MISTRA
The Swedish Foundation for
Strategic Environmental Research

Background paper

# Designing for reduced chemical hazards in the product value chain

June 13, 2018

**Authors:**
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The contents of this background paper
are the responsibility of the authors.

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# Contents

# 1 Background

The Swedish foundation for strategic environmental research, Mistra, is governed by a set of statutes which require that Mistra finances research aimed at contributing to the solution of important environmental problems. As such, Mistra works continuously to identify and define problems to be addressed. The research areas defined should be relevant for many aspects of Swedish society with further implications on a global level. The research results should be applicable and lead to changes in the outcome of societal behaviour, be this in terms of use and consumption of resources or in attitudes.

In more than twenty years of research investment, Mistra has supported a number of research programmes dealing with issues associated with the consumption of limited raw materials, use and release of chemicals and development of alternative materials. While there has been considerable improvement in how chemicals have been used, and how release of chemicals with detrimental effects on the environment has been reduced, there is still a great deal to be done. The introduction of the concepts of green chemistry and its´ uptake by academia and industry is an important step in the right direction. Researchers are developing the tools required for reducing exposure to potentially hazardous chemicals thereby reducing the risks associated. Although it would be a noble vision to eliminate risk completely, a more pragmatic approach is to develop methods for measuring and evaluating various risks in the context of societal acceptance, while working through the design process to reduce risks associated with exposure as far as possible.

Mistra's board of trustees, therefore, commissioned a background paper covering the relevant topics with a view to publishing a call for research proposals. This background paper has been written by a panel of experts representing disciplines expected to be covered by the proposals. Mistra envisages a programme which covers a wide range of topics at different levels.

## The assignment

A working group comprising international experts has drawn up this background report as documentation for Mistra's Board of trustees, ahead of a forthcoming decision on whether to call for proposals for research funds for a programme in the area described above. The group's tasks were:

- to describe the challenges of achieving acceptable levels of risk associated with exposure to chemicals from various sources through the design of material, products, processes,
- to provide an overview of the current state of the art within potentially relevant areas, both for Swedish research and in an international perspective, and
- to provide some guidelines as to the possible orientation of a new research programme.

Areas where exposure to hazardous chemicals occurs which may be particularly interesting include:

- Extraction and production of feedstocks, including fossil feedstock, which will be phased out as society achieves the goal of becoming fossil free in the future, and bio-based feedstock, which is envisaged as the replacement for fossil feedstocks.
- Processing of raw materials to produce the products required by society.
- Use and consumption of materials in the form of various products.
- Processing materials for re-use or recycling as part of an end of life scenario.

# 2 Introduction

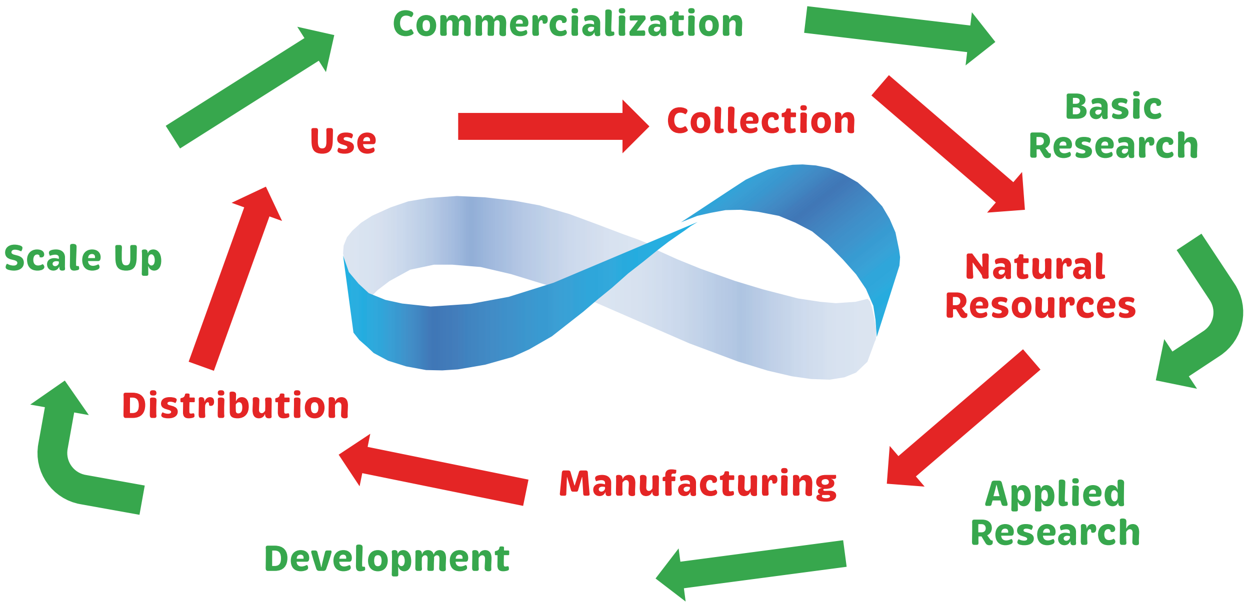
The presence of hazardous chemicals in products is one of the greatest obstacles for developing cost effective, resource-efficient, material cycles. If the full health and environmental cost of any toxic materials in a product were included in the price, that product would probably never reach the market. Today, however, these societal costs are never fully accounted for in the price consumers pay. This results in problems being pushed down the material value chain, e.g. that recycling or repair activities are hampered by the presence of hazardous chemicals in certain products. It is therefore crucial that both products and recycled material are toxic-free. This would also help encourage the take-up of re-used and recycled material.

