Chemicals in Toys

A general methodology for assessment of chemical safety of toys with a focus on elements

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Executive summary

The work described in this report was carried out on request of DG Enterprise in view of contract nr. SI2.ICNPROCE003918500. In the call for tender (ENTR/05/005), the following two objectives were defined:

1) to examine how the limit values for certain elements that are contained in toys, laid down in Annex II.II.3 of Directive 88/378/EEC on the Safety of Toys should be revised according to recent scientific knowledge and to examine whether other elements should be added to the list in that Annex (4.1.1.1);
2) to examine the way to address the content of chemicals in toys intended for children under 36 months or intended to be put in the mouth.

In the present report we present a *risk based* methodology that can be used to assess the safety of exposure to chemicals in toys. To demonstrate its use we applied this methodology to elements with the emphasis on toys intended for children under 36 months and on toys intended to be put in the mouth.

The essence of the methodology is the assumption that exposure of children to chemicals in toys may not exceed a certain health-based level (Tolerable Daily Intake, or TDI in mg/kg bw/day). Since children are also exposed to chemicals via other sources than toys we advocate that a certain percentage of the TDI should be allocated to toys. A number of arguments for the choice of this percentage are presented for elements. The actual choice of a percentage is a risk management decision and is not taken as such in this report.
In chapter 2, general issues in deriving health-based limit values (TDI) are discussed. A list of elements which is thought to be relevant to be included in the Toy Directive is presented and for each of these elements the most recent and appropriate TDI is given. Since hardly any data on the presence of elements in toys (apart from those already in the Directive) were available, it could not be demonstrated which elements are relevant for which toy materials. The presented list is therefore to be considered as a starting point from which substances can be removed when data become available to show their irrelevance for toy materials.
To assess whether the exposure of a child via toys is acceptable, exposure characteristics are required to be taken into account. Three worst case default values for oral contact were therefore defined. One for textile fibers and material that can be scraped off with teeth (8 mg), one for dry, pliable or powder-like materials like modeling clay (100 mg) and one for liquid material like finger paint (400 mg). Also default values for mouthing times for children < 3y of age (3h) and for toys intended to be put in the mouth for children > 3 y of age (1h) were derived. Beside that, guidance is given on how to assess exposure to chemicals in toys following inhalation or dermal contact (chapter 3).

When the contact or exposure scenarios to a toy are defined, information is needed on the amount of chemical that actually will migrate from the toy material. Chapter 4 describes and compares different migration test methods. Mouthing can be simulated by means of extraction with artificial saliva or water. This method will suffice for both organic compounds as well as elements. Ingestion can be simulated with a current migration test according to EN71-3. This method will suffice for elements, but will not be generally applicable to other substances.
The possibility to make use of limit values derived for chemicals in the scope of the Food Contact Material (FCM) legislation is explored in chapter 5. In principal, it may be possible that substances with low migration in the FCM framework (< 0.05 mg/kg food or fluid) may be directly allowable in toys without further testing. However, this can only be allowed when it is assured that the toy material / matrix (of the finished product) is identical to that tested in the FCM framework and when the testing conditions conform to Directive 82/711/EEC and 90/128/EEC, are relevant for toy exposure. Even then, there are some uncertainties because FMC involves static migration while mouthing involves dynamic migration. Furthermore, the FCM concept allows exposure that may be higher than the fraction of TDI that is allowable for toys (at least for elements, see chapter 8). Therefore, this extrapolation should only be used after sufficient experimental validation data become available showing that such an approach is indeed safe. For the time being, we recommend not to extrapolate FCM migration limits to toys.
Two other possibilities to use the FCM framework are derived TDIs and the negative lists. When TDIs have been derived for substances in the FCM framework, these can be directly used to derive limit values according to the methodology in the present report. Also it can be decided by risk management, to consider the negative lists of the FMC framework relevant for toys. In that case, chemicals from this lists may not be used in toys.
In chapter 6, analytical issues like sampling and the use of correction factors are discussed. It is proposed that a single sample can be used for compliance testing and that all accessible parts of a toy must comply with EN 71-3. If a toy consists of different materials, subsamples should be taken from each material. In contrast to the present limit values for elements, correction values are recommended not to be included in the limit values.

Finally, in chapter 7 a methodology based on the findings in the preceding chapters and applicable to any kind of substance in any kind of toy is presented. The use of this methodology will be illustrated for elements in chapter 8 on toys intended for children < 3 years of age and toys intended to be put in the mouth (> 3 years of age). In this chapter also a proposal for migration limit values for the elements proposed in chapter 2 is presented.

The analysis as made in this report makes clear that on various topics further research is required. Recommendations for further actions are given at the end of each chapter.

Risk-Based Methodology

The methodology is set up according to a general approach which can be used for any type of chemical. Conform the assignment, the methodology is specifically applied to inorganic elements resulting in a proposal for an update of the (migration) limit values for this group of chemicals in toys intended for children < 3 y of age and for toys intended to be put in the mouth.

The basis of our approach is:

Exposure of children to substances in toys should not exceed a certain health-based level (in mg/kg bw/day)

In this approach, for elements we have chosen a chronic limit value as the relevant health-based limit level. Exposure to chemicals from toys (e.g. when mouthed) is characterized by daily exposure during a period of maximum 1-2 years. This would support the use of a sub-chronic limit value. However, subchronic limit values are not routinely available for all chemical substances. Chronic health-based limit values on the other hand are routinely available for most chemical substances, at least for the oral route and assure an adequate level of protection. Therefore, in the case of elements, it is proposed to use the concept of the Tolerable Daily Intake (TDI) for setting limit values for elements in toys.

Especially in the case of elements, children are also exposed via other sources. Therefore we allocate a certain fraction of the TDI to exposure via toys. The allocation of the size of that fraction is clearly a risk management issue. In chapter 8 arguments for the allocation are provided.

For elements, therefore, the basic approach can be re-stated as:

The exposure of children to chemicals in toys may not exceed X% of the TDI (in mg/kg bw/day)

As further guidance on how to apply this approach we offer three options that can be used to check whether a particular toy can be assessed as safe.

OPTION 1: Use of migration data

This is conceptually the same principle as the present methodology described in EN 71-3. In contrast to EN 71-3 the derivation of migration limits is made transparent in this report.
It is recognized that exposure to a chemical can only result in exposure when the chemical is first released from the matrix (thus is: bioaccessible). The migration method as described in EN 71-3 uses an acid extraction for the release of elements from a toy matrix, and is valid for assessing exposure via the oral route (and also for dermal exposure). This option can only be used if one exposure route dominates the others with respect to the fraction of the dose that actually leads to systemic exposure. For children < 3y of age and for toys that are intended to be put in the mouth, oral exposure is the most relevant route of systemic exposure. For elements in toys intended for children < 3 years, migration limits are derived for three different types of toys: solid (easily to break or bite off), liquid or sticky material and for material to be scraped off. For toys intended to be put in the mouth (> 3y) only the limit for scraped off material is relevant, because children of this age display less mouthing behaviour. For elements, it is assumed that when migration limits for oral exposure are derived, these cover both mouthing and ingestion.
The basic principle is the following:

The child shall not be exposed to a certain chemical (element) > X% of TDI

Therefore:
The leachable amount of element from a maximum amount of toy that can be ingested divided by body weight of child should be below X% of TDI.

Using the default values derived in chapter 3 for ingestion and body weight, and using X% of the TDI as a basis, migration limit values can be calculated for elements.
In chapter 8, four tables are presented, where migration limit values are calculated for 3 different fractions of the TDI (5, 10 and 20%). The choice of the actual percentage is a risk management decision.
Three tables refer to children < 3 years of age (ingestion via scraping off material, solid and liquid or sticky material) and one refers to toys intended to be put in the mouth (> 3y).

OPTION 2: Use of product (toy material) composition data

In this option the chemical safety of the toy is demonstrated by documentation on the amounts of elements present in the toy materials. In this option one can use chemical analyses of the raw materials used for making the toy. If chemical analyses of all the raw industrial

materials are available and show only trace amounts of elements or such low levels that the total amount in toys is < X% TDI, then additional testing is not necessary. This documentation can then show the chemical safety of the product.

The following calculation can be used for demonstrating the safety of a toy.

$$\frac{\text{Element in toy (mg/kg toy material) x weight of toy material (kg)}}{\text{Body weight child (kg)}} < \text{X\% TDI}$$

In this approach it is assumed that the element is completely released at once from the product and available for exposure. Bioaccessibility is thus 100%.

This approach should be viewed as a kind of 'waiver-opportunity' for further testing. Those producers that have data available to demonstrate the absence of elements (or other substances) in their material can use those data for compliance with the X% TDI limit. The X% TDI value is therefore again the ultimate limit value. Since at present it might be difficult for all producers (and importers) to get hold on this information, in the future, under REACH this will probably improve.

OPTION 3: Use of a quantitative risk based approach

The use of this option is recommended in the following cases:

- Chemicals in toys for which exposure via inhalation may occur
- Chemical in toys for which more than one exposure route contribute significantly to the systemic exposure
- When the results of a migration test indicate that the bioaccessible amount may exceed the relevant health-based limit value for the chemical under consideration, and it can be demonstrated that default factors used for the derivation of these limit values are not relevant for the toy under consideration. Because a number of (worst case) assumptions are being made in option 1, option 1 is a conservative approach and may not be relevant for specific types of toys. For example, in option 1 (and 2) it is assumed that the measured migration will occur daily. In reality this may not be true for all kinds of toys. Furthermore, the EN 71-3 acidic test system is worst case in a sense that for elements the highest migration occurs in the acid environment, simulating the stomach, whereas absorption of most substances occurs in the less acidic small intestine. Additionally, most of the elements present in the tested matrix will be released in the first test, the migration may be lower in reality. A second extraction (e.g. day 2 of mouthing) will usually not release the same amount of element.

Option 3 provides the opportunity to demonstrate the chemical safety of a product even if the values of the initial migration test are higher than the values listed in chapter 8. This can be achieved by using a number of specific exposure scenarios (chapter 3) and – if desired – refined migration testing (chapter 4). In essence, option 3 can be seen as an EC-type[1] examination. This option should only be used when it can be argued convincingly that the default factors used in option 1 are not relevant for the toy under investigation.

[1] EC type examination is the procedure by which an approved body, called 'Notified Body' ascertains and certifies that a model of a toy satisfies the essential requirements of the Directive Safety of Toy

How to read this report?

The methodology presented in this executive summary, and that is discussed in detail in chapter 7 is the result of discussions as laid down in the other chapters.
We recommend the reader to start reading the ‘simple’ version of the methodology described in the executive summary and then go to chapter 7. When more guidance or background information is needed on specific issues, the reader is referred to the respective chapters.

A number of the issues that are discussed in this report were also raised by the CSTEE. These are answered in chapter 2 to 8. For a short overview of these issues and separate comments, see Appendix I.

1 Introduction and approach

The work described in this report was carried out on request of DG Enterprise in view of contract nr. SI2.ICNPROCE003918500. In the call for tender (ENTR/05/005), the following two objectives were defined:

1) to examine how the limit values for certain elements that are contained in toys, laid down in Annex II.II.3 of Directive 88/378/EEC on the Safety of Toys should be revised according to recent scientific knowledge and to examine whether other elements should be added to the list in that Annex (4.1.1.1);
2) to examine the way to address the content of chemicals in toys intended for children under 36 months or intended to be put in the mouth

1.1 Background

The permissible levels of 'bioavailable' elements from toys as laid down in Council Directive 88/378/EEC, were actually derived in a June 1985 advice by the *Scientific Advisory Committee to examine the toxicity and ecotoxicity of chemical compounds*, as published in report EU 12964 EN.

The Committee chose an approach based on literature data concerning normal weekly intakes of metals via the diet by adults in the EU, as selected from literature. It was assumed that children (with assumed body weight of up to 12 kg) would have an intake of 50% of the adult weekly intake levels (both expressed as µg/week). Leaching from toys should not contribute more than 10% of the dietary intake, the Committee stipulated. Subsequently the Committee evaluated the toxicology of the elements dealt with, which included comparison with WHO *Provisional Tolerable Weekly Intakes* where available. In this evaluation consideration was given to children's sensitivity regarding toxicity and toxicokinetics (absorption) as far as possible. Based on these evaluations the Committee determined whether for individual elements the figure of 10% of normal dietary intake being permissible for leaching from toys, needed adjustment. For antimony, barium, mercury and selenium the toxicity evaluation did not warrant lowering the figure of 10%. For barium, however, the percentage was lowered to 5% because of the high normal dietary intake for this element. For arsenic and chromium the percentage was lowered to 0.1% and 1.0%, respectively, because of their known carcinogenicity and mutagenicity via the oral route. For cadmium the percentage was lowered to 5% because the normal dietary intake already approached the WHO *Provisional Tolerable Weekly Intake* for the element. For lead the percentage was lowered to 1% because of the known high sensitivity of children for lead neurotoxicity.

In Annex 2 to the Opinion of the Committee the approach was summarized. The following table was derived from this annex:

Table 1-1 Permissible intake of certain elements, derived from Annex 2 of the June 1985 advice by the Scientific Advisory Committee to examine the toxicity and ecotoxicity of chemical compounds, as published in report EU 12964 EN.

	Sb	**As**	**Ba**	**Cd**	**Cr**	**Pb**	**Hg**	**Se**
Adult intake (µg/week)	30	1400	7000	175	400	1000	70	700
Children's intake (µg/week)	15	700	3500	87.5	200	500	35	350
Assumed contribution from toys	10%	0.1%	5%	5%	1%	1%	10%	10%
Children's daily permissible intake from toys in µg	0.2	0.1	25	0.6	0.3	0.7	0.5	5

Note that subsequently, in Standard EN 71-3: 1994, these levels were converted to migration limits expressed as mg/kg toy. For this conversion it was assumed that a child ingests 8 mg of toy material per day, based on which concentrations of 'bioavailable' elements in toy materials could be calculated. These concentrations were converted to migration limits from toys expressed as mg/kg toy after adjusting 'to minimize the exposure of children to toxic elements and to ensure analytical feasibility.'

In their call DG Enterprise was seeking a party which would be able to propose a sound methodology for setting limit values of elements present in toys. Several years ago CEN already put effort in the development of such an approach, but was confronted with scientific criticism by the EU Scientific Committee on Toxicity, Ecotoxicity and the Environment (CSTEE). The opinion of the CSTEE on 'Assessment of the bioavailability of certain elements in toys' distinguished two main topics, i.e. 1) suitability of the proposed limit values and 2) the necessity of updating the standard EN-3:1994.

The following issues were addressed by the CSTEE and/or by DG Enterprise in their call and will be considered in the present report:

1) Choice of elements: what elements should toys be analyzed for.
2) Intake of toy-material: what is the daily intake of toy material for children to be considered.
3) Definition for bioavailability: The CSTEE recommends to change the definition for bioavailability from *the soluble extract having toxicological significance*' into *the amount of each element in the toy which could be absorbed into the systemic circulation of a child*.
4) A single representative or not: The CSTEE does not accept that it is possible to take a single representative from many toys because of their heterogeneous nature. Sampling is a critical step in the enforcement and testing for compliance, that is often overlooked. In this report it will be studied if a single sample is representative for the

whole toy, or if several sub-samples have to be taken and analyzed. This will depend on the nature of the toy as some toys may consist of different parts.

5) Limit values and maximum bioavailability: how to deal with correction factors for analytical variation.
6) Health-based limit values: latest scientific knowledge and associated revisions of tolerable daily intakes (TDI) and average daily intakes (ADI) should be reviewed and special focus should be paid to the potential sensitivity of children.
7) Bioavailability or migration: should the limit values for elements be expressed in terms of bioavailability or in terms of migration?
8) Toys intended for different ages. One of the discussion points identified is whether different toys intended to be used for different ages should be distinguished. If so, then several exposure scenarios have to be established for different ages.
9) Food Contact Materials. It was proposed by DG Enterprise to examine whether the food contact materials (FCM) framework could provide a basis for setting limit values in toys.
10) Analytical test methods. It is stated that corresponding analytical test methods should be available.

1.2 Approach

In this report a general methodology is presented to derive limit values for chemicals in toys. The methodology is set up according to a general approach which can be used for any type of chemical. However, because the first objective of the assignment involves deriving new limit values for inorganic elements in toys, a proposal for an update of relevant (migration) limit values for this group in toys will be given.

The basis of the whole approach is in essence the same as that for the current derivation of migration limit values for toys, as laid down in the Toy Directive and in EN 71-3, namely :

The exposure of children to chemicals in toys should not exceed a certain health-based level (in mg/kg bw/day)

In the approach, it is determined to what level a chemical may be present in toy material in order to reach a certain defined level of exposure.

General issues in the derivation of TDIs were described. A major objective for the present report was to update the toxicological information and health-based limit values (TDIs) on individual elements. The original list of the 8 elements was extended with 10 additional elements. As far as possible, review of recent, existing evaluations conducted by recognized international bodies were used. Because of the specific focus on toys and on elements, several special issues were addressed like e.g. children as a sensitive subgroup and background

exposure. In view of dermal contact with toys, available information on ‘local effects upon dermal contact,’ is reviewed.

Assessing the exposure involves the consideration of child specific exposure scenarios and exposure factors such as those related to playing behaviour and physiological characteristics. Information is collected that can be used for different levels of exposure assessments, varying from simple exposure duration factors to guidance for specific cases where an extensive exposure assessment is desired. For the definition of the amount of toy that children can be exposed, to simple weighing experiments were carried out.

Concepts and migration tests as used in the Food Contact Material (FCM) Framework were considered for their applicability for risk assessment of toys. Different migration tests were described and compared, both with respect to exposure to toy material and to Food Contact material. A proposal was made on how to sample and how to make use of correction factors.

The risk-based methodology that is presented in this report, is illustrated with three options that can be used assess whether the certain health-based level is not exceeded.

This project started in January 2006. An Interim report was presented to DG Enterprise on March 31, and the final draft version on June 30.

For this project an Advisory Team was invited with individuals representing the toy industry, risk assessment and risk management groups. During the preparation of the report 2 times our Advisory Team was consulted. The team consisted of the following individuals:
Dr. S. Stefanovic, SGS, Spijkenisse, Mr. E. van Woensel, Mattel Europe, Ms A. Knaap, Former Chair of Former chair of the FCM Committee, Dr. P. Bragt, Dutch Food and Consumer Product Safety Authority, Dr. P. Hakkinen, JRC, Ispra.

The first meeting was on March 6, 2006, about 2 months after the start. Discussed were the selection of the list of elements, the exposure scenarios and the first principles of the methodology. The second meeting was on June 15, 2006, where the draft final report was discussed and suggestions were given for a more clear presentation of the methodology.

We highly appreciate all their valuable comments !

2 Elements and their Health-Based Limit Values (TDIs)

2.1 Introduction

Basic to our methodology for deriving limit values for toys, is the Health-based Limit Value that is usually denoted as the Tolerable Daily Intake or TDI. The TDI denotes the daily dose of a chemical than can be ingested daily throughout the entire lifetime without adverse effects for the individual in question. Using the TDI as the basis differs from the approach previously used to derive the permissible levels of 'bioavailable' elements from toys as laid down the Council Directive 88/378/EEC. As already explained above in the Introduction, the levels as specified in this Directive were based on a previous advice (from 1985) by the *Scientific Advisory Committee to examine the toxicity and ecotoxicity of chemical compounds (CSTEE)*. The approach chosen by this Committee was based on weekly intakes of metals via the diet by adults in the EU, as selected from literature. Of these normal weekly intakes percentages ranging from 0.1 to 10% were allocated as allowable exposure from playing with toys. These percentages were chosen based on toxicological evaluation of the elements in question. Thus, this approach did not use health-based limit values (TDIs) as the point of departure but toxicological information was used only in determining the percentage that exposure through toys was allowed to add to normal dietary background exposure (see the Introduction for further description of the 1985 derivation by the *Scientific Advisory Committee to examine the toxicity and ecotoxicity of chemical compounds*).

A major objective for the present report was to update the toxicological information and health-based limit values (TDIs) on individual elements. As described in section 2.2, we extended the original list of the 8 elements with 10 additional elements we consider relevant with respect to toy-related exposures. Relevant toxicological information for the 18 elements is presented concisely as toxicity profiles, containing for each element the basic information deemed most relevant in the context of toy-related exposures. Available existing limit values (TDIs) and their derivation are described in these profiles, from which the value considered most suitable for use in the present context of evaluating toy-related exposures is then selected. Given the time schedule of the project and the mostly huge toxicological data bases available for the elements reviewed, use of existing evaluations and TDI-derivations was inevitable. As will be seen hereafter, existing evaluations conducted by recognized international bodies were available for all elements. Moreover, for virtually all elements this included evaluations conducted after the year 2000.

Because of the specific focus on toys and on elements, several special issues are addressed in the profiles, like children as a sensitive subgroup and background exposure. Further, in view of dermal contact with toys, available information on 'local effects upon dermal contact' was

reviewed. Absorption from the gastro-intestinal tract is an important issue for elements and accordingly existing knowledge on this point is discussed in the profiles.

