessible, Interoperable and Reusable) and GDPR (General Data Protection Regulation) compliant data infrastructure will be further developed, including capability of doing decentralized data analyses, needed for existing cohort data. Existing cohort data cannot be made open access due to former agreements, but new data will be made open access via the Yoda system.

• ‘Innovation ...with industry....sensor development, ...omics, ...biomarker development, ...bioinformatics, ...data processing ...management’. Innovations take pace with several industrial partners: Owlstone Medical: technology for exhaled volatile organic compound (VOC) analyses; VTEC-Engineering: development of the wearable sensor system; LifeGlimmer: data analytics, bioinformatics for omics and biological pathway analysis and text mining; Interaktiv: development of online working-life exposome toolbox and the interactive tool for exploring the working-life exposome and exposure-response associations.

• ‘Proposals are expected to respond to ...policy/regulatory need where the exposome approach would be useful to solve a scientific issue to underpin better regulation’. EPHOR focusses on developing an exposome approach to improve working-life health. Ensuring a safe and healthy work environment for the over 217 million workers presently in the EU is a strategic goal for the European Commission. The characterization of work-related exposures within EPHOR is relevant to issues addressed in recent communications by DG Employment, Social Affairs & Inclusion (EMPL). Examples are: ‘Legislation on the protection of workers from exposure to cancer-causing chemicals at work’ and ‘Improving the prevention of work-related diseases by tackling existing, new & emerging risk’. EPHOR responds timely ‘to solve a scientific issue to underpin better regulation’.

• ‘Overarching Human Exposome Project, ...overall coordination’. Recent projects (HEALS, EXPOOMICS, Helix) have focused on mixed exposures such as air quality in relation to timing of exposure; biological pathway discovery resulting from bioinformatics on omics data; processing ...management'.

1.3 Concept and methodology

1.3.1 Concept

1.3.1.1 The Exposome: a promising concept for reducing the burden of non-communicable diseases

NCDs are the leading cause of morbidity worldwide, being responsible for 61% of the global burden of disease, a proportion that is on the rise[8]. The contribution of genetic risk factors to NCDs is very modest[9], estimated between 10-30%. Therefore, a very large proportion of NCDs have non-genetic causes. The risk of NCDs could be reduced by modifying these non-genetic factors, which in turn has a major impact on health and wellbeing. However, a large proportion of these non-genetic factors remain unaccounted for, given that the Global Burden or Disease Study has estimated that currently known non-genetic risk factors explain only around 46% of the disease burden. Effective prevention is hampered by this limited insight into the specific and quantitative role non-genetic factors play in the total burden of disease. The associations with disease are often multifactorial, involving interactions between genetic and non-genetic risk factors. Increased vulnerability for different population groups or life stages is also likely. Studying non-genetic factors is difficult due to the fact that these factors are numerous, partly undefined and vary greatly between people and over time. The exposome, which encompasses all non-genetic risk factors experienced during a person’s life (external exposome) and its relation to biological responses inside the human body (internal exposome), is a promising concept for exploring the complex relationships between environment and disease[7]. The exposome concept has introduced a more holistic approach to environmental health sciences allowing for investigating combined exposures, in their relation to health, at different levels[10], namely at the overarching societal level, the more general urban and occupational environments, individual lifestyle and behaviour, and the individual internal environment with biological and physiological processes (Figure 1.3.1). Taking an exposome approach therefore enables us to: 1) map the totality of an individual’s exposure; 2) to assess the extent
Taking an exposome approach can have important economic and societal impacts. Improving working-life health is a strategic and ongoing goal for the EU.

Ensuring a safe and healthy work environment for the over 217 million workers presently in the EU is a strategic goal for the European Commission. As risks for workers' health and safety are broadly similar across the EU, there is a clear role for the Union in helping Member States to address such risks more efficiently and in ensuring a level playing-field throughout the EU. The impact of workplace exposures on worker employability, business productivity and performance, and national level competitiveness has been recognized by policy makers. Consequently, well-designed occupational safety and health (OSH)-policies and strategies have been in place for the past 25 years[11]. Despite these policies, poor health among the European workforce due to occupational exposures remains an issue with respect to loss of quality of life, absenteeism, work incapacity, early retirement or premature mortality. A better understanding of the working-life exposome, in relation to the development of NCDs will contribute to ensuring a healthier and more productive workforce. This enables reducing pressure on, and increasing the sustainability of, the healthcare system. Further, Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) is a regulation of the European Union, adopted to improve the protection of human health and the environment from the risks that can be posed by single chemicals. Having an understanding of exposure beyond single chemical use is one of the big gaps in current risk assessments under REACH, which EPHOR will help bridge.

Demographic change

The EU Strategic Framework on Health and Safety at Work 2014-2020 has identified demographic change including an ageing workforce as one of the key challenges. The Framework draws attention to the need to make risk assessment diversity-sensitive paying attention to age, gender and other demographic characteristics[12] Indeed, nationality, age, gender and previous and current employment conditions have been pinpointed as factors increasing the risk for developing occupational injuries[12]. The working population aged over 55 in the EU is expected to increase by at least 16% between 2010 and 2030[13] due to an aging population combined with an extended working-life span. Challenges facing an aging workforce include vulnerability for developing NCDs due to concomitant age-related diseases. Even in healthy ageing, resilience to risk factors may be reduce. Reduced health contributes to a marked decrease in workforce participation. In addition, over the last decades, female participation in the workforce has risen, with women increasingly working during pregnancy and nursing, resulting in potential peri-natal and post-natal occupational exposures. Work-related risks to women's safety and health less studied[14]. Very little attention and resources are being directed towards identification of work-related risks experienced specifically by women. An exposome approach will provide knowledge on these vulnerable groups.
Rapidly changing nature of work
The nature of work has shifted in the last decades in terms of self-employment, migrating workers, variety of jobs over a lifetime and precarious work (non-standard employment that is poorly paid, insecure, unprotected, or cannot support a household). This shift is due to changes in the economy, population demographics, migration, and the availability of advanced technologies and digitalization and leads to more heterogeneous exposure patterns. These patterns complicate traditional exposure assessment which is typically based on groups of workers with homogeneous exposures working in a specific company or industry during their working-lifetime. The exposome approach is more focused on individuals or smaller exposure groups and will be better suited for this ‘new world of work’ compared to traditional exposure and risk assessment approaches.

A holistic perspective on health and wellbeing
Working and lifestyle are intertwined. On the one hand, a person’s work and employment may affect social life general exposures and lifestyle. On the other hand, exposure to lifestyle factors impose a direct threat to workers’ health and thereby has an impact on workers’ productivity. Therefore, factors that contribute to health problems previously considered as being unrelated to work are increasingly acknowledged as related to work. Examples of this holistic view are underlined by the total worker health initiative launched by the US National Institute for Occupational Safety and Health (https://www.cdc.gov/niosh/TW/) and by workplace related initiatives in the EU on lifestyle determinants for promotion of the overall wellbeing of workers. The exposome approach will aid policy makers and occupational health practitioners with guiding and developing these holistic strategies by providing evidence on the interactions and importance of occupational and non-occupational exposures.

1.3.1.3 The working-life contributes significantly to the exposome of most people
Until now, the working-life has been largely neglected in exposome studies despite the fact that working-life makes up the largest proportion of the total lifespan (Figure 1.3.2). Also, many occupational exposures are higher and more complex than exposures in the outdoor or home environments. In addition, working-life encompasses important vulnerable life stages including the reproductive period and part of later life aging. Lastly, working is closely interconnected to lifestyle/behaviour (e.g. diet, physical activity, smoking and alcohol consumption) and socio-economic status. While being in the workforce mainly has a positive impact on these factors, certain occupational exposures may have negative impacts, such as shift work on diet. The relative importance of the working-life to the exposome in its contribution to several NCDs is of a similar magnitude to general environmental risk factors such as urban air pollution and obesity\(^{(15)}\).

1.3.1.4 Concept behind the EPHOR approach: the development of a working-life exposome toolbox
The exposome concept has been recognized as a great opportunity for prevention, but also has generated considerable discussion, both about the feasibility of performing exposome research and applying exposome knowledge for health

![Figure 1.3.2: Expected contribution of the working-life exposome to the total exposome.](image)

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prevention. Collaboration between different research disciplines and stakeholders is needed to fulfil the exposome potential. Collaboration starts with synergism in terminology, as well as better data sharing and more optimal use of existing data[10, 16]. Therefore, the main objective of EPHOR is to develop a working-life exposome toolbox containing: 1) better and more knowledge on how multiple exposures within the working-life exposome relate to NCDs; 2) tools for scientists to expand current exposome knowledge in relation to health; 3) tools for policy makers and occupational health practitioners to obtain data for developing evidence-based and cost-effective preventive actions and policies.

The tools in this toolbox will include data on the working-life exposome: exposome data, exposure-response data, and methods and models for obtaining and analysing these data. In addition, the toolbox will contain methods and models for performing health and economic impact assessment based on exposome data.

Figure 1.3.3 shows the type of data, methods and models that will be developed within EPHOR and will become available in the toolbox. EPHOR will embrace the exposome paradigm in order to advance knowledge on the heterogeneous working-life exposure patterns in relation to the common NCDs, including: 1) complex interactions between exposures; 2) identification of vulnerable life stages and subgroups; 3) mechanistic insights, including identification of biomarkers of early disease; and 4) exposure-response associations for more short-term and higher resolution exposures. Methodologically, obtaining these different aspects of the exposure-response associations requires a combination of two different study approaches: systematic analyses for a wide range of NCDs in a large population making use of the large body of existing data (EPHOR mega cohort) combined with more detailed analyses in case studies with newly collected exposome data.

The triangles in Figure 1.3.3 give an indication of the differential type of exposome data that will be used and type of exposure-response data that are obtained with these study approaches. These approaches and data are described in more detail in 1.3.1.5. Briefly, the EPHOR mega cohort will rely mainly on different sources of existing data for job-based exposure assessment at a group level. In the case studies, new exposure data will be collected, enabling more individualized exposome assessment of external exposures and internal exposures in biological samples. Here, existing data will also be used, but to a more limited extent for retrospective exposure assessment. The boxes at the bottom show the methods that are needed and developed in EPHOR. Briefly, besides methods for study design (described in 1.3.1.5), methods for collection, storage and analyses of existing and new exposome data (described in 1.3.1.6), and methods for health impact assessment will be developed (1.3.1.7). EPHOR does not encompass an EU wide burden of working-life disease study. It rather provides methodology and a demonstration of how to use (EPHOR) data on the working life exposome in relation to health for performing impact assessments.

Figure 1.3.3: EPHOR combines two study approaches (EPHOR mega cohort and focused case studies) with differential exposome data and exposure-response data. This requires the development of a range of methods.

1.3.1.5 Study design: combining 2 approaches making use of new and existing data

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The EPHOR mega cohort

Most of our current knowledge on occupational health is based on population-based or occupational-based cohort studies. These studies focus on specific occupational situations or exposures, or involve add-ons within population-based cohort studies initially designed with a much broader focus. Europe has a long tradition of occupational health research and currently has some of the most valuable population-, industry- and occupation-based cohorts worldwide. These existing cohorts have collected a wealth of data on lifetime occupational histories, also including information on more general characteristics of the population. These existing studies are invaluable resources for obtaining a detailed understanding of the working-life exposome in relation to health. Within EPHOR, a mega cohort will be constructed based on large-scale pooling data from multiple individual cohort studies. Pooling of cohorts is essential to achieve sample sizes that are sufficient to:

1) Move away from single exposure, single disease evaluations to the agnostic exposome-based exploration of (combinations of) risk factors in relation to multiple NCDs, including rare exposures and rare diseases.
2) Identify vulnerable life stages (e.g. young adult life, reproductive life, ageing life) and population subgroups (e.g. gender, socio-economic groups) in which these risk factors result in more pronounced or different health effects.

Focussed case studies collecting new data

More individual and high-resolution level external and internal exposure data are needed to:
3) Provide mechanistic insights and identify early markers of disease.
4) Study exposure-response relations with individual level data at a high resolution in time, e.g. the effect of short-term exposures.

Within the case studies EPHOR takes two angles: 1) Taking a disease angle by using population-based cohorts with high quality data on respiratory health considering a wide range of working-life exposures in relation to respiratory health; 2) Taking an exposure angle by using industry-based or occupation-based cohorts with high quality data on shift work. This angle explores the association between shift work and other related exposures in relation to a wide range of (intermediate) health endpoints. More details on these case studies are described in 1.3.1.9.

1.3.1.6 Working-life exposome methodology needed

Uncovering a person’s exposome requires complete, accurate and time-resolved individual-level external exposure data capturing the variety and dynamics of a multitude of exposures. Recent technological advances have provided opportunities for the collection, storage and analyses of these data. EPHOR proposes to further develop and combine some of the advances described below for application to the working-life exposome.

Collection of new high-resolution external exposure data

Conventional external exposure assessment employs passive or active sampling with subsequent laboratory analyses for one or a few substances, resulting in time-weighted average (TWA) concentrations. Sampling and laboratory costs limit the number of samples. Recent advances enable more convenient personal level sampling for a wider range of exposures[17-19]. Firstly, wearable sensors and smart technologies provide expanded temporal and spatial detail. Sensors require less human field worker effort and costs, while enabling the possibility of collecting a wider range of exposures by combining sensors into one system. Using a system with multiple sensors, and applying them throughout the day at work and away from work, enables the generation of individualized and more complete exposure profiles. This is particularly useful for addressing heterogeneous exposure patterns due to the rapidly changing nature of work, or for assessing both exposure at and outside the workplace. Sensors also have potential to provide real-time feedback to workers to help them better understand their exposures. In future interventions, this enables the improvement of behaviour and practices to reduce exposures.

Secondly, new passive sampling methods allow for easier collection of larger amounts of exposure samples for laboratory analyses: wristbands for personal sampling[20] and electrostatic dust collection for stationary sampling[21]. Advances in analytical chemistry and informatics enable targeted screening of a wider range of substances, allowing to move beyond the single exposure paradigm. These techniques allow to investigate potentially exposure combinations that could not be studied in the past.

Exposure assessment making use of existing data in cohorts

Exploitation of the EPHOR mega cohort proposed, requires high-quality large-scale systematic harmonised exposure assessment. A job-exposure matrix (JEM) is a tool used to assess exposure to potential hazardous agents in large populations[22]. A JEM consists of a job axis and an exposure axis, and occasionally a time dimension. It translates job histories into specific (semi-) quantitative exposures in a systematic and unbiased way, representing a highly efficient and reproducible methodology. Several national JEMs have been developed in Europe[23-28], but differences in occupational coding systems, exposure definitions and exposure measures complicate the comparison of JEMs develop for different studies or populations. The EPHOR mega cohort involves pooling data from different countries,
requiring the development of a standardized European wide JEM. In addition, existing JEMs have some limitations. Firstly, JEMs are available mainly for more traditionally studied occupational risk factors (e.g. specific chemicals in dust). JEMs do not cover emerging new risk factors, non-occupational factors and differences in exposure levels across gender or industries. New knowledge on working-life exposures becomes continuously available, which may be useful for enhancing JEMs. Large data sources with relevant data exist (e.g. ECHA REACH database on production volumes/chemical use), but their use in population-based research is limited due to a lack of standardization. New powerful data mining techniques are needed to make better use of these data sources for harmonized exposure assessment in pooled cohort studies. Secondly, a major challenge related to the utilization of JEMs is the process of translating a job title into meaningful exposure estimates. Before a JEM can be linked, free text fields from job histories need to be coded using standardized occupational coding systems across studies (e.g. ISCO-68, ISCO-88). This process is time consuming and automatic coding based on text mining is currently being explored. Lastly, current job coding systems have been developed for economic purposes but often do not optimally reflect exposure categories. More optimized coding systems for exposure assessment are currently absent.

**Collection of new high-resolution internal exposure data**

The internal exposome aims to characterize internal markers related to exposure or biological effects. This contributes to understanding how internal exposure originated from external exposure, in relation to adverse health effects. The use of biomarkers is not new, but until now involves single exposure biomarkers (e.g. urinary metabolite) or biological effect (e.g. acetylcholinesterase inhibition). In contrast, omics approaches allow for the detection and quantification of (ideally) all biomolecules (e.g. DNA, mRNA, metabolites, proteins). Omics may contribute to exposome studies, in particular when applied to accessible biological samples, taken at various moments in time. Omics can represent biomarkers of different exposures, for example multiple compound blood levels and metabolites. In addition, omics can detect past exposures via so called ‘imprints’, e.g. CpG DNA methylation patterns. Therefore, omics enable the study of biological pathways across a continuum from multiple exposure, towards early health changes, and onwards to disease. Thereby generating hypotheses regarding development of exposure-related disease and corresponding biomarkers.

There are several scientific challenges that limit the application of omics. Omics data are often collected from invasive matrices (blood) within a limited number of individuals/timepoints. However, biological markers vary over time, between people and across tissues. The development of methods for collection of less invasive matrices, like urine or exhaled breath (EB), enables more widespread sample collection. This improves understanding of time effects and interindividual variability in omics responses.

In addition to omics, recent attention is directed towards volatile organic compounds (VOCs) in exhaled breath. Exhaled breath can contain thousands of VOCs originating either as products of the body’s metabolism (endogenous VOCs) or originating from the exposome (exogenous VOCs). The dual origin of VOCs in breath means that breath analyses can provide valuable information about the volatile fraction of the internal and external exposomes. For instance, breath can contain VOCs inhaled during a shift at a factory, providing specific information about an individual’s external exposome, as well as volatile metabolites resulting from internal processes caused by the exposure, e.g. inflammation of lung tissues. Improved knowledge on how EB VOCs relate to occupational exposures and (early) health effects is needed, to enable the full deployment of non-invasive monitoring.

**Data storage and interpretation**

The human exposome data structure is a high-dimensional collection of highly heterogeneous exposure variables. Given the scale needed in exposome studies, data will be provided by many institutes. Easy to use data management tools are needed to safely collaborate between countries and institutes on data during the research project and to facilitate re-use thereafter. Pooled analyses (analysing the original data all together) are preferred over meta-analyses (combining summary statistics from separate analyses). However, pooling of raw data may face ethical and legal challenges. Innovative approaches are being developed for decentralized data analysis, enabling pooled data analysis to be carried out as if one had full access to all the individual data from study participants.

Data analytical methods are needed, capable of handling multiple exposures in exposure-response analyses and complex interdependent exposure-time-response relationships (ETR). In addition, new data mining approaches are needed to use new and existing data sources for the development of: 1) updated JEMs; 2) automated coding systems; and 3) improved coding systems for job-based exposure assessment (see Exposure assessment making use of existing data in cohorts). Lastly, methods for interpretation of the high dimensional variety of omics data on different biological levels are needed, also with respect to modelling underlying complex biological pathways. Analysing complex biomarker and omics data requires integration with biological and toxicological knowledge. This enables comparison with known biological or toxicological processes that are being described at OECD (Organisation for Economic Co-operation and Development) level in structured representations of biological effects: adverse outcome pathways (AOPs) and related molecular initiating event (MIEs).
1.3.1.7 Methods needed for assessing the impact of the working-life exposome

For translation of these new types of model results into actionable insights, new methods for risk assessment and health and economic impact assessment are needed. Current health impact assessments and evaluations of policy and other interventions are generally based on a single exposure-single health effect model. The global burden of disease study[30] is an example of a global study on impacts of a wide spectrum of risk factors. However, for optimal use of exposome data in impact assessment, frameworks and models should be able to incorporate data from complex exposure scenarios. This includes multiple exposures and early markers of exposure/disease along biological pathways. This will allow for more targeted and science-based policies. As an example, an outcome such as sleep disturbance will be related to various risk factors, including shift work, diet, physical activities, etc., of which some will be correlated. Hence, the health impact assessment may require that this complexity is considered when estimating the impact of interventions. If risks vary by subgroups, policies or interventions may be targeted towards specific vulnerable groups, (e.g. specific SES, women). Furthermore, impact assessment from and evaluations of interventions may be done using intermediate markers of disease, rather than the (clinical) health outcome. Lastly, current impact models mostly use mortality or disability adjusted life years (DALY), while for the working-life more specific health metrics, like working-life expectancy and working years lost, are more useful.

1.3.1.8 Selected case studies

Rationale behind case study 1: Respiratory health and the working-life exposome

Chronic obstructive pulmonary disease (COPD) and asthma are common chronic diseases. Occupational and non-occupational exposures both contribute substantially to the burden of asthma and COPD[31]. The evidence originates from data based on the ‘one exposure, one disease’ principle[32], which severely hampers a valid estimation of the true importance of the totality of occupational and related non-occupational exposures for health. Considering the totality of exposures is crucial since most individuals are daily exposed to a multitude of potentially hazardous exposures. Furthermore, understanding the key biological pathways between occupational exposures and lung disease is limited. Biomarkers exist, with a clear relation to COPD and lung function, for example proteins YKL 40 and CC16, which interact with smoking for lung disease risk. However, the impact of occupational exposures on these proteins and in turn lung disease is unknown[33, 34]. In addition, for preventive measures, it is important to know the exposure metric of interest, i.e. the roles of short- and long-term exposures in relation to lung function and disease. Acute declines in lung function during a working day related to occupational exposure is well known, and biomarkers are available for short-term non-occupational effects of exposure to e.g. ozone, but biomarkers are mostly unavailable for occupational exposures. Recently, biological pathways linking short-term airborne particulate matter and loss of lung function was suggested among 9/11 WTC catastrophe rescue workers. Lastly, insight into impacts on vulnerable subgroups is critical to tailor preventive measures. There are some indications of gender differences in age-related effects on lung function and effects of occupational exposures on lung disease[35]. Still, the results are not conclusive. This complex exposure situation involving both occupational and non-occupational risk factors and genetic make-up, as well as the need for better insights in relevant exposure metrics and biological pathways, is particularly relevant. To obtain a more complete picture of how both short- and long-term working-life exposures are related to respiratory health, the two EPHOR study approaches will be combined. The evidence on working-life risk factors of respiratory health in the EPHOR mega cohort will be complemented with state-of-the-art methods for new data collection on the external and internal exposome. This will advance knowledge on how long- and short-term occupational and non-occupational exposures interact with individual biological pathways in relation to respiratory disease risk. We will further identify gender differences. The focus on this major working-life health outcome is particularly important in the view of the prolonged productive working-life.

Rationale behind case study 2: Night shift work and the working-life exposome

Experimental and epidemiological evidence shows that long-term disruption of endogenous circadian rhythms, in particular due to exposure to light during the biological night, may be associated with a wide range of common NCDs, including cancers, cardiovascular diseases and major metabolic disorders (obesity and type 2 diabetes) [36-38]. The prevalence of circadian disruption in human populations is high and increasing due to expanding human activities over the 24-hour day in both the working and the general population. The need of establishing the long-term impact of circadian disruption on health, the understanding of biological pathways and the application of population and individual prevention policies is a priority for health across all ages. In 2007, the International Agency for Research on Cancer (IARC/WHO) concluded that “shift work that involves circadian disruption is probably carcinogenic to humans”[36]). This mainly based on animal experimental evidence with only limited human evidence on shift work and breast cancer[39, 40]. The public health consequences of this evaluation are important, since about 20% of the workforce in Europe is doing some non-standard work schedule. Individual chronotype is a human attribute with genetic basis that reflects the circadian phase of entrainment[41]. Chronotype correlates with diurnal preference, an attribute reflecting personal preference for activities in the morning or evening. Diurnal preference and chronotype may affect shift work adaptation and evening types (subjects with a later circadian phase) may adapt faster to night
shift work. Genetic variation, related to chronotype, may also affect adaptation and effects of circadian disruption on health. Circadian disruption may also affect behaviour, lifestyle and even other work-related risk factors due to fatigue. These are, however, understudied areas of research limiting the prediction of individual risk and planning of prevention policies. This complex exposure situation involves both occupational and non-occupational risk factors and genetic make-up. There is a need for better insights in relevant exposure metrics and biological pathways, particularly relevant in the context exposome research. By complementing the evidence on shift work in the EPHOR mega cohort with state-of-the-art methods for assessing the external and internal exposome, we will uniquely advance knowledge on how the long-term and short-term occupational and non-occupational environment (including behaviour and lifestyle) interact with the genetic make-up of individuals, and disease risk and identify mechanistic pathways and potential gender differences. The focus on this major exposure in affecting around 20% of the population is particularly important in view of the prolonged productive.

1.3.1.9 Technology readiness level (TRL)
The activities within EPHOR have a TRL of 2-5. The first scientific definitions of the general exposome concept can be considered as TRL2. Under TRL2, EPHOR further defines the working-life exposome. At TRL3, experimental proof for the exposome concept has been established in general population studies (2010-2017). EPHOR will take initial experimental proofs of the exposome concept (which were TRL3) further towards the working-life exposome. This involves the further development and validation of methods and technologies in pilot experimentation (TRL4) before application in cohort studies (TRL5). For example, the development of a wearable sensor system (WP2) will involve pilot experiments in a few individuals before application in the cohorts. Existing JEMs will be further harmonized, made more specific and data rich and evaluated before application in cohorts to evaluate working-life risk factors for NCDs (at TRL5). Omics and exhaled breath analyses will be developed in WP3, which is also at TRL4. In summary, EPHOR activities at TRL4 entail the adoption and further testing of exposome technologies and concepts at small scale, prior to using these in the context of characterizing the working-life exposome within cohort studies. EHPOR will also develop towards TRL5. An integrated approach of a dynamic EuroJEM, wearable sensor technology and passive sampling for improved external exposure assessment, biomonitoring, omics and biological pathways, and data technologies will be applied for characterizing the working-life exposome in relation to NCDs for the first time in the EPHOR mega cohort and case studies (e.g. at the scale of several ten-millions of individuals). In addition, methods for assessing the health and economic impact of the working-life exposome will be developed and applied. Together, this represents testing the working-life exposome concept and associated technologies in a relevant environment (TRL5).

1.3.1.10 Stakeholder involvement
Figure 1.3.4 gives an overview (including explanation of the abbreviations used in this section) of the four groups of stakeholders and their involvement in EPHOR. The vertical arrow represents the full endeavour of uncovering the working-life exposome in relation to NCDs. The dotted lines show the contribution of the EPHOR project at TRL2-5 (further developments after EPHOR are outlined in section 1.4.2). Creating full insight in the complex associations between working-life exposures and health (both during and after EPHOR), requires scientists for developing new methods for assessing the working-life exposome and its relation to NCDs and performing exposome studies and technology developers for developing new technologies that enable these methods. For ultimately applying this knowledge base to prevent NCDs related to working-life, policy makers and occupational health practitioners will use the data, methods and models for the development and implementation of more effective preventive measures. For optimal implementation other stakeholders are also involved: government agencies, employers and employees, general health practitioners and insurance companies. Technology developers also play a role in prevention since the technologies used for science can also be developed to enable interventions.

To ensure that the project activities and outcomes are relevant to these different stakeholder groups and assure that the outcomes are sustainable into the future, stakeholders will be involved in stakeholder consultations organized within WP11. During the project relevant stakeholders will be identified and consulted with respect to the development of wearable sensor systems, the development of relevant hypothetical intervention scenarios for impact assessment and the working-life exposome toolbox development. In addition, a wider range of stakeholders representing all groups shown in Figure 1.3.4 will invited for a stakeholder symposium on the results of EPHOR. The inventory of stakeholders in figure 1.3.4 will be used as a basis and expanded on for involving the relevant stakeholders for these consultations and workshops. Also, some stakeholders will be even closer involved in the project activities:

Technology developers and scientists in the consortium: The consortium consists of scientists and technology developers. The projects exploitation and dissemination strategy detail the transfer of EPHOR outcomes to other technology developers and scientists. Three partners TNO, FIOH and STAMI are members of the PEROSH network.
of occupational safety and health institutes and several partners are represented in the boards of the relevant scientific societies and expert groups

**End-user stakeholders in the advisory board:** The end-user stakeholders will be represented in the advisory board: ICOH representing occupational hygiene practitioners, EUOSHA representing EU government, ECETOC representing scientists within industry and HSE and NIOSH representing scientists within national agencies. NIOSH will also be an ambassador to the US for working life exposome data, methods and tools. The tripartite advisory board consisting of government, industry and scientists will advise the EPHOR consortium on how to align the EPHOR project research activities with their needs optimizing the relevance of the project activities, contributing to sustainability of the toolbox and efficient future implementation of EPHOR results for reduction prevention of NCDs (see Table 3.2.2).

**Table 1.3.1: National and international research activities on which EPHOR builds**

<table>
<thead>
<tr>
<th>Project</th>
<th>Output from project that will feed into EPHOR</th>
</tr>
</thead>
<tbody>
<tr>
<td>OMEGA-NET (the Network on the Coordination and Harmonisation of European Occupational Cohorts), (2017-2021). Funded by: EU COST Association. (Core management group: STAMI, ISGLOBAL, KI, UU)</td>
<td>Collaboration of European occupational, industrial and population cohorts, including registry-based cohorts, with occupational information facilitates an integrated research strategy. Inventory of these cohorts. Harmonised existing occupational exposure and health outcome information. Feeds into WP5.</td>
</tr>
<tr>
<td>European Human Biomonitoring Initiative (HBM4EU) (2017-2021) Funded by EU (TNO, UU, IOM, KUL, FIOH)</td>
<td>Mechanistic modelling of benzene exposure, reviews on biomonitoring of occupational exposures, methods</td>
</tr>
<tr>
<td>Project</td>
<td>Output from project that will feed into EPHOR</td>
</tr>
<tr>
<td>------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>HEALS, EXPOsOMICS, Helix Funded by EU (TNO, IOM, UU, ISGLOBAL)</td>
<td>First EU exposome projects studying Multiple exposure health relationships, use of sensor data, omics and big data analysis approaches in exposome/epidemiology studies addressing the general public or vulnerable individuals (e.g. children). This forms the basis for EPHOR approach, feeding into WP1, 3, 4.</td>
</tr>
<tr>
<td>BRUSH Funded by the European Research Council (UiB)</td>
<td>Clinical examinations in ECRHS study, translating into in 3 EPHOR study centres in WP6</td>
</tr>
<tr>
<td>“Nordic Occupational register – a tool for estimation of the potential workplace and population level interventions” Funded by Nordforsk. (FIOH)</td>
<td>Metrics relevant for estimating the impact of work environment on NCDs and working-life expectancy.</td>
</tr>
<tr>
<td>OPERAS Funded by the French ANSES (UU)</td>
<td>Text mining methodology for automated coding of free text occupational histories (for French and Dutch), feeds into WP4 and 5.</td>
</tr>
<tr>
<td>CEFIC LRI funded projects (TNO, IOM)</td>
<td>Approaches for modelling of internal exposure for use in occupational risk assessment, feeds into WP4.</td>
</tr>
<tr>
<td>RobotAnalyst project <a href="http://www.nactem.ac.uk/robotanalyst/">http://www.nactem.ac.uk/robotanalyst/</a> Funded by MRC (UNIMAN)</td>
<td>Machine learning to transform the way in which evidence-based health reviews are conducted, including descriptive clustering for search, feeds into WP2 and 4.</td>
</tr>
<tr>
<td>Manchester Molecular Pathology Innovation Centre (MMPathIC) Funded by MRC/EPSRC (UNIMAN)</td>
<td>Text Mining tools and infrastructure for biomedical text mining, linking together different types of information about potential biomarkers which may be dispersed across documents of different types, feeds into WP2 and 4.</td>
</tr>
<tr>
<td>Open Mining Infrastructure for Text and Data (OpenMinTeD) project (EU H2020) (UNIMAN)</td>
<td>Interoperable text mining infrastructures for biomedicine, feeds into WP4.</td>
</tr>
<tr>
<td>Big Mechanism Funded by DARPA (UNIMAN)</td>
<td>Deep machine reading methods for extracting mechanistic interactions and their interpretations from the literature, feeds into WP4.</td>
</tr>
<tr>
<td>Crosswalks Funded by ANSES (INSERM)</td>
<td>Transcoding of French job codes for using CANJEM in Constances, feeds into WP4 and 5.</td>
</tr>
</tbody>
</table>

Within the H2020-SC1-2019 call, in total 9 projects were funded forming a network of projects, the European Human Exposome Network. Project members of EPHOR will participate actively in this European Human Exposome Network to share knowledge and best practices.

### 1.3.2 Methodology

EPHOR is structured around 10 interconnected work packages (Figure 1.3.5). Methods for collection, storage and interpretation of working-life exposome data are developed in WP1-4. Application and demonstration of these methods for better and more complete knowledge of the working-life exposome in relation to NCDs will be done in WP5-7. Methods for assessing the impact of the exposome will be developed in WP8. The working-life toolbox will be developed in WP9. In WP10, besides dissemination and exploitation, several stakeholder workshops will be held during the course of the project in collaboration with WP1, 8 and 9.
The research question addressed is: *How can we apply recent advances in external exposure assessment for the collection of more complete external exposome data at individual level?*

This WP includes integrating different methods for generating more complete individual level exposure data for each subject. An exposome system must gather data over time, and therefore must involve relatively ‘low demanding and low maintenance’ technologies, which are agreeable for participant use over longer periods of time. Within this WP we will use a combination of such technologies to obtain a wide range of exposures. A wearable sensor system will be developed (VTEC responsible). This will build on a wearable sensor system previously developed which already includes sensors for particulate matter, temperature and humidity, currently undergoing calibration experiments and field testing by TNO (section 1.3.11). The sensor system has wireless communication that communicates the data securely via a base station to a cloud based database. We will combine this with gathering information on a wide spectrum of chemical exposures using silicone wristbands, and on biological exposures using passive environmental sampling. To supplement the data collection on these exposures, we will also include a digital questionnaire to help us understand activities and exposures which will help put these exposures into context, and which are more difficult to capture with the sensor system and passive sampling. This combination of sensors, passive sampling and a questionnaire covers important risks and helps to improve the assessment of the working-life exposome. A protocol for applying these combined methods (Figure 1.3.6) will be developed, tested in a feasibility study and made available to WP6, 7 and 8. Engagement of relevant stakeholders (WP10) will occur at the beginning and course of EPHOR.

**1.3.2.2 WP2 Standardized assessment of multiple exposures in large populations**

The research question addressed is: *How can we develop a dynamic tool for state-of-the-art retrospective external working-life exposure assessment, including all relevant occupational and non-occupational exposures (taking into account e.g. gender differences), to be used in EPHOR and future cohorts studies across the EU?*

In order to keep up with the changing world, and subsequent changing exposures at workplaces, we will develop a validated and standardized dynamic tool for state-of-the-art exposure assessment. This dynamic EuroJEM is capable of including new exposure data, also beyond EPHOR. The work will build on the inventory of existing JEMs in the OMEGA-NET Cost Action (section 1.3.11). Several partners of the EPHOR consortium have developed JEMs for broad spectrum of exposures. Therefore, the EPHOR consortium has access to the majority of the existing JEMs in
Europe (Table 1.3.2). These JEMs will be harmonised to form the basis of EuroJEM. A protocol for including new data into EuroJEM will include methods for searching and collecting new data from literature (incl. text mining in collaboration with WP4), exposure databases (e.g. ECHA REACH) or other databases, reports and (Bayesian) decision criteria to determine if and how to revise exposure estimates in EuroJEM. The protocol will be applied to expand EuroJEM to include a higher granulation (e.g. gender specific or industry specific) of exposure estimates.

Table 1.3.2. Existing job-exposure matrices in Europe that are available to the EPHOR consortium

<table>
<thead>
<tr>
<th>Job-exposure Matrices</th>
<th>Agents</th>
<th>Time resolved</th>
<th>Region-specific</th>
<th>Available at</th>
</tr>
</thead>
<tbody>
<tr>
<td>SYN-JEM</td>
<td>Respirable crystalline silica, chromium, nickel, asbestos, PAH</td>
<td>Yes</td>
<td>Southern Europe, Western Europe, Nordic Countries, Germany, UK, France, CEE, Canada</td>
<td>UU</td>
</tr>
<tr>
<td>DOM-JEM</td>
<td>Respirable crystalline silica, chromium, nickel, asbestos, PAH, diesel exhaust, biological dusts, endotoxins, animal contact</td>
<td>No</td>
<td>-</td>
<td>UU</td>
</tr>
<tr>
<td>ALOHA +</td>
<td>Dusts, pesticides, solvents, metals</td>
<td>No</td>
<td>-</td>
<td>UU</td>
</tr>
<tr>
<td>BENJEM</td>
<td>Benzene</td>
<td>Yes</td>
<td>-</td>
<td>UU</td>
</tr>
<tr>
<td>ISOPS</td>
<td>Occupational prestige</td>
<td>No</td>
<td>-</td>
<td>UU</td>
</tr>
<tr>
<td>ELF - JEM</td>
<td>extremely low-frequency magnetic fields (ELF-MF)</td>
<td>No</td>
<td>-</td>
<td>UU</td>
</tr>
<tr>
<td>Shock - JEM</td>
<td>Electric Shocks</td>
<td>No</td>
<td>-</td>
<td>UU</td>
</tr>
<tr>
<td>Noise JEM</td>
<td>Noise</td>
<td>Yes</td>
<td>Denmark</td>
<td>AU</td>
</tr>
<tr>
<td>Lifestyle JEM</td>
<td>Smoking, alcohol</td>
<td>Yes</td>
<td>Denmark</td>
<td>AU</td>
</tr>
<tr>
<td>Day light JEM</td>
<td>Day light</td>
<td>Yes</td>
<td>Denmark</td>
<td>AU</td>
</tr>
<tr>
<td>NOCCA</td>
<td>28 agents (chemical and non-chemical factors)</td>
<td>Yes</td>
<td>Nordic countries</td>
<td>FIOH/KI</td>
</tr>
<tr>
<td>Asthma JEM</td>
<td>Asthmagens</td>
<td>No</td>
<td>-</td>
<td>On request</td>
</tr>
<tr>
<td>Lux JEM</td>
<td>Illuminance (lux) and outdoor work.</td>
<td>Yes</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Psyk - JEM</td>
<td>Job strain and bullying</td>
<td>No</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>JEM-Constances</td>
<td>Biomechanical factors</td>
<td>Yes</td>
<td>France</td>
<td>INSERM</td>
</tr>
<tr>
<td>HCWJEM, HCWTREM</td>
<td>Task-based hospital factors among health care workers</td>
<td>Yes</td>
<td>The Netherlands</td>
<td>On request</td>
</tr>
<tr>
<td>Dutch Asbestos JEM</td>
<td>Asbestos</td>
<td>Yes</td>
<td>Finland</td>
<td>FIOH</td>
</tr>
<tr>
<td>FINJEM</td>
<td>Chemical agents</td>
<td>Yes</td>
<td>Finland</td>
<td>FIOH</td>
</tr>
<tr>
<td>FINJEM</td>
<td>Microbiological agents</td>
<td>Yes</td>
<td>Finland</td>
<td>FIOH</td>
</tr>
<tr>
<td>FINJEM</td>
<td>Physical agents</td>
<td>Yes</td>
<td>Finland</td>
<td>FIOH</td>
</tr>
<tr>
<td>FINJEM</td>
<td>Lifestyle factors: smoking, alcohol, diet, physical exercise, overweight</td>
<td>Yes</td>
<td>Finland</td>
<td>FIOH</td>
</tr>
<tr>
<td>Physical exposures</td>
<td>heavy physical work, kneeling/squatting, whole body vibration, heavy lifting, arm elevation, awkward trunk posture, biomechanical load</td>
<td>Yes</td>
<td>Finland</td>
<td>FIOH</td>
</tr>
<tr>
<td>Psychologica l factors</td>
<td>high demands, low control, high job strain, low social support, monotonous work</td>
<td>Yes</td>
<td>Finland</td>
<td>FIOH</td>
</tr>
<tr>
<td>UV JEM</td>
<td>Occupational UV exposure (artificial &amp; solar)</td>
<td>Yes</td>
<td>Finland</td>
<td>FIOH</td>
</tr>
<tr>
<td>NORJEM</td>
<td>Mechanical work exposures</td>
<td>Yes</td>
<td>Norway</td>
<td>STAMI</td>
</tr>
<tr>
<td>NORJEM</td>
<td>Psychosocial factors</td>
<td>Yes</td>
<td>Norway</td>
<td>STAMI</td>
</tr>
</tbody>
</table>
within job titles and also new exposures (e.g. emerging risks, non-occupational risks etc.). In addition, the use of optimized and dynamic coding systems (as opposed to the current systems used that were designed for economic purposes) will be investigated. For example, depending on the exposure of interest, job categories can be merged or separated to reduce exposure variability within occupational job categories to improve the performance of the JEMs.

1.3.2.3 WP3 Internal exposure and effect assessment using biomonitoring, omics and minimally invasive biomarker development

The research questions addressed are: How can the internal exposome be assessed in order to propose internal exposure estimates and biological pathways in WP6,7? Can VOCs or omics profiles in exhaled breath be used as a non-invasive marker of exposure or (early) effects?

WP3 will coordinate and perform the analyses of both markers of exposure (e.g. metals, organic chemicals, VOCs, PAH) and effect (DNA/RNA, and proteome alterations) in traditional matrices (blood, urine). A protocol will be developed for collection of biomaterials (Figure 1.3.7 gives an overview of all biomaterials) in WP 6 and 7. In addition, biomarker analyses takes place in WP 3. A tiered analytical approach along a biological sequence will be followed to efficiently analyse the samples for a broad spectrum of biomarkers and omics. Additionally, identification of non-invasive markers is a key component in identification and development of biomarkers. Therefore, non-invasive targeted and non-targeted exposome markers of the lung will be developed based on exhaled breath (EB). A relevant matrix as occupational exposure occurs mainly through inhalation with an immediate impact on the lung. Exhaled breath condensate (EBC) will be analysed for epigenomics and proteomics. Comparing these data with similar data obtained from blood, allows to address interorgan differences in biological pathways, which creates knowledge for developing non-invasive exposure and effect monitoring using EBC. In addition, EB will be analysed for VOCs. EB collection will be done using the OWL designed ReCIVA, built to address problems that have impacted breath-based research over the last 40 years.

1.3.2.4 WP4 Working-life exposome data management and analytics platform

The following research questions will be addressed: How can high-performance/high throughput computing and storage of existing and new EPHOR data be facilitated for all consortium members providing them with efficient access, while ensuring compliance with the GDPR and FAIR principles? How can new data interpretation and mining methods be adapted/developed – in particular to augment JEMs, biomonitoring, omics and personalized sensing data – for simultaneous analyses of multiple exposure-response relationships in occupational cohorts?
For data management, we will customise Yoda (text box 1) for large amounts of research data during all stages of EPHOR. A framework will be developed using DataSHIELD [39, 41] for joint decentralised analyses across cohorts either through meta-analysis or pooling of the individual cohorts (WP5). Existing cohort data do not become available after the project since these were collected in the past under different data sharing agreements. New cohort data collected in EPHOR (WP6,7) will become available in the Yoda data platform through the Toolbox (WP9).

New methods: Exposure-response analyses: Methods capable of handling multiple exposures in exposure-response analyses will be developed for WP5-7, including variable selection methods as originally developed for machine learning (e.g. penalized regression). Additional methods will be explored either identifying groupings in a data-driven way, or by forcing logical groupings of exposures [45], such as by chemical class using a battery of latent class and clustering approaches. For correctly handling complex exposure-time-response relationships (ETR), compartmental (multi-state) models, (two-stage) clonal expansion models, and exposure rate models have all been successfully applied, but it is not yet clear how they compare in terms of data requirements and inference. We will compile these methods, apply and compare them in the EPHOR mega cohort (WP5). In parallel we will investigate to what extent existing ETR models can be modified to allow for multiple exposures and nonlinear exposure-response relations, and to incorporate biological data to strengthen these models (effect markers, omics [46]). The agnostic analyses in the EPHOR mega cohort will involve multiple comparisons and therefore potentially suffer from false positive findings. Hierarchical regression will be used as general approach, including Semi-Bayes adjustment, that aims at improving the validity of standard maximum-likelihood estimates in the presence of multiple comparisons by incorporating similarities between the exposures of interest in a second-stage model [47]. We will further develop this method and apply this to the EPHOR mega cohort to identify new exposure-disease associations and use the outcomes within WP2 to evaluate and improve EuroJEM.

New methods: Artificial intelligence (AI) methods for automated and flexible coding of job titles for exposure assessment: Data mining will be applied to develop an expert system, which mimics the labour intensive process performed by human experts, for automated coding of free text occupational histories into conventional job codes, as needed in WP5. This work will build on the OPERAS project at UU (section 3.1.6), extending to different EU languages. The system will result in a decision support tool, where codes with low reliability will be flagged by the expert system to assure a final check by a human expert. Improved coding methods will also be developed for more flexible coding, allowing for different coding structures depending on the risk factor. We will expand on existing descriptive clustering approaches to map job descriptions and estimated exposures using previous expert assessments of exposure and develop candidate cluster labels into a common semantic vector space by using context-sensitive embeddings, such as Context2vec [48] and ELMo [49]. This will support the straightforward assignment of meaningful and exposure dependent descriptive labels to clusters of occupations. Context-sensitive embeddings allows us to learn a low dimensional but informative distributed vector representation of documents and phrases (words, terms, relations, events, etc.), which allows detection of semantic similarities between them. The number of labels (keywords) used for each cluster can subsequently be used for automated coding. This work will build on the RobotAnalyst project (section 1.3.1.11) and will be used in WP2.

New methods: Internal mechanisms and biological pathways connecting external exposures and health: In order to integrate external exposure, biological pathways, health outcome and impaired body functions, omics and biomarker output of WP3 will be used to map omics, exposure and effect data in WP6 and 7 onto qualitative and quantitative adverse outcome pathways (AOPs). This mapping involves the collection of data on molecular initiating events MEIs of AOPs, and AOPs themselves, of relevance to occupational health. The latter involves specifically the functional integration of information from gene, chemical, disease databases with relevant tools (e.g. GeneMANIA [50]) and results from text mining (INDRA, Big Mechanism, NaCteM, MMPaThiC, PathText, OpenMinted, section 1.3.1.11). This work leads to a set of qualitative toxicological causal (AOP) networks. Several subsequent modelling approaches are foreseen: 1) physiology based toxicokinetic modelling to link external exposure to biomonitoring/omics levels (WP6 and 7) to target organ concentrations, in particular at the site of the MIE; 2) quantitative description of the MEIs (e.g. Km value, Ki value, IC50 value), in relation to these predicted target organ concentrations to propose a likelihood of MIE/AOP activation within the case study from WP6 and WP7; and 3) use
of predefined AOP/toxicological networks to aid in the analysis of omics data to infer biological pathway based exposure-response relationships (e.g. Bayesian). This work will build on various previous/ongoing projects (HBM4EU, HEALS, CEFIC LRI projects) (section 3.1.11).

1.3.2.5 WP5 EPHOR mega cohort
The following research questions will be addressed: What are the most important working-life risk factors for the development of cancers, cardiovascular, respiratory, musculoskeletal, mental, metabolic and neurodegenerative diseases across the life course? Do working-life exposures (including occupational, lifestyle and SES) interact in their relation to NCDs? Are some subpopulations, such as gender based sub groups, more vulnerable? Can critical exposure time windows across the life course be identified or does temporal variation modify health effects? Can previously unknown working-life risk factors be identified? Can transgenerational effects of working-life exposures be observed in offspring?

This WP will build on the OMEGA-NET EU COST Action (described under 3.1.6) led by STAMI and ISGLOBAL. We will extend and further develop this unique inventory of European cohorts, with extensive information on employment and occupational exposures, to create a working-life exposome mega cohort (EPHOR mega cohort), resulting in the largest pooling of occupational cohorts ever undertaken. At proposal stage, through the consortium members, we have access to at least 40 cohort studies adding up to nearly 21 million subjects across different European regions and time periods (Table 1.3.3), which will be expanded during the project. In addition, we have access to at least 6 mother—child cohorts with occupational data on the mother during pregnancy and more than 2 million children (not shown). Innovative and de-centralized approaches for data storage and analyses will be used, based on the Yoda data management platform and DataSHIELD technology (WP4). Within Yoda, the EPHOR mega cohort will be combined with the newly elaborated EuroJEM (WP2), covering a multitude of workplace exposures and general life exposures, including both lifestyle, general life exposures and socio-economic status. Due to the large and unprecedented sample size, it will be possible to study multiple health outcomes including rare effects and vulnerable subgroups (including gender), as well as the effects of multiple occupational and general life exposures occurring either simultaneously or sequentially, and temporal variation of exposure occurring over the working-life (incl. critical time periods).