The concept of the circular economy has been well described and promoted (Ref Ellen MacArthur Foundation website). Keeping materials in a closed loop from natural resources through manufacturing, distribution, use and collection is a goal that we must strive for. Unfortunately, many products and their constituent components have not been invented to be consistent with this concept. Current economic linear system with linear resource flow still rules and each part in the product value chain is optimized separate.

It is critical that existing products be redesigned, and new products be initially designed to be consistent with circularity principles. As new products are conceived, it is important that the intellectual ecology (ref JCW Bioneers presentation) of invention be in constant contact with the realities of the supply chain. As R&D proceeds through basic research, applied research, development, scale up and commercialization, feedback from the materials economy need be appreciated. The image of the Mobius strip is useful for this concept (see Figure 1). Where a circular surface has a twist placed in it so that it if one follows the surface it requires two

**FIGURE 1.** The concept of the Circular economy expressed as the Mobius strip with the Research and Development cycle superimposed

ELLEN MACARTHUR FOUNDATION: *HTTPS://WWW.ELLENMACARTHURFOUNDATION.ORG/*; JOHN WARNER KEYNOTE AT BIONEERS CONFERENCE, SAN RAFAEL, CA 17 OCTOBER 2010, *HTTPS://VIMEO.COM/101562284*



transits through the circle to return to the point of origin. This image represents constant communication between inventors, industry and society.

As any group considers an issue relating to human health and the environment, the desire to arrive at a system close to perfection is quite understandable. Unfortunately, we must acknowledge that there are significant gaps in toxicology and environmental health knowledge. And as time moves forward, we will see several revisions of this knowledge as new research occurs. Because of the importance of these issues, it must be realised that we do not have the luxury of time. Thus, we urge that we accept that any program in this area must continuously evolve over time.

# 3 Scope

The natural environment, humans and all other creatures and plants that inhabit it are continuously exposed to chemicals of natural and manufactured origin. Some of these chemicals can be harmful while most are probably benign. It is reasonable to assume that a better quality of life can be achieved by limiting the consequences of exposure to these harmful, or hazardous, chemicals. Knowing the nature of hazardous chemicals it is probably also reasonable to assume that the complete eradication of exposure to hazardous chemicals cannot be achieved. Attempts should therefore be concentrated on limiting the risks involved as far as possible.

In preparing for a background document a number of limitations and requirements were considered as relevant for a pending call for research proposals:

- Mistra's area of research is to contribute towards the solving of important environmental problems. In this aspect environmental is taken in a broad sense including living and working environments throughout society, together with what is considered to be the natural environment.
- Hazardous chemicals can be of natural origin or the products of human, anthropogenic, activities, which may include the relocation of chemicals of natural origin. For the purpose of this document hazardous is mainly concerned with the anthropogenic chemicals.
- Exposure to hazardous chemicals can occur during many phases from the extraction of raw materials, through manufacture, use to end of life, recycling and ultimate destruction. Exposure may be through unintentional release as a result of chemical incidents, general release from products or lack of knowledge about properties, or the result of intentional release as in the use of pesticides or treatment of waste. The consequences of exposure could be acute effects such as poisoning due to exposure to relatively high doses of hazardous chemicals over a very short time-period or chronic where the effect could be due to assimilation of chemicals at lower levels over a life-time.
- Steps taken to mitigate exposure to hazardous chemicals should be communicated clearly together with an analysis of the risks being addressed and the difficulty in reducing risk to zero.

As can be seen the problem of exposure to hazardous chemicals is very complex and will not be solved by a single measure of package of measures. Modern societies have developed alongside, and arguably because of, products and materials made by the use of chemical processes. Society must learn to balance the benefits gained from the use of these products with the necessity of limiting the negative effects of exposure to hazardous chemicals contained therein.

Mistra envisages a research programme which takes into consideration the source and level of exposure to various chemicals and how adverse effects can be avoided by designing chemicals, processes, products, and use in such a way that risks are minimised, ideally by elimination of their intrinsic hazards. In addition to resulting in new products on the market the programme is also expected to impact on the teaching and understanding of chemistry and related subjects at all levels.

# 4 Concepts and Definitions

## Exposure vs Intrinsic Hazard

When assessing the risk posed to human health and the environment of any given material there are traditionally two quantitative components that are considered; the extent of likely exposure to the materials and the level of intrinsic hazard. Mitigating risk by exposure control has historically been the typical approach. Measures to reduce exposure may, for example, involve the wearing gloves to protect the skin, goggles to protect the eyes, masks to protect the lungs and scrubbers and filters to protect the air, land and seas. While society has been and will continue to be dependent on exposure control to some extent, it must be acknowledged that this is an imperfect approach. From a financial perspective any exposure mitigating technology will always add to the cost of any technology or process. The materials, employee trainings and other corollary safeguard mechanisms come at a price. But, in addition to the added cost, there is the reality that exposure mitigating approaches can unfortunately fail for a variety of foreseeable and unforeseeable reasons because accidents happen. Either through human error or natural disaster, history is full of examples where safeguards designed to limit exposure have failed leading to tragic consequences. Another consequence of dealing with risk by attempting to control exposure of a hazardous material is that this approach often pushes the risk to some other population within the supply chain prior to adoption of the exposure mechanism.

