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1 ACKNOWLEDGEMENTS

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Further consultation with colleagues of the European Center for Nanotoxicology⁹ (EURO-NanoTox), of the European NanoSafety Cluster¹⁰ (NSC) and of the sub-working group named "Industrial Innovation Liaison (i2L)"¹¹ (which is part of the WG E “Safer by Design, innovation and regulation” of the NSC) improved the interdisciplinary and international collaboration in this important topic.

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¹ http://www.r2r-biofluidics.eu/
² http://hi-responseh2020.eu/
³ http://www.nano-inspired.eu/
⁴ http://www3.ubu.es/nanogentools/
⁵ https://www.bionanonet.at/projects/sbd-at
⁶ http://www.bionanonet.at/projects/nanoprodex
⁷ http://nanoreg.eu/
⁹ http://www.bionanonet.at/index.php/about-nanotoxicology
¹⁰ http://www.nanosafetycluster.eu/
¹² http://www.euro-nanotox.at/
¹³ http://www.nanosafetycluster.eu/
2 CONSIDERATION OF NANOSAFETY AND ECONOMIC VIABILITY

Emerging technologies such as nanotechnology are surrounded by uncertainties with regard to technological (im)possibilities, financial rewards and societal implications. Within the development and innovation process, clarity about the safety surrounding these new technologies is one of the most important conditions for acceptance of the technology. Particularly for nanomaterials, a subclass of the entire nanotechnology playing field, safety is an essential point of attention due to the uncertain risks [1, 2].

Moreover, safety has been identified by the EU Commission as a vital empowering issue for the success of engineered nanomaterials (ENM) and nanotechnologies. Uncertainties related to the safety of these materials and technologies have created a major obstacle for industry and down-stream actors to invest into nanotechnology research and produce new exploitable innovations. Indeed, the EU Commission considers that concerns on safety related to ENM and associated technologies are a major bottleneck for the willingness of European companies in various industry sectors to invest into nanotechnologies, and hence Europe is lagging behind the US and Japan in this highly competitive area [3].

Eliminating hazards at the design or planning stage is often easier and cheaper to achieve than making changes later when the hazards become real risks in the workplace. Thus, throughout the project we will consider Safe-by-Design (SbD) approaches [4] and will cover materials, processes and the product respectively.

To properly address possible safety issues, we propose a sustainable safety concept with a balanced approach between design for manufacturing and design for safety aiming to:

- create a real-life relevant risk profile for a given material/process (identification of potential exposure scenarios)
- reduce uncertainty related to potential hazards,
- analyse occupational (both at lab and pilot scale) and environmental exposure using of qualitative and semi-quantitative tools to prioritize them,
- optimise production processes and related parameters, and
- maximise safety along the entire value chain of the used nanomaterial via implementation of the SbD concept in the innovation and development phases of the pilot plant.
3 KEY ELEMENTS OF SAFE-BY-DESIGN

The SbD approach is promoted to boost innovation capacity by reducing late development failures. The impact of this approach is shown by several on-going nano-related environment, health and safety (EHS) activities, e.g., on European level consolidated within the EU NanoSafety Cluster (ref. to Working Group E of the NanoSafety Cluster and subgroup industrial innovation liaison-i2L) [5, 6]. Safe-by-Design actions focus on hazard/risk avoidance rather than address them as an exposure. Through the SbD approach, a timely insight can be acquired by innovators and regulators with the ultimate goal of striving for negligible risks and avoidance of adverse impact on products (e.g., bans) [7].

The concept of SbD (see Figure 1) was discussed and seen as an approach that can be used supplementary to and prior to regulation. A tailored and timely approach is required (instead of conducting risk assessment at the end of the innovation chain) to enable regulation to help guide the production of safe nanomaterials and products prior to market entry. SbD aims at such a timely dialogue between relevant stakeholders much earlier in the innovation process. In this way insight can be obtained about potential risks and these can be monitored to guide decision making throughout material selection and product development.

Figure 1: Illustration of the Safe-by-Design (SbD) concept.
4 SAFETY STRATEGY FOR THE R2R BIOFLUIDICS PROJECT

Originally, R2R Biofluidics aims to create surface nanostructures in macroscopic polymer foils using stamps and imprinting techniques. However, it turned out in simulations and preliminary experiments, that microstructures are more suitable instead of nanostructures, thus “nano-related” safety issues can thus be excluded. In order to appropriately address any (chemical) safety issues and ensure the safety and health of employees engaged in R2R innovation chain, the safety/SbD concept for the R2R Biofluidics project is basically grounded on the classical safety assessment (CSA) framework [8] including:

- Hazard Assessment
- Exposure Assessment
- Risk Characterisation
The SbD concept encompasses the following steps:

### Pre-Design
- Identify the breadth of workplace hazards that need to be considered
- Identify the roles and responsibilities of various parties in relation to the project, and establish collaborative relationships with parties who can influence the design outcome
- Decide the criteria against which risk will be evaluated

### Concept Development
- Conduct a preliminary hazard analysis to gather sufficient information concerning potential risks. Consider what could happen, where it could happen and when = Hazard Assessment
- Identify the extent to which exposure/risk actually occurs = Exposure Assessment

### Design options
- Consult with key people who have the specialised knowledge and/or capacity to control or influence the design, (workers, engineers, project managers and safety and health representatives), to identify and assess risks = Risk Characterisation
- Implement solutions from recognised standards. Identify hazards that can be adequately addressed by applying risk controls from existing standards if appropriate
- Conduct a risk assessment process for hazards which have no suitable solutions in recognised standards

### Design Synthesis
- Select the optimum solution. Balance the costs of implementing the design against the benefits derived
- Apply the Hierarchy of Control to try to achieve the highest level of control (see section 6.1.1 for more detail)

