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D9.3 Legal and Ethics Management Handbook
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D9.3 Legal and Ethics Management Handbook

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PROJECT No. 965196

Innovative tools to study the impact and mode of action of micro and nanoplastics on human health: towards a knowledge base for risk assessment

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1. ACRONYMS AND ABBREVIATIONS

GA	• Grant Agreement
CA	• Consortium Agreement
MNPLs	• Micro and Nanoplastics
WHO	• World Health Organization
ICMJE	• International Committee of Medical Journal Editors
GDPR	• General Data Protection Regulation
DPO	• Data Protection Officer

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2. EXECUTIVE SUMMARY

The exponential increase in the production/use of plastic translates into a parallel increase of environmental plastic- waste that is continuously degraded into micro and nanoplastics (MNPLs). Information on the MNPLs effects on human health is still preliminary and, furthermore, the limitations in current methodologies prevent accurate human exposure/risk assessment.

In this context, PLASTICHEAL aims at providing new methodologies and solid scientific evidence to regulators by combining the use of breakthrough research and validated test methods to set the knowledge basis for adequate risk assessment of MNPLs.

PLASTICHEAL will be supported by an innovative experimental approach that will first generate human exposure estimates after identification, measurement, and characterization of MNPLs present in the environmental air, water and food sources, as well as in human biological samples of population groups with potential high MNPLs exposure levels (biomonitoring study) by means of adapting the existing analytical methodology proven useful for fibres and nanomaterials. Those estimates will then be complemented/ correlated with the output of kinetic models using data on MNPLs translocation, accumulation, and destabilization of the Gastrointestinal and Respiratory Tracts, and with the MNPLs toxicokinetic in blood and secondary organs using in vivo models. Thereafter, immune effects, transforming effects, genotoxic effects, impact on transcriptome/epigenome/secretome (i.e. omics), stemness imbalance and potential molecular mechanisms of action and adverse outcome pathways in blood, primary and secondary organs will be studied under *in vitro*, *in vivo*, and *ex vivo* short and long-term (co)exposure settings.

To ensure the impact of PLASTICHEAL's developed methodology and gained knowledge on current and future regulation, a continuous dialogue will be established from the beginning of the project with policy makers and other key stakeholders of the plastic value chain.

PLASTICHEAL is part of the European Cluster for Understanding Impacts of Micro- and Nano-plastics on Human Health (CUSP).

This deliverable summarises the legal aspects that this project abides by as well as the ethical principles that should be considered in all phases of the project.

More information on the ethics requirements can be found in the deliverables of work package 10 *Ethics*. The research in PlasticHeal involves work on cells, animals and on different cohorts of volunteers. The ethical aspects regarding research work with the different subjects are summarised here. Especial care is taken regarding information to volunteers and management of their personal data and rights on them.

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3. LEGAL ASPECTS

As specified in art. 7 of the GA, the beneficiaries will implement the action as described in GA Annex 1 and in compliance with the provisions of the Agreement and all legal obligations under applicable EU, international and national regulation. In case of non-compliance the grant amount may be reduced or other measures may be taken.

The specific aspects regarding the PlasticHeal project are detailed in the Grant Agreement and the Consortium Agreement

3.1. Grant Agreement

The Grant Agreement sets out the rights and obligations and the terms and conditions applicable to the grant awarded to the beneficiaries for implementing the PlasticHeal project.

It contains the following sections:

- Terms and Conditions
- Annex 1 Description of the action
- 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
- Annex 5 Model for the certificate on the financial statements
- Annex 6 Model for the certificate on the methodology

The Grant Agreement is signed by the coordinator and the EU. Beneficiaries access to it through the accession form. Beneficiaries should guide their work and expenses on the PlasticHeal project by the information contained in the Grant Agreement.

3.2. Consortium Agreement

The relationships among the institutions involved in the project are regulated by the Consortium Agreement. This document provides more specific details about the governance structure and the running of the project.