The field of green chemistry is based on the philosophy that it is much better to deal with risk by addressing the intrinsic hazard of a material. The fields of toxicology and environmental health sciences have evolved over the years to begin to understand the molecular mechanisms of hazard. If risk is mitigated by reducing intrinsic hazard, then the costs and liabilities associated with attempts to control exposure are proportionately reduced throughout the entire value chain. Chemists and chemical engineers, by better understanding the implications of molecular structure on the negative consequences to human health and the environment, can design materials that avoid chemical structures likely to be associated with toxicity. This approach reduces the costs in the long run for organizations as they will require less materials and training for the mitigating equipment and consequence of accidents through human error or natural disaster.

Of course, it will take a great deal on continuous research and development to invent these new materials that are intrinsically safer and, thus, society will continue to be dependent on exposure controls. So, for technologies that have no green chemistry alternatives available yet, we must focus on technologies that continuously control and monitor exposure.

## Chemical/Materials, Products and Systems

The product value chain is a hierarchical system starting with the materials or chemicals as the simple building blocks. Products are the ensamples or aggregates of materials and systems are ecologies of products [Dubberly 2017]. The hazardous emissions and exposure from chemicals and materials will normally be carried from the simple building blocks into the aggregates of materials and to the final products. However, synergistic effects in the ecologies of products at the highest level might complicate and add to exposure profiles and eventually prohibit a safe re-use. Thus, initially avoiding the use of basic chemicals providing hazardous exposures in the hierarchical value chain by use of less hazardous alternatives whenever possible will benefit the recycling concept and the circular economy.

## Policy versus Technology

There are various forms of policy and policy changes which can influence the uptake of environmentally beneficial or environmentally benign technologies. In EU member states such as Sweden, policy initiatives can arise and be implemented at the level of the EU as well as at the national or local level. Policy can be implemented in a number of ways. Perhaps legalisation is one of the best known instruments to implement policy objectives but other measures can include the drafting of policy documents, taxation policies or the use of targets to meet policy objectives, for example, the reduction in greenhouse gas emissions.

One of the most familiar pieces of legislation related to the safety of chemicals in the EU is the Regulation for Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH). It is of major importance when considering the use of chemical substances and even the substitution of less hazardous substances. REACH is a highly complex piece of legislation which entered into force on 1 June 2007. Consequently, it has been EU law for more than ten years. The scope of REACH is, in principle, all chemical substances though other sectoral legation may be relevant such as Directive 2009/128/EC which has the effect of establishing a framework for Community action to achieve the sustainable use of pesticides. A lot of work has been undertaken in recent years to ensure that REACH can address manufactured nanomaterials

A major objective of REACH is to protect human health and the environment from any hazards posed by the use of chemicals. It also aims to enhance the competitiveness of the EU chemicals industry; and at the same time, it encourages the use of alternative methods to reduce the use of animal testing.

In addressing the hazard assessment of chemical substances, a key characteristic of REACH is that it places the burden of proof on companies, which must identify the risks linked to the substances they manufacture and market in the EU. They must also demonstrate to how the substance can be safely used by identifying relevant risk management measures. If the risks cannot be managed, authorities can restrict the use of substances in different ways. In the context of REACH, a long-term goal is to ensure that the most hazardous substances will be substituted with less dangerous ones. In this context, the European Chemicals Agency (ECHA), the EU institution which implements REACH, has developed a substitution strategy. This is a policy which encourages the replacement of harmful chemicals by boosting the availability and adoption of safer alternatives and technologies. It highlights networking, capacity building, and improving access to data, funding and technical support as key areas for action.

The strategy is linked to the EU priorities of a more circular and bio-based economy, the sustainable manufacture and use of chemicals and a non-toxic environment. The European Commission introduced a Circular Economy Action plan in 2015. In January 2018 the European Commission adopted a new set of measures, aimed at implementing this plan. This package includes documentation on plastics, a report on critical raw materials, as well as an important Communication on the Interface between chemicals, products and waste legislation. This document has many suggestions and questions on how best to move forward to a more effective circular economy, which is work still underway.

It is important that hazard and risk assessments are transparent in REACH registrations and can be evaluated by a third party. However, it is well know that this possibility is limited creating potential conflict of interests (Ingre-Khans, et al., 2016). REACH will lead to increased availability of toxicological data, but not to the extent that would be needed to achieve a sound scientific basis for hazard assessment of all individual substances covered by the legislation (Hansson and Rudén, 2010).

Policies are undoubtedly important in influencing the direction of technology innovations. However, from the perspective of the innovator policy can be an unreliable guide as it can change over time, often becoming more restrictive but sometimes also more relaxed. In addition, policy can be costly to enforce for industry diverting funds away from innovation of better solutions. Ideally, if innovation is based on environmentally friendly technologies and has superior performance compared with traditional solutions, they are less prone to changes in legislation and companies will spend less resources making sure there is no risk to humans and the environment.

## Some examples of Industry Sectors

### Mining

Mining has been an important business in Sweden for over a 1,000 years and Sweden is the leading supplier of metals within the EU with around 80 million tonnes being mined. Over 90% of the iron ore produced in the EU originates from Sweden (The Swedish Trade & Invest Council, 2016). Although the environmental impact of mining in Sweden has been much reduced, there are still problems with emission of pollutants into the air, surface water and groundwater. According to a Swedish Environmental Protection Agency's report, 89 million tonnes of mine waste was produced in 2010. Mine waste and unused mines, and in particular that from sulfidic ores, left exposed to water and wind can result in drainage of acidic, metal-rich leachate into the environment.