The individual toxicity profiles for the 18 elements are attached to the present report as Appendix II.

2.2 Update of list of Elements

The original list as laid down in Council Directive 88/378/EEC was as follows:
Antimony
Arsenic
Barium
Cadmium
Chromium (trivalent, hexavalent)
Lead
Mercury
Selenium

It proved very difficult to get information on the presence of additional elements in different toy material, especially since routinely toys are only tested for the above 8 elements as specified in the Directive. As far as information was received, no conclusions can be drawn about which elements occur most frequently and/or whether some elements are specific for particular toys/toy materials. Therefore we used the following strategy: in addition to the present list of 8 elements, we used the list for Food Contact Materials and a list that contains elements that are found in the waste phase of plastics.

The 'Synoptic Document' (EU, 2005) lists the monomers and additives notified to the EU (EFSA, SCF) as substances which may be used in the manufacture of plastics or coatings intended to come into contact with foodstuffs. Some of the materials used for food packaging may also be used in toys, therefore it is reasonable to assume that these elements included in the 'Synoptic', will also be present in toys. These elemental additives supplement the above list of 8 elements. Based on the Synoptic Document the following elements/ions are added to the above list of eight:

Aluminum
Boron
Cobalt
Copper
Manganese
Silver
Tin (inorganic)
Tin (organic
Zirconium

Although only *in*organic elements were to be considered with regard to limit values in toys in the present report (see chapter 1, objective 1) it is noted that, for tin organic forms may be added to synthetic materials as bio-stabilizer. Following a request by DG Enterprise, we have listed organotins for review, based on the rationale that their much higher toxicity compared to inorganic tin warrants specific attention for these chemicals.

Recently a survey was carried by RIVM on the use and waste-disposal of synthetic materials (RIVM, 2006). This work was carried out on behalf of the Inspection of the Netherlands' Ministry of Housing, Spatial Planning and the Environment following EU Council Regulation (EEC) No 259/93 of 1 February 1993 on the supervision and control of shipments of waste within, into and out of the European Community. The survey includes an inventory of metals present in waste due to use in synthetic materials. Of these the following are in addition to those already listed above:

Molybdenum
Nickel
Strontium
Titanium
Zinc

Given their low toxic potency, molybdenum, zirconium and titanium are considered not to be relevant for inclusion in the Directive and therefore no toy limit value was derived for these three elements.

2.3 Update of TDIs

2.3.1 Derivation of toxicological limit values

Toxicological limit values such as the Tolerable Daily Intake (TDI) for contaminants and the Acceptable Daily Intake (ADI) for compounds applied intentionally in the production of foods, are a long-established tool within chemical risk assessment. Toxicological evaluation of chemical substances aimed at derivation of such limit values is carried out by various national and international bodies. Within the EU various expert panels of the European Food Safety Authority (EFSA) evaluate toxicological dossiers on different categories of chemical agents relevant for food (food additives, food contact materials, contaminants, pesticides etc.). Another important international body specifically active in the food area is the Joint Expert Committee on Food Additives (JECFA), which is a programme of the World Health Organisation (WHO) dealing with both food additives and food contaminants. The International Programme on Chemical Safety (IPCS) also of the WHO deals with environmentally relevant chemicals in its Enviromental Health Criteria. Within the EU, the Existing Substances Programme comprehensively evaluates chemicals that have a wide use in industry and in consumer products. In the USA the Environmental Protection Agency

routinely derives Reference Doses (RfDs) for a wide range of environmental chemicals whereas the US Agency for Toxic Substances and Disease Registry (ATSDR) does similar work for soil contaminants.

Two general approaches are used in the toxicological evaluation, i.e the threshold approach and the non-threshold approach. The latter is used for genotoxic carcinogens, the former for all other compounds. As will be seen hereafter, of the elements dealt with here, only hexavalent chromium falls under the category of genotoxic carcinogens. The non-threshold approach involves linear extrapolation from observed tumour incidences to risk-specific doses such as one in a million for lifetime exposures. The latter level is often called the Virtually Safe Dose. The threshold approach uses a No Observed Adverse Effect Level (NOAEL) or Lowest Observed Adverse Effect Level (LOAEL) which is divided by uncertainty factors, leading to a limit value (TDI, ADI). Because the threshold approach is applied for almost all elements included in this report, it is discussed further below.

In the toxicological evaluation, findings in individual experiments are judged as to their relevance against those in other studies and other species. For each study and each endpoint a NOAEL is to be derived. Based on a full evaluation of all toxicity data available for the compound under scrutiny an overall-NOAEL is then selected that will serve as the basis for limit value derivation. The overall-NOAEL should be the highest relevant dose where no (adverse) effect was observed. As has been pointed out in numerous publications, the NOAEL has important statistical limitations relating to the design of the study from which it derived. Increasingly an alternative measure, the Benchmark Dose (BMD), is being used as point of departure in limit value derivation.

In order to derive a health-based limit value, uncertainty factors (US terminology) or assessment factors (EU Existing Substances Program) are applied to the overall NOAEL or BMD in order to extrapolate from experimental animals to humans (interspecies extrapolation; default value is 10) and from humans to sensitive humans (intraspecies extrapolation; default value is 10). The use of these factors is a default approach fraught with considerable uncertainty. In recent years the trend has been to use, wherever possible, factors based on compound-specific biological data. This use of data-derived uncertainty factors was first advocated in IPCS (1994), where traditional 10-fold factors were subdivided in factors for toxicokinetics and toxicodynamics, thus allowing a more structured use of existing data, with the goal of making more reliable extrapolations. As can be seen in the profiles, in many of the evaluation for the elements that are the subject of the present report, applied factors tend to be lower than 100 (the traditional default). This is due to the toxicity database, that often included usable human data (obviating the need of animal to human extrapolation), and the fact that several elements are essential nutrients and their toxicity has to be judged against their daily requirements.

2.3.2 Specific Issues

2.3.2.1 Children as a sensitive group

In the context of toy-related exposures any specific toxicological information on children's susceptibility is highly relevant. This topic has raised considerable interest in recent years, going back to the seminal report *Pesticides in the diets of infants and children* published by US National Research Council in 1993 (NRC, 1993). Regulatory bodies and toxicological advisory committees working on their behalf, are increasingly paying attention to this topic in their reviews of individual chemicals. The US-ATSDR in its Toxicological Profile series on individual chemicals systematically reviews available information on children's susceptibility. In these documents ATSDR also provides some general considerations on this topic. EFSA also where relevant addresses the issue in its evaluations for individual chemicals. For the present report a general discussion of children's susceptibility was not considered necessary, this being available elsewhere. The available chemical-specific information, however, was selected and summarised.

The TDI as a limit value is intended to be protective for (potentially) sensitive subgroups in the population which includes children as a group. Nevertheless, data bases on which TDIs are based vary widely in the degree to which experiments and observations address this specific sensitivity of children or young animals. For lead, for instance, this issue has been investigated extensively and the TDI for lead is actually based on its neurotoxic potential for children. For other elements available data in this area are fragmentary only and their TDIs are based on studies with exposure to adult humans or (young-)adult animals. Of course the uncertainty factors used in deriving TDIs are selected taking into account such limitations but, especially in the present context of toy-related exposure, special attention seemed warranted. This was given specifically in selecting suitable TDIs, where those values were chosen expected to be providing the most adequate protection for children.

2.3.2.2 Local effects upon dermal contact

When children play with toys dermal contact occurs. Therefore information on direct effects by potentially released elements on the skin is relevant and accordingly is included in the toxicity profiles. Thus the potential for producing dermal irritation and sensitization was reviewed for individual elements. Again the ATSDR documents were a primary source of information on this issue. As was to be expected, dose-response information for these effects is scarce. This kind of studies is mostly carried with high concentrations and mostly no attempt is made to determine NOAELs for skin irritation and sensitization. For the latter endpoint this situation is beginning to change where for example methods are being developed that allow quantification of sensitizing potential (using Mouse Local Lymph Node-assay results). For the elements reviewed here, however, irritation and sensitization data were of a qualitative nature only. Exceptions to this are chromium and nickel, two well known inducers of contact dermatitis. For these elements the dose/concentration-response has been examined in a large number of tests.

2.3.2.3 Absorption

For chemicals in general but for elements especially, absorption in the gastrointestinal tract is an important factor on which the ultimate risk posed by an exposure will depend. When using a TDI in the assessment of any given exposure, consideration should be given to the concept of the internal dose, which is the dose actually reaching the blood stream after external exposure via the mouth, skin or lungs. Gastro-intestinal absorption and the concept of bioavailability are of prime importance here. In depth discussion of these topics is provided in chapter 4. A crucial point with reference to the TDI is that it represents an *external* dose (ingested amount per kg body weight/day), ultimately based on an experiment with its own specific bioavailability. The bioavailability of the external dose of any *exposure,* from toys for instance, mostly will be different from that in the experiment from which the TDI was derived. Consequently in comparing exposure with the TDI this may lead to unwarranted conclusions, which should be avoided by the proper consideration of differences in bioavailability as sketched. For this reason, information on gastro-intestinal absorption is included in the toxicity profiles.

As can be seen in the profiles, for elements frequently much information on gastro-intestinal absorption is available. Typically a wide range in absorption percentages is found in different experiments, reflecting strong matrix effects for this group of chemicals.

2.3.3 Background exposure

Any toy-related exposures to elements take place against a background of exposure to the same element via other exposure routes such as food or non-food consumer products. When using the TDI as a tool in safety evaluation, the most relevant comparison in principle is with total exposure instead of only one specific exposure. Thus background exposure is relevant also in the present context and this background exposure should be considered when making an informed choice on which part of the TDI can responsibly be allocated to the specific exposure route of toys.
Exposure assessment for elements and for chemicals in general is a highly complex field of study, not in the least because of the wide variation in exposure situations and human activities pertaining to them. Equally important, certainly for elements, are variations, both natural and man-made, in concentrations in air water and food across countries. Thus data on normal background levels of elements in these compartments and of estimates of daily general population exposures usually will always provide a partial picture only. This certainly goes for the data as presented in the individual profiles: the normal background as estimated there should be seen as an indication of the real background exposure of children across the European Union.

As can be seen in the individual profiles, data specifically on children’s exposures are not available for all elements, even when using data from non-European countries. Where such

data gaps existed either the adult estimate was adopted or this estimate was adjusted to a value considered more reflective of what would be a typical children's exposure level.

2.3.4 Method of literature review

As already stated above, given the time schedule of the project and the mostly huge toxicological data bases available for the elements reviewed, we chose to use existing evaluations and TDI-derivations. Evaluations conducted by recognized international bodies were available for all elements. Moreover, for virtually all elements this included evaluations conducted after the year 2000. Thus, a retrograde approach was chosen, in which critical use was made of TDIs or other relevant health-based limit values as proposed by recognized international scientific expert groups such as those of the WHO (JECFA, IPCS, JMPR) and the EU (SCF, EFSA Existing Substances). Adequate reviews of sufficiently recent date being available for all elements, no further literature search for original publications was considered necessary. Table 2-1 provides some basic information of the primary sources of information that were used.

Table 2-1 Major toxicological review documents

Publisher, name	**Description of contents**	**Limit value**
EU Risk Assessment Reports	In depth review all toxicity endpoints, all exposure scenarios quantified	MOS calculation
EFSA opinions	Review of all toxicity endpoints, data on food exposure	TDI or UL
ATSDR Toxicological profiles	Comprehensive review of all toxicity endpoints, data on exposure via all routes	Acute, intermediate and chronic MRLs
OEHHA Drinking-water	Comprehensive review of oral toxicity endpoints, comprehensive review of exposure via food	Drinking-water guideline
IPCS Environmental Health Criteria	Comprehensive review of all toxicity endpoints, data on exposure via all routes	Guidance values for risk assessments
US-EPA Toxicological review	Comprehensive review of all toxicity endpoints, brief review of exposure via all routes	RfD
RIVM Review Soil contaminants	Brief review of all toxicity endpoints, estimate of total background exposure (non-soil-related)	TDI
JECFA food contaminants	Comprehensive review of oral toxicity endpoints, comprehensive review of exposure via food	TDI

These review documents embody a critical evaluation of all relevant toxicological and environmental data and represent the risk assessment consensus among recognized experts. The TDIs as selected for the elements dealt with here, must therefore be regarded as

optimally reflecting the scientific state-of-the-art. As such they provide a solid basis for the toxicological part of the present report. For detailed discussion of specific toxicological endpoints and of individual toxicity studies the reader is referred to the review documents as referenced in the individual toxicity profiles.

2.3.5 Updated TDIs for elements

For toxicological profiles on the individual elements, see Appendix II. In Table 2-2, an overview is given of updated TDIs. Also presented in the table is information on background exposure and risks for local skin effects.

Table 2-2 TDIs, background exposure and skin irritation/sensitisation risk for elements

	TDI		Background exposure child (µg/kg bw/day)	Skin irritation and sensitisation contact risk (qualitative indication)
	Value (µg/kg bw/day)	Reference		
Aluminum	750	Newly derived	300	Low
Antimony	6	WHO, 2003	0.53	Unknown
Arsenic	1.0	RIVM, 2001	0.4-0.7	Low
Barium	600	ATSDR, 2005	9	Unknown
Boron	160	EFSA, 2004a	80	Low
Cadmium	0.5	RIVM, 2001	0.45	Low
Chromium trivalent	5	RIVM, 2001	1	Low
Chromium hexavalent	5[a]	RIVM, 2001	0.1[b]	High
Cobalt	1.4	RIVM, 2001	0.6	Medium
Copper	83	SCF, 2003a	60	Low
Lead	3.6	JECFA, 1993, RIVM, 2001	2.0	Low
Manganese	30 (160)[c]	OEHHA, 2004	130	Unknown
Mercury	2	IPCS, 2003	0.1	Medium
Nickel	10	Newly derived	8	High
Selenium	5	SCF, 2000, RIVM, 1998	2	Low
Silver	5	US-EPA, 1996a	1.3	Low
Strontium	600	US-EPA, 1996b	18	Unknown
Tin inorganic	2000	JECFA, 2001	290	Unknown
Tin organic	0.25	EFSA, 2004b	0.083	High
Zinc	500	SCF, 2003b	350	Low

a This value only takes into account non-carcinogenic effects by hexavalent chromium; for the carcinogenic effect by hexavalent chromium a highly uncertain Virtually Safe Dose of 0.0053 µg/kg bw/day has been proposed by OEHHA (1999). A new drinking-water cancer bioassay with hexavalent chromium is being conducted within the US-NTP.

b Estimate for a child playing on CCA-treated timber as given in EU-RAR (2005).

c The value of 30 µg/kg bw/day applies to exposures **above** normal dietary intake For the current method of calculation of the allowable toy-related exposure level (10% of the TDI) this TDI was converted to a value usable for evaluating total daily exposure (inclusive of normal dietary intake). Thus for manganese a figure of 160 µg/kg bw/day was used for calculation (estimated background added to 'non-dietary' TDI).

2.4 Recommendations

At present, research on elements in toys is directed exclusively at the elements already included in the Directive. We recommend further research on which elements are present in toys by means of chemical analysis of a representative sample of toy (materials), in time allowing the removal of any irrelevant elements from the list while others might be added. More in general it would be useful if Industry could prove, by means of measurements already available, which of these elements are irrelevant.

3 Exposure to chemicals in toys

To warrant the safety of using elements and other chemicals in toys and toy material requires demonstration that the level of exposure of children to these chemicals does not exceed relevant health-based limit values. Assessing this exposure involves the consideration of child specific exposure scenarios and exposure factors such as those related to playing behaviour and physiological characteristics. This chapter will evaluate the available information on exposure scenarios and factors of toys and toy material, such as exposure pathways and activity patterns. As discussed in chapter 7, it is not always necessary to perform a detailed exposure assessment for chemicals in toys or toy materials. This chapter provides information that can be used for different levels of exposure assessments, varying from simple exposure duration factors to guidance for specific cases where an extensive exposure assessment is desired. The information can also be used for an EC type examination[2]. Where possible, default values for exposure factors will be provided that may be used in the exposure assessments.

3.1 Categories of toys and toy materials

Within the EU, regulations on toys are harmonized, based on Council Directive 88/378/EEC on the approximation of the laws of Member States concerning the safety of toys. The definition for 'toy' used in Council Directive 88/378/EEC is as follows:

'Any product or material designed or clearly intended for use in play by children of less than 14 years of age'

Annex I of Directive 88/378/EEC provides a list of articles that are not regarded as toys, which is included in appendix III.
Depending on its purpose, toys can be categorized based on different criteria. A review of toy categories used for legislative and other purposes is given in Appendix IV.

In summary, it is possible to categorize toys based on different criteria: possible safety hazard, type of material, type of use, intended age groups and type of exposure.
For the purpose of general safety of toys, including mechanical and thermal safety, it may be most relevant to categorize toys based on possible safety hazards. However, for elements in particular, no groups of toys can be identified that may pose the greatest risk of exposure to elements.

[2] EC type examination is the procedure by which an approved body, called 'Notified Body' ascertains and certifies that a model of a toy satisfies the essential requirements of the Directive Safety of Toy

For the purpose of determining which migration tests are appropriate, it may be relevant to categorize toys based on the material of which they consist.
A relevant way of categorizing toys for the purpose of safety evaluations and setting limits for elements and other chemicals in toys is based on exposure information, such as contact routes and exposure scenarios.
Intended age group categories are often used to determine whether a toy is suitable for children under 3 years of age. The value of basing exposure categories on intended age groups for the purpose of setting limits for elements and other chemicals is discussed extensively in the next paragraph.

3.2 Age-related exposure

One objective of this project is to examine the way to address the content of chemicals in toys intended for children under 36 months or intended to be put in the mouth. For the exposure assessment, it is possible to include exposure scenarios specific for young children, in particular mouthing and ingesting toy material, and crawling over toy surfaces. However, the question arises whether it is justified to include these scenarios only in exposure assessments for toys intended for children under 36 months or intended to be put in the mouth, and not for toys intended for older children.

According to EU Council Directive 88/378/EEC, toys which might be dangerous for young children (under 36 months) need to be labelled 'not suitable for under 36 months/three years'. Particular risks relating to young children cited in Annex II of the Directive are

- Toys and their component parts, and any detachable parts of toys which are clearly intended for use by children under 36 months must be of such dimensions as to prevent their being swallowed and/or inhaled
- Toys containing inherently dangerous chemicals or preparations must bear a warning stating that the toys must be kept out of reach of very young children.

It could therefore be argued that exposure assessment for toys labelled not suitable for children under 36 months will not need to include exposure scenarios specific for children under 36 months, because these toys should not be accessible to children of this age. However, the EU Council Directive 88/378/EEC also states that 'toys may be placed on the market only if they do not jeopardize the safety and/or health of users or third parties *when they are used as intended or in a foreseeable way, bearing in mind the normal behaviour of children*'. Although certain toys are not intended for young children, the odds that they will mouth toys can be considered relatively high. In addition, in the EN 71-3 standard it is stated: 'For the purposes of this standard, the following criteria are considered appropriate in the categorisation of sucking, licking or swallowing: toys intended for children up to 6 years of age, i.e. all accessible parts and components where there is a probability that those parts or components may come into contact with the mouth' The CSTEE (2004) concluded that it is

foreseeable that children under 6 will have access to toys intended for children over 6. CSTEE stated that these toys might also pose a risk for children under 6 and should therefore be tested.
Indeed, many families consist of children of different ages, and it can be anticipated that young children will often have easy access to toys owned by their older siblings. Mouthing hands and objects is natural behaviour for babies, infants and toddlers (Van Engelen et al., 2004). Indeed, the list of objects mouthed by children under 36 months, as observed in several mouthing studies, consisted of many items (not just toys) not intended for children under 36 months (DTI, 2002; Juberg et al., 2001; De Groot et al., 1998; Smith and Norris, 2003). In fact, Smith and Norris (2003) reported that at least an estimated 75% of items that were mouthed by children in their study were considered not intended to be mouthed. Hence, young children having access to toy material intended for older children can be considered 'use in a foreseeable way'. It is therefore not justified to exclude exposure scenarios specific for young children from the exposure assessment simply based on the intended age category of the toy under consideration.
It has been argued that there has to be a degree of carer responsibility and supervision of young children, in particular those who still have tendency to mouth everyday objects and toys. It is common knowledge that toys containing small parts are unsuitable for children under 36 months of age due to the choking hazard. Parents and other caregivers can be expected to keep toys containing small parts out of reach from children under 36 months. However, toxic hazards are not visible on the toy itself. The toy may be labelled unsuitable for children under 36 months of age on the packaging, but in practice, package materials are disposed of and the information is lost. In addition, some toys appear to be labelled inappropriately, as shown by a market survey of plastic toys by the Dutch Food and Consumer Product Safety Authority (VWA, 2005). The sampled toys included a number of bath baby toys which were labelled unsuitable for children under 36 months or which were not labelled at all, although these toys are likely to be mouthed by young children.