### Design Completion
- Test, trial or evaluate the design solution
- Finalise the design and prepare risk control plans for the lifecycle of the product

Within this project, the SbD approach covered materials (i.e., resist formulations, adhesion-promoting molecules, coating materials, biomolecule candidates), processes (i.e., mastering and imprinting) and the products/demonstrators (DEM) (i.e., point-of-care diagnostic device = DEM1 and neuron-based drug screening device = DEM2) respectively (see Fig. 2). Existing data on potential toxicity of materials/structures (e.g., biocompatibility tests according to ISO 10993 [9] provided by Tecnalia.) were screened, evaluation of processes (with special focus on workers safety) were conducted, and screening of potential safety concerns along the life-cycle (consumer and environmental issues) led to evidence of safety for the products of this project. Moreover, by implementing ISO standards like ISO 10993, the R2R Biofluidics project contributes to
the United Nations Sustainable Development Goals (SDGs)\textsuperscript{14}, more precisely to the Sustainable Development Goal No. 3: Good Health and Well-being - Ensure healthy lives and promote well-being for all at all ages.

Additional value was added by continuous collaboration with the EU NanoSafety Cluster via contributing project outputs, as well as taking into account SbD aspects published within the cluster.

Figure 2: Innovation chain of the R2R Biofluidics project. Process steps where safety issues where evaluated are marked in green.

\textsuperscript{14}https://www.undp.org/content/dam/undp/library/corporate/brochure/SDGs_Booklet/Web_en.pdf
5 RESULTS OF THE SAFETY ASSESSMENT

5.1 EVALUATION OF SAFETY ISSUES OF RESIST MATERIALS

Hazard assessment/information gathering is an essential part of managing health and safety risks. A safe workplace is more easily achieved when people involved at the design stage communicate with each other about potential risks and work together to find solutions. By drawing on the knowledge and experience of other people, including workers, more informed decisions can be made about how the material/structure or/and the process can be designed to eliminate or minimise risks.

Thus, as a first step a demand-driven and detailed questionnaire (see Appendix I) was shared with resist material manufacturer and roll-to-roll (R2R) manufacturer to identify potential hazards and safety issues related to the production and design of materials for R2R-imprintig processes. This initial assessment also involved close collaboration with technical developers (of the resist formulation) and production experts to identify possible hazard flows as well as evaluation of cytotoxicity/genotoxicity data. Evaluation of safety issues included biocompatibility studies of the coating materials and the device surfaces in an on-going manner across the span of the whole project, following the protocols described in the ISO 10993 “Biological evaluation of medical devices”. This is especially important for demonstrator 2 (DEM2) (see Fig. 3) since, in the intended application, it is crucial to avoid biasing the results regarding the biological response of the cells because of materials leaching out contaminating substances in the culture medium.

ISO 10993-5:2009 describes test methods for assessing the *in vitro* cytotoxicity of medical devices. These methods specify the incubation of cultured cells in contact with a device and/or extracts of a device either...
directly (direct contact) or through diffusion (indirect contact). The in vitro tests were designed to determine the biological response of mammalian cells and potential cytotoxic effects of medical devices and materials that enter in their compositions. According to the ISO 10993-5 related to the biological evaluation of medical devices, if the cell viability for the highest concentration of the sample extract (100% extract) is higher than 70%, the material shall be considered non-cytotoxic.

Some of the resist formulations showed cytotoxic potential. Following the SbD approach the toxic formulations were optimized/changed while maintaining the desired requirements of the product specification. In order to evaluate the efficiency of the SbD strategy, cytotoxicity tests of “re-designed” formulations were conducted. Cytotoxicity data of modified formulations showed promising results, since toxicity was successfully “design-out” via changing the resist composition (e.g., use less volatile monomers, or less irritant initiators).

However, new risks may emerge as products are modified. Thus, safety can be further enhanced by constantly reviewing the design and checking that the design meets safety standards in each of the lifecycle phase. Additionally, potential risks along the whole life-cycle (production, handling & use and end-of-life processes) and environmental safety aspects were considered (e.g., appearance of volatile, inhalable substances /compounds from the resist, solvents, environmental impacts related to waste handling/disposal, see sections 5.2 and 5.4).

5.2 EVALUATION OF SAFETY ISSUES OF R2R BASED ADVANCED MANUFACTURING PROCESSES

As described in 5.1 we started with the information gathering process, which is split up in two individual steps. The starting point was the collection of general information, which are important for R2R Biofluidics project partners with regard to safety via a questionnaire survey (see Appendix 1). In the second step, BioNanoNet visited JOANNEUM RESEARCH – MATERIALS (i.e. roll-to-roll (R2R) manufacturer) to gain deep and detailed insight into real working conditions on-site (e.g., current working conditions). In addition, potential hazardous properties of used resists and potential exposure scenarios were identified, considering possible worker exposure as well as environmental release of hazardous materials. In-depth interviews with technical developers and production experts at the sites of industrial partner were performed to identify the potential source(s) of safety issues during manufacturing processes by reviewing the type of process, process flow, material inputs and discharges, and work practices (protocol template for on-site company visits see Appendix 2). The on-site visit also included a guided tour through the lab facilities, discussions/face-to-face meetings with technical developers, production experts as well as health and safety managers.

Figure 4 shows an image of the R2R-UV-NIL pilot plant. For R2R fabrication a liquid UV-curable imprint resist is coated on a floating foil. A clear benefit is that the resist composition can be varied and/or additives can be added to the resin, which allows for the modification of the refractive index of the structured layer. This allows much higher flexibility in exploiting all potential optical effects compared to thermal imprinting into a single polymer foil material. On its way through the R2R machine, the coated foil passes the imprinting unit which contains the shim that is mounted on a steel roller. The pressure that is needed to transfer the topographic shim pattern into the resist is applied by a soft rubber-coated counter roller pressing the substrate against the shim [10].
Each individual innovation process step was evaluated in order to identify possible exposure scenarios. The results of the exposure assessment indicated low evidence of risk that may arise for humans or the environment during the manufacturing process. The reason for this that the R2R-UV-NIL process is a fully automatic system designed for cost- and time effective large scale fabrication of optical elements. The tool deposits the complete material stack in an unbroken process chain, which guarantees safe working conditions. Environmental release/risk is not expected since tasks are performed under safeguarded conditions and appropriate waste management measures are in place.