### Cosmetics, Personal Care and Household Chemicals

Because of the direct exposure to people's bodies or their home environments of cosmetics, personal care products and household cleaners, there has been much research on the potential impact on human health and the environment. Many ingredients have been identified and continue to be determined to be potential harmful. While some have immediate alternatives available, there are many unmet needs that still have not had safer alternatives discovered or invented.

### Pharmaceuticals

The pharmaceutical industry is highly regulated, and the negative consequences of human and veterinary drugs must already be carefully determined and controlled. Unfortunately, manufacturing processes of pharmaceutical often create substantial amounts of hazardous waste. Also, active pharmaceuticals are increasingly appearing in the environment as unmetabolised drugs in human excretion, inappropriate disposal of unused prescriptions, and veterinary drugs enter the environment through manure, slurries and other biosolids.

### Performance Materials

A large and important group of performance materials is the plastics. The main components of all plastics are the basic polymer, which is then compounded with necessary additives for the specific application. Additives can be pigments and colourants, processing aids, antioxidants, inorganic fillers to provide strength, (brominated) flame retardants etc. Moreover, very few polymers except the polyolefins are directly miscible, so the desirable recycling is facing two main issues: polymer non-compatibility and unknown substances in mixtures collected for re-use. Here especially the latter issue can cause unknown emissions of hazardous substances in the environment (Stenmark, 2017; Nordic Council of Ministers, 2017).

### Industrial Chemicals

Industrial chemicals cover tens of thousands of very different chemicals employed in a multitude of industrial sectors, where especially manufacturers and other workers are exposed to hazards. One striking example is in liquid products based on low boiling organic solvents (e.g. paints with coalescing agents and other surface coatings), where the solvents are often deliberately evaporated and special care to avoid exposure is needed. Aromatic and/or halogenated solvents should be replaced whenever possible by green solvents. Another concern is for analytical laboratories where the use of toxic solvents (trichlorobenzene, acetonitrile, tetrahydrofuran, dimethylformamide, etc.) for chromatographic purposes is necessary, however, method development to replace with less toxic solvents are strongly encouraged.

### Food, feed and fisheries

Agricultural chemicals, additives, and undesirable contaminants can potentially affect not only the consumer, but also the environment, farm animals, companion animals and workers (e.g. farmers, food and feed manufacturers). In addition, agriculture and aquaculture causes environmental exposure of trace elements added to feed. Agricultural chemicals, such as pesticides for example, may be necessary to use to ensure food and feed supply but have also been associated with disease and environmental disasters. There is therefore a need to be able to accurately predict their effects on humans and non-target organisms. Food and feed additives, such as some colourants and flavourings, may also have health effects which arguably may not always be scientifically justified by their nutritional benefits. Here a combination of improved hazard characterisation, replacement with safer alternatives, as well as public education of the potential risks and benefits would be helpful. However, although chemicals deliberately added to food and feed or incorporated as a direct consequence of food and feed production strategies, the cumulative risk from exposure to chemicals occurring in food is dominated by contaminants (Danish Environmental Protection Agency, 2017). Solutions to remove contaminants from feed materials has great potential to reduce human exposure to undesirable substances. For example, the content of dioxins and dioxin-like PCBs in feed for farmed salmon can be reduced by activated carbon filtering of fish oil going into the feed (Berntssen et al., 2010a) or by substituting fish oil in fish feed for land-based alternatives with low contents of organic pollutants (Berntssen et al., 2010b).

### Forestry

There are a number of countries in which forestry is an important economic sector. Sweden is a good example. More than two thirds of Sweden is covered by forests. The vast majority of this area is given over to commercial forestry; consequently, commercial forestry plays an important role in the Swedish economy. In 2011, products of the forestry sector accounted for 7.4 per cent of Sweden’s exports. This achievement was second to only that of Finland in the EU. Almost all of forest land in Sweden is used for commercial forestry, of which, 81 per cent held by private owners; the remainder being held by the state or other public institutions. About 5 per cent of forest land is protected as national parks, nature reserves, and habitat protection areas or as nature conversation agreements. Many forestry areas in private hands are protected by the owners on a voluntary basis.

Despite these measures, 861 forest species are endangered according to the Swedish Red List. These include the western taigas, coniferous species as well as a number of hardwood species. Needless to say, there are many other species of plants and animals which depend on these species and ecosystems. Sweden has a series of environmental quality objectives (EQAs) which include a "Sustainable forests" objective. According to a number of studies, this objective is unlikely to be met by 2020 which is the foreseen deadline for implementation.

In terms of the use of chemicals used in the forestry industry, pesticides are of major importance. They include prophylactic insecticides, such as synthetic pyrethroids and neonicotinoids, which are used to prevent insects from eating the bark of young tree seedlings. These are likely to have unintended impacts on non-target insect species. They may also have a damaging effect on the health of workers unless appropriate personal protection measures are used. At the same time, pulp and paper mills discharge water that includes as well as lignin, alcohol, and inorganic material such as cholates, chlorinated and metal compounds. All of this contributes to soil and water pollution.