Table 1.3.3: Cohorts with occupational exposure data (occupation recorded at least twice) available to the consortium at EPHOR proposal stage. Some of these cohorts also have specific data on occupational exposures (data not shown)

<table>
<thead>
<tr>
<th>Cohort Name</th>
<th>Country</th>
<th>Available</th>
<th>Cohort type</th>
<th># subjects</th>
<th>Occup (≥2)</th>
<th>Health outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>DOC*X (Danish Occupational Cohort)</td>
<td>DK</td>
<td>AU</td>
<td>Reg</td>
<td>6.200.000</td>
<td>x x x x x x x</td>
<td>CVD Met</td>
</tr>
<tr>
<td>Finnish Nationwide Working-age Cohort</td>
<td>FI</td>
<td>FIOH</td>
<td>Reg</td>
<td>2.500.500</td>
<td>x x x x x x</td>
<td>CVD Met</td>
</tr>
<tr>
<td>Norwegian Working Age Cohort</td>
<td>NO</td>
<td>STAMI</td>
<td>Reg</td>
<td>4.000.000</td>
<td>x x x x x x</td>
<td>CVD Met</td>
</tr>
<tr>
<td>Norwegian 1967-1976 Birth Cohort</td>
<td>NO</td>
<td>STAMI</td>
<td>Reg</td>
<td>626.928</td>
<td>x x x x x x</td>
<td>CVD Met</td>
</tr>
<tr>
<td>AFA-CVD</td>
<td>SE</td>
<td>KI</td>
<td>Reg/occ</td>
<td>6.000.000</td>
<td>x x x x x x</td>
<td>CVD Met</td>
</tr>
<tr>
<td>New working-life, Sweden</td>
<td>SE</td>
<td>KI</td>
<td>Reg/occ</td>
<td>8.800</td>
<td>x x x x x x</td>
<td>CVD Met</td>
</tr>
<tr>
<td>Health 2000 cohort</td>
<td>FI</td>
<td>FIOH</td>
<td>Pop/reg</td>
<td>14.829</td>
<td>x x x x x x</td>
<td>CVD Met</td>
</tr>
<tr>
<td>Health 2011 cohort</td>
<td>FI</td>
<td>FIOH</td>
<td>Pop/reg</td>
<td>503.316</td>
<td>x x x x x x</td>
<td>CVD Met</td>
</tr>
<tr>
<td>The HUNT Study 1-4 (1984-2019)</td>
<td>NO</td>
<td>Request</td>
<td>Pop</td>
<td>1.000</td>
<td>x x x x x x</td>
<td>CVD Met</td>
</tr>
<tr>
<td>Constances</td>
<td>FR</td>
<td>INSERM</td>
<td>Pop</td>
<td>60.000</td>
<td>x x x</td>
<td>CVD Met</td>
</tr>
<tr>
<td>AH2012-18</td>
<td>DK</td>
<td>AU</td>
<td>Pop</td>
<td>10.000</td>
<td>x x x</td>
<td>CVD Met</td>
</tr>
<tr>
<td>ECRHS (International)</td>
<td>Int</td>
<td>AU</td>
<td>Pop</td>
<td>13.961</td>
<td>x x x x x x</td>
<td>CVD Met</td>
</tr>
<tr>
<td>EPIC-LIFEWORK</td>
<td>NL</td>
<td>UU</td>
<td>Pop</td>
<td>14.829</td>
<td>x x x x x x</td>
<td>CVD Met</td>
</tr>
<tr>
<td>Amigo-LIFEWORK</td>
<td>NL</td>
<td>UU</td>
<td>Pop</td>
<td>18.000</td>
<td>x x x x x x</td>
<td>CVD Met</td>
</tr>
<tr>
<td>GCAT</td>
<td>ES</td>
<td>Global</td>
<td>Pop</td>
<td>503.316</td>
<td>x x x x x x</td>
<td>CVD Met</td>
</tr>
<tr>
<td>Biobank</td>
<td>UK</td>
<td>Request</td>
<td>Pop</td>
<td>20.625</td>
<td>x x x x x x</td>
<td>CVD Met</td>
</tr>
<tr>
<td>Gazel</td>
<td>FR</td>
<td>INSERM</td>
<td>Occ</td>
<td>1.800</td>
<td>x x x</td>
<td>CVD Met</td>
</tr>
<tr>
<td>SMASH</td>
<td>NL</td>
<td>TNO</td>
<td>Occ</td>
<td>18.000</td>
<td>x x x</td>
<td>CVD Met</td>
</tr>
<tr>
<td>CODI</td>
<td>NL</td>
<td>TNO</td>
<td>Occ/Pop</td>
<td>10.000</td>
<td>x x x</td>
<td>CVD Met</td>
</tr>
</tbody>
</table>

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In addition to the evaluation of exposures which have been previously defined as known or suspected in relation to health and for which JEMs have been developed and combined (EuroJEM), a hierarchical modelling approach will be taken to identify potential previously unknown or non-suspected exposures. This will be done by first assessing the association between job title and NCDs and in a second step add EuroJEM based exposure factors to these models. For jobs for which EuroJEM does not explain the association between job and NCDs, probably unknown or non-suspected exposures are responsible (as they are not part of EuroJEM), laying the ground for new hypotheses. Further, we will perform more targeted analyses for respiratory health and shift work exposures to support the case studies (WP6, 7) with exposure-response data at the EPHOR mega cohort scale. We will combine these large epidemiological analyses based on data of several million employed persons followed-up in relation to multiple outcomes with two targeted exposome studies focusing on extensive exposure assessment, biological pathways leading to disease and impaired body functions (WP6&7). WP5 will collaborate intensively with WP6 and 7, but due to the limited lead time, analyses will be performed in parallel and will provide parallel and supporting evidence on respiratory disease and night shift work, respectively (Figure 1.3.8). Protocols for future studies converging on this parallel evidence will be developed in collaboration between these WPs and provided to the toolbox (WP9). Cohort data and exposure-response results will also be used as input into WP8 for simulations of study populations and for the development of health impact assessment tools, respectively.
1.3.2.6 WP6 Case study 1: Working-life exposome, lung function, and obstructive lung disease among men and women

The following research questions will be addressed: How does long-term and short-term working-life exposome affect lung function, asthma and COPD? Is this influenced by gender and age? What are key biological pathways and markers for exposure and respiratory health effects associated with the working-life exposome?

We will collect new data in subjects in existing cohorts with existing exposome data, providing the opportunity to study both long and short-term exposures in relation to respiratory health, e.g. lung function decline, including biological pathway analyses. The study population is based on two population-based cohorts (Figure 1.3.9) with abundant information on health including lung function, asthma and COPD, anthropometric measures, biological samples and life-long job histories with a planned follow-up in 2021: the European Community Respiratory Health Survey (ECRHS\[51\]) and the French Constances cohort\[52\]. 10 ECRHS and 2 Constances study centres from 7 European countries (Spain, France, Sweden, Norway, Estonia, Iceland and Denmark) and Australia will be included. Study coordinators are partners in EPHOR (UiB: included ECRHS centres; INSERM: Constances). Follow up of three ECRHS study centres has been funded (section 3.1.11). In EPHOR, 2500 subjects who participated in ECRHSIII 2010-12 and 1500 who participated in Constances in 2012-16 will be invited. A participation rate of 75% is expected, resulting in 3000 individuals with follow-up data. Follow-up will include, blood sampling, urine sampling, measurement of lung function (EasyOne spirometer), questionnaires (respiratory symptoms, occupational history since last follow-up). Long-term occupational exposure will be assessed using EuroJEM (WP2). Based on incidence data from ECRHS\[52\] combined with age of the cohorts (49-76y in ECRHS, 20-80y in Constances) at least 100 new asthma cases and 150 new COPD cases are anticipated at planned follow-up (2021). A subgroup will be selected for more detailed short-term (one week) external and internal exposure assessment based on disease status and current exposure (EuroJEM): 100 incident asthma cases, 100 incident COPD cases, and 200 controls with no current respiratory disease of which 150 have current occupational exposure to...
occupational particulate matter and 50 do not. New exposure data will be collected and analysed in collaboration with WP1. WP3 for short-term external and internal exposure effects respectively. Information on exposure mechanistic and health outcome data will be combined in complex models integrating external exposure, to biological pathway, to lung function and respiratory health (in collaboration with WP4). We will combine this evidence with the evidence from WP 5 and protocols for future studies converging on this parallel evidence will be developed (Figure 1.3.8).

1.3.2.7 WP7 Case Study 2. Exposome studies on shift work and health

The following research questions will be addressed: How does long-term and short-term working-life exposome among shift workers affect key body functions and ageing, in relation to the development of non-communicable diseases (NCDs) and mortality? Is this influenced by gender or age? What are key biological pathways for health effects associated with night shift in relation to other exposome factors?

We will collect new data, providing the opportunity to study both long- and short-term exposures in relation to key functions of disease and ageing and biological pathway analyses, in combination with the pooling of partial exposome information of several previous small scale shift work studies. The new exposome study on unusual (night) working hours will enrol and collect detailed information and extensive biological samples from 800 workers in Spain, Sweden and the Netherlands having worked day and/or night shifts for varying time periods (Figure 1.3.10).

The study will involve sampling in a new population in a car industry in Barcelona of long-term rotating male and female workers, new sampling from the Nightingale cohort in the Netherlands that includes both night and day shift female nurses\(^{[53]}\) (n=60,000), and sampling from the Athos cohort (Stockholm county council, n=60,000, \(\text{https://ki.se/en/imm/project-working-hours-and-health}\)).

Exposome protocols (WP1, external; WP3, internal) will be applied. The exposome protocol will also incorporate analyses to evaluate key body functions and ageing closely related to the development of NCDs and mortality through a combination of biomarkers, biochemical analyses, harmonized tests, clinical evaluations and questionnaires. These will include cognitive development, lung function, cardiometabolic parameters and metabolic syndrome, obesity, assays on neurodegenerative status, liver assays, mental health, and hallmarks of ageing\(^{[54]}\) including telomere attrition (in 400 subjects a full protocol will be employed including physical testing, for the other 400 a limited protocol will only include the biomarker based analyses). Information on exposure, pathway and outcome data will be combined to develop complex models integrating exposure, to impaired body functions, aging and disease outcomes (with WP4). In addition, three existing studies on night shift workers available to the consortium from Norway, Spain and The Netherlands (Norwegian Nurses cohort, HORMONIT and Klokwerk available to STAMI, ISGLOBAL and UU, respectively\(^{[55]}\)) will be included, for replication of study results. This will provide a paradigm for the incorporation of exposome data in connection with more classical approaches in occupational epidemiology to identify risks, quantify risks and personalize risks. We will combine this evidence with the evidence from WP 5 and protocols for future studies converging on this parallel evidence will be developed (Figure 1.3.8).

1.3.2.8 WP8 Impact assessment of the working-life exposome

The following study questions will be addressed: How can we incorporate the exposome concept and working-life specific health metrics into the models currently used to determine health and economic impact? Which objective criteria need to be in place in order to determine if exposome-based complexity is beneficial to improve health impact assessment and the effect of interventions?

Since no methods for impact assessment of exposome data in terms of multiple exposures and correlation structures exist a conceptual framework will be made. The current approach for the global burden of disease model\(^{[56]}\) will be used as the basis for transforming the single-exposure, single-outcome approach into a complex, multi-factorial exposure-outcome approach, taking into account correlations and interactions, including socio-economic status and incorporating information about differential exposures and susceptibilities for vulnerable populations, where

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available. Incorporation of work-specific health impact metrics, including working-life expectancy and working years lost, will build on previous work by FIOH\textsuperscript{56}. Development of the conceptual framework into an impact assessment model will be done based on simulations since the full EPHOR exposome-response evidence will not become available until the last phases of the project. The exposure, demographic and socio-economic profiles of the simulated cohorts will be based on data from WP2 and 5 and information obtained from the literature. For demonstrating the applicability of the impact assessment models to policy makers and occupational health practitioners, a set of hypothetical intervention scenarios will be developed (policy interventions, workplace interventions to control exposure, behavioural intervention etc.), with the benefit of stakeholder consultations (collaboration with WP10). In addition to estimating the impact of interventions on clinical health outcomes, concepts for impact assessment of exposome data using biological markers will be developed, incorporating concepts from the biological pathways (WP4,6,7). Such approaches would enable combination of health impact modelling with quantitative or qualitative evaluations of interventions, in relation to external exposures.

1.3.2.9 WP9 Working-life exposome toolbox
The research question addressed is: \textit{How can the data and methods developed by EPHOR be made available in a toolbox that can be used by stakeholders (health scientists, policy makers, and occupational health practitioners) to improve their understanding and management of the working-life exposome in relation to NCDs?}

The toolbox will be, in terms of IT format, a website hosted as part of the project website during the project. The data methods, and models from WP1-8 will be made available to the stakeholders

An interactive tool will be made for exploring and visualizing the exposome and exposure-response data. The tool may resemble the CAREX exposure and risk visualization tool developed in Canada (https://www.carexcanada.ca/). This tool will be developed based on stakeholder consultations to align with their specific needs.

Methods and models for collecting, storing and analysing working-life exposome data developed in WP 1-8 will be made available to scientists outside the consortium. These methods include protocols, proof of concepts, a decision support and an adverse outcome visualization tool and tutorials. In addition, two online searchable databases will be made available to scientists: EuroJEM and an inventory of EU cohorts with occupational data. Impact assessment methods and guidance will be made available to policy makers. A selection of the methods for collection, storage and analyses will be made available to occupational health practitioners. These methods will be further developed into practicable protocols, demonstrations and software tools. The involvement of different groups of occupational stakeholders during the development of all aspects of the toolbox, ensures alignment with the values, needs and expectations of these stakeholders. Responsible research and innovation (www.rri-tools.eu/nl/about-rri) are a ‘cross-cutting issue’ in Horizon 2020 research, promoting ‘science with and for society’ and bringing research to the wider public. Through the working life exposome toolbox, EPHOR will bring exposome science to policy makers, occupational health practitioners and even individual workers will be explored. Related trends like citizen science and the quantified self, which are accelerated by technological innovation, offer new possibilities for exposome research. The tools will also be shared through a common European Human Exposome Network platform.

1.3.2.10 WP10 Dissemination and exploitation
Besides dissemination and exploitation (described in section 2) this WP involves stakeholder consultations that are needed for the developments in WP1 (wearable sensor system), WP8 (impact assessment modelling) and WP9 (working-life exposome toolbox development). Stakeholder consultations will include both face-to-face consultations in the form of discussion tables and symposia as well as questionnaire based consultations in order to prepare the face to face consultations with the stakeholder groups identified under 1.3.1.10.

1.3.3 Gender dimension
The gender aspect is specifically considered in EPHOR. There is some evidence that work-related risks to women's health have been underestimated. This underestimation may be due to differences in exposure levels for men and women performing the same job but also to differences in vulnerability between males and females. A gender-neutral approach to female worker participation when female workers started to increasingly enter the job market has contributed to less attention and resources being directed towards specific prevention of work-related risks experienced by women. Within EPHOR, differential exposures within the same job (WP2) and differences in vulnerability for acquiring health effects due to working-life exposome (WP5-7) will be specifically investigated, providing the knowledge base for prevention that is taking the gender dimension into account.

1.4 Ambition
An overview of the ambition of EPHOR during and beyond the project is given in Figure 1.4.1
1.4.1 Ambition of developments within the EPHOR project

1.4.1.1 The working-life exposome

**Short state-of-the-art:** The exposome concept has been around for over a decade. Exposome is distinguished from traditional epidemiologic approaches by three characteristics: 1) exposure assessment of more complete and individual-level exposure data compared to previous single exposure estimates; 2) expanded exposure assessment across multiple exposure domains, in contrast to single exposures in a single domain; 3) the integration of external and internal exposure data; and 4) the use of the resulting high-dimensional information in combination with existing biological knowledge to obtain multiple exposure–response relationships, vulnerable subgroups and individuals, and biological pathways.

**Gap:** The implementation of the exposome concept into human health studies has been limited due to a lack of methods and infrastructure for the comprehensive and individual level exposure assessment. In addition, study designs and analytic methods lack that accommodate specific aspects of the exposome, such as high-dimensional external and internal exposure data and multiple windows of vulnerability. In addition, working-life exposures have been largely neglected until now.

**Beyond state-of-the-art:** Within EPHOR, two complementary approaches for studying the working-life exposome will be developed and applied: one based on making use of the rich resource of existing cohort studies with working-life data and one making use of recent innovations for acquiring new high resolution external and internal exposure data. Both approaches require specific developments for collection, storage and analyses of exposome data. Combination of these approaches derives complementary working-life exposome insights uniquely advancing the working-life exposome knowledge base. The following paragraphs detail some more specific innovations beyond the state-of-the-art to be delivered by EPHOR.

**Figure 1.4.1:** Overview of the ambition during the EPHOR project and beyond

1.4.1.2 Assessment of working-life external exposures

**Short state-of-the-art:** Methods for measuring occupational exposures mainly rely on active (air pump in combination with capturing device) or passive diffusion methods. Subsequent laboratory analyses, to produce a time-weighted average concentration, e.g. 8hrs, involve a large part of manual handling by trained personnel. These methods make exposure sampling burdensome for both field workers and study subjects and laborious with many logistical challenges resulting in high costs. This limits the number of samples and the amount of contextual information present in the collected data. Due to the challenges above, taking exposure samples on a large scale in cohort studies is not feasible and the use of direct measurements in cohort studies is very limited. In some cases, mostly in industry- or occupation-based cohorts, a limited number of exposure measurements are taken and generalized over a limited number of “similar exposed groups” (SEGs), e.g. based on job title. Due to the retrospective character and size of most of the cohort studies, JEMs, expert judgment or decision rules are the norm for exposure assessment. These assessments can be both qualitative and quantitative.

**Gap:** The SEG approach, both in terms of applying JEMs and using exposure measurements, stands in clear contrast with the complexity of workplace with heterogeneity in exposure between workers within the same job, as well as temporal (day-to-day) variability in exposure. Ignoring this heterogeneity may result in exposure misclassification.
Especially given the changing world of work, exposure situations will become more and more dissimilar. In addition, the methods currently available usually provide time integrated levels over one work day and are not suitable for the simultaneous collection of exposures outside of work.

**Beyond state-of-the-art 1**: EuroJEM will include all types of occupational exposures, including chemical, physical, ergonomic, work organizational, and psychosocial aspects but also non-occupational aspects such as lifestyle. EuroJEM will also consider regional (across EU), gender-, and time-related variability in exposure. For ensuring usability in future applications beyond EPHOR, EuroJEM will be dynamic, with protocols updating EuroJEM with the most recent knowledge and data, based on data mining.

**Beyond state-of-the-art 2**: The maturation of lightweight, miniaturized and technically advanced (low-cost) sensors has the potential to transform exposure assessment technologies in the occupational setting. These new technologies are expected to change the landscape of traditionally used time-integrated sampling methods by enabling the collection of vaster amounts of working-life exposome data of not only groups of workers, but also of specific individuals in a population, due to the lower (operational) cost and the potential for sensors placed on individuals and carried both in the workplace but also outside the workplace. In addition, sensor data can be collected for prolonged periods of time (in contrast to the 8hrs traditionally sampled for occupational exposures) and will provide data with a higher sampling resolution in time providing insights in exposure patterns inside and outside the workplace over weeks or months. Although real-time sensor equipment has already been applied in research studies aimed at managing acute safety hazards such as toxic substances in hazardous occupational environments (e.g. confined spaces) and in exposome studies focusing on e.g. air pollution, the application of sensors for assessment of exposure in the context of the working-life exposome is in its infancy. Within EPHOR a sensor system will be developed that is able collect, store and analyse a combination of relevant working-life exposures. This system will be tested and subsequently applied in both population- and industry-based cohort studies. The system, including specific protocols, will be made available in the toolbox for exposure scientists and epidemiologists, but also for occupational health practitioners which are also facing the limitations of current exposure sampling methods. The wearable sensor system will provide occupational health practitioners with the technology to collect the large scale and individual level high resolution exposure data needed to assess when, where and why exposures occur, providing the basis for (individualized) exposure interventions.

### 1.4.1.3 The influence of external exposures on biological pathways reflecting exposure or disease

**Short state-of-the-art**: Biological pathways are currently being explored to provide estimates of internal exposure. This involves single-molecule based biomonitoring/analytical chemistry to, one-by-one, identify and characterize chemicals (parent compounds) associated with working-life related exposures. Aside parent compounds, markers that reflect metabolism are used to estimate (internal) exposure. Examples are SPMA for benzene and 1-OH-pyrene for polycyclic aromatic hydrocarbons. Some markers reflect early signs of internal exposure and health damage e.g. haemoglobin adducts from the carcinogen acrylamide. Various recent/running EU projects are concerned with biomonitoring and/or early omics-derived markers/signatures of changing health status and disease in relation to exposure. Examples are HEALS (metals, pesticides, endocrine disruptors), HBM4EU (e.g. perfluoro compounds, disiocyanates); EXPOsOMICS (air and water pollution) and the recently started OBERON (endocrine disruptors). These projects mainly focus on the general population, or specific vulnerable groups (e.g. children), but (again) largely neglect the role of occupation/working-life.

**Gap**: The effects of the totality of exposures individuals are faced with during their working-life (e.g. chemical, mechanical, psychological stress) and interactions with lifestyle related factors (incl. diet, physical activity, sleeping patterns) are unknown with respect to biological pathways and markers reflective of early signs of changing health and disease development.

**Beyond-state-of-the-art**: Within the case studies, specifically addressing the working-life period, agnostic and targeted omics and multi assays together with bioinformatics and pathway-based approaches will be used to: (1) identify and characterize internal biomarker/marker signatures that reflect multiple simultaneous external working-life related exposures; (2) identify biological markers and pathways indicative of early exposome-related health damage; and (3) identify causal markers that directly link exposure to disease outcome, mechanistically. Beyond state-of-the-art is also multidisciplinary data integration e.g. integration of adverse outcome pathways data concepts from the toxicological domain within the analysis and interpretation of biological pathway data from omics technologies applied on working life exposome data.

### 1.4.2 Ambition beyond the EPHOR project: development into TRL 9

Working-life exposures will no longer be neglected and will be a part of all future exposome studies in adult populations. This involves the full and cost-efficient implementation of the working-life exposome in any type of increasingly larger human studies to understand any external exposure scenario in relation to any short/medium/long-
term health endpoint. Immediately beyond EPHOR, the knowledge and methods developed will be taken to a TRL6 and 7 level, involving their further and wider application in case studies for: 1) verifying the findings on multiple exposure-multiple response relationships at a wider scale; 2) follow-up studies based on the combined results of the EPHOR mega cohort and targeted exposome case studies within EPHOR on respiratory health and shift work; and 3) new targeted case studies unveiling more detailed exposure-response associations for different disease end-points and exposure situations. In addition, TRL6-7 will involve the initial implementation of the working-life exposome within occupational health practice, e.g. the application of wearable sensor systems for exposure assessment or the application of newly identified biomarkers for identification on people at risk for developing health effects. Ultimately, TRL8 and 9 include the experimentation of full deployment, and deployment itself, of the working-life exposome concept in future science and (occupational) health practice applications. The ultimate innovation will be efficient and cost effective acquisition of complete and accurate individual level exposure data on all relevant working-life exposures. This is achieved by deployment of automated labour extensive and fully data-driven exposure assessment methodologies, based on all available state-of-the-art exposure data and knowledge or based on the newest sensor technology, e.g. multiparameter sensors for internal and external exposome assessments, or both. Data will be automatically combined in a database and will be available for data-mining and analysis by health scientists. Based on these studies the interrelation between urban and occupational exposures, lifestyle factors and socio-economic parameters (i.e. the exposome) in their association with health, including individual susceptibility and biological pathways leading to physiological changes will be fully understood. This will enable fast health and economic impact assessment, taking into account vulnerable sub groups and life stages for policy making, for any type of foreseen exposure scenario. Within occupational health practice, deployment of the working-life exposome concept will entail the fully automated assessment at individual level of exposures and (early) health effects in (near) real-time, taking vulnerability into consideration. These innovations will involve the integration with the Internet of Things enabling personalized or group-based automated exposure and risk management at the workplace (workplace health management dashboard dash boards) jointly with personalized advice systems (e.g. personalized coaching apps) to prevent interactions with general life exposures in relation to health.

References


2. Impact

2.1 Expected impacts

2.1.1 Contribution to the impacts mentioned in the work programme

Innovation in environmental health sciences, in particular for external and internal exposure assessment and data management

External exposure assessment in environmental health sciences, in particular occupational environmental health sciences, are still predominantly based on time-consuming and expensive field work and laboratory analysis in combination with expert judgment. Moreover, internal exposures are mostly neglected. With the currently available research tools for exposure assessment, data handling and analyses, only single exposure - single health outcome relationships can be studied. Complex associations between exposures and health effects, including biological pathway insights will not be revealed. Revealing these associations requires a set of sophisticated research tools and knowledge that is currently not available.

EPHOR will deliver sophisticated technologies, tools and methods for collecting, storing and analysing accurate individual- or subgroup-level working-life exposome data in a standardised and automated way (described below). With these tools, the research approach will shift from a ‘one exposure-one disease’ hypothesis-driven approach to a data-driven integrative approach revealing the complex picture between multiple exposures and health effects. It will open up a wealth of new research directions in (occupational) health sciences. This shift can be clearly demonstrated by the ambitious goal of the EPHOR project, which is to apply novel tools for pooling, mining and analysing existing EU cohorts with nearly 21 million subjects (EPHOR mega cohort) to identify new associations between (combinations of) known and unknown working-life exposome risk factors and NCDs. This approach will include the identification of vulnerable life stages and population subgroups (e.g. based on gender, region or job title). Another ambitious goal of EPHOR is the identification of links between exposure and biological pathways (i.e. AOPs: Adverse Outcome Pathways), including discovery of biological markers of exposure and/or early effects and role of these in disease development. For this purpose, high throughput external exposure data generation will be combined with internal exposure (omics, non-invasive monitoring) measurements.

The ultimate innovation will be that groups of workers will be equipped with multiparameter sensors for internal and external exposome assessments, to assess real time personal exposures/early effects. These assessments will be automatically combined with additional relevant data, such as job history, in a database and will be available for data-mining and analysis by health scientists. With the tools delivered by the EPHOR project, this futuristic view comes a step closer. Specifically, EPHOR will deliver the following working-life exposome research tools:

- A searchable database with at least 40 existing European cohorts (including a link to the data in the Yoda database that has been generated in the EPHOR project) with data on the working-life exposome. These cohorts contain a wealth of data on occupational histories and more general population data from nearly 21 million subjects, which are available in existing European occupation-, industry-, and population-based cohorts. These data will enable, for the first time, the agnostic exploration of (combinations of) risk factors in relation to multiple NCDs, including rare exposures and rare diseases and the identification of vulnerable life stages and population subgroups (e.g. based on gender or socio-economic context) in which these risk factors result in a more pronounced or a different health effect.

- EuroJEM: A dynamic EuroJEM (Job-exposure Matrix) to enable, for the first time, harmonised assessment of a wide range of occupational and related non-occupational exposures of subgroups (e.g. based on regions, type of industry, gender or age) when pooling cohorts at the EU level. This much larger scale of exposome studies will speed up the understanding of working-life health hazards by assessing multiple exposures in relation to disease, even for subgroups and specific lifetime stages.

- Data and text mining tools: Protocols for text mining to automatically code job titles, and protocols for mining currently unused data sources for more optimal exposure assessment and updating the EuroJEM even after EPHOR has ended.

- Data analysis tools: Protocols for analysis of multiple exposures-responses relationships to understand, in populations, multiple health effects and diseases resulting from combined exposures.

- High throughput data generation tools: A flexible system, developed towards commercialization by VTEC, with which single parameter sensors can easily be combined to generate customized, wearable, multiparameter sensor systems to be used for assessing both occupational and non-occupational exposures. OWL have developed a system for non-invasive collection/analysis of VOCs in exhaled breath. This technology will be further developed into a non-invasive device for detection of biomarkers of exposure and disease. The system will be commercialised by OWL.
• **Mechanistic biological pathways** tools to connect external exposure with omics and biomarker data to determine the internal impact of exposures. These tools are also improved by using existing (text-mined) toxicological, biological and clinical knowledge.

• **Yoda database** sustainable and capable of storing and assisting the analysis of heterogeneous and high-dimensional working-life exposome data. Includes capabilities for decentralized data analyses needed for existing cohort data that cannot be ‘physically’ brought together in a single location due to standing privacy and ethics agreements on these cohorts. The data generated within EPHOR will become publicly available through Yoda.

All working-life exposome research tools for health scientists, as described above, will become available in the toolbox that will also contain tools for policy makers and occupational health practitioners (hygienists and physicians).

**Enabling researchers and policy makers to continuously include new knowledge in the policy making process by using the toolbox to generate data and information**

EPHOR will create a new and growing scientific knowledge base on the working-life exposome in relation to NCDs, providing the basis for data-driven and effective policy making. Scientists will directly make use of the knowledge base in the policy making process. This, through their role in expert groups that advise policy makers on guidance and limit values, e.g. the joint task force of RAC (Risk Assessment Committee ECHA, which manages the REACH process) and SCOEL (Scientific Committee on Occupational Exposure Limits). In the future, scientifically proven disease mechanisms and early markers of disease will enable more individualised prevention of disease by identifying individuals at risk for developing disease and may form the basis for setting more accurate exposure guidance and limit values.

Apart from the above described tools for scientists, the toolbox will contain valuable tools and methods for generating direct input data for policy makers:

• **Interactive visualisation tools for occupational exposure and disease** will make available data on exposure and exposure-response associations, e.g. showing per gender, job title, country and/or region. The tool will visualise this information in maps, graphs or tables by combining a variety of search terms, e.g. job title, gender or region, and therefore can generate new insights on exposure levels and the burden of disease of particular subgroups.

• **Health impact- and economic impact assessment tools** to assess the effect of the working-life exposome on the burden of disease and associated costs and to compare the effects of different intervention scenario’s. For impact assessment, input data are needed on exposures and exposure-response associations. The information collected during the project that is made available via the interactive visualization tool can be used as input.

The toolbox will also be invaluable for **occupational health practitioners**. Besides the interactive visualisation tool described, the toolbox will contain protocols adapted to their specific needs for external and internal exposome data collection and interpretation (wearable sensor systems; (non-invasive) testing of biomarkers). These practical tools will enable the practitioners to develop effective and data-driven workplace interventions and exposure management strategies at the population-, subgroup-, or even individual level.

The toolbox will remain available for all stakeholders after the project and kept up to date by adding new tools and protocols. See non-commercial exploitation under 2.3.1.3 These updates will be the responsibility of the host of the toolbox. Moreover, we aim to update the interactive visualisation tool for occupational exposure and disease with the newest data and also add burden of disease data (TNO will be in the lead and will attract funding to make this possible).

**Better prediction of disease risk by acquisition of new knowledge on the influence of external exposures on biological pathways at different life-stages and identification of early signs of health damage caused by environmental factors**

EPHOR will identify early signs of health damage caused by working-life exposures on the basis of disturbances in biological pathways. Their role in the association between the working-life exposome and key health endpoints and NCDs, will be clarified. With focus on shift workers, respiratory exposures, in relation to lung function, metabolic function and respiratory diseases. This will allow for the identification of vulnerable subgroups of workers with increased disease risks. Novel omics approaches in EPHOR, e.g. combination of cfDNA and proteome analysis in exhaled breath condensate and VOC metabolites in exhaled breath, will contribute to non-invasive ways of identifying these early signs. Through a targeted dissemination strategy, these associations and methods for non-invasive monitoring will be brought to the attention of stakeholders such that measures can be taken to protect vulnerable groups.
2.1.2 Other impacts

- **Improved health of EU citizens, savings on health care expenditures and socio-economic costs.** EPHOR will identify risk factors for developing NCDs in all workers and in vulnerable subgroups. These risk factors include complex interactions of occupational and non-occupational origin and, at present, unknown exposures that would never have been identified without the sophisticated research tools from EPHOR. As the research tools will stay available after the project, the knowledge base on working-life risk factors is expected to increase rapidly. Based on the increased understanding of these, policy makers and occupational health practitioners can use the toolbox to protect (vulnerable) workers from hazardous exposures. This protection will reduce NCDs and eventually lead to a reduction of healthcare and other socioeconomic costs, e.g. due to absenteeism.

- **EPHOR will stimulate innovation by SMEs and industry** in e.g. the area of sensors, biomarker tests and diagnostics and IT/data analysis for assessing exposures and early responses. Ultimately leading to do-it-yourself apps for EU citizens/workers and occupational hygiene dashboards for occupational health practitioner. See section 2.3.

- The web-based risk assessment tools and protocols in the toolbox will **improve the capacity of SME and self-employed workers to put effective and efficient risk assessment in place** because health risk assessment procedures likely become simpler and less costly in the end. Microenterprises represent almost 93% of all enterprises in the EU. Only 69% of microenterprises declare that they perform regular occupational safety and health risk assessments (against 96% for larger enterprises). This is not because they are not willing to protect their workers, but is related to limited financial, technical and human resources, as well as to a lack of awareness and expertise. In addition, microenterprises may consist of workers being self-employed which cannot be monitored through their employer. All stakeholders, including the enterprises themselves, agree that making exemptions for SMEs regarding proper safety and health risk assessment is not the right approach, as it may potentially lower the protection level of their workers.

- At the same time, there is a trend towards a decreasing acceptance of industrial risks within the EU. This potentially results in a strive towards complete risk avoidance by downward adjustment of exposure limits. To accommodate with these lowering limits, high costs for industry may develop. In line is a recent statement made by a company in an ECHA document summarizing the collected comments on a new proposal for limit values for benzene in the workplace: “Routine personal exposure monitoring of workers at the petrochemical complex indicate that it would not be possible to comply with the proposed exposure limit changes without significant investment and changes in methods of working. Without the intention here to neglect the importance of evidence-based quantitative exposure/risk assessment, this may lead to loss of jobs in Europe because of companies leaving Europe for less stringent continents”7. EPHOR will result in a better understanding of the exposure risks and will enable industry to take **more effective science-based measures**. This avoids overexposures because of better exposure assessment tools, while at the same time preventing being costly overcautious. In turn, this will **contribute to the preservation of industrial activities within Europe**.

- Contribution to the **UN Sustainable development goals** for 2030. EPHOR will result in new policies and preventive actions to improve safety during working-life and herewith contributes to the following SDGs:
  - **SDG 3.9.** A substantial reduction of the number of deaths and illnesses from hazardous chemicals and air, water and soil pollution and contamination by 2030. This is exactly what EPHOR aims at: EPHOR will identify risk factors and facilitate the development of new policies and measures to protect the EU workforce from hazardous exposures, thereby reducing mortality and morbidity.
  - **SDG 8.8.** Protect labour rights and promote safe and secure working environments for all workers, including migrant workers, in particular female migrants, and those in precarious employment. EPHOR will secure working environments by implementing new policies and measures to protect health of the EU workforce. EPHOR will deliver tools for more individualized exposure/risk assessment. These are needed for precarious working conditions in which people’s exposure circumstances become more and more dissimilar and a ‘one size fits all’ risk assessment approach as currently taken does not suffice.
  - Within the frame of the European Human Exposome Network, EPHOR will contribute to a better prediction of disease risks by acquisition of new knowledge on the influence of external exposures on biological pathways at different life-stages

2.2 Barriers and risks

The EPHOR project delivers new knowledge for policy development, such as new guidance, limit values or even new concepts for external and internal exposure levels. However, policy making is a time-consuming process and the adoption of novel approaches will last at least 5-10 years. The challenge will be to get companies and occupational health practitioners to implement working-life exposome-based interventions before they are legally obliged to do
so. Development and implementation of new interventions and procedures will initially increase the costs. However, in the longer term, the investments will result in economic benefits because of less absences and less incapacitated workers. Forerunner companies, that luckily exist and with whom EPHOR partners are already in contact, will be aware of these longer term economic benefits and feel responsible for their workers health. They will implement new safety measures on a voluntary basis. However, other companies may fall behind until they are legally obliged by new policy.

Privacy, confidentiality and unclarity about ownership of personal (health) data are major concerns, which could hamper implementation of exposome assessments. These concerns are becoming increasingly scrutinized at national and international levels, e.g. for personalized medicine. Exposome-based prevention can be considered as personalized prevention and, as such, extends the scope of personalised medicine. Therefore, it will deal with the same concerns. Large-scale implementation of exposome assessments can only be realized when these concerns are clarified, and users have confidence in personal data protection. As the field of personalized medicine is ahead of exposome-based prevention, EPHOR is confident, however, that timely solutions will be ready (e.g. https://www.dtls.nl/fair-data/personal-health-train/).

A data privacy/ownership issue specific for the working-life exposome results from the fact that workers would need to be monitored not only at the working place, but also outside work. Many workers will strongly believe that employers should not be informed on their private situation. They may be reluctant to wear sensors that provide private life data to their employer. Also, disclosing data showing vulnerability towards certain working conditions may promote distress of becoming unemployed. It is also expected that some individuals do not want to know their individual exposure-related disease risks, and lack willingness to undergo exposome measurements. Especially in case where risks are either unavoidable (genetic predisposition or disease has already progressed), or invoked by lifestyle factors that are either impossible or difficult to adapt from a behavioural perspective. However, many of the occupational exposome risk factors are amendable and therefore very suitable for early detection.

The exposome approach fits in with the increasing attention for preventive health care. However, a shift from curative towards preventive health care faces numerous challenges, including the reshaping of current health care models. Specifically, for the working-life exposome, this requires collaborative models between general- and occupational health practitioners, workers, employers and health insurers. In particular, whenever the costs associated with exposome assessments and resulting health advices need to be accommodated. The data, impact assessment models and tools generated by EPHOR will facilitate effective communication between these professional groups and contributes to the creation of such collaborative models.

2.3 Measures to maximize impact

2.3.1 Dissemination and exploitation of results

The dissemination and exploitation strategy will be defined within the dissemination and exploitation plan (WP10). The dissemination section of the plan will identify: outputs to be disseminated, target audiences, appropriate communication tools and channels to reach target audiences, key messages to be ascertained, frequency of dissemination, responsible Partners for dissemination actions. A first outline of the plan is presented in Table 2.2.1. The first version of the plan will be finalized in month 6 and this version and yearly updates will be sent to the consortium partners for input and subsequently to the General Assembly for approval. The yearly updates will be included in the periodic and final reports and will contain a list of completed and planned activities. At the end of the project, a final exit version will outline a strategy for post-project dissemination.

2.3.1.1 Dissemination

As EPHOR has broad and varied implications for multiple stakeholder groups, their early and systematic engagement will be key to successful implementation of the knowledge, tools and methods that will result from the project. Therefore, EPHOR will implement a rigorous communication and dissemination strategy, the objectives of which are:

- To engage all consortium partners in the planned process of awareness raising that should occur throughout and beyond the duration of the project;
- To build awareness of the project outputs and to ensure that the outputs are visible to and understood by all relevant stakeholder groups;
- To support community building by ensuring that target audiences receive information appropriate to their needs, thus reinforcing a wide network of interested stakeholders;
- To foster societal and economical interest to effectively translate the knowledge generated by the project into new technologies and products to the advantage of the stakeholders.

The dissemination approach will be adjusted to the target audiences, specifically:

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• Employers and employer organizations;
• Employees and employee organizations, general public;
• Occupational health practitioners, hygienists and physicians (organisations)
• National- and EU policy makers in the area of occupational health;
• SMEs and industry in the area of sensors, IT, big data and bioinformatics, health apps, biological monitoring and diagnostics;
• Scientists, e.g. exposure assessors, epidemiologists, toxicologist.

2.3.1.2 Available tools for dissemination
In WP10, a wide variety of dissemination tools and channels will be available to ensure awareness of all stakeholders with the project goals and results:

- A distinctive **project logo** and house-style templates for all documents and presentations used for dissemination will be developed to increase familiarity with the EPHOR project. These templates will also include appropriate reference to EU funding.
- A **website** with the project goals, methodology, news items, results, events and links with relevant organisations. During the project, the toolbox will be hosted as part of this website.
- **Scientific publications** in gold and green open-access, peer-reviewed journals and direct dissemination of scientific publications through the EPHOR website.
- **Oral- and poster presentations** at (inter)national conferences, incl. International Commission on Occupational Health (ICOH), International Epidemiology in Occupational Health (EPICOH), International Society for Exposure Science/Epidemiology (ISES/ISEE).
- **Scientific symposia, sessions, workshops for scientists**, linked to (inter)national conferences during which different aspects of the project will be presented in a coherent way.
- A dedicated **LinkedIn** account to present regular updates of the project.
- **Articles** will be written in specialized magazines (e.g. directed at policy makers, occupational health practitioners or industry). These are often at the national level, in local language, including infographics.
- **Press release in national media** that will be reached through the consortium partners, e.g. via universities press offices.
- Two **project leaflets** will present the main elements of the project (first leaflet, to create awareness), and its achievements (second leaflet) for distribution at sessions/symposia where project partners will be present and at the final stakeholder workshop.
- During the project, 3 **stakeholder workshops** will be organised for policy makers, occupational health practitioners, employees, workers and employers, where input will be requested with respect to the features of the toolbox and the development of the sensor system. This will not only ensure that these will optimally fulfil the user needs, but it will also raise awareness on the future availability, thereby stimulating their use.
- **Final stakeholder workshop** to present the results and to demonstrate the toolbox to the stakeholders, specifically employees and workers (organisations), employers (organisations), occupational health practitioners and policy makers. Discussion sessions will be organised to encourage interaction. This will include a discussion session with interested parties of the EU Parliament (Committees, rapporteurs).
- **European Human Exposome Network** website to jointly disseminate the findings of the nine projects funded in the network. This will increase visibility and thereby impact. Within the European Human Exposome Network a joined dissemination and stakeholder strategy will be developed to support and strengthen each other and the joined European Human Exposome Network. This is described in WP 12.

#### Table 2.3.1: Outline of the dissemination plan.

<table>
<thead>
<tr>
<th>Stakeholder</th>
<th>Dissemination goal</th>
<th>Instruments</th>
<th>Anticipated impacts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Employees and workers (organizations), general public</td>
<td>Clarifying the relevance of the working-life exposome and its relation to health; engaging them during study design phases of the project to create awareness and possible interest in participation. Presenting project results.</td>
<td>Website, LinkedIn, press releases, project leaflets, final stakeholder workshops</td>
<td>Increased awareness on exposome and health; Empowerment; Increased willingness to accept exposome technologies, e.g. sensors for assessing working-life exposures and (early) health effects and to take preventive measures. The final impact will be enhanced health.</td>
</tr>
<tr>
<td>Employers (organizations)</td>
<td>Clarifying the relevance of the working-life exposome and its</td>
<td>Website, LinkedIn, press releases, final</td>
<td>Increased awareness of the working-life exposome; Economic</td>
</tr>
<tr>
<td>Stakeholder</td>
<td>Dissemination goal</td>
<td>Instruments</td>
<td>Anticipated impacts</td>
</tr>
<tr>
<td>-------------</td>
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<td>--------------------</td>
</tr>
<tr>
<td></td>
<td>relation to health and economic implications; Presenting project results.</td>
<td>conferenc stakeholders workshop</td>
<td>benefits (less sick leave); Improved health contributing to keeping an ageing workforce resilient and productive.</td>
</tr>
<tr>
<td>Occupational health practitioners</td>
<td>Presenting new (combined) risk factors in the working-and general environment; Raising awareness on the availability and use of new sensor systems for exposure assessments and protocols for assessment of biomarkers for early health effects of working-life exposures; Presenting the toolbox;</td>
<td>Website, LinkedIn, Articles in specialized magazines and (medical) journals, conference presentations, project leaflets, final conference, stakeholder workshops</td>
<td>Implementation methods for exposure and risk assessment and of protective procedures and measures at the workplace; shifting towards a concept for the totality of worker health</td>
</tr>
<tr>
<td>National- and EU policy makers</td>
<td>Presenting results on the health risks of working-life exposures; Raising awareness on the availability of the toolbox to enhance the policy making process.</td>
<td>Website, LinkedIn, articles in specialized magazines, final conference, stakeholder workshop</td>
<td>New policies for health and safety at the workplace</td>
</tr>
<tr>
<td>SMEs and industry developing technology</td>
<td>New opportunities for innovation</td>
<td>Website, LinkedIn, articles in specialized magazines, attendance at trade fairs, project leaflets.</td>
<td>Innovation; Strengthened competitive position of EU industry, see below (Market)</td>
</tr>
<tr>
<td>Scientists</td>
<td>Presenting new scientific knowledge on the working-life exposome; Raising awareness on the availability of the toolbox.</td>
<td>scientific publications /presentations at conferences, symposia and workshops. Website, LinkedIn, project leaflet</td>
<td>Improving scientific understanding of the (working-life) exposome; Innovative approaches for exposome research making use of existing data and collecting new data; ensuring European leadership in world-wide exposome research.</td>
</tr>
</tbody>
</table>

**2.3.1.3 Exploitation**

The exploitation section of the dissemination and exploitation plan will describe how the project deliverables can be (commercially) exploited. Three main areas for exploitation of results have been identified: non-commercial exploitation, generic commercial exploitation and commercial exploitation by EPHOR partners. Awareness raising on the opportunities for exploitation will be based on the dissemination strategy described above. Agreement and future exploitation will be discussed during the project lifespan.

**Non-commercial exploitation:**

A sustainable toolbox for policymakers, health scientists and occupational health practitioners. During the EPHOR project, the toolbox will be placed onto the EPHOR website. The sustainability of the toolbox is guaranteed because TNO is willing to host the toolbox as part of their Exposome Programme after the EPHOR project. However, also other options will be investigated, specifically hosting by EU OSHA and hosting by one of the partners as a commercial exploitation. A procedure for updating the toolbox will be developed during the course of the project, involving peer-review by WP leaders to assure scientific quality.

The anonymized cohort data generated in the EPHOR project will be stored in the Yoda data management platform. Yoda is the UU institutional research data repository, and is registered as such with re3data.org. The data will become available to the research community through a link in the toolbox.

**Generic commercial exploitation.**

Occupational risk factors both existing and new, identified in the EPHOR project will offer SMEs and industry in different sectors a wealth of new opportunities for innovation. Furthermore, the tools developed in the project will speed up the identification of additional risk factors after the project. Examples of innovative products for which the EPHOR project will lay the foundation are customizable wearable sensor systems for multifactorial personal exposure measurements and non-invasive breath tests and biomarker tests for assessing exposures and health.
early health effects. Ultimately, non-invasive biomonitoring of exposures or effects may also be incorporated in multiparameter wearable sensor systems, providing also the possibility to monitor fluctuations in these internal markers (as opposed to the snapshots taken now). In addition, IT companies can develop dashboards and apps for monitoring and managing working-life exposures. These interfaces can provide direct feedback to occupational health practitioners or workers, based on exposure data collected with sensor systems or non-invasive monitoring of exposure or early markers of effect. This feedback could, for example, include warnings and recommendations regarding the working life exposome and health of the end user. Several IT companies currently offer dashboards for industrial process and work flow optimization based on sensor systems and the IoT, ‘connected worker or connected workplace’ type products. The results of this project will enable broadening the scope of these products into the field of health and safety. In addition, more individualized personal apps or dashboards may be developed for self-management of both work and related non-work related exposures.

**Commercial exploitation of project results by the project partners**

LIFE targets the eHealth and health app markets focusing on occupational health in regard to the exposome and aims to provide a new generation of science-based models and tools. Based on new, non-invasive biomarkers and biological pathways identified in the EPHOR project, LIFE envisages to develop, beyond EPHOR, a mobile app that has access to relevant user data and will supply warnings and recommendations based on the user’s internal and external exposome in their working-life. These will relate to safety at work, diet, habits, exercise, etc. and take into account changes in their working-life environment and thus support improved health and well-being. LIFE foresees a market launch of this app within 1.5 years after the end of the project. VTEC will develop and commercialize a flexible system where single parameter sensors can be plugged in to generate wearable, multiparameter sensor systems. In the project, a multiple wearable sensor will be developed and commercialized that simultaneously measures light, dust, sound, sleep, physical activity level, stress and location. It will result in high throughput generation of data with research-specific combinations of sensors. With this system, VTEC can address the market for occupational protective equipment with an expected market size $67.6 billion by 2023. OWL is a global diagnostic company developing non-invasive breath tests for early detection of disease. It has the world’s only commercial breath biopsy laboratory and is a market leader in breath-based diagnostics. The project is expected to generate IP on novel biomarkers of exposure and related effects in breath. Based on these biomarkers, OWL will develop non-invasive breath biomonitoring tools for occupational health that will give early warning of disease progression to allow preventative action. After the project OWL will work to validate biomarkers associated with exposure and if successful plan to launch a test onto the market >2023. Initially OWL will develop a research product for exposome and biomonitoring research using breath as a non-invasive sampling method. In the medium term, OWL plans to develop validated tests to enable policymakers and health professionals to utilise non-invasive breath sampling. The results of the project will enable policymakers to set standards for non-invasive breath biomonitoring in occupational health. Occupational health professionals will be able to use breath tests to identify at risk individuals for the impact of exposures on their health. INTER will: be involved in the development and hosting (during the project) of the EU project website; develop the toolbox part of the EU website (results task 9.1-9.4); provide access to software tools and protocol/guidelines/factsheets/video’s etc.; develop online and searchable databases based on offline (excel) tables; provide interactive tool based on a table with different options for visualisations; provide input to user experience workshops with stakeholders.

### 2.3.1.4 Data management

Table 2.3.2 shows the data used in the project. During the project, pseudonymized data will be stored in the Yoda database. After the project, the data will be anonymized and made open access. Storage of these data will be based on the FAIR principles and comply with GDPR. Only the anonymized data will be open access and will become available through a link in the toolbox (see Table 2.2.2). A full Data Management Plan describing in detail the data to be collected and how it will be curated will be produced in WP10 at the start of the project. The Consortium Agreement that will be developed as part of WP11 will specify the ownership and access to key knowledge, including IP and data. The principle investigators who will lead the studies that are included in the EPHOR project are based within organisations with extensive track records in data collection and management, and have validated systems in place for doing so and the necessary IT infrastructure to ensure data security. The project will comply fully with the data protection requirements in each of the countries where it is implemented.

**Table 2.3.2: Data generated in the project**

<table>
<thead>
<tr>
<th>Data type</th>
<th>WP</th>
<th>WP leader</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exposure data generated with a wearable sensor system on exposure to light, dust, sound, sleep, physical activity level, stress and location and passive sampling, questionnaire data regarding exposure-related activities.</td>
<td>1</td>
<td>IOM</td>
</tr>
</tbody>
</table>
Biomarker and omics data related to blood-, urine-, exhaled air-, exhaled breath condensate- and lung function parameters; Anthropometrics, data from questionnaires on occupational history, lifestyle and occupational factors; Data from a wearable sensor system on exposures to light, dust, sound, sleep, physical activity level, stress and location. Passive sampling of chemicals and biological exposures.

2.3.1.5 Strategy for IP protection and knowledge management

The Consortium Agreement (CA), based on the DESCA 2020 model version 1.2.4, will detail, further to its provisions regarding responsibility, governance and financial issues, the agreements relating to management of knowledge. In particular, the CA will address 1) ownership and transfer of background and foreground; 2) publication rights and limitations; 3) access rights for implementation and for use of the project results; and 4) non-disclosure of information outside the consortium. All partners will list their included Background in an agreement on Background attached to the CA that has to be approved by all partners before the project starts. Where several beneficiaries have jointly carried out work generating foreground they shall have joint ownership and establish an agreement regarding the allocation and terms of exercising such joint ownership.

Throughout the project, all project partners will screen their work on results that may qualify for IP protection. At the earliest possible stage, they will inform their local IP representative and WP leader on the newly identified IP, and he/she will bring forward the IP protection initiative to the Daily Management Team for further discussion in the Executive Board. For implementation, each partner will follow the procedures already in use at their own organisation or Technology Transfer Office.

Confirmation of the right to publish is also subject to the agreement of the Executive Board during the lifetime of the project, and done by e-mail, and thereafter (with due acknowledgement to the project and Commission co-funding). Procedures will be proposed and agreed in the General Assembly to ensure that patentable knowledge will not be published before IP has been protected. Therefore, before publication, the project partners will submit the material to the Executive Board that will perform a screening on patentable knowledge. In case of major issues, the General Assembly will decide.

