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Guidance for risk assessment of chemicals in consumer articles and products

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Guidance for risk assessment of chemicals in consumer articles and products

Editing:

Helle Buchardt Boyd
Poul Bo Larsen,

DHI Environment and Toxicology

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1401 Copenhagen K
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Helle Buchardt Boyd

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Contents

Foreword

This guidance document has been prepared as a tool for the competent authorities of the EU member states in preparing health risk assessments for chemicals found in various non-food consumer articles[1], destined or likely to come into contact with consumers. The purpose is to ensure uniform and consistent methods applied in the risk assessments among the competent authorities in the member states of the EU.

The management of the Community Rapid Information System 'RAPEX' is established under Article 12 and of the notification procedure established under Article 11 of Directive 2001/95/EC (the General Product Safety Directive).

Guidance for risk assessment has already been given in the Commission decision 2010/15[2] laying down guidelines for the management of the Community Rapid Information System 'RAPEX'. However, according to same decision, the guidelines should be regularly updated. The present guidance document on risk assessment should be viewed as a contribution to such an update on the area of chemicals in articles.

Even though the General Product Safety Directive and the Community Decision 2010/15 says that risk assessments should be performed, there is no guideline as to how to perform this risk assessment in the case of chemicals contained in or leaching from consumer products in the form of articles, except a referral to the REACH regulation and guidance documents. It is the purpose of this guidance document to provide a brief guidance with reference to authoritative guides, including the REACH guidance documents developed by ECHA.

This guidance document was prepared by DHI Denmark (Helle Buchardt Boyd and Poul Bo Larsen) for the Danish Environmental Protection Agency (Shima Dobel and Elisabeth Paludan) in November - December 2013.

[1] Article: means an object which during production is given a special shape, surface or design which determines its function to a greater degree than does its chemical composition (as defined in article 3(3) in the REACH regulation).
[2] Commission decision of 16 December 2009 laying down guidelines for the management of the Community Rapid Information System 'RAPEX' established under Article 12 and of the notification procedure established under Article 11 of Directive 2001/95/EC (the General Product Safety Directive) (notified under document C(2009) 9843) (2010/15/EU).
http://ec.europa.eu/consumers/safety/rapex/docs/rapex_guid_26012010_en.pdf

1. Introduction

RAPEX is established as the EU rapid alert system that facilitates the rapid exchange of information between Member States and the Commission on measures taken to prevent or restrict the marketing or use of products posing a serious risk to the health and safety of consumers with the exception of food, pharmaceutical and medical devices, which are covered by other mechanisms.

As of 2010, the system also facilitates the rapid exchange of information on products subject to EU harmonisation regulation and posing a serious risk to the health and safety of professional users as well as on those posing a serious risk to other public interests protected via the relevant EU legislation (e.g. environment and security). Both measures ordered by national authorities and measures taken 'voluntarily' by producers and distributors are reported by RAPEX.

Every Friday, the Commission publishes a weekly overview of the products posing a serious risk as reported by the national authorities (the RAPEX notifications). This weekly overview gives information on the product, the identified risk and the measures that were taken in the notifying country. Since 2013, the Commission also publishes notifications on products posing less than serious risk as well as notifications on professional products and on those posing a risk to other public interests protected via the relevant EU legislation (e.g. environment and security).

According to the Commission decision 2010/15, Member States have a legal obligation to notify the Commission when the following four notification criteria are met:

- the product is a consumer product, and
- the product is subject to measures that prevent, restrict or impose specific conditions on its possible marketing or use ('preventive and restrictive measures'), and/or
- the product poses a serious risk to the health and safety of consumers, and
- the serious risk has a cross-border effect

Before an authority of a Member State decides to submit a RAPEX notification, it is required to perform an appropriate risk assessment in order to assess whether a product to be notified poses a serious risk to the health and safety of consumers and thus whether the RAPEX notification criteria are met.

In the cases where existing legal limit values for certain substances in certain commodities are exceeded, the risk is not acceptable and appropriate restrictions are taken into use. However, the level of risk must be determined before reporting to RAPEX. According to Commission decision 2010/15: "Non-compliance with limit values does not automatically mean that the product presents a 'serious risk' (which is the highest risk level covered by these guidelines). Therefore, to ensure appropriate risk reduction measures, a risk assessment will be required for those parts of a product that do not comply with or are not covered by legislation or a standard." Serious risks are those which give a high probability of irreversible or long-term (more than 6 months) damage to the body. Even though a risk is not deemed serious, it may still be unacceptable if it exceeds a legal limit.

In cases of chemical contents or leaching/migration of chemicals, where no specific limit values are available, a more detailed risk assessment must be carried out. In the following chapters and annexes it will be described and demonstrated how such a risk assessment should be carried out.

In order to provide guidance and demonstration on how to perform a risk assessment of chemical substances leading to determination of the risk level, we are in the following describing the four elements of risk assessment, namely hazard identification, hazard characterisation, exposure assessment and risk characterisation. In addition we provide some of the terms usually employed in risk assessment, and their definitions. In a separate chapter we provide references to where different tools can be found, which may be useful for the risk assessor. In three annexes we have given brief examples of risk assessment of chemical substances in articles reported by the Danish EPA: one of which was clearly exerting serious risk; one where the risk level is subject to controversy, and one where the risk level was deemed low.

2. The Elements of Risk Assessment

Among toxicologists internationally, there is general consensus that a risk assessment consists of the following elements:

Hazard identification
Hazard characterisation
Exposure assessment
Risk characterisation

In the following, these elements will be described in more detail.

The risk assessment follows after the situation where a chemical substance has been found in a consumer product, and there is suspicion that the substance may cause adverse effects during the use of the product, either as intended or likely to be used.