### Waste and Recycling

The hazardous properties of waste should determine the way in which the waste is handled and treated. However, information about the intrinsic properties and contents of hazardous chemicals in waste is not easily available for the recycling industry. Analysing and testing the content in an exhaustive manner is often difficult or even impossible by existing methods. Lack of knowledge about the content of hazardous chemicals could lead to implications in the choice of recycling methods and consequently a risk of adverse negative human health and environment effects (Belleza & Youhanan, 2017). Depending on how the waste is treated, different types of exposure sceneries may be relevant, e.g;

- When products containing hazardous chemicals are materially recycled to be used in new products with the risk of emitting hazardous chemicals both to the user and to the environment.
- When incorrectly sorted hazardous waste is mixed with combustible waste and incinerated in conventional waste incineration plants with the risk of emitting hazardous chemicals through air emission and via the ashes produced in the incineration plants.
- When hazardous waste is incorrectly classified as non-hazardous and re-used in construction with the risk that hazardous chemicals leach out to the environment over time or in a next cycle.

# 5 Technological State of the Art and Challenges

## Implications of entire value chain collaboration/cooperation

An important part of reaching non-toxic and resource-efficient material cycles is collaboration throughout the entire value chain of the product. Today, there are shortcomings and inconsistencies in how hazardous chemicals are regulated in the different parts of a product's value chain (Molander, 2015). Absences of harmonisation and holistic responsibility on hazardous chemicals may lead to problems being pushed down the chain (e.g. post-consumer products being classified as hazardous waste). As such, optimization of a product design and content in one part of the chain can cause problems in another. Furthermore, as product value chains often consist of many actors, and challenges regarding information and traceability often arise.

We need collaboration to improve material design to give a holistically effective performance of a product throughout its lifecycle(s) via e.g. resource efficiency, functionality, recyclability, and upgradability over longer time perspectives. New business models and responsibilities could also improve collaborations and create more incentive to design effective and smart for several cycles.

## Technologies to reduce negative impacts on human health and the environment

While it might seem obvious that chemists and chemical engineers should invent and design future products that have reduced impact on human health and the environment, it is important to acknowledge the difficulties that prevent widespread realisation. Creating safer products is ultimately a molecular exercise that resides with individuals trained in chemistry and materials science. Unfortunately, if one reviews the academic programs offered at virtually all universities worldwide, with very few exceptions, the curricula provided to students has no training in toxicology to humans or the environment. As students leave academia and head to careers designing new products, they are currently not given the appropriate skills to anticipate negative consequences to health. Any long-term solution to addressing issues of toxicity and sustainability will have to involve a modification of how chemists and material scientists are trained. The fields of toxicology and environmental health sciences are quite robust and are constantly discovering the molecular mechanisms that are responsible for negative impacts on human and environmental health. Unfortunately, there is an intellectual disconnect where scientists and engineers who are trained to design and invent new materials and processes are not connected to these fields and do not have adequate training on how to benefit from this knowledge.

We must create mechanisms to bridge the gap between the fields of science that invent and design new molecules with the fields of science that seek to understand their negative consequences. We must not only focus on students in universities that will be the future practitioners of chemistry and materials scientists, but we must find ways to provide the necessary tools to existing industrial chemists and engineers as well. Training programs to access the wealth of information that already exists regarding the molecular mechanisms of negative impacts on human health and the environment and a process to ensure to that this information is constantly updated with new knowledge must be created and disseminated.  Three areas where existing information exists and is constantly being updated are regulatory lists, mechanistic insights, and predictive computational tools.

Several governmental and non-governmental organizations create and maintain lists of molecules and classes of compounds. REACH, OECD and the Environmental Working Group are three examples of organisations that create and maintain such lists. These lists are often used when a material is being commercialised - well after it has been invented. There needs to be a user-friendly conduit to connect these lists to individuals involved in the design stage of materials and processes.

The fields of toxicology and environmental health sciences are scientific disciplines with their own degree programmes and which scientists dedicate their careers to master. While it is impractical and probably unnecessary to suggest that designers of molecules and materials learn the entire curricula of these fields, there should be some minimum training to ensure that they obtain enough fundamental understanding to communicate, interact, and use this knowledge. Computation tools and databases that provide some predictions of potential negative impacts on human health and the environment based on molecular structure already exist to some extent. They are continuously being improved and expanded. Unfortunately, most practicing chemists and materials scientists are often unaware of these tools, or do not have sufficient training to use them adequately. By creating better access of these tools and customising them to chemists and engineers designing new products and processes, not only will products be potentially safer but through continuous improvement the tools themselves will overtime get better.

## Designing Improved Hazard Screening Technologies

### Needs

There is a need to move away from the current chemical hazard assessment paradigm relying primarily on experiments in surrogate organisms to predict effects on humans, companying animals, and the environment. On the 07 February 2018, the REACH database contained 145,297 unique substances approximately half of which will require toxicity data for hazard identification and characterisation. As a further perspective The Carcinogenic Potency Database (CPDB) reports that only 1,547 chemicals had undergone long-term animal cancer tests as of 2011. Adding to these numbers are novel materials, such as nanomaterials for which there is no clear testing strategy in many areas.

There is an important question of how representative surrogate species, such as rats, are of the species the assessment is aimed to protect?  Humans are of course not rats and there are numerous examples of how biochemistry, physiology and anatomy of rodents make them to deviate from responses in human (Hartung, 2009). The society is also increasingly unhappy about animal testing, which has created a drive to Reduce, Refine and Replace (“3Rs”) animals in laboratory experiments (https://youtu.be/2hxUMpYF0_Y). What is ultimately needed is animal-free technologies and methods, which can increase efficiency, accuracy and speed of toxicity testing, whilst at the same time reducing the cost. A sensible approach to improve hazard assessment of chemicals is to optimise the use of existing information about structurally similar substances, along with cell culture-based methods, to prioritise chemicals and guide testing strategies such that animal testing is only carried out when deemed necessary (Hartung, 2009). The link between activity of a chemical at the molecular level and the apical manifestation of toxicity at the organism (or population) level is underpinned by the Adverse Outcome Pathway framework (Schroeder et al., 2016). This concept has been the basis for the Federal 'Tox21' programme in the USA in which a high-throughput screening programme is used to assess the potential of 10,000 chemicals to disrupt biological pathways (Thomas et al., 2018).