Discussions revealed that possible safety issues can almost be excluded during handling the resist and related tasks like curing using high UV-intensities, etc. However, UV curing resists, coatings and adhesives, like all chemistries, do have some health and safety concerns. Those concerns are no greater than for conventional chemistries and in many cases are actually less of a concern. When evaluating the safety concerns associated with the handling of a product in a production environment, there are three basic routes of exposure for every chemical – ingestion, inhalation and contact. Oral toxicity can easily be avoided by following good hygiene practices. A major concern with conventional chemistry is the fact that these formulations contain chemicals that are volatile. Volatile chemicals (VOCs) may release vapours that can then be inhaled by workers. Typical UV formulations do not contain solvents and do not contain VOCs. This eliminates the considerable health risks associated with vapour inhalation [11].

Since the primary concern with UV materials is skin contact (no inhalation or ingestion), the response is to establish a program to minimize or eliminate contact. Use protective clothing, gloves, eye glasses and even full-face shields whenever possible. In addition, barrier creams and lotions are effective but should only be

Figure 4: a) Cliche mounted in the R2R machine; b) imprinted structures of Run 1 during operation c) R2R-UV-NIL pilot plant at Joanneum Research in Weiz
used in conjunction with gloves. If contact does occur with a UV material, wash the affected area with soap and water. Do not use solvents. These procedures are nothing more than good industrial hygiene and should be implemented regardless of the chemistry being used [12].

Since there is a strong link between WP3 (Materials) and WP4 (R2R processing) (i.e., safety is influenced by the resist composition as well as by the processing equipment) we have integrated SbD strategies from WP3 and WP4 to one unified SbD concept (illustrated in Fig. 5).
Fig. 5: SbD concept for evaluation of safety issues related to resist composition and processing equipment.
5.3 EVALUATION OF SAFETY ISSUES OF COATING MATERIALS/BIOMOLECULE CANDIDATES

Neuronal cells do not normally adhere to most materials, thus making it necessary to coat the base substrate material (foil + non-toxic rest) with adhesion-promoting molecules, which can be any of the following (or combinations of the following): biomimetic peptides or ECM components, adhesion molecules, polyamino acids and polycations, organosilanes and self-assembled monolayers. As previously described in 5.1., biocompatibility tests were performed based on ISO 10993-5:2009 test methods to assess the in vitro cytotoxicity of medical devices after coating the DEM2 substrate with various adhesive species (see Fig. 6).

Figure 6: Schematic illustration of the concept for the neuron based drug screening device. Cytotoxicity biocompatibility studies of DEM2 substrate modified with diverse adhesive biomolecules were conducted (highlighted in colour).
Figure 7: SbD concept for evaluation of safety issues related to coating materials/biomolecule candidates for DEM2.

Following the SbD concept (see Fig. 7) the toxic formulations were optimized/changed/modified (e.g., changing functional groups such as thiol groups and/or carboxylic groups, using different biomolecule candidates like Poly-D-lysine, Collagen I, Fibronectin, Laminin etc.). After implementation of the SbD concept, resist fulfilled the requirements to be considered as a candidate in final application of DEM 2, which are:

i) Non-toxic for cells;

ii) PC 12 cell number adhesion response;

iii) Neuronal like morphology after 24h of adhesion;

iv) Neuronal like differentiation with nerve growth factor (NGF);

v) Primary neuronal cells adhesion.
5.4 EVALUATION OF SAFETY AND REGULATORY ISSUES OF DEMONSTRATOR 1 & 2

One challenge of medical devices (e.g., point-of-care diagnostic devices, screening devices) and suppliers is to pass through the complex regulatory requirements and get approval from the respective authority of the particular country. On top of regulatory requirements and innovative products, they should deal with inevitable associated risks. Risks cannot be avoided completely, however they can be greatly minimised if companies are aware of those impending risk and follow effective risk management measures as dictated by the legal framework.

5.4.1 REGULATORY FRAMEWORK FOR MEDICAL DEVICES

On 5 April 2017, two new Regulations on medical devices were adopted, and they entered into force on 25 May 2017. These replace the existing Directives:


The new rules will only apply after a transitional period. Namely, 3 years after entry into force for the Regulation on medical devices (spring 2020) and 5 years after entry into force (spring 2022) for the Regulation on in vitro diagnostic medical devices.

The Commission welcomes the adoption of its proposal for two Regulations on medical devices which establish a modernised and more robust EU legislative framework to ensure better protection of public health and patient safety.

5.4.1.1 REGULATION (EU) 2017/745 – ANNEX I GENERAL SAFETY AND PERFORMANCE REQUIREMENTS

Annex I of the Regulation (EU) 2017/745 contains extremely important aspects related to safety and performance requirements of medical devices. Most important information is quoted on the following pages:

#3 Manufacturers shall establish, implement, document and maintain a risk management system

"Risk management shall be understood as a continuous iterative process throughout the entire lifecycle of a device, requiring regular systematic updating. In carrying out risk management manufacturers shall:

(a) establish and document a risk management plan for each device;
(b) identify and analyse the known and foreseeable hazards associated with each device;
(c) estimate and evaluate the risks associated with, and occurring during, the intended use and during reasonably foreseeable misuse;
(d) eliminate or control the risks referred to in point (c) in accordance with the requirements of Section 4;

(e) evaluate the impact of information from the production phase and, in particular, from the post-market surveillance system, on hazards and the frequency of occurrence thereof, on estimates of their associated risks, as well as on the overall risk, benefit-risk ratio and risk acceptability; and

(f) based on the evaluation of the impact of the information referred to in point (e), if necessary amend control measures in line with the requirements of Section 4.