The items covered in the CA are:

- Section 1: Definitions
- Section 2: Purpose
- Section 3: Entry into force, duration and termination

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- Section 4: Responsibilities of Parties
- Section 5: Liability towards each other
- Section 6: Governance structure
- Section 7: Financial provisions
- Section 8: Results
- Section 9: Access Rights
- Section 10: Non-disclosure of information
- Section 11: Miscellaneous
- Section 12: Signatures
- Attachment 1: Background included
- Attachment 2: Accession document
- Attachment 3: List of Third Parties for simplified transfer according to Section 8.3.2.
- Attachment 4: Identified Affiliated Entities according to Section 9.5

3.3. Amendments and changes to Consortium Agreement

During the development of the project, it may be necessary to introduce changes to annexes 1 and 2. In this case an amendment to the Grant Agreement will be requested.

The amendment should be requested by the coordinator to the project officer after the approval of the Steering Committee.

Budget changes that do not involve subcontracting and do not involve changes in the description of the action can be addressed internally as long as the project officer is informed about the need of these changes.

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4. ETHICAL ASPECTS

Ethics is a fundamental aspect of all research project and one of the main requirements for EU funded projects

The research in PlasticHeal involves work on cells, animals and on different cohorts of volunteers this involves a variety of ethical aspects that have to be considered. Especial care is taken regarding information of volunteers and management of their personal data and rights on them.

The EU ensures the fulfilment of all applicable ethics regulations from the proposal phase of the project. This is done through the Ethics self-assessment that all consortia have to include in their proposal.

4.1. Ethics self-assessment

During the proposal preparation phase all proposals have to undergo an ethics self-assessment[1] where they revise whether their research involves any aspects that require ethic supervision out of the following list.

1. Human embryos & foetuses
2. Human beings
3. Human cells or tissues
4. Personal data
5. Animals
6. Non-EU countries
7. Environment, health & safety
8. Dual use
9. Exclusive focus on civil applications
10. Potential misuse of research results
11. Other ethics issues

The aspects with ethical impact identified in the Plasticheal project were:

1. Human beings
2. Human cells or tissues
3. Personal data
4. Animals
5. Environment, health & safety

[1] https://ec.europa.eu/research/participants/data/ref/h2020/grants_manual/hi/ethics/h2020_hi_ethics-self-assess_en.pdf

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These ethical aspects have given rise to a dedicated work package to this issue, *WP10 Ethics requirements*. Furthermore, there is an ethic advisor (Dr. Josep Santaló) within the advisory board that will supervise all ethical aspects.

Dr Josep Santaló is a UAB lecturer who is conducting research in Life and Health Sciences. He is also a member of the UAB's Ethics Committee on Animal and Human Experimentation CEEAH[2] .

Within WP10 the following deliverables and milestones are programmed. The table below summarises the content of each ethics deliverable. These deliverables can be consulted for further information on the different aspects.

Deliverable title and content:	
D10.1; Due in month 3	H - Requirement No. 1
1. Procedures and criteria that will be used to identify/recruit research participants 2. Involvement of vulnerable individuals/groups. Justification for their participation and the measures to protect them. 3. Copy of the informed consent procedures that will be implemented for the participation of humans. 4. Templates of the informed consent/assent forms and information sheets (in language and terms intelligible to the participants). 5. Details on incidental findings policy. 6. Copies of opinions/approvals by ethics committees and/or competent authorities for the research with humans.	
D10.2; Due in month 3	HCT - Requirement No. 2
1. Details on types of commercial cell/tissue and provider. 2. Details on human cell/tissue types that will be obtained within the project. 3. Details on human cell/tissue types in case they are obtained from another project. 4. Copies of relevant documents for using, producing or collecting human cells or tissues (e.g., ethics approval, import licence, accreditation/designation/authorisation/licensing).	
D10.3; Due in month 3	POPD - Requirement No. 3
1. Confirmation on the appointment of a Data Protection Officer (DPO) whose contact details will be made available to all data subjects involved in the research. Detailed data protection policy for the project for host institutions not required to appoint a DPO under the GDPR. 2. Description of the anonymisation/pseudonymisation techniques that will be implemented. 3. Detailed information on the informed consent procedures regarding data processing.	