Publication policies: The publication policy for peer-review papers will be laid down in a dedicated section of the Consortium Agreement. This includes agreements between the project partners with respect to authorship, target journals for publication, internal review process, open access policies, criteria for publication in gold open access journals, the prior notice period for planned publication, process and grounds on which an objection can be put forward to the planned publication. WP10 will supervise the publication process.

Open access: The project partners will endeavour to select the best scientific journals especially for key papers, whilst also assuring open access without restriction. Each partner will upload publications stemming from the project to the research repositories at their organisations (if available). The publication policy will outline to each participant their obligations to ensure open access is provided to deposited publications via a repository at the latest: 1) on publication, if an electronic version is available for free via the publisher, or 2) within six months of publication in any other case. However, there are also high impact journals which tend not to be open access unless you pay. Therefore, the management has allocated budget for 5 gold publications to support the cost of gold open access of the key papers resulting from the project. After that, all partners will be encouraged to use other no-cost “gold” and “green” open access journals. In addition, prior to external availability via Journals, all EPHOR publications will be collected in a project specific repository (e.g. Zeno, Mendeley) for sharing within the scientific community.

2.3.2 Communication activities

All target audiences will be kept informed on the project achievements through both dissemination and communication activities. Dissemination and communication is closely interlinked, and thus important communication activities have been described in detail in section 2.2. In Table 2.3.3 below, the discussion topics and communications channels that are especially relevant for two-way interactions between EPHOR and its target audiences are highlighted. The discussion topics will be formulated in an easy to understand form in order to facilitate a dialogue with a wide audience.

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Table 2.3.3: communication activities in EPHOR

<table>
<thead>
<tr>
<th>Target audience</th>
<th>Key discussion topics</th>
<th>Communication channels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Policy makers, occupational health practitioners, employers, workers and employees</td>
<td>Features of the toolbox</td>
<td>Stakeholder workshops on the features of the toolbox and the multiparameter sensor</td>
</tr>
<tr>
<td>Employees and workers (organisations), employers (organisations), occupational practitioners and policy makers</td>
<td>Content of the toolbox</td>
<td>Final workshop with discussion sessions</td>
</tr>
<tr>
<td>All stakeholders</td>
<td>Discussion topics will be linked to important project results</td>
<td>A LinkedIn account will be established together with a discussion group on LinkedIn to present results and receive feedback.</td>
</tr>
</tbody>
</table>

3. Implementation

3.1 Work plan — Work packages, deliverables

3.1.1 Overall structure of the work plan

The 10 scientific WPs delivering project outcomes are strongly inter-related and grouped as follows.

Methods for collection, storage and interpretation of working-life exposome data: WP1 focuses on the development of new technologies for collecting external exposome data. In WP2, the dynamic EuroJEM will be developed to determine a wide range of occupational and related non-occupational factors across Europe. WP3 focusses on (non-invasive) internal exposure.

Exposome studies for better and more complete knowledge on the working-life exposome in relation to NCDs: In WP5, the EPHOR mega cohort is developed, by pooling existing cohorts. Associations between complex exposure patterns and health are investigated, including the effect of life stage. For WP5, the dynamic EuroJEM (WP2) is the most important input. In addition, there will be extensive interaction with WP4 for decentralized data analytics. In WP6 and 7 new working-life exposome data are collected. In WP6 the focus is on studying the effect of the both long-term and short-term working-life exposome on respiratory health. While WP7 focusses on the effect of shift work and related working-life exposures on key functions of disease and (early) health effects. Both WP6 and 7 will apply the methods for new external (WP1) and internal (WP3) exposure assessment. In addition, EuroJEM will be applied in these WPs and there will be intensive collaboration with WP4 for centralized data management and analyses.

Methods for impact assessment of the exposome: WP8 focusses on the development of health and economic impact assessment of working life exposome data that will provide knowledge on complex interactions and disease mechanisms. WP8 will use cohort data from WP5 and exposure prevalence from the application of the dynamic EuroJEM from WP2 for simulations during method development and the results of WP5, 6 & 7 for demonstration of the methods.

Project outcomes: WP9 will develop the working-life exposome toolbox with input from WP1-8. Finally, WP10 will focus on the dissemination, communication and exploitation. Stakeholder consultation is concentrated in WP10 interacting intensively with WP1,8 and 9.

Key interrelationship between the WPs are shown in Figure 3.1.1. A detailed overview of the timing and tasks per WP is presented in the Gantt chart (Figure 3.1.2).
Methods for collection, storage and interpretation of working life exposome data

WP1: New technologies for external exposome and health
WP2: Standardized assessment of multiple exposures in large populations
WP3: Internal exposure and effect assessment using biomonitoring, omics and minimally invasive biomarker development
WP4: Working life exposome data management and analytics platform

Better and more complete knowledge of the working life exposome in relation to NCDs

WP5: EPHOR Mega Cohort
WP6: Working life exposome, lung function, and obstructive lung disease among men and women
WP7: Exposome studies on shift work and health

Methods for impact assessment of the exposome

WP8: Impact assessment of the working life exposome

WP9: Working life exposome toolbox
WP10: Dissemination & exploitation

WP11: Project management
WP 12: European Human Exposome Network Activities
WP 13: Ethics

Figure 3.1.1: Overview of WPs with the most important interrelations
<table>
<thead>
<tr>
<th>WPs / Tasks</th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
<th>Year 4</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>3 6 9 12</td>
<td>15 18 21 24</td>
<td>27 30 33 36</td>
<td>39 42 45 48 51 54 57 60</td>
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<td>WP1 - New technology for external exposome and health</td>
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<tr>
<td>Task 1.1 Development the wearable sensor system</td>
<td>D1.3</td>
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<tr>
<td>Task 1.2 Passive sampling: Protocol development and lab analyses</td>
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<td>D1</td>
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<tr>
<td>Task 1.3 External exposome protocol development for the case studies</td>
<td></td>
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<td>D1.2</td>
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<tr>
<td>Task 1.4 Processing of sensor data</td>
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<td>D1.5</td>
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<tr>
<td>WP2 - Standardized assessment of multiple exposures in large populations</td>
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<tr>
<td>Task 2.1 Collecting and defining existing JEMs</td>
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<td>D2.1</td>
<td>D2.5</td>
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<tr>
<td>Task 2.2 Harmonizing existing JEMs</td>
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<td>D2.2/</td>
<td>D2.3/D2.4</td>
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<tr>
<td>Task 2.3 Protocol for including new data in EuroJEM</td>
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<tr>
<td>Task 2.4 Development of new and more specific JEMs</td>
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<tr>
<td>Task 2.5 Evaluation and transition into dynamic EuroJEM</td>
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<tr>
<td>WP3 - Internal exposure and effect assessment using biomonitoring, omics and minimally invasive biomarker</td>
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<tr>
<td>Task 3.1 Protocol development</td>
<td>D3.1</td>
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<tr>
<td>Task 3.2 Targeted and agnostic common biomonitoring, omics and biomarker development</td>
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<td>D3.4</td>
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<tr>
<td>Task 3.3 Method development for non-invasive monitoring</td>
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<tr>
<td>Task 3.4 Bioinformatics analysis of omics data and stratification of exposomes</td>
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<tr>
<td>WP4 - Working life exposome data management and analytics platform</td>
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<tr>
<td>Task 4.1 Data management platform</td>
<td>D4.4</td>
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<tr>
<td>Task 4.2 Development of new data interpretation methods</td>
<td>D4</td>
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<tr>
<td>WP5 - EPHOR mega cohort</td>
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<tr>
<td>Task 5.1 Extension and further development of a searchable web-based database</td>
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<tr>
<td>Task 5.2 Creation of EPHOR mega cohort</td>
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<td>D5.2</td>
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<tr>
<td>Task 5.3 Systematic epidemiological analyses to investigate known and new risk factors</td>
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<tr>
<td>WP6 - Working life exposome, lung function, and obstructive lung disease among men and women</td>
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<tr>
<td>Task 6.1 Protocol development, ethical approval and coordination of field studies</td>
<td>D6.1</td>
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<tr>
<td>Task 6.2 Conduct of the field studies: exposome and health data collection</td>
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<td>D6.2</td>
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<tr>
<td>Task 6.3 Statistical analyses exposure response associations/disease prevention</td>
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<td>WP7 - Exposome case studies on night shift work and health</td>
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<tr>
<td>Task 7.1 Development of protocols, ethical approval and coordination of field studies</td>
<td>D7.1</td>
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<td>Task 7.2 Conduct of field studies: exposome and health data collection</td>
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<td>D7.2</td>
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<tr>
<td>Task 7.3 Harmonization and incorporation of exposure, omics and aetiological information</td>
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<td>Task 7.4 Integrated statistical analysis, development of predictive models</td>
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</table>

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Figure 3.1.2: Gantt Chart of the EPHOR project

<table>
<thead>
<tr>
<th>WPs / Tasks</th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
<th>Year 4</th>
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<td>WP8 - Impact Assessment</td>
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<td>Task 8.1 Exposomic burden of disease model</td>
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<td>Task 8.2 Working life specific health metrics for impact assessment</td>
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<td>Task 8.3 Exposomic health impact assessment</td>
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<td>Task 8.4 Tools and guidance for impact assessment</td>
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<td>WP9 - EPHOR working life toolbox</td>
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<td>Task 9.1 Interactive visualisation tool for exploring the current work</td>
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<td>Task 9.2 Tools for working life exosposome data collection, storage and analysis</td>
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<td>Task 9.3 Tools for external and internal exposome data collection at intervention sites</td>
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<td>Task 9.4 Tools for health impact assessment for policy makers</td>
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<td>Task 9.5 Toolbox website development and coordination of the tools</td>
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<td>WP10 - Dissemination, Communication and Exploitation</td>
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<td>D10.3</td>
<td>D10.4</td>
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<td>Task 10.1 Communication and Dissemination Plan</td>
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<td>Task 10.2 Exploitation and IP management</td>
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<td>Task 10.3 Workshops with stakeholders</td>
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<tr>
<td>WP11 - Project management</td>
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<td>D11.2</td>
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<td>D11.4</td>
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<td>Task 11.1 Scientific, financial and contractual management</td>
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<td>Task 11.2 Data management plan</td>
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<td>Task 11.3 Privacy and ethical management</td>
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<td>Task 11.4 Contribute to overarching Human Exposome Project</td>
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<tr>
<td>WP12 - European Human Exposome Network Activities</td>
<td>D12.1</td>
<td>D12.2</td>
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<td>Task 12.1 Governance of the Network</td>
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<td>Task 12.2 Set up an external Network Advisory Board</td>
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<td>Task 12.3 Periodic Human Exposome Network meetings</td>
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<td>Task 12.4 Joint strategy for communication and dissemination and linking to policy</td>
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<td>Task 12.5 Joint working groups</td>
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<tr>
<td>WP13 - Ethics requirements</td>
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</tbody>
</table>
WP12 describes activities of the common European Human Exposome Network, as mandated by the Collaboration Agreement signed between 9 projects issued from the same call “SC1-BHC28-2019: The Human Exposome Project: a toolbox for assessing and addressing the impact of environment on health”:

- ATHLETE: 874583 - Advancing tools for human early lifecourse exposome research and translation
- EPHOR: 874703 - Exposome project for health and occupational research
- EQUAL-LIFE: 874724 - Early environmental quality and life-course mental health effects
- EXIMIOUS: 874707 - Mapping exposure-induced immune effects: connecting the exposome and the immunome
- EXPANSE: 874627 - Exposome powered tools for healthy living in urban settings
- HEAP: 874662 - Human exposome assessment platform
- HEDIMED: 874864 - Human exposomic determinants of immune mediated diseases
- LONGITOOLS: 874739 - Dynamic longitudinal exposome trajectories in cardiovascular and metabolic noncommunicable diseases
- REMEDIA: 874753 Impact of exposome on the course of lung diseases

The Table below describes all the deliverables that will be submitted by the Network projects.

<table>
<thead>
<tr>
<th>Overview of all Deliverables of common WP</th>
<th>Project(s) in charge of the deliverable</th>
<th>Month of delivery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Report 1 Handover document to next coordinating team</td>
<td>EXPANSE (D10.1) and HEAP (D12.1)</td>
<td>15</td>
</tr>
<tr>
<td>Report 2 Handover document to next coordinating team</td>
<td>ATHLETE (D12.4) and EQUAL-LIFE (D11.1)</td>
<td>30</td>
</tr>
<tr>
<td>Report 3 Handover document to next coordinating team</td>
<td>LONGITOOLS (D10.1) and EXIMIOUS (D9.1)</td>
<td>45</td>
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<tr>
<td>Report 4 Joint Network Advisory Board</td>
<td>EPHOR (D12.1) REMEDIA (D8.1) and HEDIMED (D12.1)</td>
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<tr>
<td>Report 5 Dissemination and Communication strategy</td>
<td>ATHLETE (D12.1) and EQUAL-LIFE (D11.2)</td>
<td>3</td>
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<tr>
<td>Report 6 Network website</td>
<td>HEAP (D12.2)</td>
<td>6</td>
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<tr>
<td>Report 7 Update Dissemination and Communication strategy</td>
<td>LONGITOOLS (D10.2) and EXIMIOUS (D9.2)</td>
<td>36</td>
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<tr>
<td>Report 8 Policy Strategy</td>
<td>EPHOR (D12.2) REMEDIA (D8.2) and HEDIMED (D12.2)</td>
<td>18</td>
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<tr>
<td>Report 9 Updated policy strategy</td>
<td>ATHLETE (D12.5) and EQUAL-LIFE (D11.3)</td>
<td>54</td>
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<td>Report 10 List of Working Groups and ToR for the WGs</td>
<td>EXPANSE (D10.2) and HEAP (D12.3)</td>
<td>3</td>
</tr>
</tbody>
</table>

3.2.1 Project Management Team (PMT)

The organisational structure of EPHOR is presented in Figure 3.2.1.
Figure 3.2.1 Organisation structure of EPHOR

The PMT will be responsible for day-to-day management of the EPHOR project. This includes:
1) Preparation of the scientific and financial progress reports for the EC
2) Organizing all meetings and teleconferences related to management and providing minutes
3) Maintaining project procedures and coordinating the work of the executive bodies
4) Managing the review of the critical project deliverables, which will be done in cooperation with the EAB
5) Defining and carrying out the actions to be taken to promote gender equality
6) Liaising with the Financial and Control Department of TNO for support regarding financial management and all legal aspects of the project. TNO has extensive experience in EU Framework Programmes and successfully participated in over 270 FP7 projects, of which TNO coordinated around 50 projects, with a total own budget around €160 million. TNO has a dedicated EU Business & Contracts team which manages projects through the application and negotiation phases. A dedicated EU accountancy team handles the financial issues of running projects.

The PMT will be consist of the Project Coordinator (PC) (Anjoeka Pronk, TNO, F), a Supportive Scientific Coordinator (SSC) (Rob Stierum, TNO, M), a Project Manager (PM) (Astrid Kruizinga, TNO, F) and a project assistant for practical organisation. The PC, Anjoeka Pronk, is very experienced in coordinating international and multidisciplinary projects. She participates in relevant EU projects: (1) HEALS, focussing on assessing the external exposome by combining sensor data and models, (2) HBM4EU, focussing on biomonitoring and integrated modelling of occupational exposures, and (3) EXPOSOGAS (WP lead) focussing on applying the exposome concept to optimise health and safety in the oil and gas industry.

3.2.2 General Assembly (GA)

The General Assembly (GA) consists of one representative of each consortium partner, chaired by the Project Coordinator. Each partner shall be entitled to send one voting representative to the GA. The representatives to the GA will be of sufficient management level to commit their organisation to the project-related decisions of the GA. The decisions that need approval by the GA include:
1) Major changes of the work plan, planning or budget (also consultation with the EC Project Officer needed)
2) Entrance or exit of partner(s), Change of Coordinator or WP Leader
3) Major ethical issues
4) Any unforeseen major non-scientific or technical issues
5) Taking decisions on IP matters and knowledge management when issues arise.

Decisions will be taken by consensus where possible, otherwise they require that at least two-thirds of the Project partners vote in favour of a particular proposition. The partners agree to abide by all decisions of the GA. The GA will meet once a year in person at the full consortium meetings, and at ad hoc occasions as arranged by the PMT.
3.2.3 Executive Board (EB)

The Executive Board (EB) consists of all WP Leaders, the privacy and ethical coordinator, PC, SSC and PM, chaired by the representative of the Coordinator (the PC). Tasks include:
1) Monitoring and evaluating progress of the WPs against the defined milestones and deliverables and expenditures in relation to the budget
2) Decision making about the future direction of the project on basis of the milestone achievements
3) Prepare issues that should be decided by the General Assembly, e.g. IPR, major changes in work plan/budget, amendment of the terms of the EU contract and the Consortium Agreement
4) Measures in the framework of quality, privacy and ethical issues
5) Finding solutions for conflicts that cannot be solved by the WP leaders alone
6) Discuss and update the possible risks in the project and contingency plans
7) Approval of deliverables and progress reports, and assessment of milestones
8) Organizing WP meetings with multiple WP’s to assure sufficient interlinking between the WPs

The EB meetings will be held at least twice a year at the consortium meeting and if needed, as arranged by the PMT.

3.2.4 WP leader

Each WP will be led by a WP leader. The tasks include:
1) Assuring the content and quality of the work within their WP and timely delivery of the milestones and deliverables
2) Monitoring progress and reporting on progress to the PMT and EB
3) Supervising management of IP, knowledge management and innovation management in their respective WPs
4) Organizing and chairing WP meetings

WP's will meet regularly, live as well as by teleconferencing. Live meetings will be during the consortium meetings. All meetings will be supported by written minutes defining agreed actions and will monitor progress against deliverables, milestones, risks and contingency. The WP-leaders and co-leads are listed in table 3.2.1.

<table>
<thead>
<tr>
<th>Lead</th>
<th>Co-lead</th>
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</thead>
<tbody>
<tr>
<td>WP1 IOM:</td>
<td>TNO: Eelco Kuijpers (M)</td>
</tr>
<tr>
<td>WP2 KI: Maria</td>
<td>FIOH: Svetlana Solovieva (F)</td>
</tr>
<tr>
<td>WP3 KU Leuven:</td>
<td>KI: Karin Broberg (F)</td>
</tr>
<tr>
<td>WP4 UU:</td>
<td>TNO: Rob Stierum (M)</td>
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<tr>
<td>WP5 STAMI:</td>
<td>ISGLOBAL: Michelle Turner (F)</td>
</tr>
<tr>
<td>WP6 AU:</td>
<td>TNO: Anjoeka Pronk (F)</td>
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<tr>
<td>WP7 ISGLOBAL:</td>
<td>UU: Roel Vermeulen (M)</td>
</tr>
<tr>
<td>WP8 UNIMAN:</td>
<td>FIOH: Svetlana Solovieva (F)</td>
</tr>
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<td>WP9 TNO:</td>
<td>IOM: Miranda Loh (F)</td>
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<td>WP10 TNO:</td>
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<tr>
<td>WP13 TNO:</td>
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</table>

3.2.5 Privacy and Ethical committee

Within EPHOR a privacy and ethical committee is formed. The ethical committee exists of representatives of the WP’s in which ethical and/or privacy issues play a role (i.e. WP1, 5, 6 and 7). The ethical committee is chaired the privacy and ethical coordinator, Tina (Stamatia) Garani-Papadatos, who is a professor of Public Health Ethics. The ethical committee will have meetings during every consortium meeting and will review all documents in the relevant WP’s to discuss ethical and privacy issues and assure compliance with EU and national legislation.

3.2.6 External Advisory Board (EAB)

To assure alliance with stakeholders the EPHOR project will be supported by the External Advisory Board (EAB). The EAB will consist of a limited number of external experts that will be selected on the basis of their profound and long-lasting expertise in the field of research and will represent several stakeholder groups. The EAB members will be invited at least once per year to the consortium meetings of the project (after signing appropriate confidentiality agreements with all partners in the consortium), where they can advise the EB mainly on implementation, dissemination and relevance to stakeholders. The members of the advisory board are listed in table 3.2.2.
Table 3.2.2: Members of the External Advisory Board

<table>
<thead>
<tr>
<th>Stakeholder group</th>
<th>Organization</th>
<th>Person involved (indicated and approved by the organisation)</th>
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</thead>
<tbody>
<tr>
<td>Occupation health practitioner</td>
<td>ICOH (International Commission on Occupational Health [<a href="http://www.icohweb.org/site/homepage.asp">www.icohweb.org/site/homepage.asp</a>]</td>
<td>Dr. Jukka Takala, President</td>
</tr>
<tr>
<td>Industry (scientific representation)</td>
<td>ECETOC (European Centre For Ecotoxicology and toxicology of Chemicals [<a href="http://www.ecetoc.org/">http://www.ecetoc.org/</a>]</td>
<td>Olivier de Matos, Secretary General</td>
</tr>
<tr>
<td>Scientists within government agencies</td>
<td>HSE (Health and Safety Executive) [<a href="http://www.hse.gov.uk/">www.hse.gov.uk/</a>]</td>
<td>Dr. Nick Warren, Science lead for one of five HSE’s science hubs: ‘Taking Responsibility for Health’</td>
</tr>
<tr>
<td></td>
<td>NIOSH (National Institute for Occupational Safety and Health) [<a href="https://www.cdc.gov/niosh/">https://www.cdc.gov/niosh/</a>]</td>
<td>Dr. John Snawder, Research Toxicologist</td>
</tr>
<tr>
<td>Independent external ethics advisor</td>
<td>To be determined after the start of the project</td>
<td>To be determined after the start of the project</td>
</tr>
</tbody>
</table>

3.2.7 European Human Exposome Network

Together with the other eight project funded under the SC1-BHC-28-2019 call EPHOR will form a European Human Exposome Network. EPHOR will be represented in this network by the PC and, depending on the topic, WP leaders and/or other project members. Within the network also working groups will be formed to stimulate collaboration on common topics. The representatives of EPHOR in these working groups will be selected from the project members and will depend on the topic.

The Network Advisory Board (NAB) will be set up to oversee the activities of the European Human Exposome Network and facilitate links to international activities, relevant stakeholder communities, infrastructures and dissemination channels. The NAB will advise on 1) the network strategy on linking research results to policy; 2) the network communication and dissemination strategy; 3) linking to international activities and initiatives; and 4) the joint working groups.

3.2.8 Communication and Reporting

The communication strategy will be based on three pillars: the day-to-day communication, the web-based communication and the project meetings. The day-to-day communication between the partners will mainly take place by telephone and e-mail. The PMT will actively stimulate and facilitate a smooth communication and interaction between all researchers involved in the project. The web-based communication will consist of an external, public website and an internal, password restricted web-based shared working environment (e.g. SharePoint-based). On the internal site all relevant project documents (reports, meeting minutes, presentations, etc.) will be posted and project members can download and upload data and documents.

The following project meetings will be organised:
- Kick-off meeting at the start of the project, in presence of all project members;
- GA meetings, at least once a year;
- EB meetings, at least 4 times a year, face-to-face or by telephone conference;
- Consortium meetings, in total 8 meetings (including kick off meeting); The consortium meetings will have both separate WP sessions and sessions with various WP’s to stimulate the interlinking;
- WP meetings, whenever considered necessary for the progress of the WP;
- Review meetings (to be organised by PMT in agreement with the EC Project Officer)

In order to obtain maximum efficiency, the various meetings will, whenever possible, be organised in conjunction, e.g. GA and EB meetings will be combined with review meetings or general progress meetings.
3.2.9 Decision making/milestones

A detailed description of the responsibilities of GA and EB and the decision making process (including voting procedure) will appear in the Consortium Agreement (CA, based on the DESCA model for Horizon 2020), that will be signed by all partners before the official start of the project. A major tool for making technical decisions during the execution of the project is the assessment of identified milestones.

3.2.10 Quality assurance

All partners will perform their part of the work according to their internal quality control and assurance procedures, e.g. with respect to experimental procedures and review of reports. If necessary, quality issues will be on the agenda of the EB meetings, possibly resulting in preventive or corrective actions. The overall quality of the execution of the research programme is also controlled by the use of milestones and deliverables, and updated timetables within the project. The WP Leaders will regularly (at least 4 times a year, e.g. by telephone conference) inform the PMT on the detailed progress of the WP, on the status of milestones and deliverables, and on possible problems or delays. All deliverables have to be approved by the EB. The milestones will be assessed by the EB and, if appropriate, decisions or selections will be approved.

3.2.11 Innovation management

The degree of innovation that can be reached by the results of the project, does not only depend on the technical achievements, but also on the market needs and parallel technical developments. Therefore, the project partners will continuously be stimulated to keep abreast of the newest developments with regard to market requirements, product and process innovations, patent applications and scientific/technical publications in their respective research areas or industrial branches. The WP Leaders will actively collect any such developments, and the Executive Board will evaluate the possible need for modification of the research programme in order to maintain the innovative perspective of the project. Apart from this response to external developments, also internal accomplishments like an unexpected technical invention that might lead to even more impact than the originally planned solution, will be assessed for possible upgrading of the research programme. Eventually, the General Assembly will approve such innovation-driven (proposals for) changes to the research plan and, if necessary, the Project Coordinator will take appropriate action towards the EC.

3.2.12 Critical risks

In view of the highly innovative character of the proposed research, several risks are identified that may occur during the implementation of the EPHOR project. The monitoring of these risks, and the reporting of new, as yet unidentified risks, will be a task of everyone involved in EPHOR. Overall, it is the responsibility of the Executive Board to assess the possible occurrence of the risks, and to decide on the mitigation measures or, eventually, a modification of the workplan. The monitoring of these risks will be performed at least every 6 months.

3.3 Consortium as a whole

The working-life exposome is a multidisciplinary endeavor. This means that a consortium by definition should be multidisciplinary, including experts on external exposure assessment, internal exposure assessment, data management and data-analysis including both epidemiologists and (system) biologists for mechanistic insights. In addition, since many new technologies are applied, technology developers are needed. To estimate the societal and economic impact of the working-life exposome sociologists and economists are needed. And finally, in order to ensure the construction of a toolbox with workable tools for the different stakeholders the involvement of applied scientists is needed.

The EPHOR consortium consists of 19 partners from 12 European countries. The consortium is well balanced in terms of organizational structure as given below:

- Research Organisations: TNO, ISGLOBAL, IOM, STAMI, INSERM, FIOH
- Private for Profit entities: VTEC, LIFE, OWL, INTER
- Higher or Secondary Education Establishments:, AU, KI, KUL, UNIMAN, UU, PDA, UiB, CUT
- Health care: SLL

With respect to the gender balance in the consortium, there is a good female representation with the coordinator and 6 out of 11 WP leaders being female. The consortium is balanced in senior and mid-career researchers. Furthermore, several PhD students will be trained in the field of exposome science.

The complementarity and synergy offered by the EPHOR partnership results in a consortium that as a whole offers substantially more than just the sum of each of its individual parts. Beyond the immediate consortium, coordinated dialogue and active collaboration with a variety of stakeholders (through WP10 and the EAB) will ensure further
Table 3.3.1: Core Competences of EPHOR Partners and Their Relevance with Required Expertise

<table>
<thead>
<tr>
<th>Participant</th>
<th>Core competences/ Assets</th>
<th>Core activities in EPHOR</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNO</td>
<td>External and internal exposome, occupational exposure assessment, sensor methods/point-of-care biomarker assays, epidemiology, systems biology, biological pathway modelling and data mining. Applied science, collaboration with industry and SME. Experience in acquiring, managing major projects. Impressive track record in managing EU-funded projects. Cohorts; see Table 1.3.3.</td>
<td><strong>Overall Coordination</strong>&lt;br&gt;WP1: Feasibility study sensors; passive sampling wristbands; Processing of sensor data;&lt;br&gt;WP2: Data mining for protocols for updating EuroJEM;&lt;br&gt;WP3-4: Data mining, coordination of pathways analyses;&lt;br&gt;WP6: Exposure-response data analyses, pathways;&lt;br&gt;WP8: Impact assessment using biological pathways&lt;br&gt;<strong>WP9: Lead,</strong> coordination of toolbox&lt;br&gt;<strong>WP10: Lead,</strong> plan for dissemination, communication and exploitation; exploitation and IP management;&lt;br&gt;<strong>WP11: Lead,</strong> project management</td>
</tr>
<tr>
<td>ISGLOBAL</td>
<td>Vice-chair OMEGA-NET. Pioneer exposome studies. Epidemiology on environmental, occupational and genetic factors and cancer, respiratory diseases and child health. Exposure assessment, bioinformatics, biostatistics. Cohorts: see Table 1.3.3.</td>
<td>WP3: Luminex, sex steroid analyses, omics data analysis&lt;br&gt;WP5: Data analyses in EPHOR mega cohort; focus on shift work&lt;br&gt;WP6: New data collection in 2 ECRHS centres&lt;br&gt;<strong>WP7: Lead,</strong> coordination of field work (car factory); coordination of data analytics</td>
</tr>
<tr>
<td>IOM</td>
<td>(Personalized) Exposure assessment, using e.g. sensors for air pollution and physical activity. Epidemiology, health effects, mechanisms of disease, statistics.</td>
<td><strong>WP1: Lead,</strong> Protocol development sensor system; WP5: Involved in EPHOR mega cohort analysis&lt;br&gt;WP6-7: Assist in sensors application in field study and data analysis&lt;br&gt;WP8: Burden of disease modelling&lt;br&gt;WP9: Tools: coordination for occupational health practitioners; contribution for policy makers&lt;br&gt;WP10: Organization of stakeholder workshops</td>
</tr>
<tr>
<td>AU</td>
<td>Epidemiology/toxicology of aerosols. Occupational exposures and respiratory diseases. Head ECRHS Denmark. Infrastructure for register-based research, clinical fieldwork, environmental exposure assessment. Statistics, data management. Environmental microbiome analysis. JEMs: see Table 1.3.2 Cohorts: see Table 1.3.3.</td>
<td>WP1: Laboratory analyses of biological exposures in passive dust samples, contribution to feasibility study&lt;br&gt;WP2: Development of new and more specific JEMs; Contribute to EuroJEM&lt;br&gt;WP3: Input sample collection protocol&lt;br&gt;WP4: Input on exposure output modelling&lt;br&gt;WP5: Data analyses on respiratory health in the EPHOR mega cohort;&lt;br&gt;<strong>WP6: Lead,</strong> development of protocol and coordination of field studies; new data collection in ECRHS centres; coordination of data analyses;</td>
</tr>
<tr>
<td>KI</td>
<td>Exposure/risk assessment, epidemiology, environmental/ occupational medicine (cancer, respiratory, CVD), toxicology, physiology, omics, biomonitoring. JEMs: see Table 1.3.2 Cohorts: see Table 1.3.3.</td>
<td><strong>WP2: Lead,</strong> coordination of development of dynamic EuroJEM and harmonizing existing JEMs&lt;br&gt;WP3: Omics (mtDNA/telomere length analyses)&lt;br&gt;WP5: Application of EuroJEM and data analyses in the EPHOR mega cohort;&lt;br&gt;WP6: Application of EuroJEM; data analyses;&lt;br&gt;WP7: Conducting field study Sweden; Application of EuroJEM; data analyses;&lt;br&gt;WP8: Assist in health impact assessment&lt;br&gt;WP9: Development of tool for exposome and exposome-response data, including EuroJEM</td>
</tr>
<tr>
<td>KUL</td>
<td>Environmental medicine, toxicology, hygiene. Biological effects (nanoparticles, solvents</td>
<td><strong>WP3: Lead,</strong> PAH, cotinine, cortisol, clinical chemistry, 8-OHdG, epigenomics, pyrosequencing, DNA methylation and proteomics analyses; new technology for non-invasive</td>
</tr>
<tr>
<td>Participant</td>
<td>Core competences/ Assets</td>
<td>Core activities in EPHOR</td>
</tr>
<tr>
<td>-------------</td>
<td>-------------------------</td>
<td>-------------------------</td>
</tr>
<tr>
<td>monomers), (epi)genetic effects, pulmonary toxicology, clinical-epidemiology. Monitoring airborne exposures, Analytical Chemistry for biomonitoring. Cohorts: see Table 1.3.3.</td>
<td>Monitoring airborne exposures. Analytical Chemistry for biomonitoring. Cohorts: see Table 1.3.3.</td>
<td>Monitoring airborne exposures. Analytical Chemistry for biomonitoring. Cohorts: see Table 1.3.3.</td>
</tr>
<tr>
<td>Chair Omega-NET: connecting EPHOR and OMEGA-NET. Work environment and occupational health, medicine, epidemiology, biology, chemistry, toxicology, psychology and sociology. EXPO database for airborne chemicals and biologicals. Cohorts: see Table 1.3.3.</td>
<td>WP2: Contribute to EuroJEM; evaluation and transition into dynamic EuroJEM, using EXPO db WP3: Contribution transcriptomics analyses from WP6-7 Assist in case studies; WP4: Exposure-outcome modelling, job coding, hierarchical analysis WP5: Lead, coordination of EPHOR mega cohort; WP6: Assist in data analysis WP7: Analyses of telomere length (with WP3). WP9: Co-coordination interactive tool for exposome and exposome-response data</td>
<td>WP2: Contribute to EuroJEM; evaluation and transition into dynamic EuroJEM, using EXPO db WP3: Contribution transcriptomics analyses from WP6-7 Assist in case studies; WP4: Exposure-outcome modelling, job coding, hierarchical analysis WP5: Lead, coordination of EPHOR mega cohort; WP6: Assist in data analysis WP7: Analyses of telomere length (with WP3). WP9: Co-coordination interactive tool for exposome and exposome-response data</td>
</tr>
<tr>
<td>Computational expertise. Epidemiology. Chemical exposure risk assessment/management. JEMs: see Table 1.3.2 Cohorts: see Table 1.3.3.</td>
<td>WP4: Lead, data management (Yoda) development of data analyses methods: multiple exposures-outcomes modelling; ETR models; hierarchical analyses, automated job coding; WP5: Creation of EPHOR mega cohort, facilitating decentralised data sharing and analysis WP6-7: coordination of data transfer into Yoda, contribute to data analytics WP8: Development of conceptual model for impact assessment of exposome data; counterfactual modelling for impact assessment;</td>
<td>WP4: Lead, data management (Yoda) development of data analyses methods: multiple exposures-outcomes modelling; ETR models; hierarchical analyses, automated job coding; WP5: Creation of EPHOR mega cohort, facilitating decentralised data sharing and analysis WP6-7: coordination of data transfer into Yoda, contribute to data analytics WP8: Development of conceptual model for impact assessment of exposome data; counterfactual modelling for impact assessment;</td>
</tr>
<tr>
<td>Epidemiology. Organisation of human cohorts. Emphasis: cancer; MSD; psychosociology, occupational exposure, social and determinants of health behaviour. Cohorts: see Table 1.3.3.</td>
<td>WP2: Contribute to EuroJEM WP4: Expert opinion on automated job coding WP5: Support to data analyses WP6: Protocol development, new data collection and data analysis in CONSTANCES cohort</td>
<td>WP2: Contribute to EuroJEM WP4: Expert opinion on automated job coding WP5: Support to data analyses WP6: Protocol development, new data collection and data analysis in CONSTANCES cohort</td>
</tr>
<tr>
<td>Public health ethics, bioethics, research integrity, and human rights, privacy issues</td>
<td>WP4,6,7,11: privacy and ethics</td>
<td>WP4,6,7,11: privacy and ethics</td>
</tr>
<tr>
<td>Sensor principles/implementation. Customized sensors. wearable sensor system (dust and noise). IT platforms for large scale sensor system deployment: application knowledge;</td>
<td>WP1: Development wearable sensor system; commercialisation of wearable sensor system technology; WP10: Involved in stakeholder workshop on perception wearable sensor system implementation</td>
<td>WP1: Development wearable sensor system; commercialisation of wearable sensor system technology; WP10: Involved in stakeholder workshop on perception wearable sensor system implementation</td>
</tr>
</tbody>
</table>
### Participant | Core competences/ Assets | Core activities in EPHOR
--- | --- | ---
**machine learning; artificial intelligence; data connectivity management; cloud processing; Apps.** | WP6: New data collection in ECRHS centres; Contribute to data analytics; |
**Respiratory medicine. Environmental determinants. Multi-centre cohort studies. Cohorts: see Table 1.3.3.** | WP3: Integration of omics data; analysis of omics data; pathway analysis for stratification of exposomes; WP4: Support in text mining; WP9: Visualisation of adverse outcome pathways for toolbox; prototyping mobile app support near/after end of project |
**Bioinformatics and Systems biology modelling for personalized medicine and biomarker discovery, semantic data analytics and integration. High-performance computing, data management. smartphones/tablet, for testing mobile apps** | WP3: Analyses of VOCs in EB; development of non-invasive biomarker discovery; WP6-7: Providing breath collection stations /ReCIVA® and assistance; WP10: Involved in stakeholder workshop on perception of use of breath biopsies in working-life exposome. |
**Breath Biopsy Collection. ReCIVA® breath sampler VOCs. Breath Biopsy Lab - world’s only dedicated commercial laboratory for breath analysis. TD-GC-MS for biomarker discovery in breath. Data analyses pipeline.** | WP9: Interactive toolbox development (IT part); web-based access to software tools; protocols/guidelines/factsheets; searchable databases; data visualisations; WP10: Development EPHOR project website. |
**Web applications, content management and software development.** | WP3: Participate in biomonitoring and omics activities, specifically analysis of metals |
**Environmental Health, biomarkers biomonitoring, metabolomics. Agilent GC-MS/MS Triple Quadrupole Mass Spectrometer. Agilent Intuvo 9000 Gas Chromatograph.** | WP2: Contribution and evaluation of JEMs WP5: Data management WP7: Field-work in case study |
**Occupational medicine, ergonomics, occupational hygiene** | **3.4 Resources to be committed**

Table 3.4.1: 'Other direct cost' items (travel, equipment, other goods and services, large research infrastructure) for each participant if the sum of the costs for ‘travel’, ‘equipment’, and ‘goods and services’ exceeds 15% of the personnel costs

<table>
<thead>
<tr>
<th>1/TNO</th>
<th>Cost (€)</th>
<th>Justification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Travel</td>
<td>38,700</td>
<td>Travel to meetings by employees</td>
</tr>
<tr>
<td><strong>Equipment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Other goods and services</strong></td>
<td>241,300</td>
<td></td>
</tr>
<tr>
<td>Travel</td>
<td>15,813.87</td>
<td>Travel to meetings by employees</td>
</tr>
<tr>
<td><strong>Equipment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other goods and services</td>
<td>105,600</td>
<td>Direct costs for analyses in WP3</td>
</tr>
<tr>
<td>--------------------------</td>
<td>---------</td>
<td>---------------------------------</td>
</tr>
<tr>
<td></td>
<td>55,000</td>
<td>Costs for meeting with PI of cohorts and access to cohorts in WP5</td>
</tr>
<tr>
<td></td>
<td>55,500</td>
<td>Consumables for collection of data in WP6</td>
</tr>
<tr>
<td></td>
<td>90,000</td>
<td>Consumables for collection of data in WP7</td>
</tr>
<tr>
<td></td>
<td>3,000</td>
<td>Audit report</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>324,913.87</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>5/KI</th>
<th><strong>Cost (€)</strong></th>
<th><strong>Justification</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Travel</strong></td>
<td>17072.49</td>
<td>Travel to meetings by employees</td>
</tr>
<tr>
<td><strong>Equipment</strong></td>
<td>111,000</td>
<td>Direct costs for analyses in WP3</td>
</tr>
<tr>
<td></td>
<td>15,000</td>
<td>Costs clinical studies</td>
</tr>
<tr>
<td></td>
<td>5,000</td>
<td>Audit report</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>148,072.49</td>
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</table>

<table>
<thead>
<tr>
<th>6/KUL</th>
<th><strong>Cost (€)</strong></th>
<th><strong>Justification</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Travel</strong></td>
<td>16,187.25</td>
<td>Travel to meetings by employees</td>
</tr>
<tr>
<td><strong>Equipment</strong></td>
<td>548,000</td>
<td>Direct costs for analyses in WP3</td>
</tr>
<tr>
<td></td>
<td>5,000</td>
<td>Audit report</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>569,187.25</td>
<td></td>
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</table>

<table>
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<tr>
<th>7/STAMI</th>
<th><strong>Cost (€)</strong></th>
<th><strong>Justification</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Travel</strong></td>
<td>17236.05</td>
<td>Travel to meetings by employees</td>
</tr>
<tr>
<td><strong>Equipment</strong></td>
<td>93,000</td>
<td>Direct costs for analyses in WP3</td>
</tr>
<tr>
<td></td>
<td>5,000</td>
<td>Audit report</td>
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<tr>
<td><strong>Total</strong></td>
<td>115,236.05</td>
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</table>

<table>
<thead>
<tr>
<th>10/INSERM</th>
<th><strong>Cost (€)</strong></th>
<th><strong>Justification</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Travel</strong></td>
<td>18,287.62</td>
<td>Travel to meetings by employees</td>
</tr>
<tr>
<td><strong>Equipment</strong></td>
<td>150,000</td>
<td>Consumables for case study in WP6</td>
</tr>
<tr>
<td></td>
<td>5,000</td>
<td>Audit report</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>173,287.62</td>
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</table>

<table>
<thead>
<tr>
<th>12/PDA</th>
<th><strong>Cost (€)</strong></th>
<th><strong>Justification</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Travel</strong></td>
<td>9,828.03</td>
<td>Travel to meetings by employees</td>
</tr>
<tr>
<td><strong>Equipment</strong></td>
<td>25,000</td>
<td>Costs for sensor systems to be used in WP6 and 7</td>
</tr>
<tr>
<td></td>
<td>10,000</td>
<td>Materials and electronica for developing the prototype to be used in WP1</td>
</tr>
<tr>
<td><strong>Other goods and services</strong></td>
<td>9,828.03</td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>54,377.57</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>13/VTEC</th>
<th><strong>Cost (€)</strong></th>
<th><strong>Justification</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Travel</strong></td>
<td>19,377.57</td>
<td>Travel to meetings by employees</td>
</tr>
<tr>
<td><strong>Equipment</strong></td>
<td>25,000</td>
<td>Costs for sensor systems to be used in WP6 and 7</td>
</tr>
<tr>
<td></td>
<td>10,000</td>
<td>Materials and electronica for developing the prototype to be used in WP1</td>
</tr>
<tr>
<td><strong>Other goods and services</strong></td>
<td>54,756</td>
<td>Costs for analyses in WP3</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>54,756</td>
<td></td>
</tr>
</tbody>
</table>
18/CUT | Cost (€) | Justification |
--- | --- | --- |
Travel | 9,697,30 | Travel to meetings by employees |
Equipment | | |
Other goods and services | 10,000 | Costs for analyses in WP3 |
Total | 19,697,30 | |

4. Members of the consortium

4.1. Participants (applicants)

4.1.1 Organisatie voor Toegepast Natuurwetenschappelijk Onderzoek TNO

<table>
<thead>
<tr>
<th>Participant</th>
<th>Organisatie voor Toegepast Natuurwetenschappelijk Onderzoek TNO</th>
<th>Participant No.</th>
<th>1</th>
<th>Short name</th>
<th>TNO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Function</td>
<td>Coordinator</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Persons in charge</td>
<td>Anjoeka Pronk, Astrid Kruizinga, Rob Stierum</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Short description of the organisation

TNO (Nederlandse Organisatie voor toegepast-natuurwetenschappelijk Onderzoek TNO) is one of the major non-profit contract research organisations in Europe. With a staff of ~3500 and annual turnover of 580 M€, TNO is executing research in order to achieve impact on the following themes: Healthy Living, Industrial Innovation, Urbanisation, Energy, and Defence, Safety and Security. The Research Group Risk Analysis for Products In Development (RAPID) consists of 60 high level (PhD, MSc) experts including toxicologists, epidemiologists, immunologists, chemists, occupational hygienists, exposure assessment experts, statisticians, bioinformaticians and computational modelers. We are working on the interdisciplinary assessment and mitigation of health risks due to exposure to potentially hazardous chemicals/materials via the (occupational-) environment. RAPID adopts, develops and integrates science based models and methods to predict these potential risks. RAPID is primarily concerned with the application of in silico and desk-based research, performed on public data and data generated in collaborative or B2B projects. Aside, RAPID is highly experienced within EU and international funded research projects (8 coordinating, ~30 participating, over the past 10 years). Specific disciplines of relevance to EPHOR are exposure assessment and sensor-based exposome technologies, statistics, systems biology modelling, bioinformatics and systems toxicology, and risk assessment.

Tasks in the project

WP leader of WP 9, 10 and 1. Further TNO will be mainly involved in WP 1, 3, 4 and 8 (task leads)

Experience: projects or activities/infrastructure

TNO is partner in: (1) HEALS, (Health and Environment-wide Associations based on Large population Surveys) at present the largest EU exposome project (http://www.heals-eu.eu/). TNO coordinates the omics activities for HEALS and is involved in internal exposure modelling. In addition, TNO is active in external exposure assessment and modelling WPs; (2) EU Twinning Exposogas (https://www.exposogas.eu/) in the application of the exposome concept to optimise health and safety in the oil and gas industry (together with IOM and CUT) (WP leader); (3) HBM4EU (https://www.hbm4eu.eu/), the European biomonitoring project, in which TNO is participating in occupational field studies as well as bioinformatics to integrate external exposure towards internal exposure and effects (AOPs) (4) EUROTOXrisk, (http://www.eu-toxrisk.eu/) in which TNO provides expertise in toxicology, toxicoinformatics, innovative testing strategies. In occupational exposure/risk assessment, TNO developed worker exposure models that are applicable as first tier tool, e.g. Stoffenmanager, which has a specific application Stoffenmanager nano, or a higher tier tool to predict exposure, i.e. Advanced Reach Tool (ART).

A description of any significant infrastructure and/or any major items of technical equipment, relevant to the proposed work

A large number of databases and in silico tools are developed/present at RAPID to assist in sensor based exposure assessment, and computational modelling. Examples are exposure models ART/dART, and DIAMONDS (Datawarehouse Infrastructure for Applications, Models and Ontologies towards Novel Design and Safety), allow for the comparison of chemical data, toxicogenomics and toxicological data. Biomolecular data computing framework (BDC) integrates biomolecular computing tools (e.g. omics data integration tools), access to chemical-disease databases (e.g. CTD, pathway databases (e.g. KEGG, AOP wiki), and other software & hardware environments like KNIME & HADOOP for work-flow management. Generic PBPK model in R Shiny
Anjoeka Pronk, PhD (senior scientist) (F). Registered epidemiologist. Interdisciplinary researcher on environmental and occupational exposure and risk assessment, health impact assessment and epidemiology. She heads the TNO exposome program. Within this program, sensors and exposure modelling are combined in order to provide actionable individualized (e.g. citizens or patients) or group based (e.g. governments) feedback on exposures. In addition, the application of internal markers for more individualized risk assessment is investigated. >50 publications on exposure assessment, epidemiology and exposome. She participates in relevant EU projects HEALS and HBM4EU and coordinates the WP on Researcher Capacity within EU Twinning Exposogas. She also coordinates exposome projects for the Dutch government and the private sector. She has set up several collaborations with industry e.g for the development of point of care biomarker assays and for the application of (wearable) sensor systems for personalized exposure assessment.

Rob Stierum, PhD, European Registered Toxicologist (senior scientist) (M). Interdisciplinary researcher on toxicology, human chemical risk assessment and innovative technologies. Heads the systems toxicology, toxicoinformatics, omics and integrative safety data sciences (internal exposome) activities at TNO. Extensive expertise in acquisition and coordination of M€ research projects/or associated work packages in these areas: e.g. CEFIC-LRI, FP7 HEALS, EU H2020 CalIBRAte, Netherlands Toxigenomics Centre and FP6 EU Carcinogenomics. ~60 publications/ book chapters in the areas of genomics and toxicoinformatics/bioinformatics, exposure assessment, carcinogenesis, DNA repair.

Eelco Kuijpers, PhD (medior scientist) (M), Researcher on exposure assessment, risk assessment and epidemiology. His main fields of interest are exposure assessment for risk assessment, risk management and epidemiology, exposome studies and sensor applications. Extensive knowledge in measuring and assessing (occupational) exposure using new technology (e.g. sensors), modeling exposure using several methods and stakeholder involvement. He was involved/coordinates studies related to sensor applications and exposome research in HEALS, and is instrumental in establishing the international collaboration for occupational exposome together with NIOHS (USA) and HSE (UK). ~20 publications on exposure and risk assessment/management, epidemiology, sensor applications.

Shaji Krishnan, PhD (senior scientist) (M), is experienced in mathematical modeling (> 25 years). His interests are in developing mathematical models and fundamental data structures/high-throughput data-integration schemes to characterize health and progressive shifts towards disease from a system dynamic (complexity theory) perspective. Applications of these in toxicogenomics, immune health, and exposure studies. He currently advises one PhD student in developing a computational hepatic model. 30 publications in the areas of mathematics, physiological models (satiety, type2 diabetes), and machine/deep learning models, semiconductors, chemometrics.

Astrid Kruizinga, MSc (project manager) (F), is a senior project manager. Her main fields of interest are health and risk assessment. She managed several international projects in the area of risk assessment and knowledge investment projects and has been involved in the FP7 project iFAAM (WP leader) and was grant holder of the EU COST Action Imparas.

### Selected publications and/or products, services


4.1.2 Fundacion privada instituto de salud global Barcelona

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<tr>
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<td>Manolis Kogevinas, Michelle Turner, Xavier Basagaña, Gemma Castaño Vinyals</td>
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</table>

Short description of the organisation

ISGlobal is a cutting-edge institution with capacity to address global public health challenges through research, translation and education, with 407 members and 42 research groups. ISGlobal has an ambitious vision as a world-class centre in research, translation and education in Global Health. The tenure track faculty is integrated by 42 group leaders, including 2 ERC. The center manages an annual budget of 24 M€, of which about 17 M€ correspond to competitive funding, especially BMGF and the EC. During 2017, ISGlobal researchers have participated in 48 international projects, coordinating 20 of them. In 2017, the scientific activity produced 440 indexed articles, 75% in Q1 IF journals and 42% in D1. In 2014-15, Scimago ranked ISGlobal amongst the best 6% research centres worldwide in two size independent bibliometric indicators: normalized impact factor and excellence with leadership. Complementarily, health policy activities place ISGlobal in the Top-20 Health Policy Think-Tanks, and the 4th in Europe (U. Pennsylvania Index Report). ISGlobal received the Human Resources Excellence in Research accreditation (HRS4R) from the European Commission in 2015. ISGlobal has been a pioneer in exposome studies in Europe and has considerable experience in advanced methods in exposure assessment, omics and complex analyses.

