KEMI
Swedish Chemicals Agency

Increasing children's protection through REACH

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KEMI
Swedish Chemicals Agency

The Swedish Chemicals Agency is supervisory authority under the Ministry of the Environment. We work in Sweden, the EU and internationally to develop legislation and other initiatives to promote good health and improved environment. We monitor compliance of applicable rules on chemical products and substances in articles and we carry out inspections. We review and authorise pesticides before they can be used. Our environmental quality objective is A non-toxic environment.

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Foreword

The Swedish Chemicals Agency (KemI) has been assigned by the Swedish Government to produce an Action plan for a toxic-free everyday environment 2011-2014 with special emphasis on children. The assignment includes reporting on measures and activities needed to tighten up the EU legislation to reduce the risk faced by people in their everyday lives on being exposed to hazardous chemicals. Reducing the chemical risks in everyday life is also a step towards attaining the parliamentary environmental objective of a Non-Toxic Environment.

In the Action plan, there is a particular focus on protecting children and adolescence better as they may be more vulnerable than adults to the effects of chemicals. The fact that children cannot independently choose their living environment also gives the society a particular responsibility to create a healthy environment free of harmful chemical substances.

This report has been conducted as part of a government assignment received by KemI to review the workings and possible future developments of REACH. The report focuses on the extent to which the REACH regulation takes into account children’s sensitivity to chemical exposure, describes a desired future scenario with regard to the protection of children under REACH and suggests a way forward in the form of an action plan.

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The views and recommendations expressed in this report are the author's own and do not reflect necessarily the view of KemI.

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Sammanfattning

På uppdrag av regeringen genomför Kemikalieinspektionen (KemI) en översyn av Reach-förordningen (EG nr 1907/2006) med syfte att identifiera eventuella brister och föreslå framtida insatser för ett ökat skydd för vår hälsa och miljön. Ett område inom detta uppdrag rör skyddet av barn. Det är känt att barn kan vara mer känsliga för kemikaliepåverkan än vuxna. Detta beror på den utveckling av komplexa organsystem och funktioner som sker tidigt i livet, med början under fosterstadiet och upp i vuxen ålder, men också på grund av skillnader i beteende mellan barn och vuxna. Att barn upptäcker världen krypandes och genom att stoppa saker i munnen är en anledning till att de kan exponeras för högre halter av fler kemikalier, till exempel via damm, jämfört med vuxna.

Denna rapport behandlar i vilken utsträckning Reach i dagsläget tar hänsyn till att barn kan vara särskilt känsliga för kemikalier, beskriver ett önskat framtidsscenario vad gäller skydd av barn under Reach samt föreslår en handlingsplan med åtgärder för att närma sig det önskade framtidsscenariot. Rapporten bygger på beskrivningar och analyser av Reach lagtext, dess bilagor och tillhörande vägledningsdokument.

Nutidsanalysen visar att det finns ett behov av att stärka de nuvarande restriktionerna och kraven i Reach för att säkerställa en hög skyddsnivå för foster, barn och ungdomar med avseende på kemiska hälsorisker. De åtgärder som föreslås i handlingsplanen, som syftar till att nå ett önskat framtidsscenario där barn skyddas från exponering för farliga kemikalier, innefattar bland annat att hänsyn tas till alla relevanta exponeringskällor med avseende på barn vid riskbedömning, att den information som krävs i registreringsprocessen innefattar barn-relevanta och känsliga endpoints, att kraven för särskilt farliga ämnen stärks och att nya metoder och ny kunskap, till exempel vad gäller hormonstörande ämnen och blandningars toxicitet, kontinuerligt efterfrågas respektive implementeras i lagstiftningen. Det är viktigt att poängtera att det i arbetet för ett ökad skydd av barns hälsa också ofta innebär att även vuxna skyddas bättre från att exponeras för skadliga kemikalier. Flera av de förslag som lyfts fram i handlingsplanen utgör därför generella riskminskningsåtgärder.

Summary

A government assignment with the aim of reviewing the workings and possible future developments of the Registration, Evaluation, Authorisation and restriction of Chemicals (REACH) Regulation (EC) No 1907/2006 is currently undertaken by the Swedish Chemicals Agency (KemI). One area within this assignment concerns the protection of children. It is known that children may be more sensitive to chemical insult than adults. This is due to the development of complex organ systems and functions during early life, but also due to differences in behavior between children and adults. The crawling and mouthing behavior of children is one reason why they may be exposed to higher levels of more chemicals, e.g. via dust, relative to adults.

This report addresses the extent to which REACH currently takes into account children's sensitivity to chemicals, lays down a desired future scenario as regards the protection of children under REACH, and finally it proposes an action plan with measures aiming to target the desired future scenario. The report builds upon descriptions and analyses of the REACH legal text, its annexes and associated guidance documents.

It is concluded that there is a need to strengthen the current restrictions and requirements under REACH in order to ensure a high level of protection of fetuses, children and young adults from chemical health risks. The measures proposed in the action plan include, among other things, that all relevant sources of exposure are taken into account when assessing the health risk of children, that the information and test methods required in the registration process cover sensitive endpoints of relevance to children, that the requirements concerning substances of very high concern are strengthened and that new methods and knowledge to a greater extent are continuously reviewed and used to update the regulatory requirements. The latter concerns e.g. endocrine disrupting compounds (EDCs) and mixture toxicity.

It is important to point out that the work for a better protection of children's health often also means protecting adults from exposure to harmful chemicals. Several of the proposals in the action plan are therefore not specific for children, but measures that will lead to a general risk reduction.

1 Background

The Swedish Chemicals Agency (KemI) has identified and emphasized that there is need to increase the protection of children from exposure to harmful chemicals in both national and EU chemicals legislations in several reports. In the action plan for a non-toxic living 2011-2014 it is for example highlighted that children and adolescents are more vulnerable to chemical exposure than adults and that special consideration should be taken to endocrine-disrupting chemicals (EDCs) due to the growing concern that exposure to these chemicals early in life may negatively affect health at later time points (Swedish Chemicals Agency, 2011a). Report 3/11 on chemicals in articles suggests risk reduction strategies and policy instruments with a special focus on children (Swedish Chemicals Agency, 2011b). Last year report 1/12 provides a comprehensive overview of EU chemicals legislations as well as identifications of shortcomings and needs for development of the EU rules (Swedish Chemicals Agency, 2012). These reports all emphasize that efforts are needed for further implementation and development of the Registration, Evaluation, Authorisation and restriction of Chemicals (REACH) Regulation (EC) No 1907/2006 (EC, 2006) in order to ensure a high level of protection of children's health.

The present report differs from previous reports in that it focuses on the extent to which the REACH regulation takes into account children's sensitivity to chemical exposure (section 2), describes a desired future scenario with regard to the protection of children under REACH (section 3) and suggests a way forward in the form of an action plan (section 4). This report has been conducted as part of a government assignment received by KemI to review the workings and possible future developments of REACH.

To scrutinize the REACH regulation with respect to the protection of children from harmful effects of chemicals is important because REACH is the main EU regulation providing data and risk assessments for industrial chemicals and which thereby constitutes the foundation for many, both regulatory and voluntary, decision processes, including restrictions. The data that are gathered in the REACH registration process will for example be used for hazard classification according to the regulation on classification, labeling and packaging of substances and mixtures (CLP) (EC, 2008). As the CLP classifications are used for prioritizing chemicals for restrictions in a number of different contexts, such as under the Toys Safety Directive, it connects back to the REACH registration process. It is thus of importance that the information requirements in REACH include data generation and/or gathering of already existing data that consider the sensitivity of children.

In addition to REACH there are a number of product-specific directives that more or less takes children's sensitivity to chemical insult into account. The most comprehensive and straight-forward directive that aims to protect children from chemical health risks is the Toys Safety Directive (EU, 2009), which restricts the use of hazardous chemicals in toys. However, children are not only exposed to chemicals via products and articles specifically intended for children, but also via everyday products and articles, such as textiles, building materials, paints and lacquers. The chemical risks associated with these everyday products are currently managed by REACH, why it is important that also REACH effectively protects children's health.

For the purpose of this report, the United Nations' definition of "child" in the Convention on the Rights of the Child has been used as a guiding principle. The Convention defines a child as a person below the age of 18, unless the laws of a particular country set the legal age for

adulthood younger (Article 1) (UN, 1989). As many organ systems and body functions are developing until adulthood, such as the nervous and immune systems, it is important to also include the sensitive periods of development that occurs during adolescence.

2 Analysis of the present situation

This section provides information on diseases and disorders identified to be of particular relevance for assessing chemical hazards and risks to children and to what extent REACH currently takes into account children's sensitivity for chemical substances in its requirements to generate toxicity information and characterize risks. More specifically, the following questions are addressed:

Effect data: information requirements and test methods

- To what extent and in what way are relevant and sensitive endpoints covered?
- To what extent and in what way are sensitive life stages covered?

Exposure assessment

- Children are exposed to chemicals to a greater extent than adults in relation to their body weight – how is this knowledge used in the regulatory setting?
- We are exposed to the same and structurally similar chemicals emitted from several sources – are all relevant sources of exposure taken into account in building exposure scenarios under REACH?

Assessment factors

- To what extent and in what way are assessment factors as recommended by REACH taking children's sensitivity to chemical exposure into account?

2.1 Diseases and disorders of relevance to children

Effects of relevance to investigate when assessing risks to children's health include adverse effects that are prevalent and/or increasing in children, especially effects that may be initiated during critical periods of development and for which chemicals have been identified as risk factors, such as reproductive impairments, certain cancers, obesity, diabetes, developmental neurotoxic effects, and asthma and allergies (WHO/UNEP, 2013; Karolinska Institutet (and references therein), 2013).

There is an increasing concern that a number of reproductive impairments on the rise are associated to chemical exposures. There is for example mounting evidence that the testicular dysgenesis syndrome (TDS), which encompasses poor semen quality, hypospadias (malformations of the penis), cryptorchidism (non-descending testes) and testicular cancer, can in part be associated to chemical exposure, in particular to chemicals with endocrine-disrupting properties (EEA, 2012). The semen quality of a large proportion of young men in some EU Member States is so poor that is has been stated to "seriously affect their chances of siring children" and it is estimated that up to 40 % of men's fertility is impaired in some countries (WHO/UNEP, 2013; EEA, 2012). There is a reported increase in boys born with congenital malformations, such as hypospadias and cryptorchidism. These male reproductive health disorders are believed to originate from disturbances during fetal and early postnatal development. (WHO/UNEP, 2013; EEA, 2012) Exposure to polybrominated diphenyl ethers (PBDEs) and mixtures including PBDEs and phthalates via breast milk has for example been

associated with cryptorchidism in male infants (Main et al., 2007; Krysiak-Baltyn et al., 2012).