[2] https://www.uab.cat/web/ceeah/presentation-1345735629010.html

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4. Templates of the informed consent forms and information sheets (in language and terms intelligible to the participants).

D10.4; Due in month 3	EPQ - Requirement No. 4

1. Information about the possible harm to the environment caused by the research and the measures that will be taken to mitigate the risks.
2. Proof that appropriate health and safety procedures conforming to relevant local/national guidelines/legislation are followed for staff involved in this project.

D10.5; Due in month 6	A - Requirement No. 5

1. Copies of relevant authorisations for animal experiments.
2. Copies of training certificates/personal licenses of the staff involved in animal experiments.
3. Details on number of animals to be used in the experiments.

D10.6; Due in month 18	GEN - Requirement No. 6

1. Appointment of an independent advisor to monitor the ethics issues involved in this project and how they are handled. This Advisor must be consulted in particular on the ethics issues related to the involvement of human participants (patients and healthy volunteers-workers) and personal data management.
2. A report by the Ethics Advisor at the end of each reporting period.

D10.7; Due in month 36	H - Requirement No. 7

For each clinical study:

1. A report on the status of posting results in the study registry(s), including timelines if/when final posting of results is scheduled after end of funding period.

D10.8; Due in month 24	H - Requirement No. 8

For each clinical study, 'Midterm recruitment report'

1. Deliverable to be scheduled for the time point when 50% of the study population is expected to have been recruited. The report shall include an overview of recruited subjects by study site, potential recruiting problems and, if applicable, a detailed description of implemented and planned measures to compensate delays in the study subject recruitment.

D10.9; Due in month 36	H - Requirement No. 9

For each clinical study, the following documents/information (in one package) prior to enrolment of first study subject:

1. Final version of study protocol as submitted to regulators/ethics committee(s),
2. Registration number of clinical study in a WHO-or ICMJE- approved registry (with the possibility to post results)
3. Approvals (ethics committees and national competent authority if applicable) required for invitation/enrolment of first subject in at least one

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clinical centre. Updates on the recruitment status will be reported periodically.	

In WP10 there is milestone 22: *Possession of authorization of Ethics Committees for human/animal experiments*. This milestone is due in month 3, however the Project Officer has been informed that this milestone will be delayed due to the time needed to obtain the authorization from the Ethics Committee. Furthermore, the target populations/groups from the biomonitoring studies are not yet completely defined, therefore it is not possible to ask for this permission yet.

Ethical aspects will be carefully observed during the whole development of the Plasticheal project.

All the requested documentation, authorisations or reports from ethics committees will be gathered prior to the beginning of the activity and kept on file at the disposal of the EC.

All ethical aspects involved in EU, national and local regulation will be observed.

4.2. Ethics regulations and recommendations

The PlasticHeal project will abide to the following regulations and recommendations.

Charter of Fundamental Rights of the European Union[3]

The Charter of Fundamental Rights of the European Union collects economic, social and political rights of EU residents. It was enforced with the Treaty of Lisbon on December 2009. The Charter is based on the European Convention on Human Rights (ECHR), European Social Charter, the case-law of the European Court of Justice and pre-existing provisions of European Union law.

The Charter contains 54 articles grouped in the following seven sections: dignity, freedoms, equality, solidarity, citizens' rights and justice, and interpretation and application of the Charter.

This charter must be applied by the EU institutions and its member states when implementing EU law.

European Code of Conduct for Research Integrity[4]

The European Code of Conduct for Research Integrity was published in 2011 and revised in 2017. It is a framework that sets the principles for research

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integrity as well as the good research practices and the violations of research integrity and how to handle them.

Beneficiaries will ensure that their researchers will follow the guidelines presented in this code.