Tasks in the project

ISGlobal will lead WP7 “Exposome studies on night shift work and health”; co-lead WP5 “EPHOR mega cohort” also involving data analysis on shift work; contribute with the exposome cohorts in Spain (GCAT); participate in WP3 (Luminex and sex steroid analyses); participate in WP6 with the ECRHS-Spain cohort; participate to lesser extent in all other WPs.

Experience: projects or activities/infrastructure

This project builds on institutional capacity in environmental exposure assessment, epidemiology, and exposome research developed through previous EC funded projects including:

A description of any significant infrastructure and/or any major items of technical equipment, relevant to the proposed work

Scientific environment: ISGlobal is one of the largest global health institutions in Europe and provides a hub of excellence in research and health care. Evaluation, Support and Prevention unit: Oversees the management of research, providing quality improvement management (BPC, BPL, ISO), methodological and ethical support for research projects and methodological and ethical support for clinical trials.

Medical Library: provides all necessary scientific information for research and ongoing training by acquiring, cataloguing, preserving and making available suitable collections of books, journals and documents in any format. Bioinformatics unit: Provides researchers with services of consultation, planning next generation sequencing (NGS) and other genomic and transcriptomic experiments, NGS data processing, analysis and management, software and database development, bioinformatics training, and access to high-performance computing resources.
Geographic Information System (GIS): The unit has capacity to map and model exposure and health information by implementation geospatial technologies. The use of a relational database allows to process big volumes of data efficiently.

**Curriculum Vitae**

**Professor Manolis Kogevinas** (male) is a senior researcher at ISGlobal. His research focuses on the evaluation of environmental, occupational and genetic factors in relation to cancer, respiratory diseases and child health. In recent years he has conducted research on the effects of circadian disruption on health and in studies on the exposome. He has published more than 600 scientific papers in peer-reviewed journals. He has been the President of the International Society for Environmental Epidemiology (ISEE) in 2016-2017.

**Michelle Turner** (female), PhD, is an Assistant Research Professor at ISGlobal. Her primary research interest is examining environmental and occupational determinants of health in large-scale epidemiological studies. Most recently, she was unanimously elected as Vice-Chair and Grant Holder of the 28-country European Cooperation in Science and Technology Action “Coordination and Harmonization of European Occupational Cohorts (OMEGA-NET)”. She was also recently elected as Secretary-Treasurer 2019-2020 of the International Society for Environmental Epidemiology.

**Xavier Basagaña** (male), PhD. He joined CREAL-now ISGlobal Campus MAR-in 2008 as an Assistant Research Professor in Biostatistics. His main lines of research include: Statistical methods to produce valid interferences in observational studies; Relationships between extreme temperatures and health; and Relationships between air pollution and health.

**Gemma Castaño Vinyals** (female) is a senior Scientific Project Manager at ISGlobal. She is involved in several projects regarding non-communicable diseases and environmental exposure, specifically working in the multicase-control study including high incidence tumours in Spain, in studies on circadian disruption, studies on occupational health, and studies on radiation epidemiology.

**Selected publications and/or products, services**


4.1.3 **Institute of Occupational Medicine**

<table>
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<td>Miranda Loh, Susan Young</td>
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**Short description of the organisation**

The Institute of Occupational Medicine (IOM; [http://www.iom-world.org](http://www.iom-world.org)) is a major independent centre of scientific excellence in the fields of occupational and environmental health, hygiene and safety. Established in 1969 and fully independent since 1990 with a strong ethos of multidisciplinary collaborative research, including epidemiology, human exposure assessment, statistical methods, health effects and mechanisms of disease, central to IOM’s research and consultancy in occupational, environmental and public health. This work is conducted in the EU, UK, Asia, Africa and North America, including Government departments, international agencies, industry associations, local authorities and industrial and commercial companies. IOM is a WHO Collaborating Centre in Occupational Health and provides reviews for policy support on emerging occupational health issues for the European Commission and European Parliament. IOM has considerable project experience, participating in over 40 EU Framework projects, as well as numerous national and international projects both as a coordinator and as a partner.

**Tasks in the project**

IOM leads WP1, including the development of the external exposome study protocol, and liaises with WPs 4, 6, 7, 9, and 10. IOM will also lead Task 1.3. IOM will play an active role into stakeholder engagement in WP10
HEALS (partner) The main aim of the Health and Environment-wide Associations based on Large population Surveys (www.HEALS-eu.eu) project was to develop a methodology to collect data on internal and external exposure within an exposome paradigm and to relate this to health information. EU Twinning Exposogas (https://www.exposogas.eu/) in the application of the exposome to optimise health/safety in the petrochemical industry (together with TNO and CUT). Revising the Good Work, Good Health Guidelines (VS/2017/0366) Review and updating of guidance for EU telecoms industry. Return to work after cancer: developing guidance and case studies to aid employers manage health and safety issues Systematic review, case studies and guidance to aid in the management of H&S of workers returning to work after cancer CITISENSE (IOM were a partner) Development of sensor-based Citizens' Observatory Community for improving quality of life in cities. Occupational l-health in the Singapore Construction Sector: Cancer/Respiratory Diseases The research estimated the occupational cancer and COPD health burden in the construction sector in Singapore.

A description of any significant infrastructure and/or any major items of technical equipment, relevant to the proposed work

NA

Curriculum Vitae

Dr. Miranda Loh (F) is a Senior Scientist working in the Centre for Human Exposure Science. She has been involved in evaluating air pollution and physical activity sensors and is using a multi-stressor indoor and personal exposure assessment system, based on sensor technology, that can be used in exposome studies as part of HEALS. Her work on environmental health extends also to Asia, as PI for the Air Pollution Impacts on Cardiopulmonary disease in Beijing: An integrated study of Exposure Science, Toxicogenomics & Environmental Epidemiology (APIC-ESTEE) funded by the British Natural Environment Research Council, the Medical Research Council, and China’s National Natural Science Foundation.

Dr. Karen Galea (F). Karen Galea leads the team of exposure scientists. She holds a PhD in Environmental Medicine, MSc in Occupational Hygiene and First class Honors in Environmental Health. Experienced as an exposure scientist, project leader and supervisor on a wide range of human exposure assessment projects. She has a special interest in large-scale occupational and residential field measurement campaigns, involving pesticide, diesel exhaust, silica, crude oil exposures, dermal exposure assessment and low costs sensor technologies.

Professor Damien McElvenny (M) is a biostatistician and is principal epidemiologist with > 30 years’ experience. He has a master’s degree in statistics from the University of Sheffield and a PhD in epidemiology from the London School of Hygiene and Tropical Medicine. He is a member of the International Commission on Occupational Health, the International Epidemiology Association and the Society for Social Medicine. He has recently been made an honorary member of the Society for Occupational Medicine and Honorary Senior Research Fellow at Manchester University. He leads a number of epidemiological projects at IOM including cohort studies of workers in the rubber, hard-metal and lead industries.

Dr. Joanne Crawford (F) leads the Ergonomics and Human Factors section. Joanne has over 25 years’ experience in research and consultancy in ergonomics and human factors. As a Chartered Ergonomist and Human Factors Specialist, she has directed a large number of research projects which have included systematic reviews, case study based research, stakeholder engagement and larger surveys and workplace assessments. Her research has encompassed a wide range of workplace and broader issues including the impact of ageing on ability to work, knowledge transfer for OSH professionals, rehabilitation and return to work after cancer, air pollution and behaviour and a number of projects examining musculoskeletal disorders. She has also been involved in a number of EU projects including e-capacit8, CITI-SENSE and the ongoing NANOREG2 project.

Dr. Ioannis Basinas (M) Ioannis is a senior scientist within the Exposure Science section of our Research Division. His research interests focus on the establishment and application of improved methods for quantitative exposure assessment based on statistical and mathematical modelling approaches. Ioannis has substantial experience in the assessment of exposure to organic dusts and the related health risks. Previously he was responsible for one of the largest exposure assessment studies on personal bio-aerosol exposures of farmers ever accomplished. He has also been involved in several studies aiming to guide and optimize exposure control
strategies for bio-aerosol exposures in farm workplaces, and extensively worked towards the assessment of the burden of historical exposures to organic dusts. Currently he is involved in several projects related to the assessment of exposure to engineered nanomaterials, organic dusts, and the evaluation of Tier 1 models used under REACH. Ioannis won the Thomas Bedford Memorial Prize in 2018.

Ms Susy Young (female) is the Research Operations Manager at the IOM and works closely with our scientists on project management activity of all research and large consulting projects. She has more than 25 years’ experience working in a scientific environment, 20 of which have been in managing research quality and progress. She is responsible for coordinating all research and large consulting projects within the IOM, which include managing the financial and administrative aspects of the work, especially for large projects that we are coordinating/leading e.g. BIORIMA (H2020), APIC (NERC), TAPHIA (MRC).

Selected publications and/or products, services


4.1.4 Aarhus Universitet

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<tr>
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<th>Participant No. 4</th>
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<td>Persons in charge</td>
<td>Vivi Schlünssen</td>
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Short description of the organisation

Aarhus University (AU) was founded in 1928. It has 39,000 students; about 1,800 PhD students – of which one in four has a foreign nationality - and close to 850 postdoctoral scholars together with 11,500 employees (2017). AU has four faculties which cover the entire research spectrum – basic research, applied research, strategic research and research based advice to the authorities.

In recent years AU has been moving up the most important university ranking lists. In 2018 the university was number 111 at the Leiden Ranking and number 123 of 17,000 universities on the Times Higher Education World University Ranking (2019). The Department of Public Health works to promote public health. We conduct research into the health challenges facing society – to promote health and to prevent, treat and alleviate disease. The Research group Headed by Schlünssen and Sigsgaard performs epidemiological and toxicological studies of aerosol effects on human health. Key priorities are occupational exposures and respiratory diseases. The Department is part of Danish Ramazzini Centre, a regional research network on occupational and environmental medicine. Further information and key figures can be found at [http://www.au.dk/en/about](http://www.au.dk/en/about) and [http://www.ramazzini.dk/](http://www.ramazzini.dk/)

Tasks in the project

coordinates WP6: Working life exposome, lung function, and obstructive lung disease among men and women. Involved in WP1,2,3,4,5,8,9,10

Experience: projects or activities/infrastructure

A description of any significant infrastructure and/or any major items of technical equipment, relevant to the proposed work

- A well-equipped laboratory for clinical field studies and analysis of environmental exposures
- Infrastructure for clinical fieldwork
- Infrastructure for register-based research
- Access to statistical and data-management expertise
- Collaboration with Department of microbiology with expertise in analysis of environmental microbiome

Curriculum Vitae

Vivi Schlünssen, MD (F), Professor. Department of Public Health, Environment, Occupation and Health, Danish Ramazzini Centre, Aarhus University/ the National Research Centre for the Working Environment, Copenhagen. Specialist and former consultant in Occupational Medicine. Research profile: Respiratory diseases, allergy and exposure assessment, mainly in the Public Health and the occupational field. 150+ peer reviewed papers, H index GOS 33. Former head of Danish Society for Occupational and Environmental Medicine. Chairman of The Danish Working Environment Authority’s board for occupational exposure limits.

Torben Sigsgaard, MD, PhD (M), Professor & Head of Post Graduate Prg in Public Health, Department of Public Health, Environment, Occupation and Health, Danish Ramazzini Centre, Aarhus University. Research profile: Respiratory diseases, allergy, Epidemiological as well as toxicological studies emphasis on environmental and occupational exposures; Twentyeight completed and six current PhD students. Papers in peer reviewed journals: 200+ H-factor 39 SCI. Book chapters: 9. Former head of assembly Epidemiology and Occupation, European Respiratory Society & WG Organic Dust, ICOH.

Henrik Kolstad, MD, (M), Professor, Department of Occupational Medicine, Danish Ramazzini Centre, Aarhus University Hospital. Consultant in occupational medicine. Research profile: Epidemiology of occupational exposures (chemical substances, noise, shift work, psychosocial factors) and health effects (cancer, mental disorders, cardiovascular and respiratory diseases) and exposure assessment. More than 140 peer reviewed papers, H-Index 31 WoS. Head of Danish Ramazzini Centre.

Selected publications and/or products, services


4.1.5 Karolinska Institutet

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<tr>
<th>Participant</th>
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<td>Maria Albin, Håkan Tinnerberg, Karin Broberg, Jenny Selander</td>
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Short description of the organisation

*Karolinska Institutet (KI)* is the only Swedish university focusing especially on biomedical sciences. KI ranks as one of the world’s leading medical universities, aiming at excellence in research, which accounts for 40 per cent
of all medical research in Sweden. About 80 per cent of KI’s income is devoted to research, distributed among around 750 research groups covering all medical fields. Research at KI has a strong European dimension with ~200 projects supported by EU FP6, of which 28 were coordinated by KI. Within FP7 323 and 36 coordinated as well as 31 European Research Council Grants. Within H2020 until now awarded 177 contracts. KI is also a major European beneficiary of funds from the National Institutes of Health in the U.S. The Institute of Environmental Medicine (IMM; https://ki.se/en/imm/startpage) is a research department at KI and provides authorities in Sweden and EC as well as international organisations (e.g. WHO) with expertise on environmental health risk assessments. Research at IMM is carried out in four major areas: epidemiology, toxicology, physiology, environmental and occupational medicine. IMM has about 350 employees and associates, The Unit of Occupational Medicine at IMM has a multidisciplinary team with 56 members and associates, including 4 professors, 3 assistant professors, 5 post docs, and 8 PhD students. The yearly budget is 2.5 million Euro mainly from external funding (Swedish Research Council, Swedish Research Council for Health, Working Life and Welfare, AFA Insurance; VINNOVA-the Swedish Innovation agency, and the Nordic council of Ministers). Many associates work at the clinical Centre of Occupational and Environmental Medicine, serving the County of Stockholm. The Unit of Metals and Health at IMM is a team with 10 members and associates, including 3 professors, 1 assistant professor, 1 post doc, and 5 PhD students The yearly budget is 1.3 million Euro with mainly external funding (e.g. Swedish Research Council for Health, Working Life and Welfare). Researchers at the unit participate in health risk assessments, for a.o. EFSA, the Swedish Chemicals Agency, and the American Academy of Sciences.

**Tasks in the project**

KI will coordinate WP2 and participate in WP3, WP4, WP5, WP6, WP7, WP9 and W10.

**Experience: projects or activities/infrastructure**

KI has long experience in epidemiology often creating and using job-exposure matrices for exposure assessment in large register-based studies. The construction of a new comprehensive multidimensional Swedish job-exposure matrix (SweJEM) is such an undertaking serving major research programs including cardiac diseases in people of working age (https://ki.se/en/news/multimillion-grant-to-ki-researcher-from-afa-forsakring); and effects on the mother and child of occupational exposures during pregnancy (https://ki.se/en/imm/projects-occupational-epidemiology-and-chemical-exposure-assessment). Other projects focus on working hours (based on individual records form 2009 and on for 60,000 subjects) and cardiovascular disease, birth outcomes, and cancer; psychosocial factors, ergonomics and work-life participation and return-to-work. A new research field is new employment relations, including precarious work (https://ki.se/en/imm/the-new-world-of-work). Current projects involving advanced biomarker analyses addresses health risks of welding fumes, PAH exposure, and nanocellulose.

**A description of any significant infrastructure and/or any major items of technical equipment, relevant to the proposed work**

Significant infrastructure for the EPHOR project is the comprehensive multidimensional job-exposure matrix SweJEM, and large population-based multi-generational cohorts (up to 9 million) with extensive information on job history, socioeconomics, often life-style factors, and multiple health outcomes. Further, infrastructure enables the analytical and molecular laboratory for metallomics and (epi)genetic biomarker analysis, as well as bioinformatic competence for targeted and non-targeted analyses.

**Curriculum Vitae**

**Maria Albin:** MD, PhD, Professor (Occupational Medicine) (F). Head of the Unit of Occupational Medicine, and has published extensively mainly in the fields of occupational cancer, respiratory and cardiovascular disease, but lately also on working-life expectancy. She is member of the advisory board to the Swedish Work Environment Authority, and served in the Swedish national commission on inequalities in health. Member of the core management committee in two COST-actions.

outcomes including mental health, cardiovascular and chronic kidney diseases as well as occupational injuries.

**Karin Broberg:** PhD, Professor (Genetic Occupational and Environmental Medicine) (F). She is the head of the Unit of Metals and Health, and professor in Occupational and Environmental Medicine at Lund University, Sweden. Her research focuses on genetic and epigenetic mechanisms of work-related diseases in different occupations, e.g. welders and PAH-exposed workers. Her research is mainly based on epidemiological studies combining advanced assessments of exposure with biomarkers of early disease, including omics. Member of two COST-actions.

**Jenny Selander:** MSc, PhD, Assistant Professor (Occupational and Environmental Medicine) (F). Unit of Occupational Medicine at the Institute of Environmental Medicine, Karolinska Institutet. The main focus of her...
research is on Physical (noise, vibration) and chemical (particles, solvents etc) exposure and its effect on pregnancy, cardiovascular disease and cancer. She has many ongoing studies and collaborations within this area of research, for instance within NORDSOUND and NOCCA (The Nordic Occupational Cancer study).

Håkan Tinnerberg, Certified Occupational Hygienist, Assistant professor (Occupational hygiene) (M). His main research focus is about methods for exposure assessment in epidemiological studies, especially for chemical exposures. He is involved in the development of SweJEM, and has long experience from assessing exposures from different environments, among them PAH, isocyanates, and welding fumes.

Selected publications and/or products, services

4.1.6 Katholieke Universiteit Leuven

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<td>Lode Godderis, Manosij Ghosh</td>
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Short description of the organisation
KU Leuven (academic staff ~7296) is currently by far the largest university in Belgium in terms of research funding and expenditure (EUR 475 million in 2017), and is a charter member of LERU. KU Leuven conducts fundamental and applied research in all academic disciplines with a clear international orientation. Ranked as the 21st European university (Times Higher Education). Listed as the first European university (Reuters Top 100). > 400 projects in H2020 approved. 11th place of European HES institutions hosting ERC grants. Since 1972 124 spin offs. The Department of Public Health and Primary Care is a multidisciplinary department with a focus on community health, best practice and health policy. Within the Dept. the Centre for Environment and Health (CEH) studies the impact of/interaction with environment in relation to health. CEH works in the field of environmental medicine, toxicology and hygiene. Key research lines include biological effects of (nano)particles, organic solvents and monomers, genetic/epigenetic effects, mechanisms in pulmonary toxicology, clinical-epidemiological effects of occupational and environmental exposures and diseases. CEH is composed of two laboratories closely related, with convergent scientific and research interests. The laboratory for Occupational and Environmental Toxicology, with expertise in epidemiological and toxicological research on the effects of air pollution and respiratory toxicants on lung and cardiovascular parameters. The laboratory for Occupational and Environmental Hygiene specialized in monitoring airborne and biomonitoring of urinary contaminants. Moreover, the CEH has a close collaboration with several national and international research centers, mutuality’s and occupation health providers.

Tasks in the project

Experience: projects or activities/infrastructure
The laboratory has an expertise in the development and validation of sampling and analytical methods for assessing occupational exposure to stress (saliva cortisol levels) and occupational exposure to chemical agents (in air, on skin and in urine). All used analytical methods are either based on available reference methods (NIOSH, OSHA, MDHS,…) or in-house developed and validated. The laboratory has been granted formal accreditation, according to the Belgian Royal Decree of 31 March 1992, for different sampling and analytical methods. The most recent certification is published on December 20th, 2012. As an accredited lab, the laboratory maintains a quality system, as described in the European Standard EN ISO/IEC 17025 “General requirements for the competence of testing and calibration laboratories”. General lab procedures and analytical methods are well described in our quality handbook and in various SOPs (Standard Operating Procedures). The laboratory also participates in interlaboratory comparison tests (2 times per year). Projects: Human biomonitoring of chemical exposure in the workplace: method development and application to chromatome study: methods based upon Exhaled Breath Condensate. European Human Biomonitoring Initiative. The ‘Maternal Nutrition and Offspring’s Epigenome’ (MANOE) study. Parental Pesticide and Offspring Epigenome study (PaPOE)

A description of any significant infrastructure and/or any major items of technical equipment, relevant to the proposed work


Curriculum Vitae

Lode Godderis (M): Full professor at the Centre for Environment and Health of the University of Leuven. He investigates the impact of environment on health by unravelling the underlying epigenetic mechanism and also the reverse how health can affect work (dis)ability. He leads the division of the Laboratory of Occupational and Environmental Hygiene. The lab analyses air samples and biological samples of workers. He is also director Knowledge, Information and Research at IDEWE (External Service for Prevention and Protection at Work) where he leads a team specialized in questionnaire studies on psycho-social risks and analysis of medical data for companies and sectors. He is the current chair of Modernet: an international network for development of techniques for discovering trends in work-related diseases and tracing new and emerging risks. A full list of projects and publications are available at: http://www.kuleuven.be/wieiswie/en/person/00005874.

Manosij Ghosh (M): FWO post-doctoral fellow at the Centre for Environment and Health, KU Leuven. He studies the cellular and molecular mechanisms of nanoparticle and ultrafine particle toxicity. This includes unravelling epigenetic mechanisms that regulate gene activity and the proteome in response to external stimuli in a translational study design. As a senior post-doctoral fellow, he is involved in several collaborative projects aiming to understand the impact of environmental and occupational factors on Epigenome, together with Prof Lode Godderis and Prof Peter Hoet. A full list of publication is available at: https://www.kuleuven.be/wieiswie/en/person/00095907

Selected publications and/or products, services

4.1.7 Statens Arbeidsmiljøinstitutt (National Institute of Occupational Health), Norway

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</table>

**Short description of the organisation**

Statens Arbeidsmiljøinstitutt (STAMI) is the Norwegian research institute on work environment and occupational health, funded by the Ministry of Labour and Social Affairs, and collaborating with the social partners in Norwegian working life. STAMI has approximately 120 employees from various professional backgrounds, such as medicine, epidemiology, biology, chemistry, toxicology, psychology and sociology, performing interdisciplinary research. STAMI has received good evaluations on occupational health research. In addition to research, STAMI also gives advice to the Norwegian authorities for work environment, partners of the working life (employers’ and employees organisations), and organises training courses for Occupational Health Service professionals and occupational toxicology. The Department of Occupational Medicine and Epidemiology has approximately 20 employees, most medical doctors and other health professionals, involved in research, 15 with PhD. The department also has an outpatient clinic for assessment of patients with possibly occupational and work-related diseases, with 3 residents in training for speciality in Occupational Medicine.

**Tasks in the project**

STAMI will lead WP5, *EPHOR mega cohort*, and participate in WP2 by co-leading task 2.5 on evaluation and transition into dynamic EuroJEM, and participating in other WP2 tasks. STAMI will also participate in WP3, WP4, WP6, WP7, WP8, WP9, WP10, and WP11.

STAMI (IS Mehlum) is the Chair of OMEGA-NET and will work to develop strong linkages between OMEGA-NET and EPHOR.

**Experience: projects or activities/infrastructure**

**Ingrid Sivesind Mehlum**

- 2 other projects (systematic reviews) supported by the Nordic Council of Ministers:
  - *The impact of the working environment on work retention of older workers* (2016–2017)

**A description of any significant infrastructure and/or any major items of technical equipment, relevant to the proposed work**

*EXPO*, the Norwegian national database for airborne chemical and biological work environment exposure measurements, will be used in WP2, *Task 2.3 Protocol for including new data in EuroJEM*, to collect new exposure data, as well as in *Task 2.4 Development of new and more specific JEMs*.

In WP7, STAMI will perform analyses of biomarkers of ageing (telomere length). These analyses will be performed at the Department of Chemical and Biological Work Environment of STAMI, which has experience with such analyses (Samulin Erdem J et al 2017, *Cancer Med*. 2017, 6(8):1988–1997. doi: 10.1002/cam4.1135) and all necessary methods and instrumentation.
Ingrid Sivesind Mehlum (female), MD PhD, Specialty in Occupational Medicine, Chief physician and Department head of Occupational Medicine, Dept. of Occup. Med. and Epidemiology. Chair of COST Action OMEGA-NET. Network on the Coordination and Harmonisation of European Occupational Cohorts (CA 16216).

Since 2000, she has been involved in several projects at STAMI, and has been PI or co-PI of many of these, most based on national registry data or survey data, with aim to study work-related health problems in the population, and the impact of working conditions on gender differences and social inequalities in health. She has also worked in Occupational Health Services (part-time for 15 years) and in the Norwegian Labour Inspection Authority (9 years in total, 4 years full-time, 5 years part-time).

Selected publications and/or products, services


4.1.8 The University of Manchester

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<tr>
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<tbody>
<tr>
<td>Function</td>
<td>WP8 lead</td>
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<tr>
<td>Persons in charge</td>
<td>Martie van Tongeren</td>
</tr>
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Short description of the organisation

The University of Manchester was created in 2004 by bringing together the Victoria University of Manchester and UMIST. The University of Manchester is the UK’s largest single-site university, and ranked 8th in Europe in the 2018 Academic Ranking of World Universities. > 4,000 staff active in research, 25 Nobel Prize winners, and income in excess of £1 B. The University has extensive experience of administering EU funding, having participated in 395 FP7 projects including 27 Marie Curie ITNs, and is currently participating in 244 H2020 projects including 16 Marie Curie ITNs. It has the largest ever capital investment programme in UK higher education, with more than £750m invested since 2004 in buildings, research infrastructure and core technologies, integrating clinical, life sciences, engineering and physical sciences. Together with its partner, Manchester University NHS Foundation Trust (MFT; a linked 3rd party in DOHART-NET), the University of Manchester also forms the largest clinical academic campus in the UK, and has unrivalled influence over the local health ecosystem through Health Innovation Manchester, which is responsible for transforming the health of the region with the first devolved health and social care budget in the UK.

Tasks in the project

UNIMAN leads WP8, contribute in particular to WP1 (external exposome and data analyses), WP2 (protocol development and dynamic EUROJEM vs2), WP4 (text mining), and provide input into WP5 and WP9. Input on health economics health impact analysis (WP8) and statistical components. Providing text mining pipeline/coding to support the understanding of exposome (WP4) and provide input in protocol development for updating JEMs (WP2).

Experience: projects or activities/infrastructure

[Open Mining Infrastructure for Text and Data (OpenMinTeD) project](https://example.com) for interoperable text mining infrastructure that unites the efforts of several key players in the text mining world. [SHECAN – Socio-economic, health and environmental impact of possible amendments to the EC Carcinogens and Mutagens Directive](https://example.com) Project to provide a robust assessment of the health, socioeconomic and environmental impacts associated with a
A description of any significant infrastructure and/or any major items of technical equipment, relevant to the proposed work

National Centre for Text Mining, www.nactem.ac.uk, the first publicly funded centre in the world, specializing in biomedical text mining. Professor Ananiadou is the Director of the centre since 2005.

Curriculum Vitae

Prof Martie van Tongeren (M) is professor of Occupational and Environmental Health. He leads The Health and Occupation Research network (THOR), which is a national occupational health surveillance schemes in the UK, which collects medically certified data on occupational disease. His main expertise is in occupational and environmental exposure assessment and has collaborated in a wide range of international collaborations, including epidemiological projects (occupational exposures and brain tumours), health impact assessment (SHECAN – health and economic impact assessment of changes to the EC carcinogen directive) and risk assessment of nanomaterials.

Dr. Luke Munford (M) is an academic health economist. He was worked on numerous aspects of economics and health economics, including: the effectiveness and cost-effectiveness of medical technologies; analyzing large scale public policies such as pay-for-performance schemes; investigating the determinants and consequences of health, ill-health, and health inequalities; and the spatial patterns and clustering of public health. He currently holds a prestigious MRC Skills Development Fellowship, as well as grants from the ESRC, NIHR, Health Foundation, and Northern Health Services Alliance.

Dr. Matthew Gittins (M) is an applied medical statistician in the Centre for Biostatistics. Matthews PhD investigated through empirical and simulated data factors influencing the dose-response and short term lag structure associated with exposure to air pollution and temperature on mortality (Pneumonia, COPD, and Ischemic Heart Disease). More recently Matthew has been working on large scale observational epidemiology studies investigating occupational health, autoimmune disease, stroke, and renal failure using large observational datasets such as Biobank and the Stroke Sentinel National Audit Programme (SSNAP).

Professor Sophia Ananiadou (F), Professor in Computer Science, Director National Centre for Text Mining (NaCTeM, www.nactem.ac.uk) the 1st publicly funded text-mining centre in the world, Turing Fellow, Deputy Director Data Science Institute, University of Manchester. >10 years active in the field of text mining, with particular emphasis in biomedicine. Internationally leading within top 30 most cited scholars worldwide in text mining (h-index 51). Research areas: the automatic extraction of concepts and their normalization, the development of large scale terminologies for biomedicine using distributional semantics, string similarity measures, and alignment, e.g., BioLexicon and development of scalable semantic search systems for indirect association mining FACTA+ and for massive analysis of full papers e.g. Europe PubMedCentral (3.4M papers) all supported by an interoperable text mining platform, Argo (OpenMinted).

Selected publications and/or products, services

5. Carder, M; Darnton, A; Gittins, M; et al. Chest physician reported, work-related, long latency respiratory disease in Great Britain EUROPEAN RESPIRATORY JOURNAL Volume: 50 Issue: 6 Article Number: 1700961 Published: DEC 1 2017.

4.1.9 Utrecht University

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<td>Persons in charge</td>
<td>Prof. Roel Vermeulen, Dr. Susan Peters</td>
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**Short description of the organisation**

The Institute for Risk Assessment Sciences (IRAS), Utrecht University is a leading institute in the field of environmental health risk assessment in Europe. Within the Netherlands Utrecht University is ranked first in the Shanghai Academic Ranking of World Universities (ARWU) and in Life Sciences and Medicine according to QS World Rankings. Worldwide Utrecht University is ranked 52nd in the ARWU. The IRAS is a partnership between the faculties of Medicine and Veterinary Medicine that has an excellent research organisation and a widespread international network. Besides (occupational) epidemiologists the IRAS hosts biostatisticians, exposure scientists, physicians and data managers, all relevant for the present proposal. Specifically, the Environmental Epidemiology Division of IRAS conducts research on environmental contributors (non-genetic factors including lifestyle, environmental, occupational exposures) to various non-communicable diseases. The institute has a strong track-record in combined risk assessments using the Exposome and One Health paradigms.

**Tasks in the project**

WP-leader WP4. Data management and analytical platform (Yoda) for all other WPs. Task-leader within WPs 2, 5, 7

**Experience: projects or activities/infrastructure**

PI of the EPIC-NL study, which is a combination of two Dutch cohorts that together contribute almost 8 percent (n=40,092) of the individuals to the EPIC pooled cohort. Detailed characterization of environmental, lifestyle, and dietary factors is available for all individuals in the cohort. In addition, a blood sample was taken for each individual at inclusion into the cohort and is stored at -80 degrees Celsius. In 2011 and in 2015 EPIC-NL participants received a questionnaire in which (among other factors) their exposure to shift work was assessed. Coordinates the NIGHTINGALE study, which is a prospective cohort study and has a study population of almost 60,000 (former) nurses. Approximately 50% of participants donated toenails for DNA analyses. Questionnaires compatible to the one used in EPIC-NL were used to assess exposure to occupational risk factors including shiftwork. Coordinates the AMIGO study, which is a prospective cohort study of 15,000 individuals randomly sampled from the general population. Questionnaires compatible to the one used in EPIC-NL were used to assess exposure to occupational risk factors including shiftwork. Developed several Job Exposure Matrices (DOMJEM, ALOHA, BENJEM, EMF-JEM, Shock-JEM) and have built several exposure databases containing occupational exposure measurements (e.g. DERMDAT, Synergy, Benzene). Partner in EU FP7 EXPOSOMICS. EXPOSOMICS aims to develop a new approach to assess environmental exposures, primarily focusing on air pollution and water contaminants. Using ‘omic’ techniques the collected exposure data is linked to biochemical and molecular changes. Partner in HBM4EU project. HBM4EU uses human biomonitoring to assess human exposure to chemicals in Europe, to better understand the associated health impacts and to improve chemical risk assessment. IRAS is involved in several work packages, primarily focused on human exposure to mixtures of chemicals, emerging substances, and integrated modeling of exposure-biomarker-health relationships. Partner in OMEGA-NET. Occupation and paid employment is an essential component of adult life and a major determinant of health and healthy ageing. Europe currently has some of the most valuable occupational, industrial, and population cohorts worldwide. The lack of integration of these cohorts hampers the optimal exploitation of these resources, essential to underpin evidence-based interventions and policy. The overarching concept of OMEGA-NET is to create a network to optimize the use of occupational, industrial, and population cohorts at the European level.

A description of any significant infrastructure and/or any major items of technical equipment, relevant to the proposed work

Prof Vermeulen is co-chair of the exposome board and coordinator of the Utrecht Exposome hub. The Utrecht Exposome hub combines research on both the external exposome, focusing on sensing, exposure modelling, and e- and m-Health applications, and on the internal exposome, focusing on microbiomics. By combining these research areas, we aim to develop successful prevention and intervention strategies.
Roel Vermeulen (M) Professor of Environmental Epidemiology and Exposome Science, Institute of Risk Assessment Sciences, Utrecht University, The Netherlands. Adjunct Professor, Public Health department, University Medical Center Utrecht, The Netherlands Visiting Professorship, Imperial College London, London, UK. Prof. Vermeulen’s scientific research focuses on environmental risk factors for cancer and neurological diseases with a strong emphasis on integrating epidemiology, high quality exposure assessment, and molecular biology into multidisciplinary investigations. He is the PI of several large case-control and prospective studies in occupational and the general population. One of his main research areas is the exploration of new methods for quantifying the external and internal exposome. Prof. Vermeulen has served on many international committees including the WHO and the National Toxicology Program in the US. He is a member of the Dutch Expert Committee for Occupational Standards of the Dutch Health council. He is elected chair of the International Commission on Occupational Health (ICOH), Scientific Committee on Epidemiology in Occupational Health (EPICOH) in 2015.

Susan Peters (F) Assistant Professor, Institute of Risk Assessment Sciences, Utrecht University, The Netherlands Research Fellow, Neurology Department, University Medical Centre Utrecht, The Netherlands. Dr. Peters is an occupational epidemiologist within the team of Prof. Vermeulen at the Institute of Risk Assessment Sciences. Her research interests are exposure assessment science and chronic disease epidemiology, mainly focusing on external causes of neurodegenerative disorders. She has extensive experience working with large datasets, both from cohort and case-control studies. Dr. Peters has over 90 international peer-reviewed publications. She has served on various international committees, including for the world health organisation (WHO) and scientific committees for conferences on exposure science and occupational health, and editorial boards for international journals.

Selected publications and/or products, services


4.1.10 Institut National de la Sante Et de la Recherche Medicale

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<tr>
<td>Persons in charge</td>
<td>Marie Zins, Marcel Goldberg</td>
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Short description of the organisation

INSERM is a public research organisation in France entirely dedicated to human health. Its objective is to promote the health of all by advancing knowledge about life and disease, treatment innovation, and public health research (https://www.inserm.fr/en/about-inserm).

INSERM-UMS 11 (Population-Based Epidemiological Cohorts Unit) is a unit of INSERM. UMS 11 is managing Gazel and Constances, two large population-based cohorts. Gazel is composed of 20 000 subjects aged 35-50 at inception in 1989, almost 30 years ago; all were working in the national utility company at that time and are retired now. Constances is a representative sample of 200 000 persons of the French adult population aged 18-69 at inception; recruitment began in 2012 and will be completed in 2019. In both cohorts, numerous data on occupational factors and health useful for the project were prospectively collected and are available for research.

Tasks in the project

We will contribute to different WPs, (in particular WP5,6) thanks to the availability of the data of the CONSTANCES cohort composed of 200,000 French people aged 18-69 at inception. Numerous available data on occupational exposure and health will be used.

Experience: projects or activities/infrastructure

UMS 11 is involved in several research consortia:
A description of any significant infrastructure and/or any major items of technical equipment, relevant to the proposed work

CONSTANCES Cohort: composed of 200,000 subjects aged 18-69 at inclusion; subjects benefit from a comprehensive health examination at inclusion, including a full battery of cognitive and physical functioning test as young as 45; follow up includes a questionnaire every year, a new health examination every 5 years and permanent linkage to health, socioeconomic and mortality national databases; the major outcomes collected include quality of life, morbidity (main diseases), disability, frailty, mortality; for subjects aged 45 and more, cognitive and physical functioning; a biobank of 85,000 subjects is under construction (blood and urine). Full job histories and linkage with job-exposure matrices allow for the assessment on occupational exposure to different types of agents.

Curriculum Vitae

Dr. Marie Zins, MD, PhD (F), is the Director of INSERM-UMS 11. Her background is in medicine, public health and epidemiology. Her main personal field of interest if the study of social and occupational determinants of and health behaviours. As PI or co-investigator on several studies, she has a long experience in managing large prospective and complex data sets

Professor Marcel Goldberg (M) is Emeritus Professor of Epidemiology and Public Health at Paris Descartes University and was for a long time the director of an INSERM research Unit on occupational and social epidemiology. His main scientific fields of interest are occupational epidemiology (cancer, musculoskeletal disorders, psychosocial factors and methods of evaluation of occupational exposure), and social epidemiology (determinants of health inequalities). Marcel Goldberg is also co-PI of the CONSTANCES cohort.

Selected publications and/or products, services


4.1.11 Finnish Institute of Occupational Health

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<tr>
<th>Participant</th>
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<tr>
<td>Persons in charge</td>
<td>Svetlana Solovieva</td>
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Short description of the organisation

The Finnish Institute of Occupational Health (FIOH, www.ttl.fi) is a multidisciplinary research and specialist organisation that focuses on well-being at work, research, advisory services and training. It operates under the Ministry of Social Affairs and Health as an independent legal entity and has around 500 employees. FIOH has offices in Helsinki, Kuopio, Oulu, Tampere and Turku and is divided into two research and service centers: Occupational Health and Occupational Safety. FIOH aims to improve Finnish work life on the level of individual workers, workplaces, organisations, and society at large, through: (1) applied research and developmental projects, focusing on applied research and developmental projects in collaboration with national and international research institutes, universities, and public and private organisations; (2) market-priced services for private and public organisations; (3) training for occupational health and safety specialists, employers and workers; (4) specialist advisory services for the government; and (5) disseminating information to key stakeholders and general public.
FIOH’s top management is committed to constantly developing their management system in accordance with the SFS ISO EN 9001:2015 standard, which is based on the process approach and the management of quality and risks.

Tasks in the project
FIOH will have lead/co-lead tasks in WP2 (Standardized assessment of multiple exposures in large populations) and WP9 (Toolbox). FIOH will also participate in WP5 (Occupational exposure mega cohort and analyses) and WP8 (Impact assessment).

Experience: projects or activities/infrastructure

**MSD @ Lifecourse Consortium**, coordinated by Prof. Eira Viikari-Juntura. Aimed to produce new knowledge on occurrence and common occupational and non-occupational risk factors for musculoskeletal and cardiovascular diseases to be targeted in future interventions. **Assessment of physical and psychosocial occupational exposures: development of a job exposure matrix for large scale epidemiological studies on musculoskeletal disorders**, led by Adj. Prof. Svetlana Solovieva. Within this project JEM for physical and psychosocial work-related factors was developed and validated. **Systematic analysis of the effect of work-related diseases on work participation in Finland: Potential of work-targeted interventions**, led by Adj. Prof. Svetlana Solovieva. Aim is to produce a comprehensive and systematic view on the effect of work-related diseases on permanent withdrawal from the labour force and productive work participation among the Finnish workforce and estimate potential of work-targeted interventions to enhance work participation. **Nordic Occupational register – a tool for estimation of the potential workplace and population level interventions**, International project involving three Nordic countries is led by Adj. Prof. Svetlana Solovieva. Aim is to produce comprehensive systematic knowledge on the effect of common chronic diseases on work participation among the Nordic workforce and to estimate the impact of work environment and ill-health on working life expectancy. **Occupational risk factors and neurodegenerative disease (Alzheimer disease) and Risk of Parkinson Disease Associated with Solvent Exposures in Finland** both in which Sanni Uuksulainen coordinated the use of FINJEM exposure estimates and conversion work between different occupational codings. **Chemicals and work** (Sanni Uuksulainen) – Dissemination project on 10 most common chemical exposures in Finland including use description, updated exposure data, risk assessment and risk management methods. **Developing FINJEM exposure assessments for fine dust** (Sanni Uuksulainen). Aim is to produce estimates for respirable dust and carry out literature review of exposure to ultrafine particles. **Development of REACH exposure scenarios** (Sanni Uuksulainen) - research project with methanol initiative exposure scenarios.

A description of any significant infrastructure and/or any major items of technical equipment, relevant to the proposed work
FIOH has the computational requirements (hardware and software) and expertise to contribute to the project. Researchers and experts from FIOH developed the FINJEM with detailed information on chemical, microbiological and physical agents, and JEM for physical and psychosocial work-related factors. FIOH also has access to several population and occupational cohorts.

**Curriculum Vitae**

Adj. Professor **Svetlana Solovieva**, PhD (F) has PhD in both applied mathematics and epidemiology. She is an expert in the epidemiological aspects of the effects of occupational risk factors and ill-health on work participation, as well as in epidemiological methods and advanced statistical analyses of register and longitudinal cohort data. She will be involved in WP2, WP5, WP8 and WP9.

Professor **Eira Viikari-Juntura**, MD, PhD (F), specialist in physical medicine and rehabilitation, an expert in the epidemiological aspects of the effects of occupational and health-related factors as well as societal change on return-to-work and work participation. She will be involved in WP5 and WP8.

**Sanni Uuksulainen**, MSc, Senior Specialist/ Occupational Hygienist (F) is specialist in chemical exposure assessment, risk characterisation and management, consultation and training. Sanni is responsible for the FINJEM, its updating and development and is a member of NOCCA JEM development group. She has also been acting as supervisory authority according to the environmental legislations (mainly air, water and soil protection). She will be involved in WP2 and WP9.

**Taina Leinonen**, D.Soc.Sc. Specialized researcher (F) is an expert in epidemiological methods and analyses of register and longitudinal cohort data. She will be involved in WP5 and WP8.

**Selected publications and/or products, services**


4.1.12 Panepistimio Dytikis Attikis

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<tr>
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<th>PANEPISTIMIO DYTIKIS ATTIKIS</th>
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<td>Persons in charge</td>
<td>Stamatia Garani-Papadatos</td>
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**Short description of the organisation**

The PANEPISTIMIO DYTIKIS ATTIKIS (PDA), Athens, Greece and particularly the Department of Public and Administrative Health (DPH) is involved in extensive educational activity in the field of Public Health Ethics and Human Rights at a post-graduate level. This includes mainly education of public health professionals, within PDA as well as in collaboration with other academic institutions and Universities. The DPH has been active in the Bioethics field, including participation in research projects, seminars and lectures. Moreover, Stamatia (Tina) Garani has long-time involvement in many international committees.

**Tasks in the project**

T 1.3. Ethical Management, Review of legal and ethical requirements, Participation in the Ethics Committee.

**Experience: projects or activities/infrastructure**


**A description of any significant infrastructure and/or any major items of technical equipment, relevant to the proposed work**

The Department of Public Health of the National School of Public Health

**Curriculum Vitae**

**Dr. Tina (Stamatia) Garani-Papadatos (F):** Law Degree (University of Athens), Master of Arts in Medical Law and Ethics -King’s College (London), PhD (Dept of Forensic Medicine of the Faculty of Medicine -University of Athens). Short trainings at Imperial College-London, Harvard School of Public Health, Association of Schools of Public Health of the European Region (ASPHER). Since 1990 member of the academic staff of the National School of Public Health in Athens-Dept of Public Health. Visiting Lecturer in higher education institutions in Greece. Participation in various EU research projects, (Project on Persistent Vegetative State, PRIVIREAL, TEMPE, EPICC, Deinstitutionalization Ethics, EURECNET, ENERI). Deputy member of the National Authority of Medically Assisted Reproduction (2005-2010). Member of ad hoc Expert Committees of the Council of Europe, National representative of Greece- Committee on Bioethics (DH-BIO). Chair of the DH-BIO (2009-11). Independent expert of the EU DG Research and Innovation (Ethics Sector) and of the European Research Council.

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Selected publications and/or products, services


4.1.13 VTEC Engineering BV

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<tr>
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<td>Persons in charge</td>
<td>Jan Mink</td>
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Short description of the organisation

About us. VTEC Engineering, located in Eindhoven, The Netherlands, was founded in 2011 and its experience dates back to the 1980s at the time of the invention and first production of the 780 nm Compact Disk lasers. We are an independent organic growing company developing, manufacturing and selling high tech products. VTEC Engineering is part of the Dutch Persistence group. **Sensors.** We create sensors for enhancing the fitness experience, improving and monitoring the work and living conditions and monitoring of tools in harsh environments. We provide design services: Sensors for fitness environmental and maintenance, Module prototyping, Application specific testing. Our core expertise is in the field: Sensor principles and implementation, R&D and production of entire products, Hardware and software platforms for large scale deployment, Customized sensors **Internet of Things (IOT).** Intelligence is the purpose of applying IOT, after producing the validated monitoring data it is converted to information for understanding to help for control and strategy definition. For our current products we return the intelligence to help people to grow their fitness level and creates insight in the environmental air pollution and working conditions to enable improvement activities. We provide services: Bringing application requirements into solutions, Vertically integrated service. Our core expertise is: Application knowledge, Machine learning and Artificial intelligence, Data connectivity, App development, Cloud processing, App and data management.

Tasks in the project

The task of VTEC is to develop the sensors (WP1) and make the validated data available for analysis and feedback. Next to that, we will participate in the definition of the required parameters and the evaluation of the feasibility and case studies.

Experience: projects or activities/infrastructure

**Waternomics** – IOT platform to increase the awareness and improve the efficiency of use of potable water. Pilots executed in airport Linate Milano, Households in Thermi and Engineering building of University Campus in Galway. **EDOCAL** – project to show the feasibility of optical technologies for early detection of cancer in the esophagus in Cooperation with AMC in Amsterdam and Ninewells Hospital in Dundee.

A description of any significant infrastructure and/or any major items of technical equipment, relevant to the proposed work

VTEC is able to design and build complete prototypes for sensors, IOT applications and laser test setups.

Curriculum Vitae

**Jan Mink (M)** Founder & CEO graduated cum-laude from the University in Eindhoven (Physics) while working full time with Philips Electronics. After graduation he continued his career at Philips in a number of technical and managerial functions, while he was intermittently also involved in the foundation of several start-ups on a.o. semiconductor optical amplifiers, photonics, sensors and IOT the latter at VTEC Lasers & Sensors. VTEC Engineering BV was founded in 2014 for executing and supporting the European activities.

**Iris Bokkes (F)** Master Biomedical Engineering at Rijksuniversiteit Groningen, The Netherlands. Expertise on: auditory biofeedback device to improve partial weight bearing compliance; Development of insole for detection of 3D stress for diabetic patients; smart safety kit, including sound, fine dust and posture sensors in working environment; development of data analysis and dash board for real time feedback; development of fine dust sensor system to measure air pollution in urban environments.
Saujan Ghimire (M) Development, deployment and testing of software and software platform for supporting 100 fit20 studios remotely and in real time. Building generic testing and tools platform for cloud storage and analysis.

Jingjing Wang (F) Embedded software for insole sensor system. Building embedded and app software for Smart Safety kit and fit20 platform. Expert in prototyping of sensors and apps.

Lu Xia (F) Master Degree of Electrical Engineering. Application of different methods to develop models based on large set of experimental data, such as linear regression, neural network, and Gaussian process regression for machine learning, based on Matlab programming.

Zhaohan Liu (F). BSc Electrical engineering following MSc on Electrical Engineering (Eindhoven University of Technology, Eindhoven). Photonics Engineer. Experience in 25G high speed DML/EML chip characterization (DC/RF) and analysis; Experience in high speed modulator layer stack design; Experience in fiber(array)-to-chip alignment; Experience in building and testing RF over fiber link in large quantity; Experience in controlling and setting mode-hop free tunable laser for OCT application

**Selected publications and/or products, services**

1. Jan Mink and Yingying Lu, “WATERNOMICS: Low cost sensors and systems for collecting water usage in three pilots”, in 36th IAHR World Congress (IAHR 2015), The Hague, the Netherlands, 2015

### 4.1.14 University of Bergen

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**Function** Contribute to WP6

**Persons in charge** Cecilie Svanes

**Short description of the organisation**

The University of Bergen (UiB) is an internationally recognised research university. Academic diversity and high quality are fundamental for UiB, which is the most frequently cited university in Norway. The Department of Global Public Health and Primary Care (IGS) at the Medical Faculty of UiB undertakes research and research training in a wide spectrum of disciplines including: occupational medicine, epidemiology, statistics, physiotherapy, social pharmacy, genetic counselling, nursing, ethics and general practise. The Centre for International Health (CIH) at IGS aims to improve health in the poorer countries of the world, through research, teaching and capacity building. CIH collaborates with partners across UIB, Norway and the world. CIH is responsible for the UiB strategy area Global Challenges, and hosts the Centre of Excellence, the Centre for Intervention Science in Maternal and Child Health. Professor Svanes and her research group leads large population based multi-centre cohort studies of respiratory health and disease and other NCDs, addressing environmental determinants, early life and preconception origins a.o.
Tasks in the project
Involved in WP6. Leads and coordinates the protocol development for the 11 study centers from European Community Respiratory Health Survey (ECRHS) and Constances including co-ordinating the ethical approvals from all study centres.

Experience: projects or activities/infrastructure
UiB is involved in 109 FP7 projects - 38 coordinated by UiB. To date, UiB has been awarded 96 projects under H2020 of which 34 are coordinated by UiB. H2020 project ALEC “Ageing Lungs In European Cohorts”, WP-leader. RCN FRIPRO top researcher project “Preconception exposures and related epigenetic mechanisms in asthma and allergies”, PI.