### *In silico* methods

The use of existing data on effects of chemicals on a given endpoint to predict the properties of other chemicals is known as (Quantitative) Structural Activity Relationship ((Q)SAR) methods. (Q)SARs are statistically based methods in which relevant features of chemicals are encoded using chemical descriptors, or fragments (Nicolotti et al., 2014). The molecular descriptors encode physicochemical properties, such as atomic composition, sub-structures, hydrophobicity, surface area charge, and molecular volume. (Q)SARs can predict effects on biological target molecules (toxicodynamics) as well as toxicokinetic properties governing uptake, metabolism and excretion. (Q)SARs are becoming increasingly sophisticated and accurate in their predictive abilities, but are still primarily used in absence of empirical data to bridge data-gaps.

### *In vitro* assays

There are already in vitro tests which are widely used in risk assessment, primarily for identification of genotoxic potential. An ever-increasing number of in vitro toxicity tests are being developed, typically focussing of Molecular Initiating Events (first point of chemical disruption of a biological process) and Key Events (critical junctures) in Adverse Outcome Pathways, linking chemical-biological interactions with toxicity. Such in vitro testing may be especially useful for assessment of receptor mediated effects, such as endocrine disruption and dioxin-like activity. Several genetically modified cells exist for assessment of activation of nuclear receptors, including the yeast YES assay for oestrogens, and the CaluxTM family of mammalian cell based assays for detection of activation of oestrogens, androgens and some other nuclear receptors, including AHR and PPAR. Other cell-based assays report on effects on other commonly affected proteins, such as enzymes, G-coupled protein receptors, protein kinases, protein phosphatases, ion channels, and transporters.

A major challenge for in vitro tests is to relate effects at a cellular level to relevant adverse outcomes at the organismal level. In ecotoxicology this is particularly challenging since an environmental concentration needs to be related to a quantitative effect on variables, such as survival, growth and reproduction that could influence population health. There is also an issue with the relevance of the concentration of a toxicant tested in cell culture relative to the predicted environmental concentration. In other words, how can a concentration of a test item in a cell culture medium be translated to an environmental concentration? Presently, only one cell culture based system can address this problem; primary cultures of fish gills can be grown on permeable supports and tolerate direct exposure of the test item in water (Walker et al., 2008). To aquatic organisms the water itself is often the most important exposure route and the gills are multifunctional organs that are exceptionally sensitive to many toxicants. This system has also been used to investigate bioaccumulation and metabolism of environmental pharmaceuticals (Stott et al., 2014; Stott et al., 2015).

### Omics technologies

The term genomics was originally coined to describe the study of genes in the context of the chromosome. Following this, the profiling of all RNA expressed in a cell, tissue, or organism, was called transcriptomics. Analogously the global analysis of protein abundance and modifications was dubbed proteomics, and simultaneous analysis of all metabolites became known as metabolomics (or metabonomics). Together these relatively novel technologies are usually collectively referred to as Omics technologies. Toxicogenomics is then the application of genomics to toxicology. The underlying paradigm for most toxicogenomics studies found in the literature is that the interaction between a toxicant and a biomolecule results in a change in gene expression and/or protein processing. The change in gene expression can be a Molecular Initiating Event (e.g., AHR activation) or Key Event in Adverse Outcome Pathways, or a compensatory response to restore disrupted homeostasis. In either case, omics has the power of identifying metabolic pathways, components, and systems affected by toxicants and are valuable to delineate the mechanisms of toxicity to populate Adverse Outcome Pathway scheme, which form the framework for 21st Century Toxicology.

Omics can be used to identify biomarkers and expression signatures ('fingerprints') associated with exposure to groups of chemicals and/or their effects. Gene expression signatures can be obtained through use of machine-learning in which the minimum number of genes are derived that can with high reliability identify a condition, which might be exposure to a chemical or a certain pathological outcome (Erstad et al., 2018). Gene expression signatures as developed through network-based differential connectivity analysis are being increasingly used in drug development to predict therapeutic and undesirable effects of drugs (Mulas et al., 2018). Chemical connectivity analysis of transcriptomics datasets has also been used to identify toxicological resemblance of chemicals based on similarities in gene expression profiles (Wang et al., 2016).

### What still needs to be developed

As pointed out earlier, toxicology knowledge and tools that are accessible to designers of chemicals and materials are lacking. Beyond basic training in principles of modern predictive toxicology, there is a need to invent appropriate in silico tools for synthetic chemists harnessing existing (Q)SAR principals and technologies, and also to expand these through incorporation of chemical connectivity networks indicative of specific toxicological properties. Deployment of in silico tools in hazard characterisation of chemicals relies on the confidence in extrapolation to toxicologically relevant effects at the organismal level. There is much to be gained from use of existing information to identify and build on Adverse Outcome Pathways, which when perturbed beyond homeostatic control results in an adverse health effect. Finally, there is a need to build understanding of the genetic basis for variabilities in responses between individuals and, even more so, across species.