#4 Risk control measures adopted by manufacturers for the design and manufacture of the devices shall conform to safety principles, taking account of the generally acknowledged state of the art. To reduce risks, Manufacturers shall manage risks so that the residual risk associated with each hazard as well as the overall residual risk is judged acceptable. In selecting the most appropriate solutions, manufacturers shall, in the following order of priority:

(a) eliminate or reduce risks as far as possible through safe design and manufacture;

(b) where appropriate, take adequate protection measures, including alarms if necessary, in relation to risks that cannot be eliminated; and

(c) provide information for safety (warnings/precautions/contra-indications) and, where appropriate, training to users.

#5 In eliminating or reducing risks related to use error, the manufacturer shall:

(a) reduce as far as possible the risks related to the ergonomic features of the device and the environment in which the device is intended to be used (design for patient safety), and

(b) give consideration to the technical knowledge, experience, education, training and use environment, where applicable, and the medical and physical conditions of intended users (design for lay, professional, disabled or other users).

#6 The characteristics and performance of a device shall not be adversely affected to such a degree that the health or safety of the patient or the user and, where applicable, of other persons are compromised during the lifetime of the device, as indicated by the manufacturer, when the device is subjected to the stresses which can occur during normal conditions of use and has been properly maintained in accordance with the manufacturer’s instructions.

#7 Devices shall be designed, manufactured and packaged in such a way that their characteristics and performance during their intended use are not adversely affected during transport and storage, for example, through fluctuations of temperature and humidity, taking account of the instructions and information provided by the manufacturer.

#8 All known and foreseeable risks, and any undesirable side-effects, shall be minimised and be acceptable when weighed against the evaluated benefits to the patient and/or user arising from the achieved performance of the device during normal conditions of use."
5.4.2 DEMONSTRATOR 1: POINT-OF-CARE DIAGNOSTIC (POC) DEVICE

Related to demonstrator 1 (DEM1) we focussed on the identification of potential safety issues related to the product. Most foreseeable risks are related to proper management of medical waste throughout the waste chain (from where it is generated to where it is eventually disposed of).

Discarded (used and unused) devices are classified as healthcare (clinical) waste. It is important that a procedure is in place for the safe disposal of biological waste in accordance with the appropriate health and safety and/or infection control legislation. It is the responsibility of the service provider to ensure that appropriate occupational health advice is provided to staff implementing POC devices [15].

Environmental Regulation requires waste producers to adequately describe their waste using both a written description and by indicating the appropriate European Waste Catalogue (EWC) code(s) [16]. Discarded medical devices are classified using the same EWC code 18 01 03 as other potentially infectious healthcare wastes. Discarded devices should be placed in UN type approved waste containers suitable for clinical waste (UN 3291); these should be rigid and puncture proof. As most medical devices contain only small amounts of blood or tissue this waste would be considered low risk and so suitable for pre-treatment and disposal. Also when considering the disposal of quarantined medical devices in their 2011 annual report Annex M the Advisory Committee on Dangerous Pathogens (ACDP) stated that [17]:

“Members were presented with two options for disposal of the instruments originally collected. Both proposed disposal routes were based on a limited body of evidence describing the destruction of infectivity by an incineration temperature of 1000°C for 15 minutes”.

The existence in health-care facilities of bacteria resistant to antibiotics and chemical disinfectants may also contribute to the hazards created by poorly managed health-care waste. It has been revealed that plasmids from laboratory strains contained in health-care waste were transferred to indigenous bacteria via the waste disposal system [18]. Moreover, antibiotic-resistant *Escherichia coli* have been shown to survive in an activated sludge plant, although there does not seem to be significant transfer of this organism under normal conditions of wastewater disposal and treatment [19]. Thus special attention should be drawn to waste disposal of DEM1, since DEM1 will be used for the detection of Methicillin resistant *Staphylococcus aureus* (MRSA). MRSA-containing material and waste which could be contaminated with MRSA, are to be disposed of as waste pertaining to Group B (infectious biological waste) [20]. Healthcare waste, including used devices can only be treated or disposed of in facilities with the appropriate authorisations (waste management licences / permits), and reference should be made to European Waste Catalogue (EWC) codes for the type of waste accepted by the facility. Currently, medical devices are managed in three ways [17, 21]:

- Specialist clinical waste for incineration;
- Treatment (autoclave) at waste facility to render them safe e.g. remove the infectious risk, prior to sending for recycling;
- Disposal, treatment (autoclaves) at waste facility with no subsequent recycling.

*S. aureus* and MRSA can survive for between seven days and seven months on hard surfaces, with the length of survival dependent on conditions such as temperature and humidity [22]. This means that in any setting — community or healthcare — there is a risk that surfaces that are not cleaned and disinfected regularly or correctly can harbour MRSA. Frequent touching of these surfaces can transfer MRSA to hands, which may
then possibly contaminate other surfaces or transmit the pathogens to people. Thus, frequent cleaning and disinfection of potentially contaminated surfaces and equipment is an important step. According to guidance from the Centers for Disease Control and Prevention, it is important to select a disinfectant that has been approved by the Environmental Protection Agency (EPA) to kill *S. aureus* or MRSA.

To conclude, elementary personal hygiene is important for reducing risks of infections and breaking the infection chain when medical waste is being handled. Hence, we highly recommend regular hand hygiene with soap and water or an alcohol-based hand sanitizer should be practiced by anyone who has a MRSA infection, those in close contact with them, and healthcare workers who are caring for patients with MRSA\(^{15}\). On the other hand, we do also recommend to dispose the contaminated material/device (i.e. DEM1) in the infectious waste bin and autoclave it (or, if there is no autoclave, incinerate it).