A description of any significant infrastructure and/or any major items of technical equipment, relevant to the proposed work
Extensive experience with leading, developing and performing large international population based cohort studies: Professor Svanes has been a member of ECRHS steering committee since 1996, and has conceived and leads the RHINESSA multi-generation multi-center population-based cohort study.

Curriculum Vitae
Cecilie Svanes (F), professor MD PhD, shares her time between clinical and scientific work. She is a professor at Centre for International Health, a specialist in respiratory medicine and a consultant in occupational respiratory medicine. Svanes is an international top-expert on environmental determinants in early life for respiratory health and disease. Svanes is a member of the Steering Committee of the ECRHS, the world’s largest international study of asthma and allergies in adults, which results are disseminated in >500 scientific articles and guide current health care policies. She has conceived and leads the generation study RHINESSA. Svanes has an extensive and exponentially increasing scientific track record with a high scientific achievement, especially given limited time in fulltime research (H index WoS 45). Her work has been highly cited (WoS 6305 citations) and has impact on policy (cited in >15 policy documents, altmetric.com) and practice (>10 textbooks of medicine). Svanes’ main strengths as a scientist are original and innovative thinking, excellent network building capacity and expertise on environmental determinants in early life for respiratory health and disease.

Selected publications and/or products, services
4.1.15 LifeGlimmer GmbH

<table>
<thead>
<tr>
<th>Participant</th>
<th>LifeGlimmer GmbH</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Function</strong></td>
<td>Data Analytics and Bioinformatics SME for omics and pathway analysis, (semantic) data integration, and text mining</td>
</tr>
<tr>
<td><strong>Persons in charge</strong></td>
<td>Vitor Martins dos Santos, Christopher Hardt</td>
</tr>
</tbody>
</table>

**Short description of the organisation**
LifeGlimmer is an international Berlin-based company providing advanced solutions for the full research pipeline in bioinformatics, metabolic modeling, data management and integration in systems & synthetic biology. We offer tailored scientific solutions to solve complex problems in the biosciences. Our solutions facilitate the elucidation of the mechanisms underlying basic cellular processes in different organisms, and help translate this knowledge into applications of biotechnological, medical and environmental interest. In the biomedical domain, our key areas of activity include genome-scale and dynamic modelling, semantic data analytics and integration, and bioinformatics for personalised medicine and biomarker discovery. In synthetic biology we focus on the understanding and (re-)design of industrial processes. We collaborate extensively with academic, industrial and clinical partners nationally and internationally.

**Tasks in the project**
Involved in WP4 and WP9. (Semantic) Integration of omics data. Analysis of omics data / Pathway analysis for stratification of exposomes. Support in text mining (information extraction, language support). Visualisation of adverse outcome pathways for toolbox. Prototyping mobile app support near/after end of project

**Experience: projects or activities/infrastructure**

**A description of any significant infrastructure and/or any major items of technical equipment, relevant to the proposed work**

**Curriculum Vitae**
**Professor Dr. Dipl.-Ing. Vitor Martins dos Santos** (M). CSO of LifeGlimmer GmbH(Germany), has a PhD degree in Biotechnology (1992) from the College of Biotechnology, Porto, Portugal. He has done Postdocs in Molecular. Microbiology (CSIC, Granada Spain), Genomics (TIGR, Md, USA and Environmental Biotechnology (GBF, Braunschweig, Germany). He has lead the Systems and Synthetic Biology group at the Helmholtz Centre for Infection Research, Braunschweig, Germany as well as the Centre for Systems & Synthetic Biology, Wageningen University, The Netherlands. He had been the President of the Dutch Society of Biotechnology (2011-2014). He has coordinated and. participated in a substantial number of EU, national and international projects in the areas of systems biology and medicine, synthetic biology and computational biology. He has over 120 publications, 10 patents, founded 3 companies and has advised academia and industry extensively, having been. regularly involved also in science research policy.

**M.Sc. Christopher Hardt** (M) Computational Biologist, has a degree in Bioinformatics (2007) from the Free University of Berlin, Germany. He joined LifeGlimmer GmbH in 2017 working primarily on network analysis, text mining, data integration, machine learning and health software/app development. Until 2016 he worked at the Max Planck Institute for Molecular Genetics in Berlin focusing on genome analysis, systems biology as well as evolutionary genetics.

**Dr. Lorna Morris** (F) has a PhD in Biochemistry and Molecular Biology and an MSc in Computer Science. She has fifteen years of experience working as a computational biologist and scientific software developer in a range of fields, from oncology to plant taxonomy. Previously she worked on breast cancer functional genomics at the University of Cambridge, before joining the Biodiversity Informatics group at the Botanical Museum, Berlin. In 2017 she joined LifeGlimmer GmbH working primarily on next-generation-sequence and pathway analysis to...
elucidate the biological mechanisms of disease. She uses an iterative approach, working closely with clinicians and laboratory researchers to facilitate their research questions (from experimental design and data collection to data analysis, visualisation and final delivery of results).

Dr. Erno Lindfors (M) has PhD in Computational Systems Biology, Aalto University School of Science, Espoo, Finland (2011) and a MSc in Electrical and Communications Engineering, Helsinki University of Technology, Espoo, Finland (2005). After functions as software engineer and postdoc in network analysis and metabolomics, he joined Lifeglimmer in 2013, where he focuses on semantic data analytic, integration and visualization.

Selected recent publications and/or products, services

1. **SAPP: functional genome annotation and analysis through a semantic framework using FAIR principles.**

2. **Systems-level modeling of mycobacterial metabolism for the identification of new (multi-) drug targets.**

3. **SyNDI: Synchronous Network Data Integration framework.**

4. **Computational Network Analysis for Drug Toxicity Prediction.**

5. **ToxDB: pathway-level interpretation of drug-treatment data.**

### 4.1.16 Owlstone Medical Limited

<table>
<thead>
<tr>
<th>Participant</th>
<th>Owlstone Medical Limited</th>
<th>Participant No.</th>
<th>16</th>
<th>Short name</th>
<th>OML</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Function</strong></td>
<td>Exhaled breath collection + chemical and data analysis</td>
<td></td>
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<tr>
<td><strong>Persons in charge</strong></td>
<td>Max Allsworth, Chief Science Officer, Owlstone Medical Ltd.</td>
<td></td>
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</table>

**Short description of the organisation**

Owlstone Medical is a global diagnostics company developing non-invasive breath based tests for the early detection of disease, precision medicine and exposure. Its vision is to save 100,000 lives and $1.5 billion in healthcare costs by realising the enormous promise of breath-based diagnostics through the development and application of Breath Biopsy®. Breath Biopsy operates by detecting volatile organic compounds (VOCs) produced as products of metabolic processes within the body or as a result of chemicals from external sources such as environmental exposure. These VOCs may be linked to the presence of a disease or it’s early precursors such as inflammation or oxidative stress. The Breath Biopsy platform includes ReCIVA®, a proprietary breath sample collection device and the world’s only commercial Breath Biopsy Laboratory located in Cambridge, UK. Owlstone Medical’s technology is in use at over 100 clinical sites around the world and has been deployed in clinical trials for the early detection of cancer and is used by large pharmaceutical companies including AstraZeneca and GlaxoSmithKline, through precision medicine partnerships researching methods to enable therapeutics to be deployed more effectively.

**Tasks in the project**

Involved in WP3. Development of methods for the analysis of occupation specific exposure related VOCs. Providing breath collection stations for sampling at multiple workplaces. Chemical analysis of collected samples using TD-GC-MS in the Breath Biopsy Laboratory. Analysis of breath sample data, including quantification of target VOCs and discovery of exposure related biomarkers, with reference and correlation to data collected from subjects within the study by other techniques - e.g. known blood and urine-based biomarkers of exposure

**Experience: projects or activities/infrastructure**
Breath Biopsy technology currently in use at >100 sites worldwide. Breath Biopsy Lab - The world’s only dedicated commercial laboratory developed specifically for analysis of exhaled breath using TD-GC-MS. Research service contracts in place for projects with world leading pharmaceutical companies and medical institutions including GSK, AstraZeneca, Mayo Clinic. LuCID – clinical trial looking for VOC biomarkers in breath related to lung cancer, ~2000 samples collected across hospital sites in the UK and Europe. PAN - 1,500 patient study to detect multiple cancers via breath, in association with Cancer Research UK, based at Addenbrookes Hospital, Cambridge, UK. IPF Catalyst - OML winners of £240,000 grant to develop breath biomarkers for early detection of Idiopathic pulmonary fibrosis. Innovate UK funded asthma study - In collaboration with University of Manchester, £250,000 grant to identify breath biomarkers for the diagnosis of asthma and to guide effective treatment. >100 peer reviewed papers and posters. 43 patents granted and pending.

A description of any significant infrastructure and/or any major items of technical equipment, relevant to the proposed work

Breath Biopsy Lab - world’s only dedicated commercial laboratory for breath analysis using TD-GC-MS. Proprietary TD-GC-MS methods developed specifically for biomarker discovery in breath.

Breath Biopsy Collection Stations, incorporating the MacRobert award winning, CE marked ReCIVA breath sampler. Data analysis pipeline - OML’s proprietary data analysis includes confounder analysis to improve test performance.

Curriculum Vitae

Dr. Max Allsworth, Chief Science Officer (M) Dr. Allsworth is the Chief Science Officer at Owlstone Medical and has over 15 years of experience in the development of trace chemical detection technologies. He has developed sensor technologies for a vast range of applications including personal safety, food contamination and environmental monitoring. At OML he is responsible for the technical development of the breath capture devices and the analytical techniques behind biomarker identification. He has pioneered the development and application of Owlstone’s unique technologies to detect traces of chemicals in complex environments and at ever lower concentrations. Previous roles have included Senior Scientist for Kidde Research and then United Technologies Corporation after a company acquisition. Max has a multidisciplinary background primarily in physics, chemistry and material science with a doctorate in condensed matter physics and also has over a dozen patents to his name.

Selected publications and/or products, services

2. Breath Biopsy Services: [https://www.owlstonemedical.com/services/](https://www.owlstonemedical.com/services/).

4.1.17 Interaktiv GmbH

<table>
<thead>
<tr>
<th>Participant</th>
<th>Interaktiv GmbH</th>
<th>Participant No.</th>
<th>17</th>
<th>Short name</th>
<th>INTER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Function</td>
<td>IT partner</td>
<td></td>
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<tr>
<td>Persons in charge</td>
<td>Jörg Zell</td>
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</table>

Short description of the organisation

Interaktiv GmbH is a Cologne Germany-based web agency specializing in sophisticated content management and software development based on open source technologies, mainly Python and Plone CMS. With a team of 15 software engineers, designers, project managers and online marketeers we build state-of-the-art web applications, serving customers in Germany and abroad.

Tasks in the project

- Development and hosting (during the project) of the EU project website
- Development of the toolbox part of the EU website (results task 9.1-9.4)
- Make available/provide access to software tools and protocol/guidelines/factsheets/video’s etc.
- Develop online and searchable databases based on offline (excel) tables
- Interactive tool based on a table with different options for visualisations
- User experience workshops with stakeholders

Experience: projects or activities/infrastructure
Knowledge database for the German Cancer Society: We developed publication databases, enterprise search systems and a content management system during this ongoing project.

Development, maintenance and support for all CMS servers of the Uniklinik Köln "uk-koeln.de"

Leitlinienprogramm Onkologie: We developed a content management system for medical guidelines with interfaces for content publishing on different apps/devices and visualizations of treatment options as flow charts.

A description of any significant infrastructure and/or any major items of technical equipment, relevant to the proposed work

Interaktiv’s development environment contains well established processes and equipment: version control systems for code development, automatic builds and deployments (continuous integration) as well as separated server environments for development, staging and production. Error tracking and monitoring is performed using systems like Sentry and Nagios.

Curriculum Vitae

Jörg Zell, (M), CEO, project management: 20+ years of experience in project management, web application projects, Professional Scrum Master.

Johanna Lenhard, (F), COO, project management, Professional Scrum Master.

Martin Bodatsch, (M), COO, user experience consulting expert, design.

Mevissen, Jan (M), software engineer, 12 years of development experience as backend developer for websites, intranets and web applications, Professional Scrum Developer.

Lukas Guziel, (M), software engineer, 7 years of development experience as backend developer for websites, intranets and web applications, Professional Scrum Developer.

Marcel Liebischer, (M), software engineer, 13 years of development experience as backend developer for websites, intranets and web applications, Professional Scrum Developer.

Thomas Kastenholz, (M), software engineer, 7 years of development experience as frontend and backend developer for websites, intranets and web applications, Professional Scrum Developer.

Selected publications and/or products, services

1. Suzuki websites, intranets, web applications: [https://motorrad.suzuki.de/](https://motorrad.suzuki.de/), [https://handel.suzuki.de/heubach](https://handel.suzuki.de/heubach) (Sample URL of a dealership)
2. Knowledge portal designed to simplify the search for sources and resources in the fields of health and the social participation: [https://www.wissensportal-lsbt.de/](https://www.wissensportal-lsbt.de/)
3. The Guidelines International Network (G-I-N) has the world's largest international guideline library: [http://www.g-i-n.net/](http://www.g-i-n.net/)
5. University of Bonn: [https://www.uni-bonn.de/](https://www.uni-bonn.de/)

4.1.18 Cyprus University of Technology

<table>
<thead>
<tr>
<th>Participant</th>
<th>Cyprus University of Technology</th>
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</thead>
<tbody>
<tr>
<td>Function</td>
<td>Partner in WP3</td>
</tr>
<tr>
<td>Persons in charge</td>
<td>Konstantinos Makris</td>
</tr>
</tbody>
</table>

Short description of the organisation

Cyprus International Institute for Environmental and Public Health (CII), within the CUT System: The Institute was established in 2004 by the Government of Cyprus and Harvard University (Harvard School of Public Health), marking the identity and vision of the Institute, to address environmental and public health issues in Cyprus and the region (Eastern Mediterranean, northern Africa, Middle East. The goal of CII is the promotion of environmental and public health in the region through research and education. The main focus of CII research is to improve understanding of the relationship between exposures to environmental risk factors individual behavior and lifestyle patterns with human disease. Ischemic heart disease, stroke, diabetes, lung cancer (and traffic accidents) are the five leading contributors to premature mortality/morbidity in Cyprus. The underlying risk
factors are poor diet, obesity, failure to control blood pressure, cholesterol, blood sugar, smoking, inadequate physical activity and ambient air pollution. CII researchers are actively engaged in work relevant to all of these topics, and improving ways to promote the inclusion of this information in risk and decision analysis to inform public policy. The CII is ready and equipped to continue its educational, research and outreach related mission using the existing human resources and infrastructure. Our immediate concern is how to expand and grow the CII organization, University of Ioannina, Greece. His knowledge centers around the areas of health and environmental science.

**Tasks in the project**

WP3. Participate in biomonitoring and omics activities. Specifically on analysis of metals

**Experience: projects or activities/infrastructure**


A description of any significant infrastructure and/or any major items of technical equipment, relevant to the proposed work

**Agilent GC-MS/MS Triple Quadrupole Mass Spectrometer**
The laboratory is a spacious facility housing wet and dry research benches, tools, and equipment.

The laboratory houses both environmental and biological samples preparation equipment such as liquid-liquid (LLE) and solid phase (SPE) extraction set-up (Biotage off-line automated module), solvent evaporator (N-EVAP 111, Nitrogen evaporator, Organomation Associates Inc., USA), and analytical instrumentation such as gas chromatograph coupled with a triple quadrupole mass spectrometer (GC/MS/MS) (Agilent 7890A/7000B GC/MS/MS with split/splitless, PTV, and CoC inlets, 7693A automatic liquid sampler, Mass Hunter software, Fiehn GC/MS metabolomics RTL library, and Mass Profiler Professional features), and an inductively coupled plasma mass spectrometer (ICP-MS) (Thermo XSeries 2, Thermo Scientific, Germany).

**Agilent Intuvo 9000 Gas Chromatograph System.** Other equipment/capabilities include temperature controlled incubator, shaker, and centrifuge.

**Curriculum Vitae**

**Professor Konstantinos Makris** (Male), M.S., PhD (University of Florida, USA) is Associate Professor of environmental health at the Dept. of Environmental Health, Harvard University. He is the Director of the Master’s program in Environmental Health within the CII. Dr. Makris leads the exposome-based water and health lab which aims to minimize the human health risk associated with chronic exposures to environmental chemicals. Towards this goal, his team applies improved exposure assessment protocols that refine the degree of association with metabolic health outcomes, participating in human studies in Cyprus, Greece, France, Kuwait, the Netherlands, and Norway. His laboratory is equipped with state-of-the-art instrumentation valued at >0.5M euros to generate its own biomarker and metabolomics data. Since 2009, Prof. Makris has received > 1.2 million euros in external funding from the EU, the Cyprus RFp, the BBMRI-LPC biobanking network in the EU, and the National Institutes of Environmental Health Sciences Center at Harvard University. He has produced over 85 peer-reviewed journal articles and >40 conference proceedings. Prof. Makris was invited by the Cyprus Parliament Senate Committee on Environment and Health to provide expert testimony about the environmental health consequences for the surrounding populations after the Mari tragedy/explosion.

**Dr. P. Charisiadis** (Male), is an organic chemist and serves as postdoctoral fellow with Prof. Makris team. He holds B.Sc. in Chemistry, M.Sc. in Analytical Chemistry Techniques & Applications, and Ph.D. in Chemistry from the Department of Chemistry, University of Ioannina, Greece. His knowledge centers around the areas of
analytical chemistry, and in particular with various chromatographic and spectroscopic techniques. His research interests are in the development and implementation of methodologies for the isolation and identification of analytes from complex matrices, including those of biological samples. There are also 7 PhD students currently at CII and two other lab researchers.

**Selected publications and/or products, services**


### 4.1.19 Stockholm Lans Landsting

<table>
<thead>
<tr>
<th>Participant</th>
<th>Stockholm Lans Landsting</th>
<th>Participant No.</th>
<th>Short name</th>
<th>SLL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Function</td>
<td>Participation in WP2, WP5, and WP7</td>
<td>19</td>
<td>SLL</td>
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</tr>
<tr>
<td>Persons in charge</td>
<td>Maria Albin, Theo Bodin, Katarina Kjellberg, Pernilla Wiebert</td>
<td></td>
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</tbody>
</table>

**Short description of the organisation**

**Stockholm Lans Landsting (SLL)** is the legal name of Region Stockholm, responsible for all publicly-financed healthcare and public transport in Stockholm County. Around two million people live in the county. Region Stockholm is one of Europe's largest healthcare providers, offering everything from telephone advice about self-care to advanced specialist care at university hospitals.

**Healthcare Provision Stockholm County (SLSO)** is a part of Region Stockholm / Stockholm Lans Landsting. SLSO is responsible for all care provided by the county council apart from emergency hospitals and offers care at all stages of life. SLSO have just over 11,200 employees in total. Over the course of a year, SLSO offers five million outpatient visits and 600,000 inpatient care days. SLSO collaborates closely with Karolinska Institutet (KI) in research and in education.

The division for **Research and Development** includes 7 centres with a strong focus on R&D and also on primary prevention, including nationally and internationally leading expertise in occupational and environmental medicine, social medicine, health economics, suicide prevention, psychiatry, and primary health care research.

**The Centre for Occupational and Environmental Medicine** (Centrum för Arbets- och Miljömedicin, CAMM), Division for Research and Development, serves the region of Stockholm with the overall aim of contributing to a good working health and environmental health in the population. To this end the organisation supports the health service in the region with a polyclinic mainly focused on occupational disease, performs epidemiological surveillance and risk assessment, develops new methods for exposure assessment and performs a far-reaching knowledge dissemination in relation to key stakeholders. CAMM has currently around 60 employees, of which around half have a PhD degree, representing multidisciplinary competence in e.g. occupational medicine, occupational dermatology, ergonomics, occupational hygiene, biostatistics, and work psychology. The Centre has a close collaboration with the corresponding unit at Karolinska Institutet (Unit of Occupational Medicine).

**Tasks in the project**

SLL will participate mainly in WP2 (contribution and evaluation of JEMs) and in WP7 (responsible for Swedish field study), but also in WP5 (data management)

**Experience: projects or activities/infrastructure**

Occupational hygienists at CAMM has been key in the development of SweJEM at KI. The Centre has over the years been highly successful in providing logistics and data management for follow-up of the Swedish birth cohort BAMSE, which recently completed the 24 year clinical examinations. Recently several projects have started focusing on working hours, health and wellbeing for staff employed by Region Stockholm strongly supported by the HR-department.

**A description of any significant infrastructure and/or any major items of technical equipment, relevant to the proposed work**
Infrastructure for complex field studies. Well established networks for performing studies of health effects of working night shifts within Region Stockholm.

### Curriculum Vitae

**Maria Albin;** MD, PhD, Professor (Occupational Medicine) (F) is senior physician and head of the Centre of Occupational and Environmental Medicine (as well as of the Unit of Occupational Medicine at KI), and has published extensively mainly in the fields of occupational cancer, respiratory and cardiovascular disease, but lately also on working-life expectancy. She is member of the advisory board to the Swedish Work Environment Authority, and served in the Swedish national commission on inequalities in health. Member of the core management committee in two COST-actions.

**Theo Bodin;** MD, PhD, Assistant Professor (Occupational and Environmental Medicine) (M). His main research focus is epidemiological studies on precarious employment arrangements and environmental exposures such as heat, noise and air pollution. Previous and on-going projects study a variety of health outcomes including mental health, cardiovascular and chronic kidney diseases as well as occupational injuries. He has coordinated complex field studies on heat stress and chronic kidney disease and is currently leading a research program on health-effects of non-standard employment.

**Katarina Kjellberg.** PhD (Ergonomics) (F). Her main research focus is epidemiological studies on physical and psychosocial working conditions in relation to health outcomes and a sustainable working life. Main outcomes are musculoskeletal disorders, cardiovascular diseases, work ability and early exits from the labor market through long-term sick leave, disability pension, unemployment and other exit routes. Other research areas are social inequalities in health, health effects of precarious employment conditions, and occupational rehabilitation.

**Pernilla Wiebert:** Certified Occupational and Environmental Hygienist, PhD (Occupational Hygiene) (F). Her research is focused on development and application of job-exposure matrices in epidemiological studies on occupational respiratory and cardiovascular diseases as well as birth outcomes and cancer. She is a member of the NOCCA-group (The Nordic Occupational Cancer study) developing and harmonizing JEMs for the Nordic countries. She is also involved in the development of the chemical part of SweJEM in collaboration with FIOH.

### Selected publications and/or products, services


### 4.2. Third parties involved in the project (including use of third party resources)

The following participants do not have any third parties involved:
Partner 2 (IS Global) does have third parties involved:

<table>
<thead>
<tr>
<th>Does the participant plan to subcontract certain tasks (please note that core tasks of the project should not be sub-contracted)</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Does the participant envisage that part of its work is performed by linked third parties</td>
<td>N</td>
</tr>
<tr>
<td>Does the participant envisage the use of contributions in kind provided by third parties (Articles 11 and 12 of the General Model Grant Agreement)</td>
<td>Y</td>
</tr>
</tbody>
</table>

Consorci Parc de Salut Mar de Barcelona (PSMar) is a third party (Article 12) of ISGlobal providing as an in-kind contribution free of charge the expertise and work of Prof. Kogevinas. Work will be conducted on the premises of ISGlobal. Prof. Kogevinas will mainly be responsible for WP 7 and furthermore be involved in all WP’s where ISGLOBAL is contributing. The value of the in-kind work is estimated to be 116,120 EUR.

| Does the participant envisage that part of the work is performed by International Partners (Article 14a of the General Model Grant Agreement)? | N |

Partner 4 (AU) does have third partners involved:

| Does the participant plan to subcontract certain tasks (please note that core tasks of the project should not be sub-contracted) | Y |
Within WP 6 a follow up is proposed in two population-based cohorts with abundant information on health including lung function, asthma and COPD, anthropometric measures, biological samples and life-long job histories with a planned follow-up in 2021: European Community Respiratory Health Survey (ECRHS) and the French Constances cohort. More specifically, we include 10 ECRHS and 2 Constances study centers from 7 European countries and Australia (Spain, France, Sweden, Norway, Estonia, Iceland, Australia and Denmark).

Funding of the follow up data collection for the following centers: Sweden (3 centers) and Iceland will go through subcontracting.

It was decided not to include those centres as partners, since in that case their role would be limited to perform the data collection. In the contract for subcontracting agreements will be made regarding ethical approval, protocol to follow, data sharing, open access of data to ensure that the deliverables of the EPHOR proposal can be met.

Since it is a follow up study of an existing cohort, it is not possible to acquire multiple quotations, since others will not have access to the participants.

In line with article 10 of the Grant agreement, the best value for money principle does NOT in all cases require competitive selection procedures. The subcontracting performed by partner 4 (AU) provides a unique cohort including relevant (follow up) personal data. No other partners can provide such data so competitive selection is not an option.

| Does the participant envisage that part of its work is performed by linked third parties | N |
| Does the participant envisage the use of contributions in kind provided by third parties (Articles 11 and 12 of the General Model Grant Agreement) | N |
| Does the participant envisage that part of the work is performed by International Partners (Article 14a of the General Model Grant Agreement)? | N |

Partner number 7 (KUL) does have third parties involved:

| Does the participant plan to subcontract certain tasks (please note that core tasks of the project should not be sub-contracted) | Y |

- Analyses of melatonin in the serum samples collected in WP 7. These analyses are an important aspect of the evaluation of the effect shift work on health and none of the partners have the required expertise. We reserve 12,000 Euro for these analyses. For these analyses a quotation will be asked from at least three companies. Selection will be based on price, scientific quality and timing to assure best value for the budget.
- Analyses of the Genome Wide Association Study (GWAS) in samples collected in WP 6 and 7. These analyses are important to link genetic polymorphisms to exposure and health responses. This help to explain the ultimate effects of the occupational exposome on health, in relation to genetic factors. None of the partners have the required expertise, at least with respect to wet laboratory analysis (bioinformatics expertise to integrate GWAS analysis with other types of data analyses is available within the consortium). Selection of subjects and DNA isolation will be done at the consortium partners, whereas Genome DNA sequencing will be done at a service provider. We reserve 32,000 Euro for these analyses. A quotation will be asked from at least three companies. Selection will be based on price, scientific quality and timing to assure best value for the budget.

| Does the participant envisage that part of its work is performed by linked third parties | N |
4.3 Financial support to third parties

Not applicable

5. Ethics and security

5.1 Ethics

Relevant legislation:

All research conducted in the EPHOR project will comply with the international, EU and national law, in particular:

- WMA Declaration of Helsinki.

Below, the ethical issues per WP, and how these will be addressed are described.

Besides the ethical issues focussing on the participants of the clinical studies, the relevant health and safety procedures confirming to the relevant local/national guidelines/legislation will be followed by the staff involved in the project.

WP1

1) Ethical issues related to research with human beings

Goal of the study:

The objective is to test the practicality and acceptability for study participants and researchers of an external exposome protocol to measure a suite of personal working life exposures. The protocol will consist of 1) a set of wearable sensors to measure dust, light, sound; 2) use of passive chemical (using wristbands) and biological (with an electrostatic dust sheet) exposure sampling methods; 3) questionnaire regarding activities that influence exposure. The outcomes are real time, minute-by-minute personal exposure measurements of dust, light, and sound; chemical exposures to organic compounds, biological exposures as measured by endotoxin; exposure related activity question answers regarding time activity patterns and information on exposures.

The feasibility study will include a small sample of people in several countries (currently suggested to be the Netherlands and the United Kingdom). Because this is a feasibility study, we will recruit at least 12 participants per country.

Outcomes:

- Primary outcome: Feasibility of using the sensors by persons in the case studies both from a scientific point of view and a participant point of view.
- Secondary outcomes relate to adjustment of the protocol.

Recruitment procedure:

Recruitment will occur through each partners’ networks and through the stakeholder networks. The study participants are anticipated to have a variety of occupations. All subjects will be provided information about the study in the local languages prior to enrolment. The participants will be asked to provide informed consent after recruitment and before the start of the protocol.

Informed consent procedure:

All participants involved in field studies will give informed consent for participation in the study, sample collection and data collection (where applicable) prior to taking part in the studies. The study will be explained, and a participant information letter will be provided in a language and in terms they can fully understand. It will be stated that
participation is voluntary, and that participation can be refused or participants can withdraw without consequences. The information sheet will describe the aims, methods and implications of the study, the nature of participation and any benefits, risks or discomfort that might ensue. The procedures that will be implemented in the event of unexpected or incidental findings (in particular when the participants have the right to know, or not to know, about any such findings) will also be described.

In- and exclusion criteria:

- **Inclusion criteria:** Aged between 18-65 years; Be able and willing to use the sensor system, wear passive wristbands, answer questions in the primary language of the country, and agree on placement of a biological sampling device in their home.
- **Exclusion criteria:** Not aged between 18-65 years; Unable or unwilling to use the sensor system and wear passive wristbands, unwilling to answer questions, and don’t allow to place a biological sampling device in their home.

**Physical interventions and risks:**
Not applicable.

**Possible benefits, burden and potential impacts for the participants in the study:**

- **Benefits:** Participants will receive feedback on their exposures during the time of the study. Moreover, they will be involved in developing a system that will be of use to scientific study and contribute to further development of exposure management in the future.
- **Possible burden:** The participants will be asked to wear sensors and answer questions regarding their exposure or exposure related behaviour and their experience with the study. They may not be used to wearing sensors, but every effort will be made to ensure that the sensor system is as user friendly and unobtrusive as possible.

**Ethical approval:**
Ethical approval will be obtained through the National Health Service Research Ethics Committee for medical or health related research involving human subjects.

**WP3**

1) **Ethical issues related to research with human samples**

**Goal of the study:**
In WP3, samples will be analysed that have been collected from cohorts in WP 6 and 7. The analysis takes place in Belgium (KU Leuven), UK (Owlstone), Spain (IS Global), Sweden (KI), Norway (STAMI), Cyprus (CUT). The types of samples that will be analysed in WP3 include frozen whole blood/ peripheral blood mononuclear cells (Epigenomics/ transcriptomics), plasma/ serum (proteomics, cfDNA), urine, exhaled breath condensate (proteomics, cfDNA), DNA/RNA (targeted epigenetics, transcriptomics) and saliva (for cortisol awakening response). Samples that are already available are stored in accordance with the ethical guidelines described by the cohort owners. All other samples to be used in WP3 will be freshly collected after obtaining ethical clearance. All samples will be collected and shipped according to standard operation procedures (SOPs). Material transfer agreements (MTAs) will be signed for the shipment of all biological samples from each cohort to the sites where the analysis will be performed.

All samples will be pseudonymised by the clinical centres before the samples are send to the participants performing the analysis in WP3. The list coupling the code with the identity of the donor will be kept by the clinical centers according to the national and EU regulation that applies. After the project is finished, the samples will be stored for additional 5 years to address additional scientific questions generated from the project. Informed consent for secondary use will be obtained.

During the project, pseudonymized data resulting from the analysis will be stored in secured databases at the sites where the samples have been analysed and in YoDa at the UU. After anonymization, the data will become available open access. No confidential personal information will be retained.

**Ethical approval:**
Ethical approval for sample collection will be obtained by the researchers managing the cohorts in WP6 and WP7.
WP5
Ethical issues related to personal data

Goal of the study:
Previously collected personal data (including use of pre-existing data sets or sources, merging existing data sets) will be analysed to identify working life risk factors for the development of major NCDs, e.g., cancer, cardiovascular and respiratory diseases, across the life course.

These data will be collected from the mega cohort established in the EPHOR project that consists of at least 23 cohorts. These will be occupational and population cohorts, as well as registry-based cohorts, and combinations of different types. The mega cohort will contain data from at least 23 million individuals. Data will not include identifiers, such as name or personal identification number. Individuals are considered to not be directly or indirectly identifiable, due to the large numbers and the lack of identifiers in the data.

The following types of data will be used:
- Occupational title and industry, preferably measured at several time points (at least twice) over the life-course of each individual;
- Demographic data: Gender, age, country of cohort;
- Health outcome data on major specific NCDs, including cancer, respiratory, cardiovascular, and metabolic diseases, and musculoskeletal, mental, and neurodegenerative disorders;
- Outcome data may be based on registry linkage (e.g., cancer, hospital diagnoses, mortality, sickness absence diagnoses), measurements (e.g., lung function, BMI, blood glucose), or self-reported symptoms (e.g., respiratory, mental) or physician-diagnosed disease (e.g., asthma, COPD), depending on what is available.

If available, the following types of data may also be used:
- Measured/monitored exposures of specific interest for WP6 and 7, in particular night shift work and working hours (WP7), and known and suspected risk factors for respiratory disease (WP6);
- Lifestyle factors (e.g., physical activity, tobacco and alcohol use);
- Education level (SES indicator).

The processed data will be anonymous. The databases will be accessed through the decentralized data analyses functions of YoDa (UU) that are needed for existing cohort data that cannot be “physically” brought together in a single location due to standing privacy and ethics agreements on these cohorts.

Ethical approval:
Ethical approval has been obtained for individual cohort studies, including for secondary use, previously, or will be obtained for this study from all relevant local/regional/national ethics boards.

WP6
1) Ethical issues related to research with human beings

Goal of the study:
A population-based study with a focus on lung function, asthma and COPD. The overall objective is to evaluate how the working life exposome impacts lung function, asthma and COPD, which biological pathways are involved, and how this is influenced by sex, life style factors and age. 4000 individuals from 12 centres in 7 European countries (Spain, France, Sweden, Norway, Estonia, Iceland, Denmark) and Australia will be included. For a subgroup of 100 with incident asthma, 100 with incident COPD, 150 high occupationally exposed and 50 low occupational exposed, an extended collection of short-term occupational exposure, blood, urine and exhaled air samples will be collected for analysis in WP3. The ethical issues associated with sample collection are described in WP3.

Outcomes:
- Primary outcomes: Decline in lung function, incidence of asthma and COPD.
- Secondary outcomes: Biological signatures and pathway analysis for early respiratory effects. In a selection of subjects, external exposures will be measured through the use of sensors including: real time, minute-by-minute personal exposure measurements of dust, light, and sound; chemical exposures to organic compounds (e.g. polychlorinated biphenyls, Polycyclic aromatic hydrocarbons, methylated naphthalenes, musk compounds, organochlorine pesticides, organophosphate esters); biological exposures as measured by endotoxin; and exposure related activity question answers regarding time activity patterns and information on
exposures. The latter includes: time spent at home, work, transport; whether they live near a busy road or other sources of air pollution; work and residential history.

**In- and exclusion criteria:**

- **Inclusion criteria:** Individuals who participated in ECRHS III and Constances in the included centres.
- **Exclusion criteria:** Recent cardiac attack, or a severe chronic cardiac disease. Low lung function (FEV1 < 50% of expected). Current TB treatment. Recent infectious airway disease.

**Recruitment procedure:**

2500 individuals who participated in ECRHS III and 1500 who participated in Constances in 2012-16 (12 study Centres in total) will be recruited. A participation rate of 75% based on earlier study waves is expected. All subjects will be provided information about the study in the local languages prior to enrolment. The participants will be asked to provide informed consent after recruitment and before the start of the protocol.

**Informed consent procedures:**

See WP1.

**Physical interventions and risks:**

Breath samples will be collected using the ReCIVA Breath Sampler, a device for the non-invasive and repeatable capture of breath VOCs (volatile organic compounds).

Blood samples will be taken. Short-term discomfort may be possible in connection with blood sampling, including a minor risk of a bruise. To limit the discomfort blood samples will be taken by trained staff.

**Possible benefits, burden and impacts for the participants in the study:**

- **Benefits:** The participants will receive the results of the lung function test and will be referred to a health evaluation if we experience incidental findings.
- **Burden:** It could be a burden for some persons to be confronted with a bad lung function test.

The collected samples will be analysed in WP3 (see WP3 for the ethical issues).

**2) Ethical issues related to personal data**

In WP6, previously collected data from existing cohorts will be analysed and new data will be generated.

2a) **Analysis of existing data**

Data (lung function data, life style factors, sex, weight, age, exposure data) from the ECRHS/Constances cohort will be analysed to identify risk factors for lung function, asthma and COPD. Informed consent for secondary use of the data is available. All data will be pseudonymized.

The databases will be accessed through the decentralized data analyses functions of YoDa (UU), needed for existing cohort data that cannot be ‘physically’ brought together in a single location due to standing privacy and ethics agreements on these cohorts.

2b) **Collection and analysis of new data**

In the EPHOR project, new data will be collected and processed. Blood parameters, urine parameters, exhaled breath condensate parameters, lung function parameters from spirometry, anthropometrics, and data from questionnaires. These data will be stored in YoDa (UU) and will be pseudonymized.

**Data from non-EU countries**

In WP6 data will be collected in various centres of which the centres in Norway, Estonia, Iceland and Australia are based outside the EU. The personal data (new and existing) collected in these centres will be imported to the EU for the EPHOR project. These data include blood parameters, urine parameters, exhaled breath condensate parameters, lung function parameters from spirometry, anthropometrics, and data from questionnaires. A declaration confirming compliance with the laws of the country in which the data was collected will be added to the ethical approval documents during the project. In the case of biological samples, relevant import licences will be arranged.
Technical and organisational measures to safeguard the rights of the research participants and details of the security measures to prevent unauthorised access to personal data.

Each of the participating centres has established publicly available procedures to safeguard rights of research participants. These include organisational and technical measures:

**Organisational measures:**
- Keep track of who has accessed the stored data;
- Keep track of whether data is being exported;
- Drafting Responsibility assignment matrix (RAM);
- Use of Trusted Third Party.

**Technical measures:**
- Pseudonymization of research data and separating identifying and non-identifying data in separate files;
- Technical restriction on access to data and limitation of data processing;
- Encryption;
- Use of secure terminals, secure servers and secure cloud servers.

**Informed consent procedures:**
See WP1.

The processed data will be relevant and limited to the purposes of the project (‘data minimisation’ principle) because:
- Contact details are necessary to reach out to the participants to ask them to participate, and also to use satellite mapping of specific exposures linked to their residential address
- No financial information is required;
- Age and sex are necessary for appropriate statistical analysis;
- Weight, length, life style data will be collected next to lung function parameters because they can be covariates/cofounders in the relation to lung function.

**Anonymisation/pseudonymization techniques:**
All individuals are identified by a unique study number assigned when they entered the ECRHS/Constances cohort. Only use this number is used. The key file between the study id number and personal id number is kept secured. The data need to be pseudonymized because this is a follow-up study and we need to be able to merge data from earlier study waves.

Pseudonymization of research data will be done by separating identifying and non-identifying data in separate files using a new study ID. Code for merging with initial ID and name will be kept under confidential conditions with restricted access.

If requested, we will inform participants for the results of the study and their personal data. Pseudonymization will only be broken for this reason. Under these conditions, the use of identifiable personal data in our research does not cause a disproportionate infringement of the privacy of the data subjects.

**Details of the data transfers (type of data transferred and country to which it is transferred – for both EU and non-EU countries):**
Both questionnaire data and biological samples will be transferred within EU partners of the project for analysis. These will follow signed DTAs and secure transfer, per protocol for the biological samples and the YoDa system will be used for the questionnaire data and the analyses of biological samples data. All partners have extensive experience in international research including biological samples.

**Processing special categories of personal data:**
We will process genetic data. This forms part of the main aims of the project per indication of the European’s Commission H2020 call for exposome projects. Processing of sensitive data is absolutely necessary for scientific research purposes of the EU call. The use of these data will serve public interest. In addition, specific safety measures will be taken following standard procedures in similar projects of the participating centres. Explicit consent will be requested from the research participants.

The processed data will be pseudonymized and stored in the YoDa database.
**Ethical approval:**

The ethical approval will be obtained in each of the 11 study centres from 7 different countries:

- Denmark: De Videnskabsetiske Komitéer For Region Midtjylland
- Norway: Regional Ethics Committee West Norway
- Sweden (Göteborg, Uppsala Umeå): Regional Ethical Review Board in Uppsala
- Estonia: Research Ethics committee of the University of Tartu
- Iceland: National Bioethics committee of Iceland
- Spain (Albacete and Huelva): Ethics Committee of the Parc de Salut Mar, Barcelona (Comité etic d’investigacio clinica (CEIC)- Parc de Salut Mar, Barcelona)
- Australia, Melbourne: Monash university Human research ethics committee

**WP7**

1) Ethical issues related to research with human beings

**Goal of the study:**

The overall aim is to evaluate the effect of unusual working hours, including night work and extended working hours on health by developing targeted and agnostic research approaches to examine how external work environment and lifestyle exposures may affect major health-related biological pathways and impaired body functions. The new exposome study on (night) unusual working hours will collect detailed information and extensive biological samples from up to 800 workers in Spain, Sweden and The Netherlands having worked day and/or night shifts for varying time periods. The study will apply a state-of-the-art exposome protocol.

Workers will be recruited from: care industry in Barcelona (Spain) (long term rotating man and women), night and day-shift female nurses from the Nightingale cohort in The Netherlands (Pijpe et al, 2014) and municipal workers from an administrative cohort (Sweden).

**Outcomes:**

- **Primary outcomes:** intermediate biological pathways based on biomarker analyses; body functions (lung function, kidney function, markers for cardiovascular diseases such as cholesterol and triglycerides).
- **Secondary outcomes:** none.
- **Important covariates:** Age, sex. In a selection of subjects, external exposures will be measured through the use of sensors including: real time, minute-by-minute personal exposure measurements of dust, light, and sound; chemical exposures to organic compounds (e.g. polychlorinated biphenyls, polycyclic aromatic hydrocarbons, methylated naphthalenes, musk compounds, organochlorine pesticides, organophosphate esters); biological exposures as measured by endotoxin; exposure-related activity question answers regarding time activity patterns and information on exposures. The latter includes: time spent at home, work, transport; whether they live near a busy road or other sources of air pollution; work and residential history.

**In- and exclusion criteria:**

- **Inclusion criteria.** Workers (equal proportion of women and men) in a car factory, Barcelona, who are doing rotating shift work. Nurses samples from an existing cohort study in The Netherlands (Nightingale study; women). Men and women who had been enrolled in a study on council workers in Stockholm in the health sector. All participants will be volunteers.
- **Exclusion criteria:** Included subjects with basic knowledge of local languages (practically all workers in the studies/workplaces included, comply this criterion)

**Recruitment procedure:**

Different strategies will be followed in the three centres. Enrolment will be voluntary in all centres and all subjects will be provided information about the study in the local languages prior to enrolment. In Barcelona, study participation will be offered to all workers doing rotating shifts through the Medical department of the company and the workers’ Health and Safety committee. In The Netherlands participants will be randomly selected from the existing cohort. A similar procedure will be followed in Sweden.
Informed consent procedures:
See WP1.

Physical interventions and risks:
Blood samples and saliva samples will be taken. Short-term discomfort may be possible in connection with blood sampling, including a minor risk of a bruise. To limit the discomfort blood samples will be taken by trained staff.

Possible benefits, burden and potential impacts for the participants in the study:
- Benefits: There are no direct benefits for the person.
- Burden: Minimal burden, possible bruise when taking blood. No burden is foreseen for urine and breath samples.

The collected samples will be analysed in WP3 (see WP3 for the ethical issues).

2) Ethical issues related to personal data

In the EPHOR project, new data will be collected and processed. By means of intermediate biological pathways based on biomarker analyses, we will study body functions (lung function, kidney function, and markers for cardiovascular diseases such as cholesterol and triglycerides).

Technical and organisational measures to safeguard the rights of the research participants and details of the security measures to prevent unauthorised access to personal data

Each of the participating centres has established publicly available procedures to safeguard rights of research participants. These include organisational and technical measures:

Organisational measures:
- Keep track of who has accessed the stored data;
- Keep track of whether data is being exported;
- Drafting Responsibility assignment matrix (RAM);
- Use of Trusted Third Party.

Technical measures:
- Pseudonymization of research data and separating identifying and non-identifying data in separate files;
- Technical restriction on access to data and limitation of data processing;
- Encryption;
- Use of secure terminals, secure servers and secure cloud servers.

Informed consent procedures:
See WP1.

The processed data will be relevant and limited to the purposes of the project (‘data minimisation’ principle) because:
- Contact details are necessary to reach out to the participants to ask them to participate, and also to use satellite mapping of specific exposures linked to their residential address;
- No financial information is required;
- Age and sex are necessary for appropriate statistical analysis;
- Weight and length of the participants are necessary because they may be correlated with the working conditions examined. Similarly, a wide range of lifestyle and work factors will be requested. Some of these factors, for example chronotype- the tendency to be a morning or evening person- may be important to evaluate risks in population groups with specific characteristics.

Anonymisation/pseudonymization techniques:
Pseudonymization of research data will be done by separating identifying and non-identifying data in separate files using a new study ID. Code for merging with initial ID and name will be kept under confidential conditions with restricted access.
If requested, we will inform participants for the results of the study and their personal data. Pseudonymization will only be broken for this reason. Under these conditions, the use of identifiable personal data in our research does not cause a disproportionate infringement of the privacy of the data subjects.

Details of the data transfers (type of data transferred and country to which it is transferred – for both EU and non-EU countries):
Both questionnaire data and biological samples will be transferred within EU partners of the project for analysis. These will follow signed DTAs and secure transfer, per protocol for the biological samples and the YoDa system will be used for the questionnaire data and the analyses of biological samples data. All partners have extensive experience in international research including biological samples.

Processing special categories of personal data:
We will process genetic data. This forms part of the main aims of the project per indication of the European’s Commission H2020 call for exposome projects. Processing of sensitive data is absolutely necessary for scientific research purposes of the EU call. The use of these data will serve public interest. In addition, specific safety measures will be taken following standard procedures in similar projects of the participating centres. Explicit consent will be requested from the research participants.
The processed data will be anonymized and stored in the YoDa database.

Ethical approval:
The clinical study will be approved by corresponding local scientific ethical committees for each of the 3 centres included in the study:
- Ethical Committee PS Mar, Barcelona
- Institutional Review Board, NKI, The Netherlands
- Swedish Review Board
### Implementation of requirements of the Ethics Review

<table>
<thead>
<tr>
<th>Required no and category</th>
<th>Concern</th>
<th>To be addressed in</th>
<th>WP Participants involved</th>
<th>Month work will start</th>
<th>Available / submitted to commission Month</th>
<th>Comments</th>
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<tr>
<td>Environmental protection and safety</td>
<td>The applicant must demonstrate that appropriate health and safety procedures conforming to relevant local/national guidelines/legislation are followed for staff involved in this project. This must be confirmed in the grant agreement before signature.</td>
<td>Consortium agreement</td>
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<td>TNO</td>
<td>Before start</td>
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<td>Humans</td>
<td>The applicant must clarify whether invasive physical procedures will be used and what measures will be taken to minimise possible pain, and include this information in the grant agreement before signature.</td>
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<td>n.a.</td>
<td>TNO</td>
<td>Before start</td>
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<td>participation of humans must be submitted as a deliverable.</td>
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<td>Copies of opinions/approvals by ethics committees and/or competent</td>
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<td>rights of data subjects or the processing of genetic, biometric</td>
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and/or health data have been established under the national legislation of the country where the research takes place and submit a declaration of compliance with respective national legal framework(s).

The host institution must confirm that it has appointed a Data Protection Officer (DPO) and the contact details of the DPO are made available to all data subjects involved in the research. For host institutions not required to appoint a DPO under the GDPR a detailed data protection policy for the project must be submitted as a deliverable.

In case of further processing of previously collected personal data, an explicit confirmation that the beneficiary has lawful basis for the data processing and that the appropriate technical and organizational measures are in place to safeguard the rights of the data subjects must be submitted as a deliverable.

The beneficiary must evaluate the ethics risks related to the data processing activities of the project. This includes also an opinion if data protection impact assessment should be conducted under art.35 General Data Protection Regulation 2016/679. The risk evaluation and the opinion must be submitted as a deliverable.

In case personal data are transferred from the EU to a non-EU country or international organisation, confirmation that such transfers are in accordance with Chapter V of the General Data Protection Regulation 2016/679, must be submitted as a deliverable.

A description of the technical and organisational measures that will be implemented to safeguard

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<tr>
<th>Description</th>
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the rights and freedoms of the data subjects/research participants must be submitted as a deliverable.

A description of the security measures that will be implemented to prevent unauthorised access to personal data or the equipment used for processing must be submitted as a deliverable.

| Third countries | Details on the materials which will be imported/to/exported from the EU must be submitted as a deliverable. | D13.4 | 13 | 4 (AU), 7 (STAMI), 12 (PDA), 14 (UiB), 19 (SSL) | 1 | 12 |
|                 | Copies of import/export authorisations, as required by national/EU legislation must be submitted as a deliverable. | D13.4 | 13 | 4 (AU), 7 (STAMI), 12 (PDA), 14 (UiB), 19 (SSL) | 1 | 12 |
|                 | In case activities undertaken in non-EU countries raise ethics issues, the applicants must ensure that the research conducted outside the EU is legal in at least one EU Member State and submit a confirmation as a deliverable. | D13.4 | 13 | 4 (AU), 7 (STAMI), 12 (PDA), 14 (UiB), 19 (SSL) | 1 | 12 |
| **General**     | An independent, external Ethics Advisor must be appointed to monitor the ethics issues as part of the scientific advisory board and be included in the missions already identified in the project. | D13.5 | 13 | 1 (TNO), 12 (PDA) | 1 | 6 |
5.2 Safety

The EPHOR project:

does NOT involve activities or results raising security issues

does NOT involve 'EU-classified information' as background or results
Annex A: Essential information to be provided for proposals including clinical trials/studies/investigations/cohorts

Introduction

In the EPHOR project three studies will be performed:

1. A feasibility study to test a protocol for applying the sensors in cohort studies, including methods for exposure data analyses. (WP1)

2. A population-based cohort study to investigate Working life exposome, lung function, and obstructive lung disease among men and women (WP6)

3. An industry-based cohort study to investigate the effect of shift work in the exposome concept on health

In this document the details of these studies are described.