To identify toys for which exposure scenarios specific for young children should be considered, the approaches related to the EU measures recently adopted for phthalates in toys and child articles may be helpful. In 1999, the EU adopted measures prohibiting the placing on the market of toys and childcare articles intended to be placed in the mouth by children under three years of age made of soft PVC containing one or more of 6 specific phthalates (DINP, DEHP, DBP, DIDP, DNOP, BBP) (Council Directive 1999/815/EC).
In response to these measures, Denmark has prohibited the use of phthalates in toys and childcare products for children under three years of age (Statutory Order No. 151, 1999). However, the Danish Environmental Protection Agency is often faced with the problem whether or not a toy is suitable for children under three years of age. To help producers, importers and buyers of toys, decisions regarding this issue are made public in the form of a list of toys suitable for children under three years old, which is updated regularly[3]. Guidelines

[3] Available at http://www.mst.dk

are also provided by the CEN, which are partly based on the extensive Age Determination Guidelines prepared by the US CPSC (discussed in Appendix IV). However, due to the use of often subjective criteria, even the most extensive age determination guideline may still not avoid all ambiguity on the suitability of a particular toy for a certain age group.

An alternative approach has been used in the amendment of Council Directive 76/769/EEC on the marketing and use of certain dangerous chemicals and preparations. The amendment restricts the use of DEHP, DBP and BBP in all toys and childcare articles. The restrictions for the use of the other phthalates DINP, DIDP and DNOP are less severe for reasons of proportionality. The use of these phthalates is restricted only in toys and childcare articles which can be placed in the mouth by children. To help identifying toys and childcare articles or parts of toys and childcare articles which can and those which can not be placed in the mouth by children, a guidance document has been prepared[4].

Similarly, decisions on whether the exposure assessment for a toy should include exposure scenarios specific for young children can be based on the suitability of the toy for children under 36 months of age. However, the question of suitability may lead to much discussion for certain toys. In addition, it may be inappropriate to use different criteria for phthalates than for other possible hazardous chemicals. It is therefore recommended to base this decision on whether the toy can or can not be placed in the mouth by children and/or whether the toy can be crawled on. The guidance document which will be used for the phthalate regulations can be applied to identify toys that can be placed in the mouth. A separate guidance document would need to be drafted for toys than can be crawled on.

In conclusion, similar to the EU measures adopted on phthalates and similar to the conclusion of the CSTEE (2004), we propose that the exposure assessment of all toys which do not contain small parts or long chords (or are otherwise dangerous from a physical-mechanical point of view), but can be placed in the mouth or can be crawled on by children should include exposure scenarios specific for young children, regardless of the intended age category of the toy. However, this is clearly a risk management decision. Therefore, throughout the current report, exposure scenarios specific for young children will only be considered for toys <u>intended</u> for children under 3 years of age.

[4] http://ec.europa.eu/enterprise/chemicals/legislation/markrestr/guidance_document_final.pdf

3.3 Exposure scenario categories

To set appropriate limits for chemicals in toys, information on the exposure to these chemicals in toys is needed. The route and level of exposure to chemicals in toys is linked to both the physico-chemical properties of the chemical and to how the toy is used by the child, which can be described by exposure scenarios. The following paragraphs will discuss which exposure scenarios are relevant for toys, and special reference will be made to elements in toys.

3.3.1 Direct ingestion

As discussed earlier, direct ingestion of toy and toy material can be assumed to occur mainly by children under 3 years of age due to the oral exploration behaviour that is natural at this age (Van Engelen et al., 2004). Toys intended for children this age are regulated such that they should not contain small detachable parts that may pose a choking hazard. These parts should therefore also not be accessible for ingestion. However, some liquid toys used by children under 36 months of age such as finger paint are easily swallowed. Toys that consist of dry, brittle, powder-like or pliable material, such as chalk crayons, plaster or modelling clay may also be ingested, for example via hand-mouth contact. In addition, some toys may have a layer of paint or other coating, or textile fibres that may easily be scraped off and swallowed. Ingestion of scraped off material is also relevant for toys intended for older children which are intended to be placed in the mouth, such as whistles. The direct ingestion scenario can be relevant for elements in toys.

Figure 3-1 Example of scraping off material: girl chewing on pencil

3.3.2 Mouthing

Similar to the direct ingestion scenario described above, mouthing of toys can be assumed to occur mainly by children under 36 months of age. In fact, some toys available on the market are specifically designed to be mouthed, such as teething rings. It should be noted that mouthing behaviour studies demonstrated that children mouth on a broad range of items, including toys and other items not intended to be mouthed (De Groot et al., 1998; DTI, 2002; Juberg et al., 2001; Reed et al., 1999; Smith and Norris, 2003; Tulve et al., 2002). Although the dimensions of some toys may be such that they cannot be placed in the mouth, ridges can

still be sucked on. In addition, some toys intended for children over 3 years of age are intended to be placed in the mouth. The mouthing scenario can be relevant for elements in toys.

Note: For many toys, both mouthing and direct ingestion may occur. Depending on the properties of the toy and on physico-chemical properties of the chemical under consideration, one of these scenarios will likely be more relevant for systemic exposure than the other. Only the most relevant scenario will need to be considered.

Figure 3-2 Example of mouthing: a teething blanket

3.3.3 Inhalation via evaporation

A number of toys may release chemicals in the air via evaporation, such as the solvent in a felt pen. To evaporate, the chemical would need to be quite volatile to be available for inhalation. This route of exposure is therefore not relevant for elements. In general, this route is likely to be less relevant for systemic exposure if oral exposure also occurs. For toys releasing volatile chemicals that may cause local effects in the lungs, this exposure scenario should be considered.

3.3.4 Inhalation via dust or spray

Some toys may release considerable amounts of dust, such as plaster mix and crayons (for example, when beating out a brush). Other toys may release chemicals in the air via a spraying system. At present, very few examples of toys in the form of sprays are known. Some doll perfume sprays are available already, but these may be regulated under the cosmetics directive. Nevertheless, more toy sprays may be marketed in the future.
Contrary to evaporating chemicals, chemicals in sprays or dust do not necessarily need to be volatile to be available for inhalation. Again, although the oral route may be more relevant for the systemic exposure to chemicals in these toys, the inhalation route of exposure may need to be considered for chemicals which may cause local effects in the lungs, for example respiratory sensitizers.

Figure 3-3 Example of a toy in the form of a spray: spray chalk

3.3.5 Skin contact

Most if not all toys will at some point contact some part of the skin. Many toys are handled with the hands, but some may also be contacted by skin of other body parts, such as foot contact with a canvas on which children may jump, and arm and leg contact with costumes. Dermal exposure to elements in such toys is especially relevant for sensitizing elements such as nickel. For example, the Danish EPA found levels of 2.96 µg/g nickel in so-called 'slimy' toys (Danish EPA, 2005). These toys were not expected to contain nickel and the detected levels are assumed to be contaminations from the manufacture of the products, e.g. from the use of nickel-containing catalysts. For systemic exposure, this exposure route is probably not very relevant for elements, as the dermal uptake is very low (chapter 4).

Figure 3-4 Example of skin contact other than hands with a toy: a baby gym play mat

3.3.6 Eye contact

Eye contact may not seem a relevant exposure category for toys, as it has been reported that most injuries with toys are of a physical rather than a chemical nature (Consument en Veiligheid, 2001). However, this report was based on analysis of data on cases of eye injury reported in an injury information system, which registers accidents for which patients underwent medical first aid treatment in a selection of Dutch hospitals. Injuries of lesser seriousness such as eye irritancy are not registered in this system, but could potentially occur when, for example, a chemical in finger paint ends up on the hands and subsequently contacts the eyes when they are rubbed. However, effects such as eye irritancy are of such mild and transient nature that it may be considered irrelevant. For the remainder of this report, this scenario will therefore not be considered further.

3.3.7 Summary

The wide range of available toys results in many different possible exposure scenarios. Six general exposure scenarios have been described that should cover the most relevant ways of exposure to chemicals in toys: direct ingestion, mouthing, inhalation via evaporation, inhalation via dust or spray, and skin contact.
As with the creation of any categories, the exposure scenario categories described above have been created with a specific toy and toy material in mind. It would be convenient to provide lists of toy types for each exposure scenario category, based on which exposure scenario is relevant for the exposure assessment of a certain chemical in a certain toy. However, this approach bears the risk that certain (new) toys and toy materials will not be listed in any category. The heterogeneity of toy types complicates the creation of categories which will cover every single toy on the market. In addition, one particular toy may consist of several parts and materials to which different ways of exposure may occur. The next section will outline an alternative approach using exposure information to identify the relevant exposure scenarios for the exposure assessment of elements (and other chemicals) in toys.

3.4 Identification of relevant exposure scenarios

As more than one exposure scenario may be relevant for one particular type of toy, it is proposed to determine the relevant exposure scenarios on a case-by-case basis, by means of a scenario selection tree, rather than providing rigid groups of toy types for each category. A scenario selection tree for toys intended for children under 3 years of age has been designed (Figure 3-5). The scenario selection tree can also be used for toys intended for children over 3 years of age, although the oral scenarios (direct ingestion and mouthing) may not be relevant for this age group, unless the toy is intended to be placed in the mouth.

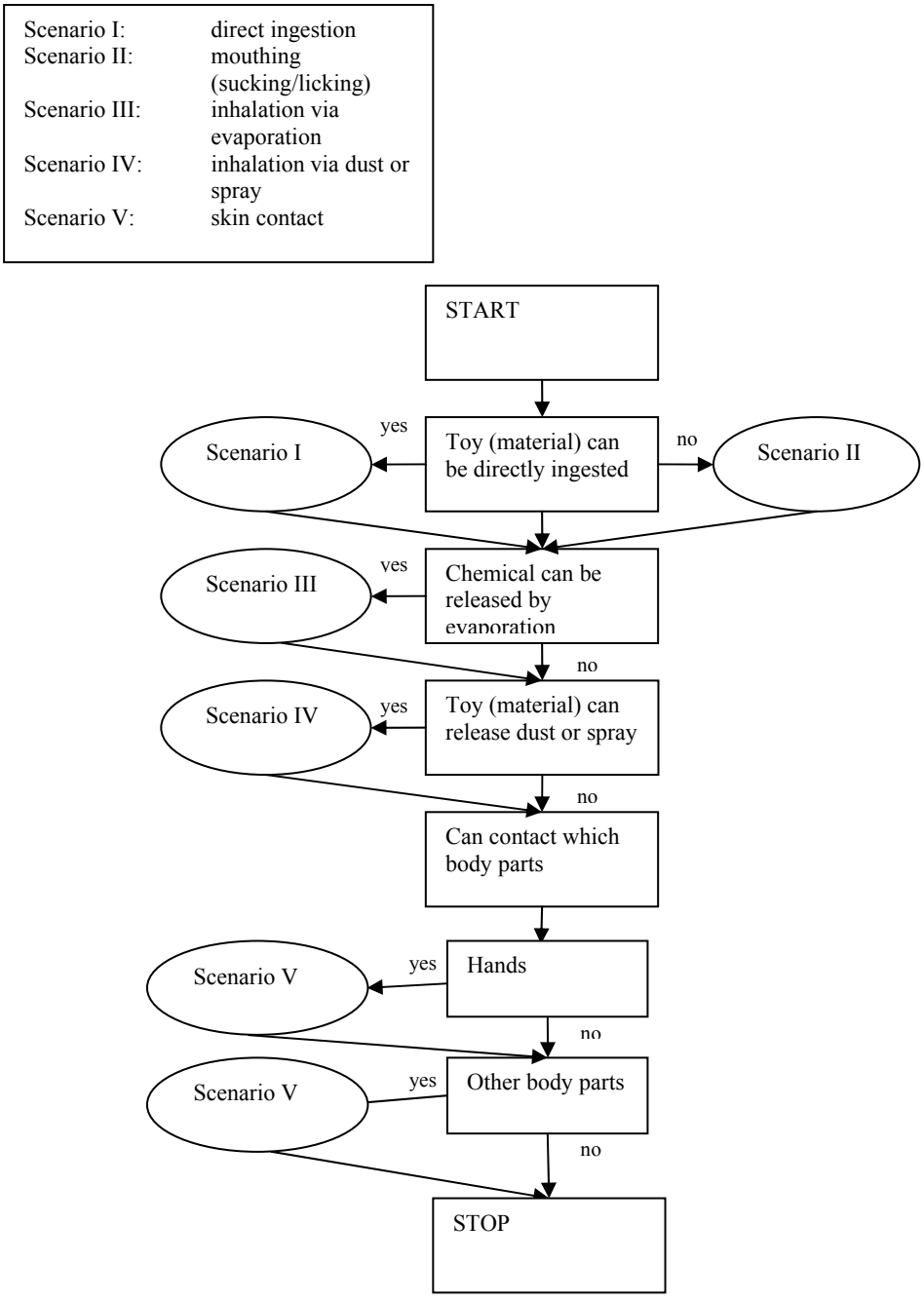

Figure 3-5 Exposure scenario selection tree

In using the scenario selection tree as depicted in Figure 3-5, the following questions need to be answered:

1) Can the toy (material) be directly ingested? For all liquid toys such as finger paint, it is assumed that it can be directly ingested. Some toys may be covered with layers of for example paint, which may easily be scraped off during mouthing of a toy. Potential exposure to chemicals in this layer should be assessed by means of the direct ingestion scenario.

Most toys for which no toy material can be ingested, can still be mouthed. It should be noted that even if the dimensions of the toy are such that they cannot be placed in the mouth, it can still be licked and sucked on.

2) Can the chemical of interest be released from the toy by evaporation? Some toys may contain volatile substances (not relevant for elements) that may be released during use.
3) Can the toy release dust or spray? For example, while using crayons, chalk dust may be released and subsequently inhaled.
4) Which body parts can the toy contact? For example, a book will predominantly contact the hands, whereas a baby play gym mat may contact face, arms and legs as well.

3.4.1 Examples of using the exposure scenario selection tree

To demonstrate the use of the scenario selection tree, some examples of toys are given below: modelling clay, crayons and a baby gym play mat.

3.4.1.1 Modelling clay

1) Can the toy be directly ingested? Yes, parts of clay are small enough to be placed in the mouth and swallowed. Exposure scenario I needs to be considered.
2) Can the chemical of interest be released from the toy by evaporation? If a volatile chemical is used in the modelling clay, this may be released. In this case, exposure scenario III needs to be considered
3) Can the toy release dust or spray? No, the consistency of modelling clay does not directly indicate significant dust formation and clay is not available in spray form.
4) Which body parts can the toy contact? Modelling clay is handled with the hands. It is unlikely to significantly contact skin of other body parts. Exposure scenario V needs to be considered for hands.

3.4.1.2 Crayons

1) Can the toy be directly ingested? Yes, even if the dimensions of a crayon are such that it cannot be directly ingested, parts of brittle crayons can easily be bitten off. Exposure scenario I needs to be considered.
2) Can the chemical of interest be released from the toy by evaporation? If a volatile chemical is used in the crayon, this may be released. In this case, exposure scenario III needs to be considered.
3) Can the toy release dust or spray? Yes, crayons that are made of powder-like material such as chalk may generate considerable amounts of dust when used. Exposure scenario IV needs to be considered.
4) Which body parts can the toy contact? Crayons are handled with the hands and are unlikely to significantly contact skin of other body parts. Exposure scenario V needs to be considered for hands.

3.4.1.3 Baby gym play mat

1) Can the toy be directly ingested? No, the dimensions of a baby gym play mat are of such dimensions that it cannot be directly ingested. Corners or parts of the play mat can be licked and sucked on, exposure scenario II needs to be considered.
2) Can the chemical of interest be released from the toy by evaporation? If a volatile chemical is used in the play mat, this may be released. In this case, exposure scenario III needs to be considered
3) Can the toy release dust or spray? No, the material the play mat is generally made of (textile) does not indicate significant dust formation. Spray is also irrelevant.
4) Which body parts can the toy contact? A baby may crawl or lie on the play mat, exposing face, (possibly bare) hands, arms and legs. Exposure scenario V needs to be considered for hands and other body parts.

NOTE: The use of the scenario selection tree is primarily meant to prevent overlooking any relevant exposure scenarios, by selecting all scenarios that might possibly occur. As a result, some of the exposure scenarios selected may seem irrelevant for a certain chemical-toy combination. It is up to the exposure assessor to provide arguments for omitting the consideration of a specific exposure scenario. The (ir)relevance of a selected scenario will also become clear by simply plugging in the exposure factor values in the mathematical formula used to calculate the exposure, as outlined in the next section.

3.5 Formulas and variables for exposure assessments

Once the relevant exposure scenarios for a particular type of toy have been determined, the exposure to chemicals such as elements can be assessed by using the applicable mathematical formulas related to the scenarios and the appropriate values for the variables, or exposure factors. This section covers information on the mathematical formulas and exposure factors for each exposure scenario listed in the scenario selection tree. Where possible, default values are given, many of which have been taken from the fact sheet on children's toys made for the ConsExpo program, a software package for deriving quantitative exposure assessments (Bremmer et al., 2002). It is not possible to present default values for each type of toy. Calculation of the exposure assessments therefore depends to a great extent on the sound judgment of the exposure assessor.
It should be noted that the resulting exposure assessments are rough estimates due to the use of very simple pragmatic mathematical formulas which oversimplify real exposure. In addition, the selection of realistic worst case parameter values results in an assessment that may considerably overestimate exposure. More exact exposure assessments are possible with the use of mathematical models which may describe the exposure more precisely, such as the higher tier models in ConsExpo (Delmaar et al., 2005). The assessment may further be refined by using probabilistic methods (Bosgra et al., 2005).

The information in this section applies to chemicals in toys in general and may not always be relevant for elements. Special reference to elements will be made where applicable.

3.5.1 Frequency of exposure

The exposure levels calculated with the formulas given below refer to one exposure event, i.e. one event of playing with the toy. For comparison with health-based limit values that are related to chronic exposure such as the TDI, the exposure levels can be assumed to occur daily. However, for some toy types, daily exposure may not be realistic. Exposure assessments for these toys need to be adjusted accordingly. Where possible, defaults will be provided per exposure scenario.

3.5.2 Direct ingestion

The amount of element (or other chemical) ingested can be calculated as:

$$D = A \times w_f / W_{body}$$

with

A	:	amount of toy (material) swallowed	[kg]
w_f	:	weight fraction of the chemical in the toy (material)	[mg/kg]
W_{body}	:	body weight of the exposed person	[kg]

The parameter values needed for this calculation are:

A : amount of toy material swallowed, which depends on whether the toy is made of dry or liquid, pliable or otherwise sticky material, or whether the ingested material is from scraping off a toy layer.

- Toys consisting of dry, brittle, pliable or powder-like material. For some toys, a considerable amount of material may be bitten off or ingested via hand-mouth contact, such as chalk crayons, modelling clay and plaster powder.
  For chalk crayons, ConsExpo's fact sheet on toys derived a rough default value of 6 mg/min as a default, based on studies on ingestion of soil by children (cited in Bremmer and Van Veen, 2002). It was further assumed that children play with crayons for 45 minutes. Total amount swallowed during one event is then 6 x 45 = 270 mg. To illustrate how much this amount approximately is, we weighed parts of clay (Figure 3-6) and chalk crayon (Figure 3-7 and 3-8).

Figure 3-6: 270 mg modelling clay material

Figure 3-7: 270 mg chalk crayon material

Figure 3-8: 290 mg chalk crayon material

Based on these simple weighing experiments, the default of ingesting 270 mg appears to be quite an overestimation. For risk assessments within the Dutch Soil Protection Act, a default of 100 mg is now used for ingestion of soil by children (Otte et al., 2001). It is proposed that this value is used as a default for ingested amount of dry, pliable or powder-like toy materials, although further research is warranted.

It is emphasized that this default applies to children under 3 years of age only, as these children display most mouthing behaviour.
The ingestion of 100 mg by children is considered reasonable, but may not occur daily. For exposure assessment refinement purposes, we propose to use a frequency of 1/week for this ingestion default when the exposure is compared to a chronic health-based limit value. This is a rough estimate and needs further research.

- Toys consisting of liquid material. The amount of liquid toy material that may be ingested via hand-mouth contact is likely considerably higher than for dry material. For finger paint and other products that stick to the skin, ConsExpo's fact sheet on toys derived a default value of 30 mg/min (Bremmer and Van Veen, 2002). It was

further assumed that children play with finger paint for 45 minutes. Total amount swallowed is then 30 x 45 = 1350 mg.

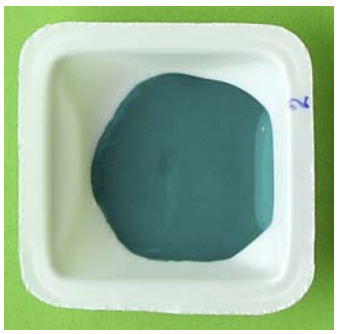

Figure 3-9: 1350 mg finger paint

Figure 3-10: 290 mg finger paint

The pictures above show that this amount may be an overestimation, although 100 mg may be too little. We propose to use a value of 400 mg as a default, but again, this value is a rough estimate and needs further research.