According to the code and as stated in the GA, the fundamental principles of research integrity are:

- 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

The code details what good research practices consist of in the following aspects:

- Research Environment
- Training, Supervision and Mentoring
- Research Procedures
- Safeguards
- Data Practices and Management
- Collaborative Working
- Publication and Dissemination
- Reviewing, Evaluating and Editing

The code also sets guidelines regarding violations of Research Integrity. Research misconduct is traditionally defined as fabrication, falsification, or plagiarism. These are recognised as the most serious forms of violation. However, the unacceptable practices are not limited to them. Violations and allegations of misconduct should always be dealt in a consistent and transparent fashion with Integrity and fairness.

A summary of the most remarkable ethics aspects that will arise in the project is presented in the section below

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5. ETHICAL MONITORING IN PLASTICHEAL

The main ethical aspects of the PlasticHeal project are related to the experimentation with human cells and tissues, animals and human volunteers, as well as the avoidance of damages to the environment and to the workers. All these aspects will be closely monitored by the ethics commission.

5.1. Ethics commission

The ethics commission is formed by Susana Pastor (UAB), Cyrill Bussy (UNIMAN), José Antonio Domínguez Benítez (IGTP), Laura Martínez Alarcón (IMIB), Tiina Santonen (FIOH) and it will be in contact with External Independent Ethics Advisor from the Advisory Board (Josep Santaló, UAB)

Furthermore, the Ethics Commission will make sure the project complies with

- Ethics in research
- Data management regulations of the EU, member states, and participating institutions
- Code of conduct, Guidelines, and Best practices of the relevant professional associations.

5.2. Human cells and tissues

PlasticHeal will use different type of commercial cell lines for its research, most of them will be from the American Type Culture Collection (ATCC) mainly involving pulmonary, intestinal and bone marrow.

Regarding *ex vivo* experiments, the cells/tissue that will be obtained within the project include peripheral blood from healthy donors and from chronic pulmonary disease patients.

For the biomonitoring studies several populations will be analysed (chronic kidney disease patients, green-house workers and different plastic-related workers). From all the populations the main tissue collected will be peripheral blood. For workers, urine will also be collected.

All permits for work with these cells will be obtained before the start of the experiments.

Further information can be found in deliverable 10.2 *HCT - Requirement No. 2.*

5.3. Experimentation with animals

The use of animals in PlasticHeal will happen within WP4 *Fate, evolution & effects at tissue level in model organisms.* The experiments will aim at assessing MNPLs fate and effects in mice. Adult mice will be chronically exposed to MNPLs via food or air, and different samples will be obtained for its analysis.

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The research using animal models used as proxy to emulate humans is justified since it is likely to bring benefits by improving our knowledge on potential toxicity and adverse effects of micro and nanoplastics.

All studies and procedures will be designed keeping in mind Russel and Burch's Three R's: Reduce, Refine, and Replace. Reduce: number of animals will be kept to the minimum requirement to achieve statistical significance. Refine: During the timeline of experiment, animals will be hosted in enriched environment in line with current animal work guidelines. Replace: we have replaced vertebrate animals (rodents) with less sentient animals and with advanced human cell-based cell culture systems when possible.

The laboratory at The University of Manchester that will carry out the experiments with rodents has a long experience in handling experimental animals and is authorized for this work.

Further information can be found in deliverable 10.5 *A - Requirement No. 5*.

5.4. Human research volunteers

The assessment of the human exposure to MNPLs will require the participation of three different cohorts of participants. The three cohorts are patients, healthy volunteers and industry workers. Study protocols will have to be approved by ethics boards previous to the beginning of the study.

Sample collection

Data samples will be obtained from the different population groups, their participation will be voluntary and they will be informed they can revoke it at any time. All participants will have to fulfil some participation criteria (that will differ from group to group) and they will be informed about the different aspects of the study as well as about the data protection policy. Participants will have to sign an informed consent form in order to enter the study. All the documentation provided to the participants will be translated in the local language.

The group of patients will be formed by with chronic kidney disease patients and from chronic pulmonary disease patients. They will be recruited through Clinical University Hospital Virgen de la Arrixaca and through Hospital Universitari Germans Trias I Pujol.