WP1: Feasibility study of external exposome protocol

Identifier

WP1: Feasibility study of external exposome protocol

Study design and endpoints

Study design

The objective is to test the feasibility of using an external exposome protocol to measure a suite of personal exposures in a study of the working life exposome. This feasibility study will provide information on the practicality of the protocol for study participants and researchers. The final protocol will be revised based on this feasibility study before implementation in case studies of shift workers and a general population study of respiratory health. The study participants are anticipated to have a variety of occupations, so the protocol will need to be broadly applicable. The protocol will consist of 1) a set of wearable sensors to measure dust, light, sound, along with physical activity levels, heart rate, and sleep; 2) use of passive chemical (using wristbands) and biological (with an electrostatic dust sheet) exposure sampling methods; and 3) a questionnaire regarding activities that influence exposure.

The feasibility study will include a small sample of people in several countries (currently suggested to be the Netherlands and the United Kingdom), which would cover a selection of the countries of the case studies. Because this is a feasibility study, we will recruit at least 12 participants per country. The participants will be asked to provide informed consent after recruitment and before the start of the feasibility study. Results will be summarized, and used to finalise the case study exposure protocol.

Primary and secondary endpoint(s)

The primary outcome of the feasibility study is to assess the feasibility of using the sensors by persons in the case studies both from a scientific point of view and a participant point of view. Secondary outcomes relate to adjustment of the protocol based on participant and researcher feedback.

Relevant guidance documents

There are no relevant guidance documents for this study applicable.

Regulatory status and activities
Regulatory / ethics status
Relevant for this study is regulation (EU) 2016/679 regarding the protection of natural persons with regard to the processing of personal data and on the free movement of such data (GDPR).

Scientific advice / protocol assistance
EPHOR will have a privacy and ethical coordinator as partner (PDA) to assure we meet ethical and privacy guidelines. Furthermore, EPHOR will have a scientific advisory committee.

Qualification advice
Not applicable

Subjects/population(s)
The study populations will be employed people who are anticipated to be similar to the populations of the case studies, which are working aged adults in a variety of occupations.
Inclusion criteria:
- Aged between 18-65 years
- Be able and willing to use the sensor system, passive wristbands, answer questions in the primary language of the country, and placement of a passive environmental biological sampling device in their home.

Exclusion criteria:
- Not aged between 18-65 years
- Unable or unwilling to use the sensor system, passive wristbands, answer questions in the primary language of the country, and placement of a biological sampling device in their home.

Statistical analysis plan(ning) and power calculation
Our target sample size is 30 (at least 12 per country). Because this is a feasibility study for a protocol, and the primary aim is to determine the acceptability and practical application of the protocol, this number is adequate to capture a range of potential situations. The datasets will be checked on missing and duplicate data, on the range of the data and on correct read-in and calculations of the variables. All transformations, calculations and changes (if any) in datasets will be controlled and recorded. Statistical analysis will be limited to data QA/QC and descriptive methods summarizing the data, including range, mean, median, standard deviation.

Cumulative safety and efficacy information

Cumulative safety information
Not applicable

Cumulative efficacy information
Not applicable

Conduct

Schedule for study conduct including timelines for key study milestones

Protocol development is anticipated to take one year. The ethics application will be submitted at the end of the first year to the relevant bodies in each country. Approval is expected within three months.

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1 Key study milestones will be scrutinised during the time course of the project. Significantly delayed key study milestones (e.g. FPFV) might lead to the termination of the grant agreement.
• First Patient (or study subject), First Visit (FPFV): Month 15
• Last Patient (or study subject), First Visit: Month 16
• Last Patient (or study subject), Last Visit: Month 17
• End of Study (including data analysis): Month 24

Description of recruitment strategy
Recruitment will occur through each partners’ networks. We will also go through our stakeholder network. We anticipate to be able to recruit at least 7 subjects per month, based on a previous project. In the event that recruitment is slower, we will extend the study time, but we anticipate being able to complete the study within 6 months post-ethical approval, as the study sample is small.

Description and assignment of intervention
Not applicable (no intervention).

Study management, study monitoring, data and sample management
Subjects will be given a subject information leaflet explaining the study’s aims and objectives. The test purpose and procedures will be explained to each subject and each will be given an opportunity to ask questions prior to them providing consent for themselves to participate on the study by means of a signed Subject Consent Form, which will cover the terms and conditions of the sensors as well as exposure samples and questionnaire data. Subjects will be informed that they are allowed to withdraw at any time and without explanation.

Data collected under this project will be subject to compliance with the General Data Protection Regulation (GDPR) and any local data laws.

All researchers will be trained in the ethics of human subject research and in the appropriate information governance. Subject names and contact information will be kept in a separate file, linked with the person’s ID code for the study. This will be kept encrypted on a password protected computer. Only personnel authorized by the study will have access to this and any other files containing private information. Any paper documents with subject information will be kept in a locked cabinet, and only study personnel will have access to the keys.

A data management system (Yoda) will be used to securely store and share data via the internet, ensuring that only authorized study personnel have access. The stored data will be encrypted. Any data to ultimately be made public will be adequately de-identified. No potentially identifying data will be revealed in any public data or data publication.

Data collected using sensors will be uploaded to an online portal using an anonymous account. Data from these applications will be synchronized to the EPHOR data repository via an Application Protocol Interface (API). Only pseudonymized data can be downloaded for subsequent tabulation and statistical analysis. Subjects will be assigned a unique identification code that does not include any identifying information. Information such as residential address and phone number will be kept in a separate, encrypted database and will not be linked to subject data in analyses.

The documentation of this study consists of the study protocol, correspondence, report, raw data, source documents or authenticated copies of these. For privacy reasons, documents containing data of individual subjects will be identified only by their pre-entry or entry number.

Information with personal identifiers will be retained for the timescale set out by local partner Research Procedures. Anonymous matched data may be retained for future research, but without any link to personal identifiers (e.g. date of birth converted to age at last birthday, etc.).

Electronic devices will be re-used throughout the study. In all cases, data will be downloaded and removed from the device before re-use in another household and for another subject. Each device will be assigned a unique ID, which will be linked with any identifiers, such as a serial number, for the device, and will not be changed during the study. This will allow researchers to track any issues that may come up with certain devices. The device ID used for each subject will be recorded and entered into a database.
Passive samplers will be logged with a unique sample ID. These will be associated with a chain of custody form, that will be filled out by each person handling the samples, and which will be kept with the samples. These forms will only use household and sample ID numbers for identification. The location and status of samples throughout their life cycle (i.e. from laboratory to home, back to laboratory, to any further analysis) will be logged in a database. Any associated measurements or treatments of the sample will also be logged in this database. If the sample is sent outside of the institute for analysis, courier tracking will be used, and appropriate transit conditions will be used (e.g. use of a cooling box or other method for storage, next day delivery, etc.). Recipients will be required to sign and send the original of the chain of custody form back to the research institute, keeping a copy. All transactions will be logged in the sample database.

Audits of the data collection and processing procedures will be taken throughout the project. For example:

- An audit of the data collection process employed by the fieldworkers will be carried out at regular project meetings.

- Most of the data collected will not be manually entered. Research staff will be responsible for checking that data is uploaded to the data portal during the collection period for each subject and to the database during and after the collection period.

- All devices will be tested at the institute before use in the field. Tests will include co-location, reliability for the sampling time, and comparison with a reference instrument, if available.

- Approximately 10% of passive samples will be co-located duplicates and 10% will be blank.

- If required the sponsor/investigator will submit a summary of the progress of the trial to the ethics committee once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events (SAE), serious adverse reactions, other problems, and amendments.

The investigator will inform the subjects and the reviewing ethics committee of any issue that is deemed by the investigator to pose danger to the subjects and for which the disadvantages of participation may be significantly greater than was foreseen in the research proposal. The study will be suspended pending further review by the ethics committee, except insofar as suspension would jeopardise the subjects’ health. All subjects will be kept informed by the investigator.

The investigator will report the SAEs to the accredited ethics committee that approved the protocol, as soon as possible, and no later than 15 days after the investigator has first knowledge of the serious adverse events. SAEs that result in death or are life threatening should be reported expedited. The expedited reporting will occur not later than 7 days after the responsible investigator has first knowledge of the adverse event. This is for a preliminary report with another 8 days for completion of the report. All AEs will be followed until they have abated, or until a stable situation has been reached.

Sponsor, coordinating centre(s) and committees
Not applicable

Study medication
Not applicable

Clinical centres
The study will be performed in the United Kingdom and the Netherlands.

Orphan designation
Not applicable

‘Unit costs per patient’ for clinical trials / studies / investigations
Not applicable
WP 6 Respiratory case study

Identifier
WP6 respiratory case study

Study design and endpoints

Study design
The overall aim is to evaluate how the working life exposome impacts lung function, asthma and COPD, which biological pathways are involved, and how this is influenced by sex, lifestyle factors and age. We hypothesise occupational exposures to have a significant negative impact on lung health. We use two population-based cohorts with existing information on health status including lung function, asthma and COPD, biomaterial and life-long job histories. We include 12 centres from 7 European countries (Spain, France, Sweden, Norway, Estonia, Iceland, Denmark) and Australia. Ten of the centres are part of the European Community Respiratory Health Survey (ECRHS), and the two French centres are part of the Constances population-based cohort. 2000 individuals from ECRHS and 1000 from Constances are included in a follow-up investigation in 2021 with measurements of exposure, omics and health outcome. A subgroup of 400 are further included in a short-term study with cross week measurements of exposure, omics and health outcome.

Primary and secondary endpoint(s)
This is an observational study.
Primary outcomes: Decline in lung function, incidence of asthma and COPD
Secondary outcomes: Biological signatures and pathway analysis for early respiratory effects
Important covariates: Age, gender, anthropometric measures smoking status, socioeconomic status, comorbidity. In a selection of subjects external exposure will be measures through the use of sensors including: real time, minute-by-minute personal exposure measurements of dust, light, and sound; chemical exposures to organic compounds (e.g. Polychlorinated biphenyls, Polycyclic aromatic hydrocarbons, Methylated naphthalenes, Musk compounds, Organochlorine pesticides, Organophosphate esters); biological exposures as measured by endotoxin; and exposure related activity question answers regarding time activity patterns and information on exposures. The latter includes: time spent at home, work, transport; whether they live near a busy road or other sources of air pollution; work and residential history.
This is an observational population-based study. Incident cases of asthma and COPD is prioritised in omics analysis and in the short-term cross week study.

Relevant guidance documents
We will follow Good epidemiological practice (Guidelines from International Epidemiological association (http://ieaweb.org/).

Regulatory status and activities

Regulatory / ethics status
The clinical study will be approved by national or regional scientific ethical committees for each of the 11 centres included in the study. Furthermore, we will adhere to the General Data Protection Regulation (EU) 2016/679.

Scientific advice / protocol assistance
The project will have a privacy and ethical coordinator as partner to assure we meet ethical and privacy guidelines. Furthermore, the project will have a scientific advisory committee. Of note, all participating centres have already ethical approval for already collected data.
The ethical approval for ECRHSIII / Constances obtained in each of the 11 study centres from 7 different countries:

**Denmark**: De Videnskabsetiske Komitéer For Region Midtjylland, M-20110106

**Norway**: Regional Ethics Committee West Norway 2010/759

**Sweden (Göteborg, Uppsala Umeå):** Regional Ethical Review Board in Uppsala. And the number of the decision is 2010/432

**Estonia**: Research Ethics committee of the University of Tartu (UT REC) 209T-17 and 225/M-24

**Iceland**: National Bioethics committee of Iceland VSNb2011090016/0315

**Spain Albacete**: Clinical Research Ethics Committee (Comité Ético y de Investigación Clínica del Complejo Hospitalario Universitario de Albacete. Servicio de Salud de Castilla - La Mancha: SESCAM) n° 06/13.

**Spain Huelva**: Subcommittee on Health Research. Juan Ramón Jiménez Hospital and Associated Centres in the province of Huelva.


**Australia, Melbourne**: Monash university Human research ethics committee Project # CF11/1818-2010001012

**Qualification advice**

Not relevant for the current study

**Subjects/population(s)**

Inclusion criteria. Individuals who participated in ECRHS III and Constances in the included centres.

Exclusion criteria: recent cardiac attack, or a severe chronic cardiac disease. Low lung function (FEV1 <50% of expected). Current TB treatment. Recent infectious airway disease

Definition of sub-populations if subgroup analysis is intended.

For a subgroup of 100 with incident asthma, 100 with incident COPD, 150 high occupationally exposed and 50 low occupational exposed an extended collection of short-term occupational exposure, biomaterial and further analysis of omics and biomarkers will be performed.

**Statistical analysis plan(ning) and power calculation**

We perform a follow-up of existing cohorts, please see above. We anticipate having 3000 individuals with a mean follow-up time of 9 years. This leave us with abundant power to examine the impact of long-term occupational exposome on change in lung function in mixed-effects models, even in subgroups (women/men, age groups, non-smokers, different socioeconomic positions). For a subgroup of 400 individuals we will have abundant information at two time-points about omics and biomarkers in a paired design where individuals serve as their own control, leaving us with sufficient power to fulfil our objectives.

A description of the statistical methods to be applied is described in WP4 of the proposal.

**Cumulative safety and efficacy information**

**Cumulative safety information**

Not relevant – an observational study
Cumulative efficacy information
Not relevant – an observational study

Conduct

Schedule for study conduct including timelines for key study milestones
We will start screening the subjects in month 18 and the data collection will run until month 30.
- First Patient (or study subject), First Visit (FPFV): 18
- Last Patient (or study subject), First Visit: 29
- Last Patient (or study subject), Last Visit: 30
- End of Study (including follow-up and data analysis): 46

Description of recruitment strategy
We invite 2500 individuals who participated in ECRHSIII and 1500 who participated in Constances in 2012-16 (12 study Centres in total), and we expect a participation rate of 75% based on earlier study waves. The examination can take place in the 12 centres independent of each other, therefore it is possible to start independently. Still with lower than anticipated participant rates we have the power to meet the study objectives.

Description and assignment of intervention
Not relevant – an observational study

Study management, study monitoring, data and sample management
Based on protocols developed in Task 6.1 the data collection takes place in 11 already established ECRHS/Constances centres with an established infrastructure and competences to perform the data collection. The data collection will be monitored by the partners AU and UiB. Adverse event report will take place according to national regulation, but will at a minimum be recorded to the national/regional scientific ethical committee. Data will be entered locally based on protocols developed in Task 6.1, but will be transferred to WP4 for further data management and analyses.

Sponsor, coordinating centre(s) and committees
Not relevant – an observational study

Study medication
Not relevant – an observational study

Clinical centres
Aarhus, Denmark
Bergen, Norway
Sweden:
- Göteborg
- Uppsala
- Umeå
Tartu, Estonia
Iceland
Australia, Melbourne
Spain:
- Huelva
- Albacete
France
- Constances center 1
- Constances center 2
WP 7: Shift work case study

Identifier
WP7 shift work case study

Study design and endpoints

Study design
The overall aim is to evaluate the effect of unusual working hours, including night work and extended working hours on health by developing targeted and agnostic research approaches to examine how external work environment and lifestyle exposures may affect major health-related biological pathways and impaired body functions. The new exposome study on (night) unusual working hours will enrol and collect detailed information and extensive biological samples from up to 800 workers in Spain, Sweden and The Netherlands having worked day and/or night shifts for varying time periods and will apply a state-of-the-art exposome protocol. The study will be based in a car industry in Barcelona of long-term rotating male and female workers, new sampling from the Nightingale cohort in The Netherlands that includes both night and day-shift female nurses (Pijpe et al, 2014) and sampling from an administrative cohort of municipal workers in Sweden.

Primary and secondary endpoint(s)
This is an observational study.
Primary outcomes: intermediate biological pathways based on biomarker analyses; body functions (lung function, kidney function, markers for cardiovascular diseases such as cholesterol and triglycerides)
Secondary outcomes: none
Important covariates: Age and gender. In a selection of subjects external exposure will be measures through the use of sensors including: real time, minute-by-minute personal exposure measurements of dust, light, and sound; chemical exposures to organic compounds (e.g. Polychlorinated biphenyls, Polycyclic aromatic hydrocarbons, Methylated naphthalenes, Musk compounds, Organochlorine pesticides, Organophosphate esters); biological exposures as measured by endotoxin; and exposure-related activity question answers regarding time activity patterns and information on exposures. The latter includes: time spent at home, work, transport; whether they live near a busy road or other sources of air pollution; work and residential history.

Relevant guidance documents
We will follow Good epidemiological practice (Guidelines from International Epidemiological association (http://ieaweb.org/)

Regulatory status and activities

Regulatory / ethics status
The clinical study will be approved by corresponding local scientific ethical committees for each of the 3 centres included in the study. Furthermore, we will adhere to the General Data Protection Regulation (EU) 2016/679.
**Scientific advice / protocol assistance**

EPHOR will have a privacy and ethical coordinator as partner (PDA) to assure we meet ethical and privacy guidelines. Furthermore, the project will have a scientific advisory committee. Of note, all participating centres have already ethical approval for already collected data.

**Qualification advice**

Not relevant for the current study

**Subjects/population(s)**

Inclusion criteria. Workers (equal proportion of women and men) in a car factory, Barcelona, who are doing rotating shift work. Nurses samples from an existing cohort study in The Netherlands (Nightingale study; women). Men and women who had been enrolled in a study on council workers in Stockholm in the health sector. All participants will be volunteers.

Exclusion criteria: Included subjects with basic knowledge of local languages (practically all workers in the studies/workplaces included, comply this criterion)

Definition of sub-populations if subgroup analyses is intended. Stratified analyses by gender and by chronotype (tendency for morning/evening activities)

**Statistical analysis plan(ning) and power calculation**

There are many outcomes to be evaluated and the power differs depending on the specific intermediate outcome. The sample size has been defined so as to have very high power for main effects (i.e., for alpha of 0.05, power of 80%), ratio of night to day workers of 1, and outcome (this could be levels of HDL or a parameter related to gene expression) in day workers of 30% prevalence we would be able to identify Relative risks of 1.3 or less. The higher number of included subjects is because some factors are rare and we will need higher power and also because we are interested in effect modification e.g., by chronotype, and there the power becomes very low unless we have big samples like we propose.

A variety of statistical tests will be applied: Individual cosinor analysis will be used to evaluate circadian rhythms. Regression (depending on outcomes different types of regression) and correlation analyses, GAMs (generalised additive models), DAGs (directed acyclic graphs) for confounder selection.

**Cumulative safety and efficacy information**

**Cumulative safety information**

Not relevant – an observational study

**Cumulative efficacy information**

Not relevant – an observational study

**Conduct**

**Schedule for study conduct including timelines for key study milestones**

We will start screening the subjects in month 12 and the data collection will run until month 24.

- First Patient (or study subject), First Visit (FPFV): 12
- Last Patient (or study subject), First Visit: 23
- Last Patient (or study subject), Last Visit: 24
- End of Study (including follow-up and data analysis): 46

**Description of recruitment strategy**

Different strategies will be followed in the three centres. Enrolment will be voluntary in all centres and all subjects will be provided information about the study in the local languages prior to enrolment. In Barcelona, study participation will be offered to all workers doing rotating shifts through the Medical
Description and assignment of intervention
Not relevant – an observational study

Study management, study monitoring, data and sample management
Planned strategy for study/trial management. An international steering committee will be overall responsible for development of protocols and filed study. Local committees with project managers will run the study in each centre. These committees will include a specialist in QC for biological samples (collection, process and storage). Regular contacts will be established using electronic media for the international committee.
Study monitoring plan. Monitoring will be in practice daily or weekly during the field study. The overall committee will have monthly meetings to monitor progress through the use of numbers of recruited participants, non-response, item non-response (item: specific aspects of the protocol, for example use of sensors), QC for biological samples, QC for environmental and epidemiological information collected.
Adverse event reporting: No major adverse effects are expected, there are no interventions. If during blood drawing we have any event, the corresponding medical services will be immediately notified.
Data collection and management: Data will be transferred immediately through a secure server to the local coordinating centres where QC will be done. Specific protocols will be applied for the biological samples that will require rapid transfer and processing of the blood samples that will require storage in either -20 Celsius or -80 Celsius depending on the sample, while urine samples will be stored (initially in -4 Celsius) at the place of collection and later at -20 Celsius. Information on all data collected will be immediately recorded. All centres have established protocols for this.

Sponsor, coordinating centre(s) and committees
Not relevant – an observational study

Study medication
Not relevant – an observational study

Clinical centres
- NL. Utrecht University. One of the two coordinating centres for the Nightingale nurses’ cohort study. Internationally known for studies in the occupational environment including circadian disruption and studies on exposome
- Spain. ISGlobal. Responsible for the conduct of the shift work study in Spain. One of the largest research centres in Europe in Environmental/Occupational health with extensive experience in studies on circadian disruption and the exposome.
- Sweden. Karolinska Institute, Institute of Environmental medicine. One of the largest research centres in Europe in Environmental/Occupational health with extensive experience in record linkage studies and the exposome.

Orphan designation
Not relevant

’Unit costs per patient’ for clinical trials / studies / investigations
Not applicable.
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<tr>
<td></td>
<td>Maximum grant amount</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| A.1 | Employees (or equivalent) | | | |
| A.2 | Natural persons under direct contract | | | |
| A.3 | Seconded persons | [A.6 Personnel for providing access to research infrastructure] | | |
| A.4 | SME owners without salary | | | |
| A.5 | Beneficiaries that are natural persons without salary | | | |
| A.6 | Total (internal) | | | |
| A.7 | Total (external) | | | |
| A.8 | Total (all) | | | |
| A.9 | Total (non-funded) | | | |
| A.10 | Total (all) | | | |

### Notes
1. See Article 6 for the eligibility conditions.
2. Indirect costs already covered by an operating grant (received under any EU or Erasmus funding programme; see Article 6.5 (b)) are ineligible under the GA. Therefore, a beneficiary/linking third party that receives an operating grant during the action’s duration cannot declare indirect costs for the year(s)/reporting periods covered by the operating grant, unless it can demonstrate that the operating grant does not cover any costs of the action (see Article 6.2.E).
3. This is the theoretical amount of EU contribution that the system calculates automatically (by multiplying all the budgeted costs by the reimbursement rate). This theoretical amount is capped by the ‘maximum grant amount’ (that the Commission decided to grant for the action) (see Article 5.1).
4. The ‘maximum grant amount’ is the maximum grant amount decided by the Commission. It normally corresponds to the requested grant, but may be lower.
5. Depending on its type, this specific cost category will or will not cover indirect costs. Specific unit costs that include indirect costs are: costs for energy efficiency measures in buildings, access costs for providing trans-national access to research infrastructure and costs for clinical studies.
6. See Article 5 for the forms of costs.
7. Unit: hours worked on the action; costs per unit (hourly rate) - calculated according to the beneficiary's usual accounting practice.
8. See Annex 2 'Additional information on the estimated budget' for the details (costs per hour; hourly rate).
9. Unit and costs per unit: calculated according to the beneficiary's usual accounting practices.
10. Flat rate: 25% of eligible direct costs, from which are excluded: direct costs of subcontracting, costs of in-kind contributions not used on premises, direct costs of financial support, and unit costs declared under budget category F if they include indirect costs (see Article 6.2.E).
11. See Annex 2 'Additional information on the estimated budget' for the details (costs, costs per unit).
12. See Annex 2 'Additional information on the estimated budget' for the details (units, costs per unit, estimated number of units, etc).
13. Only specific unit costs that do not include indirect costs.
14. See Article 9 for beneficiaries not receiving funding.
15. Only for linked third parties that receive funding.

### Table
<table>
<thead>
<tr>
<th>Form of costs</th>
<th>Unit size</th>
<th>Estimated eligible costs</th>
<th>EU contribution</th>
<th>Information for indirect costs</th>
<th>Additional information</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Actual</td>
<td>Reimbursement rate</td>
<td>Maximum EU contribution</td>
<td>Maximum grant amount</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Actual</td>
<td>Total costs</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Actual</td>
<td>Flat-rate value</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Calculations
- Formula: $k = \frac{h \times \text{Total costs}}{100}$
- Formula: $j = \frac{a + b + c + d + e}{5}$
- Formula: $n = \frac{m}{100}$

### Estimation
- Estimated costs: 11 981 851.64
- EU contribution: 872 808.11
- Maximum EU contribution: 872 808.11
- Maximum grant amount: 872 808.11
ADDITonal INFORMATION ON THE ESTIMATED BUDGET

- Instructions and footnotes in blue will not appear in the text generated by the IT system (since they are internal instructions only).
- For options [in square brackets]: the applicable option will be chosen by the IT system. Options not chosen will automatically not appear.
- For fields in [grey in square brackets] (even if they are part of an option as specified in the previous item): IT system will enter the appropriate data.

⚠️ Transitory period: Until SyGMA fully supports Annex 2a, you must prepare it manually (using this template by choosing and deleting the options/entering the appropriate data). For the ‘unit cost tables’: either fill them out manually or use currently existing tables from Annex 1 or the proposal. The document can then be uploaded in SyGMA and attached to the grant agreement.

**Unit cost for SME owners/natural beneficiaries without salary**

1. Costs for a /SME owner//beneficiary that is a natural person/ not receiving a salary

Units: hours worked on the action

Amount per unit (‘hourly rate’): calculated according to the following formula:

{[the monthly living allowance for researchers in MSCA-IF actions / 143 hours]}
multiplied by
{[country-specific correction coefficient of the country where the beneficiary is established]}

The monthly living allowance and the country-specific correction coefficients are set out in the Work Programme (section 3 MSCA) in force at the time of the call:

- for calls before Work Programme 2018-2020:
  - for the monthly living allowance: **EUR 4 650**

- for calls under Work Programme 2018-2020:
  - for the monthly living allowance: **EUR 4 880**
  - for the country-specific correction coefficients: see Work Programme 2018-2020 (available on the Participant Portal Reference Documents page)

[additional OPTION for beneficiaries/linked third parties that have opted to use the unit cost (in the proposal/with an amendment): For the following beneficiaries/linked third parties, the amounts per unit (hourly rate) are fixed as follows:

- beneficiary/linked third party [short name]: EUR [insert amount]
- beneficiary/linked third party [short name]: EUR [insert amount]

[same for other beneficiaries/linked third parties, if necessary] ]

Estimated number of units: see Annex 2
Energy efficiency measures unit cost

2. Costs for energy efficiency measures in buildings

Unit: m² of eligible ‘conditioned’ (i.e. built or refurbished) floor area

Amount per unit*: see (for each beneficiary/linked third party and BEST table) the ‘unit cost table’ attached

* Amount calculated as follows:
   \( \text{EUR} 0.1 \times \text{estimated total kWh saved per m² per year} \times 10 \)

Estimated number of units: see (for each beneficiary/linked third party and BEST table) the ‘unit cost table’ attached

Unit cost table (energy efficiency measures unit cost)\(^1\)

<table>
<thead>
<tr>
<th>Short name beneficiary/linked third party</th>
<th>BEST No</th>
<th>Amount per unit</th>
<th>Estimated No of units</th>
<th>Total unit cost (cost per unit x estimated no of units)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^1\) Data from the ‘building energy specification table (BEST)’ that is part of the proposal and Annex 1.
Grant Agreement number: [insert number] [insert acronym] [insert call identifier]

H2020 Template: Annex 2a (Additional information on the estimated budget)

**Research infrastructure unit cost**

### 3. Access costs for providing trans-national access to research infrastructure

**Units**: see (for each access provider and installation) the ‘unit cost table’ attached

**Amount per unit**: see (for each access provider and installation) the ‘unit cost table’ attached

* Amount calculated as follows:
  
  average annual total access cost to the installation (over past two years) / 
  average annual total quantity of access to the installation (over past two years)

**Estimated number of units**: see (for each access provider and installation) the ‘unit cost table’ attached

**Unit cost table (access to research infrastructure unit cost)**

<table>
<thead>
<tr>
<th>Short name access provider</th>
<th>Short name infrastructure</th>
<th>Installation</th>
<th>Unit of access</th>
<th>Amount per unit</th>
<th>Estimated No of units</th>
<th>Total unit cost (cost per unit x estimated no of units)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>No</td>
<td>Short name</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Clinical studies unit cost**

### 4. Costs for clinical studies

**Units**: patients/subjects that participate in the clinical study

**Amount per unit**: see (for each sequence (if any), clinical study and beneficiary/linked third party) the ‘unit cost table’ attached

* Amount calculated, for the cost components of each task, as follows:

  **For personnel costs:**

  For personnel costs of doctors: ‘average hourly cost for doctors’, i.e.:

  \[
  \text{certified or auditable total personnel costs for doctors for year N-1} / \text{estimated number of hours to be worked by doctors for the task (per participant)}
  \]

  For personnel costs of other medical personnel: ‘average hourly cost for other medical personnel’, i.e.:

  \[
  \text{certified or auditable total personnel costs for other medical personnel for year N-1} / \text{estimated number of hours to be worked by other medical personnel for the task (per participant)}
  \]

---

2 Unit of access (e.g. beam hours, weeks of access, sample analysis) fixed by the access provider in proposal.
3 In exceptional and duly justified cases, the Commission/Agency may agree to a different reference period.
4 In exceptional and duly justified cases, the Commission/Agency may agree to a different reference period.
5 Data from the ‘table on estimated costs/quantity of access to be provided’ that is part of the proposal and Annex 1.
For personnel costs of technical personnel: ‘average hourly cost for technical personnel’, i.e.:

\[ \text{certified or auditable total personnel costs for technical personnel for year N-1} \]

\[ \times \left( \begin{array}{c}
[1720 \times \text{number of full-time-equivalent for technical personnel for year N-1}] \\
\times \text{number of hours to be worked by technical personnel for the task (per participant)}
\end{array} \right) \]

‘total personnel costs’ means actual salaries + actual social security contributions + actual taxes and other costs included in the remuneration, provided they arise from national law or the employment contract/equivalent appointing act

For consumables:

For each cost item: ‘average price of the consumable’, i.e.:

\[ \left( \begin{array}{c}
\text{certified or auditable total costs of purchase of the consumable in year N-1} \\
\times \text{number of items purchased in year N-1}
\end{array} \right) \times \text{estimates number of items to be used for the task (per participant)} \]

‘total costs of purchase of the consumable’ means total value of the supply contracts (including related duties, taxes and charges such as non-deductible VAT) concluded by the beneficiary for the consumable delivered in year N-1, provided the contracts were awarded according to the principle of best value-for-money and without any conflict of interests

For medical equipment:

For each cost item: ‘average cost of depreciation and directly related services per unit of use’, i.e.:

\[ \left( \begin{array}{c}
\text{certified or auditable total depreciation costs in year N-1 + certified or auditable total costs of purchase of services in year N-1 for the category of equipment concerned} \\
\times \text{total capacity in year N-1}
\end{array} \right) \times \text{estimates number of units of use of the equipment for the task (per participant)} \]

‘total depreciation costs’ means total depreciation allowances as recorded in the beneficiary’s accounts of year N-1 for the category of equipment concerned, provided the equipment was purchased according to the principle of best value for money and without any conflict of interests + total costs of renting or leasing contracts (including related duties, taxes and charges such as non-deductible VAT) in year N-1 for the category of equipment concerned, provided they do not exceed the depreciation costs of similar equipment and do not include finance fees

For services:

For each cost item: ‘average cost of the service per study participant’, i.e.:

\[ \left( \begin{array}{c}
\text{certified or auditable total costs of purchase of the service in year N-1} \\
\times \text{total number of patients or subjects included in the clinical studies for which the service was delivered in year N-1}
\end{array} \right) \]

‘total costs of purchase of the service’ means total value of the contracts concluded by the beneficiary (including related duties, taxes and charges such as non-deductible VAT) for the specific service delivered in year N-1 for the conduct of clinical studies, provided the contracts were awarded according to the principle of best value for money and without any conflict of interests

For indirect costs:

\[ \left\{ \left\{ \text{cost component ‘personnel costs’ + cost component ‘consumables’ + cost component ‘medical equipment’} \right\} \right. \]

\[ - \left\{ \text{costs of in-kind contributions provided by third parties which are not used on the beneficiary’s premises + costs of providing financial support to third parties (if any)} \right\} \]

\[ \times 25\% \]
The estimation of the resources to be used must be done on the basis of the study protocol and must be the same for all beneficiaries/linked third parties/third parties involved.

The year N-1 to be used is the last closed financial year at the time of submission of the grant application.

Estimated number of units: see (for each clinical study and beneficiary/linked third party) the ‘unit cost table’ attached

Unit cost table: clinical studies unit cost

<table>
<thead>
<tr>
<th>Task, Direct cost categories</th>
<th>Resource per patient</th>
<th>Costs year N-1</th>
<th>Costs year N-1</th>
<th>Costs year N-1</th>
<th>Costs year N-1</th>
<th>Costs year N-1</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Beneficiary 1 [short name]</td>
<td>Linked third party 1a [short name]</td>
<td>Beneficiary 2 [short name]</td>
<td>Linked third party 2a [short name]</td>
<td>Third party giving in-kind contributions 1 [short name]</td>
</tr>
<tr>
<td>(a) Personnel costs:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Doctors</td>
<td>n/a</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Other Medical Personnel</td>
<td>Phlebotomy (nurse), 10 minutes</td>
<td>8,33 EUR</td>
<td>11,59 EUR</td>
<td>10,30 EUR</td>
<td>11,00 EUR</td>
<td>9,49 EUR</td>
</tr>
<tr>
<td>- Technical Personnel</td>
<td>Sample Processing (lab technician), 15 minutes</td>
<td>9,51 EUR</td>
<td>15,68 EUR</td>
<td>14,60 EUR</td>
<td>15,23 EUR</td>
<td>10,78 EUR</td>
</tr>
<tr>
<td>(b) Costs of consumables:</td>
<td>Syringe</td>
<td>XX EUR</td>
<td>XX EUR</td>
<td>XX EUR</td>
<td>XX EUR</td>
<td>XX EUR</td>
</tr>
<tr>
<td></td>
<td>Cannula</td>
<td>XX EUR</td>
<td>XX EUR</td>
<td>XX EUR</td>
<td>XX EUR</td>
<td>XX EUR</td>
</tr>
<tr>
<td></td>
<td>Blood container</td>
<td>XX EUR</td>
<td>XX EUR</td>
<td>XX EUR</td>
<td>XX EUR</td>
<td>XX EUR</td>
</tr>
<tr>
<td>(c) Costs of medical equipment:</td>
<td>Use of -80° deep freezer, 60 days</td>
<td>XX EUR</td>
<td>XX EUR</td>
<td>XX EUR</td>
<td>XX EUR</td>
<td>XX EUR</td>
</tr>
<tr>
<td></td>
<td>Use of centrifuge, 15 minutes</td>
<td>XX EUR</td>
<td>XX EUR</td>
<td>XX EUR</td>
<td>XX EUR</td>
<td>XX EUR</td>
</tr>
<tr>
<td>(d) Costs of services</td>
<td>Cleaning of XXX</td>
<td>XX EUR</td>
<td>XX EUR</td>
<td>XX EUR</td>
<td>XX EUR</td>
<td>XX EUR</td>
</tr>
<tr>
<td>(e) Indirect costs (25% flat-rate)</td>
<td></td>
<td>XX EUR</td>
<td>XX EUR</td>
<td>XX EUR</td>
<td>XX EUR</td>
<td>XX EUR</td>
</tr>
</tbody>
</table>

Task No. 2

... 

Amount per unit (unit cost sequence 1): XX EUR XX EUR XX EUR XX EUR XX EUR

Sequence No. 2

Task No. 1

---

6 Same table as in proposal and Annex 1.
### H2020 Templates: Annex 2a (Additional information on the estimated budget)

<table>
<thead>
<tr>
<th>XXX</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>(a) Personnel costs:</strong></td>
</tr>
<tr>
<td>- Doctors</td>
</tr>
<tr>
<td>XXX</td>
</tr>
<tr>
<td>- Other Medical Personnel</td>
</tr>
<tr>
<td>XXX</td>
</tr>
<tr>
<td>- Technical Personnel</td>
</tr>
<tr>
<td>XXX</td>
</tr>
<tr>
<td><strong>(b) Costs of consumables:</strong></td>
</tr>
<tr>
<td>XXX</td>
</tr>
<tr>
<td>XXX</td>
</tr>
<tr>
<td>XXX</td>
</tr>
<tr>
<td><strong>(c) Costs of medical equipment:</strong></td>
</tr>
<tr>
<td>XXX</td>
</tr>
<tr>
<td>XXX</td>
</tr>
<tr>
<td><strong>(d) Costs of services:</strong></td>
</tr>
<tr>
<td>XXX</td>
</tr>
<tr>
<td><strong>(e) Indirect costs (25% flat-rate)</strong></td>
</tr>
<tr>
<td>XX EUR</td>
</tr>
</tbody>
</table>

#### Task No. 2

...  

**Amount per unit (unit cost sequence 2):**  
XX EUR | XX EUR | XX EUR | XX EUR | XX EUR

...  

**Amount per unit (unit cost entire study):**  
XX EUR | XX EUR | XX EUR | XX EUR | XX EUR
ANNEX 3

ACCESSION FORM FOR BENEFICIARIES

FUNDACION PRIVADA INSTITUTO DE SALUD GLOBAL BARCELONA (ISGLOBAL),
established in C ROSSELLO 132 PLANTA 05, BARCELONA 08036, Spain, VAT number:
ESG65341695, (‘the beneficiary’), represented for the purpose of signing this Accession Form by the
undersigned,

hereby agrees

to become beneficiary No (‘2’)
in Grant Agreement No 874703 (‘the Agreement’)

between NEDERLANDSE ORGANISATIE VOOR TOEGEPAST
NATUURWETENSCHAPPELIJK ONDERZOEK TNO and the European Union (‘the EU’),
represented by the European Commission (‘the Commission’),

for the action entitled ‘Exposome project for health and occupational research (EPHOR)’.

and mandates

the coordinator to submit and sign in its name and on its behalf any amendments to the Agreement,
in accordance with Article 55.

By signing this Accession Form, the beneficiary accepts the grant and agrees to implement it in
accordance with the Agreement, with all the obligations and conditions it sets out.

SIGNATURE

For the beneficiary

Antoni PLASÈNCIA with ECAS id nplasena signed in the
Participant Portal on 09/12/2019 at 13:29:50 (transaction id
Sigld-92695:
Ysge5bzzrK6CF0yxHvLzRGE1dwURaJmr9iEPzYhEK87
Vr2BsuELW0Ema17wa7wyzvuzzqVExyJL4lK7dh4HbmYm-
pJZsgsw0KgszaRezgPiqC-
v0Sa4Gount2RZ30tzLkKDGhmwlCccl3pTHmgVeiZ0tL).
Timestamp by third party at
Mon Dec 09 13:29:57 CET 2019
ANNEX 3

ACCESSION FORM FOR BENEFICIARIES

INSTITUTE OF OCCUPATIONAL MEDICINE (IOM), established in Research Avenue North, Riccarton 45, EDINBURGH EH14 4AP, United Kingdom, (‘the beneficiary’), represented for the purpose of signing this Accession Form by the undersigned,

hereby agrees

to become beneficiary No (‘3’)
in Grant Agreement No 874703 (‘the Agreement’)

between NEDERLANDSE ORGANISATIE VOOR TOEGEPAST NATUURWETENSCHAPPELIJK ONDERZOEK TNO and the European Union (‘the EU’), represented by the European Commission (‘the Commission’),

for the action entitled ‘Exposome project for health and occupational research (EPHOR)’. and mandates

the coordinator to submit and sign in its name and on its behalf any amendments to the Agreement, in accordance with Article 55.

By signing this Accession Form, the beneficiary accepts the grant and agrees to implement it in accordance with the Agreement, with all the obligations and conditions it sets out.

SIGNATURE

For the beneficiary

Chris OWENS with ECAS id nowensch signed in the Participant Portal on 09/12/2019 at 12:58:29 (transaction id Sigld-91891-
QWX1m9jUkzLXNYXH04DnhDkza9JgPy5g09MzwugbySp
LbgWVerNybEODqHwetGboM8Xwu57bb8wGo7w5CDfa
PZWRp_jgZscgs90KggsRzR0qJG-
YSc40Duer0m2Q994AHyY4P1MqnpcsCX9GevN3hyj).
Timestamp by third party at Mon Dec 09 12:58:37 CET 2019
ACCESSION FORM FOR BENEFICIARIES

AARHUS UNIVERSITET (AU), established in NORDRE RINGGADE 1, AARHUS C 8000, Denmark, VAT number: DK31119103, (‘the beneficiary’), represented for the purpose of signing this Accession Form by the undersigned,

hereby agrees

to become beneficiary No (‘4’) in Grant Agreement No 874703 (‘the Agreement’)

between NEDERLANDSE ORGANISATIE VOOR TOEGEPAST NATUURWETENSCHAPPELIJK ONDERZOEK TNO and the European Union (‘the EU’), represented by the European Commission (‘the Commission’),

for the action entitled ‘Exposome project for health and occupational research (EPHOR)’.

and mandates

the coordinator to submit and sign in its name and on its behalf any amendments to the Agreement, in accordance with Article 55.

By signing this Accession Form, the beneficiary accepts the grant and agrees to implement it in accordance with the Agreement, with all the obligations and conditions it sets out.

SIGNATURE

For the beneficiary

Morten Hollaender BEECK with ECAS id nbeecmo signed in the Participant Portal on 16/12/2019 at 09:07:29

(transaction id SigId-213149-JZwbbi88SPvLd5tzaBnsE3cuwYcJMYVQOuDgpuyZA2IO2d9TUnrBncmZWOsFEsK23HJCgorU02zctB8jeU-jejZh5ccsw0KgszaRezzPigG-S8dYaqzP1EZsQhEw3FkJPggzleUEueus2L24Jy3L7oHW).

Timestamp by third party at Mon Dec 16 09:07:35 CET 2019
ANNEX 3

ACCESSION FORM FOR BENEFICIARIES

KAROLINSKA INSTITUTET (KI), established in Nobels Vagt 5, STOCKHOLM 17177, Sweden, VAT number: SE202100297301, (‘the beneficiary’), represented for the purpose of signing this Accession Form by the undersigned,

hereby agrees

to become beneficiary No (‘5’)
in Grant Agreement No 874703 (‘the Agreement’)

between NEDERLANDSE ORGANISATIE VOOR TOEGEPAST NATUURWETENSCHAPPELIJK ONDERZOEK TNO and the European Union (‘the EU’), represented by the European Commission (‘the Commission’),

for the action entitled ‘Exposome project for health and occupational research (EPHOR)’.

and mandates

the coordinator to submit and sign in its name and on its behalf any amendments to the Agreement, in accordance with Article 55.

By signing this Accession Form, the beneficiary accepts the grant and agrees to implement it in accordance with the Agreement, with all the obligations and conditions it sets out.

SIGNATURE

For the beneficiary

Bjorn KULL with ECAS id nkulbjor signed in the Participant Portal on 09/12/2019 at 18:21:13 (transaction id SigId-103187-3tUlahhC7tpQhwzoxVj6D5xocQl4di1Y21el7angDY3iQMzqw8659A79bDqV2XLUrAbzzidzeYi6EK0zwxmjh-3pJZscqsw0KgzaRezqPigG-LEnE4lmzhFvdUvcWStVn8spUWogzvqswZzxo1EFUU7S). Timestamp by third party at Mon Dec 09 18:21:19 CET 2019
ANNEX 3

ACCESSION FORM FOR BENEFICIARIES

KATHOLIEKE UNIVERSITEIT LEUVEN (KUL), established in OUDE MARKT 13, LEUVEN 3000, Belgium, VAT number: BE0419052173, (‘the beneficiary’), represented for the purpose of signing this Accession Form by the undersigned,

hereby agrees

to become beneficiary No (‘6’)
in Grant Agreement No 874703 (‘the Agreement’)

between NEDERLANDSE ORGANISATIE VOOR TOEGEPAST NATUURWETENSCHAPPELIJK ONDERZOEK TNO and the European Union (‘the EU’), represented by the European Commission (‘the Commission’),

for the action entitled ‘Exposome project for health and occupational research (EPHOR)’.

and mandates

the coordinator to submit and sign in its name and on its behalf any amendments to the Agreement, in accordance with Article 55.

By signing this Accession Form, the beneficiary accepts the grant and agrees to implement it in accordance with the Agreement, with all the obligations and conditions it sets out.

SIGNATURE

For the beneficiary

Elke LAMMERTYN with ECAS id nl师范mel signed in the Participant Portal on 11/12/2019 at 17:05:18 (transaction id SigId-152423-tBetGtXnpmMeKuM2MWAHqewpo8347Ls0UUCHUBVQoQiwUjwJULhBT580UW2hCFY9bXTafTB8X4MwPgGdlyv-jpJzscgw0KgszaRezxgPpqG-mfQo3U8FGzLUKJtcr7mQ1ocRClzn5cUFgB0BlpYRDkJJo) . Timestamp by third party at Wed Dec 11 17:05:27 CET 2019
ANNEX 3

ACCESSION FORM FOR BENEFICIARIES

STATENS ARBEIDSMILJOINSTITUTT (STAMI), established in GYDAS VEI 8, OSLO 0363, Norway, (‘the beneficiary’), represented for the purpose of signing this Accession Form by the undersigned,

hereby agrees

to become beneficiary No (‘7’)
in Grant Agreement No 874703 (‘the Agreement’)

between NEDERLANDSE ORGANISATIE VOOR TOEGEPAST NATUURWETENSCHAPPELIJK ONDERZOEK TNO and the European Union (‘the EU’), represented by the European Commission (‘the Commission’),

for the action entitled ‘Exposome project for health and occupational research (EPHOR)’.

and mandates

the coordinator to submit and sign in its name and on its behalf any amendments to the Agreement, in accordance with Article 55.

By signing this Accession Form, the beneficiary accepts the grant and agrees to implement it in accordance with the Agreement, with all the obligations and conditions it sets out.

SIGNATURE

For the beneficiary

Margrethe SCHONING with ECAS id nschonim signed in
the Participant Portal on 19/12/2019 at 08:48:21
(transaction id SigId-4078- CxLxuNgAnhnQ3xvQwpAh6clmXpXg4B4Zubgn1Ula1N2Sf 6aYb8kpmz56DEehynXm8zijAec6ckWtjszXsRLsW- jpJZscgew0KHFPjKROQQg-
nP9dZUdy2Sigmmd0yIyFyK1CjbElxGuGtWfRUneiyrO). Timestamp by third party at
Thu Dec 19 08:48:28 CET 2019
ANNEX 3

ACCESSION FORM FOR BENEFICIARIES

THE UNIVERSITY OF MANCHESTER (UNIMAN), established in OXFORD ROAD, MANCHESTER M13 9PL, United Kingdom, VAT number: GB849738956, (‘the beneficiary’), represented for the purpose of signing this Accession Form by the undersigned,

hereby agrees

to become beneficiary No (‘8’)
in Grant Agreement No 874703 (‘the Agreement’)

between NEDERLANDSE ORGANISATIE VOOR TOEGEPAST NATUURWETENSCHAPPELIJK ONDERZOEK TNO and the European Union (‘the EU’), represented by the European Commission (‘the Commission’),

for the action entitled ‘Exposome project for health and occupational research (EPHOR)’.

and mandates

the coordinator to submit and sign in its name and on its behalf any amendments to the Agreement, in accordance with Article 55.

By signing this Accession Form, the beneficiary accepts the grant and agrees to implement it in accordance with the Agreement, with all the obligations and conditions it sets out.

SIGNATURE

For the beneficiary

Andrew WALSH with ECAS id nwishadr signed in the Participant Portal on 08/12/2019 at 09:07:40 (transaction id SigId-79787-
emHy8vuILEodKGPKkzWx1V4m34kl3BC4OhKS3pdfG2Lsu
jROikAVhwucliFeqSg3xzRpzF1OjzYzpfJgmTmip-
pJZscgsw0KgszaRezqPiqG-
B9LQqvJQY7eFCBQ27paFxx0n8zOeALjN8SYkxF4s9iGQ).
Timestamp by third party at Sun Dec 08 09:07:46 CET 2019
ANNEX 3

ACCESSION FORM FOR BENEFICIARIES

UNIVERSITEIT UTRECHT (UU), established in HEIDELBERGLAAN 8, UTRECHT 3584 CS, Netherlands, VAT number: NL001798650B01, (‘the beneficiary’), represented for the purpose of signing this Accession Form by the undersigned,

hereby agrees

to become beneficiary No (‘9’)
in Grant Agreement No 874703 (‘the Agreement’)

between NEDERLANDSE ORGANISATIE VOOR TOEGEPAST NATUURWETENSCHAPPELIJK ONDERZOEK TNO and the European Union (‘the EU’), represented by the European Commission (‘the Commission’),

for the action entitled ‘Exposome project for health and occupational research (EPHOR)’.

and mandates

the coordinator to submit and sign in its name and on its behalf any amendments to the Agreement, in accordance with Article 55.

By signing this Accession Form, the beneficiary accepts the grant and agrees to implement it in accordance with the Agreement, with all the obligations and conditions it sets out.

SIGNATURE

For the beneficiary

Wouter DHERT with ECAS id ndhewout signed in the Participant Portal on 08/12/2019 at 19:48:38 (transaction id SigId-80524-XfJ3R3AieGqmBH3ZUwvSA0La6qjZB75E2DKXTf3oDWhN
NZwWShCmG5okEUt3efQG3ygOnxzmn1F33WzjCWAwOl
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Timestamp by third party at Sun Dec 08 19:48:45 CET 2019
ACCESSION FORM FOR BENEFICIARIES

INSTITUT NATIONAL DE LA SANTE ET DE LA RECHERCHE MEDICALE (INSERM),
established in RUE DE TOLBIAC 101, PARIS 75654, France, VAT number: FR31180036048, (‘the beneficiary’), represented for the purpose of signing this Accession Form by the undersigned, hereby agrees

to become beneficiary No (‘10’)
in Grant Agreement No 874703 (‘the Agreement’)
between NEDERLANDSE ORGANISATIE VOOR TOEGEPAST NATUURWETENSCHAPPELIJK ONDERZOEK TNO and the European Union (‘the EU’), represented by the European Commission (‘the Commission’),

for the action entitled ‘Exposome project for health and occupational research (EPHOR)’.

and mandates

the coordinator to submit and sign in its name and on its behalf any amendments to the Agreement, in accordance with Article 55.

By signing this Accession Form, the beneficiary accepts the grant and agrees to implement it in accordance with the Agreement, with all the obligations and conditions it sets out.