It is emphasized that this default applies to children under 3 years of age only, as these children display most mouthing behaviour.
Similar to the ingestion default for dry, brittle, powder-like and pliable materials, an ingestion of 400 mg may occasionally occur, but not daily. For the purpose of an exposure assessment refinement, when comparing exposure to a chronic health-based limit value, we propose to use a frequency of 1/week as a default. This is a rough estimate and needs further research.

- Layers of toy material scraped off. The amount of toy material scraped off with the teeth while mouthing a solid toy is likely considerably lower than the amount of liquid, pliable or sticky toy material that may be ingested. In the fact sheet on toys, a single ingestion of paint from a toy car is estimated based on the product volume (0.05 cm^3) and density of paint (2 g/cm^3). This amounts to a total of 0.1 g (Bremmer et al., 2002). However, this value is considered an overestimation. The weight of paint material scraped off from a pencil and textile fibers pulled off a pluche toy are in the order of magnitude of the 8 mg used in the current EN-71 (see Figure 3-11 to

3-16). It is therefore recommended to keep this value as a default for ingested layers of scraped off toy material.

In contrast to the previous two defaults for ingested amounts, this default also applies to toys intended to be mouthed by children over 3 years of age. Furthermore, with regard to frequency, it is assumed that the small amount of 8 mg material can be scraped off from a toy every day.

Figure 3-11: 8.6 mg of textile fibres from a pluche toy

Figure 3-12: 1.3 mg of textile fibres from a pluche toy

Figure 3-13: 8 mg of scraped off chalk crayon material

Figure 3-14: 8 mg of modelling clay material

Figure 3-15: 8 mg of scraped off pencil material

Figure 3-16: 0.5 mg scraped off pencil material

w_f : fraction of the chemical in the toy material. This depends entirely on the material the toy consists of and no default values can be given. The total amount of chemical migrated from the toy (material) can also be used, for example if composition data of the material are not available. The amount of migrated chemical depends entirely on the chemical- material combination and should be assessed with methods described in chapter 4.

W_{body} : body weight of the exposed child. The risk assessment work of the CEN/TC 52/WG9 used 10 kg for the mass of a child (European Committee for Standardization (CEN), 2003). Mean, standard deviation and 25th percentile default values for body weight of Dutch children from 1.5 months to 17.5 years have been given in the general fact sheet of ConsExpo (Bremmer et al., 2006):

Table 3-1 Mean, standard deviation and 25th percentile default values for body weight of Dutch children from 1.5 months to 17.5 years. Source: Bremmer et al., 2006, derived from a study by TNO in 2000.

Age		**Body weight [kg]**		
Months	Years	Mean	SD	25th percentile
1.5		4.65	0.52	4.30
4.5		6.75	0.79	6.21
7.5		8.30	1.0	7.62
10.5		9.45	1.1	8.69
13.5		10.3	1.2	9.47
	1.5	11.1	1.9	9.85
	2.5	13.9	2.1	12.5
	3.5	16.0	2.9	14.1
	4.5	18.4	3.1	16.3
	6.5	23.1	3.8	20.6
	9.5	32.4	6.0	28.4
	12.5	44.8	8.1	39.3
	13.5	50.0	9.0	43.9
	16.5	62.9	9.0	56.8
	17.5	65.3	10	58.2

- If the direct ingestion will be done by young children displaying mouthing behaviour, the body weight for this age needs to be used. According to the table above, the 10 kg value used by the CEN approximately corresponds to the 25th percentile body weight of Dutch children aged 1.5 years. The study by the DTI (2002) reported that children aged 6-9 months display the highest mouthing durations for toys. The 25th percentile body weight for this age group (i.e. 7.5 months in the table above) is 7.62 kg. A body weight of 7.5 kg is suggested as a default.
- For ingestion of scraped off toy material from toys intended to be mouthed for children over 3 years of age, the bodyweight of a child of approximately 3-4 years of age should be used. The 25th percentile of Dutch children 3.5 and 4.5 years of age is 14.1 and 16.3 kg, respectively. A default value of 15 kg is proposed.

3.5.3 Mouthing

The amount of element or other chemical ingested via mouthing can be calculated as:

$$D = A \times w_f / W_{body} \times (1 - \exp(-\frac{R_m \times S}{A \times w_f} \times t))$$

with

A	:	the total amount of product that is being mouthed	[kg]
R_m	:	rate at which the chemical migrates from the product (per unit area)	[kg/m^2.s]
S	:	the surface area of the product that is being mouthed	[m^2]

wf	:	weight fraction of the chemical in the product	[fraction]
t	:	mouthing time	[s]
W_{body}	:	body weight of the exposed person	[kg]

The parameter values needed for this calculation are:
A : the total amount of toy that is being mouthed. This amount can be determined by calculating the volume of the (part of the) toy that can be mouthed and multiplying this value with the density of the material of which the toy is made. In the ConsExpo fact sheet for toys, the volume for a teething ring, a cuddly toy and a plastic doll have been estimated at 20, 50 and 100 cm^3, respectively (Bremmer et al., 2002). To illustrate, for a doll made of plastic with a density of 1 g/cm^3, the total amount that can be mouthed is 100 x 1 = 100 g. In practice, the amount of toy that can be mouthed highly depends on the dimensions of the toy and therefore should be determined on a case by case basis.

R_m : the rate at which a chemical migrates from the product. Methods of migration tests will be discussed in chapter 4.

S : the surface area of the (part of the) toy that is being mouthed. The risk assessment work of the CEN/TC 52/WG9 for organic chemicals assumed a value of 10 cm^2 for the area of toy mouthed (European Committee for Standardization (CEN), 2004). The same value is used in ConsExpo's fact sheet on toys, which was based on a study by Könemann (1998). The value of 10 cm^2 probably refers to the surface area of a toy that can be placed in the mouth at once. However, considering that a toy may be mouthed for three hours (as discussed below), a much larger surface area may be covered. Again, as for amount of toy being mouthed, this depends highly on the dimensions of the toy and should be determined on a case by case basis.

wf : fraction of the chemical in the toy (material). This depends entirely on the material the toy consists of and no default values can be given. The total amount of chemical migrated from the toy (material) can also be used, for example if composition data of the material are not available. The amount of migrated chemical depends entirely on the chemical- material combination and should be assessed with methods described in chapter 4.

t : Mouthing time. The risk assessment work of the CEN/TC 52/WG9 for organic chemicals assumed a value of 3 hours per day for the duration of mouthing (European Committee for Standardization (CEN), 2003). The value of 3 hours was adopted by the CSTEE opinion of 1998, 6^{th} plenary meeting in the framework of the risk assessments of phthalates in toys. In ConsExpo's fact sheet on toys, default mouthing times for toys for mouthing and other toys have been calculated based on a study from De Groot et al. (1998):

Table 3-2 Default mouthing times for toys for mouthing and other toys. Based on: De Groot et al. (1998)

Age [months]	**Default mouthing times [minutes per day]**	
	Toys for mouthing	Other toys
4.5	11	27
7.5	21	63
13.5	0	9
18	0	3

Similar average mouthing times have been reported by Juberg et al. (2001).
Two new studies have been published since. The first study was conducted by the UK Department of Trade and Industry (DTI), which reported mean and maximum mouthing times of toys and other items for children of different age groups up to 5 years of age (DTI, 2002; Smith and Norris, 2003). Children aged 6–9 months displayed the most mouthing behaviour. For this group, the mean mouthing time on toys was 39 minutes.
A second study was published by the US Consumer Product Safety Commission which conducted an observational study of mouthing activity by 169 children aged 3-36 months (Babich et al., 2004). From this study, daily mouthing times for selected objects can be calculated by multiplying the hourly mouthing duration (min/h) with the daily exposure time. The hourly mouthing duration is defined as the time per hour that the article is actually in the child's mouth or touching the lips. The daily exposure time is defined as the time a child is awake and not eating and is estimated by the model:

T_{day} = 9.46 + 0.0375 x Age (months)

For children between 3 and 36 months of age, exposure time is thus roughly 10 hours. Using the mean or 95% hourly mouthing duration data of the study and an exposure time of 10 hours, the calculated mouthing times are:

Table 3-3 Calculated mouthing times, as derived from Babich et al. (2004)

Age group studied [months]	Object mouthed	Mean hourly mouthing duration [min/h]	95% hourly mouthing duration [min/h]	Mean daily mouthing time [min]	95% daily mouthing time [min]
3-11	Soft plastic toys	0.13	0.69	1.3	6.9
	Soft plastic teethers, rattles	0.19	0.44	1.9	4.4
	Non-soft plastic toys, teethers, rattles	1.8	6.5	18	65
12-23	Soft plastic toys	0.18	0.88	1.8	8.8
	Soft plastic teethers, rattles	0.02	0.1	0.2	1.0
	Non-soft plastic toys, teethers, rattles	0.56	1.8	5.6	18
24-36	Soft plastic toys	0.07	0.21	0.7	2.1
	Soft plastic teethers, rattles	0.02	0.00	0.2	0.00
	Non-soft plastic toys, teethers, rattles	0.21	0.94	2.1	9.4

The observed mean mouthing times of these studies are significantly lower than the value of three hours as used by the CSTEE. However, the use of this value can be clarified when one takes into account the skewness of the data, as it has been observed in these mouthing studies that few children mouth objects for a long period and many children mouth objects for a short time or not at all (Greene, 1998). For example, in the DTI study, the mean mouthing time by children aged 6-9 months was 39 minutes, whereas the maximum mouthing time for toys was 3 hours and 46 minutes (DTI, 2002; Smith and Norris, 2003). Similarly, in the study by Juberg et al. (2001), the mean and median daily mouthing durations of non pacifiers (including teethers and toys) by children aged 0-18 months were approximately 35 and

15 minutes, respectively, whereas daily mouthing durations of over 300 minutes were also observed.
To safeguard the relatively small group of children that display these longer mouthing times, it is recommended to continue using three hours as a default for mouthing duration. However, this example of highly variable mouthing durations supports the use of probabilistic methods to adequately assess the exposure to chemicals in toys that can be mouthed.
As can be seen in the table above, toys intended to be mouthed by children under 36 months are not necessarily mouthed for longer durations than other toys.

A different value for mouthing duration can be used for toys that are intended for older children and intended to be placed in the mouth, such as whistles and balloons. Although no data was found on the mouthing duration of such toys, it can be assumed that the duration is shorter than the mouthing duration by young children. A default value of one hour is proposed for mouthing duration of toys intended for older children and intended to be placed in the mouth, although this value is quite arbitrary and further research on this is warranted.

W_{body} : Body weight of the child. For toys intended for young children, the body weight of children displaying most mouthing behaviour (6-9 months of age, approximately 7.5 kg) should be used, as in the direct ingestion model. For toys intended to be placed in the mouth by older children such as whistles, the body weight of a child of approximately 3-4 years of age should be used. The 25th percentile of Dutch children 3.5 and 4.5 years of age is 14.1 and 16.3 kg, respectively. A default value of 15 kg is proposed.

3.5.4 Inhalation via evaporation

For volatile chemicals, the mean event concentration in the air can be calculated as follows:

$$< Cair >= \frac{1}{T} \times \frac{A \times w_f}{V} \times \int_0^T e^{-qt} dt = \frac{1}{T} \times \frac{A \times w_f}{V} \times \frac{1}{q} \times (1 - e^{-qT})$$

where:

C_{air}	: concentration of chemical in the room air	[mg/m^3]
A_o	: product amount	[mg]
wf	: weight fraction of the chemical in the total product	[fraction]
V	: room volume	[m^3]
q	: ventilation rate of the room (number of air changes per time unit)	[1/hr]
t	: exposure duration	[hr]

Subsequently, the amount inhaled can be calculated by :

$$A_{inh} =< Cair > \times Q_{inh} \times T$$

where:

A_{inh} : amount inhaled [mg]

Q_{inh} : inhalation rate [m^3/hr]

The parameter values needed for this calculation are:

A_o : Amount of the toy containing the volatile chemical. This is practically the weight of the whole toy.

wf : Weight fraction of the chemical in the toy material. This depends entirely on the material the toy consists of and no default values can be given

V : Room volume. Mean, standard deviation and 25th percentiles for room volumes in Dutch homes have been given in the general fact sheet of ConsExpo:

Table 3-4 Room volumes in Dutch homes. Source: Bremmer et al. (2006)

	Volume		
Space	Mean [m^3]	s.d.	25th percentile
living room	74	23	58
kitchen (incl. open kitchen)			
bedroom 1	22	9.6	15
bedroom 2	35	11.2	27
bedroom 3	28	8.3	22
	21	7.6	16

In the absence of information on which room is used, a default volume of 20 m^3 is usually used.

q : Ventilation rate of the room (number of air changes per time unit). Measurements of ventilation rates in Dutch homes and abroad have been given in the general fact sheet of ConsExpo (Bremmer et al., 2006). Default 25th percentiles for ventilation rates in Dutch homes:

Table 3-5 Default 25th percentile room ventilation rates in Dutch homes. Source: Bremmer et al. (2006)

Room	Ventilation rate [h^{-1}]	Q
the whole house	0.6	3
living room	0.5	3
kitchen	2.5	3
bedroom	1	3
bedroom (window open)	2.5	3
bathroom	2	3
toilet	2	3
shed	1.5	3
garage	1.5	3
default, if room is unspecified	0.6	3

t : Exposure duration is the time during which a child is exposed to the evaporated chemical. The US EPA child-specific exposure factors handbook cites a study by Timmer et al. (1985) in which the playing activity for five different age groups varying from 3 to 17 years of age children is reported to be between 14 an 267 minutes per day (US EPA,

2002). The Danish EPA quotes an American study which observed average play activity times of 47 – 70 minutes for children 1 to 17 years of age, with 90 percentiles of 120 to 255 minutes (Danish EPA, 2005). The playing duration is likely to vary significantly per toy and information on this is probably known best by the manufacturer of the toy. It has to be emphasized that the exposure duration may be longer than the actual play time with the toy in question, because the child may still reside in the room where the chemical has evaporated after playing with the toy. The daily exposure time as defined by Babich et al. (2004) as the time a child is awake and not eating can be used as a worst case value, which was approximately 10 hours.

Q_{inh} : Inhalation rate. The US EPA child-specific exposure factors handbook recommends using an inhalation rate default value of 4.5 m^3/day for children under one year of age (US-EPA, 2002). For children aged 3-5 years, an inhalation rate default value of 8.3 m^3/day is recommended. We propose to take over these defaults.

Due to the wide variation in toys that may release a chemical via evaporation, a default for frequency of exposure cannot be given.

NOTE : A more accurate exposure assessment to a chemical evaporating from a toy may be achieved with the evaporation mode of the 'exposure to vapour' model in ConsExpo (Delmaar et al., 2005).

3.5.5 Inhalation via dust or spray

The concentration of the chemical available for inhalation via dust or spray can be calculated using the same formula as that used for the inhalation via evaporation scenario. However, not all particles or droplets can be inhaled and reach the lower areas of the lungs (the alveolar region). This depends on the size of the particles or droplets. To assess exposure via this pathway, the particle size distribution of the spray or dust must be known. In the European Norm EN 481, size fraction definitions for measurement of airborne particles have been given (1994). Based on this norm, it is estimated that dust particles or spray droplets which can be inhaled and reach the alveolar region will mostly have a diameter below 5 µm, although particles with diameters up to 15 µm can still reach the alveolar region. Particles with a diameter between 5 and 15 µm will mostly only reach the thoracic region and can be taken in orally. Larger particles will mostly fall directly to the floor. Based on this, the fraction of product released in the air with particles or droplets below 15 µm can be used for the parameter 'product amount'.
For dust generated by chalk crayons, a default can be derived from a study by Stopford (Stopford, 2003)[5]. The respirable aerosol production (particles < 4 µm) generated during chalk and pastel drawing activities for 30 minutes was found to be 364 ± 272 µg (mean ±

[5] http://duketox.mc.duke.edu/cpscdust3.pdf

standard deviation), whereas total dust formation was 855 ± 590 µg. A rough estimate of particles below 15 µm generated is 500 µg, which can be used as a default.
For spray, the particle size distribution depends strongly on the solvent, the propellant and the nozzle size. We currently have no information on these factors for toy sprays and therefore, and no default can be given.

NOTE: A more accurate exposure assessment to a chemical released in dust or spray may be achieved with the spray model in ConsExpo (Delmaar et al., 2005).

3.5.6 Skin contact

The amount of a chemical on skin per skin area (L_{derm}) or per body weight (D) can be calculated as follows:

$$L_{derm} = A_o \times S_{contact} \times F_{leach} / S_{exp}$$

And the external dose as:

$$D = A_o \times S_{contact} \times F_{leach} / W_{body}$$

where

F_{leach}:	the leachable fraction	[fraction]
A_o:	amount of product in contact with skin	[kg]
$S_{contact}$:	skin contact factor	[fraction]
S_{exp}:	the surface area of the exposed skin	[m^2]
W_{body} :	the body weight of the exposed person	[kg]

The parameter values needed for this calculation are:

F_{leach} : leachable fraction, the amount of chemical that migrates to the skin per unit amount of toy. This value can be determined with migration tests, which will be discussed further in chapter 4.

A_0 : amount of toy in contact with the skin. This is practically the weight of the toy.

$S_{contact}$: skin contact factor, used to account for the fact that the product is only partially in contact with the skin. For example, for a costume this factor has been estimated to be 0.7, since part of the costume will be on top of underwear and as such not in direct contact with the skin (Bremmer and Van Veen, 2002). The skin contact factor varies too much with the type of toy to be able to provide a default value.

S_{exp} : The surface area of the exposed skin. Mean, standard deviation and 25th percentile default values for body surface area of Dutch children from 1.5 months to 17.5 years have been given in the general fact sheet of ConsExpo (Bremmer et al., 2006):

Table 3-6 Mean, standard deviation and 25th percentile default values for body surface area of Dutch children from 1.5 months to 17.5 years. Source: Bremmer et al. (2006).

Age		Body surface [m^2]		
Months	Years	mean	SD	25th percentile
1.5		0.283	0.020	0.270
4.5		0.364	0.026	0.346
7.5		0.419	0.031	0.398
10.5		0.459	0.033	0.437
13.5		0.490	0.035	0.467
	1.5	0.520	0.062	0.480
	2.5	0.616	0.062	0.575
	3.5	0.690	0.076	0.640
	4.5	0.762	0.081	0.709
	6.5	0.902	0.093	0.841
	9.5	1.13	0.13	1.05
	12.5	1.40	0.15	1.31
	13.5	1.51	0.16	1.40
	16.5	1.75	0.16	1.65
	17.5	1.79	0.18	1.67

In addition, default percentages of body surface for different body parts have been given:

Table 3-7 Default percentagess for body surface area of different body parts of Dutch children from 3 months to 14 years. Source: Bremmer et al. (2006).

Age	Age	surface	body surface in %					
	Default value	[m^2]	Head	trunk	arms	hands	legs	feet
3 - 6 months	4.5 months	0.346	19.5	32.8	12.1	5.1	23.5	7.0
6 - 12 months	7.5	0.398	18.5	33.5	12.2	5.2	23.6	7.0
12 - 18 months	13.5	0.467	16.9	34.3	12.6	5.3	23.8	7.1
1.5 - 3 year	1.5 year	0.480	16.2	34.0	13.0	5.15	25.05	6.6
3 - 9 year	4.5	0.709	13.4	33.05	14.0	5.5	26.95	7.1
3 - 9 year	6.5	0.841	12.5	33.45	13.95	5.5	27.35	7.2
9 - 14 year	12.5	1.31	9.8	33.15	13.9	5.7	30.0	7.4

W_{body} : Body weight of the exposed child, see above for direct ingestion.

With respect to exposure frequency, dermal contact with most toys can be expected to occur on a daily basis.

3.5.7 Uptake

An essential part of the exposure assessment is formed by the uptake of a chemical by the gastrointestinal tract, lungs or skin. The exposure assessment can be significantly refined if data on the uptake of the chemical is available. A default value for uptake cannot be given,

as this is very chemical specific. It is common practice to use an uptake of 100% if no information is available.
Exposure levels via different routes can only be added when uptake is included, i.e. when looking at the internal, systemic dose.

3.5.8 Level of detail required for exposure assessments

As mentioned earlier, a detailed exposure assessment involving all exposure routes and factors as described above is not always needed to demonstrate the safety of a toy. Apart from excluding irrelevant exposure routes from the assessment, composition data of toy material or migration data in combination with some general exposure factors such as exposure frequency and bodyweight may frequently provide sufficient information to demonstrate that exposure levels will not exceed the relevant health-based limit values. This will be explained in detail in chapter 7. Nevertheless, for certain ad hoc situations, or for specific toys or chemicals, a more refined exposure assessment may be desired. This can be achieved by using the methodology presented here. In addition, for certain exposure scenarios, further refinement can be achieved by using more refined migration testing methods.