Healthy volunteers will be recruited through advertising or database in the involved institutions to act as a control group.

Industries with a suspected high plastic-exposure level will be approached and their workers will be invited to join the study.

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The biological samples collected will be mainly urine, faeces, blood, breath condensate, sputum and broncho-alveolar lavage (only for CRD patients). Participants will have to fill up a questionnaire in order to evaluate its exposure to MNPLs.

Participant Information and consent

An informed consent sheet will be signed by each participant in the studies where the different aspects of the data and sample collection and processing will be detailed. The participants will agree to the specified terms in order to be included in the study. A data sheet will be generated by the data controller for each dataset with the following information according to art. 13 GDPR:

✓ Details of the data controller (institution)

✓ Name and contact details of the data protection officer

✓ Purposes of the processing

✓ Categories of data recipients (in case of foreseen data cession)

✓ Where applicable, the fact that the processor intends to transfer personal data to a third country or international organisation

✓ Period for which the personal data will be stored, or if that is not possible, the criteria used to determine that period

✓ The existence of the right to request from the controller access to and rectification or erasure of personal data or restriction of processing concerning the data subject or to object to processing as well as the right to data portability

✓ The existence of automated decision-making, including profiling

✓ The right to lodge a complaint with a supervisory authority

As well as the following points:

✓ Name and EU reference of the project

✓ Name and reference of the data set being collected

✓ Categories of data subjects

✓ Categories of personal data

✓ Where possible, a general description of the technical and organisational security measures

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Data anonymization and incidental findings

All personal data will be pseudo anonymized before being transferred to the data processor for analysis. Only the involved clinical/occupational physicians know the link between the code and the patient/donor data. For this reason, physicians are the only persons (out of the project) able to translate the exposure biomarkers data to the patients/donors. In the case of incidental findings, it will be the clinical/occupational physicians who must decide how to communicate the patient/worker the incidental data.

Data protection (GDPR)

Each partner of the project is responsible for ensuring that their collection, processing and sharing of personal data and / or special categories of personal data follow Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 (the General Data Protection Regulation (GDPR)) and other applicant regulation on personal data.

Each institution will appoint a Data Protection Officer (DPO) for the project; furthermore, for each data set, a controller from the involved institution will be appointed, who will report to the institution`s DPO.

Further information regarding the involvement of human volunteers can be found in deliverables 10.1 *H - Requirement No. 1 and* 10.3 *POPD - Requirement No. 3;*

5.5. Damage to the environment and to PlasticHeal workers

All laboratories involved in the European PlasticHeal project have extensive experience in handling and working with nanoparticles and some working with mutagens and/or carcinogens, which provides an area of work with maximum protection and safety measures, both for the worker and for the environment.

Exposure to MNPLs is ubiquitous, and therefore it will be difficult to discern their origin and what percentage of environmental exposure is due to the work originated from the project. The main risks to the environment of MNPLs arising from the PlasticHeal project are:

- Formation of solid and liquid waste containing MNPLs.
- Aerosol formation.

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Technical, organizational and spill control measurements are already implemented in the consortium lab to avoid risk to staff and to the environment.

Further information can be found in deliverable 10.4 *EPQ - Requirement No. 4*.

5.6. Continuous ethics monitoring

The Ethics commission will continuously monitor the observance of the different regulations regarding ethics with the support of the External Independent Ethics Advisor (Dr. Josep Santaló, UAB). Dr. Santaló will provide an Ethics report at the end of each reporting period (deliverable 10.6).

The progress of the different experiments will be supervised and in particular all the participation of human volunteers in the different studies will be carefully monitored in the different stages:

- Before the beginning of the volunteers' recruitment, the study protocols will be submitted to the ethics committees and registered with an approved registry. Deliverable 10.8 will be submitted with this information.
- During the recruitment, the process will be carefully monitored in order to detect an address any recruitment problems that may arise. At mid-recruitment deliverable 10.9 will be submitted with this information for each clinical study.
- At the end of the studies, deliverable 10.7 will be submitted detailing the status of the posting of results in the study registries.

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