## Creating Circularity in Systems

### Turning waste management into materials management

Managing the use and impacts of resources in our society - such as primary (geosphere) resources, secondary (waste) resources, energy, and renewable materials - needs to be approached from a broad systems perspective. Overall, resource management must be aligned with the societal goals such as achieving non-toxic and resource-efficient materials cycles. Therefore, secondary resource (waste) management should not be 'optimized' on its own but viewed as a part of resource management in general. This shift in perspective from effective parts (such as minimal impacts at end-of-pipe) to an effective system involves an extensive transformation within society (e.g. steering mechanisms and policy approaches). Such a shift will require decontaminating and reducing the entropy of circular flows while taking full advantage of the functional value of the resources over several cycles (Graedel et al., 2011 pg 14).

New innovations are also required. Proactive organisations need to get ahead of the legislation by voluntarily taking the initiative and showing the opportunities of new solutions. Actors in the different stages of the materials life cycle must cooperate to create an understanding of the different needs and opportunities available. In such collaborations, issues such as mixing and incidental contamination should be addressed to maintain material value through several cycles.

Clear requirements and criteria from the material processing and production industries are also needed so that 'upstream' actors can effectively establish relevant handling and treatment of secondary materials. From a regulatory point of view, international End-of-Waste criteria would contribute to creating circularity in the systems. By creating knowledge and cooperation throughout the chain, systems and techniques can be further developed with common goals, enabling the value and quality of materials to be maintained over long periods.

### Keeping toxic materials in "closed loops" is not ideal

While seeking closed loop processes for the chemical industries we must be careful not to see this as an avenue to perpetuate the continued use of hazardous materials. It is certainly better to keep materials, even hazardous materials, in a continuous cycle than to have them ending up in landfills. However, we must acknowledge that the ultimate solution is for materials in a closed loop be rendered harmless or replaced by intrinsically safe materials. Moving exposure to hazardous materials from one population to another, even if they are better trained and have adequate exposure control technologies, does not eliminate the potential for accidents by human failure or natural disaster.

### Technologies to maintain or increase value in re-use

Technologies need to be developed, as add-ons to recycling systems, which either remove hazardous chemicals or render them harmless by modification. This may result in a degradation in the value chain but could be acceptable for some product classes. At some stage the value must be regenerated through a refinement process which should involve removal of hazardous substances and other contaminants.

# 6 Educational Imperatives

## Targets

The pertinent novel mind-set that waste should be considered an indispensable and valuable resource requires educational imperatives at various levels. A deposit system on beer cans and PET bottles have worked well in the Nordic countries for several years based on a reasonably returned deposit and an operational collection system (normally within the supermarkets). Many consumers appear willing to recycle various types of waste provided the collection systems are well thought out and easy to use. The awareness and training of the children on these issues should start already in the families, which should also be assisted by the municipalities and other public authorities through information and advertisements. Teaching material (videos, educational games, exercises) should be prepared for the school system from the first grade on and through high school and the children taught that used consumer products and materials are valuable resources that can be re-used and are an indispensable part of a circular economy. At the universities part of the curriculum for chemists and materials scientists should be toxicology and include assessment of hazardous exposure and emissions from chemicals, products and recycled materials and how to handle these issues. In industry and at production sites the workers should periodically be trained in minimising waste that cannot be re-used and handling the improved recycling systems.

Future, progressive legislation encouraging the coming more positive mind-set that waste is an indispensable resource in combination with reasonable logistics for industry and consumer waste disposals will hopefully and eventually contribute to the circular economy.

## Themes to be included in the educational curriculum

### Green Chemistry

Green chemistry is a field of chemistry that seeks to design chemical products and processes that reduce or eliminate the use and/or generation of hazardous substances. The book Green Chemistry: Theory and Practice was published in 1998 and describes the 12 principles of green chemistry (Anastas and Warner, 1998). Several educational organisations throughout the World are now helping to design new curricula for students in schools and universities that teach how to implement these principles (Box 1).

### Life Cycle Analytics

Health- and environmental impacts are caused by every product, and different products give rise to different types of impacts throughout their life cycles: from extraction of raw materials, through production and use, to final disposal. As a result, from a growing consumption of products and goods, both direct and indirect health and environmental effects caused by pollution and resource depletion

**BOX 1: The Twelve Principles of Green Chemistry**

1. Prevention. It is better to prevent waste than to treat or clean up waste after it is formed.
2. Atom Economy. Synthetic methods should be designed to maximize the incorporation of all materials used in the process into the final product.
3. Less Hazardous Chemical Synthesis. Whenever practicable, synthetic methodologies should be designed to use and generate substances that possess little or no toxicity to human health and the environment.
4. Designing Safer Chemicals. Chemical products should be designed to preserve efficacy of the function while reducing toxicity.
5. Safer Solvents and Auxiliaries. The use of auxiliary substances (solvents, separation agents, etc.) should be made unnecessary whenever possible and, when used, innocuous.
6. Design for Energy Efficiency. Energy requirements should be recognized for their environmental and economic impacts and should be minimized. Synthetic methods should be conducted at ambient temperature and pressure.
7. Use of Renewable Feedstocks. A raw material or feedstock should be renewable rather than depleting whenever technically and economically practical.
8. Reduce Derivatives. Unnecessary derivatization (blocking group, protection/deprotection, temporary modification of physical/chemical processes) should be avoided whenever possible.
9. Catalysis. Catalytic reagents (as selective as possible) are superior to stoichiometric reagents.
10. Design for Degradation. Chemical products should be designed so that at the end of their function they do not persist in the environment and instead break down into innocuous degradation products.
11. Real-time Analysis for Pollution Prevention. Analytical methodologies need to be further developed to allow for real-time in-process monitoring and control prior to the formation of hazardous substances.
12. Inherently Safer Chemistry for Accident Prevention. Substance and the form of a substance used in a chemical process should be chosen so as to minimize the potential for chemical accidents, including releases, explosions, and fires.