### 5.4.3 DEMONSTRATOR 2: NEURON BASED DRUG SCREENING DEVICE

For manufacturers of medical products containing viable cells of human origin, ISO 13022:2012 [23] specifies procedures to be used in processing and handling, as well as those to be used in identifying the hazards and hazardous situations associated with such cells, in order to estimate and evaluate the resulting risks, to control these risks, and to monitor the effectiveness of that control. Furthermore, this International Standard outlines the decision process for the residual risk acceptability, taking into account the balance of residual risk and expected medical benefit as compared to available alternatives.

Hazards typical of medical products manufactured utilizing viable human materials, could be:

a) contamination by bacteria, moulds, yeasts or parasites;  
b) contamination by viruses;  
c) contamination by agents causing Transmissible Spongiform Encephalopathies (TSE);  
d) contaminating material responsible for undesired pyrogenic, immunological or toxicological reactions;  
e) decomposition of the product and degradation products caused by inadequate handling;  
f) hazards related to the tumorigenic potential of the cell types used;  
g) complications resulting from unintended physiological and anatomical consequences (this includes unintended migration of cells, unwanted release of biologically active substances such as hormones and cytokines, and unintended interactions between cellular and non-cellular components of the product);  
h) failure of traceability;  
i) complications resulting from the material eliciting an unintended immunogenic reaction.

The following documents, are normatively referenced in 13022:2012 and are indispensable for its application.

- ISO 13485, Medical devices — Quality management systems — Requirements for regulatory purposes [24]
- ISO 14971, Medical devices — Application of risk management to medical devices [25]
- ISO 22442-1, Medical devices utilizing animal tissues and their derivatives — Application of risk management [26]

As already mentioned in 5.4.1 most foreseeable risks are related to proper management of medical waste throughout the waste chain. Clinical waste may contain toxic chemicals/drugs and could pose contamination risks to both people and the environment. Poor management of wastewater and sewage sludge can result in

the contamination of water and soil with pathogens or toxic chemicals. DEM2 belongs to the waste category “Biohazardous Waste” and therefore has to be collected as biologically contaminated waste in a designated container lined by an autoclave bag (marked with the biohazard symbol) followed by biohazardous waste treatment. The purpose of solid biohazardous waste treatment is biological inactivation in a manner that reduces hazardous exposure risk for lab personnel and the environment. This can be achieved by autoclave treatment of waste or treatment and disposal through a medical waste disposal contractor (i.e., licensed medical waste hauler) who will autoclave or incinerate the waste\textsuperscript{16,17}.

5.4.4 IMPACT ON ENVIRONMENTAL SAFETY

Treatment and disposal of healthcare waste may pose health risks indirectly through the release of pathogens and toxic pollutants into the environment. The disposal of untreated health care wastes in landfills can lead to the contamination of drinking, surface, and ground waters if those landfills are not properly constructed. Thus, the treatment of health care wastes with chemical disinfectants can result in the release of chemical substances into the environment if those substances are not handled, stored and disposed in an environmentally sound manner.

Incineration of waste has been widely practised, but inadequate incineration or the incineration of unsuitable materials results in the release of pollutants into the air and in the generation of ash residue. Incinerated materials containing or treated with chlorine can generate dioxins and furans, which are human carcinogens and have been associated with a range of adverse health effects. Incineration of heavy metals or materials with high metal content (in particular lead, mercury and cadmium) can lead to the spread of toxic metals in the environment. Only modern incinerators operating at 850-1100 °C and fitted with special gas-cleaning equipment are able to comply with the international emission standards for dioxins and furans. Alternatives to incineration such as autoclaving, microwaving, steam treatment integrated with internal mixing, which minimize the formation and release of chemicals or hazardous emissions should be given consideration in settings where there are sufficient resources to operate and maintain such systems and dispose of the treated waste \[19\].

5.4.5 END-OF-LIFE MANAGEMENT

The EU Directive 2012/19/EC (on Waste Electrical and Electronic Equipment (also known as WEEE II) \[27\] represents the EU’s latest effort to increase recycling of and reduce waste from electrical and electronic equipment. Under WEEE II, EU Member States must achieve collection rates of 45% beginning in 2016 and collection rates of 65% by 2019. Most important, all categories of electrical and electronic equipment, including medical devices and \textit{in vitro} medical devices, are subject to WEEE II recovery targets.

In order to achieve the recovery targets established in WEEE II, manufactures/producers are required to establish processes and systems to ensure the safe and effective collection and recovery of most electrical and electronic waste. Medical devices such as \textit{in vitro} diagnostic medical devices, where such devices are expected to be infective prior to end of life, and active implantable medical devices are excluded from the scope of WEEE II. Manufacturers are also encouraged to maximise the use of recoverable and recyclable materials in their products, and to design products in order to facilitate the dismantling and recovery of

\textsuperscript{17} https://umibiomedical.com/5-types-biohazardous-waste/ Accessed March 14, 2019.
Recyclable materials. Manufacturers are required to appoint an authorised representative in each EU Member State, who is legally responsible for fulfilling the manufacturer’s responsibilities under WEEE II.

In addition to the requirements of WEEE II, medical device manufactures may be subject to other EU directives and regulations addressing the control and recycling of electrical and electronic waste. These include for example EU Directive 2011/65/EU on the restriction of the use of hazardous substances (RoHS II) [28].
6 RECOMMENDED SAFETY MEASURES

6.1 OVERALL STRATEGY IN ESTABLISHING SAFETY MEASURES

- The primary consideration is to adopt appropriate preventive measures in order to directly remove the hazards at source, such as by elimination or substitution. If such measures are not possible, segregation of the chemicals or the processes or other control measures should be taken. The use of personal protective equipment should only be considered a supplementary means or as the last resort to minimize workers’ exposure to the hazards.