3.6 Conclusions

- We conclude that it is foreseeable that children under 3 years old will have access to toys intended for children over 3 years old, unless these toys contain small parts or long cords, because caregivers commonly know that such toys should be kept out of reach from children displaying mouthing behaviour. This conclusion concurs with the conclusion of the CSTEE.
- Six exposure scenario categories can be identified that may be relevant for toys: direct ingestion, mouthing, inhalation via evaporation, inhalation via dust or spray, skin contact and eye contact. It is anticipated that exposure to chemicals via eye contact will not lead to effects of a serious nature and this contact scenario is therefore not considered further.
- The exposure scenarios relevant for a particular type of toy can be identified using the exposure scenario decision tree.
- Exposure via the scenarios can be assessed by using adequate formulas and exposure factor values.
- Exposure factor values are often highly uncertain and rough estimates are used until more adequate information becomes available.
- Based on simple weighing experiments, the default for ingested amount of 8 mg of toy material can be supported when the toy material is scraped off. For other toy materials such as liquid and powder-like materials, other defaults need to be used.
- For all exposure routes, the exposure assessment can be significantly refined if data on the uptake of the chemical is available.

3.7 Recommendations

- We propose that the exposure assessment of all toys which do not contain small parts or long chords (or are otherwise dangerous from a physical-mechanical point of view), but can be placed in the mouth or can be crawled on by children should include exposure scenarios specific for young children, regardless of the intended age category of the toy.
- Many default values for exposure factors are highly uncertain and further research in this area is warranted. More information is especially needed on:
    - frequency and amounts ingested of toy material;
    - mouthing durations for toys intended to be put in the mouth for children over 3 years of age;
    - mouthing amounts and surfaces;
    - playing durations for different types of toys;
    - amounts of dust (and particle size distributions) generated by chalk, plaster and other powder-like toys.

4 From toy to internal exposure – migration versus bioavailability

4.1 Introduction

Not all the chemicals in a toy represent a hazard for the child's health. Part of the chemicals will remain in the toy even after mouthing the toy or swallowing (parts of) it. Therefore, in guidance document EN 71-3 migration limits are set for 8 elements (Sb, As, Ba, Cd, Cr^{3+} and Cr^{6+}, Pb, Hg, and Se), which simulate the contact of toy material with stomach acid (European Committee for Standardization (CEN), 1994). This acidic solution probably represents a worst case scenario for elements. This is however not necessarily the case for organic compounds. Legislation for most organic substances is laid down in guidance documents EN 71-9, EN 71-10, and EN 71-11.

The aim of this chapter is twofold:

1. to evaluate the use of migration and bioavailability data in risk assessment for substances in toys;
2. to evaluate these data more in particular for the 8 elements (Sb, As, Ba, Cd, Cr, Pb, Hg, and Se) and some additional inorganic substances indicated in chapter 2 (Al, B, Co, Cu, Mn, Sn, Ni, and Sr) in the 'safety of toys' Directive.

To that end the following issues will be addressed:

A. Oral bioavailability:
- definition and the various sub-processes that can be distinguished
- description of various migration and physiologically based extraction tests
- pros and cons of these tests
- applicability of migration and physiologically based extraction tests in risk assessment of chemicals in toy matrices
- comparison to migration tests applied for food contact materials

B. Bioavailability after inhalation:
- experimental determination
- applicability in risk assessment of chemicals in toys

C. Dermal bioavailability:
- experimental determination
- applicability in risk assessment of chemicals in toys

4.2 Oral bioavailability

4.2.1 Definition of oral bioavailability

In Council Directive 88/378/EEG bioavailability is defined as '*the soluble extract having toxicological significance'* (European Committee for Standardization (CEN), 1988). In the opinion of the Scientific Committee on Toxicity, Ecotoxicity and the Environment (CSTEE) on 'assessment of the bioavailability of certain elements in toys' it is stated that this is not in line with the general understanding of the term which is '*the amount of each element in the toy which could be absorbed into the systemic circulation of a child'* (Scientific Committee on toxicity, 2004).

The term bioavailability is subject to various interpretations. Different points of view exist partly depending on the scientific background of the investigator. For example, in human nutritional sciences, the concept of bioavailability is regarded as the efficiency with which nutrients are utilized (Schümann et al., 1994; Wienk et al., 1999). In pharmacology, oral bioavailability characterizes the fraction of a dose that reaches the systemic circulation after oral administration (Schümann et al., 1994; Chiou, 2001). Also different definitions of bioavailability exist in fields such as ecotoxicology, et cetera, which fall outside the scope of this report.

The pharmacology definition of bioavailability is considered to be the most appropriate within the present context, i.e. *the fraction of a substance present in toy material that reaches the systemic circulation (of a child)*. This is a broadly applicable definition, whereas the definition in nutritional sciences focuses on the nutritive value of feed and food. The CSTEE has recommended using a slightly different definition than the pharmacology definition, as the CSTEE definition is "the amount of each element in the toy which *could be* absorbed into the systemic circulation of a child", rather than the amount that *reaches* the systemic circulation. Therefore, the definition by the CSTEE can be interpreted as bioaccessibility (F_B), a prerequisite step before a compound can become bioavailable, see section 4.2.2. The bioaccessible fraction (F_B) represents the maximum amount of contaminant potentially available for transport across the intestinal epithelium, and can be investigated by the release of the element from toy in conditions similar to conditions in the human gastrointestinal tract.

The link between the definition of bioavailability by Council Directive 88/378/EEG and the definition by the CSTEE is that the systemic fraction of a toxic compound is in general a better measure for toxicity than external exposure. In general this is true. However, for some compounds the internal fraction is not a better measure for toxicity, for example for compounds that locally exert toxicity, e.g. skin irritation by nickel.

The definition by Council Directive 88/378/EEG (‘*the soluble extract having toxicological significance’*) is very broad and therefore difficult to translate to simple non-animal tests to estimate the bioavailable fraction.

According to the pharmacology definition (‘*the amount of each element in the toy that is absorbed into the systemic circulation of a child’*), bioavailability is best determined by measuring the concentration of chemical in the blood of a human being or animal in time. Usually, bioavailability is determined by comparison of the chemical concentration in blood in time after intravenous administration, i.e. 100% bioavailable by definition, versus the concentration in blood in time after the administration of interest. In section 4.2.2, the sub-processes of bioavailability are addressed in order to find a starting point for estimating bioavailability.

4.2.2 Sub-processes of oral bioavailability

According to the general interpretation in pharmacology, oral bioavailability is defined as the fraction of an orally administered dose that reaches the systemic circulation. We have conceptually subdivided oral bioavailability (F) into three major processes (Brandon et al., 2006; Oomen et al., 2005; González-Soto et al., 2000; Danish EPA, 2005; Oomen et al., 2004a; Babich et al., 2004; Versantvoort et al., 2004). Figure 4-1 describes these processes. After ingestion, the contaminants may be partially or totally **released from its matrix**, a toy in the present case, during digestion in the gastro-intestinal tract. The fraction of the contaminant that is mobilized from the matrix into the digestive juice is defined as the **bioaccessible fraction (F_B)** and represents the maximum amount of contaminant potentially available for transport across the intestinal epithelium.
F_A represents the fraction of bioaccessible contaminant that is **transported from the lumen across the intestinal epithelium** and into the portal vein or the lymph, thus representing the absorption.
The contaminants may be **metabolized** in the intestinal epithelium or the liver, which is referred to as the first-pass effect. The fraction of *un*metabolised contaminant after passing the liver (**F_H**) will be transported throughout the body by the systemic circulation, and may exert toxicity in organs and tissues. Consequently, the orally bioavailable fraction of a contaminant is the resultant of the three steps: bioaccessibility, transport across the intestinal epithelium, and the first-pass effect (see Figure 4-1 and equation 1):

$$F = F_B \times F_A \times F_H \qquad (1)$$

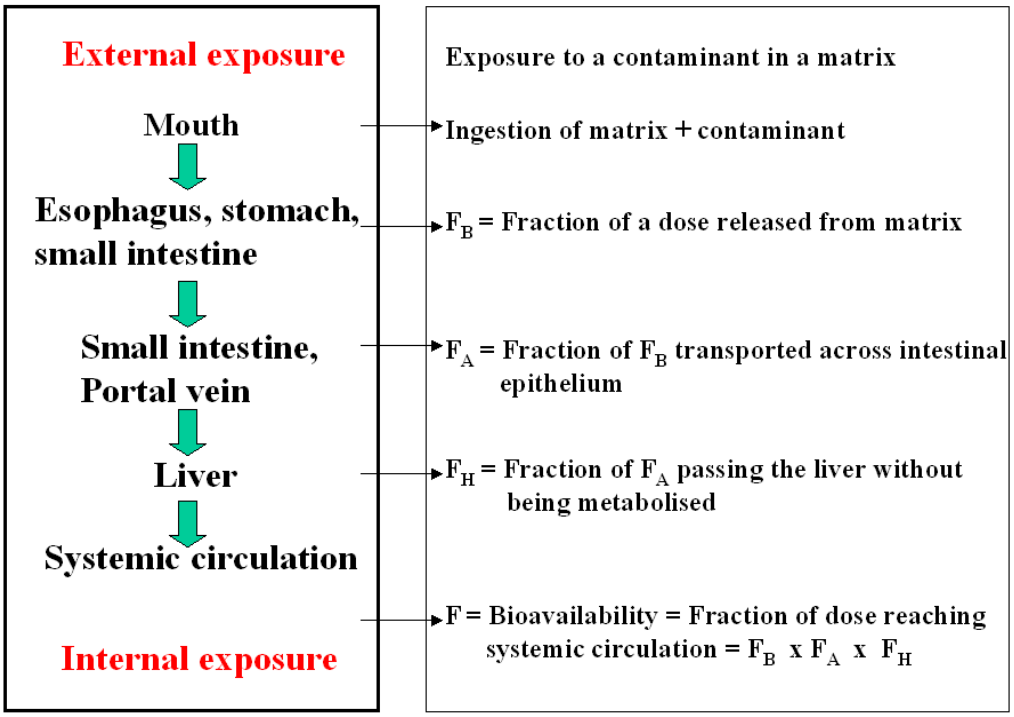

Figure 4-1 Various steps of oral bioavailability (F) of a compound in toy matrix.

To our experience the matrix in which the contaminant is ingested, i.e. toy, food, water, soil etcetera, is a determining factor in the fraction of the contaminant that becomes bioaccessible (Oomen et al., 2006; Versantvoort et al., 2005; Brandon et al., 2006). Therefore, bioaccessibility can be used to investigate the difference in bioavailability of a substance from two different matrices (see section 4.3). It is possible that the matrix in which the contaminant is ingested may affect the absorption of the contaminant. For an example and for further information on this issue we refer to Oomen et al. (Oomen et al., 2006). Presently, we assume that the matrix of ingestion only influences the sub-process of bioaccessibility.

The bioaccessible fraction, F_b, can be determined in vitro, by simulating the physicochemical conditions of the human gastrointestinal tract. Several in vitro methods exist that aim to determine the bioaccessible fraction of a contaminant (Oomen et al., 2002a). In most cases, such tests have been applied to investigate the bioavailability of contaminants from soil (exposure to contaminants via hand-to-mouth behaviour). Oomen et al. also developed a physiologically based extraction test for contaminants in toys, making difference between scenario's for 1) mouthing, 2) swallowing, and 3) mouthing followed by swallowing.

4.3 Relative bioavailability in risk assessment

In order to correctly apply bioavailability of compounds in toy material in the risk assessment of these compounds, one should use *relative bioavailability*. This means that the bioavailability should be considered for both the exposure assessment as well as for the toxicological information available. For example, the risk assessment of ingested material can be refined by taking into account the fraction that migrates to the gastric juice and the absorption over the intestinal wall. In this way, the internal (systemic) exposure is determined. However, if we compare such an internal exposure with toxicological data, also a correction for the bioavailability in the toxicological test should be used. For example, if the toxic substance was provided in the food to rats, one should take into account the fraction that was released from the food matrix in the stomach and the absorption over the intestinal wall. If such corrections are not made, we implicitly assume that the bioavailability in the exposure and the toxicological condition is similar.
An example for toys: when the bioavailability of a compound in the toxicological study underlying the TDI is 60%, and the bioavailability of the same compound from a certain toy material is 20%, the relative bioavailability is 20%/60% is 0.33.

The correct application of relative bioavailability in the present framework of chemicals in toys is difficult. As indicated in section 4.2.2, bioavailability consists of several sub-processes. One of these processes is bioaccessibility, which we aim to study by migration of the chemical from toy into artificial saliva or gastric juice. Assuming that the difference in bioavailability from the matrix used in the study underlying the TDI and the toy matrix can be explained by the difference in bioaccessibility only, a relative bioaccessibility instead of a relative bioavailability can be used. A relative bioaccessibility is preferred, as the outcome of the migration test can be considered to be a measure of bioaccessibility. However, ideally also the bioaccessibility of the matrix used in the study underlying the TDI should be known. Sometimes information is available on the bioavailability of the compound of interest in the study underlying the TDI, but information on the bioaccessibility is usually not available. Therefore, if relative bioavailability is to be used correctly in the present framework, further research is needed on the bioaccessibility of the compounds of interest from the matrix used in the studies underlying the TDI is necessary. Also, attention should be paid to the possibility that relative bioavailability cannot always be translated directly into relative bioaccessibility (this assumes that absorption and metabolism of the compound are the same in the study underlying the TDI and for the toy matrix).
An example of application of relative bioavailability and relative bioaccessibility in risk assessment can be found for lead in soil (Oomen et al., 2006). In this report, the bioavailability of lead from soil is used relative to the bioavailability of dietary lead, e.g. the matrix in the studies underlying the TDI of lead.

If a methodology incorporates sufficient margins of safety, the issue of relative bioavailability can be neglected. It can be argued that for most elements the presently proposed methodology in chapter 8 is safe without correction for relative bioavailability. The outcome of the migration test is expected to give a worst case value for bioaccessibility due to the low pH value of the extraction medium. This assumption is based on several observations that the bioaccessibility of elements is much higher in the stomach compartment compared to the intestinal compartment of a physiologically based in vitro digestion model (Oomen et al., 2003c; Oomen et al., 2004b; Oomen et al., 2002b). The acid environment of the stomach compartment is considered to be similar to the extraction according EN 71-3, whereas the extraction in the intestinal compartment is probably a better measure for bioavailability as absorption of elements occurs in the intestine. Because direct in vivo data that verify the statement that the methodology incorporates sufficient margins of safety are lacking, further research on this issue is recommended.

4.4 Tests to estimate the orally bioavailable fraction of a contaminant from toy

Bioavailability is presently defined as the fraction of an orally administered dose that reaches the systemic circulation, see section 4.2.1. Bioavailability refers to a physiological process. Therefore, true bioavailability of a compound from toy can only be tested in humans or animals, for example by determination of the blood concentration in time after oral and intravenous application. For simplicity and in order to avoid animal testing, a few methods have been developed to estimate the bioavailability or part of the process determining the bioavailability *in vitro*, i.e. in the laboratory. The different migration and physiologically based extractions tests are listed in Appendix V.

4.4.1 Tests for inorganic compounds

Policy on the safety of toys in European Member States has been laid down in Council Directive 88/378/EEC. In this Directive requirements for the total bioavailable amount are listed for several elements, see Table 4-2. The bioavailable amount was used in the Directive as it was considered that the bioavailable fraction of a substance in toys is more important than the total content of potentially dangerous substances, i.e. internal exposure is considered to be more predictive for toxicity than the dose (Commission of the European Communities, 1985). In this sense, the intention of the use of bioavailability by Council Directive 88/378/EEC is in line with the pharmacological definition of bioavailability, see section 4.2.1. In the European Standard 71-3 these bioavailability requirements are translated to limits of migration, also listed in Table 4-1 (European Committee for Standardization (CEN), 1994). For the translation of allowed bioavailability to limits of migration a daily intake of 8 mg toy is assumed. In addition, adjustments were made to minimize the exposure of children to toxic elements by lowering the migration limit for barium and selenium, and to ensure analytical feasibility by increasing the migration limit for antimony, arsenic, and

chromium (Danish EPA, 1998). For comparison, the maximum bioavailable concentrations in toy materials based on 8 mg of ingested toy material would be 25 mg Sb/kg, 12.5 mg As/kg, 3125 mg Ba/kg, 75 mg Cd/kg, 37.5 mg Cr/kg, 87.5 mg Pb/kg, 62.5 mg Hg/kg, and 625 mg Se/kg (Danish EPA, 1998), whereas the migration limits listed in Table 4-2 are proposed by EN 71-3 (European Committee for Standardization (CEN), 1994).

The migration of elements from toy is according EN 71-3 assessed with chemical extraction tests (European Committee for Standardization (CEN), 1994). Generally, a 0.07 M hydrochloric acid solution of 50 times the mass of the test portion (and preferentially a sample mass of 100 mg or more, with exceptions) is used. The pH is adjusted in the presence of toy to pH 1.0 to 1.5, and the chemical is extracted from the toy matrix during 1 h with agitation and 1 h without agitation, see Appendix V for details on the migration tests. This extraction medium, hydrochloric acid solution, is considered to simulate gastric juice (Commission of the European Communities, 1985). For the elements listed in EN 71-3 simulated gastric juice was used as it was argued that this is a more stringent extraction medium than saliva, providing an additional margin of safety in the evaluation of possible intake of these compounds by children (Commission of the European Communities, 1985).

Some non-EU countries use different migration tests. For example, Canada has its own legislation and test methods, see Appendix V, which uses different extraction solutions which could lead to other outcomes for the migration. However, the majority of the non-EU countries also use the CEN 71-3 migration test for the 8 different elements.

Beside the chemical extraction tests, there are several physiologically-based extraction tests to simulate mouthing in order to minimise over- or underestimation of migration/bioaccessibility of the *in vivo* situation. Most of these tests were developed and used to determine the release of organic compounds, e.g. phthalates, from toys and other consumer products. Only Iliano et al. (1988) and RIVM (Oomen et al., 2005; Oomen et al., 2004a; Oomen et al., 2003b) have actually looked at the release of elements from toys using physiologically-based extraction tests (see Appendix V).

Table 4-1 Requirements based on total bioavailable amount of element resulting from the use of toys per day according to Council Directive 88/378/EEC, and migration limits according to EN 7 1-3.

Element	Limit of total bioavailable amount per day (88/378/EEC) (μg)	Limit of migration from toy material (EN 71-3) (mg/kg) [1]			Limit of migration for modelling clay and finger paint (EN 71-3) (mg/kg) [2]		
		Without analytical correction	Analytical correction factor (in %)	After analytical correction[3]	Without analytical correction	Analytical correction factor (in %)	After analytical correction[3]
Antimony (Sb)	0.2	60	60	150	60	60	150
Arsenic (As)	0.1	25	60	63	25	60	63
Barium (Ba)	25.0	1000	30	1429	250	30	357
Cadmium (Cd)	0.6	75	30	107	50	30	71
Chromium (Cr)	0.3	60	30	86	25	30	36
Lead (Pb)	0.7	90	30	129	90	30	129
Mercury (Hg)	0.5	60	50	120	25	50	50
Selenium (Se)	5.0	500	60	1250	500	60	1250

[1] Limits of migration for any toy material detailed in EN 71-3, except for modelling clay and finger paint. Due to the precision of the analytical methods the result of a migration test is corrected. The analytical correction to which the result of the migration test should be subjected is listed. In the next column the corresponding limits of migration have been accounted for the analytical correction, i.e. if less than the latter amount migrates out of the EN 71-3 tests the toy complies with the requirements.

[2] Limits of migration for modelling clay and finger paint. In analogy with the limits for other toy materials the analytical correction and the migration limits accounted for analytical correction are listed, see also 1).

[3] In EN 71-3, the analytical correction is calculated from the value of the measured migration. For example, if the analytical result of lead is 120 mg/kg, an analytical correction of 30% is applied. The adjusted analytical result is:

$$120 - \frac{120 \times 30}{100} = 120 - 36 = 84$$

This adjusted analytical result is below the requirements of 90 mg/kg. In the present table the analytical requirements are used to calculate the migration limit that is allowed after analytical correction.

Assumptions supporting EN 71-3

- The present methodology of EN 71-3 to determine the bioavailable amount of an element from toy is probably an overestimation of the actual bioavailable amount after ingestion of toy matrix. For, extraction in an acid extraction medium simulating gastric juice is performed. Absorption of compounds takes place in the intestine, with an environment of higher pH (pH 5.0-7.5). The bioavailability in the intestinal phase can be considered to be lower for these elements than in the stomach environment due to their dependence on the pH (Oomen et al., 2004a; Oomen et al., 2003b).
- Another important aspect of EN 71-3 is that always ingestion of toy material is considered, assuming that this also is protective for mouthing the toy (Commission of the European Communities, 1985). Based on the physicochemical nature of saliva and gastric juice this is true.
- It is not considered that a large surface may be mouthed on, whereas only 8 mg of toy is considered to be ingested. Therefore, the bioavailable amount of a substance from toy during mouthing may be greater than after ingestion of 8 mg of toy. For elements, usually a small amount migrates into artificial saliva, whereas much more migrates in the stomach and intestinal compartment due to the low pH environment of the stomach (Oomen et al., 2003a). Therefore, it can be anticipated that for elements migration determined by the methodology of EN 71-3 can be used as a worst case value for both ingestion and mouthing, although additional research on this issue is recommended for verification. However, for other compounds sucking may give higher bioavailability amounts of a substance than ingestion.