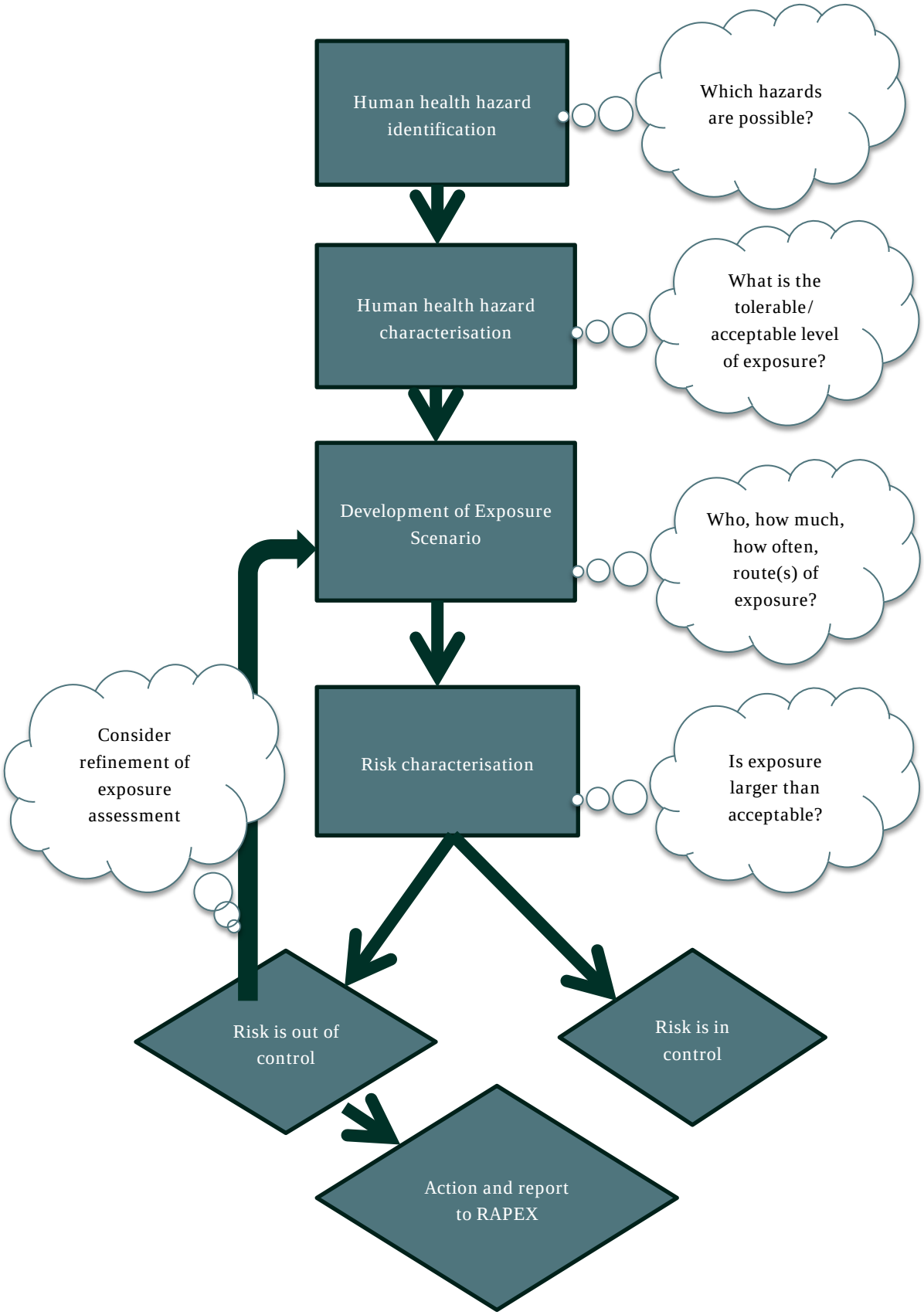

FIGURE 2-1 FLOW OF THE RISK ASSESSMENT PROCESS AND THE QUESTIONS WHICH SHOULD BE ADDRESSED

2.1 Hazard identification

Hazard identification is the task of determining the adverse effects of a chemical, which could possibly harm people. In this initial step of the risk assessment, hazards are only identified, not quantified.

According to the Commission Decision 2010/15 hazard identification and assessment is the same as determining the severity of the injury.

The hazard identification should consider all relevant endpoints after both acute and repeated, longer term exposure.

If the substance or substance group of question is already classified as hazardous, the classified hazards should of course be taken into consideration, but there is also a need to consider effects which may not have been the subject of classification.

Effects may be divided into those occurring after

- Short duration of exposure, e.g. a single day.
- Repeated exposure, from a few days up to daily for a lifetime if the item in question lasts that long.

Toxicological end-points considered should at least be:

- Acute mortality/toxicity.
- Skin/eye/ respiratory tract irritation and corrosivity.
- Skin and respiratory tract sensitisation.
- Repeated dose toxicity (e.g. toxicity to functions and specific organs e.g. neurotoxicity and immunotoxicity).
- Mutagenicity/ genotoxicity.
- Carcinogenicity.
- Toxicity to reproduction (effects on fertility and development).
- Endocrine disruption

2.1.1 Data search

Data on hazards may be obtained by looking at the ECHA web site for information using the chemical name or CAS no. Data on classification and industry self-classification of substances can be found at the Classification & Labelling Inventory at the web site: http://echa.europa.eu/web/guest/information-on-chemicals/cl-inventory-database.

Other databases, such as HSDB, Toxline, Toxnet and PubMed may be used to retrieve data on hazards. Whole reviews of substances are often available in documents from ECHA, WHO/IPCS, OECD, and ATSDR and in the opinions from the EU Scientific Committees (see also chapter 3 for where to find relevant references and tools).

2.1.2 Read-across and (Q)SAR ((Quantitative) Structure Activity Relationship)

If the chemical formula of the substance is known, but data on one or more end-points are scarce, read-across and QSAR modelling may serve as a means of assessing the likeliness of the substance exerting a particular effect based on the knowledge of other substances with similar structural features, and it may also be possible to get an idea of the dosage required to give that effect.

However, making read-across or QSAR modelling requires expert knowledge. Various commercial QSAR computer tools exist, but there are also a few public ones, such as:

The OECD QSAR toolbox, which can be found here: http://www.qsartoolbox.org/

The Danish (Q)SAR database, which can be found here: http://qsar.food.dtu.dk/

VEGA, which can be found here: http://www.vega-qsar.eu/

2.2 Hazard characterisation

Hazard characterisation is the task of finding out how large doses it takes to get poisoned by a chemical.

The purpose of the hazard characterisation is to find the critical effect (the adverse effect(s) observed at the lowest exposure level, i.e. the Lowest Observed Adverse Effect Level, LOAEL), and the corresponding critical dose without any adverse effect i.e. the No Observed Adverse Effect Level (NOAEL), which is the highest dose level just below the LOAEL and without any adverse effects. These critical dose levels may be found based on data on experience in humans or (more often) from experimental animal testing.

The unit of the **critical dose** is usually given as mg/kg body weight (bw), and is denoted NOAEL (no observed adverse effect level) or NOEL (no observed effect level). A critical *concentration* in air may be given in mg/m^3 and is denoted as a NOAEC or NOEC.