SIGNATURE

For the beneficiary

Laurence PARMANTIER with ECAS id nparmlau signed in the Participant Portal on 10/12/2019 at 13:31:20

Transaction id: SigId-1171b3-ylt1ayxNL0cczL81OB8fw7R3vlNefM36Alm9udkUJzhvS0DZj1nxzhUeQRFk3KJllh8uaCirx35lmmnDljgJZ5cgsw0KqszraRezqPngQ8qkyIndjwGgJWMDRBlUOchVsx5S0V2Iwebfd2Uj).

Timestamp by third party at Tue Dec 10 13:31:26 CET 2019
ACCESSION FORM FOR BENEFICIARIES

TYOTERVEYSLAITOS (FIOH), established in TOPELIUKSENKATU 41 B, HELSINKI 00250, Finland, VAT number: FI02202669, (‘the beneficiary’), represented for the purpose of signing this Accession Form by the undersigned,

hereby agrees

to become beneficiary No (‘11’)
in Grant Agreement No 874703 (‘the Agreement’)

between NEDERLANDSE ORGANISATIE VOOR TOEGEPAST NATUURWETENSCHAPPELIJK ONDERZOEK TNO and the European Union (‘the EU’), represented by the European Commission (‘the Commission’),

for the action entitled ‘Exposome project for health and occupational research (EPHOR)’.

and mandates

the coordinator to submit and sign in its name and on its behalf any amendments to the Agreement, in accordance with Article 55.

By signing this Accession Form, the beneficiary accepts the grant and agrees to implement it in accordance with the Agreement, with all the obligations and conditions it sets out.

SIGNATURE

For the beneficiary

Antti KOIVULA with ECAS id nkoivant signed in the Participant Portal on 11/12/2019 at 09:48:53 (transaction id SigId-134646-
v1KQyk1QKLzhW7OwkqwtCl2nJuX4xH1KR2cXG8tvJHJCJYa
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jpJZscgsowKgszraRezqPigG-
0EFRFuZGJ3YUoSkrsJkJLPoPV7btwQ5srBbB2J81Yrf4).
Timestamp by third party at Wed Dec 11 09:49:01 CET 2019
ANNEX 3

ACCESSION FORM FOR BENEFICIARIES

PANEPISTIMIO DYTIKIS ATTIKIS (PDA), established in PETROU RALLI KAI THIVON, AIGALEO 122 44, Greece, VAT number: EL997018536, (‘the beneficiary’), represented for the purpose of signing this Accession Form by the undersigned,

hereby agrees

to become beneficiary No (‘12’)
in Grant Agreement No 874703 (‘the Agreement’)
between NEDERLANDSE ORGANISATIE VOOR TOEGEPAST NATUURWETENSCHAPPELIJK ONDERZOEK TNO and the European Union (‘the EU’), represented by the European Commission (‘the Commission’),

for the action entitled ‘Exposome project for health and occupational research (EPHOR)’.

and mandates

the coordinator to submit and sign in its name and on its behalf any amendments to the Agreement, in accordance with Article 55.

By signing this Accession Form, the beneficiary accepts the grant and agrees to implement it in accordance with the Agreement, with all the obligations and conditions it sets out.

SIGNATURE

For the beneficiary

[Signature]

11

ANNEX 3

ACCESSION FORM FOR BENEFICIARIES

VTEC ENGINEERING BV (VTEC), established in KASTANJELAAN 400, EINDHOVEN 5616 LZ, Netherlands, VAT number: NL853153449B01, (‘the beneficiary’), represented for the purpose of signing this Accession Form by the undersigned,

hereby agrees

to become beneficiary No (‘13’)

in Grant Agreement No 874703 (‘the Agreement’)

between NEDERLANDSE ORGANISATIE VOOR TOEGEPAST NATUURWETENSCHAPPELIJK ONDERZOEK TNO and the European Union (‘the EU’), represented by the European Commission (‘the Commission’),

for the action entitled ‘Exposome project for health and occupational research (EPHOR)’.

and mandates

the coordinator to submit and sign in its name and on its behalf any amendments to the Agreement, in accordance with Article 55.

By signing this Accession Form, the beneficiary accepts the grant and agrees to implement it in accordance with the Agreement, with all the obligations and conditions it sets out.

SIGNATURE

For the beneficiary

Jan MINK with ECAS id nminkaab signed in the Participant Portal on 09/12/2019 at 09:24:55 (transaction id 8lgdl-83576-
Yaf3kG4KrKBZTF1Z5s6gbchU2ZKoAptk6xgpiBrmwGuHs2k-
pW754eQqmLbR3n4JAYTXNbc4hfipr9prkaXJ8IW-
jpZsogsw0KqszrRezzpPiqG-
qR51XQKczga51FTGXCslC9JmB0OGoU3soWINOw50R-
W). Timestamp by third party at Mon Dec 09 09:25:00 CET 2019
ANNEX 3

ACCESSION FORM FOR BENEFICIARIES

UNIVERSITETET I BERGEN (UiB), established in MUSEPLASSEN 1, BERGEN 5020, Norway, VAT number: NO874789542MVA, (‘the beneficiary’), represented for the purpose of signing this Accession Form by the undersigned,

hereby agrees

to become beneficiary No (‘14’)
in Grant Agreement No 874703 (‘the Agreement’)
between NEDERLANDSE ORGANISATIE VOOR TOEGEPAST NATUURWETENSCHAPPELIJK ONDERZOEK TNO and the European Union (‘the EU’), represented by the European Commission (‘the Commission’),

for the action entitled ‘Exposome project for health and occupational research (EPHOR)’.

and mandates

the coordinator to submit and sign in its name and on its behalf any amendments to the Agreement, in accordance with Article 55.

By signing this Accession Form, the beneficiary accepts the grant and agrees to implement it in accordance with the Agreement, with all the obligations and conditions it sets out.

SIGNATURE

For the beneficiary

Magnus HOLTERMANN with ECAS id nholtmag signed in the Participant Portal on 10/12/2019 at 10:40:47

(transaction id SigId-1103335-Vidwxyx4zVDt1NdRkWzaHgCcCc9YRkYzby9GQPlgSscVjmCUwNifRLebzvqFCHzzzTncEDevm8YQtB2kJEVcbs5l6-3jpJZscgsw0KgszaRezqPigG-pnfszd80dMQWxjt2auH6jpcenzyZ41GzNaYWKmWxcXQ).

Timestamp by third party at
Tue Dec 10 10:40:53 CET 2019
ANNEX 3

ACCESSION FORM FOR BENEFICIARIES

LIFEGLIMMER GMBH (LIFE), established in MARKELSTRASSE 38, BERLIN 12163, Germany, VAT number: DE282940451, (‘the beneficiary’), represented for the purpose of signing this Accession Form by the undersigned,

hereby agrees

to become beneficiary No (‘15’)
in Grant Agreement No 874703 (‘the Agreement’)

between NEDERLANDSE ORGANISATIE VOOR TOEGEPAST NATUURWETENSCHAPPELIJK ONDERZOEK TNO and the European Union (‘the EU’), represented by the European Commission (‘the Commission’),

for the action entitled ‘Exposome project for health and occupational research (EPHOR)’.

and mandates

the coordinator to submit and sign in its name and on its behalf any amendments to the Agreement, in accordance with Article 55.

By signing this Accession Form, the beneficiary accepts the grant and agrees to implement it in accordance with the Agreement, with all the obligations and conditions it sets out.

SIGNATURE

For the beneficiary

Mechthild SCHULTE with ECAS id nschumec signed in the Participant Portal on 11/12/2019 at 16:52:23 (transaction id SigId-151985-ZvVQzGnet1s9COXescXLMMm21LIPgTGBdQRzc3vSRhjkffjVKKrAJlecXGOzJ31WwXGnKNGOIl4uzNk3ta0qzQqR35jpJZscgsw0KgszaRezggPisG-Mwocm4Wc2S9q2NwFUsjHhxLcpFOuS8tMzggJVXo4QNnm). Timestamp by third party at Wed Dec 11 16:52:31 CET 2019
ANNEX 3

ACCESSION FORM FOR BENEFICIARIES

OWLSTONE MEDICAL LIMITED (OWL), established in 183 CAMBRIDGE SCIENCE PARK, MILTON ROAD, CAMBRIDGE CB4 0GA, United Kingdom, VAT number: GB260449214, (‘the beneficiary’), represented for the purpose of signing this Accession Form by the undersigned,

hereby agrees

to become beneficiary No (‘16’)

in Grant Agreement No 874703 (‘the Agreement’)

between NEDERLANDSE ORGANISATIE VOOR TOEGEPAST NATUURWETENSCHAPPELIJK ONDERZOEK TNO and the European Union (‘the EU’), represented by the European Commission (‘the Commission’),

for the action entitled ‘Exposome project for health and occupational research (EPHOR)’.

and mandates

the coordinator to submit and sign in its name and on its behalf any amendments to the Agreement, in accordance with Article 55.

By signing this Accession Form, the beneficiary accepts the grant and agrees to implement it in accordance with the Agreement, with all the obligations and conditions it sets out.

SIGNATURE

For the beneficiary

Martin Cartwright with ECAS id n002kshr signed in the Participant Portal on 10/12/2019 at 15:42:39 (transaction id SigId-122525-8c9X7zMIPWAhzQ3GGrqzGxspqztTompYxXU8hHzdcQdAVzuNTU SW2BHEoQoa3l2xUGi4Wk6H0yS1sSWEDYXysYoBodw S-jpJZgcwsw0KqszarEzgzPj@gmail- R52gPoNW2oF0gqT77nYyX4APoLo6zT0BD05UkUMx71) . Timestamp by third party at Tue Dec 10 15:42:48 CET 2019
ANNEX 3

ACCESSION FORM FOR BENEFICIARIES

INTERAKTIV GMBH (INTER), established in MAX PLANCK STR 6-8, KOLN 50858, Germany, VAT number: DE210904165, (‘the beneficiary’), represented for the purpose of signing this Accession Form by the undersigned,

hereby agrees

to become beneficiary No (‘17’)
in Grant Agreement No 874703 (‘the Agreement’)

between NEDERLANDSE ORGANISATIE VOOR TOEGEPAST NATUURWETENSCHAPPELIJK ONDERZOEK TNO and the European Union (‘the EU’), represented by the European Commission (‘the Commission’),

for the action entitled ‘Exposome project for health and occupational research (EPHOR)’.

and mandates

the coordinator to submit and sign in its name and on its behalf any amendments to the Agreement, in accordance with Article 55.

By signing this Accession Form, the beneficiary accepts the grant and agrees to implement it in accordance with the Agreement, with all the obligations and conditions it sets out.

SIGNATURE

For the beneficiary

Jörg Zell with ECAS id n002oo1u signed in the Participant Portal on 07/01/2020 at 11:33:43 (transaction id SigId-14843: UKT1flgAzhZFHP6ZsRusf4A1pxcROT9uFzBcswRBO/E4WwFNWdp8ouyz7FcllySpQ1hrK0lu8wV9YJZD00-rS0vSrmBGrYCFw1Qw5x00u-öYakChh6k4QbwOjR0uS6I77BFcLj0vGXMS1znFngMX5). Timestamp by third party at
Tue Jan 07 11:33:49 CET 2020
ANNEX 3

ACCESSION FORM FOR BENEFICIARIES

TECHNOLOGIKO PANEPISTIMIO KYPROU (CUT), established in ARCHBISHOP KYPRIANOS 31 SAVINGS COOPERATIVE BANK BUILDING 3RD FLOOR, LEMESOS 3036, Cyprus, VAT number: CY90002687H, (‘the beneficiary’), represented for the purpose of signing this Accession Form by the undersigned,

hereby agrees

to become beneficiary No (‘18’)
in Grant Agreement No 874703 (‘the Agreement’)

between NEDERLANDSE ORGANISATIE VOOR TOEGEPAST NATUURWETENSCHAPPELIJK ONDERZOEK TNO and the European Union (‘the EU’), represented by the European Commission (‘the Commission’),

for the action entitled ‘Exposome project for health and occupational research (EPHOR)’.

and mandates

the coordinator to submit and sign in its name and on its behalf any amendments to the Agreement, in accordance with Article 55.

By signing this Accession Form, the beneficiary accepts the grant and agrees to implement it in accordance with the Agreement, with all the obligations and conditions it sets out.

SIGNATURE

For the beneficiary

Andreas ANAYIOTOS with ECAS id nanayian signed in the Participant Portal on 13/12/2019 at 00:40:05
(transaction id SigId-183717- TIlknQxyxjLiJvkhjtmzzeMDQChmnzTyok8WzdDk81mXK39 jiTzz9EIDCgDFgJYXYibDymzXKaPhc1TcqUqeDam- jpJZsge5w0KgszaRezgPjGQmYujipDfTzmDzUjizLxskdzcPGrifXZzursQXzwFe).
Timestamp by third party at Fri Dec 13 00:40:17 CET 2019
ACCESSION FORM FOR BENEFICIARIES

STOCKHOLMS LANS LANDSTING (SLL), established in HANTVERKARGATAN 45, STOCKHOLM 104 22, Sweden, VAT number: SE23210001601, (‘the beneficiary’), represented for the purpose of signing this Accession Form by the undersigned,

hereby agrees

to become beneficiary No (‘19’)

in Grant Agreement No 874703 (‘the Agreement’)

between NEDERLANDSE ORGANISATIE VOOR TOEGEPAST NATUURWETENSCHAPPELIJK ONDERZOEK TNO and the European Union (‘the EU’), represented by the European Commission (‘the Commission’),

for the action entitled ‘Exposome project for health and occupational research (EPHOR)’. 

and mandates

the coordinator to submit and sign in its name and on its behalf any amendments to the Agreement, in accordance with Article 55.

By signing this Accession Form, the beneficiary accepts the grant and agrees to implement it in accordance with the Agreement, with all the obligations and conditions it sets out.

SIGNATURE

For the beneficiary

Viktoria BJOERK with ECAS id nbjoevik signed in the Participant Portal on 30/12/2019 at 15:54:01 (transaction id SigId-3418- HvBcZmi4W3W1WASPnmcKt9QPxoVzwHKSmCaCBgBqH gPotr6npWCTYIIEoc19xzW3u7xzJ8eqT10chzK4zj8XaTzW- rS0vSmrBGYCFw1Qw5x00fu- rUqSuc5YA5Va0WdzhyqQcchtzoWBTQXnuJZ3PPAktxO)
. Timestamp by third party at Mon Dec 30 15:54:08 CET 2019
**FINANCIAL STATEMENT FOR [BENEFICIARY [name]/ LINKED THIRD PARTY [name]] FOR REPORTING PERIOD [reporting period]**

<table>
<thead>
<tr>
<th>A. Direct personnel costs</th>
<th>B. Direct costs of subcontracting</th>
<th>[C. Direct costs of fin. support]</th>
<th>D. Other direct costs</th>
<th>E. Indirect costs</th>
<th>[F. Costs of ... ]</th>
<th>Total costs</th>
<th>Receipts</th>
<th>EU contribution</th>
<th>Reimbursement rate %</th>
<th>Maximum EU contribution</th>
<th>Requested EU contribution</th>
<th>Additional information</th>
</tr>
</thead>
<tbody>
<tr>
<td>A.1 Employees (or equivalent)</td>
<td>A.4 SME owners without salary</td>
<td>C.1 Financial support</td>
<td>D.1 Travel</td>
<td>E.1 Costs of large research infrastructure</td>
<td>F.1 Costs of ...</td>
<td>Total costs</td>
<td>Receipts</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A.2 Natural persons under direct contract</td>
<td>A.5 Beneficiaries that are natural persons without salary</td>
<td>C.2 Prizes</td>
<td>D.2 Equipment</td>
<td>D.4 Costs of paid research infrastructure</td>
<td>F.2 Costs of ...</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A.3 Seconded persons</td>
<td>A.6 Personnel for providing access to research infrastructure</td>
<td></td>
<td>D.3 Other goods and services</td>
<td>D.5 Costs of internally invoiced goods and services</td>
<td></td>
<td></td>
<td></td>
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</tr>
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</table>

**Form of costs**

<table>
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<tr>
<th>Actual</th>
<th>Unit</th>
<th>Unit</th>
<th>Actual</th>
<th>Actual</th>
<th>Actual</th>
<th>Actual</th>
<th>Unit</th>
<th>Flat rate 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>Total b</td>
<td>No hours</td>
<td>Total c</td>
<td>d</td>
<td>[e]</td>
<td>f</td>
<td>[g]</td>
<td>Total h =0.25 x (a+b+c+d+e+f+g+h)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>25%</td>
</tr>
</tbody>
</table>

For the last reporting period: that all the receipts have been declared (see Article 5.3.3).

The beneficiary/linked third party hereby confirms that:
The information provided is complete, reliable and true.
The costs declared are eligible (see Article 6).

The costs can be substantiated by adequate records and supporting documentation that will be produced upon request or in the context of checks, reviews, audits and investigations (see Articles 17, 18 and 22).

For the last reporting period: that all the receipts have been declared (see Article 5.3.3).

1. Please declare all eligible costs, even if they exceed the amounts indicated in the estimated budget (see Annex 2). Only amounts that were declared in your individual financial statements can be taken into account later on, in order to replace other costs that are found to be ineligible.

2. See Article 6 for the eligibility conditions.

3. The indirect costs claimed must be free of any amounts covered by an operating grant (received under any EU or Euratom funding programme; see Article 6.2.E). If you have received an operating grant during this reporting period, you cannot claim indirect costs unless you can demonstrate that the operating grant does not cover any costs of the action.

4. The indirect costs claimed must be free of any amounts covered by an operating grant (received under any EU or Euratom funding programme; see Article 6.2.E). If you have received an operating grant during this reporting period, you cannot claim indirect costs unless you can demonstrate that the operating grant does not cover any costs of the action.

5. Flat rate: 25% of eligible direct costs, from which are excluded: direct costs of subcontracting, costs of in-kind contributions not used on premises, direct costs of financial support, and unit costs declared under budget category F if they include indirect costs (see Article 6.2.E)

6. Only specific unit costs that do not include indirect costs
ANNEX 5

MODEL FOR THE CERTIFICATE ON THE FINANCIAL STATEMENTS

➢ For options [in italics in square brackets]: choose the applicable option. Options not chosen should be deleted.
➢ For fields in [grey in square brackets]: enter the appropriate data

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TERMS OF REFERENCE FOR AN INDEPENDENT REPORT OF FACTUAL FINDINGS ON COSTS DECLARED UNDER A GRANT AGREEMENT FINANCED UNDER THE HORIZON 2020 RESEARCH FRAMEWORK PROGRAMME

INDEPENDENT REPORT OF FACTUAL FINDINGS ON COSTS DECLARED UNDER A GRANT AGREEMENT FINANCED UNDER THE HORIZON 2020 RESEARCH FRAMEWORK PROGRAMME
Terms of Reference for an Independent Report of Factual Findings on costs declared under a Grant Agreement financed under the Horizon 2020 Research and Innovation Framework Programme

This document sets out the ‘Terms of Reference (ToR)’ under which

[OPTION 1: [insert name of the beneficiary] (‘the Beneficiary’)] [OPTION 2: [insert name of the linked third party] (‘the Linked Third Party’), third party linked to the Beneficiary [insert name of the beneficiary] (‘the Beneficiary’)]

agrees to engage

[insert legal name of the auditor] (‘the Auditor’)

to produce an independent report of factual findings (‘the Report’) concerning the Financial Statement(s) drawn up by the [Beneficiary] [Linked Third Party] for the Horizon 2020 grant agreement [insert number of the grant agreement, title of the action, acronym and duration from/to] (‘the Agreement’), and

to issue a Certificate on the Financial Statements’ (‘CFS’) referred to in Article 20.4 of the Agreement based on the compulsory reporting template stipulated by the Commission.

The Agreement has been concluded under the Horizon 2020 Research and Innovation Framework Programme (H2020) between the Beneficiary and [OPTION 1: the European Union, represented by the European Commission (‘the Commission’)] [OPTION 2: the European Atomic Energy Community (Euratom,) represented by the European Commission (‘the Commission’)] [OPTION 3: the [Research Executive Agency (REA)] [European Research Council Executive Agency (ERCEA)] [Innovation and Networks Executive Agency (INEA)] [Executive Agency for Small and Medium-sized Enterprises (EASME)] (‘the Agency’), under the powers delegated by the European Commission (‘the Commission’).

The [Commission] [Agency] is mentioned as a signatory of the Agreement with the Beneficiary only. The [European Union][Euratom][Agency] is not a party to this engagement.

1.1 Subject of the engagement

The coordinator must submit to the [Commission][Agency] the final report within 60 days following the end of the last reporting period which should include, amongst other documents, a CFS for each beneficiary and for each linked third party that requests a total contribution of EUR 325 000 or more, as reimbursement of actual costs and unit costs calculated on the basis of its usual cost accounting practices (see Article 20.4 of the Agreement). The CFS must cover all reporting periods of the beneficiary or linked third party indicated above.

The Beneficiary must submit to the coordinator the CFS for itself and for its linked third party(ies), if the CFS must be included in the final report according to Article 20.4 of the Agreement.

The CFS is composed of two separate documents:

- The Terms of Reference (‘the ToR’) to be signed by the [Beneficiary] [Linked Third Party] and the Auditor;

---

1 By which costs under the Agreement are declared (see template ‘Model Financial Statements’ in Annex 4 to the Grant Agreement).
The Auditor’s Independent Report of Factual Findings (‘the Report’) to be issued on the Auditor’s letterhead, dated, stamped and signed by the Auditor (or the competent public officer) which includes the agreed-upon procedures (‘the Procedures’) to be performed by the Auditor, and the standard factual findings (‘the Findings’) to be confirmed by the Auditor.

If the CFS must be included in the final report according to Article 20.4 of the Agreement, the request for payment of the balance relating to the Agreement cannot be made without the CFS. However, the payment for reimbursement of costs covered by the CFS does not preclude the Commission [Agency,] the European Anti-Fraud Office and the European Court of Auditors from carrying out checks, reviews, audits and investigations in accordance with Article 22 of the Agreement.

1.2 Responsibilities

The [Beneficiary] [Linked Third Party]:

• must draw up the Financial Statement(s) for the action financed by the Agreement in compliance with the obligations under the Agreement. The Financial Statement(s) must be drawn up according to the [Beneficiary’s] [Linked Third Party’s] accounting and bookkeeping system and the underlying accounts and records;
• must send the Financial Statement(s) to the Auditor;
• is responsible and liable for the accuracy of the Financial Statement(s);
• is responsible for the completeness and accuracy of the information provided to enable the Auditor to carry out the Procedures. It must provide the Auditor with a written representation letter supporting these statements. The written representation letter must state the period covered by the statements and must be dated;
• accepts that the Auditor cannot carry out the Procedures unless it is given full access to the [Beneficiary’s] [Linked Third Party’s] staff and accounting as well as any other relevant records and documentation.

The Auditor:

• [Option 2 if the Beneficiary or Linked Third Party has an independent Public Officer: is a competent and independent Public Officer for which the relevant national authorities have established the legal capacity to audit the Beneficiary].
• [Option 3 if the Beneficiary or Linked Third Party is an international organisation: is an [internal] [external] auditor in accordance with the internal financial regulations and procedures of the international organisation].

The Auditor:

• must be independent from the Beneficiary [and the Linked Third Party], in particular, it must not have been involved in preparing the [Beneficiary’s] [Linked Third Party’s] Financial Statement(s);
• must plan work so that the Procedures may be carried out and the Findings may be assessed;
• must adhere to the Procedures laid down and the compulsory report format;
• must carry out the engagement in accordance with this ToR;
• must document matters which are important to support the Report;
• must base its Report on the evidence gathered;
• must submit the Report to the [Beneficiary] [Linked Third Party].
The Commission sets out the Procedures to be carried out by the Auditor. The Auditor is not responsible for their suitability or pertinence. As this engagement is not an assurance engagement, the Auditor does not provide an audit opinion or a statement of assurance.

1.3 Applicable Standards

The Auditor must comply with these Terms of Reference and with:

- the International Standard on Related Services (‘ISRS’) 4400 Engagements to perform Agreed-upon Procedures regarding Financial Information as issued by the International Auditing and Assurance Standards Board (IAASB);
- the Code of Ethics for Professional Accountants issued by the International Ethics Standards Board for Accountants (IESBA). Although ISRS 4400 states that independence is not a requirement for engagements to carry out agreed-upon procedures, the [Commission][Agency] requires that the Auditor also complies with the Code’s independence requirements.

The Auditor’s Report must state that there is no conflict of interests in establishing this Report between the Auditor and the Beneficiary [and the Linked Third Party], and must specify - if the service is invoiced - the total fee paid to the Auditor for providing the Report.

1.4 Reporting

The Report must be written in the language of the Agreement (see Article 20.7).

Under Article 22 of the Agreement, the Commission[, the Agency], the European Anti-Fraud Office and the Court of Auditors have the right to audit any work that is carried out under the action and for which costs are declared from [the European Union] [Euratom] budget. This includes work related to this engagement. The Auditor must provide access to all working papers (e.g. recalculation of hourly rates, verification of the time declared for the action) related to this assignment if the Commission [, the Agency], the European Anti-Fraud Office or the European Court of Auditors requests them.

1.5 Timing

The Report must be provided by /dd Month yyyy/.

1.6 Other terms

[The [Beneficiary] [Linked Third Party] and the Auditor can use this section to agree other specific terms, such as the Auditor’s fees, liability, applicable law, etc. Those specific terms must not contradict the terms specified above.]

______________________________
[legal name of the Auditor] [legal name of the [Beneficiary][Linked Third Party]]
[legal name of the [Beneficiary][Linked Third Party]]
[legal name & function of authorised representative]
[name & function of authorised representative]
[dd Month yyyy] [dd Month yyyy]
[dd Month yyyy]
Signature of the Auditor
Signature of the [Beneficiary][Linked Third Party]

---

2 Supreme Audit Institutions applying INTOSAI-standards may carry out the Procedures according to the corresponding International Standards of Supreme Audit Institutions and code of ethics issued by INTOSAI instead of the International Standard on Related Services (‘ISRS’) 4400 and the Code of Ethics for Professional Accountants issued by the IAASB and the IESBA.
Independent Report of Factual Findings on costs declared under Horizon 2020 Research and Innovation Framework Programme

(To be printed on the Auditor’s letterhead)

To
[ name of contact person(s)], [Position]
[ [Beneficiary’s] [Linked Third Party’s] name ]
[ Address]
[ dd Month yyyy]

Dear [Name of contact person(s)],

As agreed under the terms of reference dated [dd Month yyyy]

with [OPTION 1: [insert name of the beneficiary] (‘the Beneficiary’) ] [OPTION 2: [insert name of the linked third party] (‘the Linked Third Party’), third party linked to the Beneficiary [insert name of the beneficiary] (‘the Beneficiary’) ],

we

[name of the auditor ] (‘the Auditor’),

established at
[full address/city/state/province/country],

represented by
[name and function of an authorised representative],

have carried out the procedures agreed with you regarding the costs declared in the Financial Statement(s)3 of the [Beneficiary] [Linked Third Party] concerning the grant agreement [insert grant agreement reference: number, title of the action and acronym] (‘the Agreement’),

with a total cost declared of
[total amount] EUR,

and a total of actual costs and unit costs calculated in accordance with the [Beneficiary’s] [Linked Third Party’s] usual cost accounting practices’ declared of

[sum of total actual costs and total direct personnel costs declared as unit costs calculated in accordance with the [Beneficiary’s] [Linked Third Party’s] usual cost accounting practices] EUR

and hereby provide our Independent Report of Factual Findings (‘the Report’) using the compulsory report format agreed with you.

The Report

Our engagement was carried out in accordance with the terms of reference (‘the ToR’) appended to this Report. The Report includes the agreed-upon procedures (‘the Procedures’) carried out and the standard factual findings (‘the Findings’) examined.

3 By which the Beneficiary declares costs under the Agreement (see template ‘Model Financial Statement’ in Annex 4 to the Agreement).
The Procedures were carried out solely to assist the [Commission] [Agency] in evaluating whether the [Beneficiary's] [Linked Third Party's] costs in the accompanying Financial Statement(s) were declared in accordance with the Agreement. The [Commission] [Agency] draws its own conclusions from the Report and any additional information it may require.

The scope of the Procedures was defined by the Commission. Therefore, the Auditor is not responsible for their suitability or pertinence. Since the Procedures carried out constitute neither an audit nor a review made in accordance with International Standards on Auditing or International Standards on Review Engagements, the Auditor does not give a statement of assurance on the Financial Statements.

Had the Auditor carried out additional procedures or an audit of the [Beneficiary's] [Linked Third Party's] Financial Statements in accordance with International Standards on Auditing or International Standards on Review Engagements, other matters might have come to its attention and would have been included in the Report.

Not applicable Findings
We examined the Financial Statement(s) stated above and considered the following Findings not applicable:

<table>
<thead>
<tr>
<th>Explanation (to be removed from the Report):</th>
</tr>
</thead>
<tbody>
<tr>
<td>If a Finding was not applicable, it must be marked as ‘N.A.’ ('Not applicable') in the corresponding row on the right-hand column of the table and means that the Finding did not have to be corroborated by the Auditor and the related Procedure(s) did not have to be carried out.</td>
</tr>
<tr>
<td>The reasons of the non-application of a certain Finding must be obvious i.e.</td>
</tr>
<tr>
<td>i) if no cost was declared under a certain category then the related Finding(s) and Procedure(s) are not applicable;</td>
</tr>
<tr>
<td>ii) if the condition set to apply certain Procedure(s) are not met the related Finding(s) and those Procedure(s) are not applicable. For instance, for ‘beneficiaries with accounts established in a currency other than euro’ the Procedure and Finding related to ‘beneficiaries with accounts established in euro’ are not applicable. Similarly, if no additional remuneration is paid, the related Finding(s) and Procedure(s) for additional remuneration are not applicable.</td>
</tr>
</tbody>
</table>
Example (to be removed from the Report):

1. The Beneficiary was unable to substantiate the Finding number 1 on ... because ....
2. Finding number 30 was not fulfilled because the methodology used by the Beneficiary to calculate unit costs was different from the one approved by the Commission. The differences were as follows: ...
3. After carrying out the agreed procedures to confirm the Finding number 31, the Auditor found a difference of ___________ EUR. The difference can be explained by ...

Further Remarks

In addition to reporting on the results of the specific procedures carried out, the Auditor would like to make the following general remarks:

Example (to be removed from the Report):

1. Regarding Finding number 8 the conditions for additional remuneration were considered as fulfilled because ....
2. In order to be able to confirm the Finding number 15 we carried out the following additional procedures: ....

Use of this Report

This Report may be used only for the purpose described in the above objective. It was prepared solely for the confidential use of the [Beneficiary] [Linked Third Party] and the [Commission] [Agency], and only to be submitted to the [Commission] [Agency] in connection with the requirements set out in Article 20.4 of the Agreement. The Report may not be used by the [Beneficiary] [Linked Third Party] or by the [Commission] [Agency] for any other purpose, nor may it be distributed to any other parties. The [Commission] [Agency] may only disclose the Report to authorised parties, in particular to the European Anti-Fraud Office (OLAF) and the European Court of Auditors.

This Report relates only to the Financial Statement(s) submitted to the [Commission] [Agency] by the [Beneficiary] [Linked Third Party] for the Agreement. Therefore, it does not extend to any other of the [Beneficiary’s] [Linked Third Party’s] Financial Statement(s).

There was no conflict of interest\(^4\) between the Auditor and the Beneficiary [and Linked Third Party] in establishing this Report. The total fee paid to the Auditor for providing the Report was EUR ___________ (including EUR ___________ of deductible VAT).

We look forward to discussing our Report with you and would be pleased to provide any further information or assistance.

[legal name of the Auditor]
[name and function of an authorised representative]
[dd Month yyyy]
Signature of the Auditor

---

\(^4\) A conflict of interest arises when the Auditor's objectivity to establish the certificate is compromised in fact or in appearance when the Auditor for instance:
- was involved in the preparation of the Financial Statements;
- stands to benefit directly should the certificate be accepted;
- has a close relationship with any person representing the beneficiary;
- is a director, trustee or partner of the beneficiary; or
- is in any other situation that compromises his or her independence or ability to establish the certificate impartially.
Agreed-upon procedures to be performed and standard factual findings to be confirmed by the Auditor

The European Commission reserves the right to i) provide the auditor with additional guidance regarding the procedures to be followed or the facts to be ascertained and the way in which to present them (this may include sample coverage and findings) or to ii) change the procedures, by notifying the Beneficiary in writing. The procedures carried out by the auditor to confirm the standard factual finding are listed in the table below.

If this certificate relates to a Linked Third Party, any reference here below to ‘the Beneficiary’ is to be considered as a reference to ‘the Linked Third Party’.

The ‘result’ column has three different options: ‘C’, ‘E’ and ‘N.A.’:

- ‘C’ stands for ‘confirmed’ and means that the auditor can confirm the ‘standard factual finding’ and, therefore, there is no exception to be reported.
- ‘E’ stands for ‘exception’ and means that the Auditor carried out the procedures but cannot confirm the ‘standard factual finding’, or that the Auditor was not able to carry out a specific procedure (e.g. because it was impossible to reconcile key information or data were unavailable).
- ‘N.A.’ stands for ‘not applicable’ and means that the Finding did not have to be examined by the Auditor and the related Procedure(s) did not have to be carried out. The reasons of the non-application of a certain Finding must be obvious i.e. i) if no cost was declared under a certain category then the related Finding(s) and Procedure(s) are not applicable; ii) if the condition set to apply certain Procedure(s) are not met then the related Finding(s) and Procedure(s) are not applicable. For instance, for ‘beneficiaries with accounts established in a currency other than the euro’ the Procedure related to ‘beneficiaries with accounts established in euro’ is not applicable. Similarly, if no additional remuneration is paid, the related Finding(s) and Procedure(s) for additional remuneration are not applicable.

<table>
<thead>
<tr>
<th>Ref</th>
<th>Procedures</th>
<th>Standard factual finding</th>
<th>Result</th>
<th>(C / E / N.A.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>ACTUAL PERSONNEL COSTS AND UNIT COSTS CALCULATED BY THE BENEFICIARY IN ACCORDANCE WITH ITS USUAL COST ACCOUNTING PRACTICE</td>
<td>The Auditor draws a sample of persons whose costs were declared in the Financial Statement(s) to carry out the procedures indicated in the consecutive points of this section A. (The sample should be selected randomly so that it is representative. Full coverage is required if there are fewer than 10 people (including employees, natural persons working under a direct contract and personnel seconded by a third party), otherwise the sample should have a minimum of 10 people, or 10% of the total, whichever number is the highest) The Auditor sampled _______ people out of the total of _______ people.</td>
<td></td>
<td></td>
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</tbody>
</table>

### A.1 PERSONNEL COSTS

For the persons included in the sample and working under an employment contract or equivalent act (general procedures for individual actual personnel costs and personnel costs declared as unit costs)

To confirm standard factual findings 1-5 listed in the next column, the Auditor reviewed the following information/documents provided by the Beneficiary:

- a list of the persons included in the sample indicating the period(s) during which they worked for the action, their position (classification or category) and type of contract;
- the payslips of the employees included in the sample;
- reconciliation of the personnel costs declared in the Financial Statement(s) with the accounting system (project accounting and general ledger) and payroll system;
- information concerning the employment status and employment conditions of personnel included in the sample, in particular their employment contracts or equivalent;
- the Beneficiary’s usual policy regarding payroll matters (e.g. salary policy, overtime policy, variable pay);
- applicable national law on taxes, labour and social security and any other document that supports the personnel costs declared.

The Auditor also verified the eligibility of all components of the retribution (see Article 6 GA) and recalculated the personnel costs for employees included in the sample.

#### Further procedures if ‘additional remuneration’ is paid

To confirm standard factual findings 6-9 listed in the next column, the Auditor:

- reviewed relevant documents provided by the Beneficiary (legal form, legal/statutory

<table>
<thead>
<tr>
<th>Ref</th>
<th>Procedures</th>
<th>Standard factual finding</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>A.1</td>
<td>PERSONNEL COSTS</td>
<td>1) The employees were i) directly hired by the Beneficiary in accordance with its national legislation, ii) under the Beneficiary’s sole technical supervision and responsibility and iii) remunerated in accordance with the Beneficiary’s usual practices.</td>
<td>(C / E / N.A.)</td>
</tr>
<tr>
<td></td>
<td>2) Personnel costs were recorded in the Beneficiary’s accounts/payroll system.</td>
<td></td>
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<tr>
<td></td>
<td>3) Costs were adequately supported and reconciled with the accounts and payroll records.</td>
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<td></td>
<td>4) Personnel costs did not contain any ineligible elements.</td>
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<tr>
<td></td>
<td>5) There were no discrepancies between the personnel costs charged to the action and the costs recalculated by the Auditor.</td>
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<tr>
<td></td>
<td>6) The Beneficiary paying “additional remuneration” was a non-profit legal entity.</td>
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<tr>
<td>Ref</td>
<td>Procedures</td>
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<tr>
<td></td>
<td>Delegate the Beneficiary’s usual policy on additional remuneration, criteria used for its calculation, the Beneficiary’s usual remuneration practice for projects funded under national funding schemes...;</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>o recalculated the amount of additional remuneration eligible for the action based on the supporting documents received (full-time or part-time work, exclusive or non-exclusive dedication to the action, usual remuneration paid for projects funded by national schemes) to arrive at the applicable FTE/year and pro-rata rate (see data collected in the course of carrying out the procedures under A.2 ‘Productive hours’ and A.4 ‘Time recording system’).</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

‘ADDITIONAL REMUNERATION’ MEANS ANY PART OF THE REMUNERATION WHICH EXCEEDS WHAT THE PERSON WOULD BE PAID FOR TIME WORKED IN PROJECTS FUNDED BY NATIONAL SCHEMES.

IF ANY PART OF THE REMUNERATION PAID TO THE EMPLOYEE QUALIFIES AS "ADDITIONAL REMUNERATION" AND IS ELIGIBLE UNDER THE PROVISIONS OF ARTICLE 6.2.A.1, THIS CAN BE CHARGED AS ELIGIBLE COST TO THE ACTION UP TO THE FOLLOWING AMOUNT:

(A) IF THE PERSON WORKS FULL TIME AND EXCLUSIVELY ON THE ACTION DURING THE FULL YEAR: UP TO EUR 8,000/YEAR;

(B) IF THE PERSON WORKS EXCLUSIVELY ON THE ACTION BUT NOT FULL-TIME OR NOT FOR THE FULL YEAR: UP TO THE CORRESPONDING PRO-RATA AMOUNT OF EUR 8,000, OR

(C) IF THE PERSON DOES NOT WORK EXCLUSIVELY ON THE ACTION: UP TO A PRO-RATA AMOUNT CALCULATED IN ACCORDANCE TO ARTICLE 6.2.A.1.

Additional procedures in case “unit costs calculated by the Beneficiary in accordance with its usual cost accounting practices” is applied:

Apart from carrying out the procedures indicated above to confirm standard factual findings 1-5 and, if applicable, also 6-9, the Auditor carried out following procedures to confirm standard

<table>
<thead>
<tr>
<th>Result</th>
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<tbody>
<tr>
<td>(C / E / N.A.)</td>
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<tr>
<td>7) The amount of additional remuneration paid corresponded to the Beneficiary’s usual remuneration practices and was consistently paid whenever the same kind of work or expertise was required.</td>
</tr>
<tr>
<td>8) The criteria used to calculate the additional remuneration were objective and generally applied by the Beneficiary regardless of the source of funding used.</td>
</tr>
<tr>
<td>9) The amount of additional remuneration included in the personnel costs charged to the action was capped at EUR 8,000 per FTE/year (up to the equivalent pro-rata amount if the person did not work on the action full-time during the year or did not work exclusively on the action).</td>
</tr>
<tr>
<td>10) The personnel costs included in the Financial Statement were calculated in accordance with the Beneficiary’s usual cost accounting practice. This methodology was consistently...</td>
</tr>
</tbody>
</table>
### Procedures

**Factual findings 10-13 listed in the next column:**
- obtained a description of the Beneficiary’s usual cost accounting practice to calculate unit costs;
- reviewed whether the Beneficiary’s usual cost accounting practice was applied for the Financial Statements subject of the present CFS;
- verified the employees included in the sample were charged under the correct category (in accordance with the criteria used by the Beneficiary to establish personnel categories) by reviewing the contract/HR-record or analytical accounting records;
- verified that there is no difference between the total amount of personnel costs used in calculating the cost per unit and the total amount of personnel costs recorded in the statutory accounts;
- verified whether actual personnel costs were adjusted on the basis of budgeted or estimated elements and, if so, verified whether those elements used are actually relevant for the calculation, objective and supported by documents.

<table>
<thead>
<tr>
<th>Ref</th>
<th>Procedures</th>
<th>Standard factual finding</th>
<th>Result (C/E/N.A.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>Obtained a description of the Beneficiary’s usual cost accounting practice to calculate unit costs.</td>
<td>Used in all H2020 actions.</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>The employees were charged under the correct category.</td>
<td>11) The employees were charged under the correct category.</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>Total personnel costs used in calculating the unit costs were consistent with the expenses recorded in the statutory accounts.</td>
<td>12) Total personnel costs used in calculating the unit costs were consistent with the expenses recorded in the statutory accounts.</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>Any estimated or budgeted element used by the Beneficiary in its unit-cost calculation were relevant for calculating personnel costs and corresponded to objective and verifiable information.</td>
<td>13) Any estimated or budgeted element used by the Beneficiary in its unit-cost calculation were relevant for calculating personnel costs and corresponded to objective and verifiable information.</td>
<td></td>
</tr>
</tbody>
</table>

**For natural persons included in the sample and working with the Beneficiary under a direct contract other than an employment contract, such as consultants (no subcontractors).**

To confirm standard factual findings 14-17 listed in the next column the Auditor reviewed following information/documents provided by the Beneficiary:
- the contracts, especially the cost, contract duration, work description, place of work, ownership of the results and reporting obligations to the Beneficiary;
- the employment conditions of staff in the same category to compare costs and;
- any other document that supports the costs declared and its registration (e.g. invoices, accounting records, etc.).

<table>
<thead>
<tr>
<th>Ref</th>
<th>Procedures</th>
<th>Standard factual finding</th>
<th>Result (C/E/N.A.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>14</td>
<td>The natural persons worked under conditions similar to those of an employee, in particular regarding the way the work is organised, the tasks that are performed and the premises where they are performed.</td>
<td>14) The natural persons worked under conditions similar to those of an employee, in particular regarding the way the work is organised, the tasks that are performed and the premises where they are performed.</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>The results of work carried out belong to the Beneficiary, or, if not, the Beneficiary has obtained all necessary rights to fulfil its obligations as if those</td>
<td>15) The results of work carried out belong to the Beneficiary, or, if not, the Beneficiary has obtained all necessary rights to fulfil its obligations as if those</td>
<td></td>
</tr>
<tr>
<td>Ref</td>
<td>Procedures</td>
<td>Standard factual finding</td>
<td>Result (C / E / N.A.)</td>
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<tr>
<td></td>
<td></td>
<td>results were generated by itself.</td>
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<tr>
<td>16)</td>
<td>Their costs were not significantly different from those for staff who performed similar tasks under an employment contract with the Beneficiary.</td>
<td></td>
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<tr>
<td>17)</td>
<td>The costs were supported by audit evidence and registered in the accounts.</td>
<td></td>
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</tbody>
</table>

For personnel seconded by a third party and included in the sample (not subcontractors)

To confirm standard factual findings 18-21 listed in the next column, the Auditor reviewed following information/documents provided by the Beneficiary:

- their secondment contract(s) notably regarding costs, duration, work description, place of work and ownership of the results;
- if there is reimbursement by the Beneficiary to the third party for the resource made available (in-kind contribution against payment): any documentation that supports the costs declared (e.g. contract, invoice, bank payment, and proof of registration in its accounting/payroll, etc.) and reconciliation of the Financial Statement(s) with the accounting system (project accounting and general ledger) as well as any proof that the amount invoiced by the third party did not include any profit;
- if there is no reimbursement by the Beneficiary to the third party for the resource made available (in-kind contribution free of charge): a proof of the actual cost borne by the Third Party for the resource made available free of charge to the Beneficiary such as a statement of costs incurred by the Third Party and proof of the registration in the Third Party’s accounting/payroll;

18) Seconded personnel reported to the Beneficiary and worked on the Beneficiary’s premises (unless otherwise agreed with the Beneficiary).

19) The results of work carried out belong to the Beneficiary, or, if not, the Beneficiary has obtained all necessary rights to fulfil its obligations as if those results were generated by itself..

If personnel is seconded against payment:

20) The costs declared were supported with documentation and recorded in the
<table>
<thead>
<tr>
<th>Ref</th>
<th>Procedures</th>
<th>Standard factual finding</th>
<th>Result (C / E / N.A.)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>o any other document that supports the costs declared (e.g. invoices, etc.).</td>
<td>Beneﬁciary’s accounts. The third party did not include any profit.</td>
<td></td>
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<td><strong>If personnel is seconded free of charge:</strong></td>
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<tr>
<td></td>
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<td>21) The costs declared did not exceed the third party’s cost as recorded in the accounts of the third party and were supported with documentation.</td>
<td></td>
</tr>
<tr>
<td>A.2</td>
<td><strong>PRODUCTIVE HOURS</strong></td>
<td>To conﬁrm standard factual ﬁndings 22-27 listed in the next column, the Auditor reviewed relevant documents, especially national legislation, labour agreements and contracts and time records of the persons included in the sample, to verify that:</td>
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<td>o the annual productive hours applied were calculated in accordance with one of the methods described below,</td>
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<td>o the full-time equivalent (FTEs) ratios for employees not working full-time were correctly calculated.</td>
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<td>If the Beneﬁciary applied method B, the auditor veriﬁed that the correctness in which the total number of hours worked was calculated and that the contracts speciﬁed the annual workable hours.</td>
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<td>If the Beneﬁciary applied method C, the auditor veriﬁed that the ‘annual productive hours’ applied when calculating the hourly rate were equivalent to at least 90 % of the ‘standard annual workable hours’. The Auditor can only do this if the calculation of the standard annual workable hours was performed correctly.</td>
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<td>22) The Beneﬁciary applied method [choose one option and delete the others]</td>
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<tr>
<td></td>
<td></td>
<td>[A: 1720 hours]</td>
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<tr>
<td></td>
<td></td>
<td>[B: the ‘total number of hours worked’]</td>
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<tr>
<td></td>
<td></td>
<td>[C: ‘standard annual productive hours’ used correspond to usual accounting practices]</td>
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<td></td>
<td>23) Productive hours were calculated annually.</td>
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<tr>
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<td></td>
<td>24) For employees not working full-time the full-time equivalent (FTE) ratio was correctly applied.</td>
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<tr>
<td>Ref</td>
<td>Procedures</td>
<td></td>
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</tbody>
</table>
|     | hours can be supported by records, such as national legislation, labour agreements, and contracts.  

**Beneficiary's Productive hours** for persons working full time shall be one of the following methods:

A. **1720 annual productive hours** (pro-rata for persons not working full-time)  
B. **The total number of hours worked by the person for the Beneficiary in the year** (this method is also referred to as ‘total number of hours worked’ in the next column). The calculation of the total number of hours worked was done as follows: annual workable hours of the person according to the employment contract, applicable labour agreement or national law plus overtime worked minus absences (such as sick leave or special leave).  
C. The standard number of annual hours generally applied by the Beneficiary for its personnel in accordance with its usual cost accounting practices (this method is also referred to as ‘standard annual productive hours’ in the next column). This number must be at least 90% of the standard annual workable hours.  

‘Annual workable hours’ means the period during which the personnel must be working, at the employer’s disposal and carrying out his/her activity or duties under the employment contract, applicable collective labour agreement or national working time legislation.  

<table>
<thead>
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<th>Standard factual finding</th>
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</table>
|     | If the Beneficiary applied method B.  
25) The calculation of the number of ‘annual workable hours’, overtime and absences was verifiable based on the documents provided by the Beneficiary.  
25.1) The Beneficiary calculates the hourly rates per full financial year following procedure A.3 (method B is not allowed for beneficiaries calculating hourly rates per month).  
     | If the Beneficiary applied method C.  
26) The calculation of the number of ‘standard annual workable hours’ was verifiable based on the documents provided by the Beneficiary. |
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<tr>
<th>Ref</th>
<th>Procedures</th>
<th>Standard factual finding</th>
<th>Result (C / E / N.A.)</th>
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<tbody>
<tr>
<td>A.3</td>
<td><strong>HOURLY PERSONNEL RATES</strong></td>
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<tr>
<td>I) For unit costs calculated in accordance to the Beneficiary's usual cost accounting practice (unit costs):</td>
<td></td>
<td>27) The ‘annual productive hours’ used for calculating the hourly rate were consistent with the usual cost accounting practices of the Beneficiary and were equivalent to at least 90% of the ‘annual workable hours’.</td>
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<tr>
<td>If the Beneficiary has a &quot;Certificate on Methodology to calculate unit costs&quot; (CoMUC) approved by the Commission, the Beneficiary provides the Auditor with a description of the approved methodology and the Commission’s letter of acceptance. The Auditor verified that the Beneficiary has indeed used the methodology approved. If so, no further verification is necessary.</td>
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<tr>
<td>If the Beneficiary does not have a &quot;Certificate on Methodology&quot; (CoMUC) approved by the Commission, or if the methodology approved was not applied, then the Auditor:</td>
<td></td>
<td>28) The Beneficiary applied [choose one option and delete the other]:</td>
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<tr>
<td>o reviewed the documentation provided by the Beneficiary, including manuals and internal guidelines that explain how to calculate hourly rates;</td>
<td></td>
<td>[Option I: “Unit costs (hourly rates) were calculated in accordance with the Beneficiary’s usual cost accounting practices”]</td>
<td></td>
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<tr>
<td>o recalculated the unit costs (hourly rates) of staff included in the sample following the results of the procedures carried out in A.1 and A.2.</td>
<td></td>
<td>[Option II: Individual hourly rates were applied]</td>
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<tr>
<td>II) For individual hourly rates:</td>
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<tr>
<td>The Auditor:</td>
<td></td>
<td>29) The Beneficiary used the Commission-approved methodology to calculate hourly rates. It corresponded to the organisation's usual cost accounting practices and was applied consistently for all</td>
<td></td>
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<tr>
<td>o reviewed the documentation provided by the Beneficiary, including manuals and internal guidelines that explain how to calculate hourly rates;</td>
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</tbody>
</table>
activities irrespective of the source of funding.