increases. No matter the size or type of negative impact a product causes, most of the environmental attributes are determined early in the product development phase when materials and product specifications are selected. McAloone & Bey (2011) estimated that around 80% of the environmental profile of a product is fixed during the design of the concept. It is therefore important to integrate both health and environmental considerations early during a product's development phase, to minimise negative impacts and potential hazards throughout its life cycle without compromising other design criteria such as quality, cost, functionality, and circularity.

Life cycle assessment (LCA) is one of the most well-known concepts that can support the implementation of designing for reduced negative impacts. LCA has gained broad acceptance as a tool to quantify both environmental and human health aspects. LCA is a holistic concept that provides quantification of resource use, ecological effects and human health impacts throughout the product's life cycle, including extraction of raw materials, production, distribution, use and circulation (Baumann & Tillman, 2004). LCA can assist in activities such as identifying the environmental performance of products, identifying environmental "hotspots" (i.e. which life cycle stages that have the most negative impacts) or developing alternative product concepts.

It is important to keep in mind some of the challenges regarding LCA in the context of design. One example is the dilemma of opportunity versus knowledge. In the early phases of product development, the window of opportunity is very wide and the opportunity to integrate environmentally beneficial features into the products is the largest. However, it is also at this stage we know the absolute least about the product resulting in difficulties to quantify the potential impacts (McAloone & Pigosso, 2018).

### Toxicology Chemists and Materials Scientists

Much of this document discusses the need to create a conduit for information flow from the toxicology and environmental health community to the inventors. In order for this communication to be successful, it will be extremely useful for the people developing models of negative impacts to human health and the environment to have some insights into the inventive process of product design. If both groups better understand one another, useful information transfer can be more efficient.

### Cross Sectorial Learning

Interdisciplinary research has many benefits but also many challenges. One of the latter is a lack of a common vocabulary and definition of concepts. Interactions between people in different fields are slowed down because of misunderstandings and misinterpretations. However, these barriers are more often based on semantic differences than conceptual discrepancies and once broken down open the possibilities for interdisciplinary synergism formed through cross sectorial learning. Ideas, methods and technologies can now be learned and applied across disciplines and new ones can be created through the merger of knowledge that previously existed isolated in separate silos. The science and knowledge needed for a design to reduce chemical hazards in the product value chain lays in several disciplines. It is therefore envisioned that a project taking on this task will likely be multidisciplinary and have a clear strategy of how to integrate the cumulative knowledge.

### Communication of Hazard and Risk

While professional toxicologist have developed thorough forms of assessment and communication of risks and hazards within their community, in general, there is a poor communication of these concepts, especially concerning the combined effect in a marketed product, to two important audiences: the consumers and the inventors of new technologies. There is, therefore, a need to develop better tools to address and communicate the results and consequences for products (Warner and Ludwig, 2016). There are three important questions that need to be addressed:

1. **How does the inventor/designer of a new products know what materials to use that will not create the next generation of problems?**

   While there exist several lists of "chemicals of concern" available, the specific criteria for being considered of low hazard, including methods and prediction tools used to assess hazard, should always be made available so that any alternative compound or product has information to anticipate unfortunate substitutions.

2. **How does a consumer know the impact of a product (as a whole) on their health and the environment?**

   Lists of ingredients that are potentially harmful is an important part of communication of risk and hazard. However, it is not always easy to anticipate synergies between ingredients, or compounds that are created during the manufacturing process. Whenever practical, testing and information on total products should be made available.

3. **Where no product is perfect, how does the consumer understand the trade-offs?**

   Nowadays, consumers are provided with information about the nutritional composition of food, drinks, and snacks, which allows them to make an informed decision about what they eat and drink. Likewise, it would be useful to provide the consumer with quantitative information regarding discreet toxicological and environment endpoints so that comparison between different products are possible.

# 7 Conclusion and recommendations

The working group recommends that a call for an interdisciplinary collaborative project is initiated addressing the need for a paradigm shift in invention, use and re-use of materials. It will have three audiences, namely inventors of materials, inventors of predictive toxicology, and inventors of educational tools and methods. The project will involve the following three themes:

1. Inventing new technologies which introduce less hazardous materials into products or facilitate removal of materials that hamper up-/re-cycling and thereby benefitting the entire value chain. The inventions will take place in collaboration with toxicologists who will inform on toxicological properties of chemicals.
2. Develop better tools to predict different toxicological properties of chemicals. These may be based on in silico predictions benefiting from existing big data or involve rapid screening systems. In either case, the tools should be developed in collaboration with material inventors who will inform on usefulness to inventors.
3. Invent better education tools and methods to facilitate learning of principles of toxicology by inventors of materials and products, synthetic chemistry by toxicologists, and inherent hazards of products by consumers.

In the execution of this research programme, the technologies and tools may be validated through case studies to test the outcome and systems developed. It is envisioned that the successful application will fulfil three conditions, namely the project must:

1. address important environmental issues in a manner that works for the whole value chain,
2. demonstrate scientific rigour, and
3. contain a clear plan of dissemination to non-technical stake holders and society.

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