A **safe dose** (a dose not considered to cause any adverse effect) is usually found by applying appropriate assessment (or uncertainty) factors to the critical dose. The unit of the safe dose (or concentration) is also usually given as mg/kg bw (or mg/m^3).

Depending on which authority is consulted, the safe dose may be denoted as explained in table 2-1.

TABLE 2-1 DIFFERENT CONCEPTS OF SAFE DOSES, THEIR DEFINITION AND EXAMPLES OF AUTHORITATIVE BODIES APPLYING THEM

Concept	Authoritative body	Definition
Acute reference dose (acute RfD)	US-EPA	An estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure for an acute duration (24 hours or less) to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime.
Reference dose (RfD)	US-EPA	An estimate, with uncertainty spanning perhaps an order of magnitude, of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Reference doses are specific to oral exposure. When assessing inhalation exposure, EPA uses "reference concentrations" (RfCs), instead of RfDs.
Derived no effect level (DNEL)	ECHA	External exposure level below which an adverse effect on human health is not expected. DNELs are population, route and frequency dependent. In specific cases DNEL may be expressed as internal exposure when adjusted by an absorption factor.
Derived minimal effect level (DMEL)	ECHA	A dose level associated to a certain calculated risk level, e.g. a 10-5 lifetime risk level for the development of cancer (i.e. the dose level associated with one extra cancer case in a population of 100,000 people during a lifetime of 70 years).
Tolerable daily intake (TDI)	WHO, EFSA	An estimate of the amount of a substance that can be taken in daily over a lifetime without appreciable health risk.
Acceptable daily intake (ADI)	WHO, EFSA	The amount of a specific substance (originally applied for a food additive, later also for a residue of a veterinary drug or pesticide) in food or drinking water that can be ingested (orally) on a daily basis over a lifetime without an appreciable health risk.
Minimal risk level (MRL)	ATSDR in USA	An estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse non-cancer health effects over a specified duration of exposure.
Benchmark dose (BMD)	WHO, EFSA, US-EPA	An exposure due to a dose of a substance associated with a specified low incidence of risk, generally in the range of 1% to 10%, of a health effect; or the dose associated with a specified measure or change of a biological effect.
Benchmark dose level (BMDL)	WHO, EFSA, US-EPA	A lower one-sided confidence limit on the BMD.
Threshold of toxicological concern (TTC)	ILSI, EFSA, US-FDA, EMA	A level of exposure for all chemicals below which there would be no appreciable risk to human health.

If you have no data, but you do know the chemical structure of the substance, TTC would be the safe dose of choice. However, if there are data indicating endocrine disruptive activity of a substance, these data should be taken into consideration, case-by-case, in deciding whether or not to apply the TTC approach.. Some QSAR estimates can also give an idea of the dose of concern. However, it is not very likely to be used in the context of RAPEX, since only notifications with a clearly defined risk are accepted.

For genotoxic carcinogens a threshold for the carcinogenic effect can seldom be set and these substances are in general considered as non-threshold substances for which a safe level cannot be determined. For substances it is important to give an estimate of the cancer risk associated to a specific dose. The starting point for this estimate is often a BMDL at T25 (the dose which is toxic to 25 percent of the test population) dose leading to a DMEL level (Derived Minimal Effect Level) which is a dose level that defines a specified (low) risk level, e.g. 10^{-6}.

In REACH a DMEL value (derived minimal effect level) may be derived which expresses a dose level associated to a certain calculated risk level e.g. a 10^{-5} lifetime risk level for the development of cancer (i.e. the dose level associated with one extra cancer case in a population of 100,000 people during a lifetime of 70 years).

A good strategy for research on a hazard characterisation for a specific chemical is to start finding one or more safe doses derived internationally by authoritative bodies, and if necessary, use more recent data to consider whether modification is necessary. If you need to characterize the hazard of a chemical substance, for which no specialist assessments are available, you may need to consult an experienced toxicological risk assessor (under peer review).

According to ECHA, a DNEL value is derived from the NOAEL or LOAEL by the application of appropriate assessment factors, AF:

$$DNEL = \frac{N(L)OAEL}{\mathrm{AF1} \times \mathrm{AF2} \times \mathrm{AF3}}$$

where the different assessment factors take into account differences in duration of exposure, interspecies differences (differences in susceptibility between experimental animals and humans), intra species differences (differences in susceptibility within the human population) and other factors such as the exposure duration and validity of the study that form the basis for the N(L)OAEL value. See also ECHA (2012c) for the principles of applying the various assessment factors.

Some examples of the use of assessment factors are given in table 2-2.

TABLE 2-2 EXAMPLES OF THE USE OF ASSESSMENT FACTORS IN DNEL DERIVATION

Parameter	Description	Applied assessment factor
Interspecies	Allometric scaling (differences in susceptibility due to difference in body size between animals and humans)	4 for rats 7 for mice 2.4 for rabbits 2 for monkeys
Interspecies	Remaining interspecies differences not pertaining to allometric scaling.	2.5
Intraspecies	Intraspecies differences (variability in suceptibility within the human population)	10
Duration	Factor accounting for extrapolation from non-chronic exposure to chronic (life-long) exposure	2 (subchronic (e.g. 90 days) to chronic) 6 (subacute (e.g. 28 days) to chronic)
Dose response considerations and other issues	LOAEL to NOAEL extrapolation, if LOAEL is used, because NOAEL has not been determined - very steep dose-response - very severe effects at the LOAEL - etc.	1-10

2.2.1 Pitfalls

From the REACH-registered substances DNEL values can be found at the ECHA-website. These values have been derived by the companies who have registered the substances. However, it may be difficult to evaluate the basis and the validity for these DNEL values.

Occupational Exposure Levels (OELs) are designed for workers in the occupational environment and therefore represent conditions that are not relevant or applicable for risk assessment of chemicals in consumer articles and products. Likewise, limit values used in other regulatory sectors should only be used with caution e.g. limit values derived for food, drinking water, medicines etc."

2.3 Exposure assessments

Before human exposure to a substance in an article can take place, the substance must be able to migrate out of or be liberated from the article. The magnitude of the migration depends on the properties of the matrix, the material of the article, and the chemical and physical properties of the chemical in question. A worst case estimate for migration can be made assuming 100% of the content migrates; or the migration can be measured under circumstances resembling real life conditions, e.g. by using artificial sweat in contact with clothes at body temperature for the duration of normal or worst case wear. Rough migrations estimates may be made from knowledge of similar cases with similar matrices or substances and in some circumstances estimations may be calculated using computer models.