- On many occasions, the substance, equipment or process can be replaced by a safer one that eliminates or minimizes the risks to an acceptable level.

- Safety measures can be realised by engineering and administrative controls. Engineering control measures such as installation of suitable types of ventilation can eliminate or lower the level of hazardous air-borne contaminants or flammable vapours and/or VOCs at source. Administrative control measures such as by implementation of safe work practices and scheduling of breaks or rotating shifts can limit worker’s time spent near the hazard thus reducing their exposure.

- It is desirable to consider safety and health aspects of the materials, processes and equipment at the design or purchase stage. This will save additional expenses and often reduce practical difficulty in subsequent adjustments to accommodate the safety features [29].

6.1.1 HIERARCHY OF CONTROL

According to the traditional hierarchy of control, the most effective hazard control strategy is the elimination of all hazards within a process (e.g. by replacing the process). If the complete elimination of hazard at source is not practical, risk should be minimised by substituting the process or compound with a less hazardous (i.e. safer) alternative.

A common known variant of the general principle of the hierarchy of control is the “STOP-principle18, [30-32] a risk management principle based on the implementation of strategic, technical, organizational and personal measures. The STOP principle gives priority to strategic measures (S), including elimination and substitution, technical measures (T), organizational and administrative measures (O), and personal protection (P). Some risk mitigation measures and recommendations are given in the next sections.

6.1.1.1 STRATEGIC MEASURES (ELIMINATION/SUBSTITUTION)

Elimination and substitution also tend to be the most difficult to implement in an existing process. If the process is still at the design or development stage, elimination and substitution of hazards may be inexpensive and simple to implement. For an existing process, major changes in equipment and procedures may be required to eliminate or substitute for a hazard.

Within the R2R Biofluidics resist properties were designed in or out at bench scale in order to “tune” the toxicity of the resist formulations, which allowed to identify optimal “windows” where both toxicity and functional activity are optimised. Even where functionality is lost as a result of lowering toxicity, key lessons regarding Safe-by-Design could be learned, and these will be fed to industry such that safety considerations are included in the design phase rather than at the product registration phase. Once the principles of SbD are established for one group of materials (e.g., resist formulations), similar principles will be transposed to other resist formulations to establish their general applicability.

6.1.1.2 TECHNICAL MEASURES (ENGINEERING CONTROLS)

The primary object of adopting engineering control is to eliminate or lower the risks at source. The main engineering control method against chemical hazards is exhaust ventilation, which provides an effective means of preventing accumulation of hazardous chemicals in the atmosphere. There are four major types of ventilation, namely, general dilution ventilation, booth ventilation, local exhaust ventilation and push-pull ventilation. Practically the ventilation methods to control inhalation and fire/explosion hazards are combined. Factors related to the materials used, such as the quantity, frequency of use, volatility, flash point, explosive limit and exposure limit should be considered.

6.1.1.3 ORGANIZATIONAL AND ADMINISTRATIVE MEASURES

Organizational and administrative measures are designed to implement operational procedures to minimise release of exposure to a working area. They involve multiple organizational measures and good housekeeping practices including cleaning and maintenance of process equipment, vacuum cleaner with an air filter, spill containment measures, workplace housekeeping, management systems, monitoring, supervision, training operating practice, personal hygiene facilities, restricted or prohibited process areas, limited workers’ exposures (shorter work times) and worker training. A list of administrative controls is provided in the table below:
Table 1: Summary of best available techniques for waste management.

<table>
<thead>
<tr>
<th>Work practices</th>
<th>Development and implementation of standard operating procedures (SOPs)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Focused workplace training and education on the SOPs</td>
</tr>
<tr>
<td></td>
<td>Establishment of good housekeeping plans</td>
</tr>
<tr>
<td></td>
<td>Maintenance and storage of equipment in good conditions</td>
</tr>
<tr>
<td></td>
<td>Preparation and training for emergency response</td>
</tr>
<tr>
<td>Good housekeeping</td>
<td>Correct stockpiling and storage for a more effective use of space</td>
</tr>
<tr>
<td></td>
<td>Dust and Dirt Removal</td>
</tr>
<tr>
<td></td>
<td>Adequate, clean and well maintained employee facilities</td>
</tr>
<tr>
<td></td>
<td>Maintain Light Fixtures</td>
</tr>
<tr>
<td></td>
<td>Spill Control</td>
</tr>
<tr>
<td></td>
<td>Tools and Equipment more efficient by preventive clean-up and maintenance</td>
</tr>
</tbody>
</table>

| Personal Hygiene practices | Washing hands after handling material and before eating, drinking or smoking |
|                           | Avoiding touching face (lips, nose, eyes) with contaminated hands |

| Education and training on PPE | When PPE is necessary |
|                              | Which PPE is necessary |
|                              | How to properly put it on, adjust, wear it and take it off |
|                              | The limitations of use of the PPE |
|                              | Proper care, maintenance, useful life and disposal of PPE |

| Emergency Preparation | Practice their emergency response skills regularly |
|                       | Prevent fatalities and injuries |
|                       | Reduce damage to buildings, stock, and equipment |
|                       | Protect the environment and the co-workers |

6.1.1.4 PERSONAL PROTECTIVE EQUIPMENT (PPE)

The primary objective of using PPE is to supplement control measures by minimizing worker’s risks of exposure to hazardous chemicals through inhalation or skin contact. Being only passive protective measures, PPE should not replace preventive measures. Appropriate PPE should be chosen with regard to the hazards and physical nature of the chemicals and their routes of entry into the human body. The MSDS information and risk assessment will help determine the PPE requirements. Before and after use, PPE should be inspected for any signs of damage. It should be regularly cleaned and stored in good condition. Contaminated PPE should be properly treated or disposed of as appropriate, and replacement sets kept readily available. Moreover, as no PPE will give long-term protection, a programme should be in place for its regular replacement.
7 REFERENCES & BIBLIOGRAPHIE

1. NanoNextNL, Safe Design of Nanomaterials – Paving the way for innovation, Action plan and green paper. 2012.
6. AJAM Sips, et al., NANoREG safe-by-design (SbD) concept. 2015.
16. SEPA, Guidance on using the European Waste Catalogue (EWC) to code waste. 2015.