For option I concerning unit costs and if the Beneficiary applies a methodology not approved by the Commission:

30) The unit costs re-calculated by the Auditor were the same as the rates applied by the Beneficiary.

For option II concerning individual hourly rates:

31) The individual rates re-calculated by the Auditor were the same as the rates applied by the Beneficiary.

31.1) The Beneficiary used only one option (per full financial year or per month) throughout each financial year examined.

31.2) The hourly rates do not include additional remuneration.
### Ref

<table>
<thead>
<tr>
<th>TIME RECORDING SYSTEM</th>
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<tr>
<td><strong>A.4</strong></td>
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</table>

To verify that the time recording system ensures the fulfilment of all minimum requirements and that the hours declared for the action were correct, accurate and properly authorised and supported by documentation, the Auditor made the following checks for the persons included in the sample that declare time as worked for the action on the basis of time records:

- description of the time recording system provided by the Beneficiary (registration, authorisation, processing in the HR-system);
- its actual implementation;
- time records were signed at least monthly by the employees (on paper or electronically) and authorised by the project manager or another manager;
- the hours declared were worked within the project period;
- there were no hours declared as worked for the action if HR-records showed absence due to holidays or sickness (further cross-checks with travels are carried out in B.1 below);
- the hours charged to the action matched those in the time recording system.

_OlY THE HOURS WORKED ON THE ACTION CAN BE CHARGED. ALL WORKING TIME TO BE CHARGED SHOULD BE RECORDED THROUGHOUT THE DURATION OF THE PROJECT, ADEQUATELY SUPPORTED BY EVIDENCE OF THEIR REALITY AND RELIABILITY (SEE SPECIFIC PROVISIONS BELOW FOR PERSONS WORKING EXCLUSIVELY FOR THE ACTION WITHOUT TIME RECORDS)._

<table>
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<tr>
<th>Procedures</th>
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32) All persons recorded their time dedicated to the action on a daily/weekly/monthly basis using a paper/computer-based system. (delete the answers that are not applicable)

33) Their time-records were authorised at least monthly by the project manager or other superior.

34) Hours declared were worked within the project period and were consistent with the presences/absences recorded in HR-records.

35) There were no discrepancies between the number of hours charged to the action and the number of hours recorded.

**If the persons are working exclusively for the action and without time records**

For the persons selected that worked exclusively for the action without time records, the Auditor verified evidence available demonstrating that they were in reality exclusively dedicated to the action and that the Beneficiary signed a declaration confirming that they have worked exclusively for the action.

36) The exclusive dedication is supported by a declaration signed by the Beneficiary and by any other evidence gathered.
<table>
<thead>
<tr>
<th>Ref</th>
<th>Procedures</th>
<th>Standard factual finding</th>
<th>Result (C/E/N.A.)</th>
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<tbody>
<tr>
<td>B</td>
<td><strong>COSTS OF SUBCONTRACTING</strong></td>
<td></td>
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<tr>
<td></td>
<td><strong>B.1</strong> The Auditor obtained the detail/breakdown of subcontracting costs and sampled</td>
<td>37) The use of claimed subcontracting costs was foreseen in Annex 1 and costs were declared in the Financial Statements under the subcontracting category.</td>
<td></td>
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<td></td>
<td>cost items selected randomly (full coverage is required if there are fewer than 10 items, otherwise the sample should have a minimum of 10 item, or 10% of the total, whichever number is highest).</td>
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<td></td>
<td>To confirm standard factual findings 37-41 listed in the next column, the Auditor reviewed the following for the items included in the sample:</td>
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<td></td>
<td>o the use of subcontractors was foreseen in Annex 1;</td>
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<td></td>
<td>o subcontracting costs were declared in the subcontracting category of the Financial Statement;</td>
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<td></td>
<td>o supporting documents on the selection and award procedure were followed;</td>
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<td>o the Beneficiary ensured best value for money (key elements to appreciate the respect of this principle are the award of the subcontract to the bid offering best price-quality ratio, under conditions of transparency and equal treatment. In case an existing framework contract was used the Beneficiary ensured it was established on the basis of the principle of best value for money under conditions of transparency and equal treatment).</td>
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<td></td>
<td>In particular,</td>
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<td></td>
<td>i. if the Beneficiary acted as a contracting authority within the meaning of Directive 2004/18/EC (or 2014/24/EU) or of Directive 2004/17/EC (or 2014/25/EU), the Auditor verified that the applicable national law on public procurement was followed and that the subcontracting complied with the Terms and Conditions of the Agreement.</td>
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<tr>
<td></td>
<td>ii. if the Beneficiary did not fall under the above-mentioned category the Auditor verified that the Beneficiary followed their usual procurement rules and respected the Terms and Conditions of the Agreement..</td>
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<td>38) There were documents of requests to different providers, different offers and assessment of the offers before selection of the provider in line with internal procedures and procurement rules. Subcontracts were awarded in accordance with the principle of best value for money. (When different offers were not collected the Auditor explains the reasons provided by the Beneficiary under the caption “Exceptions” of the Report. The Commission will analyse this information to evaluate whether these costs might be accepted as eligible)</td>
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<td></td>
<td>39) The subcontracts were not awarded to other Beneficiaries.</td>
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<tr>
<td>Ref</td>
<td>Procedures</td>
<td>Standard factual finding</td>
<td>Result (C / E / N.A.)</td>
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<td></td>
<td>For the items included in the sample the Auditor also verified that:</td>
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<td></td>
<td>o the subcontracts were not awarded to other Beneficiaries in the consortium;</td>
<td>of the consortium.</td>
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<tr>
<td></td>
<td>o there were signed agreements between the Beneficiary and the subcontractor;</td>
<td>40) All subcontracts were supported by signed agreements between the Beneficiary and the subcontractor.</td>
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<tr>
<td></td>
<td>o there was evidence that the services were provided by subcontractor;</td>
<td>41) There was evidence that the services were provided by the subcontractors.</td>
<td></td>
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<tr>
<td></td>
<td>C.1  The Auditor obtained the detail/breakdown of the costs of providing financial support to third parties and sampled ______ cost items selected randomly (full coverage is required if there are fewer than 10 items, otherwise the sample should have a minimum of 10 item, or 10% of the total, whichever number is highest).</td>
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<td></td>
<td>The Auditor verified that the following minimum conditions were met:</td>
<td>42) All minimum conditions were met</td>
<td></td>
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<tr>
<td></td>
<td>a) the maximum amount of financial support for each third party did not exceed EUR 60 000, unless explicitly mentioned in Annex 1;</td>
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<td></td>
<td>b) the financial support to third parties was agreed in Annex 1 of the Agreement and the other provisions on financial support to third parties included in Annex 1 were respected.</td>
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<tr>
<td>D</td>
<td>OTHER ACTUAL DIRECT COSTS</td>
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<tr>
<td>D.1</td>
<td>COSTS OF TRAVEL AND RELATED SUBSISTENCE ALLOWANCES</td>
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<tr>
<td></td>
<td>The Auditor sampled ______ cost items selected randomly (full coverage is required if there are fewer than 10 items, otherwise the sample should have a minimum of 10 item, or 10% of the total, whichever number is the highest).</td>
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<td></td>
<td>The Auditor inspected the sample and verified that:</td>
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<td>o travel and subsistence costs were consistent with the Beneficiary's usual policy for travel. In this context, the Beneficiary provided evidence of its normal policy for travel costs (e.g. use of first class tickets, reimbursement by the Beneficiary on the basis of actual costs, a lump sum or per diem) to enable the Auditor to compare the travel costs charged with this policy;</td>
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<td></td>
<td>o travel costs are correctly identified and allocated to the action (e.g. trips are directly linked to the action) by reviewing relevant supporting documents such as minutes of meetings, workshops or conferences, their registration in the correct project account, their consistency with time records or with the dates/duration of the workshop/conference;</td>
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<td></td>
<td>o no ineligible costs or excessive or reckless expenditure was declared (see Article 6.5 MGA).</td>
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<td></td>
<td>43) Costs were incurred, approved and reimbursed in line with the Beneficiary's usual policy for travels.</td>
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<td></td>
<td>44) There was a link between the trip and the action.</td>
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<td></td>
<td>45) The supporting documents were consistent with each other regarding subject of the trip, dates, duration and reconciled with time records and accounting.</td>
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<tr>
<td></td>
<td>46) No ineligible costs or excessive or reckless expenditure was declared.</td>
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<tr>
<td>D.2</td>
<td>DEPRECIATION COSTS FOR EQUIPMENT, INFRASTRUCTURE OR OTHER ASSETS</td>
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<tr>
<td></td>
<td>The Auditor sampled ______ cost items selected randomly (full coverage is required if there are fewer than 10 items, otherwise the sample should have a minimum of 10 item, or 10% of the total, whichever number is the highest).</td>
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<td></td>
<td>For “equipment, infrastructure or other assets” [from now on called “asset(s)’”] selected in the sample the Auditor verified that:</td>
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<td>o the assets were acquired in conformity with the Beneficiary's internal guidelines and procedures;</td>
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<td></td>
<td>47) Procurement rules, principles and guides were followed.</td>
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<td></td>
<td>48) There was a link between the grant agreement and the asset charged to the action.</td>
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<tr>
<td></td>
<td>49) The asset charged to the action was traceable to the accounting records and the underlying documents.</td>
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</table>
The Auditor recalculated the depreciation costs and verified that they were in line with the applicable rules in the Beneficiary’s country and with the Beneficiary’s usual accounting policy (e.g. depreciation calculated on the acquisition value).

The Auditor verified that no ineligible costs such as deductible VAT, exchange rate losses, excessive or reckless expenditure were declared (see Article 6.5 GA).

### D.3 COSTS OF OTHER GOODS AND SERVICES

The Auditor sampled **[insert number]** cost items selected randomly *(full coverage is required if there are fewer than 10 items, otherwise the sample should have a minimum of 10 items, or 10% of the total, whichever number is highest).*

For the purchase of goods, works or services included in the sample the Auditor verified that:

- the contracts did not cover tasks described in Annex 1;
- they were correctly identified, allocated to the proper action, entered in the accounting system (traceable to underlying documents such as purchase orders, invoices and accounting);
- the goods were not placed in the inventory of durable equipment;
- the costs charged to the action were accounted in line with the Beneficiary’s usual accounting practices;
- no ineligible costs or excessive or reckless expenditure were declared (see Article 6 GA).

In addition, the Auditor verified that these goods and services were acquired in conformity with

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<td>50)</td>
<td>The depreciation method used to charge the asset to the action was in line with the applicable rules of the Beneficiary’s country and the Beneficiary’s usual accounting policy.</td>
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<tr>
<td>51)</td>
<td>The amount charged corresponded to the actual usage for the action.</td>
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<tr>
<td>52)</td>
<td>No ineligible costs or excessive or reckless expenditure were declared.</td>
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</tr>
<tr>
<td>53)</td>
<td>Contracts for works or services did not cover tasks described in Annex 1.</td>
<td></td>
</tr>
<tr>
<td>54)</td>
<td>Costs were allocated to the correct action and the goods were not placed in the inventory of durable equipment.</td>
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<tr>
<td>55)</td>
<td>The costs were charged in line with the Beneficiary’s accounting policy and were adequately supported.</td>
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<tr>
<td>56)</td>
<td>No ineligible costs or excessive or reckless expenditure were declared. For internal invoices/charges only the cost element was charged, without any mark-ups.</td>
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</tbody>
</table>
the Beneficiary's internal guidelines and procedures, in particular:

- if Beneficiary acted as a contracting authority within the meaning of Directive 2004/18/EC (or 2014/24/EU) or of Directive 2004/17/EC (or 2014/25/EU), the Auditor verified that the applicable national law on public procurement was followed and that the procurement contract complied with the Terms and Conditions of the Agreement.

- if the Beneficiary did not fall into the category above, the Auditor verified that the Beneficiary followed their usual procurement rules and respected the Terms and Conditions of the Agreement.

For the items included in the sample the Auditor also verified that:

- the Beneficiary ensured best value for money (key elements to appreciate the respect of this principle are the award of the contract to the bid offering best price-quality ratio, under conditions of transparency and equal treatment. In case an existing framework contract was used the Auditor also verified that the Beneficiary ensured it was established on the basis of the principle of best value for money under conditions of transparency and equal treatment);

  **SUCH GOODS AND SERVICES INCLUDE, FOR INSTANCE, CONSUMABLES AND SUPPLIES, DISSEMINATION (INCLUDING OPEN ACCESS), PROTECTION OF RESULTS, SPECIFIC EVALUATION OF THE ACTION IF IT IS REQUIRED BY THE AGREEMENT, CERTIFICATES ON THE FINANCIAL STATEMENTS IF THEY ARE REQUIRED BY THE AGREEMENT AND CERTIFICATES ON THE METHODOLOGY, TRANSLATIONS, REPRODUCTION.**

### D.4 AGGREGATED CAPITALISED AND OPERATING COSTS OF RESEARCH INFRASTRUCTURE

The Auditor ensured the existence of a positive ex-ante assessment (issued by the EC Services) of the cost accounting methodology of the Beneficiary allowing it to apply the guidelines on direct costing for large research infrastructures in Horizon 2020.

57) Procurement rules, principles and guides were followed. There were documents of requests to different providers, different offers and assessment of the offers before selection of the provider in line with internal procedures and procurement rules. The purchases were made in accordance with the principle of best value for money.

(When different offers were not collected the Auditor explains the reasons provided by the Beneficiary under the caption “Exceptions” of the Report. The Commission will analyse this information to evaluate whether these costs might be accepted as eligible)

58) The costs declared as direct costs for Large Research Infrastructures (in the appropriate line of the Financial Statement) comply with the methodology described in the positive ex-ante assessment report.
In the cases that a positive ex-ante assessment has been issued (see the standard factual findings 58-59 on the next column),

The Auditor ensured that the beneficiary has applied consistently the methodology that is explained and approved in the positive ex ante assessment;

In the cases that a positive ex-ante assessment has NOT been issued (see the standard factual findings 60 on the next column),

The Auditor verified that no costs of Large Research Infrastructure have been charged as direct costs in any costs category;

In the cases that a draft ex-ante assessment report has been issued with recommendation for further changes (see the standard factual findings 60 on the next column),

- The Auditor followed the same procedure as above (when a positive ex-ante assessment has NOT yet been issued) and paid particular attention (testing reinforced) to the cost items for which the draft ex-ante assessment either rejected the inclusion as direct costs for Large Research Infrastructures or issued recommendations.

Any difference between the methodology applied and the one positively assessed was extensively described and adjusted accordingly.

The direct costs declared were free from any indirect costs items related to the Large Research Infrastructure.

D.5 Costs of internally invoiced goods and services

The Auditor sampled cost items selected randomly (full coverage is required if there are fewer than 10 items, otherwise the sample should have a minimum of 10 item, or 10% of the total, whichever number is highest).

To confirm standard factual findings 61-65 listed in the next column, the Auditor:

- obtained a description of the Beneficiary's usual cost accounting practice to calculate costs of internally invoiced goods and services (unit costs);
- reviewed whether the Beneficiary's usual cost accounting practice was applied for the Financial Statements subject of the present CFS;
- ensured that the methodology to calculate unit costs is being used in a consistent manner, based on objective criteria, regardless of the source of funding;
- verified that any ineligible items or any costs claimed under other budget categories, in particular indirect costs, have not been taken into account when calculating the costs of internally invoiced goods and services.

The costs of internally invoiced goods and services included in the Financial Statement were calculated in accordance with the Beneficiary's usual cost accounting practice.

The cost accounting practices used to calculate the costs of internally invoiced goods and services were applied by the Beneficiary in a consistent manner based on objective criteria regardless of the source of funding.

The unit cost is calculated using the actual costs for the good or service recorded in the Beneficiary’s accounts, excluding any ineligible cost or costs included in other
internally invoiced goods and services (see Article 6 GA);

- verified whether actual costs of internally invoiced goods and services were adjusted on the basis of budgeted or estimated elements and, if so, verified whether those elements used are actually relevant for the calculation, and correspond to objective and verifiable information.

- verified that any costs of items which are not directly linked to the production of the invoiced goods or service (e.g. supporting services like cleaning, general accountancy, administrative support, etc. not directly used for production of the good or service) have not been taken into account when calculating the costs of internally invoiced goods and services.

- verified that any costs of items used for calculating the costs internally invoiced goods and services are supported by audit evidence and registered in the accounts.

**USE OF EXCHANGE RATES**

**E.1** a) For Beneficiaries with accounts established in a currency other than euros

The Auditor sampled ______ cost items selected randomly and verified that the exchange rates used for converting other currencies into euros were in accordance with the following rules established in the Agreement (full coverage is required if there are fewer than 10 items, otherwise the sample should have a minimum of 10 item, or 10% of the total, whichever number is highest):

**COSTSRecorded in the accounts in a currency other than euro shall be converted into euro at the average of the daily exchange rates published in the C series of Official Journal of the European Union (https://www.ecb.int/stats/exchange/eurofxref/html/index.en.html), determined over the corresponding reporting period.**

**If no daily euro exchange rate is published in the Official Journal of the European Union for the currency in question, conversion shall be made at the average of the monthly accounting rates established by the Commission and published on its website (http://ec.europa.eu/budget/contracts_grants/info_contracts/inforeuro/inforeuro_en.cfm).**

64) The unit cost excludes any costs of items which are not directly linked to the production of the invoiced goods or service.

65) The costs items used for calculating the actual costs of internally invoiced goods and services were relevant, reasonable and correspond to objective and verifiable information.

66) The exchange rates used to convert other currencies into Euros were in accordance with the rules established of the Grant Agreement and there was no difference in the final figures.
b) For Beneficiaries with accounts established in euros

The Auditor sampled ______ cost items selected randomly and verified that the exchange rates used for converting other currencies into euros were in accordance with the following rules established in the Agreement (full coverage is required if there are fewer than 10 items, otherwise the sample should have a minimum of 10 item, or 10% of the total, whichever number is highest):

**Costs incurred in another currency shall be converted into euro by applying the Beneficiary’s usual accounting practices.**

67) The Beneficiary applied its usual accounting practices.

[legal name of the audit firm]  
[name and function of an authorised representative]  
[dd Month yyyy]  
<Signature of the Auditor>
ANNEX 6

MODEL FOR THE CERTIFICATE ON THE METHODOLOGY

- For options *in italics in square brackets*: choose the applicable option. Options not chosen should be deleted.
- For fields in [grey in square brackets]: enter the appropriate data.

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 TERMS OF REFERENCE FOR AN AUDIT ENGAGEMENT FOR A METHODOLOGY CERTIFICATE IN CONNECTION WITH ONE OR MORE GRANT AGREEMENTS FINANCED UNDER THE HORIZON 2020 RESEARCH AND INNOVATION FRAMEWORK PROGRAMME

 INDEPENDENT REPORT OF FACTUAL FINDINGS ON THE METHODOLOGY CONCERNING GRANT AGREEMENTS FINANCED UNDER THE HORIZON 2020 RESEARCH AND INNOVATION FRAMEWORK PROGRAMME
Terms of reference for an audit engagement for a methodology certificate in connection with one or more grant agreements financed under the Horizon 2020 Research and Innovation Framework Programme

This document sets out the ‘Terms of Reference (ToR)’ under which

[OPTION 1: [insert name of the beneficiary] (‘the Beneficiary’) ] [OPTION 2: [insert name of the linked third party] (‘the Linked Third Party’), third party linked to the Beneficiary [insert name of the beneficiary] (‘the Beneficiary’)]

agrees to engage

[insert legal name of the auditor] (‘the Auditor’)

to produce an independent report of factual findings (‘the Report’) concerning the [Beneficiary’s] [Linked Third Party’s] usual accounting practices for calculating and claiming direct personnel costs declared as unit costs (‘the Methodology’) in connection with grant agreements financed under the Horizon 2020 Research and Innovation Framework Programme.

The procedures to be carried out for the assessment of the methodology will be based on the grant agreement(s) detailed below:

[title and number of the grant agreement(s)] (‘the Agreement(s)’)

The Agreement(s) has(have) been concluded between the Beneficiary and [OPTION 1: the European Union, represented by the European Commission (‘the Commission’) ][ OPTION 2: the European Atomic Energy Community (Euratom,) represented by the European Commission (‘the Commission’) ][OPTION 3: the [Research Executive Agency (REA)] [European Research Council Executive Agency (ERCEA)] [Innovation and Networks Executive Agency (INEA)] [Executive Agency for Small and Medium-sized Enterprises (EASME)] (‘the Agency’), under the powers delegated by the European Commission (‘the Commission’).]

The [Commission] [Agency] is mentioned as a signatory of the Agreement with the Beneficiary only. The [European Union] [Euratom] [Agency] is not a party to this engagement.

1.1 Subject of the engagement

According to Article 18.1.2 of the Agreement, beneficiaries [and linked third parties] that declare direct personnel costs as unit costs calculated in accordance with their usual cost accounting practices may submit to the [Commission] [Agency], for approval, a certificate on the methodology (‘CoMUC’) stating that there are adequate records and documentation to prove that their cost accounting practices used comply with the conditions set out in Point A of Article 6.2.

The subject of this engagement is the CoMUC which is composed of two separate documents:

- the Terms of Reference (‘the ToR’) to be signed by the [Beneficiary] [Linked Third Party] and the Auditor;
- the Auditor’s Independent Report of Factual Findings (‘the Report’) issued on the Auditor’s letterhead, dated, stamped and signed by the Auditor which includes; the standard statements (‘the Statements’) evaluated and signed by the [Beneficiary] [Linked Third Party], the agreed-upon procedures (‘the Procedures’) performed by the Auditor and the standard factual findings
(‘the Findings’) assessed by the Auditor. The Statements, Procedures and Findings are summarised in the table that forms part of the Report.

The information provided through the Statements, the Procedures and the Findings will enable the Commission to draw conclusions regarding the existence of the [Beneficiary’s] [Linked Third Party’s] usual cost accounting practice and its suitability to ensure that direct personnel costs claimed on that basis comply with the provisions of the Agreement. The Commission draws its own conclusions from the Report and any additional information it may require.

1.2 Responsibilities

The parties to this agreement are the [Beneficiary] [Linked Third Party] and the Auditor.

The [Beneficiary] [Linked Third Party]:

• is responsible for preparing financial statements for the Agreement(s) (‘the Financial Statements’) in compliance with those Agreements;
• is responsible for providing the Financial Statement(s) to the Auditor and enabling the Auditor to reconcile them with the [Beneficiary’s] [Linked Third Party’s] accounting and bookkeeping system and the underlying accounts and records. The Financial Statement(s) will be used as a basis for the procedures which the Auditor will carry out under this ToR;
• is responsible for its Methodology and liable for the accuracy of the Financial Statement(s);
• is responsible for endorsing or refuting the Statements indicated under the heading ‘Statements to be made by the Beneficiary/ Linked Third Party’ in the first column of the table that forms part of the Report;
• must provide the Auditor with a signed and dated representation letter;
• accepts that the ability of the Auditor to carry out the Procedures effectively depends upon the [Beneficiary] [Linked Third Party] providing full and free access to the [Beneficiary’s] [Linked Third Party’s] staff and to its accounting and other relevant records.

The Auditor:

• [Option 2 if the Beneficiary or Linked Third Party has an independent Public Officer: is a competent and independent Public Officer for which the relevant national authorities have established the legal capacity to audit the Beneficiary];
• [Option 3 if the Beneficiary or Linked Third Party is an international organisation: is an [internal] [external] auditor in accordance with the internal financial regulations and procedures of the international organisation].

The Auditor:

• must be independent from the Beneficiary [and the Linked Third Party], in particular, it must not have been involved in preparing the Beneficiary’s [and Linked Third Party’s] Financial Statement(s);
• must plan work so that the Procedures may be carried out and the Findings may be assessed;
• must adhere to the Procedures laid down and the compulsory report format;
• must carry out the engagement in accordance with these ToR;
• must document matters which are important to support the Report;
• must base its Report on the evidence gathered;
• must submit the Report to the [Beneficiary] [Linked Third Party].
The Commission sets out the Procedures to be carried out and the Findings to be endorsed by the Auditor. The Auditor is not responsible for their suitability or pertinence. As this engagement is not an assurance engagement the Auditor does not provide an audit opinion or a statement of assurance.

1.3 Applicable Standards

The Auditor must comply with these Terms of Reference and with¹:

- the International Standard on Related Services (‘ISRS’) 4400 *Engagements to perform Agreed-upon Procedures regarding Financial Information* as issued by the International Auditing and Assurance Standards Board (IAASB);
- the *Code of Ethics for Professional Accountants* issued by the International Ethics Standards Board for Accountants (IESBA). Although ISRS 4400 states that independence is not a requirement for engagements to carry out agreed-upon procedures, the Commission requires that the Auditor also complies with the Code’s independence requirements.

The Auditor’s Report must state that there was no conflict of interests in establishing this Report between the Auditor and the Beneficiary [and the Linked Third Party] that could have a bearing on the Report, and must specify – if the service is invoiced - the total fee paid to the Auditor for providing the Report.

1.4 Reporting

The Report must be written in the language of the Agreement (see Article 20.7 of the Agreement).

Under Article 22 of the Agreement, the Commission, [the Agency], the European Anti-Fraud Office and the Court of Auditors have the right to audit any work that is carried out under the action and for which costs are declared from [the European Union] [Euratom] budget. This includes work related to this engagement. The Auditor must provide access to all working papers related to this assignment if the Commission[, the Agency], the European Anti-Fraud Office or the European Court of Auditors requests them.

1.5 Timing

The Report must be provided by [dd Month yyyy].

1.6 Other Terms

[The [Beneficiary] [Linked Third Party] and the Auditor can use this section to agree other specific terms, such as the Auditor’s fees, liability, applicable law, etc. Those specific terms must not contradict the terms specified above.]

<table>
<thead>
<tr>
<th>[legal name of the Auditor]</th>
<th>[legal name of the [Beneficiary] [Linked Third Party]]</th>
</tr>
</thead>
<tbody>
<tr>
<td>[name &amp; title of authorised representative]</td>
<td>[name &amp; title of authorised representative]</td>
</tr>
<tr>
<td>[dd Month yyyy]</td>
<td>[dd Month yyyy]</td>
</tr>
</tbody>
</table>

Signature of the Auditor

Signature of the [Beneficiary] [Linked Third Party]

¹ Supreme Audit Institutions applying INTOSAI-standards may carry out the Procedures according to the corresponding International Standards of Supreme Audit Institutions and code of ethics issued by INTOSAI instead of the International Standard on Related Services (‘ISRS’) 4400 and the Code of Ethics for Professional Accountants issued by the IAASB and the IESBA.
Independent report of factual findings on the methodology concerning grant agreements financed under the Horizon 2020 Research and Innovation Framework Programme

(To be printed on letterhead paper of the auditor)

To

[ name of contact person(s)]. [Position]  
[[Beneficiary’s] [Linked Third Party’s] name]  
[ Address]  
[ dd Month yyyy]  

Dear [Name of contact person(s)],

As agreed under the terms of reference dated [dd Month yyyy]  

with [OPTION 1: [insert name of the beneficiary] (‘the Beneficiary’)]  
[OPTION 2: [insert name of the linked third party] (‘the Linked Third Party’), third party linked to the Beneficiary [insert name of the beneficiary] (‘the Beneficiary’)],

we

established at

[ full address/city/state/province/country],

represented by

[name and function of an authorised representative],

have carried out the agreed-upon procedures (‘the Procedures’) and provide hereby our Independent Report of Factual Findings (‘the Report’), concerning the [Beneficiary’s] [Linked Third Party’s] usual accounting practices for calculating and declaring direct personnel costs declared as unit costs (‘the Methodology’).

You requested certain procedures to be carried out in connection with the grant(s)

[title and number of the grant agreement(s)] (‘the Agreement(s)’).

The Report

Our engagement was carried out in accordance with the terms of reference (‘the ToR’) appended to this Report. The Report includes: the standard statements (‘the Statements’) made by the [Beneficiary] [Linked Third Party], the agreed-upon procedures (‘the Procedures’) carried out and the standard factual findings (‘the Findings’) confirmed by us.

The engagement involved carrying out the Procedures and assessing the Findings and the documentation requested appended to this Report, the results of which the Commission uses to draw conclusions regarding the acceptability of the Methodology applied by the [Beneficiary] [Linked Third Party].
The Report covers the methodology used from [dd Month yyyy]. In the event that the [Beneficiary] [Linked Third Party] changes this methodology, the Report will not be applicable to any Financial Statement\(^1\) submitted thereafter.

The scope of the Procedures and the definition of the standard statements and findings were determined solely by the Commission. Therefore, the Auditor is not responsible for their suitability or pertinence.

Since the Procedures carried out constitute neither an audit nor a review made in accordance with International Standards on Auditing or International Standards on Review Engagements, we do not give a statement of assurance on the costs declared on the basis of the [Beneficiary’s] [Linked Third Party’s] Methodology. Had we carried out additional procedures or had we performed an audit or review in accordance with these standards, other matters might have come to its attention and would have been included in the Report.

**Exceptions**

Apart from the exceptions listed below, the [Beneficiary] [Linked Third Party] agreed with the standard Statements and provided the Auditor all the documentation and accounting information needed by the Auditor to carry out the requested Procedures and corroborate the standard Findings.

List here any exception and add any information on the cause and possible consequences of each exception, if known. If the exception is quantifiable, also indicate the corresponding amount.

- \(i.\) the [Beneficiary] [Linked Third Party] did not agree with the standard Statement number … because…;
- \(ii.\) the Auditor could not carry out the procedure … established because …. (e.g. due to the inability to reconcile key information or the unavailability or inconsistency of data);
- \(iii.\) the Auditor could not confirm or corroborate the standard Finding number … because ….

**Remarks**

We would like to add the following remarks relevant for the proper understanding of the Methodology applied by the [Beneficiary] [Linked Third Party] or the results reported:

Example (to be removed from the Report):

Regarding the methodology applied to calculate hourly rates …

Regarding standard Finding 15 it has to be noted that …

The [Beneficiary] [Linked Third Party] explained the deviation from the benchmark statement XXIV concerning time recording for personnel with no exclusive dedication to the action in the following manner:

**Annexes**

Please provide the following documents to the auditor and annex them to the report when submitting this CoMUC to the Commission:

---

\(^1\) Financial Statement in this context refers solely to Annex 4 of the Agreement by which the Beneficiary declares costs under the Agreement.
1. Brief description of the methodology for calculating personnel costs, productive hours and hourly rates;
2. Brief description of the time recording system in place;
3. An example of the time records used by the [Beneficiary] [Linked Third Party];
4. Description of any budgeted or estimated elements applied, together with an explanation as to why they are relevant for calculating the personnel costs and how they are based on objective and verifiable information;
5. A summary sheet with the hourly rate for direct personnel declared by the [Beneficiary] [Linked Third Party] and recalculated by the Auditor for each staff member included in the sample (the names do not need to be reported);
6. A comparative table summarising for each person selected in the sample a) the time claimed by the [Beneficiary] [Linked Third Party] in the Financial Statement(s) and b) the time according to the time record verified by the Auditor;
7. A copy of the letter of representation provided to the Auditor.

Use of this Report

This Report has been drawn up solely for the purpose given under Point 1.1 Reasons for the engagement.

The Report:
- is confidential and is intended to be submitted to the Commission by the [Beneficiary] [Linked Third Party] in connection with Article 18.1.2 of the Agreement;
- may not be used by the [Beneficiary] [Linked Third Party] or by the Commission for any other purpose, nor distributed to any other parties;
- may be disclosed by the Commission only to authorised parties, in particular the European Anti-Fraud Office (OLAF) and the European Court of Auditors.
- relates only to the usual cost accounting practices specified above and does not constitute a report on the Financial Statements of the [Beneficiary] [Linked Third Party].

No conflict of interest exists between the Auditor and the Beneficiary [and the Linked Third Party] that could have a bearing on the Report. The total fee paid to the Auditor for producing the Report was EUR ______ (including EUR ______ of deductible VAT).

We look forward to discussing our Report with you and would be pleased to provide any further information or assistance which may be required.

Yours sincerely

[legal name of the Auditor]
[name and title of the authorised representative]
[dd Month yyyy]
Signature of the Auditor

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A conflict of interest arises when the Auditor's objectivity to establish the certificate is compromised in fact or in appearance when the Auditor for instance:
- was involved in the preparation of the Financial Statements;
- stands to benefit directly should the certificate be accepted;
- has a close relationship with any person representing the beneficiary;
- is a director, trustee or partner of the beneficiary; or
- is in any other situation that compromises his or her independence or ability to establish the certificate impartially.
Statements to be made by the Beneficiary/Linked Third Party (‘the Statements’) and Procedures to be carried out by the Auditor (‘the Procedures’) and standard factual findings (‘the Findings’) to be confirmed by the Auditor

The Commission reserves the right to provide the auditor with guidance regarding the Statements to be made, the Procedures to be carried out or the Findings to be ascertained and the way in which to present them. The Commission reserves the right to vary the Statements, Procedures or Findings by written notification to the Beneficiary/Linked Third Party to adapt the procedures to changes in the grant agreement(s) or to any other circumstances.

If this methodology certificate relates to the Linked Third Party’s usual accounting practices for calculating and claiming direct personnel costs declared as unit costs any reference here below to ‘the Beneficiary’ is to be considered as a reference to ‘the Linked Third Party’.

<table>
<thead>
<tr>
<th>Please explain any discrepancies in the body of the Report.</th>
<th>Procedures to be carried out and Findings to be confirmed by the Auditor</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A. Use of the Methodology</strong></td>
<td><strong>Procedure:</strong></td>
</tr>
<tr>
<td>I. The cost accounting practice described below has been in use since [dd Month yyyy].</td>
<td>✓ The Auditor checked these dates against the documentation the Beneficiary has provided.</td>
</tr>
<tr>
<td>II. The next planned alteration to the methodology used by the Beneficiary will be from [dd Month yyyy].</td>
<td><strong>Factual finding:</strong></td>
</tr>
<tr>
<td></td>
<td>1. The dates provided by the Beneficiary were consistent with the documentation.</td>
</tr>
<tr>
<td><strong>B. Description of the Methodology</strong></td>
<td><strong>Procedure:</strong></td>
</tr>
<tr>
<td>III. The methodology to calculate unit costs is being used in a consistent manner and is reflected in the relevant procedures.</td>
<td>✓ The Auditor reviewed the description, the relevant manuals and/or internal guidance documents describing the methodology.</td>
</tr>
<tr>
<td>[Please describe the methodology your entity uses to calculate personnel costs, productive hours and hourly rates, present your description to the Auditor and annex it to this certificate]</td>
<td><strong>Factual finding:</strong></td>
</tr>
<tr>
<td>[If the statement of section “B. Description of the methodology” cannot be endorsed by the Beneficiary or there is no written methodology to calculate unit costs it should be listed here below and reported as exception by the Auditor in the main Report of Factual Findings:]</td>
<td>2. The brief description was consistent with the relevant manuals, internal guidance and/or other documentary evidence the Auditor has reviewed.</td>
</tr>
<tr>
<td>- ...</td>
<td>3. The methodology was generally applied by the Beneficiary as part of its usual costs accounting practices.</td>
</tr>
</tbody>
</table>
### Please explain any discrepancies in the body of the Report.

<table>
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<tr>
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<tbody>
<tr>
<td><strong>C. Personnel costs</strong></td>
<td><strong>Procedure:</strong> The Auditor draws a sample of employees to carry out the procedures indicated in this section C and the following sections D to F.</td>
</tr>
<tr>
<td><strong>General</strong></td>
<td>The Auditor has drawn a random sample of 10 employees assigned to Horizon 2020 action(s). If fewer than 10 employees are assigned to the Horizon 2020 action(s), the Auditor has selected all employees assigned to the Horizon 2020 action(s) complemented by other employees irrespective of their assignments until he has reached 10 employees.</td>
</tr>
<tr>
<td><strong>IV.</strong> The unit costs (hourly rates) are limited to salaries including during parental leave, social security contributions, taxes and other costs included in the remuneration required under national law and the employment contract or equivalent appointing act;</td>
<td>✓ the Auditor reviewed all documents relating to personnel costs such as employment contracts, payslips, payroll policy (e.g. salary policy, overtime policy, variable pay policy), accounting and payroll records, applicable national tax, labour and social security law and any other documents corroborating the personnel costs claimed;</td>
</tr>
<tr>
<td><strong>V.</strong> Employees are hired directly by the Beneficiary in accordance with national law, and work under its sole supervision and responsibility;</td>
<td>✓ in particular, the Auditor reviewed the employment contracts of the employees in the sample to verify that:</td>
</tr>
<tr>
<td><strong>VI.</strong> The Beneficiary remunerates its employees in accordance with its usual practices. This means that personnel costs are charged in line with the Beneficiary’s usual payroll policy (e.g. salary policy, overtime policy, variable pay) and no special conditions exist for employees assigned to tasks relating to the European Union or Euratom, unless explicitly provided for in the grant agreement(s);</td>
<td>i. they were employed directly by the Beneficiary in accordance with applicable national legislation;</td>
</tr>
<tr>
<td><strong>VII.</strong> The Beneficiary allocates its employees to the relevant group/category/cost centre for the purpose of the unit cost calculation in line with the usual cost accounting practice;</td>
<td>ii. they were working under the sole technical supervision and responsibility of the latter;</td>
</tr>
<tr>
<td><strong>VIII.</strong> Personnel costs are based on the payroll system and accounting system.</td>
<td>iii. they were remunerated in accordance with the Beneficiary’s usual practices;</td>
</tr>
<tr>
<td><strong>IX.</strong> Any exceptional adjustments of actual personnel costs resulted from relevant budgeted or estimated elements and were based on objective and verifiable information. [Please describe the ‘budgeted or estimated elements’ and their relevance to personnel costs, and explain how they were reasonable and based on objective and verifiable information, present your explanation to the Auditor and annex it to this certificate].</td>
<td>iv. they were allocated to the correct group/category/cost centre for the purposes of calculating the unit cost in line with the Beneficiary’s usual cost accounting practices;</td>
</tr>
<tr>
<td><strong>X.</strong> Personnel costs claimed do not contain any of the following ineligible costs: costs related to return on capital; debt and debt service charges; provisions for future losses or debts; interest owed; doubtful debts; currency exchange losses; bank costs charged by the Beneficiary’s bank for transfers from the Commission/Agency; excessive or reckless expenditure; deductible VAT or costs incurred during suspension of the implementation of the action.</td>
<td>✓ the Auditor verified that any ineligible items or any costs claimed under other costs categories or costs covered by other types of grant or by other grants financed from the European Union budget have not been taken into account when calculating the personnel costs;</td>
</tr>
<tr>
<td><strong>XI.</strong> Personnel costs were not declared under another EU or Euratom grant</td>
<td>✓ the Auditor numerically reconciled the total amount of personnel costs used to calculate the unit cost with the total amount of personnel costs recorded in the statutory accounts and the payroll system.</td>
</tr>
</tbody>
</table>
Please explain any discrepancies in the body of the Report.

<table>
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<tr>
<th>Statements to be made by Beneficiary</th>
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</thead>
<tbody>
<tr>
<td>(including grants awarded by a Member State and financed by the EU budget and grants awarded by bodies other than the Commission/Agency for the purpose of implementing the EU or Euratom budget in the same period, unless the Beneficiary can demonstrate that the operating grant does not cover any costs of the action).</td>
<td>✓ to the extent that actual personnel costs were adjusted on the basis of budgeted or estimated elements, the Auditor carefully examined those elements and checked the information source to confirm that they correspond to objective and verifiable information;</td>
</tr>
<tr>
<td>If additional remuneration as referred to in the grant agreement(s) is paid</td>
<td>✓ if additional remuneration has been claimed, the Auditor verified that the Beneficiary was a non-profit legal entity, that the amount was capped at EUR 8 000 per full-time equivalent and that it was reduced proportionately for employees not assigned exclusively to the action(s).</td>
</tr>
<tr>
<td>XII. The Beneficiary is a non-profit legal entity;</td>
<td>✓ the Auditor recalculated the personnel costs for the employees in the sample.</td>
</tr>
<tr>
<td>XIII. The additional remuneration is part of the beneficiary’s usual remuneration practices and paid consistently whenever the relevant work or expertise is required;</td>
<td>Factual finding:</td>
</tr>
<tr>
<td>XIV. The criteria used to calculate the additional remuneration are objective and generally applied regardless of the source of funding;</td>
<td>4. All the components of the remuneration that have been claimed as personnel costs are supported by underlying documentation.</td>
</tr>
<tr>
<td>XV. The additional remuneration included in the personnel costs used to calculate the hourly rates for the grant agreement(s) is capped at EUR 8 000 per full-time equivalent (reduced proportionately if the employee is not assigned exclusively to the action).</td>
<td>5. The employees in the sample were employed directly by the Beneficiary in accordance with applicable national law and were working under its sole supervision and responsibility.</td>
</tr>
<tr>
<td>[If certain statement(s) of section “C. Personnel costs” cannot be endorsed by the Beneficiary they should be listed here below and reported as exception by the Auditor in the main Report of Factual Findings]:</td>
<td>6. Their employment contracts were in line with the Beneficiary’s usual policy;</td>
</tr>
<tr>
<td>…]</td>
<td>7. Personnel costs were duly documented and consisted solely of salaries, social security contributions (pension contributions, health insurance, unemployment fund contributions, etc.), taxes and other statutory costs included in the remuneration (holiday pay, thirteenth month’s pay, etc.);</td>
</tr>
<tr>
<td></td>
<td>8. The totals used to calculate the personnel unit costs are consistent with those registered in the payroll and accounting records;</td>
</tr>
<tr>
<td></td>
<td>9. To the extent that actual personnel costs were adjusted on the basis of budgeted or estimated elements, those elements were relevant for calculating the personnel costs and correspond to objective and verifiable information. The budgeted or estimated elements used are: — (indicate the elements and their values).</td>
</tr>
<tr>
<td></td>
<td>10. Personnel costs contained no ineligible elements;</td>
</tr>
<tr>
<td></td>
<td>11. Specific conditions for eligibility were fulfilled when additional</td>
</tr>
</tbody>
</table>
Please explain any discrepancies in the body of the Report.

<table>
<thead>
<tr>
<th>Statements to be made by Beneficiary</th>
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<tbody>
<tr>
<td>remuneration was paid: a) the Beneficiary is registered in the grant agreements as a non-profit legal entity; b) it was paid according to objective criteria generally applied regardless of the source of funding used and c) remuneration was capped at EUR 8,000 per full-time equivalent (or up to up to the equivalent pro-rata amount if the person did not work on the action full-time during the year or did not work exclusively on the action).</td>
<td></td>
</tr>
</tbody>
</table>

D. Productive hours

XVI. The number of productive hours per full-time employee applied is [delete as appropriate]:

A. 1720 productive hours per year for a person working full-time (corresponding pro-rata for persons not working full time).

B. the total number of hours worked in the year by a person for the Beneficiary

C. the standard number of annual hours generally applied by the beneficiary for its personnel in accordance with its usual cost accounting practices. This number must be at least 90% of the standard annual workable hours.

If method B is applied

XVII. The calculation of the total number of hours worked was done as follows: annual workable hours of the person according to the employment contract, applicable labour agreement or national law plus overtime worked minus absences (such as sick leave and special leave).

XVIII. ‘Annual workable hours’ are hours during which the personnel must be working, at the employer’s disposal and carrying out his/her activity or duties under the employment contract, applicable collective labour agreement or national working time legislation.

XIX. The contract (applicable collective labour agreement or national working time legislation) do specify the working time enabling to calculate the annual workable hours.

Procedure (same sample basis as for Section C: Personnel costs):

- The Auditor verified that the number of productive hours applied is in accordance with method A, B or C.
- The Auditor checked that the number of productive hours per full-time employee is correct.
- If method B is applied the Auditor verified i) the manner in which the total number of hours worked was done and ii) that the contract specified the annual workable hours by inspecting all the relevant documents, national legislation, labour agreements and contracts.
- If method C is applied the Auditor reviewed the manner in which the standard number of working hours per year has been calculated by inspecting all the relevant documents, national legislation, labour agreements and contracts and verified that the number of productive hours per year used for these calculations was at least 90% of the standard number of working hours per year.

Factual finding:

General

12. The Beneficiary applied a number of productive hours consistent with method A, B or C detailed in the left-hand column.

13. The number of productive hours per year per full-time employee was accurate.

If method B is applied

14. The number of ‘annual workable hours’, overtime and absences was
Please explain any discrepancies in the body of the Report.

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>If method C is applied</td>
<td>verifiable based on the documents provided by the Beneficiary and the calculation of the total number of hours worked was accurate.</td>
</tr>
<tr>
<td>XX. The standard number of productive hours per year is that of a full-time equivalent.</td>
<td>15. The contract specified the working time enabling to calculate the annual workable hours.</td>
</tr>
<tr>
<td>XXI. The number of productive hours per year on which the hourly rate is based i) corresponds to the Beneficiary’s usual accounting practices; ii) is at least 90% of the standard number of workable (working) hours per year.</td>
<td>If method C is applied</td>
</tr>
<tr>
<td>XXII. Standard workable (working) hours are hours during which personnel are at the Beneficiary’s disposal preforming the duties described in the relevant employment contract, collective labour agreement or national labour legislation. The number of standard annual workable (working) hours that the Beneficiary claims is supported by labour contracts, national legislation and other documentary evidence.</td>
<td>16. The calculation of the number of productive hours per year corresponded to the usual costs accounting practice of the Beneficiary.</td>
</tr>
<tr>
<td>[If certain statement(s) of section “D. Productive hours” cannot be endorsed by the Beneficiary they should be listed here below and reported as exception by the Auditor: ]</td>
<td>17. The calculation of the standard number of workable (working) hours per year was corroborated by the documents presented by the Beneficiary.</td>
</tr>
<tr>
<td>18. The number of productive hours per year used for the calculation of the hourly rate was at least 90% of the number of workable (working) hours per year.</td>
<td></td>
</tr>
<tr>
<td>E. Hourly rates</td>
<td>Procedure</td>
</tr>
<tr>
<td>The hourly rates are correct because:</td>
<td>✓ The Auditor has obtained a list of all personnel rates calculated by the Beneficiary in accordance with the methodology used.</td>
</tr>
<tr>
<td>XXIII. Hourly rates are correctly calculated since they result from dividing annual personnel costs by the productive hours of a given year and group (e.g. staff category or department or cost centre depending on the methodology applied) and they are in line with the statements made in section C. and D. above.</td>
<td>✓ The Auditor has obtained a list of all the relevant employees, based on which the personnel rate(s) are calculated.</td>
</tr>
<tr>
<td>[If the statement of section ‘E. Hourly rates’ cannot be endorsed by the Beneficiary they should be listed here below and reported as exception by the Auditor: ]</td>
<td>For 10 employees selected at random (same sample basis as Section C: Personnel costs):</td>
</tr>
<tr>
<td></td>
<td>✓ The Auditor recalculated the hourly rates.</td>
</tr>
<tr>
<td></td>
<td>✓ The Auditor verified that the methodology applied corresponds to the usual accounting practices of the organisation and is applied consistently for all activities of the organisation on the basis of objective criteria irrespective of the source of funding.</td>
</tr>
<tr>
<td>Factual finding:</td>
<td></td>
</tr>
</tbody>
</table>

**Please explain any discrepancies in the body of the Report.**

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<tbody>
<tr>
<td>19. No differences arose from the recalculation of the hourly rate for the employees included in the sample.</td>
<td></td>
</tr>
</tbody>
</table>

**F. Time recording**

**XXIV.** Time recording is in place for all persons with no exclusive dedication to one Horizon 2020 action. At least all hours worked in connection with the grant agreement(s) are registered on a daily/weekly/monthly basis [delete as appropriate] using a paper/computer-based system [delete as appropriate];

**XXV.** For persons exclusively assigned to one Horizon 2020 activity the Beneficiary has either signed a declaration to that effect or has put arrangements in place to record their working time;

**XXVI.** Records of time worked have been signed by the person concerned (on paper or electronically) and approved by the action manager or line manager at least monthly;

**XXVII.** Measures are in place to prevent staff from:

i. recording the same hours twice,

ii. recording working hours during absence periods (e.g. holidays, sick leave),

iii. recording more than the number of productive hours per year used to calculate the hourly rates, and

iv. recording hours worked outside the action period.

**XXVIII.** No working time was recorded outside the action period;

**XXIX.** No more hours were claimed than the productive hours used to calculate the hourly personnel rates.

*Please provide a brief description of the time recording system in place together with the measures applied to ensure its reliability to the Auditor and annex it to the*
Please explain any discrepancies in the body of the Report.

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<td>Present certificate¹.</td>
<td>no time worked outside the action period was charged to the action.</td>
</tr>
</tbody>
</table>

Factual finding:

20. The brief description, manuals and/or internal guidance on time recording provided by the Beneficiary were consistent with management reports/records and other documents reviewed and were generally applied by the Beneficiary to produce the financial statements.

21. For the random sample time was recorded or, in the case of employees working exclusively for the action, either a signed declaration or time records were available;

22. For the random sample the time records were signed by the employee and the action manager/line manager, at least monthly.

23. Working time claimed for the action occurred in the periods claimed;

24. No more hours were claimed than the number productive hours used to calculate the hourly personnel rates;

25. There is proof that the Beneficiary has checked that working time has not been claimed twice, that it is consistent with absence records and the number of productive hours per year, and that no working time has been claimed outside the action period.

26. Working time claimed is consistent with that on record at the human-resources department.

¹ The description of the time recording system must state among others information on the content of the time records, its coverage (full or action time-recording, for all personnel or only for personnel involved in H2020 actions), its degree of detail (whether there is a reference to the particular tasks accomplished), its form, periodicity of the time registration and authorisation (paper or a computer-based system; on a daily, weekly or monthly basis; signed and countersigned by whom), controls applied to prevent double-charging of time or ensure consistency with HR-records such as absences and travels as well as it information flow up to its use for the preparation of the Financial Statements.
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<td>[official name of the Auditor]</td>
</tr>
<tr>
<td>[name and title of authorised representative]</td>
<td>[name and title of authorised representative]</td>
</tr>
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<td>[dd Month yyyy]</td>
<td>[dd Month yyyy]</td>
</tr>
<tr>
<td>&lt;Signature of the Beneficiary&gt;</td>
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