Exposure to a substance in an article may take place through the following routes:

- Ingestion/mouthing.
- Skin, eye and mucous membrane (e.g. vagina) contact.
- Inhalation.

Upon exposure through the above mentioned routes, absorption into the body may take place to a larger or lesser degree and result in damage to inner organs. In some instances, the external contact with body surfaces (with virtually no absorption) is sufficient to exert damage to the body, e.g. local irritation and sensitization.

In figure 2-2 it is depicted how exposure to a chemical from an article occurs in several steps involving migration, deposition (adsorption) and absorption. For the risk assessor the challenge lies in quantifying the migration, deposition and absorption.

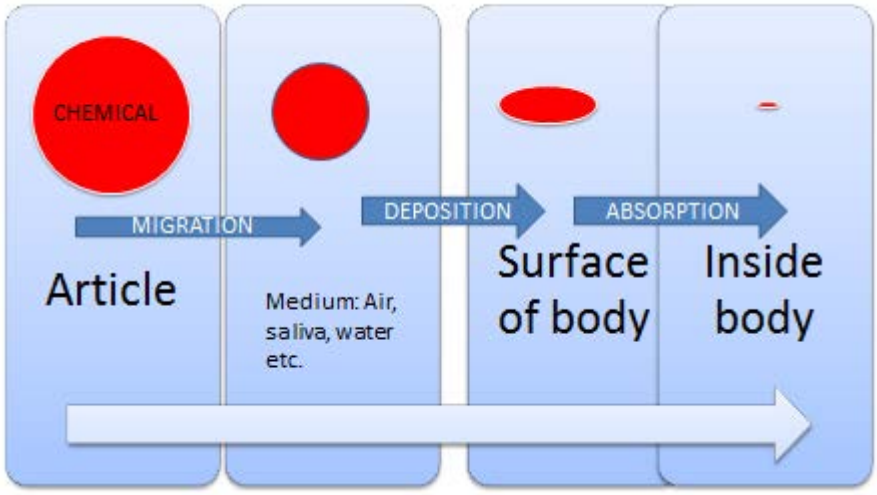

FIGURE 2-2 STEPS TO CONSIDER AND QUANTIFY IN AN EXPOSURE SCENARIO

Quantification can be made using deterministic or probabilistic methods (also known as Monte Carlo simulation). Deterministic methods will typically try to make point estimates, such as average exposure or realistic worst case exposure. Since the use conditions often vary among consumers average exposures will often underestimate the exposure for a large part of the population considered. A realistic worst case exposure is normally supposed to cover 95% of the population. If a point estimate representing a worst case exposure seems unrealistically high, such an estimate may be subject to further refinement by using probabilistic methods, which will show the likelihood

of exceeding certain predefined threshold exposures, and a sensitivity analysis of the various steps of exposure from article to body can be made.

The exposure assessment should, if possible, also take into account the background exposure of the consumer population from other sources than the article in question, such as food, drinking water and cosmetics. Even though the article can't be blamed for exposure to the substance in question from other sources, it may constitute a source which adds enough to the total exposure to constitute a level of concern.

The principles in calculations of exposure are illustrated by some examples below, whereas other more specific examples can be found in the annexes to this document.

Example of calculation of **oral exposure from an unintentionally swallowed article**:

$$D(oral) = \frac{F(oral) \cdot Fcprod \cdot n \cdot 1000}{BW}$$

Where

D(oral): intake per day and body weight in mg/kg bw/day.
F_{oral}: the mass fraction of the product ingested (g/g of product).
Fc_{prod}: the weight fraction of substance in article
n: the number of events per day
BW: is the body weight in kg of exposed person

Here 100 % migration/leaching of the chemical substance from the material is assumed as a starting point. If specific data on migration is available e.g. from experiments in artificial stomach, the exposure estimate may be further refined by this migration factor.

Example of calculation of **dermal exposure from substance in textiles**

$$D(derm) = \frac{L(derm) \cdot A(skin) \cdot n}{BW}$$

Where

D($derm$): the dermal dose per day and body weight in mg/kg bw/day
L($derm$): the dermal load in the skin that is expected due to migration in mg/cm^2
A($skin$): area of contact between product and skin in cm^2
n: the number of events per day
BW: the body weight in kg

In this equation the default rate of 100% dermal absorption is assumed. This estimate can be further refined if data is available for the substance in relation to the absorption rate.

Example of calculation of **inhalation exposure to vapours/ fumes from an article in a room**

$$D(inh) = \frac{\cdot C(air) \cdot V(inh) \cdot D(inh) \cdot n}{BW}$$

Where

D(inh): inhalatory dose (intake) of substance per day, in in mg/kg bw/day
C(air): the concentration of substance in the air in mg/m^3
V(inh): the volume of inhaled air by the person in m^3/ h
D(inh): the duration of inhalation , in hours per event.
n is the number of events per day
BW is the body weight in kg

As a default, 100% absorption of the inhaled dose is assumed. This estimate can be further refined to if data is available in relation to the absorption rate of the substance through the lungs.

2.4 Risk characterisation

In this risk assessment step the knowledge on safe levels from the hazard characterisation is combined with the data from the exposure assessment in order to evaluate whether the predicted exposure exceeds the tolerable exposure level.

Thus, the purpose of the risk characterisation is to provide a quantitative statement about the estimated exposure relative to the most appropriate limit value. The statement can be qualified in several ways. Below some examples are given.

Risk characterisation ratio, RCR (term used by ECHA)
The ratio of exposure level and DNEL:

$$RCR = \frac{estimated\ or\ measured\ exposure}{DNEL}$$

When the RCR exceeds the value of 1 this implies a toxicological concern for the exposure. The severity of this depends on the nature of the effect that is the basis for the DNEL value and the magnitude of which the value of 1 is exceeded.

If exposure occurs from several exposure routes simultaneously the overall RCR will be the sum of the RCRs by each route of exposure when RCR values for the exposure routes are calculated with respect to the same type of adverse effect: (e.g. the sum of inhalation and dermal and oral RCRs each based on DNELs on liver effects):

$$RCR_{total} = RCR_{inh} + RCR_{derm} + RCR_{oral}$$

The RCR cannot be translated to a specific probability that adverse health effects will occur. Note that an RCR exceeding 1 does not necessarily mean that adverse effects will occur, but the likelihood of adverse effect is increasing with increasing RCR, and the risk needs to be managed.