APPENDIX I - QUESTIONNAIRE FOR CONSORTIUM PARTNERS

Questions/Criteria to be asked from Industrial Partners regarding Particles/Nanomaterials:

1. What kind of Nanoparticle/Nanomaterial are you using? (please provide information on charge; registration numbers, article numbers, suppliers, reference codes of the materials (e.g. NANoREG material reference codes), etc.)

2. What kind of characterization data is available for your Nanoparticles/Nanomaterials? (Please provide characterisation data e.g. agglomeration/aggregation, crystalline phase, crystallite size, dustiness, TEM, Particle Size Distribution, Specific Surface Area, etc.)
   - Size
   - Size distribution
   - Shape
   - Morphology
   - Agglomeration/aggregation
   - Number/concentration
   - Surface area/porosity
   - Surface charge/Zeta potential
   - Reactivity/photocatalytic activity
   - Reactive Oxygen Species (ROS) generation
   - Cell viability and proliferation analysis (e.g. MTT and TUNEL assay, WST assay)
   - Surface chemistry/functionality (coatings, contaminants)
   - Solubility
   - Structure/crystallinity
   - Other please specify

3. What kind of safety data are available for your Nanoparticles/Nanomaterials? (Please provide Safety Data Sheets for your Nanoparticles/Nanomaterials, Exposure Scenarios, Tox. Screening, etc.)

4. What kind of production volumes of nanomaterials do you use?

Questions/Criteria to be asked from Industrial Partners regarding processes/production methods:

1. Which nano-relevant (refers to the presence of nanomaterial/nanoparticles in a free, matrix-bound, aggregated or agglomerated form) processes are included in developmental work of R2R BIOFLUIDICS project and/or which processes within R2R BIOFLUIDICS project include the use of Nanoparticles/Nanomaterials respectively? multiple choices possible
   - Fabrication of microfluidic channel structures by imprint lithography
   - Fabrication of optical nano/micro-structures for light coupling and guiding by imprint lithography
   - Fabrication of nano/microstructured polymer foils
   - Sol-Gel materials spray coating
   - Surface modification (topographical and chemical, e.g. coating for neuronal cell culture)
   - Surface biofunctionalization (e.g. cell adhesion molecules for capture probe immobilization, immobilization of appropriate probe-molecules)
   - Backend processing of nanostructured foils
   - Device characterization and optimization (e.g. IVD prototype DEM1 testing)
   - Performance validation of neuron based drug screening devices (DEM2 generation 1-4)
   - Bonding and actuator integration for final DEM2 devices (e.g. valves/pumps for active control of fluid perfusion and/or sensors)
   - Other please specify

2. Are these processes open or closed systems?
   - Open system(s)
☐ Closed system(s)
☐ I don’t know

3. Is there any kind of known exposure to Nanoparticles/Nanomaterials? (Occupational Safety)
☐ Yes please specify
☐ No
☐ I don’t know

4. Is there any kind of known environmental NP exposure? (e.g. rinsing processes, cleaning, etc.)
☐ Yes please specify
☐ No
☐ I don’t know

5. Your processes can be addressed to produce NOAAs (nano objects agglomerates and aggregates) (e.g. nanostructures on foils), to produce intermediate products (e.g. nano/microstructured foils) of final product/application (e.g. in-vitro diagnostic chip, neuron based high-throughput assay). What do you produce in your company, in the framework of R2R BIOFLUIDICS?
☐ Materials for R2R-imprinting processes (e.g. resist formulations)
☐ “Soft” polymer stamp with inverse structure (i.e. roller shims)
☐ Nano/microstructured foils
☐ Selective biofunctionalized nano/microstructured surfaces
☐ On-chip actuators (valves/pumps)
☐ Point-of-care diagnostic device (i.e. in-vitro diagnostic chip)
☐ Neuron based drug screening device
☐ Other please specify

6. For each nano-relevant process (in the framework of R2R BIOFLUIDICS): What are the tasks involved on it? (e.g. the process “Prototype DEM1 testing” includes the following tasks (T): (T1) Testing fluidic flow characteristics (T2) Characterizing quality of bonding (T3) Testing hybridization kinetics, (T4)…etc.

7. For each task of the processes: What are the quantities of NOAAs normally used? (e.g. grams, kilos)

8. For each task of the processes: What is the physical form of the NOAA? (e.g. powder form, dispersed in a liquid, embedded in a solid matrix).
☐ Powder form
☐ Dispersed in a liquid
☐ Embedded in a solid matrix
☐ In a coating
☐ Other please specify
☐ I don’t know

If the NOAA is in a suspension or embedded in a matrix, what is the concentration of the NOAA?