Despite improved treatment and increasing survival rates for many forms of childhood cancer, it is still one of the most common causes of death among children and young people in Sweden. Twenty percent of all deaths among children aged 1–15 are caused by cancer (Hjern, 2012). These deaths are mainly associated with brain tumors and it is not clear to what extent these may be associated with exposure to chemicals. Strong rises are seen for endocrine-related breast and prostate cancers in the EU, where the most dramatic increases are seen in countries where these cancers have not before been highly prevalent. These are the most common forms of cancers in women and men, respectively, in most industrialized countries (EEA, 2012; Hjern, 2012). The majority of the breast cancer cases are considered to be the consequence of lifestyle factors, primarily increased life spans, and environmental exposures rather than genetic factors, which are estimated to constitute for approximately 10% of the cases (EEA, 2012). As in the case of the TDS-related male reproductive impairments, there is growing evidence that breast cancer tissues are most vulnerable for interference of exogenous, and in particular endocrine active, compounds during certain developmental periods, in this case during fetal development and puberty (EEA, 2012). According to the recent WHO report on the state of the art of endocrine-disrupting chemicals (EDCs), there is a trend of earlier onset of breast development in young girls, which is a risk factor for breast cancer. This trend is seen in all countries where this has been studied (WHO/UNEP, 2013). Increasing trends are also identified for other endocrine-related cancers, e.g. in the testes, endometrium, ovaries and thyroid (WHO/UNEP, 2013). However, epidemiological evidence is very scarce or missing for linking these cancers to exposures to EDCs.

A dramatic increase is also seen in the prevalence of obesity and type 2 diabetes across the world, including in the EU (WHO/UNEP, 2013). In Sweden, the percentage of overweight children has doubled during the last two decades, although the children consume less candy and soft drinks. Studies show that 15-20 percent of Swedish children are overweight and that 3-5 percent are obese. However, more recent reports indicate that the increase in overweight children is leveling off or may even have started to decline (Hjern, 2012). Studies have shown that chemicals may play a role in the induction of obesity and diabetes. Perinatal exposure to bisphenol A (BPA) has for example shown to increase body weight and adipose tissue, elevate serum insulin and impair glucose tolerance in rats (Somm et al., 2009; Wei et al., 2011).

The burden of neurobehavioral disorders in infants, children and adolescents, including thyroid diseases that may affect the development of the brain, is recognized as high and increasing in countries where these effects have been systematically monitored. During the last decade, evidence has increased supporting the involvement of the thyroid hormone in neurodevelopmental disorders in both humans and wildlife. Deficiencies of the thyroid hormone during pregnancy have been associated with reduced IQ, autism in children and attention deficit hyperactivity disorder (ADHD) (WHO/UNEP, 2013). In Sweden, for example, 3-5 percent of children of school age are estimated to fulfill all criteria for ADHD, and that an equal percentage of other children have milder symptoms of ADHD, i.e. fulfill some of the ADHD criteria. The prescription of drugs to treat ADHD in Swedish schoolchildren increased six-fold between 2001 and 2007. This is reported to mainly be due to changes in treatment approaches (Hjern, 2012). However, only for BPA there is a large number of experimental studies demonstrating that there could be an association between various behavioral effects, such as reduced learning and memory, anxiety-related effects and changes in social behavior, and exposure to often very low doses (i.e. at doses below the

NOAEL of 5 mg/kg bw/day used for deriving the current Tolerable Daily Intake (TDI) and Reference Dose (RfD) values for BPA) during pre- and perinatal development (Beronius et al., 2013).

Asthma and other allergies are the most common chronic childhood diseases in Sweden. The incidence of allergic disorders has significantly increased and become more widespread since the mid-1900s. About 20 percent of all children are estimated to have had eczema for different periods of time during their pre-school years (Hjern, 2012). Skin sensitization that may result in eczema and contact dermatitis can be caused by for example allergenic fragrances, preservatives and other synthesized substances used in cosmetics and personal care products (Yazar et al., 2011). According to a comprehensive survey of children's environmental health conducted in 2011 by the Institute of Environmental Medicine at Karolinska Institutet, in collaboration with the National Board of Health and Welfare and Statistics Sweden, sensitivity and allergy to cosmetics and personal care products are more common in girls than boys. The fact that more girls dye their hair is one reason for this, as many hair dyes are known to be strong skin sensitizers (Karolinska Institutet (Section 6 on skin allergy), 2013). There is increasing evidence that exposure to EDCs constitute an explanatory reason for the rise in immune-related disorders, including allergies, since the immune and endocrine system are closely connected. There are for example strong associations between exposure to phthalates and the rising incidence of asthma. These findings are supported by animal studies (WHO/UNEP, 2013).

2.2 Effect data: information requirements and test methods

2.2.1 Information requirements under REACH

Current chemicals regulations have been criticized for being ineffective in protecting human health, and lately especially with regard to their protection from exposure and potential effects from EDCs (e.g. Zoeller et al., 2012; Vandenberg et al., 2013). Taking a closer look at the information requirements under REACH adheres to this description. Table 1 provides an overview of the toxicity information/data that producers and importers of industrial chemicals are required to obtain, either through testing or gathering of already available information, and submit in the registration dossier to the European Chemicals Agency (ECHA) for the different tonnage bands. *No* indicates that the information is not required for a specific tonnage band, *yes* that the information is required, and *(yes)* that the information requirement could be waived, i.e. that submission of the required information can be omitted if it can be justified as not necessary or relevant.

	REACH toxicity data				
	<1t	>1t	>10t	>100t	>1000t
Carcinogenicity	no	no	no	no	(yes)
Reproductive toxicity (two-generation)	no	no	no	(yes)	(yes)
Reproductive toxicity (one-generation)	no	no	no	(yes)	(yes)
Subchronic (90d)	no	no	no	(yes)	(yes)
Subacute (28d)	no	no	(yes)	yes	yes
Screening for reproductive toxicity	no	no	yes	yes	yes
acute toxicity second route	no	no	yes	yes	yes
acute toxicity oral route	no	(yes)	yes	yes	yes
Mutagenicity (in vitro)	no	(yes)	yes	yes	yes
skin sensitization	no	(yes)	yes	yes	yes
skin + eye irritation	no	(yes)	yes	yes	yes

Table 1: Toxicity data required by REACH for the different tonnage bands.

Reproductive and developmental toxicity should be screened for at or above 10 tonnes per year according to the OECD Technical Guidance (TG) No. 421 (Reproduction/ Developmental Toxicity Screening Test) (OECD, 1995) or No. 422 (Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test) (OECD, 1996) unless sufficient and reliable information is already available and appropriate risk management measures are implemented or relevant human exposure can be excluded (REACH, Annex VIII, 8.7.1). These tests aim to provide information on effects on male and female reproductive performance, such as the gonadal function, mating behavior and conception (ECHA, 2012a). However, due to e.g. the short duration of these studies, the limited number of selected endpoints and the relatively small number of animals in the dose groups, these screening tests are primarily used for obtaining initial information on possible effects on reproduction and/or development and for identifying if there is a need for further testing. This also means that none of these tests generally produce enough data for classification as reproductive and developmental toxicants according to the EU regulation on classification, labelling and packaging of substances and mixtures (CLP).

For substances annually produced or imported in quantities of 100 tonnes or more, reproductive and developmental toxicity can be further evaluated. However, these data requirements are flexible and should be proposed by the registrant and thereafter decided by ECHA. For substances >100 tonnes a one-generation, prenatal developmental toxicity study according to the OECD TG 414 (OECD, 2001a) can be proposed (REACH, Annex XI, 8.7.2). If a previously conducted 28-day or 90-day repeated dose toxicity study has indicated adverse effects on reproductive organs or tissues a two-generation reproductive toxicity study can also be proposed, e.g. according to the OECD TG 416 (OECD, 2001b) (REACH, Annex XI, 8.7.3). TG 416 aims to provide knowledge of adverse effects on reproduction, parturition, lactation and the postnatal development of the offspring including growth and sexual development. Both TG 414 and 416 will generate data to which the CLP criteria for classification for reproductive and developmental toxicity are applicable.

REACH states that all new *in vivo* tests should be proposed by the lead registrant and approved by ECHA. In an analysis of more than 24 000 dossiers submitted for substances produced in more than 100 tonnes per year, ECHA concludes that REACH has, so far, generated a limited number of new experimental *in vivo* studies. The dossier analysis shows that among the new *in vivo* tests (i.e. tests performed in 2009 or later) only 10 reproductive toxicity tests and 24 tests for developmental toxicity were included. This analysis also concludes that the testing proposals have so far been fewer than expected. (ECHA, 2011a)

Carcinogenicity studies may be proposed by the registrant for substances in the highest tonnage band (>1000 tonnes) if the substances have a widespread dispersive use or if there is evidence of frequent or long-term human exposure, and the substances are classified as germ cell mutagens or there is evidence that they are able to induce hyperplasia and/or pre-neoplastic lesions (REACH, Annex X, 8.9.1). Standard carcinogenicity tests can be performed according to OECD TG 451 (Carcinogenicity studies) (OECD, 2009a) or TG 453 (Combined Chronic Toxicity/Carcinogenicity studies) (OECD, 2009b), although the latter is preferred since it will be more cost- and time-efficient, as well as reduce the number of animals, without compromising data quality (OECD TG 453, paragraph 12). The duration and dosing of these carcinogen studies is normally 24 months for rodents aiming at covering the majority of the animal's life span, beginning as close as possible after weaning. These tests generate data for a variety of endpoints, including body and organ weights, haematological data, incidence of any abnormalities, and neoplastic effects. These comprehensive tests can be used for hazard classification purposes. Although hormonally mediated cancers may be detected, these carcinogenic assays are not designed to identify EDCs. Hence, hormonal carcinogens will be difficult to identify under current information requirements.

The subacute "Repeated Dose 28-day Oral Toxicity Study in Rodents" (OECD TG 407) (OECD, 2008) and the subchronic "Repeated Dose 90-Day Oral Toxicity Study in Rodents" (OECD TG 408) (OECD, 1998) provide information on a broad range of health hazards possibly resulting from repeated exposure over limited periods of time. Both guidelines include endpoints of relevance to children. When the TG 407 was revised in 1998 it was updated with parameters to detect substances with (anti)estrogenic, (anti)androgenic, and (anti)thyroid (EAT) modes of action (OECD TG 407, paragraph 2). It is however emphasized in this TG that this assay cannot be used as a screening assay for endocrine activity as it is not comprehensive or sensitive enough to identify all endocrine-active substances, or even all substances with EAT modes of action. Absence of effects mediated via these modes of action can therefore not be taken as evidence that the tested substance is not interfering with the endocrine system (OECD TG 407, paragraph 6). Several of the endpoints included in TG 407 that are of relevance for identifying endocrine-active or disrupting chemicals are optional. In a recent report from the Danish Centre on Endocrine Disrupters it is proposed that these optional endpoints are made mandatory in order to strengthen the information requirements under REACH with regard to catching EDCs (Danish Centre on Endocrine Disrupters, 2013). TG 408 includes endpoints which allow for the identification of chemicals with potential to cause neurotoxic, immunological and reproductive organ effects, which may warrant more detailed studies to enable conclusions to be drawn for these effects (OECD TG 408, paragraph 4).

Data obtained from both TG 407 and 408 can be used for hazard characterization, including classification according to CLP, and risk assessment (OECD TG 407, paragraph 4; OECD TG 408, paragraph 3). However, the results from the TG 407 assay with regard to endocrine-mediated effects should not be used alone for drawing conclusions on risk, but as a piece of information in a weight of evidence approach (OECD TG 407, paragraph 7). It is suggested

that these results are seen in the context of the OECD Conceptual Framework for Testing and Assessment of Endocrine Disrupting Chemicals (OECD TG 407, paragraph 4). These internationally validated OECD guidelines for testing and assessment of EDCs are currently not implemented under REACH as part of the information requirements. However, even if they were, these OECD test methods would not capture the full, today known, range of endocrine disrupting effects as they are mainly focused on EAT effects and effects on steroidogenesis (WHO/UNEP, 2013; OECD, 2012a). There are thus many endocrine-related functions in the body involved in the development and control of vital processes that are not considered in current testing regimes. The identification and assessment of endocrine-related effects is hampered by the lack of internationally agreed upon and validated testing strategies that adequately cover sensitive and relevant endpoints. As is pointed out in the 2013 Berlaymont Declaration on Endocrine Disrupters, this is especially the case for hormonal carcinogenesis, female reproductive health, the metabolic syndrome, obesity and other neuro-endocrine effects (Berlaymont Declaration on Endocrine Disrupters, 2013).

The generation of information on developmental neurotoxicity (DNT) is not required in REACH for any tonnage band. This means that DNT effects are not, at least not systematically, being investigated under REACH. There is an OECD guideline for testing of DNT effects, TG 426 (OECD, 2007). However, a recent study shows that testing according TG 426 may overlook DNT endpoints that are more sensitive to endocrine-active compounds than those included in the assay (Beronius et al., 2013). Analyses in this study, conducted on forty-four peer-reviewed studies investigating DNT effects, showed that few of these studies observed any effects on motor activity, which is one of the endpoints required according to TG 426 and which is often used for screening for neurotoxicity. Instead, endpoints that are not included in TG 426, such as anxiety-related effects and social and sexual behaviors, were more often reported, especially in female offspring and at very low doses. More studies supporting these observations are needed before any strong conclusions regarding the implications for toxicity testing can be made. However, these results imply that subtle neurotoxicological effects may be overlooked in studies conducted according to TG 426.

The potential of substances to cause asthma and allergies is also of high relevance to test with regard to children's health as these effects are prevalent and increasing in the young population (Hjern, 2012). Tests for identifying sensitizing and irritant/corrosive effects are required for substances produced or imported at or above one tonne per year if they fulfill certain specified criteria[1]. These requirements only include skin allergy and not sensitization via inhalation (asthma).

In summary, few chemicals will be tested under REACH for effects identified as being of particular relevance to children. Required testing for these effects are limited to high-production-volume chemicals (>10 tonnes), except for certain immunological effects, or are not required to be tested for at all. Many of the effects reported and identified here to be of relevance to children, e.g. reproductive impairments, hormonal cancers, obesity and

[1] Substances obliged to these information requirements include non-phase-in substances, phase-in substances meeting the criteria in Annex III in accordance with Article 12(1)(a) and (b), and substances produced or imported in quantities of 10 tonnes or more (REACH, Annex VII). The criteria in Annex III states that these information requirements shall apply to (a) substances for which it is predicted by (Q)SARs or through other evidence that they are likely to meet the CLP criteria for carcinogenicity, germ cell mutagenicity or reproductive toxicity (category 1A or 1B) or the criteria for PBT and vPvB substances in Annex XIII of REACH, and (b) substances with dispersive or diffuse use(s), particularly where such substances are used in consumer mixtures or articles, and for which it is predicted by (Q)SARs or other evidence that they are likely to meet the CLP criteria for any health or environmental hazard classes.

behavioral effects, can be mediated through different endocrine mechanisms that are not currently covered by the REACH information requirements. Although certain endocrine-related effects may be identified through current information requirements and recommended standard test protocols, REACH does not include specific information requirements with regard to endocrine disruption. The Danish Centre on Endocrine Disrupters recently suggested an information/testing strategy for EDCs, which included both changes to current information requirements as well as the addition of new test methods. The suggested changes comprise e.g. an extension of TG 414 by including anogenital distance and malformations of external reproductive organs as endpoints and the replacement of the two-generation reproduction toxicity study (TG 416) with the one-generation reproductive toxicity study (TG 415). TG 415 is preferred over TG 416 because it includes a number of endocrine endpoints in the juvenile and adult F1 generation, which are not required in the two-generation study. TG 415 is also considered more sensitive than TG 416 as it requires an increased number of pups to be examined. As many effects of relevance for assessing children health risks may act via the endocrine system, the Danish proposals would thus also be beneficial in this respect.

It is noteworthy that tests for capturing these children-relevant health effects will likely only be performed for a limited number of substances and/or in a non-systematic manner despite that fact that these effects are among the effects that are emphasized in REACH as being of very high concern (i.e. carcinogenic, mutagenic, reprotoxic effects according to the CLP criteria and effects of “equal level of concern”, such as endocrine-disruption). The identification of substances of very high concern (SVHCs) is connected to different regulatory requirements aiming to ensure that risks associated with these effects are adequately controlled. However, as described above, it is foreseen that tests that could trigger these regulatory actions under REACH, in particular the information and authorization requirements that apply to SVHCs, will be performed only for a limited number of chemicals.

2.2.2 Sensitive life-stages

In addition to the relevance of the endpoints, it is also of importance that the information requirements under REACH cover windows of exposure during critical periods of development in order to identify chemicals of concern with regard to children. The testing should have a broad scope concerning exposure periods to enable identification of potential effects not already known to be of relevance for assessing risks to children’s health. Figure 1 shows the life stages during which the animals are exposed to the test substance according to OECD test guidelines applicable for obtaining the subchronic and chronic *in vivo* toxicity data as required by REACH for the different tonnage bands. Figure 1 also contains a list of endpoints identified as being of relevance to children. After each endpoint it is indicated within brackets which of the OECD standard tests, as listed and numbered (1 to 5) on the y-axis, are obviously covering these children-relevant endpoints.

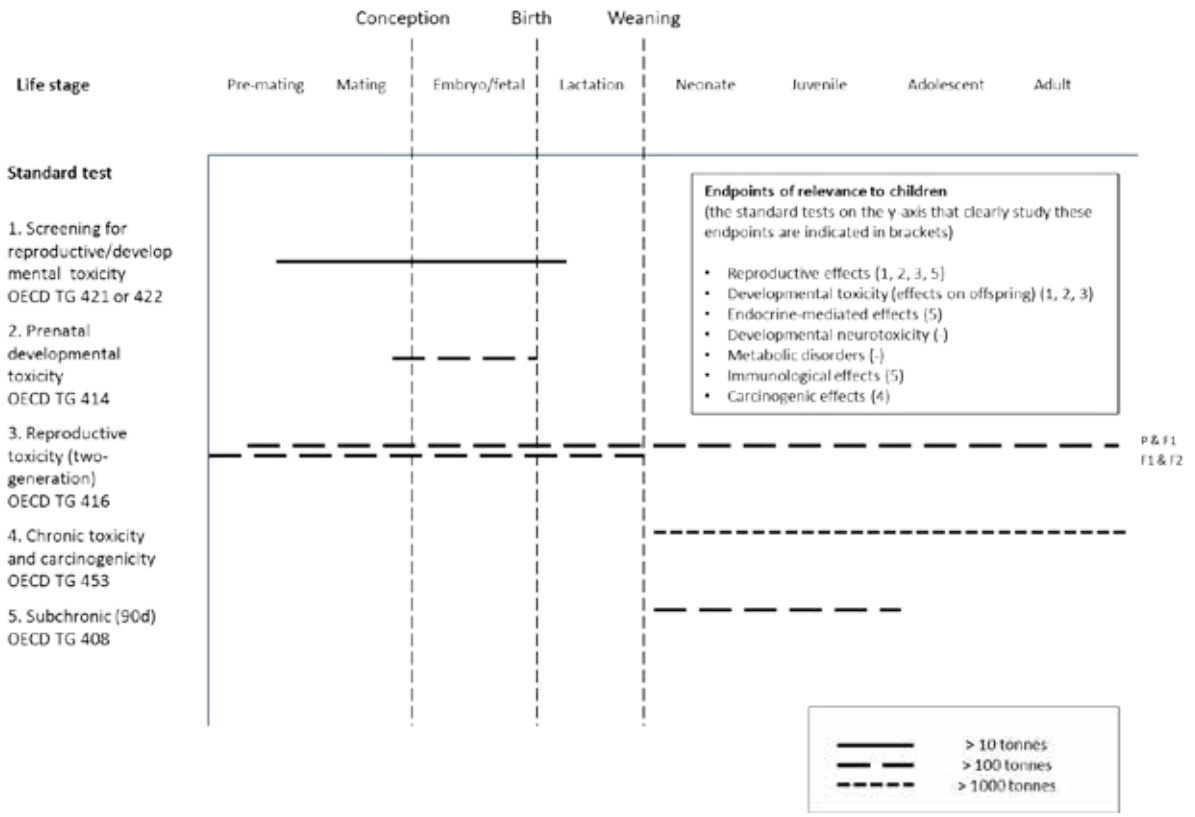

Figure 1: Exposure during different life stages in standardized test guidelines applicable for obtaining the in vivo (subchronic and chronic) toxicity data as required by REACH for the different tonnage bands.

The prenatal exposures in the reproductive and developmental screening tests (TG 421 and 422) cover certain sensitive periods of early development. However, as these tests are terminated only a few days after delivery of the pups, they are limited as tools for detecting manifestations of possible postnatal effects originating from prenatal exposures or the short period of postnatal exposure. There are a number of studies reporting associations between exposures to chemicals during critical periods of development and manifestation of (adverse) reproductive and developmental effects later in life, such as increased sensitivity to cancer in the mammary gland (WHO/UNEP, 2013). Delayed effects of exposure during critical periods of development are especially associated with endocrine-active compounds as normal functioning of the endocrine system is crucial for the development of most tissues and organ systems in the body.

Developmental and reproductive effects resulting from exposures during sensitive periods of development, including fetal development, perinatal life as well as puberty, will to a greater extent be detected by the more extensive tests, such as TGs 414 and 416, which may only be required for substances produced or imported at or above 100 tonnes per year. However, these tests are not specifically developed for identifying effects mediated via the endocrine system.

Information on the EAT-mediated effects that can be obtained by the subacute repeated dose toxicity study (TG 407) is of limited relevance for investigating and assessing hazards directed towards children as it does not cover the developmental periods most sensitive to these effects. TG 407 is not included in Figure 1 as it is not pre-defined in the guideline during which life stage(s) exposure to the test substance should occur.

The carcinogenic studies (TG 451 and 453) are comprehensive tests covering the majority of the postnatal life of the test animal. Notably the exposure period will not cover fetuses or pups pre-weaning which means that sensitive stages of development will not be covered by the exposure regimen. To fully understand the carcinogenic profile of a test substance it is important to also study if pre- and perinatal exposure to the substance could lead to (an increased sensitivity for) the development of cancer later in life.

Although the development of e.g. the nervous and reproductive systems continues up to adulthood, the developmental toxicity information as required by REACH is limited to pre- and perinatal exposure (Figure 1). Thus, there is an apparent risk that important information on possible developmental effects that are manifested in adolescents and adults or that are initiated during adolescence and adulthood are being overlooked.

In order to ensure that children's sensitivity to chemical exposures is adequately taken into account by the regulatory information requirements, there is a need for exposure regimens to cover to greater extent windows of heightened sensitive during development, including adolescence, and to subsequently evaluate as great range as possible of adverse and relevant effects that can manifest later in life. Effects to be evaluated thus also need to include endocrine-disrupting effects to a greater extent as well as developmental neurotoxic effects and inhalation sensitization currently excluded from the data requirements.

2.3 Exposure assessment

2.3.1 REACH guidance on children's exposure

Children are exposed to chemicals to a greater extent than adults in relation to their body weight. This is due to the fact that children eat, drink and breathe more than adults in relation to their body weight, as well as other differences in behavior. For example, the crawling and mouthing behavior of toddlers may also lead to exposure to higher levels of chemicals, e.g. via dust, relative to adults. (De Wit et al., 2012; Harrad et al., 2010) Studies have also indicated that levels of certain brominated flame retardants (BFRs) are higher in dust at day care centers than in homes and cars (Thuresson et al., 2012).

Due to differences in metabolic capacity, neonates and young children may furthermore metabolize toxic substances to a lesser or higher degree than adults leading to a different internal exposure in children than in adults. It has been indicated that the sometimes higher sensitivity of neonates to exposure to certain chemicals could be related to a very low metabolizing capacity (WHO, 2006).

In the REACH "Guidance on Information Requirements and Chemical Safety Assessment", Chapter R.15 on consumer exposure estimation, it is highlighted that the exposure pattern of children may be different from that of other sub-populations due to their crawling behavior and hand to mouth contact. It is also emphasized that "the children's small ratio of body size to surface area, compared to that of adults, may have a crucial effect on the exposure estimates". It is therefore stated that the exposure scenarios have to consider such exposure pathways and corresponding values for exposure determinants, such as body weight and skin surface area. (ECHA, 2012b).

In the section on oral exposure it is stated that this exposure route is of particular relevance to children as chemicals may migrate from articles as a result of sucking, chewing or licking. Another example of oral exposure especially relevant to children and that should be taken into

account in exposure estimations is the uptake of dust and soil. However, in the case of exposure via soil, consideration should be taken only if the substances in the soil can be related to emissions from consumer articles, such as textiles and building materials. (REACH Guidance, Chapter R.15).

Children, in particular small children, are also mentioned in the section on exposure to non-volatile substances. This is because house dust may present an important source of exposure to these substances and because of the mouthing behavior of small children. It is stated that small children's "exposure via house dust can account for about 50% of the total exposure" (Wormuth, 2006 in REACH Guidance, Chapter R.15). Exposure via house dust therefore needs to be considered in the chemical safety assessment (CSA). Hundred (100) mg has been proposed as a conservative estimate for house dust intake for children (Oomen, 2008 in REACH Guidance, Chapter R.15).

The guidance document presents modeling tools where these aspects can be included and references to further information on the subject. It is for example possible to assess exposure to non-volatile substances in dust, calculate exposure due to hand-mouth contact for some product/article categories (Section R.15.4.3), and there is a default value for the skin surface area of children that come into contact with different product/article categories (Table R.15-13). When using the modeling tools the registrant should check whether the default values need to be adjusted for them to be of relevance to children. One example that is given of when an adjustment of the default values may be applicable is that it sometimes might be reasonable to assume that a child ingests 100% of a substance in a consumer product or article in a single event. The algorithms that are integrated in the computer models are presented as well and can be used directly for estimating the exposure. Doing that increases the possibilities of adjusting the values. Some examples on how to use the algorithms are referred to and presented in reference databases, including how to estimate chemical exposure for school children using school bags, toy bags, erasers and pencil cases (REACH Guidance, Chapter R.15, p. 17; Appendix R.15-3).

In the REACH "Guidance on Information Requirements and Chemical Safety Assessment", Chapter R.19 on uncertainty analysis (ECHA, 2012c), guidance is provided on how to deal with uncertainty in the chemical safety assessment and methods are outlined for how to make an uncertainty analysis. The adequacy of the exposure scenario assumptions with regard to children are mentioned as a source of uncertainty. However, no specific guidance on how to deal with this uncertainty in particular is provided.

Although the REACH guidance on consumer exposure recognizes that children could be exposed to chemicals to a greater extent than adults in relation to their body weight, and provides some guidance and tools for how to take this into account in the exposure estimations, an investigation among EU member states and international organizations identified that there is a general need for improved guidance and methods for the exposure assessment of children (OECD, 2012b).

2.3.2 Sources included in the exposure scenarios

The REACH requirement to generate exposure scenarios as part of the CSA for hazardous substances produced in or imported to EU at or above 10 tonnes per year is limited to one use category at a time. Appendix R.15-1 of Chapter R.15 on Consumer exposure estimation provides a list of product and article categories which are (1) uses regulated by REACH, (2) generally considered to potentially result in significant exposures to consumers, and (3) for

which tier 1 consumer exposure estimations can be assessed using the ECETOC TRA consumer modeling tool. Each product and article category is divided into subcategories. One example of an article category with subcategories is "Plastic articles", which is further divided into "Plastic, larger articles (plastic chair, PVC-flooring, lawn mower, PC)", "Toys (doll, car, animals, teething rings)" and "Plastic, small articles (ball pen, mobile phone)". In the information provided about the ECETOC TRA tool it is stated that this list does not comprise all types of products and articles, and that registrants may have to adjust the default parameters to better fit the category of interest or directly use the algorithms provided in the guidance that are otherwise implemented in the TRA tool. However, the registrant is obliged to *consider* addressing combined risks arising from different uses of the registered substance in chapter 10 of the chemical safety report (CSR). This is advised if the same substance is used in "different consumer products or articles that could reasonably be expected to be used jointly and frequently by an average consumer" in order to avoid underestimations of the risk. This does not mean, however, that the registrant needs to carry out a risk characterization for uses of the substance that is not covered in the registrant's own registration. Therefore, the total exposure might still be underestimated if a particular registration only covers a part of the relevant uses and exposures.

2.4 Assessment factors

2.4.1 Consideration of children in setting assessment factors

The traditional assessment factor, in use in chemicals risk assessment since the 1950s, is 100. This factor is supposed to cover inter- and intraspecies differences (a factor of 10 respectively). It has also been proposed that the factors be divided into default toxicokinetic and toxicodynamic factors. Such a division offers the possibility of incorporating mechanistic information and to exchange the default sub-factors with data-derived factors (Falk-Filipsson et al., 2007).

Children are generally more sensitive to chemical exposures as complex organ systems and functions are under development, beginning during the fetal stage and continuing up to adulthood. The immune-, nervous- and reproductive systems are particularly vulnerable to the interference of exogenous compounds (Karolinska Institutet, 2013). With regard to toxicokinetics, some empirical data exist that indicate that the difference in toxicokinetics between adults and small infants (>2 yrs of age) in a significant number of cases exceeds the standard assessment factor for kinetics of 3.2 (Dorne, 2010).

Additional assessment factors for children have been proposed by several agencies (Reviewed in Falk-Filipsson et al., 2007). The US EPA´s working group for pesticides risk assessment proposed for instance a factor of 10 for children if a complete developmental toxicity database is available. When such data is missing or incomplete an extra safety factor in addition to the default inter-individual 10-fold uncertainty factor was considered appropriate. The size of the uncertainty factor would depend on the size and nature of the database (US EPA, 1999).

A similar conclusion is reached by Falk-Filipsson et al (2007), where the authors conclude that an extra inter-individual extrapolation factor for children (1–10) is motivated when the following criteria are fulfilled:

> "There are indications, obtained from for example experiments in adult animals, epidemiological studies, in vitro experiments and/or structure–activity relationships (SARs), of effects on organ systems and functions under development and maturation

> in early life and there are deficiencies in the database on such effects in young animals. Particular attention should be paid to effects on the nervous, reproductive, endocrine and immune systems and also the metabolic pathways, all of which in part develop new functional properties during childhood."

Extra factors have also been proposed for severe and irreversible effects (Falk-Filipsson et al. (and references therein), 2007), but no guidance was given on how to combine different aspects of sensitivity and severity.

The REACH guidance on characterization of dose-response for human health, Chapter R.8 (ECHA, 2012a), states that the default assessment factor of 10 for intraspecies variability is usually sufficient for protecting also children. However, it is recognized that children as well as unborn babies, i.e. the pregnant woman, may be more susceptible to adverse effects of a substance due to differences in toxicokinetics and toxicodynamics and due to specific exposures, e.g. via toys, and that such increased sensitivity should be considered when establishing a Derived No Effect Level (DNEL) (REACH Guidance, Chapter R.8). REACH opens up for an extra factor for developmental toxicity (size of factor is not specified):

> "[…]for the $DNEL_{development}$ calculation, the developing offspring should be the focus of attention […] and a higher overall assessment factor may be warranted leading to a lower DNEL value in order to protect against possible developmental toxicity." (REACH Guidance, Chapter R.8).

The REACH guidance furthermore refers to the US EPA and their recommendations to add an extra assessment factor of 10-100 for protecting children when the following criteria are (both) fulfilled:

- "There are indications, obtained from, for example, experiments in adult animals, epidemiological studies, in vitro experiments and/or SARs (structure activity relationships), of effects on organ systems and functions that are especially vulnerable under development and maturation in early life (in particular the nervous, reproductive, endocrine and immune systems and also the metabolic pathways), and
- There are deficiencies in the database on such effects in young animals." (REACH Guidance, Chapter R.8).

The reason for referring to this US EPA guidance is unclear. The reference is not stated as a recommendation, merely as a piece of information. In this respect the US EPA guidance differs compared to the REACH guidance, since the US EPA provides clear recommendations on extra assessment factors for children and also indicates criteria that should be fulfilled for this recommendation to come into force.

3 Desired future scenario as regards the protection of children under REACH

The Swedish Chemicals Agency (KemI) has previously identified that there is a need to increase the protection of children in EU chemicals legislations (e.g. Swedish Chemicals Agency, 2012; Swedish Chemicals Agency, 2011b). As a part of the Government assignment to suggest future developments of REACH, this section discusses aspects and proposes regulatory actions identified as desirable for increasing the level of protection of children from exposure to hazardous chemicals under REACH.

It is well known that children in general are more sensitive to chemical insult than adults. This is due to the fact that our most complex organs systems and functions are under development, beginning during the fetal stage and continuing up to adulthood. The immune-, nervous- and reproductive systems are particularly vulnerable to the interference of exogenous compounds. In addition, the behavior of children differs from that of adults, which affects their chemical exposure. Children eat, drink and breath more than adults in relation to their body weight and by crawling and mouthing they may also be exposed to higher levels of more chemicals, e.g. via dust, relative to adults. (Karolinska Institutet, 2013).

Therefore, if the aim is to protect children, the vulnerability of children should be explicitly addressed in the regulatory risk assessment.

3.1 Exposure

3.1.1 Taking into account children's chemical exposure patterns

Even if there are certain general guidance on when and how to take into account children's sensitivity to chemicals in estimating the exposure available in the REACH "Guidance on Information Requirements and Chemical Safety Assessment", an investigation among EU member states and international organizations pointed out a general *need for improvement of current methods and guidance for the exposure assessment of children* (OECD, 2012b). It was suggested in this investigation that, among other things, methods for assessing children's exposure could be improved by the development of "Emission Scenario Documents" for specific routes of exposure for children (e.g. toys, and color) and guidelines for how children's behavior could be accounted for in the exposure assessment.

The exposure patterns of children resemble that of adults in several aspects; we live under the same roof, share the same furniture and electronic devices and sleep in the same bed-sheets. However, in addition, certain sources of chemical exposure are mainly targeting children, e.g. toys, childcare products and materials in contact with food intended for children. The use of chemicals in these more or less children-specific products are in many cases restricted with the aim of protecting children's health, e.g. most carcinogenic, mutagenic and reprotoxic (CMR) substances, certain metals and fragrances are not allowed in toys as set out in the Toys Safety Directive (2009/48/EC). There are however exceptions from the CMR restrictions in the Toys Safety Directive if certain conditions are met and the relevant Scientific Committee has found the use to be safe. An exemption can be permitted if for example the use of a CMR-classified substance or mixture is considered to be safe in view of exposure, there are no suitable alternatives available, and if the substance or mixture is not prohibited for use in consumer articles under REACH (EU, 2009, Annex II, III Chemical properties). Another example is the ban on bisphenol A (BPA) in baby feeding bottles (directive 2011/8/EU) and

in some EU member countries also in food containers intended for children under three years of age.

As children come into direct contact with products and articles other than those intended for children, such as paper materials, electronic devices, textiles and building materials (Swedish Chemicals Agency, 2012), it would be reasonable to include the child-perspective also in regulatory risk assessments and risk management of exposures to chemicals in products and articles not directly aimed for use by children. Under REACH, this could mean that *the CSA and potential subsequent restrictions of a substance are expanded to include also exposures beyond those traditionally seen as children-specific and hence include all relevant sources of exposure of a substance.*

Children are also indirectly exposed to chemicals commonly used in everyday articles via indoor air and dust. Persistent, organic chemicals, such as brominated flame retardants (BFRs) and perfluorinated compounds tend to accumulate in dust as they are emitted from articles to indoor air. Also more easily degradable chemicals, such as phthalates and BPA, are found in household dust. We spend most of our time indoors, and babies and young children even more so and often close to the floor. Dust therefore constitutes an important source of children's total exposure to these chemicals (Karolinska Institutet (and references therein), 2013).

Since exposure of the child starts already during the fetal stage, to chemicals passing the placenta (Karolinska Institutet, 2013), it is furthermore relevant to also ensure the protection of adults, especially women of child bearing age, including pregnant and breast feeding women, from exposure to hazardous chemicals in order to ensure a high level of protection of unborn babies, newborns and young children.

3.1.2 Exposure to chemical mixtures and multiple sources

Although not children-specific, *it is also of critical importance to recognize potential mixture effects in regulatory risk assessments*, as the combined toxicity of a chemical mixture "is always higher than the individual toxic effect of even the most potent compound present" (Swedish Chemicals Agency, 2010). There are methods available for estimating mixture effects, e.g. according to the principles of concentration addition (CA) and independent action (IA) (EC, 2009), but that are not used for regulatory purposes under REACH. Given the complexity of exposure, and the countless number of possible chemical mixtures, a pragmatic approach for taking mixture toxicity into account would be to apply an additional safety factor, a mixture assessment factor, in the derivation of a Derived No Effect Level (DNEL). Taking exposures to mixtures into account could also be handled through a tiered approach: the registrant could either assess the mixture toxicity based on empirical data and from this assessment derive an appropriate assessment factor or in the absence of reliable and relevant data apply a precautionary default assessment factor.

We are also exposed to chemicals via different sources. The REACH requirement to generate exposure scenarios as part of the chemical safety assessment (CSA) for hazardous substances produced in or imported to EU at or above 10 tonnes per year is however limited to one use category at a time. Given the complex exposures, and that some chemicals has multiple uses and in order to avoid underestimations of health risks posed to children, the CSA and subsequent use restrictions under REACH should include, and sum up, exposures from all relevant sources (use categories) for each chemical.

3.2 Effects assessment

In order to enhance the protection of children, relevant and sensitive effects and endpoints to be included in the information requirements need to be identified. These effects/endpoints should comprise adverse effects that are prevalent and/or increasing in children and where chemicals have been identified as risk factors, such as obesity, diabetes, developmental neurotoxic effects, reproductive impairments, asthma and allergies and cancer (WHO/UNEP, 2013; Karolinska Institutet (and references therein), 2013), as well as any other effect/endpoint that can be considered particularly relevant to the developing fetus and the child. Some of these effects may be initiated early in life, but manifest in adulthood. Therefore it is also of importance that the information requirements under REACH cover windows of exposure during critical periods of development in order to identify chemicals of concern with regard to children.

Several of the effects/endpoints suggested above are not covered by current REACH data requirements, and for some of them no standard test guidelines are currently available. There is thus a need to develop both REACH information requirements and guidelines for performing the tests that include relevant endpoints to improve the situation. To identify which health impacts current REACH-implemented data requirements and test methods have the potential to capture and which health impacts will be missed, a systematic investigation is needed. The overall aim being that *the information required under REACH includes children-relevant endpoints and cover exposure during critical periods of development.*

Many of the diseases and impairments identified as being of importance to include in risk assessments of children's health and for which chemicals have been suggested as risk factors are considered to be hormone-related. This is understandable since the early development of many organ systems and functions in the body is regulated by the endocrine system. Information requirements for identifying endocrine-disrupting properties therefore need to be implemented under REACH. Tests for establishing a number of endocrine modes of action are currently missing.

A main REACH mechanism for restricting the use of substances is by identifying substances of very high concern (SVHC). For this regulatory tool to be effective, the data requirements under REACH need to be comprehensive enough for effectively identifying SVHCs, including endocrine-disrupting compounds (EDCs) and allergenic substances. In order to identify SVHCs, *the data obtained from the information requirements need to be sufficient for applying the criteria for the substance to be classified as a SVHC,* i.e. according to the criteria for CMRs, EDCs (criteria still lacking), sensitizers and chronic toxicity set out in the regulation on classification, labeling and packaging of substances and mixtures (CLP) and for persistent, bioaccumulative and environmental toxic (PBT) substances and very persistent and very bioaccumulative (vPvB) substances as set out in REACH[2]. This is important as substances classified as hazardous and/or PBT and vPvB are also targeted by restrictions under other legislations besides REACH, including the Toys Safety Directive.

To identify chemicals of concern with regard to children, test strategies under REACH also need to take into consideration sensitive windows of exposure to substances. As in the case of EDCs, the most sensitive windows of exposure are during critical periods of development,

[2] Currently none of the long-term tests under REACH are strictly required for any tonnage band due to waiving possibilities. 34 long-term reproductive toxicity tests have been conducted and submitted via registration dossiers out of more than 6000 registered substances (ECHA, 2011a).

such as fetal development, perinatal life and puberty (WHO/UNEP, 2013). These developmental periods are mainly covered by the more extensive tests for reproductive and developmental toxicity (OECD TG 414 and the two-generation study, e.g. OECD TG 416) and could thus also be included in any proposed testing for EDC effects at higher tiers. Recently the Extended One-Generation Reproductive Toxicity Study (OECD TG 443) (OECD, 2012c) was approved as a new option for investigating reproductive and developmental toxicity under REACH (ECHA, 2012d). In this assay, female and male rodents are exposed for two weeks before mating, continuing up to weaning of their pups. At weaning, the pups are assigned to one of three cohorts: reproductive/developmental toxicity testing (cohort 1), developmental neurotoxicity testing (cohort 2) and developmental immunotoxicity testing (cohort 3). However, as decisions can be made to omit the developmental neurotoxicity testing and/or the developmental immunotoxicity testing due to existing knowledge of the test compound and the needs of regulatory authorities, it is difficult to predict the output from this assay with regard to what data will be generated for high-volume substances. It is furthermore uncertain whether an exclusion of the second generation (F2), as would be the (default) consequence of performing the extended one-generation test instead of the two-generation test for reproductive toxicity, would lead to information being missed on effects that are delayed until or more pronounced in the F2 generation or whether the generation of data from including the F2 generation can be motivated given the additional costs (Rudén and Hansson, 2008).

To be able to apply all the SVHC criteria, a significant number of tests need to be performed, some of which are very resource consuming. To limit the need for *in vivo* testing, as a first start, *REACH priority setting concerning the lowest tonnage band should be supplemented with screening methods that can enable a reasonably reliably selection of substances for further testing for SVHC characteristics*. Production volume, which is currently the main priority-setting criterion, says little, about chemical properties and is thus not helpful in this respect. Neither are the Annex VII information requirements sufficient for an effective priority setting for further testing since the tests required for low-volume chemicals are inadequate for identifying substances with SVHC potential.

The use of quantitative structure activity relationship (QSAR) models for prioritizing low-volume chemicals for testing is another tiered feature of REACH. This approach will come into full effect in 2018, i.e. by the deadline for registration of low-volume substances. However, little guidance is currently available on what QSAR models that should be used, how to combine information from different models, and what criteria that should be applicable for substance selection. Different approaches may lead to very different priority-settings (Rybacka et al., manuscript in prep.). The tiered approach to testing in REACH could thus be further developed in order to increase the likelihood to identify (new) SVHCs. This includes further analyses of the usefulness of existing QSAR models and the development of guidance for use and interpretation of data.

3.3 Assessment factors

Assessment factors are supposed to account for uncertainties and gaps in the database when deriving the DNEL. Currently there is limited guidance available for making children specific analyses. In an OECD survey it was for example proposed that further guidance need to be developed for taking into account comparative sensitivity between age groups in the risk characterization process (OECD, 2012b). It is therefore suggested that *further guidance is needed for the derivation of children-specific DNELs,* including the application of higher

assessment factors, in the REACH ”Guidance on information requirements and chemical safety assessment, Part B: Hazard assessment”.

3.4 Data generation

In order to prevent hazardous substances from entering the market and make it into consumer products and articles and to ensure a high level of protection of children’s health, the availability of high quality toxicity data is essential. However, this fact can be in conflict with the overall aim of limiting the number of animals in toxicity studies. A long-term aim is therefore to continue to develop better strategies for priority setting as well as relevant and sensitive tests, both *in vitro* and *in vivo*.

Development of new standard tests and test guidelines is a resource- and time consuming task. An alternative or supplementary approach is to increase and improve the use of data generated by non-standard toxicity test methods, i.e. data obtained from studies not conducted according to any standardized test guidelines. This might prove to be faster and simpler than only relying on the development of additional standardized test guidelines. As a means to include children-relevant and sensitive endpoints/effects in the risk assessments of chemicals under REACH one solution can therefore be to *facilitate and improve the use of non-standard studies in the CSA*.

Although test data derived from non-standardized methods may be used in REACH, if fulfilling the conditions described in Annex XI (1.1)[3], it is foreseen that new testing proposals will focus on standardized methods conducted according to the Good Laboratory Practice (GLP) principles as “data generated by any of these methods are *per se* considered adequate for regulatory use”[4]. One way to increase the use of non-standard studies in regulatory risk assessments is to develop criteria for a systematic and transparent evaluation of reliability and relevance of non-standard studies. In addition, criteria for reporting of non-standard studies could promote an improvement in the reporting of studies that will facilitate the evaluation of these studies and thus also their use in risk assessments. (Beronius, 2013; Beronius et al., manuscript accepted for publication) Including all relevant data of sufficient reliability may fill information gaps and thereby reduce scientific uncertainty in health risk assessment conclusions, and subsequently also in chemical policy decisions.

The evaluation of the dossiers registered under REACH so far, performed by ECHA, indicates that the quality of the dossiers needs to be improved. Common shortcomings include clear information about substance identity, aspects related to the chemical safety report (CSR) (such as derivation of DNELs), and unsubstantiated use of Read Across and Waiving (ECHA, 2013). A scrutiny of REACH dossiers also shows that old data are commonly used. Data were found in the dossiers that were published over 100 years ago (Westerholm and Schenk, 2013). It is unlikely that studies that old would fulfill today’s reliability criteria. The possibility to

[3] The conditions include e.g. that the data is adequate for the purpose of classification and labelling and/or risk assessment, that there is adequate and reliable coverage of the key parameters foreseen to be investigated in the corresponding test methods referred to in Article 13(3), exposure duration is comparable to or longer than the corresponding test methods referred to in Article 13(3) if exposure duration is a relevant parameter, and adequate and reliable documentation of the study is provided.

[4] “According to REACH, Article 3(3), tests required for generating information on intrinsic properties of substances shall be conducted in accordance with the test methods included in a Commission Regulation or in accordance with other international test methods recognized by the Commission or the Agency as being appropriate. Toxicological and ecotoxicological tests and analyses shall be carried out in compliance with the principles of Good Laboratory Practice.” (ECHA, 2012b)

include also non-standard data (and Read Across and Waiving) thus warrants a discussion on the need to specify further data quality criteria (Ågerstrand, 2012).

3.5 Risk management

Strengthening the restriction of chemicals in articles under REACH, in particular articles that children come into contact with, is of high relevance for reducing children's exposure to hazardous chemicals. As suggested in KemI report no 1/12, *SVHCs, including EDCs and allergenic substances, should be banned for use in products and articles which children come into contact with.* As children come into contact with articles other than those specifically intended for children, use restrictions for SVHC under REACH should therefore ideally include all relevant sources of exposure. In line with this reasoning, KemI recently presented a proposal for a development of the existing Textile Fibre Regulation (EC) No 1007/2011 to also include restrictions on hazardous chemicals in textiles (Swedish Chemicals Agency, 2013).

Since a great share of the articles consumed in the EU Member States are imported from non-EU countries having less strict and comprehensive chemicals control, another significant strengthening of current REACH restrictions would be if *the restrictions concerning SVHCs also targeted their presence in articles imported from non-EU countries.*

Furthermore, to improve the risk management of chemicals in articles, the requirements to disseminate information on the presence of hazardous chemicals in materials and articles in the supply chain and to consumers should be extended. The information requirements are currently limited to the substances on the candidate list, and consumers need to actively request information on SVHCs in articles and have the right to receive it within 45 days. Dissemination of such information to the end-of-use stage is also lacking. Hazardous chemicals may therefore be reintroduced to the market via reused and recycled materials and articles. *Content declarations on materials and articles, initially comprising the SVHCs, would enable purchasers as well as consumers to take precautionary actions and ask for alternatives.* It would also facilitate the identification and management of sources of hazardous chemicals to which children are exposed.

There is currently no international agency or expert body that conducts and coordinates research and risk assessment on EDCs, as is for example the case for carcinogens (IARC) or Climate Change (IPCC). In order to review and coordinate available scientific knowledge and activities, *the establishment of an intergovernmental agency or expert body for EDCs should be considered*. Such organization would help promote scientific and regulatory developments within this area (WHO/UNEP, 2013). One task for such an agency or body could concern working for international harmonization of the characterization and regulation of EDCs.

3.6 Summary

In summary, the following aspects are identified as desirable for increasing the level of protection of children from exposure to hazardous chemicals under REACH:

- *The REACH "Guidance on Information Requirements and Chemical Safety Assessment, Part D: Exposure Assessment" includes clearly described methods and guidance for the exposure assessment of children.*
- *The CSA under REACH and potential subsequent restrictions of a substance are expanded to include also exposures beyond those traditionally seen as children-specific and hence include all relevant sources of exposure of a substance.*
- *Mixture effects are considered in risk assessments under REACH. A first pragmatic approach is to include an additional assessment factor for mixture toxicity.*
- *The information required under REACH includes children-relevant endpoints and cover exposure during critical periods of development.*
- *REACH priority setting concerning the lowest tonnage band is supplemented with screening methods that can enable a reasonably reliable selection of substances for further testing for SVHC characteristics.*
- *The data obtained from the information requirements of substances produced/imported at or above 10 tonnes/year are sufficient for applying the criteria for the substance to be classified as a SVHC (including EDCs and sensitizers).*
- *The REACH "Guidance on Information Requirements and Chemical Safety Assessment, Part B: Hazard Assessment" includes clear guidance for the derivation of children-specific DNELs.*
- *The systematic use of non-standard studies in risk assessment is facilitated through the implementation of comprehensive and transparent criteria for evaluation of study reliability and relevance and for reporting.*
- *SVHCs, including EDCs and sensitizers, are not allowed to be used in products and articles to which children come into contact.*
- *The restrictions concerning SVHCs target their presence also in articles imported from non-EU countries.*
- *There is a requirement to declare the content of SVHCs of materials and articles.*
- *The establishment of an intergovernmental agency or expert body for EDCs should be considered.*

4 Increasing children's protection through REACH – A proposed action plan

This action plan contains measures proposed for reaching the desired future scenario as described in section 2, where children are protected from exposure to hazardous chemicals. The measures identified as desired is here further elaborated in terms of what changes to REACH are subsequently needed. It is also here discussed how realistic the implementation of the proposed actions are.

Improving the protection of children's health often also involves protection of the general population, especially pregnant and breast-feeding women, from exposure to harmful chemicals. Several of the proposals in this action plan are therefore not only children-specific, but general risk reduction measures.

4.1 Consider all relevant sources of exposure

The REACH guidance on consumer exposure recognizes that children could be exposed to chemicals to a greater extent than adults in relation to their body weight. To this end some guidance and tools for how to take this into account in the exposure estimations are provided in the guidance (ECHA, 2012b). However, in 2011 an investigation among EU member states and international organizations identified that there is a general need for improved guidance and methods for the exposure assessment of children (OECD, 2012d). Based on this investigation, a number of proposals for follow-up work have been outlined regarding risk assessment of children's health in the OECD Environment, Health and Safety Programme. Concerning the exposure assessment, initiation of projects that look into the development of Emission Scenario Documents for specific exposure pathways for children (e.g. exposure to chemicals in toys and paints), and the development of a general guidance on addressing children's behavior in estimating the exposure to chemicals are proposed (OECD, 2012b). Furthermore, according to REACH, the registrant does not need to carry out a risk characterization for uses of the substance that is not covered in the registrant's own registration (REACH Guidance, Chapter R.15). The total combined exposure may therefore be underestimated if each registration for a particular substance only covers a part of the relevant uses and exposures.

4.1.1 Proposed action and estimated effect

Children's exposure to hazardous chemicals could be reduced if regulatory risk assessments, and potential subsequent restrictions of a substance, were not limited to exposures traditionally seen as children-specific but included all relevant sources of exposure for each substance.

To achieve this, the requirements concerning the chemical safety assessment (CSA) under REACH need to be expanded. A CSA is currently required for substances produced or imported at or above 10 tonnes per year and shall, for substances classified as hazardous, include an exposure assessment and risk characterization. To make the exposure assessment more realistic, the CSA requirements could be supplemented with an obligation to consider the combination of relevant sources of exposure for each substance. In cases where there is more than one source of exposure for a single substance, this exercise will increase the estimated exposure. This may in turn affect the outcome of the risk assessment. Increased availability of high-quality biomonitoring data, such as urine, blood or breast milk chemical

concentrations, would contribute to improve the overall quality of the exposure assessments in REACH.

4.1.2 What changes to the regulation (including annexes and guidance documents) would the proposed action require?

The guidance for exposure assessment of children should be reviewed and the need for more guidance and improved methods for exposure assessment of children considered. A concrete example is the proposed requirement to consider the combination of all relevant sources of exposure for each substance. This could be introduced in the guidance document concerning exposure scenarios and the chapter related to consumer exposure (*Guidance on Information Requirements and Chemical Safety Assessment, Part D: Exposure Assessment, Chapter R.15).* The guidance document needs to provide information that clarifies the scope, i.e. what is meant by "all relevant sources of exposure", and give clear guidance and specific examples on how to obtain such information and estimate the combined exposure from different types of sources, especially with regard to children.

4.1.3 How realistic is the proposed action?

Within the current regulatory framework it will probably be a complicated task to introduce a requirement where the registrants are obliged to gather information on exposures from uses outside of their own supply chain.

This is however done in the process of proposing a restriction of the use of a substance, mixture or article in Annex XVII, in which all relevant sources of exposure should be considered in the dossier. More specifically, it is stated in Annex XV that a restriction dossier shall consider "any relevant information from registration dossiers" and that also "other available information may be used" (REACH, Annex XV). Restriction proposals can be made by either a Member State or by the European Chemicals Agency (ECHA) on request of the European Commission. Thus, the responsibility to gather and assess all information considered relevant for the purpose of proposing and preparing a restriction is not with the chemical industry.

The suggestion also requires an explanation of what is meant by "all relevant sources of exposure". It should be noted that indirect chemical exposures of humans via the environment is currently not included in the consumer exposure assessment according to REACH. It should, however, be reported in the 'man via the environment' section in the chemical safety report (CSR). This is further detailed in Chapter R.16 (REACH Guidance, Chapter R.15). According to the REACH guidance, an indirect exposure is defined as "the exposure of humans via consumption of food and drinking water, inhalation of air and ingestion of soil which in turn are directly influenced by the releases of the substance into the environmental compartments air, water and soil" (REACH Guidance, Chapter R.15). These exposure routes are important for some chemicals and should be considered in order to give a realistic estimate of the total exposure.

4.1.4 Further work for reaching the proposed action

Further analyses are needed in order to identify a clear and transparent approach for how to turn the requirement to take into account all relevant exposure sources into manageable practice. Examples of issues that need to be clarified are how registrants will get access to information on exposures from uses outside of their own supply chain, the scope of "all

relevant sources of exposure", and methods for estimating the combined exposure from different types of sources, especially with regard to children.

4.2 Strengthen current information requirements

In order to enable identification of hazardous substances under REACH with special regard to effects on children, a prerequisite is that the information required, and thus the tests for obtaining that information, includes children-relevant and sensitive endpoints. In particular, testing for effects that can be related to diseases that are prevalent and/or increasing in children should be considered, including adverse effects that may be initiated during critical periods of development and for which chemicals have been identified as risk factors. The testing strategies will need to be broad to also enable identification of potential effects not already known to be of relevance for assessing risks to children's health.

4.2.1 Proposed action and estimated effect

Examples of adverse effects/diseases that are currently being discussed as prevalent or increasing in children and where chemicals have been proposed as a risk factor include reproductive impairments, certain endocrine-related cancers, obesity, diabetes, developmental neurotoxic effects, and asthma and allergies (WHO/UNEP, 2013; Karolinska Institutet (and references therein), 2013).

A challenge is that this could not be seen a comprehensive or final list. The causal evidence linking chemical exposure to these adverse outcomes/diseases differs in strength. Consequently, a decision on what tests and endpoints that should be considered relevant might need further deliberation and might change over time as new knowledge becomes available.

According to current REACH testing regimes, few chemicals will be tested for effects related to these diseases. The required testing related to these effects is limited to high-production-volume chemicals (>10 tonnes) or is not required to be tested for at all. Testing for immunological effects constitute the exception but is limited to skin sensitization. There are currently no tests for inhalation sensitization. Many of the effects identified to be of relevance to children are mediated through endocrine-related mechanisms, which are currently not adequately covered by the REACH information requirements.

These children-relevant health effects are among the effects that are emphasized in REACH as being of very high concern (i.e. carcinogenic, mutagenic, reprotoxic effects according to the CLP criteria and effects of "equal level of concern", such as endocrine-disruption and strong sensitization) (REACH, Art. 57).

Substances identified as having effects of very high concern are covered by different regulatory requirements aiming to ensure that risks associated with these effects are adequately controlled. However, tests sufficient for identifying substances having these properties will only be performed for a limited number of chemicals. As described above, tests for the identification of endocrine-related effects are largely lacking and tests for carcinogenicity and reproductive toxicity will – in general - only be required for the highest tonnage bands and only performed after a testing proposal from industry has been put forward and granted approval by ECHA. Only when these tests are required or available the criteria for identification of substances of very high concern (SVHCs) can be applied.

The data requirements should be designed so that they maximize the likelihood of identifying chemicals of (very high) concern. Not only for the highest tonnage bands. Towards this aim a more tiered approach to testing should be considered. A tiered test system contains rules for when and in what order the different tests should be performed. Tiered testing has been introduced in the REACH legislation. In REACH carcinogenicity testing is starting with an *in vitro* test and subsequent testing depends on the results of this test in a tiered fashion. In order to maximize the likelihood of identifying previously unidentified SVHCs, a further development of the tiered approach in REACH should be considered. The data currently required for the lowest tonnage band (first tier) should include, or be supplemented with, tests that can select potential candidates for an SVHC classification, and these candidates should be further tested to confirm (or reduce) the initial concern.

4.2.2 What changes to the regulation (including annexes and guidance documents) would the proposed action require?

The information requirements are laid down in REACH Annexes VII-X. Following the proposed changes of introducing requirements to provide additional information (1) on children-relevant effects/endpoints, and (2) for a more efficient identification of new SVHCs would require changes to Annexes VII-X.

Work on developing and validating tests and test strategies for the identification of endocrine disrupting compounds (EDCs) is ongoing. Guidelines for screening and testing of EDCs are for example available within the OECD Conceptual Framework for Testing and Assessment of Endocrine Disrupters (OECD, 2012a). The intention of this framework is, however, not to be used as a testing strategy in its current structure. However, the available set of OECD validated tests provides a basis for successively developing a tiered test system that enables identification of substances acting via the endocrine system as new tests are developed.

4.2.3 How realistic is the proposed action?

The suggested measures are considered realistic but not straightforward. The data requirements were among the most controversial issues when REACH was developed and adopted. However, since then, the issue about endocrine disrupting chemicals has emerged and new data have become available. A cornerstone in the implementation of new testing methods and strategies of relevance to children (and hormone disruption) is the upcoming definition and subsequent criteria for identifying an endocrine disruptor from the European Commission. The announcement of the EDC definition, which was planned to take place by the end of 2013, has now been postponed.

4.2.4 Further work for reaching the proposed action

For EDCs, new information and test requirements need to be based on the forthcoming EU EDC criteria. Ideally such test requirements should be arranged in a tiered approach so that some initial tests are required already at the lowest tonnage band. The combination of tests and rules for how they should be applied needs to be determined.

4.3 Increase restrictions of substances of very high concern (SVHC)

A great share of the articles sold and consumed on the EU market have been manufactured in and imported from non-EU countries where the chemicals control is less comprehensive and restrictive with regard to protecting human health than in the EU through REACH (Swedish Chemicals Agency, 2011b).

4.3.1 Proposed action and estimated effect

Imposing restrictions on identified SVHCs in imported articles would be an important step in reducing the exposure to these substances. SVHCs that have not been granted for applied uses in the authorization process should be restricted for use also in imported articles.

By restricting the use of SVHCs, including EDCs and allergenic substances, in articles that children continuously come into contact with (i.e. not only articles particularly intended for children, but also e.g. construction materials and textiles), children's exposure to these hazardous substances will be reduced. It will furthermore contribute to reduce the overall burden of exposure of hazardous chemicals.

4.3.2 What changes to the regulation (including annexes and guidance documents) would the proposed action require?

If a SVHC is not authorized for a certain use, this restriction could be listed in Annex XVII and that way it could target also the substance in imported articles.

These proposed restrictions for minimizing emissions, circulation and exposures of SVHCs could be added to the REACH legal text, Title VII (Article 56, General provisions) concerning the authorization procedures.

4.3.3 How realistic is the proposed action

The restrictions of chemicals in children's toys, according to the Toys Safety Directive (2009/48/EC), covers also imported toys. This indicates that a similar requirement under REACH is legally feasible.

The current REACH rules for consumer articles are not very comprehensive and there is a need to improve them. Increasing the restrictions of chemicals of concern in articles, including those imported from non-EU countries, is in line with the objective of the Strategic Approach to International Chemicals Management (SAICM) that is to reduce differences in chemicals control in different parts of the world. A prioritized area within this work is chemicals in articles.

4.3.4 Further work for reaching the proposed action

Changing the legal text of REACH is more complicated than changing for instance guidance documents. However, REACH is up for review every five years so there is a decision-process for considering such proposals. Nevertheless, further analyses are needed in order to identify a clear and transparent approach for how to turn this proposal into manageable practice.

4.4 Improve guidance for children-specific DNELs

An OECD scoping study was conducted in 2011 to identify methods and tools currently available for assessing chemical risks to children's health and the need for additional guidance and tools (OECD, 2012d). Based on expressed needs it was proposed that guidance for taking into account comparative sensitivity between age groups in risk characterization should be developed. It is envisaged that such guidance could be based on endpoint-specific considerations as well as route-specific considerations. (OECD, 2012b)

This proposed work to further detail the guidance concerning the hazard and risk assessment of children is applicable to the guidance that is provided for deriving children-specific Derived No Effect Levels (DNELs) under REACH. One example of where a clarification is needed concerns the reference that is made to the US EPA's recommendation to add an extra assessment factor of 10-100 for protecting children when the following criteria are (both) fulfilled:

- "There are indications, obtained from, for example, experiments in adult animals, epidemiological studies, in vitro experiments and/or SARs (structure activity relationships), of effects on organ systems and functions that are especially vulnerable under development and maturation in early life (in particular the nervous, reproductive, endocrine and immune systems and also the metabolic pathways), and
- There are deficiencies in the database on such effects in young animals." (REACH guidance, Chapter R.8)

It is unclear whether this reference is merely a piece of information or a vague, implicit recommendation to do so also within the REACH framework. The US EPA guidance differs compared to the REACH guidance in that the US EPA provides clear recommendations on extra assessment factors for children and also indicates criteria that should be fulfilled for this recommendation to come into force.

4.4.1 Proposed action and estimated effect

The need for a clear recommendation on introducing a children specific assessment factor should be considered. The guidance document should be revised so that the recommendations on the use of children specific assessment factors become clear and useful for the users of the guidance.

It is furthermore proposed that the guidance concerning children-specific assessment factors for deriving a DNEL is reviewed also with regard to the size of the recommended factor. Higher assessment factors than are recommended in REACH have been proposed in the scientific literature. For example, Dorne et al (2010) showed that the difference in toxicokinetics between adults and infants below two years of age exceeded the standard assessment factor of 3.2 for used to account for this difference in kinetics in a significant number of cases (Dorne, 2010).

4.4.2 What changes to the regulation (including annexes and guidance documents) would the proposed action require?

Changes following the proposed review of the recommendations made for children-specific assessment factors under REACH would concern changes to the guidance document.

4.4.3 How realistic is the proposed action?

Changing guidance is less complicated than changing the legal text. If the US EPA has a solution that is applicable to REACH, and that is perceived as an improvement to the REACH guidance, then this could be an incentive to make such change.

4.4.4 Further work for reaching the proposed action

The existing use of children specific assessment factors – including EPA's guidance – should be reviewed and its usefulness analyzed in the REACH context. The work suggested to be undertaken in the OECD report mentioned above concerning the development of guidance for taking into account comparative sensitivity between age groups in the risk characterization is also of relevance to follow up on in this context.

4.5 Consider mixture effects in regulatory risk assessments

Although REACH explicitly aims to "ensure a high level of protection of human health and the environment" (Article 1), it does not require consideration of mixture toxicity (what is called coincidental mixtures in REACH). Based on empirical data, it has been found that "the joint toxicity of a chemical mixture is always higher than the individual toxic effect of even the most potent compound present" (Swedish Chemicals Agency, 2010). It is therefore of critical importance to recognize (potential) mixture effects in risk assessments. In protecting the general population from exposure to harmful chemical mixtures, the protection of children will increase.

4.5.1 Proposed action and estimated effect

Requirements to consider mixture effects should be introduced in risk assessments under REACH.

There are methods available for estimating mixture effects, e.g. according to the principles of concentration addition (CA) and independent action (IA) (EC, 2009), but that are not used for regulatory purposes under REACH. Given the complexity of exposure, and the countless number of possible mixtures, mixture effects could be handled through a tiered approach: the registrant could either assess the mixture toxicity based on empirical (experimental or model) data and from this assessment derive an appropriate assessment factor or in the absence of reliable and relevant data apply a precautionary default assessment factor for mixture toxicity.

Mixture effects should be taken into account whenever considered relevant. In doing so, the vulnerability of children should be explicitly addressed in the assessment if there are reasons to believe that children are more vulnerable to exposure of the mixture than adults.

4.5.2 What changes to the regulation (including annexes and guidance documents) would the proposed action require?

The proposed action to consider mixture toxicity in under REACH could be introduced and described in guidance documents.

4.5.3 How realistic is the proposed action?

In a report by the Swedish Chemicals Agency that presents, among other things, current gaps and options for improvement concerning hazard and risk assessment of chemical mixtures

under REACH it is concluded that it is feasible to introduce a mandate into the current REACH regulation to take into account mixtures in the risk assessment (Swedish Chemicals Agency, 2010). The new Plant Protection Products (PPP) regulation (EC No 1107/2009) is mentioned as a support for this conclusion as it requires that PPPs "shall not have any harmful effects on human health, including vulnerable groups, or animal health, taking into account known cumulative and synergistic effects".

Two options are proposed for handling "coincidental mixtures" under REACH:

- Using a default mixture assessment factor (MAF)
- Conducting scenario-specific cumulative risk assessments

It is however noted that the implementation of these proposals is limited by knowledge gaps, in particular knowledge about 'typical' exposure scenarios for industrial chemicals as covered by REACH.

4.5.4 Further work for reaching the proposed action

Further analyses are needed on e.g. how to define what mixtures that are relevant to assess, and what are the (legal) implications if the mixture is considered hazardous (but not the individual substances).

4.6 Increase the use of non-standard studies in regulatory risk assessments

There is a massive body of peer-reviewed research studies available, that have not been conducted according to any standardized guidelines or GLP. Recent investigations indicate that there is a need to facilitate the use of these non-standard studies in health risk assessment (Ågerstrand et al., 2011a; Ågerstrand et al., 2011b; Beronius et al., 2013; Myers et al., 2009). An example where this could have major impact is in risk assessment of potential EDCs. Endocrine disruption has sparked a strong research interest and many non-standard studies are conducted using novel methods argued to be more sensitive than current standardized methods, e.g. when it comes to identify children-relevant effects, such as developmental neurotoxic effects (Kortenkamp et al., 2012; Zoeller et al., 2012; Beronius et al., 2013). This is illustrated by the BPA case, were the majority of *in vivo* toxicity studies reporting effects at low doses, i.e. below the lowest observed adverse effect level (LOAEL) used for the derivation of the current tolerable daily intake (TDI)[5], are non-standard developmental toxicity studies (vom Saal and Hughes, 2005 and according to our own unpublished study of the BPA low-dose literature). Importantly, neither GLP nor standardized test guidelines will automatically ensure the relevance of the study for risk assessment purposes, and it is globally discussed that standard methods may be inadequate to identify and evaluate adverse health effects caused by e.g. EDCs (e.g. EC, 2009; WHO/UNEP, 2013).

The advantage of incorporating all adequate data, i.e. reliable and relevant, to fill information gaps is addressed by regulatory agencies. ECHA recommends registrants under REACH to make full use of all existing and relevant information in the registration process (ECHA, 2013). However, data derived from non-standardized methods should fulfill certain

[5] In January 2014, EFSA suggested to temporarily lower the current TDI of 50 µg BPA/kg bw/day to 5 µg/kg bw/day based on its draft assessment of health risks from exposure to BPA (http://www.efsa.europa.eu/). Still, several of the *in vivo* developmental toxicity studies identified in the open scientific literature report significant effects of BPA at or below 5 µg/kg bw/day.

conditions, including e.g. that the data are adequate for the purpose of classification and labeling and that there is adequate and reliable coverage of key parameters (REACH, Annex XI), while studies that include standardized methods and are conducted according to the GLP principles "are *per se* considered adequate for regulatory use" (ECHA, 2011b). However, even though there is regulatory acceptance of non-standard data, such as in the REACH registration process and in the safety assessments conducted by the European Food Safety Authority (EFSA), there is a need for a structured and transparent approach to data evaluation and reporting (Beronius et al., 2014).

4.6.1 Proposed action and estimated effect

The use of non-standard studies in risk assessment needs to be facilitated. This could be done through the implementation of new criteria for evaluation of reliability and relevance of peer-reviewed studies. Existing criteria (proposed by Klimisch) will systematically attribute more weight to studies conducted according to standardized test protocols and GLP. Non-standard studies are also sometimes insufficiently reported for regulatory risk assessment purposes (e.g. Alcock et al., 2011). Clear guidance for how to report such studies would also facilitate their use in regulatory risk assessments.

4.6.2 What changes to the regulation (including annexes and guidance documents) would the proposed action require?

The proposed action to facilitate the use of non-standard studies in regulatory health and environmental risk assessments could be introduced in the REACH framework by emphasizing in the guidance document for hazard assessment (*Guidance on information requirements and chemical safety assessment, Part B: Hazard assessment*) the importance of making use of all available studies judged to be reliable and relevant. This should be coupled to references to evaluation criteria, and supplemented with clear guidance, which enables evaluation of non-standard studies in a way that is not biased towards favoring studies conducted according to standardized test guidelines and GLP.

4.6.3 How realistic is the proposed action?

EFSA goes further than ECHA in emphasizing the importance of identifying all relevant data, including published studies, reports, conference proceedings and other sources of information, and provides ample guidance how to conduct a systematic review of data for food and feed safety assessment (EFSA, 2010).

This proposal could be introduced step-wise and in a flexible manner to begin with.

4.6.4 Further work for reaching the proposed action

There are several proposals available for structured assessments of reliability and relevance of non-standard studies, as well as for reporting of such studies. A recent initiative, developed through a collaboration between Stockholm University and Karolinska Institutet, was launched at www.scirap.org. The usefulness of such a system could be further evaluated e.g. by experienced risk assessors at the relevant agencies in collaboration with industry and academia.

4.7 Extend requirements to declare chemical content

An important aspect in chemical risk reduction is the dissemination of information throughout the entire supply chain, including to consumers, about the chemical content of materials and articles.

4.7.1 Proposed action and estimated effect

Suppliers of articles should be required to declare the chemical contents of materials and articles. Initially this could apply to substances identified as SVHCs under REACH. The most important impact foreseen by making such information available is not on the level of the consumer. It should, in our view, not be the responsibility of the individual to seek and assimilate information in order to avoid hazardous chemicals in everyday life. Consumers that are provided with information about the content of hazardous chemicals in articles in a user-friendly format may change their consumption patterns, but research on the extent such information actually increases the receiver's perception of risks and subsequently changes attitudes and behavior is however diverging (e.g. Leire and Thidell, 2005). In contrast, such information can be crucial for professional buyers and retailers, as well as for NGOs and research scientists. These actors have in some cases the right competence and resources to analyze such information and make practical use of it. Making retailers aware may directly affect what they choose to buy and hence what articles will become available for consumers, including e.g. pregnant women and parents of small children. NGOs can contribute to disseminating information about the chemical contents of articles in a way that is understandable to consumers and others. And finally, the efforts to identify chemicals of emerging concern through scientific research (in environmental chemistry, exposure estimation and (eco)toxicology) would be greatly facilitated by such information.

4.7.2 What changes to the regulation (including annexes and guidance documents) would the proposed action require?

The proposed measure of requiring suppliers of articles to declare the chemical contents in an article could be added under Title IV on Information in the supply chain and to Article 33 about article suppliers' duty to communicate information on substances in articles.

4.7.3 How realistic is the proposed action?

For complex articles, with complex supply-chains, this proposal has been considered unrealistic. This assessment is however often based on a process where the content of the original article is tracked up the supply chain. If the reversed were the case, i.e. that the chemical content of different materials is declared and the information follows the part/material down the supply-chain (as for chemical products) it might be easier. The need to disseminate information on the chemical content of materials and articles downstream from suppliers is for example stressed in a UNEP Chemicals in Products Project report concerning a case study of the textile sector. (UNEP, 2011)

Increasing requirements in this area step-wise may also put pressure on industry to shorten supply-chains and develop closer partnerships with their suppliers. These are aspects that facilitate efficient information dissemination.

4.7.4 Further work for reaching the proposed action

Further work is needed to develop systems for efficient information dissemination through the supply chain, all the way from suppliers to the end users.

4.8 Establish an expert body for EDCs

There is currently no international agency or body that conducts and coordinates research and risk assessment on EDCs, as is for example the case for carcinogens (IARC) or Climate Change (IPCC). Given the magnitude and complexity of the EDC issue in relation to research as well as policy development a similar solution for EDCs should be considered.

4.8.1 Proposed action and estimated effect

In order to review and coordinate available scientific knowledge and activities with regard to EDCs, an intergovernmental agency like that of IARC or IPCC could be an option to consider, as it would help promote scientific and regulatory developments within this area (WHO/UNEP, 2013). It would also contribute in the work of reaching an international harmonization concerning the definition of EDCs and criteria for identifying EDCs in the regulatory setting. As many of our organ systems are especially susceptible to interference of endocrine-active substances during early development (WHO/UNEP, 2013), work towards a more comprehensive and systematic regulation of EDCs would be beneficial from the view of increasing the protection of children's health.

4.8.2 What changes to the regulation (including annexes and guidance documents) would the proposed action require?

The legal status of such an initiative needs to be clarified.

4.8.3 How realistic is the proposed action?

There is a pressing need for both research and policy development in the area of EDCs. Such a body could help national authorities in these processes. It requires however additional resources; probably both funding and experts. Such a body could be an important part of an EU strategy for the risk management of EDCs.

4.8.4 Further work for reaching the proposed action

Both IARC and IPCC are interesting cases that could serve as examples of how to launch a similar initiative in the area of EDCs.

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