Margin of exposure (term used by EFSA)
The MOE is the ratio between the N(L)OAEL value and the estimated exposure:

$$MOE = \frac{N(L)OAEL}{exposure}$$

i.e. the MOE value is representing the space between the critical dose and the exposure. Thus for having a protective MOE the MOE value should be at least the same magnitude as the combined assessment factors as used for the DNEL calculations).

Margin of safety, MoS (term used by SCCF and others)
In the case of a threshold effect, the Margin of Safety (MoS) can be calculated. The MoS is the ratio of NOAEL and the Systemic Exposure Dosage (SED) and thus vey comparable to the MOE.

Non-threshold effects
For non-threshold effects (e.g. non-threshold carcinogenic effect) for which data allow to quantify the risk level at a given dose level e.g. a DMEL level representing a 10^{-5} lifetime risk or a specific unit risk (i.e. the risk level associated to exposure at 1 mg/kg bw/d or 1 mg /m^3) it may be possible to calculate a specific risk level associated to the estimated daily exposure from use of the article. Based on the outcome of this estimated risk level it can then be decided whether the risk is considered acceptable or not e.g. exceeding a 10^{-5} or 10^{-6} lifetime risk level.

Aggregated and combined exposure

Aggregated exposure takes account of the total exposure to one substance from multiple different sources. In cases where there is knowledge about other major exposure sources or a big background exposure, it can be appropriate not to accept the exposure from one single specific product to "use" the full Tolerable Daily Intake or Derived No Effect Level. Instead the aggregated exposure should be calculated and used when the risk is assessed.

Using the terminology used by ECHA, the RCR would be calculated based on the aggregated exposure:

$$RCRaggregated = \frac{estimated\ aggregated\ exposure}{DNEL}$$

Combined exposure takes into account that we are exposed to multiple different substances with similar effects. The combined exposure can be estimated for a number of substances with similar effects, found in the same product or coming from multiple different sources and pathways.

Using the terminology used by ECHA, the RCR_{total} can be calculated by summing up the RCRs for each of the substances in the group. The RCR values must be based on the same type of adverse effect (e.g. the sum of RCRs for substance A, B and C based on DNELs on anti-androgenic effects):

$$RCR_{total} = RCR_{substance\ A} + RCR_{substance\ B} + RCR_{substance\ B}$$

3. Where to find the tools needed to make a risk assessment

In this chapter some useful references and links to authoritative guides for various product groups, e.g. cosmetics are provided.

3.1 Tools for hazard identification and characterisation

At the ECHA web site, http://echa.europa.eu/ toxicity data on chemical substances can be found in the REACH registrations of substances. DNEL values can also be obtained there. Note, that data from the registrations dossiers reflect the opinion of the registrants and thus cannot be considered as independent expert evaluations.

At the ECHA website, links are given to more than 140 EU risk assessment reports performed in the period up to 2008, and it is possible to find NOAELs for the specific substances in these reports. Also, DNEL values for substances subjected to the authorisation process can be found, and DNELs values used for assessment of Annex XV restriction proposals can be found. Such DNEL values have been approved by the Risk Assessment committee (RAC) at ECHA.

Guidance on how to derive a DNEL or DMEL can be found in ECHA's guidance document R8: Characterisation of dose [concentration]-response for human health (ECHA 2012c)
http://echa.europa.eu/documents/10162/13632/information_requirements_r8_en.pdf

ECHA´s practical guide 14: How to prepare toxicological summaries in IUCLID and how to derive DNELs. (ECHA, 2012b).
http://echa.europa.eu/documents/10162/13655/pg_14_on_hazard_endpoint_en.pdf

Gateway to the opinions of the EU Scientific Committees (SCCS, SCENIHR, SCHER) and others can be found here: http://ec.europa.eu/health/scientific_committees/portal/index_en.htm

Risk assessments for substances, which may be found in food, intended or accidentally, can be found at the webpage of the European Food Safety Authority, EFSA: http://www.efsa.europa.eu/. These substances may also be relevant for non-food consumer products.

The Agency for Toxic Substances and Disease Registry (ATSDR) has published numerous profiles on chemical substances. These provide an excellent starting point for obtaining data, and getting suggestions for minimal risk levels (MRLs) for various routes of exposure and durations. They can be found on the website here: http://www.atsdr.cdc.gov/

The WHO International Programme on Chemical Safety has published a series of assessment of chemicals and toolkits which may be found here: http://www.who.int/ipcs/en/

IUCLID and SIDS reports (data and hazards OECD evaluations of specific chemicals) can be found here: http://webnet.oecd.org/hpv/ui/Search.aspx.

The ESIS database provides EU-risk assessment reports on high production volume Chemicals up to 2008, and can be found here: http://esis.jrc.ec.europa.eu/index.php?PGM=ora

3.2 Tools for exposure assessment

Various tools exist to carry out exposure estimates. One of these is the Targeted Risk Assessment Tool for occupational exposure and consumer exposure developed by ECETOC (version 3 May 2012, http://www.ECETOC.org), which is the one most often referred to by ECHA.

ECHA guidance Chapter R 15: Consumer exposure estimation (ECHA 2009) http://echa.europa.eu/documents/10162/13632/r15_update_version_2_rev1_1_en.pdf. This guidance describes an efficient, step-wise and iterative procedure for the estimation of consumer exposure to substances in preparations or in articles. The appendix gives a good overview of algorithms applicable for the estimation of exposure through oral, inhalation and dermal exposure. Anthroprometic data like body weight and surface areas, respiration volume and room volumes and ventilation rates are also given.

ECHA guidance Chapter R 17: Estimation of exposure from articles (ECHA 2012) http://echa.europa.eu/documents/10162/13632/information_requirements_r17_en.pdf. This guidance presents different models for exposure assessment from articles, using the tiered approach, i.e. going from a rough estimate to more refined estimates.

Another source for exposure estimation for articles is the EIS-Chemrisk database (http://web.jrc.ec.europa.eu/eis-chemrisks/toolbox). A registration is required in order to use the database.

Background exposure from food may be found at EFSA's web page: http://www.efsa.europa.eu/

The Scientific Committee on Consumer Safety, SCCS, has published a guide in which skin areas of various parts of the body and the amounts of cream, lotion, hair shampoo etc. normally applied per day is given (SCCS, 2012):
http://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_s_006.pdf

The US-EPA regularly publishes an Exposure Factors Handbook, giving amounts of exposure to various media, including consumer products in the USA. Many of the data given there may also apply to Europeans (EPA, 2011).

Nordic Council of Ministers (2012). Existing default values and recommendations for exposure assessment – A Nordic Exposure Group Project. TemaNord 2012:505. ISBN 978-92-893-2316-1. http://dx.doi.org/10.6027/TN2012-505):
http://www.norden.org/en/publications/publikationer/2012-505/
Overview and evaluation of exposure factors, that are currently used by the authorities and industry in the exposure assessments for both adults (occupational and consumer exposure) and children in relation to REACH. Contributes to harmonisation of exposure factors by giving recommendations of most valid and representative defaults.

A guide to making probabilistic exposure assessments and Monte Carlo simulations can be found in Vose, 2000. Several computer programs exist to aid in carrying out probabilistic risk assessments, e.g. @RISK, which works as an add-in to Excel spreadsheets.

3.2.1 Exposure assessment with children in focus

RIVM report 320005005/2007: Non-food products: How to assess children's exposure? (RIVM 2007): http://www.rivm.nl/bibliotheek/rapporten/320005005.pdf

Defines appropriate exposure scenarios for children, aspects to consider and include in the micro-environment, the characteristics of the chemical, the age related behaviours and activities of the child, the resulting exposure pathways, and assumptions on the uptake of the chemical via these pathways.

Nordic Council of Ministers (2012). Existing default values and recommendations for exposure assessment – A Nordic Exposure Group Project. TemaNord 2012:505. ISBN 978-92-893-2316-1. http://dx.doi.org/10.6027/TN2012-505):
http://www.norden.org/en/publications/publikationer/2012-505/
Overview and evaluation of exposure factors, that are currently used by the authorities and industry in the exposure assessments for both adults (occupational and consumer exposure) and children in relation to REACH. Contributes to harmonisation of exposure factors by giving recommendations of most valid and representative defaults.

3.3 Tools for risk characterisation

Many of the same organisations as those mentioned above also give tools for risk characterisation. Examples can be found at:

Opinions from the Scientific Committee on Consumer Safety (SCCS), Scientific Committee on Health and Environmental Risks (SCHER), and Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) can be found by starting here: http://ec.europa.eu/health/scientific_committees/about/index_en.htm

ECHA guidance on risk characterisation can be found in guidance document Part E: Risk Characterisation: http://echa.europa.eu/documents/10162/13655/pg_15_qualitative-human_health_assessment_documenting_en.pdf

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Appendix 1: Example of risk assessment of flame retardant found in scented toys

The flame retardant tris(2-chloroethyl)phosphate (TCEP) was unexpectedly found during a GC/MS screening of scented toys (in this case a soft textile cube) intended for children under the age of 3. The amount extractable from the materials of the cube with dichloromethane was 5,800 mg/kg material. The material was a combination of textile, plastic, and rubber foam. An assessment of the risk of the flame retardant to children using this product was prepared.

Hazard identification

Data searches were carried out in the EU risk assessment reports, IUCLID and US-EPA (Toxnet, Riskline, IRIS and HSDB).

Hazards identified in animals after repeated exposure were: liver, kidney and brain damage, suspected carcinogen classified in group 3, group 2 classification is under consideration (in 2005). Classification as hazardous to reproduction in group 2 (Rep2) was also under consideration.

CLASSIFICATION (IN 2005)

Chemical substance	CAS nr.	Classification	Hazards
Tris(2-chloro-ethyl)phosphate	115-96-8	Xn;R22 Carc3;R40 N;R51/53	Harmful if swallowed Possible carcinogenic effect

SUGGESTED NEW CLASSIFICATION ACCORDING TO DRAFT RISK ASSESSMENT REPORT

Chemical substance	CAS nr.	Classification	Hazards
Tris(2-chlor-ethyl)phosphat	115-96-8	T;R22 Carc2;R45 Rep2;R60 N;R51/53	Toxic if swallowed Can cause cancer Hazardous to reproduction

Hazard characterisation

NOAEL values found in the literature for tris(2-chloroethyl)phosphate

Animal	Exposure/ study duration	Doses mg/kg body weight	Effect/organ	NOAEL mg/kg body weight/day	Reference
Rat	Orally Daily, 3 months	400; 1.000; 3.000; 8.000	weight, food intake, liver/kidneys	400	IUCLID 2000
Rat	Orally by gavage 5 d/w, 16-18 weeks	22; 44; 88; 175; 350	death, liver/kidneys	88	IUCLID 2000
Mus	Orally by gavage 5 d/w, 16 weeks	44; 88; 175; 350; 700	kidneys	350	IUCLID 2000
Mus	Oral by gavage Daily, 2 -16 weeks	44; 88; 175; 350; 700	liver/kidneys	88	IUCLID 2000
Rat	Orally by gavage, 103 weeks	44, 88	Kidney cancer Brain damage	LOAEL: 44 NOAEL: 44	RAR 2004
Rat	Orally by gavage, day 7-15 of gestation	50; 100; 200	Teratogencity, food intake	Mother: 100 Fetus: >200	RAR 2004
Mouse	Orally with diet Daily, 18 months	12; 60; 300; 1500	Kidney damage	**LOAEL: 12**	RAR 2004

The LOAEL of 12 mg/kg bw/day was selected as the point of departure (critical dose level) for the risk assessment. The critical effect was damage to the kidneys.

Exposure assessment

Relevant route of exposure was assessed to be through the skin.

A specific migration test was carried out on a sample of 5 g consisting of parts from all ingoing materials in their respective proportions in the cube. The simulant used was artificial sweat consisting of sodium chloride, ammonia, lactic acid, carbamide and water according to DS/EN 1811. Extraction in artificial sweat was carried out in 24 hours at 40 °C.

A quantitative determination of the migration of the flame retardant showed that 100% of the content migrated into the sweat simulant.

An exposure scenario was created according to the principles given in Technical Guidance Document from 2003 (TGD, 2003).

It was assumed that the area of contact was the palms of the child, corresponding to 2.2 % of the total surface area of 60.3 dm^2. Additionally, it was assumed that the entire migrated amount was absorbed at once.

The potential exposure, E, was calculated using the formula:

(1) $E = \frac{C}{a} A$, where

C is the amount of chemical in mg/kg of the article
a is the area per mass of the article, in dm^2/kg
A is the area of exposed skin in dm^2

Next, the potential amount of chemical absorbed through the skin, $U_{der,\,pot}$, was calculated using the formula

(2) $Uder, pot = \frac{E \cdot n}{BW}$, where

n is the number of exposures per day
E is the potential exposure in mg
BW is the body weight in kg
$U_{der,pot}$ is the amount of chemical potentially absorbed in mg/kg body weight/day (considering 100% skin absorption of the substance)

In this particular case, the following parameters were used as:
A $60.3 \cdot 0{,}022$ dm2
n 1 time per day
BW 15 kg

The resulting $U_{der,pot}$ was found to be 5.8 mg/kg bw/day.

Risk characterisation

The potential exposure 5.8 mg/kg bw/day evaluated against the LOAEL of 12 mg/kg bw/day, giving a margin of safety (MoS) of 2.

A MoS of 2 was deemed too small regarding:
1: allowance for extrapolation from animals to humans
2: allowance for variation among individuals
3: allowance for using LOAEL as point of departure and not NOAEL
4: allowance for serious effects such as cancer

Referring to the above mentioned points, an acceptable margin of safety was set to be at least 100.

It was noted that the type of flame retardant could be present elsewhere in the environment of a child, leading to additional exposure.

The migration test was made over 24 hours. If the liberation of the flame retardant is assumed to be linear, and the duration of exposure was only 3 hours per day, the MoS would be 17, which is still well below the acceptable 100. Simultaneous oral exposure could lead to even higher absorption, it was noted.

Conclusion

The severity of injury was kidney damage and cancer.

The probability of such effects occurring was not calculated, but a MoS of 2-17 indicates a high probability. Hence, the risk level was deemed “serious”, and it was taken off the market and reported to RAPEX.

Appendix 2: Risk assessment of erasers with DEHP

During a mapping of substances found in school supplies in 2007, a PVC eraser with a content of 35% diethylhexylphthalate (DEHP) was identified. The question was whether this eraser posed a serious risk for the consumer, a small school child.

Hazard identification

DEHP is classified as Rep2; R60-61: May impair fertility. May cause harm to the unborn child (according to Directive 67/548/EEC).

Hazard characterisation

DEHP has low acute toxicity.

The critical effect was assessed to be testicle toxicity. This was deduced from a two-generation rat study with a NOAEL of 8 mg/kg bw/day for reduction in testicle weight. Same study gave a NOAEL of 77 mg/kg bw/day for damage to reproductions. In another two-generation study on rats a NOAEL of 4.8 mg/kg bw/day for testicle toxicity and a NOAEL of 46 mg/kg bw/day for damage to reproduction was found.

The NOAEL of 4.8 mg/kg bw/day was used as point of departure (critical dose level) for the risk assessment.

Exposure assessment

The following scenario was considered:

A child of 20 kg bw swallows 0.1; 0.05 or 0.008 g of eraser daily during one hour of sucking, chewing or biting the eraser, which is measuring (1 x 3.1 x 1) cm^3 and weighing 3.79 g.
The specific value of 0.008 g of eraser was one of the chosen values, since it is the upper limit for intake of toys employed in the standards for assessment of toys in DS/EN 71-3 "Legetøj. Sikkerhedskrav. Del 3: Migration af særlige stoffer".

Extrapolation from migration tests into artificial saliva of other PVC erasers showed that the expected migration of DEHP from the eraser would be 0.23% of the 350 mg DEHP/g corresponding to 0.81 mg DEHP per g of eraser.

The oral intake was calculated from the following formula, according to principles in the TGD (2003):

$$I_{oral} = \frac{A_{oral} \cdot Fc_{migr} \cdot T_{contact} \cdot n}{BW} \cdot F_{oral}$$, where

I_{oral}	Amount of substance ingested	µg/kg bw/day
A_{oral}	Total amount of article licked or chewed at	G
Fc_{migr}	Fraction of substance migrating to saliva	µg/g
$T_{contact}$	Duration of exposure per	Minutes
n	Number of incidents per day	

BW	Body weight	Kg
F_{oral}	Fraction absorbed (bioavailable part)	100%

The oral absorption of DEHP was considered to be 100% as default.

The resulting exposure of DEHP from eraser number 12 was:

Eraser no.	Ingested amount, Qprod,oral (g)	Oral intake, Ioral (mg/kg bw/day)
12	0.1	1.75
12	0.05	0.88
12	0.008	0.14

Risk characterisation

The margin of safety (MoS), i.e. the ratio between NOAEL of 4.8 mg/kg bw/day and the oral intake was calculated as follows:

Eraser	Ingested amount, Qprod,oral (g)	Oral intake, Ioral (mg/kg bw/day)	MoS
12	0,1	1,75	2,74
12	0,05	0,88	5,45
12	0,008	0,14	34,3

As can be seen in the table above, depending on how large amounts of eraser are swallowed daily the MoS lies between 2.7 and 34.3, which is below the 100 or more which is the normally acceptable MoS, considering the data available and their quality.

When performing the migration analysis to artificial saliva, the eraser was cut in small pieces (cubes) of 2-3 mm width. This means that the surface becomes larger than the unbroken eraser. In order to illustrate this, the surface of such an eraser was cut up in cubes of 0.3 x 0.3 x 0.3 cm^3. This would give 390 pieces of eraser, each with a surface of 0.3 x 0.3 x 6 = 0.54 cm^2, i.e. a total surface of 211 cm^2. In comparison the unbroken eraser has a surface of ((3.8 x 3.1) + (3.1 x 1) + (3.8 x 1)) x 2 = 37.4 cm^2, i.e. almost a factor 6 smaller. This means that if the eraser is only licked and not swallowed the calculated exposure is overestimated by a factor of 6. This means that the MoS will be above 100 if the eraser is only licked.

Conclusion

It was assessed that the type of critical hazard was damage to reproduction and testicular toxicity. The risk was considered serious since the margin of safety was below 100.

Note: this risk assessment was subjected to review by the scientific committees, who did not agree with this conclusion, as they did not believe the intake could be as high as presumed here.

Appendix 3: Example of absence of risk: articles made of chloroprene

In many cases, findings will prompt a risk assessment, and when the steps though the risk assessment is followed, it becomes clear that the risk is not serious or even absent. The following is an example of such a case.

The case is taken from the report titled “Mapping and release of chemical substances from products made of chloroprene”, Survey of Chemical Substances in Consumer, Products, No. 51 2004, published by the Danish EPA here: http://www2.mst.dk/Udgiv/publications/2004/87-7614-767-3/pdf/87-7614-768-1.pdf

The purpose of the project was to focus on the problematic substances that appear in different consumer products of chloroprene, such as boots, waders, dive suits and supports available in retail stores in Denmark. The project comprised three phases. Firstly, mapping of consumption and consumption patterns regarding products made of chloroprene. Secondly, a screening phase for problematic substances as well as migration/exposure tests under conditions determined by "worst case" scenarios. Finally, health screening based on the results from the migration tests completed the project.

The investigation showed initially that the shops or other sales channels do not know the word chloroprene, but solely the word neoprene, which is the raw material company of DuPont Dow Elastomers' trademark for chloroprene rubber. The investigation has shown that a considerable amount of consumers gets into contact with products made from chloroprene. First of all products like support bandages, boots and waders contribute. Also the number of consumers who use wet-, semi wet -and dry suits for sport or exercise in the wet element is considerable.

The products selected comprised two types of supports, two different brands of dive gloves, a pair of dive socks, a dive hood, a pair of waders and a dive suit.

The gas chromatographic/mass spectroscopic screening through headspace and analysis of extracts of the products themselves demonstrated the presence of a fairly large number of different types of substances. For waders, the toluene level appeared to be 21 µg/g.

In total 46 chemical substances were identified and assessed for health effects in the screening phase. In the migration studies 7 “problematic” chemical substances were identified from the screening list for health effects. These chemical substances were selected for a closer assessment.

Hazard identification

Name	CAS no.	Hazard
Isophorone	78-59-1	Xn; R21/22 Harmful by skin contact and ingestion. Xi; R36/37 Irritates the eyes and respiratory organs. Carc3; R40 Potentially carcinogenic.
Toluene	108-88-3	Rep3; R63 Possible damage to the child during pregnancy. Xn; R48/20-65 Hazardous: serious health risk by longer time's exposure by inhalation. Hazardous: can result in damage to the lungs by intake. Xi; R38 Irritates the skin. R67 Vapour might give rise to bluntness and dizziness.
Phenol	108-95-2	T; R24/25 Toxic by skin contact and by ingestion. C; R34 Corrosive.
N,N-Dibutyl formamide	761-65-9	Rep3; R61 Might harm the unborn child. Xn; R20/21 Hazardous by inhalation and skin contact. Xi; R36 Irritates the eyes.
N,N-diethylthio-urea	105-55-5	Xn;R22, Harmful by ingestion. Allergic contact eczema.
N-Butyl benzene sulfonamide	3622-84-2	Harm to reproduction.

Hazard characterisation

Name	NOAEL, dose-response etc.
Isophorone	150 mg/kg
Toluene	625 mg/kg
Phenol	LOAEL = 1.8 mg/kg
N,N-Dibutyl formamide	60 mg/kg
N,N-diethylthio-urea	LD50 = 300 mg/kg
N-Butyl benzene sulfonamide	< 57 mg/kg

Exposure assessment

In order to be able to assess the exposure in "real life" of potential migration from consumer products made of chloroprene, a full-scale test with an experienced sport diver was carried out to complete the migration studies. The diving test was carried out near Marselisborg marina in Aarhus where the water is 6-7m deep near the shore. The diver dived twice on Wednesday, 19th November 2003. The temperature of the sea water was 8 °C and the temperature of the water drained from the suit was 18 – 20 °C. After the two-dive phase (65 minutes in total) and a break on shore (90 minutes), the dive suit was emptied of water on site by drawing it off from the sleeves and legs into a clean beaker. The water was then poured into a clean glass with a screw cap. The water from the dive suit was then to run off overnight so a clean beaker was placed below each of the legs of the suit. The water that ran off was combined with the water drawn off on site. The total amount of water was 155ml. A sample was taken of the sea water as reference for the migration analysis.

Converted to skin area based on 20.000 cm2 one can calculate the following concentrations of migrating chemical substances per cm^2 skin area: Isophoron 0.003 ng/cm^2, N,N-dibutylformamid 0.26 ng/cm^2, and N,N-diethylthiourea 0.28 ng/cm^2.

The migration tests carried out in the laboratory to artificial seawater did not show any migration of N,N-diethylthiourea, but in the real life exposure there was a measurable migration. The measured migration levels of chemical substances calculated by area unit were less than 1 ng/cm^2 for all substances in the "real life" experiment. For two substances i.e. isophoron and N,N dibutylformamide the results from the laboratory exposures were 11 ng/cm^2 and 20 ng/cm^2. These results were much higher than real-life. This shows the importance of carrying out migration experiments as close to actual exposure conditions as possible.

The exposure assessment was based on the exposure of an adult with a body weight of 70 kg.
For calculation of the human uptake the following exposure areas are assumed:

Knee bandage	400 cm^2
Diving hut	1,000 cm^2
Waders	6,360 cm^2
Gloves	840 cm^2
Diving suit	20,000 cm^2

The uptake was calculated by:

$$Uptake\left[\frac{g}{kg}per\ day\right] = \frac{exposed\ skin\ area\ [cm2]\cdot\ amount\ per\ area\left[\frac{g}{cm2}\right]}{body\ weight\ [kg\ ]}$$

In the calculation is was assumed that the exposure happens no more than once a day in the mount of hours that are given for each product. Further, it was assumed that 100 % of the substance is absorbed. The results of the migration tests and the diving test are calculated to amount of the substance that might be present in the body after exposure.

Risk characterisation

When the results of the exposure assessment were compared NOAELs, other dose-response data etc., it became clear that the exposure is at least a 1000 times below, i.e. the MoS is more than 1000. Hence no appreciable risk could be established.

Name	NOAEL, dose-response etc.	Values measured in the exposure assessment
Isophorone	150 mg/kg	3 µg/kg bw and 0.1 µg/kg bw
Toluene	625 mg/kg	0.4 µg/kg/bw
Phenol	LOAEL = 1.8 mg/kg	0.7 µg/kg bw
N,N-Dibutyl formamide	60 mg/kg	1.3 µg/kg bw
N,N-diethylthio-urea	LD50 = 300 mg/kg	6.7 µg/kg bw
N-Butyl benzene sulfonamide	< 57 mg/kg	2.4 µg/kg bw

Conclusion

The probability of damage was so small that the risk was considered low/not existing.

Guidance for risk assessment of chemicals in consumer articles and products

This guidance document has been prepared as a tool for the competent authorities of the EU member states in preparing health risk assessments for chemicals found in various non-food consumer articles, destined or likely to come into contact with consumers. The purpose is to ensure uniform and consistent methods applied in the risk assessments among the competent authorities in the member states of the EU.

Danish Ministry of the Environment
Environmental Protection Agency

Strandgade 29
1401 Copenhagen K, Denmark
Tel.: (+45) 72 54 40 00

www.mst.dk