9. (for each task of the processes) Is the task performed in an open/closed system? (e.g. the reactor in the chemical vapour deposition, is a closed system)
☐ Open system(s)
☐ Closed system(s)
☐ I don’t know

10. For each task of the processes: The task, is it performed with any engineering control system and/or with any specific PPE (Personal Protective Equipment)? Local ventilation system/ performed inside a fume hood/glove box, etc. (e.g. the bagging of the final product (powder) has a local ventilation system). Is there any risk management measure implemented? (e.g. specific procedures for safe handling of nano-powders during its transferring)
☐ Yes please specify
☐ No
☐ I don’t know

11. Is there any kind of known exposure to Nanoparticles/Nanomaterials? (Occupational Safety)
☐ Yes please specify
12. Do you have any quantitative/qualitative measure of worker exposure to NOAAs?
   ☐ Yes
   ☐ No
   ☐ I don’t know

If yes, which guidelines/procedure do you use to do the measurements?
   ☐ Condensation Particle Counter (CPC)
   ☐ Scanning Mobility Particle Sizer (SMPS)
   ☐ Diffusion Charger (DC)
   ☐ Electrical Low Pressure Impacter (ELPI)
   ☐ Mass Spectroscopy (MS)
   ☐ Electron Microscopy (TEM/REM)
   ☐ Other please specify

13. Can an unintended generation of NOAAs be expected from any process included in the project?
   ☐ Yes please specify
   ☐ No
   ☐ I don’t know

Questions/Criteria to be asked from Industrial Partners regarding manufactured products:

1. Is your product an end-product or will it be further processed (intermediate product is/are further used during stages of the production process)?
   ☐ Yes
   ☐ No
   ☐ I don’t know

2. Is your product an application (e.g. in-vitro diagnostic chip, neuron based high-throughput screening device)?
   ☐ Yes
   ☐ No
   ☐ I don’t know

If yes, what kind of application is your product?
   ☐ In-vitro diagnostic chip
   ☐ Neuron based high-throughput screening device
   ☐ Other please specify

3. What kind of end-product do you produce?
   ☐ In-vitro diagnostic chip
   ☐ Neuron based high-throughput screening device
   ☐ Other please specify

4. What kind of intermediate product to you produce?
   ☐ “Soft” polymer stamp with inverse structure (i.e. roller shims)
   ☐ Nano/microstructured foils
   ☐ Selective biofunctionalized nano/microstructured surfaces
   ☐ On-chip actuators (valves/pumps)
   ☐ Other please specify

5. What kind of nano-property improves the quality of the product?
   ☐ Size
   ☐ Surface charge/Zeta potential
   ☐ Shape
   ☐ High particle dispersion
   ☐ Solubility (solvents)
6. Does your product feature/show Nanostructures?
   - Yes
   - No
   - I don’t know

   If yes, which kind of Nanostructures?
   - Nanostructured (polymer) foil
   - Nanoparticles
   - Nanopowders
   - Nanorods
   - Fullerenes
   - Quantum dots
   - Atomic Quantum Clusters
   - Nanoplatelets
   - Dendrimers
   - Nanowires
   - Nanotubes
   - Nanofibers/Nanofilaments
   - Ultrathin films
   - Other please specify

7. What kind of nano-relevant characterization data is available for the end-product? (please provide characterization data, etc.)
   - Size
   - Size distribution
   - Shape
   - Morphology
   - Agglomeration/aggregation
   - Number/concentration
   - Surface area/porosity
   - Surface charge/Zeta potential
   - Reactivity/photocatalytic activity
   - Reactive Oxygen Species (ROS) generation
   - Cell viability and proliferation analysis (e.g. MTT and TUNEL assay, WST assay)
   - Surface chemistry/functionality (coatings, contaminants)
   - Solubility
   - Structure/crystallinity
   - Other please specify

8. What kind of nano-relevant safety data is available for the end-product? (please provide Safety Data Sheets, User Manuals, Guidance Documents, etc.)
   - Safety Data Sheets
   - User Manuals
   - Guidance Documents
   - Nanosafety Guidelines
   - Publications/Handbooks regarding nanosafety aspects
   - Exposure scenarios
   - REACH context
   - Other please specify

9. If you produce end-products/applications, who are the customers for your end-products?

10. If you produce an intermediary product (e.g. nano/microstructured foils) who are the users and downstream users?
11. Can you present any certificates, review, validation, inspection, etc. for your product (produced according to guideline like GMP; GLP; ISO; etc.)?
   ☐ Yes
   ☐ No

12. Do you have occupational health and/or environmental data on your product?
   ☐ Yes
   ☐ No

   If yes, what kind of data can you provide?
   ☐ data regarding release, transport, transformation, accumulation and uptake of engineered nanomaterials in the environment
   ☐ knowledge concerning the exposure to, or effects of, nanomaterials on human health and safety in occupational environments (e.g. sol-gel materials spray coating – inhalation).
   ☐ Other please specify

13. Do you have data on the release of nanoparticles from your final product/application to the final consumer (Life Cycle Assessment – from raw material extraction and conversion; to manufacture and distribution; through use, re-use, and recycling; to ultimate disposal)?
   ☐ Yes
   ☐ No

Questions/Criteria to be asked from Industrial Partners regarding the application:

1. Is your application the "end product"?
   ☐ Yes
   ☐ No

2. Is your application nano-enabled?
   ☐ Yes
   ☐ No
   ☐ I don’t know

3. Do you use Nanoparticles/Nanomaterials within your application?
   ☐ Yes
   ☐ No
   ☐ I don’t know

4. Do you use Nanostructures within your application?
   ☐ Yes
   ☐ No
   ☐ I don’t know

5. Do you provide data on the stability of your application throughout usage?
   ☐ Yes
   ☐ No
APPENDIX II - PROTOCOL TEMPLATE FOR ON-SITE COMPANY VISITS

I. NM Storage
Observations:

II. NM On-Site Transport
Observations:

- Personal protective equipment (PPE) used:
  - lab coat, protective clothing
  - gloves
  - eye protection
  - respirators

III. Processes
Description of processes:
Observations:

- Personal protective equipment (PPE) used:
  - lab coat, protective clothing
  - gloves
  - eye protection
  - respirators

IV. Cleaning, Maintenance
Observations:

- Personal protective equipment (PPE) used:
  - lab coat, protective clothing
  - gloves
  - eye protection
  - respirators

V. Waste Management
Observations: