CHEMICALS IN CONSUMER PRODUCTS

Bridging the gap between academic research and chemicals regulation

Linda Molander

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ABSTRACT

Exposure to chemicals emitting from consumer products, such as clothes, electronic devices, toys and kitchen-ware, has emerged as an issue of public health and environmental concern. The use of chemicals having endocrine disrupting properties in commercial products is receiving particular attention as low dose exposures of such chemicals have been associated with adverse effects in both human and wildlife populations. Current chemicals regulation has been criticized for not providing adequate protection of human health and the environment with regard to consumer products. The aim of this thesis has been to provide new insights and methods related to the risk assessment and risk management of chemicals in consumer products in order to ensure a safer and more sustainable use.

The comparative analyses of different EU regulatory frameworks targeting the use of chemicals in articles identified a number of shortcomings and inconsistencies in how chemicals in articles are regulated. One main conclusion from Paper I was that product specific rules are important complements to REACH as they can more easily be tailored for certain uses and exposure scenarios. In Paper II it was investigated whether the regulation of chemicals in articles according to REACH is sufficient for meeting EU environmental goals, which include rectifying environmental problems at the source. It was concluded that the prioritization of substances to be targeted by restrictions and other requirements under REACH to a greater extent should take into account substances that have been identified as posing a risk to or via the environment.

With the aim to facilitate the use of all reliable and relevant toxicity information in regulatory health risk assessment of chemicals, a method for systematic and transparent evaluation of non-standard research studies, as well as reporting guidance for such studies, were developed in Paper III. It has for example been emphasized that non-standard research studies can provide valuable information with regard to endocrine disrupting effects. Such effects are not systematically tested for in standardized studies commonly preferred in regulatory risk assessments. In Paper IV, the method for study evaluation proposed in Paper III was combined with recently developed

web-based tools that aid summarizing and visualizing toxicity data extracted from several studies. The combined use was found to comprise a promising methodology for identifying reliable and sensitive information from *in vivo* toxicity studies of relevance to consider in the risk assessment process.

The new methods and tools proposed and evaluated in this thesis will hopefully help improve the use of non-standard studies for risk assessment purposes and thereby strengthen the link between academic research and chemicals policy. In my view, this would be an important step towards improving public health protection with regard to the use of chemicals in consumer products.

SAMMANFATTNING

Vi exponeras dagligen för ett stort antal kemikalier via varor som kläder, elektronik, leksaker och köksredskap. Nuvarande kemikalielagstiftning har kritiserats för att inte ge ett fullgott skydd för människors hälsa och miljön vad gäller användningen av kemikalier i konsumentartiklar. Kemikalier med hormonstörande egenskaper har särskilt uppmärksammats, då exponeringen för sådana ämnen misstänks kunna vara en bidragande orsak till flertalet folkhälsosjukdomar och hormonrelaterade effekter som observerats i vilda djur. Huvudsyftet med arbetet som presenteras i den här avhandlingen har varit att bidra med nya kunskaper och metoder för en stärkt reglering av kemikalier i konsumentprodukter.

I avhandlingens första delarbete (Paper I) identifierades stora variationer i hur kemikalier regleras i olika typer av konsumentvaror inom EU. Skillnaderna inkluderade bland annat vilka substanser som prioriteras för reglering och vilka restriktioner och krav som de sedan omfattas av. Analysen visade också att produktspecifika regler är viktiga komplement till EU:s kemikalielagstiftning Reach, eftersom sådana regler enklare kan skräddarsys för vissa användningsområden och för skydd av särskilda grupper i befolkningen, till exempel barn. I det andra delarbetet (Paper II) undersöktes om regleringen av kemikalier i varor enligt Reach är tillräcklig för att möta EU:s miljömål, som bland annat säger att miljöproblem ska hanteras vid dess källa. Det konstaterades att Reach i större utsträckning bör prioritera kemikalier som har identifierats utgöra en risk för eller via miljön för reglering i varor.

Toxicitetsstudier som utförts enligt standardiserade riktlinjer används i stor utsträckning när kemikalier riskbedöms eftersom de anses vara tillförlitliga. Icke-standardiserade forskningsstudier kan dock bidra med värdefull information till riskbedömningar då de kan fånga upp effekter som inte undersöks i de standardiserade testerna, framför allt vad gäller hormonstörande effekter. För att underlätta användningen av toxicitetsdata från icke-standardiserade forskningsstudier i hälsoriskbedömningar utvecklades en metod för systematisk och transparent utvärdering av sådana studier i det tredje delarbetet (Paper III). I avhandlingens sista delarbete (Paper IV) kombinerades den föreslagna metoden för utvärdering av studier med ett

nytt webbaserat verktyg för sammanställning och visualisering av toxicitetsdata från flera studier. Den kombinerade användningen av utvärderingsmetoden och det webbaserade verktyget utgör en lovande metod för identifiering av vilken information som kan vara särskilt viktig att ta hänsyn till i riskbedömningssammanhang.

Min förhoppning är att de nya metoder och verktyg som föreslås och utvärderas i detta avhandlingsarbete ska förbättra användningen av icke-standardiserade studier för riskbedömningsändamål, och i och med detta stärka kopplingen mellan den akademiska forskningen och kemikalieregleringen. Detta skulle, i min mening, också innebära ett viktigt steg mot en säkrare och mer hållbar användning av kemikalier i konsumentprodukter.

LIST OF PAPERS

I. Molander L and Rudén C (2012). Narrow-and-sharp or broad-and-blunt – Regulations of hazardous chemicals in consumer products in the European Union. Regulatory Toxicology and Pharmacology 62, 523-531.

II. Molander L, Breitholtz M, Andersson PL, Rybacka A and Rudén C (2012). Are chemicals in articles an obstacle for reaching environmental goals? – Missing links in EU chemical management. Science of the Total Environment 435-436, 280-289.

III. Beronius A, Molander L, Rudén C and Hanberg A (2014). Facilitating the use of non-standard *in vivo* studies in health risk assessment of chemicals: a proposal to improve evaluation criteria and reporting. Journal of Applied Toxicology 34(6), 607-617.

IV. Molander L, Hanberg A, Rudén C, Ågerstrand M and Beronius A. Low dose effects of bisphenol A on the developing mammary gland - Combining new web-based tools to identify reliable and relevant data for regulatory risk assessment. *Manuscript.*

CONTRIBUTION TO PAPERS

I. I developed the idea for the study together with my co-author. I was responsible for carrying out the literature study and comparative analysis, as well as for writing the paper.

II. I was involved in developing the idea and responsible for carrying out the study, including the literature review and result analyses. I was responsible for writing the paper.

III. I was actively involved in all parts of the study: in the planning and execution, i.e. in developing the framework for study evaluation and the reporting guidance. I also contributed actively in writing the paper.

IV. I had the lead role in planning and performing the study, including gathering, extracting, analyzing and presenting the data. I was also responsible for writing the paper.

CONTENTS

Parts of this introduction have been reproduced from Molander (2012).

ABBREVIATIONS

BFR	Brominated flame retardant
BMDL	Lower confidence limit of a benchmark dose
BPA	Bisphenol A
CLP	Classification, Labelling and Packaging of substances and mixtures
CSA	Chemical safety assessment
DNEL	Derived no effect level
EC	European Commission
ECHA	European Chemicals Agency
EDC	Endocrine disrupting compound
GLP	Good Laboratory Practice
HAWC	Health Assessment Workspace Collaborative
NOAEL	No observed adverse effect level
OECD	Organisation for Economic Co-operation and Development
PBDE	Polybrominated diphenyl ether
PBT	Persistent, bioaccumulative, toxic
PCA	Principal component analysis
PCB	Polychlorinated biphenyl
PFC	Perfluorinated compound
PoD	Point of departure
POP	Persistent organic pollutant
REACH	Registration, Evaluation, Authorization and Restriction of Chemicals
RfD	Reference dose
RoHS	Restriction of the use of certain Hazardous Substances
SciRAP	Science in Risk Assessment and Policy
SR	Systematic review
SSD	Sewage Sludge Directive
SVHC	Substance of very high concern
TDI	Tolerable daily intake
TG	Test guideline
UNEP	United Nations Environment Programme
US FDA	United States Food and Drug Administration
vPvB	Very persistent, very bioaccumulative
WFD	Water Framework Directive
WHO	World Health Organization
WoE	Weight of evidence

1. INTRODUCTION

Exposure to low doses of chemicals emitting from everyday consumer products, such as clothes, electronic devices, toys and kitchen-ware, has emerged as an issue of public health and environmental concern. Along with improved living standards, consumption patterns have changed considerably during the last decades. The consumption of consumer articles is increasing rapidly; the international trade with articles has tripled since the 1970's (Swedish Chemicals Agency 2011a). As a consequence, there has been a shift from exposure to a limited number of chemical substances, mainly in the occupational setting, to exposure of the general population to numerous chemicals at the same time, where materials in indoor environments and food have become important sources (Swedish Chemicals Agency 2011b).

There is increasing concern that the dispersive use of chemicals in consumer products may have negative impacts on human health and the environment (Swedish Chemicals Agency 2014a; 2015). Chemicals with endocrine-disrupting properties constitute one class of chemicals that are receiving particular attention since exposure to such chemicals have been associated with increasing trends reported for endocrine-related disorders in the human population, such as breast and testicular cancers, reproductive impairments, and neurobehavioral disorders, as well as endocrine-related effects observed in wildlife (EEA 2012; UNEP/WHO 2013). Since genetic factors, changes in life style habits and an aging population cannot account for these increasing trends alone, exposure to endocrine-disrupting compounds (EDCs) has been identified as a possible contributor to the observed effects (UNEP/WHO 2013). This association is supported by a growing body of animal research studies reporting effects of EDCs at levels close to or within the range of human exposure (UNEP/WHO 2013; Vandenberg et al. 2012). Risks discussed in regard to low-dose exposures of chemicals in consumer products are therefore often centered on EDCs.

As a response to health and environmental concerns stemming from the use of hazardous chemicals in articles, a number of risk reduction initiatives, both regulatory and voluntary, that specifically target or that will indirectly affect the use of chemicals in articles have been implemented in recent years. Within the EU, the industrial chemicals regulation REACH (Registration Evaluation Authorization and Restriction of Chemicals) is currently being implemented (EC 2006). Although it first and foremost regulates chemical substances as such and mixture of substances, it includes and introduces certain new rules directed towards chemicals in articles. It is, however, being stressed that current regulatory restrictions and requirements are inadequate with regard to managing health and environmental risks of hazardous chemicals in articles (Rudén and Hansson 2010; Swedish Chemicals Agency 2011a; 2011b).

The research questions addressed in this thesis relate to different parts of the risk reduction process concerning the use of chemicals in consumer products, including evaluations of risk management strategies and how the regulatory risk assessment process can be improved in order to provide a better basis for more targeted policy decisions for health risk reduction.

1.2 AIM

This thesis concerns regulatory aspects of toxicology and aims to provide new insights to how risk assessment and risk management practices can be improved in order to ensure a safe and sustainable use of chemicals in consumer products. An overall aim has been to contribute new knowledge that can help improve public health and environmental protection by bridging the gap between academic research and chemicals regulation.

The work related to risk management in this thesis mainly addresses how health and environmental risks associated with chemicals in articles are handled through regulatory frameworks in the EU.

More specifically, the objectives of the studies presented in this thesis were to:

1. Investigate how health and environmental risks associated with chemicals in articles are managed by EU legislations, and to identify strengths and shortcomings of the included risk reduction strategies targeting chemicals in articles. (Paper I)

2. Investigate whether the regulation of chemicals in articles according to REACH is sufficient for meeting EU environmental goals. (Paper II)

3. Facilitate the use of non-standard research studies in health risk assessment by proposing criteria for systematic and transparent evaluation, and guidance for reporting, of such studies. (Paper III)

4. Explore a methodology for identifying reliable and relevant information from *in vivo* toxicity studies to be considered in the regulatory risk assessment process, by combining the criteria proposed in Paper III with the tools of another web-based resource aiming to improve health risk assessment of chemicals. (Paper IV)

In this thesis an **article** is defined in accordance with REACH (Article 3.3), i.e. “an object which during production is given a special shape, surface or design which determines its function to a larger degree than does its chemical composition”.

Consumer product is here used as a more general term that may not only include articles as defined by REACH, but also chemical products, i.e. mixtures, for consumer use, such as cosmetic and hygiene products, paints and detergents.

2 BACKGROUND

2.1 CHEMICALS IN CONSUMER PRODUCTS

2.1.1 Uses and releases of chemicals in articles

Chemicals are present in articles for different reasons. They can for example be used as constituents for the manufacturing of different materials, such as plastics, or added to the material in order for it to achieve certain functions or properties. Examples of such chemicals are perfluorinated compounds (PFCs), which act as water- and grease repellents, and phthalates, which are used as plasticizers. Other applications include the treatment of articles with biocides and finishing surfaces with paints and lacquers. Traces of chemical substances used in the manufacturing process may unintentionally also remain in the finished article where they no longer serve any purpose. (Swedish Chemicals Agency 2011a)

During the use phase, chemicals may be released from articles through leakage of additive substances, during washing and wearing or via the formation of small particles (Swedish Chemicals Agency 2011a). As a consequence, chemicals incorporated in consumer articles are subsequently found in our homes and bodies, and in different environmental compartments.

Although this thesis is mainly focused on risks associated with chemicals in consumer products during the use phase, it should be noted that chemicals can be released from products and articles during all steps of their life cycle, e.g. during the manufacturing and recycling processes, where they may pose risks to human health and the environment (Figure 1).

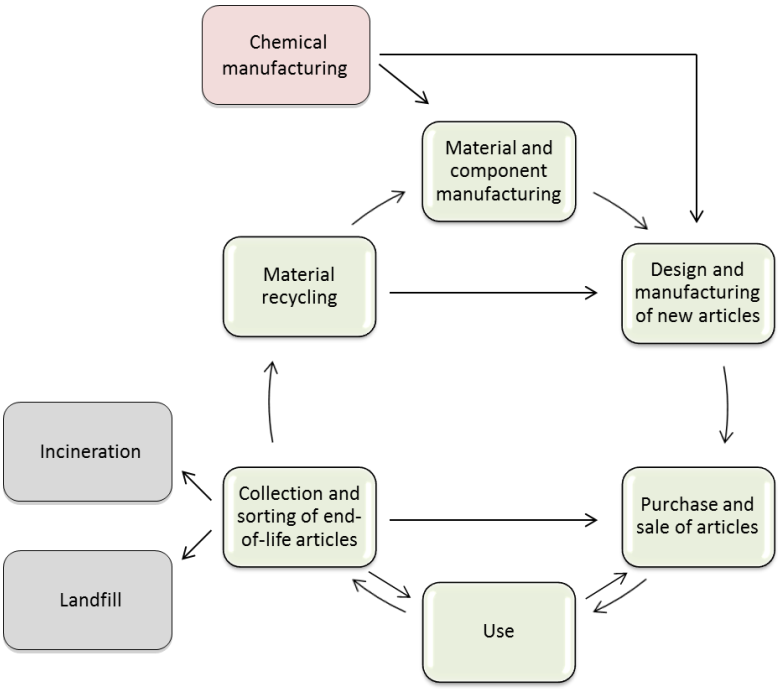

Figure 1: A simplified picture of the life cycle of chemicals used in articles. The figure is modified from the Swedish Chemicals Agency (2011a).

The manufacturing of many products and articles that are sold and used in Europe takes place outside the EU; often in countries having less restrictive and comprehensive rules for protecting human health and the environment against chemical exposures (Swedish Chemicals Agency 2011a). The consumption of articles within the EU may therefore result in significant occupational exposures and releases of known and potentially hazardous chemicals to the environment in the manufacturing countries (e.g. Fick et al. 2009). The waste phase is also associated with health and environmental problems in countries outside the EU. Articles that have been discarded within the EU, such as waste electrical and electronic equipment, are continuously being exported to countries where few risk management measures are in place for minimizing negative impacts on human health and the environment (Ongondo et al. 2011).

In recent years it has also been increasingly highlighted that chemicals with hazardous or potentially hazardous properties may be reintroduced to the market via reused and recycled materials and articles (Swedish Chemicals Agency 2014b). The newly adopted Environment Action Programme, which will guide EU environmental policy until 2020, emphasizes the importance of non-toxic and resource-efficient material life cycles (EU 2013).

2.1.2 Chemical exposure and associations to adverse outcomes

2.1.2.1 Human exposure and public health disorders

Human exposure to chemicals emitted from consumer products occur via three main routes: oral, dermal and inhalation. Oral exposure can occur via intake of food and drink, for example to chemicals that have migrated from food contact materials (Swedish National Food Agency 2011). Substances that come into contact with the skin may be dermally absorbed. Human exposure also occurs through inhalation of volatile chemicals and chemicals attached to particles in air and dust. Organic chemicals, such as flame retardants that can be released from e.g. electrical devices and furniture, have been found to accumulate in indoor dust (Mercier et al. 2011). Children may be especially targeted by these chemicals since they often spend much time indoors and close to the floor, and due to the crawling and mouthing behavior of toddlers (De Wit et al. 2012; Harrad et al. 2010).

Emissions from articles incorporated or treated with chemicals may result in long-term exposure to humans and the environment. This includes articles that stay in use for many years, such as building materials, but also articles with fast turnover, such as clothes, since chemicals included in these materials can be very persistent. However, also chemicals that degrade relatively rapidly may result in continuous exposures if emissions do not cease to occur (Swedish Chemicals Agency 2011a).

Biomonitoring studies have found that numerous chemicals representing different chemical classes are present in the human body at various levels (CDC 2009; Wood-

ruff et al. 2011). These include chemicals commonly incorporated in, and known to be released from, products and articles, such as brominated flame retardants (BFRs), perfluorinated compounds (PFCs), bisphenol A (BPA) and phthalates, as well as banned but still widespread persistent environmental contaminants, e.g. polychlorinated biphenyls (PCBs).

Based on results from epidemiological and animal toxicity and ecotoxicity studies, there is growing concern that the exposure to some of these chemicals may be a contributing factor to the increasing trends reported for some disorders and diseases seen in both human populations and wildlife, many of which are endocrine-related (UNEP/WHO 2013; EEA 2012). Some of these diseases and disorders are believed to originate from disturbances early in life, during certain developmental periods where tissues and organs are especially vulnerable for interference of exogenous compounds, and in particular those that are endocrine active (UNEP/WHO 2013; EEA 2012). In the comprehensive reports by the United Nations and World Health Organization (UNEP/WHO 2013) and the European Environment Agency (EEA 2012), it is for example stated that there is evidence from epidemiological and/or laboratory studies that suggest that male reproductive impairments, including e.g. testicular cancer and cryptorchidism (non-descending testes), may be associated with EDC exposures occurring during fetal and early postnatal life. Cryptorchidism in male infants has for example been associated with exposure via breast milk to polybrominated diphenyl ethers (PBDEs) and mixtures including PBDEs and phthalates (Main et al. 2007; Krysiak-Baltyn et al. 2012).

In women, the increased incidence of breast cancer has e.g. also been associated with developmental exposure to EDCs (UNEP/WHO 2013). Genetic factors are estimated to account only for approximately 10% of the cases. The incidence of breast cancer is mainly considered to be the consequence of lifestyle factors, primarily increased life spans, but also environmental factors including chemical exposures (EEA 2012). The developing breast tissue is believed to be particularly sensitive for interference of EDCs during fetal development and puberty (UNEP/WHO 2013; ANSES 2013).

There is concern that chemicals may play a role in the increasing trends seen in the general population also for a number of other diseases and disorders, such as obesity and diabetes, neurobehavioral disorders and asthma and other allergies (Hjern 2012; IMM 2013; Hamann et al. 2014).

2.1.2.2 Environmental risks

As for effects seen in the human population, it is often very difficult to establish causal relationships between the use of chemicals and effects observed in the environment. However, the decline in some wildlife populations, such as the seals in the Baltic sea during the 80's, have in part been attributed to reproductive failure due to certain classes of persistent organic pollutants (POPs). This association is supported by available knowledge of the endocrine-related mode of action of these chemicals as well as by the recovery of these populations following the phase-out of these POPs (UNEP/WHO 2013).

Environmental risks are also associated with chemicals currently in commercial use. The release of nonylphenol and nonylphenol ethoxylate from textiles to waste water constitutes one such example (Swedish Chemicals Agency 2013a). When released into the environment, nonylphenol ethoxylate is degraded to nonylphenol, which is persistent, may accumulate in biota and harmful to aquatic organisms. Although these substances are restricted for use within the EU, imported articles, primarily textiles, have been identified as a major source to the presence of these substances in EU aquatic environments, e.g. in Sweden (Månsson et al. 2008).

2.2 RISK ASSESSMENT AND MANAGEMENT PRACTICES

In the risk assessment process, scientific data concerning the toxicity and exposure of a chemical are combined to draw conclusions about health or environmental risks. Regulatory risk assessments of chemicals are carried out as the basis for decisions concerning the approval, restriction or phase-out of chemicals on the market. However, risk management and policy decisions do not only consider the outcome of the risk assessment, but in addition also takes into account political, economic, social and technological aspects (Leeuwen and Vermeire 2007). Figure 2 visualizes how scientific data feed into the different steps of the risk assessment process and how this process is connected to risk management.

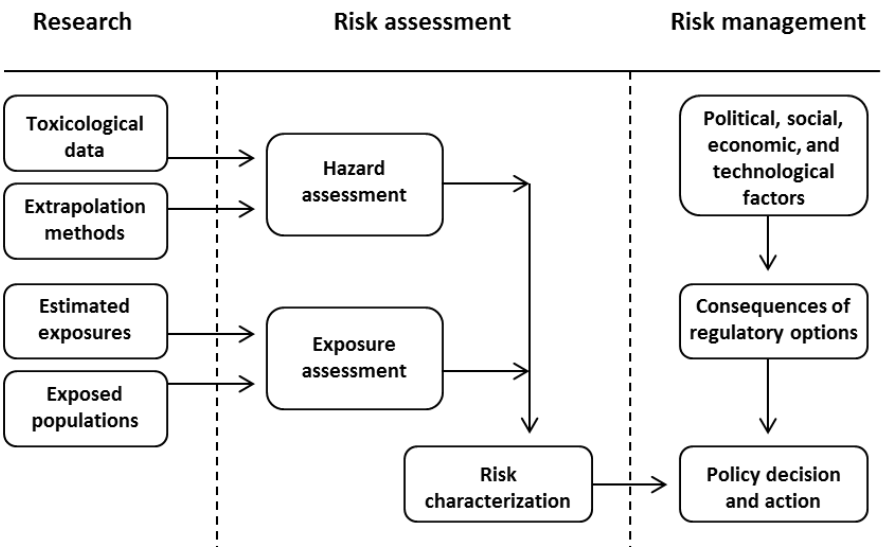

Figure 2: The structure of the risk assessment process and its connection to risk management and policy decision-making. The figure is modified from NRC (1983).

Risk assessments are often portrayed as purely scientific. However, in practice they are constantly framed by different normative assumptions. Risk assessments may therefore result in different conclusions between assessors depending on e.g. differences in expertise and experience (Beronius et al. 2010). In order to enable identification of the reasons behind different assessments, transparency is needed. To in-

crease the transparency of the process it has been argued that underlying assumptions should be made explicit (Wandall 2004).

2.2.1 The risk assessment process

A chemical risk assessment is a process performed with the overall objective to protect human health and/or the environment. Conducting a risk assessment entails a structured review and evaluation of data for identifying and characterizing the risk of adverse health or environmental effects at relevant exposure levels.

The risk assessment consists of three main parts; hazard assessment, exposure assessment and risk characterization. This conceptual framework is the same for both health and environmental risk assessment, although there are some differences in practices within each of these parts. A major difference, however, regards the aim. While health risk assessments are carried out with regard to protecting the most sensitive individuals in a population or sensitive sub-population, environmental risk assessments aim to prevent harm on the population-level in order to ensure that the function of ecosystems is protected.

Since the work related to risk assessment issues within this thesis is focused on the health risk assessment process, the components of that process are briefly described below. Guidance documents from regulatory agencies were used as references for describing the health risk assessment procedure (ECHA 2011; ECHA 2012; WHO/IPCS 2010; 2009).

The **hazard assessment** first seeks to identify the type and nature of potential adverse effects of the chemical in question (hazard identification). This is followed by the identification of the critical effect, which is the most sensitive adverse effect of relevance for human health (hazard characterization). The critical effect is further characterized by studying the relationship between doses and response. From the dose-response relationship, a point of departure (PoD) is identified for the critical effect, such as a no observed adverse effect level (NOAEL) or a lower confidence limit of a benchmark dose (BMDL), denoting the highest dose level not considered

to exert significant adverse effects in the test species. The PoD is then sometimes divided by assessment factors (also called uncertainty factors) to derive health-based guidance values, such as a tolerable daily intake (TDI), a derived no effect level (DNEL) or a reference dose (RfD), considered to indicate "safe" exposure levels for humans.

Data from animal (*in vivo*) toxicity studies are commonly used as the basis for drawing conclusions about human health risks. One important reason for this is that *in vivo* studies are performed under controlled, experimental, conditions. In contrast, epidemiological studies (i.e. studies of humans) are observational. Epidemiology can provide highly relevant information to a risk assessment, but due to the many confounding factors in such studies it may be difficult to establish clear links between health impacts and exposure to specific chemicals based on epidemiological data alone (Faustman and Omenn 2001). Uncertainties inherent in the results are for example due to the fact that humans are exposed to an uncontrolled mixture of chemicals, to differences in life style habits and genetic traits, and time latencies in the occurrence of negative health outcomes. Studies in cells or tissues (*in vitro* studies) can provide important mechanistic information to the risk assessment. *In vivo* animal tests are however often considered crucial for risk assessment since they investigate effects in intact organisms, thus providing relevant information for assessing risks to human health.

To extrapolate results from animal models to humans, assessment factors are usually applied to account for e.g. differences between and within species, differences in exposure duration and uncertainties due to lack of data (Leeuwen and Vermeire 2007).

In the **exposure assessment**, sources and levels of exposure of the chemical are identified. Exposure levels in human populations can be estimated for different exposure scenarios based on models and/or measurements. Measurements can include analyzing concentrations of a substance in e.g. food, dust and air, which can then be combined with data on intake of e.g. certain food items or respiration rates. Internal concentrations of a substance can also be measured, e.g. in urine, blood or breast milk, to estimate the total exposure of the substance, or its metabolites.

The final step is the **risk characterization**, which is a qualitative or quantitative estimation of the probability of the incidence of adverse effects under defined exposure conditions. Commonly, a comparison is made to see if the estimated human exposure levels exceed the derived "safe" levels.

2.2.1.1 Weight of evidence and systematic review

As described above, the hazard assessment entails the identification and characterization of a critical adverse effect, commonly identified from one or a few key toxicity studies. Thus, the decision to approve or restrict the use of a chemical may then in practice be based upon the results presented in a single study. However, in recent years, the importance of making use of all available data instead of focusing on evidence from one key study has been highlighted (Koustas et al. 2014; Rooney et al. 2014; UNEP/WHO 2013). The approaches used for the assessment of whole data sets are often referred to as weight of evidence (WoE) evaluation or systematic review (SR). Although these terms may have different meanings in different contexts and disciplines, in particular WoE, which is seldom clearly defined, they constitute processes for summarizing, synthesizing and interpreting a body of evidence for drawing conclusions, e.g. about the health risk associated with the exposure to a chemical.

2.2.2 Evaluation and reporting of toxicity data for risk assessment

2.2.2.1 Reliability and relevance

In the risk assessment process, available toxicity data are reviewed and evaluated in order to identify and characterize the hazardous properties of the compound. Different types of data may be used for this purpose, including information obtained from *in vitro*-, *in vivo*- or epidemiological studies. As mentioned above, data from *in vivo* toxicity studies are commonly used as the primary source of information in the health risk assessment process if available.

The evaluation of toxicity studies entails the assessment of their reliability and relevance. The reliability evaluation aims to assess the inherent "quality" of the study by e.g. considering the reproducibility of the results. According to REACH guidelines, reliability relates to "the way the experimental procedure and results are described to give evidence of the clarity and plausibility of the findings" (ECHA 2011). The relevance evaluation should assess whether the study is appropriate for investigating the risk assessment question under investigation, e.g. whether the effects or exposure scenarios studied are relevant for evaluating the risk to human health (ECHA 2011). What is considered relevant is thus context-dependent.

2.2.2.2 Standard and non-standard studies

Toxicity studies conducted according to internationally standardized test guidelines, such as the Organisation for Economic Co-operation and Development (OECD) test guidelines (TGs), and Good Laboratory Practices (GLP) are commonly by default considered to provide data adequate for regulatory risk assessment purposes (ECHA 2011). Standardized TGs and GLP have been put in place to promote high reliability of the test results, but they will not ensure the relevance of the study. Recent investigations have emphasized that there is a need to facilitate the use of non-standard studies in regulatory risk assessment (Ågerstrand et al. 2011a; Ågerstrand et al. 2011b; Myers et al. 2009). Such studies are often conducted using novel methods and endpoints and may be more sensitive and relevant than current standardized methods for investigating certain effects. This has been especially discussed with regard to EDCs, where standardized test methods have been argued to be inadequate for identifying most types of endocrine-disrupting effects. Information from non-standard studies could therefore provide critical data and fill information gaps in the risk assessment (Kortenkamp et al. 2012; Zoeller et al. 2012; Beronius et al. 2013).

The advantage of considering all adequate data, i.e. reliable and relevant, in regulatory risk assessment is however being addressed by regulatory agencies. For example, the European Chemicals Agency (ECHA) recommends registrants under REACH to make full use of all existing and relevant information in the registration process (ECHA 2013). However, even though there is regulatory acceptance of non-

standard data, the method for data evaluation that is commonly recommended by regulatory agencies does not consider the relevance of the study and will systematically attribute more weight to studies conducted according to standardized TGs and GLP (ECHA 2011; Beronius et al. 2014).

2.2.2.3 Reporting

One reason why non-standard studies are not used to the same extent as standard studies in regulatory risk assessment may also be due to insufficient reporting, from a regulatory perspective, concerning the study design, performance and results (Alcock et al. 2011; Hengstler et al. 2011; Beronius et al. 2013; Ågerstrand et al. 2014).

Since academic research may be performed for other purposes than feeding information into the regulatory process, non-standard research studies may be reported in a way that makes them less useful for risk assessment. Clear guidance for how to report such studies has therefore been suggested in order to facilitate their use in regulatory risk assessments (e.g. Ågerstrand et al. 2011b; Kilkenny et al. 2010).

2.2.3 Regulating chemicals in consumer products within the EU

As mentioned above, the outcome of the risk assessment is used as the basis for policy decisions to protect human health and/or the environment against harmful effects of chemicals. Risk management strategies can vary substantially in objective, scope, design and effectiveness. With regard to the use of chemicals in consumer products, risk management options include bans or restrictions of certain substances, mixtures or uses, and requirements, such as to disseminate information about the hazardous properties of chemicals to buyers and users. All risk management measures within EU chemicals control should rely on the precautionary principle according to the EU environmental policy (EU 2010).

While some chemical sectors are relatively well-regulated, regulations of industrial chemicals, and in particular the use of chemicals in articles, have been criticized for

not being protective enough with regard to human health and the environment. Some risk management strategies within EU chemicals regulation that intend to control the use of chemicals in articles are briefly described and discussed below.

2.2.3.1 REACH

During the last decade EU chemicals legislation has been renewed (Swedish Chemicals Agency 2012). When REACH went into force in 2007 it replaced about 40 pieces of chemicals legislation and thereby also dissolved the previous differences in requirements for what was called ”existing” and ”new” chemicals. Important reasons behind the development of REACH were that data on chemical properties should be required for all industrial chemicals, irrespective of the date of their entry to the market, and that the responsibility for assessing the risk of the chemicals was to be shifted from authorities to the chemical producers and importers (Rudén and Hansson 2006; Swedish Chemicals Agency 2012).

It has, however, been highlighted that a central problem in chemicals control is still that the required data on toxicological and ecotoxicological properties of chemicals may be insufficient for enabling a robust health or environmental risk assessment (Rudén and Hansson 2010; Swedish Chemicals Agency 2013b). The data required by REACH to be submitted to ECHA is volume-dependent; the higher the production volume of the substance, the more information about the substance is required. For chemical substances produced or imported in less than 1 ton per producer or importer and year no data is required and for substances in the tonnage band between 1 and 10 tons the data requirements are very limited. The data required for a large number of chemicals may thus not provide a sufficient basis for these chemicals to be adequately risk assessed or classified according to the hazard criteria laid down in the European regulation on classification, labelling and packaging of substances and mixtures (CLP) (EC 2008). The CLP hazard classifications are central in EU chemicals regulation as they are often used as the basis for prioritizing substances to be restricted or in other ways regulated. Further, regardless of production volume, the information requirements under REACH have been identified to be insufficient with regard to the identification of potential health effects of EDCs. Although

certain endocrine-related effects may be identified through current requirements, REACH does not include specific requirements with regard to endocrine disruption that will ensure that such effects are systematically tested for (Swedish Chemicals Agency 2013b).

Information about the chemical content of articles is rarely available to regulators, professional buyers, or consumers (Swedish Chemicals Agency 2011a; Molander and Cohen 2012). The assessment of health and environmental risks associated with the use of chemicals in consumer articles may thus be hampered by the lack of important information. The chemical safety assessment (CSA) that is required as part of the registration under REACH for hazardous chemicals produced or imported in 10 tons or more annually will generate such information for certain uses (EC 2006). Depending on how this requirement is being implemented, the CSAs have the potential to be important in contributing to the understanding of the often complex risks associated with hazardous chemicals in articles.

The identification of substances of very high concern (SVHCs) and their entry into the so-called candidate list under REACH is an important process for risk reduction of chemicals in articles. A substance may be identified as a SVHC if it meets the hazard criteria as carcinogenic, mutagenic or toxic for reproduction (category 1A or 1B), is persistent, bioaccumulative and toxic (PBT), very persistent and very bioaccumulative (vPvB), or identified as a substance "of equivalent level of concern" (EC 2006). EDCs have been identified to be of equivalent level of concern, but since no general definition of what should constitute an EDC has been agreed upon for EU regulatory purposes, no criteria for the identification of EDCs have yet been established and implemented in EU chemicals legislations. The European Commission should have announced criteria to identify EDCs by the end of 2013 (EC 2012), but it has been delayed. The forthcoming criteria for identifying EDCs will be of importance for the regulation of these compounds in consumer products.

SVHCs are intended to gradually be subject to authorization, which means that producers and importers need to apply for authorization of specific uses. If the risk associated with that use cannot be adequately controlled the authorization may not

be granted (EC 2006). Besides being the basis for the authorization process, the candidate list is also a tool for increasing and disseminating information about the presence of SVHCs in articles, particularly in the supply chain, but also to consumers upon request (EC 2006).

Since many supply chains are global, the information requirements related to the SVHCs will have impact also outside the EU. Although putting an SVHC on the candidate list does not automatically encompass any use restrictions, the list has been identified as influential in companies' work on substitution. The fact that the candidate list is regularly updated promotes chemical companies to work proactively with substitution and to find out the chemical content of their articles. (Swedish Chemicals Agency 2011a)

2.2.3.2 Product-specific directives

In addition to REACH, a number of product-specific legislations have also been implemented or updated during the last decade in the EU. These legislations regulate chemicals in different categories of articles, such as toys, electrical and electronic equipment, packaging materials and vehicles. Such product-specific rules have emerged gradually as a response to indications or occurrences of health or environmental problems. This reactive process has contributed to making EU chemicals legislations diverse and sometimes incoherent (Swedish Chemicals Agency 2011a).

3 METHODS

The work presented in this thesis was carried out as a series of literature studies. The literature mainly comprised of (1) existing and proposed regulatory acts, (2) guidance documents, and (3) toxicological studies published in the peer-reviewed scientific literature. The literature material used for the different studies of this thesis were systematically compared and analyzed.

The information used for the qualitative and quantitative analyses performed in **Papers I and II** was identified from legislative and guidance documents, and were systematically gathered in Microsoft Word and Excel tables for the comparisons.

In **Paper II**, a principal component analysis (PCA) was also conducted to investigate chemical variation between substances regulated by the legislations under scrutiny. A PCA is a data extraction technique suitable for pattern recognition analyses, where the variance of a set of variables is explained by a number of independent orthogonal variables, i.e. principal components (PC) (Abdi and Williams 2010). This way, a data set comprised of a large number of variables can be explained by a much more limited number of PCs. The names, CAS numbers and molecular structures of the chemicals were compiled in a database for the analysis. The PCA was performed by collaborative partners with expertise in the area, PL Andersson and A Rybacka, at Umeå University.

The evaluation criteria and reporting checklist proposed in **Paper III** were developed based on requirements and recommendations identified from relevant OECD toxicity test guidelines, as well as on previously published methods and guidelines for evaluating reliability and relevance of toxicity studies. The literature material was complemented with feedback from experts in toxicity testing and risk assessment in order to develop scientifically sound, relevant and user-friendly evaluation criteria and reporting guidance. The experts represented a broad range of international actors, including research institutions in Europe and the United States, the Swedish Chemicals Agency and the U.S. Food and Drug Administration (US FDA).

The Health Assessment Workspace Collaborative (HAWC) software was used for systematic extraction and collection of the toxicological data used for the analyses in **Paper IV**. HAWC is a modular web-based interface that aims to facilitate the work to be performed during different steps of the health risk assessment process (https://hawcproject.org/). The data extracted from the toxicity studies to HAWC were then summarized and presented using the visualization tools provided by this software. The evaluation of the reliability of the studies included in **Paper IV** was performed according to the criteria for *in vivo* toxicity studies developed by Beronius et al. (2014) and presented in Paper **III**.

4 RESULTS AND DISCUSSION

4.1 MANAGING RISKS OF CHEMICALS IN ARTICLES WITHIN THE EU

4.1.1 "Narrow-and-sharp" *and* "broad-and-blunt"

In **Paper I** it was examined what strategies are in place for regulating risks associated with hazardous chemicals in consumer articles in the EU. The legislations included in the comparative analysis, i.e. the Toys Safety Directive, the Restriction of Hazardous Substances (RoHS) Directive and REACH, were found to differ in several aspects, including which substances are targeted for regulation, the kind of requirements and restrictions applied to the targeted substances, and what information is provided to consumers with regard to chemical properties and content in the different article categories. One important difference concern whether the rules set out in these legislations apply to chemicals in imported articles or not. The Toys Safety Directive and the RoHS Directive apply both to articles that are produced within the EU and to those imported. However, imported articles are exempted from the authorization requirement under REACH, which constitute the key process for regulating SVHCs. In a recent report it was investigated how the REACH regulation could be modified to increase the level of protection of human health and the environment against impacts caused by SVHCs in articles (UBA 2014). Interestingly, it was concluded that one option would be to extend the authorization requirement to also cover imported articles incorporating SVHCs, and that such a modification of the legal text would not be incompatible with international trade laws. Since a large share of the articles consumed in the EU are imported from non-EU countries with less stringent chemicals regulation, the benefit of extending the authorization requirement to apply to SVHCs in imported articles were pointed out in **Paper I**, as well as in **Paper II** (see below).

Naturally, some of the differences identified between these legislations are related to their respective aim and the context in which they were developed and passed. The

differences, however, have the consequence that the same chemical may be regulated differently when used in different types of articles. Since many chemicals are used in numerous consumer applications, restricting a hazardous chemical or group of chemicals for one specific use, e.g. in certain toys, may not constitute a sufficient protection if the population intended to be protected, in this case children, continue to be exposed to these chemicals via other products and articles (Swedish Chemicals Agency 2015).

One main conclusion in **Paper I** was, however, that product directives are important complements to REACH because they can be more straight-forward and targeted in their restrictions. It was therefore suggested that it should be evaluated whether product-specific directives could be suitable also for other types of consumer products where hazardous chemicals are present and the use is widespread, such as textiles and building products. The need to extend the rules concerning the use of chemicals in textiles has thereafter been discussed, and different options on how to do this have been suggested, one being to introduce restrictions and information requirements into the already existing directive for labelling of textiles (Swedish Chemicals Agency 2013c).

4.1.2 A life cycle perspective to EU chemicals management

The EU environmental policy states that environmental damage should be rectified at source and that preventive actions should be taken according to the precautionary principle (EU 2010). Translated into the context of chemicals in articles, those principles could arguably imply that the input of hazardous chemicals into articles should be avoided or minimized in order to prevent problems from arising at the "end-of-pipe", e.g. posing risks to and via the environment. Against this background, **Paper II** investigated to what extent the restrictions and requirements pertaining to chemicals in articles in REACH were coherent with the chemical restrictions and requirements in the Sewage Sludge Directive (SSD) and the Water Framework Directive (WFD), respectively. The coherence analysis showed that the majority of the chemicals or groups of chemicals that were prioritized for phase-out under the WFD or for concentration restrictions in sludge and soil under the SSD

were allowed to be used in articles according to REACH. Incoherencies in which substances are prioritized and differences in the level of restriction between REACH and the SSD and WFD may thus constitute a possible obstacle for reaching environmental goals. It is argued in this paper that, in order to minimize risks associated with chemicals in articles to or via the environment, and at the same time enable recycling of materials free from hazardous substances, (1) the prioritization of which substances to be regulated in articles under REACH should to a greater extent take into account substances that have been identified as priority substances by the WFD or through other means as posing a risk to or via the environment, (2) suppliers should be required to declare the chemical content of articles to make the tracing and management of the sources of many environmental pollutants easier, and (3) the authorization requirement under REACH should also target SVHCs in imported articles.

4.2 IMPROVING RISK ASSESSMENT PRACTICES

Papers I and II identified shortcomings and inconsistencies in EU regulations with regard to chemicals in articles. In order for policy decisions concerning chemical risk reduction to be sharp and targeted, the toxicity data used as evidence for drawing conclusions about the health or environmental risk need to adequately identify and describe the effects of the tested chemical.

4.2.1 Facilitating the use of non-standard studies in regulatory risk assessment

It has been argued that current risk assessment practices need to be improved, e.g. by making better use of (eco)toxicity studies not conducted according to any standardized TGs or GLP (Myers et al. 2009; Ågerstrand et al. 2011b). As mentioned above, this has especially been emphasized with regard to EDCs, since current standardized test protocols are not tailored for identifying most endocrine-related effects (Kortenkamp et al. 2012; Zoeller et al. 2012; Swedish Chemicals Agency 2013b).

The work presented in **Paper III** aimed to address this issue by proposing a method to facilitate the use of non-standard studies in regulatory risk assessment. To this end, a framework consisting of criteria for evaluating reliability and relevance of *in vivo* toxicity studies was developed (Figure 3). In contrast to previously published methods for study evaluation, the method presented in **Paper III** will not by default attribute more weight to studies performed according to standardized test guidelines, such as the method proposed by Klimisch et al. (1997), which is currently recommended by regulatory agencies (e.g. ECHA 2011). Further, the proposed framework for study evaluation also provides clear guidance for evaluating the relevance of studies. Most other publically available evaluation methods are mainly focused on reliability (e.g. Klimisch et al. 1997; Schneider et al. 2009).

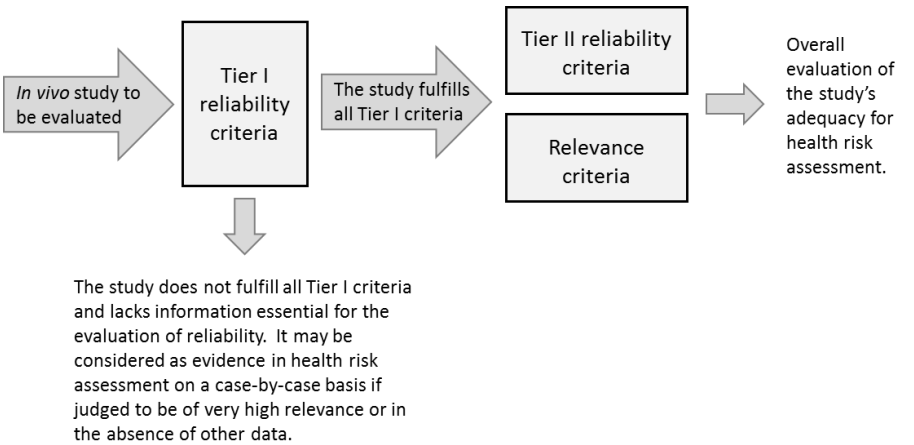

Figure 3: Structure of the proposed framework for the evaluation of toxicity study reliability and relevance with the purpose of determining the adequacy of individual studies for health risk assessment.

The reliability criteria were separated into two tiers, where Tier I comprise aspects considered most critical for evaluating study reliability (Figure 3). Thus, this two-tiered approach was aimed for quick identification of studies reliable enough and

sufficiently reported to be more thoroughly evaluated according to the Tier II criteria.

The criteria for study evaluation are publically available online at www.scirap.org as part of an initiative called the Science in Risk Assessment and Policy (SciRAP) (Molander et al. 2015). The web-based color-coding tool developed as part of **Paper III** for the purpose of applying the Tier II criteria can also be found at the SciRAP web-site. Since the publication of **Paper III**, the color-coding tool has been updated to also include the Tier I criteria. When using this tool, the evaluator addresses each criterion at a time by marking if the criterion is "fulfilled" in green, "partially fulfilled" in yellow, "not fulfilled" in red or "not applicable" in white. The Tier I criteria can only be judged as "fulfilled" or "not fulfilled". The reliability assessment can be exported to an excel sheet where the outcome is summarized in a color chart, which can be used as a basis for determining whether the study is of high, sufficient or low reliability. If red is the dominating color in the chart the conclusion may be that the study is not reliable enough to be used for risk assessment, while if it is dominated by green and/or yellow the study may be considered to be of high or sufficient reliability to serve as key or supporting evidence in a health risk assessment.

The purpose of developing a qualitative method was to enable a more flexible and transparent evaluation of reliability as compared to quantitative methods that sometimes assign a single numerical value to describe study reliability (e.g. Schneider et al. 2009).

In addition to the study evaluation framework, a checklist for reporting of *in vivo* toxicity studies was created based on the reliability and relevance criteria. The checklist thus contains items considered important to be reported from animal studies to enable an evaluation of the study's adequacy for health risk assessment. This list is intended to guide researchers on how to design, perform and report *in vivo* toxicity studies in a transparent way in line with regulatory recommendations. The reporting checklist, which is available at scirap.org, may also be used a template in

the review process as well as for providing supplementary information in scientific publications in case the publication space provided is limited.

The work presented in **Paper III** is a contribution to bridging the gap between academic research and chemicals regulation, i.e. by providing methods to facilitate the use of non-standard studies in regulatory risk assessment and, importantly, also to raise awareness among researchers regarding how to design and report their research in order to improve its use for regulatory purposes.

4.2.2 Combining new web-based tools for improved health risk assessment

In **Paper IV**, the reliability criteria suggested in **Paper III** were combined with tools of another web-based resource, the Health Assessment and Workspace Collaborative (HAWC), to explore a systematic and transparent methodology that could be used to select reliable and relevant information from *in vivo* research toxicity studies for regulatory risk assessment. *In vivo* toxicity studies investigating low-dose effects of BPA on the developing mammary gland were used for this investigation.

Effects on the mammary gland from exposure to BPA have been identified as being of potential concern to human health, most recently in EFSA's scientific opinion on health risks associated with exposure to BPA from foodstuffs (EFSA 2015). Data on these effects were however not used for the derivation of the new temporary tolerable daily intake (t-TDI) for BPA in the EU. Effects on the mammary gland were therefore considered to be of interest to further characterize in terms of type of effects investigated and reported and their distribution within the low-dose range related to the updated TDI.

Results from the mammary gland studies were extracted to HAWC, in which different visualization features were used for characterizing the results. Any differences in the type of mammary gland effects and their distribution within the low dose range were investigated by comparing the results of the whole mammary gland data set to

only those studies judged as most reliable according to the reliability criteria proposed in **Paper III**, here referred to as the SciRAP criteria.

This investigation showed that the five studies assessed as most reliable according to the SciRAP criteria to a large extent represented both the type of effects presented in the whole data set, as well as their distribution in the dose interval. Thus in conclusion, no clear relationship could be identified between the reliability of the studies as assessed according to the SciRAP criteria and the type of mammary gland effects reported or their distribution within the low dose range, respectively.

Paper IV provides an example of how these recently developed web-based tools aiming to promote systematic and transparent chemical risk assessment can be combined to identify particularly sensitive effects from reliable studies of relevance to consider for risk assessment purposes. The HAWC extraction and visualization features and the SciRAP reliability criteria were also identified as suitable tools for summarizing and evaluating data in a systematic review (SR) or weight-of-evidence (WoE) approach, currently promoted for improved chemical risk assessment.

Further, the investigation presented in **Paper IV** showed that certain information related to study design were not reported for the majority of the mammary gland studies. Poor reporting of a study will reduce its reliability, and thus hamper its use in risk assessment. As has been highlighted before, the communication needs to be strengthened between regulators and researchers, as well as journal editors, on how to evaluate and report research studies to facilitate their use in regulatory risk assessment (Ågerstrand et al. 2014).

An important outcome from applying the SciRAP reliability criteria to an actual set of toxicity studies was the identification of further developments needed to improve the SciRAP evaluation method. It was for example indicated that the Tier I criteria may need to be revised in order to avoid excluding studies that would perform well according to the Tier II criteria. A “ring test” is currently ongoing to let different categories of intended end-users, including from authorities, academia and industry, test and evaluate the usability of the SciRAP criteria and the color-coding tool in

order to further develop and improve them. Currently about 50 participants from the US, Asia and Europe have provided their feedback.

An increasing number of chemicals are being identified for having endocrine disrupting properties (UNEP/WHO 2013), many of which are used in everyday consumer products. Thus, the results presented in **Paper IV**, as well as in **Paper III**, which may have most impact with regard to the risk assessment of EDCs, contribute knowledge that can be used for better targeted policy decisions with regard to reducing risks associated with chemicals in consumer products.

5 CONCLUSIONS

The overall conclusions and recommendations from this thesis work can be summarized as follows:

- A combination of regulatory risk reduction strategies, that are of both general character and specific in targeting chemicals in articles, are recommended to ensure that health and environmental risks associated with chemicals in articles are sufficiently managed. (Paper I)

- The life cycle perspective in chemicals regulation needs to be extended for chemicals control to be effective towards reaching EU environmental objectives. Minimizing the input of hazardous chemicals into articles will help ensure that environmental goals can be met and that waste and other end-products can be reused and recycled without harming human health or the environment. (Paper II)

- There is a need to facilitate the use of non-standard research studies in regulatory risk assessment since such studies could provide sensitive and relevant information, especially with regard to EDCs. To this end the SciRAP framework for evaluating reliability and relevance of non-standard *in vivo* toxicity studies, and reporting guidance for such studies, were developed. (Papers III and IV)

- Methods that facilitate the use of non-standard studies will strengthen the link between academic research and chemicals policy, and may in extension improve public health and environmental protection with regard to the use of chemicals in consumer products. (Papers I-IV)

6 FUTURE WORK

The method suggested in **Paper III** for systematic and transparent evaluation of *in vivo* toxicity studies is under further development. A ring test is currently ongoing, in which intended users of the study evaluation method are testing and evaluating the feasibility and usability of the evaluation criteria and online color-coding tool. The outcome of the ring test will provide valuable information for further development of this resource in line with the needs of the end-users.

Based on the feedback from the ring test and our own application of the evaluation criteria in **Paper IV**, guidance for how to interpret and categorize the results of reliability and relevance assessments performed according to the SciRAP criteria is planned to be developed. It will also be investigated how the SciRAP criteria for evaluating individual toxicity studies can be incorporated into a wider WoE or SR approach, in which data from all available studies identified for a specific risk assessment or research question are summarized, evaluated and interpreted as one body of evidence.

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