4.4.2 Tests for organic compounds

EN 71-9 provides requirements for certain organic chemical compounds in toys and toy materials. Migration limits are derived for some compounds and absolute limits for others. EN 71-10 provides information on the sample preparation and the extraction procedure for these organic compounds to determine the migration. To that end, migration is determined of a sample with a surface of less than 10 cm^2 with 100 ml of deionized water as extraction medium. The extraction bottle with water and sample is rotated end-over-end for 60 ± 5 minutes at 60 ± 5 rotation per minute at 20 ± 2 ºC.

In addition, various migration and extraction tests exist to assess the release of various organic compounds such as phthalates and nitrosamines from toy articles. Mostly water (migration test) or saliva (physiologically-based extraction test) are used to determine the release after mouthing on a toy by a child.

Most of the physiologically-based extraction tests were developed and used to determine the release of phthalates from toys and other consumer products and not for other organic compounds. Examples are the Joint Research Centre (JRC) model and a model developed by the U.S. Consumer Product Safety Commission (Simoneau et al., 2001; U.S. Consumer Product Safety Commission,).

Except for the RIVM method, no migration or physiologically based extraction tests have been found in literature describing the release of organic compounds from toys using other extraction fluids representative for ingestion of the compound, e.g. stomach and/or intestinal simulant. The RIVM method (see Appendix V) is based on human physiology and is applied independently of the matrix of contaminant. The research with the in vitro digestion models by RIVM has shown that the amount extracted in the acid environment of the stomach does not represent a worst case situation for the bioavailable amount of an organic substance (Oomen, 2000). For, most organic compounds are not as susceptible for the low pH environment of the stomach as the elements considered in EN 71-3. Furthermore, the research by RIVM has shown that for many substances the release from a matrix in the intestine is highest when fed conditions are simulated in the in vitro digestion model (Oomen, 2000). The complexing capacities of the extraction juices of an in vitro digestion model are higher when fed conditions are simulated as food constituents are present, and more complexing agents such as bile and enzymes are present in digestive juices secreted during fed conditions. Therefore, the methodology of EN 71-3 to determine the bioavailable amount of elements is suitable as a worst case bioavailable amount for elements, whereas it is not applicable for organic compounds.

Both water and saliva have been used as extraction fluid in tests simulating mouthing on toy matrices. The experimental tests that aim to simulate the migration of compounds from toy matrix in saliva vary in the degree to which saliva is simulated. However, as the composition of saliva is not very aggressive or very different from water, the outcome is usually within the same order of magnitude. In a technical report of CEN TC 252/WG 9/TG 2 it is concluded that water is therefore the most proper simulant for saliva. In a report by RIVM, it was shown that slight differences in migration rate can be observed when saliva simulant is compared to water (Oomen et al., 2004a).
The migration of phthalate into saliva simulant from PVC disk resulted in a slightly better extraction in saliva than in water (Oomen et al., 2004a). It is conceivable that water is an easy and reproducible extraction medium to work with, leading to only slight differences with artificial saliva. It can therefore be used to assess the migration from toys during mouthing.

4.4.3 Recommendations for application of tests simulating ingestion and mouthing of toy matrix in risk assessment

The tests listed in Table 4-2 and recommended for application in risk assessment of substances in toys. Water can be used as an extraction medium to simulate mouthing for both elements and organic substances. Migration tests according EN 71-3 can be used to simulate ingestion of substances for elements. However, tests to simulate ingestion for organic substances are not yet available. EN 71-3 is not applicable for organic substances.

Table 4-2 Recommendations for testing mouthing and ingestion of substances in toy matrices

	Elements	Organic substances
Mouthing	**Migration into water, similar to organic substances**	**Migration into water according to EN 71-9 and EN 71-10**
Ingestion	**Migration tests according to EN 71-3** **Possibility to test migration from toy after ingestion with more complex but more physiological tests (not applicable for all elements)** **Limits of migration to be reconsidered**	**Migration tests according to EN 71-3 are not applicable for organic substances.** **Migration tests according to RIVM methodology are possible, but analytical validation is lacking (inter-laboratory testing). Relative to EN 71-3 is this a complicated method. Other tests to assess the bioavailable amount of organic substances from toys after ingestion are lacking.**

In conclusion it can be stated that the migration tests in EN 71-3 can be used as a safe method for estimating the migration of elements from a toy matrix following mouthing and ingestion. An additional plus-point is that the method has been used for a long time and is a known and well-accepted method.

If the migration test according to EN 71-3 indicates a risk, e.g. the migration exceeds the migration limit value, there is an option to refine the migration test. This can be done by linking up the migration test conditions more closely to physiology in the gastrointestinal tract. In addition, additional research on the relative bioavailability of the substance, i.e. the bioavailability of the substance from toy relative to the bioavailability from the matrix used in the studies underlying the TDI.

We recommend to express migration limits of substances from toys in mg/kg toy material. This way of expressing links the allowable migration directly to a toxicologically derived limit value, e.g. a TDI. This holds for migration into water and migration according to EN 71-3. Thus, the expression of migration limits in mg/kg toy material is applicable for the limits employed in option 1 as further detailed in section 7.3.3.1. Also when more

physiologically based tests are used, as can be the case in option 3 in section 7.3.3.3, we also recommend to express the limits as mg/kg toy material.

4.4.4 Discussion points

4.4.4.1 Mouthing

Mouthing by children on toy articles can be best simulated by migration tests, as the mouth time varies between various toy products. However, one should consider that a child sometimes not only mouths once on a toy article, but multiple times. For examples, textile cords in hoods of sweaters or other clothing materials can be mouthed on many times. The same holds for cuddly toys. In principle, such toys required multiple extractions in migration tests, as probably in time less compound will be released during mouthing. Therefore, a worst case scenario can be assumed in which case the same amount of compound is released multiple times based on a single migration experiment. Depending on the number of assumed mouthing events, this may lead to the assumption that all compound is released in time. Alternatively, the migration test can be performed multiple times to investigate the dependence of migration on the number of mouthing events.

In the same manner, the release of a compound after mechanical washing with washing detergent can be investigated. This is only relevant for clothing or stuffed toys, because wood etc will not be washed. This is probably not of use for regulatory issues, as washing is not required before use of the toy, but may be relevant for example in a case study when a realistic exposure assessment of a certain toy is necessary.

A factor that may affect the release of a compound from its matrix is whether a child chews on the toy matrix or only mouths on it. It is very difficult to simulate chewing in a migration test. Some attempts have been done by adding glass marbles to a tube containing the extraction fluid and toy matrix, and mixing the contents by rotating the tube head-over-heels or horizontal shaking (Fiala et al., 2000; Oomen et al., 2004b; Steiner et al., 1998). In this manner, the glass marbles may fall on the toy matrix in an attempt to simulate chewing, i.e. simulate that part of chewing that represents the increment of accessible surface. These experiments did not lead to large differences in the migration between the presence and absence of marbles (Fiala et al., 2000; Oomen et al., 2004b). Volunteer studies suggest that there is a difference in migration due to chewing. In the volunteer study also an outlier was observed (very high migration). A hypothesis is that by chewing small pieces of the PVC standard discs were chewed off and were completely extracted. In can therefore be concluded that the *in vitro* and *in vivo* studies give no clear picture on the effect of chewing on the migration of substances in the mouth.
The present report differentiates in a mouthing and an ingestion scenario for oral exposure to toy material. When regarding mouthing, mouthing by children on a large toy surface is considered. Obviously, children may also chew on the toy. Chewing will lead to 1) increment

of the surface area and 2) swallowing of small pieces. Hence, it can be assumed that in case it is plausible that children can chew the toy material in question into smaller pieces, it is also plausible that these small pieces will be ingested. Considering the physicochemical conditions in the mouth and in the remainder of the human gastrointestinal tract, swallowing of small pieces of toy material will most probable result in higher migration of substances than after sucking on the toy material. We therefore recommend to focus on migration simulating ingestion in case it is plausible that a child can chew the toy material into smaller pieces. When this is not the case, migration tests that focus on mouthing of large surfaces such as EN 71-10 will suffice, e.g. in EN 71-3 a disk with a surface area of 10 cm^2 is used. At present there is no standard to estimate the migration of organic substances after ingestion. Therefore, development of a test that is representative for the migration of organic substances after ingestion is highly recommended. Such a test should simulate the conditions in both the human stomach and intestine, and should consider differences in physicochemical conditions resulting from fed and fasting conditions.

Another issue with mouthing is that some very minute pieces of the toy matrix may be released from the pieces of toy introduced into the test system, and which remain in the extraction fluid even after the separation step. An example may be that small fibres are released from textile toy items, which remain in the extraction fluid even after centrifugation. Also in the real life situation textile fibres may be release from a toy during mouthing. In real life, these textile fibres will probably be ingested. An option is thus to include these minute pieces in the bioaccessible fraction. This is a worst case assumption. Note that in such a case a clear relationship between the bioaccessible amount and time will probably not be observed. Also note the potential experimental difficulties with the separation step. First the normal toy matrix should be separated from the extraction fluid by centrifugation, and then either the entire extraction fluid should be sampled or the extraction fluid should be filtered and part of the filtrate and the residue should be sampled. Otherwise, erratic results are possible.

4.4.4.2 Ingestion

Whether a person is in the fasted (after several hours of not eating and drinking) or fed state (some time after food intake), greatly affects the physicochemical conditions in the gastrointestinal tract. In the fed state, more digestive juices are secreted into the gastrointestinal tract with a higher concentration of digestive enzymes, salts, and bile. Also food remnants may be present in the fed state. Therefore, in general, more complexing agents are present in the fed state which may facilitate extraction of a substance from a matrix like toy. Therefore, for most substances, release will be highest in (artificial) digestive fluids simulating fed conditions.
On the other hand, for pH-sensitive compounds like most elements, the fasted state will lead to the greatest release of the element from toy. In the fasted state, the pH in the stomach compartment is low, sometimes as low as 1, leading to the highest release of these substances. Therefore, the hydrochloric acid solution employed in EN 71-3 with a pH

between 1 and 1.5 can be assumed to give a worst case migration of elements from toy. However, note that this does not hold for other compounds.

The amount of matrix per volume of extraction medium may cause differences in bioaccessibility. This has been shown by Oomen et al. (Oomen et al., 2004). For practical reasons it is not possible to routinely determine the migration of substances from toy matrix for several amounts of toy. In addition, in routine research on the migration of substances from toy some conservative aspects are included. However, when a detailed risk assessment is performed (option 3 in chapter 8 'use of risk based data'), the migration of various amounts of toy per volume of extraction medium should be investigated.

4.5 Dermal bioavailability

For dermal bioavailability a comparable approach of defining the process is suggested as for oral bioavailability. This means that dermal bioavailability can be defined as 'the fraction of the dose that reaches the systemic circulation following dermal contact'. Also in dermal bioavailability three processes can be distinguished, i.e.:

a. release of a substance from a toy matrix due to dermal contact
b. penetration of the substance in the skin
c. transport of the substance across the skin into the systemic circulation

Table 4-3 describes the penetration and absorption potential of the elements listed in chapter 2. In Table 2-2, chapter 2, the accompanying toxicological effects are described. Information on dermal bioavailability of metals was obtained from the publication of Hostýnek et al. (1993).

Table 4-3 Potential of a number of elements for dermal bioavailability Hostýnek et al. (1993).

Element	Skin penetration	Transport across skin
Aluminium	Generally poor. By shunt diffusion through appendages and ductal closure, leading to sweat inhibition	Unknown
Antimony		Sb_2O_3 through sweat follicles
Arsenic	poor	poor
Boron	poor	poor
Cadmium	fair	poor
Chromium	Cr^{3+}: poor Cr^{6+}: good	Cr^{3+}: poor Cr^{6+}: good/ can be reduced to Cr^{3+} during passage through the skin
Cobalt	poor	poor
Copper	Oxidised by sweat → organometallic salt: good	poor
Lead	Poor	Inorganic lead forming ligands in proteins: poor Lipid-soluble organo-lead: good
Manganese	Poor Permanganate anion: good	poor
Mercury		Depending on form of metal: fair to good
Nickel	good	poor
Selenium	unknown	unknown
Silver	good	poor
Strontium	Poor	poor
Tin	unknown	unknown
Organo-tin	good	unknown

4.5.1 Conclusions

Only in case of hexavalent chromium, permanganate ion, and mercury contamination of toys dermal bioavailability should be taken into account (see also chapter 2). Dermal absorption can be tested by using human skin (from plastic surgery or cadavers) or pig skin (closely resembles the human skin). A detailed description of these experiments can be found in literature (for example Copovi et al., 2006; Panigrahi et al., 2005; Heard et al., 2006; Cazares-Delgadillo et al., 2005); they are beyond the scope of this report.

4.6 Inhalatory bioavailability

In the present methodology, it is assumed that inhalatory bioavailability is 100% in cases it will be relevant for toys (see chapter 3). Refinements are possible, but fall beyond the scope of this report.

4.7 Ocular bioavailability

Ocular bioavailability is not assumed to be of any relevance for exposure to elements via toys (see chapter 3).

4.8 Conclusions and recommendations

- The pharmacology definition of bioavailability is considered to be the most correct in the context of toy safety, i.e. *the fraction of a substance present in toy material that reaches the systemic circulation (of a child)*. For testing on the oral bioavailability of substances from toy the definition according to the CSTEE can be used *the amount of each element in the toy which could be absorbed into the systemic circulation of a child.* The definition by the CSTEE can be interpreted as bioaccessibility (F_B), a prerequisite step before a compound can become bioavailable.
- (Oral) bioavailability (F) is conceptually seen as the resultant of three major processes, i.e. 1) release of the compound from its matrix being the bioaccessible fraction (Fb), 2) fraction being absorbed across the intestinal wall (Fa) and 3) first-pass metabolism (Fh).
- Oral bioavailability of a compound from different matrices is assumed to be driven by differences in bioaccessibility.
- Bioaccessibility can be determined experimentally by means of migration tests or by physiologically based tests.
- We recommend to express migration limits in mg/kg toy material. This way of expressing links the allowable migration of a substance directly to a toxicologically derived limit value, e.g. a TDI. This holds for migration into water (i.e. saliva simulant), migration according to EN 71-3, and for migration limits for more physiologically based in vitro digestion tests.
- Migration testing according to EN 71-3, i.e. migration into hydrochloric acid solution, is a suitable test to simply assess the bioaccessible fraction of elements from toys after ingestion. Also for mouthing migration testing according to EN 71-3 can be performed as it gives a worst case bioavailable amount.
- To refine the exposure assessment, water or artificial saliva would suffice as simulant for investigating migration of *elements* following mouthing. To that end, the

methodology of EN 71-10 that is used to study the migration of organic substances during sucking, can be applied for elements.

- Chewing on toy material will lead to 1) increment of the surface area and 2) swallowing of small pieces. Hence, it can be assumed that in case it is plausible that children can chew the toy material in question into smaller pieces, it is also plausible that these small pieces will be ingested. It can also be assumed that migration of substances from toy material is higher after ingestion than after mouthing and possibly chewing in the mouth. Therefore, we recommend to focus on ingestion in case it is plausible that a child can chew the toy material into smaller pieces. When this is not the case, migration tests that focus on mouthing of large surfaces such as EN 71-10 will suffice, e.g. in EN 71-3 a disk with a surface area of 10 cm^2 is used.
- Migration testing according to EN 71-3, i.e. migration into hydrochloric acid solution, is not suitable to estimate the bioaccessibility of organic substances from toy after ingestion of toy matrix. More sophisticated extraction media, simulating intestinal solution (for fed conditions), are required to assess the migration of organic compounds from toys. Development of a test to estimate the migration of organic substances after ingestion is highly recommended.
- Migration testing in water or artificial saliva would suffice as simulant for investigating the migration of *organic compounds* following mouthing, i.e. EN 71-10.
- The availability of validated physiologically based tests would have additional value in relation to option 3 of the general methodology proposed in chapter 7 (and 8). Further validation of such type of tests is recommended.
- In order to account for bioavailability of chemicals in the risk assessment of toys, the bioavailability of a specific chemical from the toy matrix should be compared to the bioavailability in the studies underlying the health-based limit values. However, as the methodology for the bioavailability of elements from toys according to EN 71-3 incorporates sufficient margins of safety, the issue of relative bioavailability can be neglected. When the bioavailability of elements from toys is investigated in a more sophisticated manner, attention should be paid to the derivation of relative bioavailability.
- Further research is recommended to investigate whether EN 71-3 gives conservative estimates of oral bioavailability with respect to bioavailability underlying the TDI (relative bioavailability). It is assumed that EN71-3 gives a conservative estimate for oral bioavailability but we think it is questionable whether the same is valid for *relative* bioavailability.

5 Food contact material

5.1 Introduction

Within the framework of the Food Contact Materials (FCM) a large number of migration limits for chemical substances used in the production of Food Contact Materials has been authorized. FCM are all materials and articles intended to come into contact with foodstuffs, including packaging materials but also cutlery, dishes, processing machines, containers etc. Beside that, the term includes materials and articles which are in contact with water intended for human consumption excluding fixed public or private water supply equipment.
Under the specific conditions of use, chemicals used in FCM are considered to be safe. Toys can be made from the same materials. Both FCM and toy legislation mostly focus on oral exposure. If one considers mouthing a toy (so a material in contact with a matrix, i.e. saliva), there are parallels to food contact material in contact with a matrix i.e. food or liquid.
Since a framework already exists for deriving safe levels for chemicals in FCM it was asked by DG Enterprise to examine whether the used methodology can also apply for toys. If we can come up with some kind of extrapolation from FCM limits to limits for toys, this would provide a very efficient procedure as it would not require additional testing. For both type of consumer products a safe level of contaminants is aimed at. It makes sense to the public that the same limit values apply (if a certain limit level is safe for food contact materials than it should also be safe for toys, or the other way around). For producers of (raw/finished) materials it would be convenient if one test could provide safe levels for both types of legislation. It should be noted that not all substances embraced by FCM legislation are also relevant for toys. This should be considered on a substance-specific basis.

5.2 EU Directives

The Framework Regulation (EC) 1935/2004 (L338/4) states that food contact materials shall be safe. They shall not transfer their components into the food in quantities that could endanger human health, change the composition of the food in an unacceptable way or deteriorate the taste and odor of foodstuffs.

The evaluation of chemicals used in Food Contact Materials as practiced by the EU EFSA and formerly by the EU SCF, uses a structured default approach, see Figure 5-1. In the petition dossier, data on migration of the particular chemical from the FCM matrix into foodstuffs are required. Usually this involves migration to a suitable food simulant. Depending on the level of migration toxicological information is needed. When migration is high (5 - 60 mg/kg/food), an extensive data set is needed. When migration is between 0.05 – 5 mg/kg food, a reduced data set may suffice. In case of low migration

(< 0.05 mg/kg food) only a limited data set is needed. The evaluation of all data supplied in the petitioned dossier, leads to classification of the petitioned compound on one of several lists which specify the restrictions the EU committee deems necessary. Compounds placed on lists 0, 1, 2, 3 or 4 are admitted for use and receive a Standard Migration Limit (SML) expressed as mg/kg food (simulant). An overview of various types of limit values for food contact materials is given in Figure 5-2. For compounds for which a Tolerable Daily Intake (TDI) was derived the SML is derived by multiplying the TDI with a factor of 60. This is based on the notion that a person of 60 kg could ingest up to 1 kg daily of foodstuffs in contact with packaging material. For substances where no TDI is established (reduced toxicity dossiers) fixed migration limits (restrictions) of 0.05 mg/kg food or 5 mg/kg food are allocated depending on the level of migration measured. If migration is lower than 0.05 mg/kg food, than the fixed migration limit becomes 0.05 mg/kg food. If the migration is between 0.05 and 5 mg/kg food, than the fixed migration limit becomes 5 mg/kg food. A general requirement is the overall migration limit. For plastic food contact materials the overall migration of all substances may not exceed 60 mg/kg food (simulant).

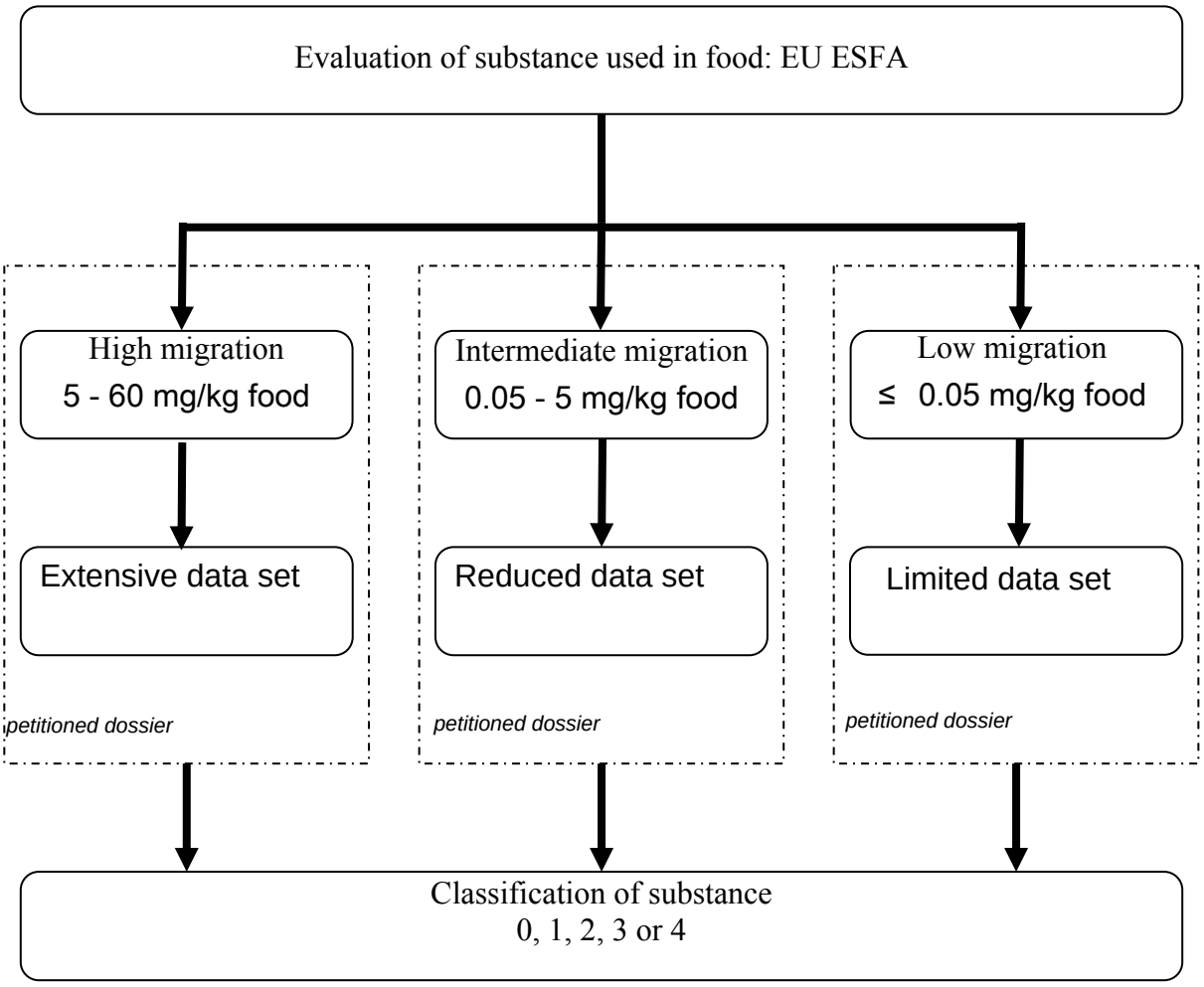

Figure 5-1 Flow chart of the evaluation of substances in food contact material according to regulations of the EU EFSA.

For some compounds the ‘QM’ or ‘QMA’ is given, which is the maximum permitted residual quantity of the substance in the finished material or article expressed as mg per kg food contact material (QM) or as mg per 6 dm^2 of the surface (of that material or article) in contact with foodstuffs (QMA).
For some compounds several limits are provided, e.g. a SML and a QM(A).

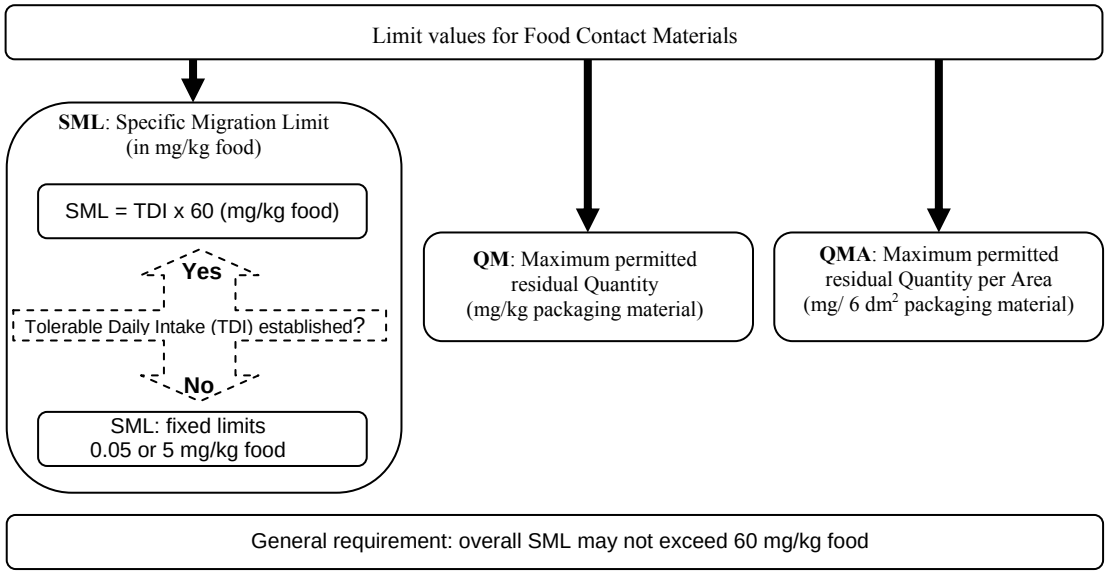

Figure 5-2 Overview of various types of limit values for food contact materials.

The Regulation distinguishes 17 groups of materials and articles which may be covered by specific measures:
Active and intelligent materials and articles
- Adhesives
- Ceramics
- Cork
- Rubbers
- Glass
- Ion-exchange resins
- Metals and alloys
- Paper and board
- Plastics
- Printing inks
- Regenerated cellulose
- Silicones
- Textiles
- Varnishes and coatings
- Waxes
- Wood

Up to now EU-wide specific measures exist for ceramics, regenerated cellulose and plastics. These measures are addressed in specific directives:

- Ceramics are regulated by Council Directive 84/500/EEC as amended by Directive 2005/31/EC. The Directive sets migration limits for **cadmium** and **lead** which might be released from decoration and/or glazing. It gives an analytical method for the determination of the migration of these substances.
- Regenerated cellulose film is regulated by Commission Directive 93/10/EEC as amended by Directive 93/111/EC. The Directive sets a positive list of authorized substances and the conditions under which they can be used. A recent amendment Commission Directive 2004/14/EC introduces changes for plastic coated regenerated celluloses film.
- Plastics are regulated by the new Commission Directive 2002/72/EC which consolidates Commission Directive 90/128/EEC and its seven amendments (Directives 92/39/EEC, 93/9/EEC, 95/3/EEC, 96/11/EEC, 1999/91/EC, 2001/62/EC and 2002/17/EC). These amendments mainly modified the lists of authorized substances such as monomers and additives.

Three groups of substances are regulated individually in specific directives, i.e. vinyl chloride monomer in plastics, nitrosamines in rubber teats and soothers and BADGE (bisphenol-A-diglycidyl ether), BFDGE (bisphenol-F-diglycidyl ether) and NOGE (Novolac glycidyl ether) in plastics and coatings.

- Vinyl Chloride Monomer (VCM) in food contact materials and articles is regulated by Council Directive 78/142/EEC. To ensure a safe product, the residual content of VCM in the finished material or article is limited to 1 mg/kg. Furthermore, VCM should not be detectable in foodstuffs. Commission Directives 80/766/EEC and 81/432/EEC give methods of analysis for VCM in the finished product and in foodstuffs.
- Nitrosamines in rubber teats and soothers are regulated by Commission Directive 93/11/EEC, which establishes specific migration limits for these substances and their derivatives.
- BADGE (bisphenol-A-diglycidyl ether), BFDGE (bisphenol-F-diglycidyl ether) & NOGE (Novolac glycidyl ether) in plastics, coatings and adhesives BADGE, BFDGE & NOGE are regulated by Commission Regulation (EC) 1895/2005. For BADGE and its partially hydrolyzed products, specific migration limit have been set at 9 mg/kg. For the chlorohydrins of BADGE the limit has been set at 1 mg/kg. Moreover, the Regulation prohibits the use BFDGE and NOGE as from 1st January 2005**.**

5.3 Migration tests food contact material

To enforce overall and special migration limits, special Directives set out procedures for compliance testing. Basic rules for migration tests such as the conditions of contact (time,

temperature, food simulants) are supplied in Council Directive 82/711/EEC and its amendments 93/8/EEC and 97/48/EC, while Council Directive 85/572/EEC gives a list of food simulants to be used in migration tests for the various types of foodstuffs.

According to Directive 82/711/EEC and 90/128/EEC, the determination of the migration of specified components in foodstuff instead of the use of simulants is permitted. The following food simulants listed in Table 5-1 should be used for migration test with food contact materials.

Table 5-1 Description of food simulants to be used to test the migration of substances from food contact materials.

Food type	**Conventional classification**	**Food simulants**	**Abbreviation**
Aqueous foods (i.e. aqueous foods having a pH > 4.5)	Foodstuffs for which tests with stimulant A only is prescribed in Directive 85/572/EEC	Distilled water or water equivalent quality	Simulant A
Acidic foods (i.e. aqueous foods having a pH < 4.5)	Foodstuffs for which tests with stimulant B only is prescribed in Directive 85/572/EEC	Acetic acid 3% (w/v)	Simulant B
Alcoholic foods	Foodstuffs for which tests with stimulant C only is prescribed in Directive 85/572/EEC	Ethanol 10% (v/v) This concentration shall be adjusted to the actual alcoholic strength of the food if it exceeds 10% (v/v?	Simulant C
Fatty foods	Foodstuffs for which tests with stimulant D is only prescribed in Directive 85/572/EEC	Rectified olive oil or other fatty food simulants	Simulant D

The design of a migration test is dependent on a) the type of food in relation to the packaging material to be tested, b) contact time between food and packaging material and c) temperature and packaging material.

In practice various FCM may come in contact with more than one type of food, for instance fatty versus acidic foods. In that case, migration into both or more food simulants should be tested.

The duration time of the migration test should correspond to the worst foreseeable conditions of contact and to any labeling information on maximum temperature for use, see Table 5.2.

Table 5-2 Guidance on the duration of the migration tests and the test temperature for food contact material.

conditions of contact in the worst foreseeable use	**test conditions**
Contact time	**test time**
t < 5 min	time corresponding to worst foreseeable use (but < 5 minutes)
5 min < t < 0.5 h	0.5 h
0.5 h < t < 1 h	1 h
1 h < t < 2 h	2 h
2 h < t < 4 h	4 h
4 h < t < 24 h	24 h
t > 24 h	240 h
contact temperature	**test temperature**
T < 5°C	5°C
5°C < T < 20°C	20°C
20°C < T < 40°C	40°C
40°C < T < 70°C	70°C
70°C < T < 100°C	100°C or reflux temperature
100°C < T < 121°C	121°C*
121°C < T < 130°C	130°C*
130°C < T < 150°C	150°C*
T > 150°C	175°C*

* this temperature shall be used only for simulant D. For simulant A, B, or C the test may be replaced by a test at 100 °C or at reflux temperature for duration of four times the time selected according to the general rules.

5.4 Comparison migration tests of food contact materials and toys

It was investigated whether a certain relationship between tests and between migration limits of substances exists by comparing migration tests for food contact materials and for toys. This would enable extrapolation of the limit of migration of (types of) compounds addressed in the food contact material legislation to the legislation of migration limits of these (types of) compounds for toys.

Within the legislation for food contact materials a range of different migration tests are possible, depending on the worst foreseeable conditions for the contact material. Four

different types of food simulant are used, the duration of the migration test varies between 0.5 h to 240 h, and the test temperature between 5 ºC and 175 ºC, whereas in EN 71-3 the migration of elements from toy material is performed at 37 ºC (European Committee for Standardization (CEN), 1994) and migration of organic substances in saliva according EN 71-10 at 20 ºC.

For the present migration tests for toys two categories can be discriminated (chapter 3):

- Mouthing a toy matrix, which can be simulated with artificial saliva or water
- Ingestion of toy matrix. In EN 71-3 this is simulated for a set of elements in which migration is measured following exposure to an acidic fluid (European Committee for Standardization (CEN), 1994). This fluid can be considered to represent (artificial) gastric juice.

When comparing the migration tests for food contact materials to migration tests for toys, two sets of migration tests of food contact materials are similar to the tests for toy matrices. This is based on physicochemical similarity of the extraction medium:

- The migration of food contact materials into water (simulant A) may correspond to the migration into saliva simulant or water.
- The migration of food contact materials into 3% acetic acid (w/v) (simulant B) may correspond to some extent to the migration into hydrochloric acid solution (generally 0.07 M adjusted to pH 1.0 to 1.5) as is applied according to EN 71-3 for several inorganic compounds in toy matrix (European Committee for Standardization (CEN), 1994).

Table 5-3 Comparison of migration tests under Toy Legislation for elements (CEN 1994) and the FCM legislation.

	Toys	**Food contact materials**
Based on aqueous solutions	Extraction into water or saliva simulant	Extraction into distilled water
Based on acidic extraction medium	Extraction into 0.07 M HCl (pH 1.0-1.5)	Extraction into 3% acetic acid (w/v) (pH ≈ 2.5 (calculated))

It is obvious that these tests only represent oral exposure. Routes like inhalation or dermal exposure are not covered in the present legislation on food contact materials.
A few examples of results from migration tests performed under toy legislation and food contact materials legislation were gathered and compared. The assumption is that comparable test designs mimic comparable processes like migration from a matrix in gastric juice. In this way results from tests with toys and tests with food contact materials might be linked. This in

turn may have as a consequence that test results *for a certain compound* with food contact materials may be predictive for *that compound* in toy material.
Although there might be similarities in composition of extraction medium, it should be noted that differences in factors like extraction time, extraction temperature, and mixing during extraction may have a huge impact on migration measured.

Other comparisons between the migration tests of food contact materials and the migration tests for toy matrices according to EN 71-3 are not expected to lead to similar, systematic results. The physicochemical characteristics of other extraction media for food contact materials such as ethanol and oil solutions are very different from the saliva or gastric juice simulants relevant for compounds in toys. Therefore, the potential difference in amount migrated is large and is not expected to be a constant factor.
It can be noted, however, that for specific material/chemical combinations, extraction with food simulants C (10% ethanol) or D (oil) oil, can result in 'worst case' extraction for toys. For example, the migration of hydrophobic compounds into oil (food simulant D) may always be greater than migration into artificial saliva/water or gastric juice. In that case, the migration test could potentially be used for toys also. However, up till now, no comparison on the migration of a compound from the same material with food simulants C and D and artificial saliva or gastric juice is available. To define the physicochemical properties of the compounds for which this 'worst case' assumption holds the migration of a large set of compounds should be investigated. At this moment only a case-by-case examination could be made which cannot be incorporated in a routine methodology.

Even for similar extraction media, the outcome of a migration test highly depends on:

1) The exact composition of the extraction medium: there is a difference in the composition of food simulant B (3% acetic acid, calculated pH about 2.5) and artificial gastric juice (0.07 M hydrochloric acid, pH 1.0-1.5).
2) Physicochemical properties of the substance of interest, e.g. lipophilic compounds are expected to be sensitive to other factors in the extraction media than for example elements
3) In general, the matrix from which the migration of a compound is investigated is different for food contact and toy material.
4) An important difference in the migration tests for food contact material and toys is that the migration tests for food contact materials are static, i.e. the food contact material and the food simulant are not stirred or mixed. On the other hand, the migration into artificial gastric juice is determined after 1 h of shaking and an additional 1 h not shaking. Dynamic testing for toy material is performed to simulate chewing in the mouth and peristaltic movements in the gastrointestinal tract. Shaking is known to dramatically increase the migration of compounds (Fiala et al., 2000; Steiner et al., 1998).
5) A direct comparison between migration of a compound into food simulant and artificial saliva or gastric juice is difficult because migration into food simulant is

usually expressed as mg/l food simulant, and migration from toy material is expressed as mg/kg toy. In section 5.6 an example is given on the obstacles one comes across in recalculating from mg/L simulant to mg/kg toy.

6) The temperature of the migration test for FCM depends on the worst foreseeable use and ranges between 5 ºC and 175 ºC. Migration tests with artificial saliva or water to investigate the migration of compounds from toys are usually performed at body temperature, i.e. 37 ºC (EN 71-3), or room temperature, 20 ºC (EN 71-10).

Even small differences in conditions of the migration test may lead to substantial differences in migration.

5.5 Comparison of migration limits of substances according to tests for food contact material and toy regulation

To illustrate the comparison of migration of substances in toy material and FCM, migration limits, migration test conditions and measured migration values are listed in the table below for two substances, lead and bisphenol-A:

5.5.1 Lead

A comparison of the migration tests and some migration data of lead from ceramics (FCM) and toy is given in Table 5-4.

Table 5-4 Comparison of the migration tests and migration data of lead from ceramics (FCM) and toy material.

	Food contact material (Council Directive 84/500/EEC)	**Toy (EN 71-3)**
Matrix	Ceramics	Toy
Migration test	Extraction in 3% (v/v) acetic acid in freshly prepared aqueous solution, at a temperature of 22 ± 2 ºC for a duration of 24 ± 0.5 h; usual lighting conditions	Hydrochloric acid 0.07 M adjusted to pH 1.0 to 1.5 in the presence of toy; Migration measured after 1 h with agitation and 1 h without agitation at 37 ± 2 ºC.
Migration limit[d]	0.8 mg/cm^2 [a] 4.0 mg/l food simulant[b] 1.5 mg/l food simulant[c] (For migration of cadmium and lead from ceramics special migration limits hold, further detailed in reference a-d).	90 mg/kg toy material (129 mg/kg after analytical correction)
Actual migration values measured	Ceramic samples bought in different shopping centers in Spain (González-Soto et al., 2000) Between 1.21 mg/l and 0.027 mg/l food simulant (15 samples)	Migration from paint scraped from wooden toys (Bouma et al., 2004) 2815 mg/kg paint (red, top) 30 mg/kg paint (mix, colored pencil) 14 mg/kg paint (white, colored pencil) 24 mg/kg paint (red, top) 11 mg/kg paint (yellow, push wagon) 11 mg/kg paint (colored pencil) 10 mg/kg paint (blue, box with blocks) 13 mg/kg paint (yellow, box with blocks) 11 mg/kg paint (blue, blocks) 169 mg/kg paint (mix, clown) 11 mg/kg paint (yellow, breakfast set)

a: Articles which cannot be filled and articles which can be filled, the internal depth of which measured from the lowest point to the horizontal plane passing through the upper rim, does not exceed 25 mm.
b: All other articles which can be filled.
c: Cooking ware; packaging and storage vessels having a capacity of more than three liters.
d: When a ceramic article does not exceed the indicated limits by more than 50%, that article shall nevertheless be recognized as satisfying the requirements if at least three other articles with the same shape, dimensions, decoration and glaze are subjected to a test carried out under the indicated conditions, and the average quantities of lead extracted from those articles do not exceed the limits set, with none of those articles exceeding those limits by more than 50%.

In addition to the comparison for lead, a comparison of the migration limits, migration tests, and some migration data of bisphenol-A from FCM and toy material is given in Table 5.5.

Table 5-5 Comparison of migration tests and migration data for bisphenol-A in the FCM framework and toys

	Food contact material	**Toy**	**Drinking ware for children**
Matrix	Plastic	Plastic	Plastic
Migration test	depends on the conditions of use (simulant, time, temperature). Static migration.	60 min at room temperature, dynamic migration	24 h at 40ºC in simulant A (water) and B (3% acetic acid)
Migration limit	SML = 0.6 mg/kg food or simulant (2002/72/EG)	0.1 mg/l (monomers) (EN 71-9, EN 71-10, EN 71-11) Concentration is measured in simulant, not expressed as mg/kg toy material.	0.03 mg/l simulant (EN 14350-2)
Actual migration values measured	Not available	0.005 – 0.5 mg/kg simulant	< 0.004 mg/l simulant

Although some scattered data on other substances are available, these data did not allow a systematic comparison as shown above. A main problem for comparing the different types of migration is that the migration limits are expressed fundamentally different, i.e. as mg/L food simulant in the framework of FCM and as mg/kg toy for the toy framework. Thus, the limits are expressed in terms of the receptor matrix for FCM and in term of the product for toys. As can be concluded from the two examples with lead and bisphenol-A, there are large differences in test conditions, units used for expressing the limit value and actual measured migration values. No consistent relation or conclusion can be drawn from this analysis.

5.6 Can the methodology of FCM be used for toys?

As stated in the introduction, it would be very efficient if migration limits for FCM could be extrapolated to toys.

In the regulation of food contact materials, substances are categorized into several lists [Synoptic document; Directive 2002/72/EC]. List 5 substances should not be used in food contact materials. For list 6 substances suspicion exists about their toxicity and data are lacking or are insufficient. Substances in section 6A are suspected to have carcinogenic properties. These substances should therefore not be detectable in food simulants by an appropriate sensitive method for each substance. Substances in section 6B are suspected to have toxic properties other than carcinogenicity. Restriction for food contact materials may be indicated. Hence, it can be considered, that the substances indicated in list 5 and 6 in the

food contact material legislation might also not be acceptable for toy materials. However, it should be stressed that such a proposal would be made from a risk management perspective and not from a risk assessment perspective.

TDIs have been listed for some substances in FCM legislation. The TDI is based on the toxicity of the substance in question, and can be indeed directly applied to derive limits of migration for toy materials. The methodology described in the present report can be used to derive a migration limit for toys, e.g. by application of a certain percentage of the TDI that can be allocated to toys, and expressing the thus obtained amount of substance as a migration limit, see chapter 7 and 8.

Other applications of limits in FCM legislation to toy legislation become more complicated. It would be practical to translate migration limits for FCM to toys. However, in practice this is not easy, since test conditions differ, the testing material differs and the results of the tests are expressed in different units (mg/l simulant (or mg/kg food) in the FCM framework vs. mg/kg toy material in the toy directive). Since in the majority (if not all) cases only the amount migrated is known but not the total amount in the starting material, expression as a fraction that is migrated is not possible, which also hinders comparison. These aspects are addressed in more detail below.

Within the FCM framework, it is required that testing conditions are relevant to the foreseeable use of the material. This foreseeable use, however, may differ widely from the conditions of toy use. Extraction time, temperature and the choice of simulant such as used in existing FCM migration tests may be such that results cannot reasonably be used for toy-related exposures because the toy exposure would need a different scenario. As to the composition of an appropriate migration medium for toys this would have to reflect the process of migration:

- to saliva during mouthing of a toy;
- to gastric juice (stomach) in case a toy fragment is ingested;
- to intestinal contents when this toy fragment moves down the GI-tract.

The FCM migration conditions do not always fulfill these criteria. Water may be used to simulate saliva as this did not result in large differences in migration, see chapter 4. It might be possible that the acetic acid solution of FCM (simulant B) can be used to simulate migration into gastric juice of the stomach. However, as the pH of gastric juice simulant (pH 1.0-1.5) is lower than the pH of the acetic acid solution (calculated pH 2.5) this is questionable, especially for pH sensitive substances. This should be investigated experimentally.
It might be possible to use oil (simulant C) as a simulant of intestinal juice, especially for hydrophobic substances. However, also this comparison is questionable as no research on this comparison has been performed up till now. Such research will have to be performed before application of a relationship between migration into oil and in a simulant of intestinal juice.

As a further complication the FCM migration test is a static process, i.e. without any kind of stirring, whereas exposure to toys via mouthing is a dynamic process, with end-over-end rotation during an hour followed by a static period of another hour. Measuring exposure during dynamic conditions has been shown to result in higher migration values than under static conditions (Fiala et al., 2000; Steiner et al., 1998). It might be possible to establish correlations for migration of substances for dynamic and static conditions. However, as this would be necessary for a large number of substances, it would require a lot of testing.

Another complicating factor is the manner of expressing migration, e.g. in mg/l simulant (or mg/kg food) in the FCM framework and in mg/kg toy material for toys. These different types of migration limits can only be translated from one type into the other type with assumptions regarding the density of the material and the depth of the material as a source for migration. For example, for substances with low migration in the FCM framework, the SML is < 0.05 mg/kg food (or < 0.05 mg/L fluid). This implicates that it is allowed to have 50 µg of a substance migrating from 6 dm^2 of food contact material. If we assume that migration from packaging materials only occurs from the first 0.5 mm depth, than it can be calculated that maximally 50 µg of a substance is allowed to migrate from 30 cm^3 of material. If we assume that the density of the material is 1 g/cm^3, 50 µg of substance is allowed to migrate from 30 g of material. This corresponds to a migration limit of 1.6 mg/kg food contact material, which could be translated to a migration limit of 1.6 mg/kg toy material. When migration occurs from as deep as 1 mm, the corresponding migration limit will be 2 times lower, i.e. 0.8 mg/kg food contact or toy material. However, the assumptions on the depth of migration and on the density of the material are disputable and depending on the material and substance in question.

Based on the above argumentation, the authors of the report think that in principle it would be possible to translate migration limits for FCM to migration limits for toys. However, this would require a considerable amount of additional experimental research regarding the investigation of relationships between migration in different solutions and between static and dynamic extraction conditions. Even then, uncertainties remain on the translation of migration limits for FCM to migration limits for toys due to the disputable assumptions that have to be made for such a recalculation, and due to the uncertainty of the safety of the migration limit for toys as the migration limit for FCM are based on different underlying assumptions. Furthermore, it is not clear which substances covered in the FCM framework are relevant also for toys.
Therefore, as we think that the amount of research required for translation of migration limits for FCM to toys is large and not fully reliable, we recommend determining the migration limits for substances in toys directly based on the approach outlined in the report.

Finally, the thus obtained calculated migration limit for toys is not necessarily safe. The basic assumptions for deriving migration limits for FCM are different than for toys. First, the limits for FCM are for adults and may comprise 100% of a TDI. This is acceptable as another worst

case assumption is used, namely that someone consumes 1 kg (or 1 L) of food that has been in contact with FCM per day. For toy material, we advise to allocate a percentage of the TDI to exposure via toys.

5.7 Conclusions and recommendations

Within the framework of the Food Contact Materials (FCM) a large number of migration limits for chemical substances used in the production of Food Contact Materials has been authorised. As both FCM and toy legislation mostly focus on oral exposure, we have presently investigated whether the methodology of the FCM can be applied to toys as this would provide a efficient procedure that would not require additional testing.

5.7.1 Conclusions

In the regulation of food contact materials, substances are categorized into several lists [Synoptic document; Directive 2002/72/EC]. List 5 substances should not be used in food contact materials. In list 6, substances are taken up for which concern exists with respect to their safety. Hence, it can be considered, that the substances indicated in list 5 and 6 in the food contact material legislation might also not be acceptable for toy materials. However, it should be stressed that such a proposal should be made from a risk management perspective and not from a risk assessment perspective.

TDIs have been listed for some substances in FCM legislation. The TDI is based on the toxicity of the substance in question and is harmonized at the European level. These TDIs can be used directly to derive limits of migration for toy materials according to the methodology described in this report.

In principle it is also possible to translate migration limits for FCM to migration limits for toys. To that end, experimental research on the relationship between various simulantia is necessary, as well as research on correlation in migration determined for static and dynamic conditions.
Furthermore, it is uncertain whether limits for FCM translated to limits for toys are by definition safe. The basic assumptions for deriving migration limits for FCM are different than for toys.

5.7.2 Recommendations

Regarding the large amount of experimental research required before migration limits for FCM can be calculated to migration limits for toys, and the uncertainty on the assumptions and safety of the thus obtained migration value for toys, we recommend not to use the migration limits for FCM but to determine migration limits for substances in toys directly based on the methodology outlined in the report.

6 Sampling and analysis for certain elements in toys

6.1 Introduction

For compliance testing of toys for certain elements, it is necessary to have a uniform approach to sampling and analysis. Compliance testing is carried out by both industry and enforcement laboratories and approached from a different point of view. Both viewpoints are taken into consideration in this chapter. Several issues were raised in the project tender. It was requested to look into the sampling strategy for testing of toys for certain elements, whether a single sample is representative or not. In EN 71-3 analytical correction values are used to correct the results. We were requested to evaluate these correction values and also the use of these factors. Other issues that are addressed in this chapter are the analysis of chromium3+/chromium6+ and organic tin compounds, repetitive use versus single testing. Comparisons are made to common practices for food contact materials, childcare articles and other toy standards. Proposals are made for sampling and analysis of toys for certain elements. These proposals are summarised in section 6.4.

6.2 Sampling

In our opinion it is essential that sampling procedures are harmonised, in order to minimise inter- and intralaboratory differences in testing the same materials. For both food contact materials and toys, sampling is not prescribed, not in the relevant EN standards neither in the relevant EU directives. In this section proposals are given on sampling and sample preparation of toys for testing for certain elements.

6.2.1 Sampling strategy

In En 71-3 it is stated that a laboratory sample for testing shall consist of a toy either in the form in which it is marketed, or in the form in which it is intended to be marketed. Toys must comply with the legal restrictions when they are sold to consumers (in retail). In principle each individual sample must be in compliance. It is the responsibility of the producer or importer of the toy to ensure that this is the case for each toy. It is therefore important that the sample that is used for testing is representative for the batch that is being put on the market. If the production circumstances change, or if different or other raw materials are being used, the toy should be tested again.

We think that toys should be tested periodically, as certain parameters that influence compliance testing are changing. These circumstances are updates of EN standards (every 5-10 years), minor or major changes to the product, changes in raw materials and changes production circumstances. In the technical dossier of a toy, a test certificate must be

present to demonstrate that the toy complies with EN 71-3. We propose that this test certificate may not be older than 5 year before the date of marketing of the toy.

Enforcement bodies can take a (representative) sample from retail for compliance testing. If this sample fails, an official measure can be taken.

6.2.2 Subsamples

In the Directive 88/378/EEG on toy safety it is required for the protection of the children's health, that the bioavailability of certain elements may not exceed certain health-based limit levels per day (see chapter 4). In EN 71-3 bioavailability levels are translated to migration limits. This translation is based on the migration of elements from all accessible parts of toys into a hydrochloric acid solution. Toy packaging materials are excluded for testing. A toy may be composed of different materials, for example wood, paint, textile, and plastic (see clause 1 of EN 71-3). In clause 4 (requirements) it is stated that all accessible parts must comply with the migration limits. We propose that this should remain unaltered.

The analytical correction values vary from 30 to 60%. Some of these values are rather high. One source of analytical variation may the inhomogeneity of the test material. It is therefore important that a (sub) sample is homogenised well. For example for coating of paint a minimum of 100 mg passing through a 0.5 mm sieve is prescribed in EN 71-3. It is well worth investigating to scrape off the entire coating, to grind this well. This entire coating is then sieved using a 0.5 mm sieve. From that fraction a 100 mg portion is taken and used for analysis. Another improvement may be to use a sieve with smaller dimensions. In this project it was not foreseen to carry out such lab experiments.

6.3 Analysis

6.3.1 Introduction

In the tender questions were raised how to apply the analytical correction values that are listed in EN 71-3. In this section correction values from testing of food contact materials and organic chemical substances in toys (EN 71-9, EN 71-10 and EN 71-11) are compared. In addition several analytical issues are addressed, such as analysis of chromium3+/chromium6+ and organic tin compounds, and repetitive versus single testing. Proposals are given how toys should be tested for certain elements.

6.3.1.1 Analytical correction values

In EN 71-3 in Table 2 analytical correction values are listed for the different elements, varying from 30 to 60%. These correction values are based on the precision data from a 1987 ring trial (see Annex D.4 of EN 71-3). In a ring trial the interlaboratory variability was

established for 8 elements. These values are used in EN 71-3 as analytical correction values to correct for the variation of the method (see chapter 4), thereby in practice increasing the migration limits for the different elements.

In Denmark in 1998 a market surveillance was carried out (Teknologisk Institut, 1998). Toys were sampled and tested for compliance with EN 71-3. The use of analytical correction values was critical in only 3 out of 10784 cases, in changing the outcome from failing to passing the test. The analytical correction values appeared to be of little practical importance. In their opinion correction values should be used to lower the limit of migration to ensure a reasonable safety margin.

For polymeric food contact materials several ring trials have been performed for specific migration of organic contaminants (EN 13130 series). Precision data are included in these standards in the Annex. These ring trials concern the migration of an organic substance in the official food simulants: distilled water (simulant A), 3% acetic acid (simulant B), 10% ethanol (simulant C) and olive oil (simulant D). The average standard deviation (interlaboratory variation) is 38% for the migration of organic substances. In 2000 the migration of diisononylphthalate from PVC standard discs in saliva simulant was tested in a ring trial (Simoneau et al., 2001). This standard PVC disc was tested for homogeneity. The interlaboratory variation using this standard disc was 30%.

The analytical variation values mentioned above show that some of the analytical correction values used in EN 71-3 (30-60%) are high. It is therefore recommended to improve the method and organise a new ring trial (see section 6.3.2.1 and also 6.4).

For food contact materials it is not custom to include this analytical variation in the standard. In our opinion analytical variation should be dealt with from different perspectives:

When a test laboratory wants to certify a test sample, they have to demonstrate compliance by proving that the migration value is below the legal limit. Therefore the migration value including analytical variation may not exceed the migration limit.
When an enforcement laboratory, such as the Dutch Food and Consumer Product Safety Authority analyses a sample, they must demonstrate that the sample exceeds the legal limit, before they can take an official measure. The migration value is corrected by subtracting the analytical variation.

As an example to demonstrate this principle the following case is elaborated. For food contact materials the specific migration limit for barium nitrate is set at 1 mg/kg (Directive 2002/72/EC). If a test laboratory wants to demonstrate compliance, the migration of this substance must be below 0.76 mg/kg (0.76 mg/kg * 130% = 1 mg/kg). When an enforcement body wants to take measures, they must demonstrate that the migration limit is exceeded. Official measures are taken when the migration exceeds 1.3 mg/kg.

In EN 71-3 the analytical variation (correction values) is used to increase the limits. The limits for elements that are proposed in the present report are based on toxicological concepts, which means safety limits to ensure the health of children. It is therefore suggested to include the precision data of EN 71-3 in an Annex of this standard and to give instructions how to use these correction factors. Our proposal is to subtract the analytical variation from the limit, from a consumer health protection point of view.

6.3.1.2 Standard reference material

It is recommended to introduce a standard reference material, which contains all the relevant elements at a relevant level. This standard reference material must be used as a quality control sample and must therefore be used in each series of analysis, to demonstrate the ability of a laboratory to correctly analyse toys for certain elements.

The precision data that are used to calculate the analytical correction values in EN 71-3 are dated from a 1987 ring trial. We suggest to organise a new ring trial, using this standard reference material. In these 20 years there has been an improvement in the precision of the analytical apparatus. Most labs have now changed to the ICP technique (Inductive Coupled Plasma). It is also important to have labs participating in the ring trial that have ample experience in testing according to EN 71-3.

6.3.1.3 Chromium3+ and Chromium 6+

In EN 71-3 a limit is set to the total amount of chromium. However, chromium6+ has a different toxicological profile compared to chromium3+. Chromium6+ is classified as carcinogenic category II (may cause cancer by inhalation) and as a skin sensitizer (Directive 67/548/EEC). From this perspective it is desirable to be able to measure chromium6+ instead of total amount of chromium. Due to the acid circumstances of analysis, chromium6+ is converted into chromium3+. Although we recognize that it is relevant to have an analytical method that can measure chromium6+, we realise that a reliable and validated method is not available yet. We are aware of the efforts of various scientific groups on developing such a method.

6.3.1.4 Organic tin compounds

Some organic tin compounds are immunotoxic compounds. It is desirable to determine these organic tin compounds not only as the element tin, but as organic substance as well. In a Dutch report (Bouma et al., 2004) methods are provided to determine the total amount of organic tin in plastic, as well as the migration into water. Only limited validation has been carried out. Furthermore this method has not been tested at other laboratories. This method therefore needs to be validated further and tested at other laboratories as well.

6.3.1.5 Repetitive versus single testing

For food-utensils intended for repeated use, three successive migration tests on the same sample have to be carried out. The result of the third test must comply with the requirements. It is assumed that the migration levels fall with increasing number of migration tests.

For childcare articles, such as soothers, soother holders, teats and drinking equipment, several EN standards have been adopted (EN 12586, EN 12868, EN1400-3 EN 14350-2). These childcare articles are intended for repetitive use. In these EN standards for childcare articles, the result of the first migration test must comply with the migration limit. The result of the first migration test is considered to be the worst-case exposure to the migrating substance. As children are a sensitive group of consumers (see section 2.3.1) a high protection level is realised. Most of the toys are intended for repetitive use. It is proposed that only one migration test is carried out and that the results form this test must comply with the legal limits, similar to childcare articles.

6.3.2 Test methods

In section 3.4 (Identification of relevant exposure scenarios) a scheme is presented for the different exposure routes. Independent of the exposure route, compliance can be easily demonstrated by determining the total amount of the elements. For all laboratories (from industry, test institutes and enforcement), it is desirable to have an easy screening test. If the sample passes the screening test, no further testing is required. If the sample fails the screening test, more in depth information on exposure can be used to demonstrate compliance.

6.3.2.1 Total amount of elements

In the methodology (see section 8.5) it is proposed to determine the total amount of elements as a screening method. In general total contents of elements are determined by destructing the material, using nitric acid and hydrogen peroxide in a microwave oven (high temperature, high pressure). Methods for destruction are not described in a standard. For tattoo inks a method is available to determine the amount of elements. This method has however not been tested for toy materials. It is advised to develop a reliable and validated method for destruction of toy material. This method can then be added to EN 71-3 in the annex.

6.3.2.2 Bioavailability

In EN 71-3 the migration of elements is studied by means of an acidic simulant. This simulant presumably substantially overestimates the migration for a toy that is mouthed. On the other hand it may also overestimate migration of elements from (parts of) toys that are ingested (see section 8.5). For that reason the National Institute for Public Health and the Environment (RIVM) developed a physiologically based in vitro digestion method (Oomen et al., 2003). This method was investigated for the migration of lead from toys and could be

used as a refinement of the exposure assessment under option 3 of the proposed methodology.

6.3.2.3 Mouthing

To simulate mouthing of the toy, the migration can be determined using the Head over Heels method. This is described in EN 71-10. A test portion of 10 cm^2 is put in a flask containing 100 ml water. This flask is rotated at room temperature for 60 minutes. The resulting solution is then analysed for certain elements. In the EN 71 part 9 to 11 series it is assumed as a worst case, that a child sucks for 3 hours per day on its toys. The limits in EN 71-9 have been corrected for this. As the migration test is carried out for only 1 hour, the result of this test should be multiplied by 3 to correct for the shorter migration time.
It should be noted that for the derivation of the migration limit values of elements, the ingestion scenario has been used and the values have not been corrected for the shorter migration time. The bioaccessibility testing as measured by the EN 71-3 migration test involves an acid extraction for 1 hour with and 1 hour without shaking (total 2 hour extraction). Since the EN 71-3 migration test is a rough and worst case simulation of reality the 2 hours testing can be regarded as being sufficient for longer periods up to 3 hours. In this sense, the difference between the 1 and 3 hour period is not really relevant.

6.4 Recommendations

In summary, the following is proposed with regard to sampling and analysis of toys for certain elements:

1) A single sample can be used for compliance testing.
2) For enforcement laboratories measures can be taken based on the results of a single sample.
3) Toy producers or importers must ensure that the sample used for compliance testing is representative for what they place on the market. Periodic testing is required if there are relevant changes in production circumstances, raw materials or in the standards. We propose that this test certificate may not be older than 5 year before the date of marketing of the toy.
4) All accessible parts of a toy must comply with EN 71-3. If a toy consists of different materials, subsamples should be made of each material.
5) It is recommended to improve the precision of the method, by optimising the sample preparation (homogeneity of the (sub) sample). This requires lab work.
6) We recommend to introduce a standard reference material that contains the elements in relevant quantities.
7) A new ring trial should be organised to establish precision data, using this standard reference material.

8) Precision data of the analytical method, including interlaboratory variation, should be included in an annex of the standard. Interlaboratory variation (analytical correction values) should not be used to increase the limit of migration of the elements. Depending on the point of view (toy producer/importer, enforcement) these precision data can used differently to decide whether a toy is in compliance or not.
9) Although toys are intended for repetitive use, the result of the first migration test must comply with the requirements.
10) It is recommended to have a method to determine the total amount of elements in toy material. Several options are available. This requires lab work.

7 Proposed general methodology for setting limit values for chemicals in toys

7.1 General introduction

As described in chapter 1 of this report, there is a need for a transparent and scientifically sound procedure for setting limit values for chemicals in toys. In the following paragraphs we will propose a methodology for setting limit values for chemicals in toys that can be used within the EU. This chapter will focus on the headlines of the methodology. In the next chapter, the proposed methodology is worked in more detail to derive migration or content limit values for elements in toys, and to provide migration limits for elements in toys.
A number of risk management issues have been encountered while developing this methodology and we will provide suggestions on how to deal with these issues. Obviously, the ultimate decisions on these issues will have to be made by the risk managers or the policy makers.
Before entering a discussion on the proposed methodology it is important to clearly describe our basic philosophy on determining the safety of the use of chemicals in consumer products. This philosophy drives the fundamental choices made in the approach we followed for setting limits of chemicals in toys. Therefore, we will first introduce our conceptual framework for safety evaluation of chemicals in consumer products with specific focus on toys. We will then show how this framework can be used to derive limits for chemicals in toys. The proposed methodology consists of three different options depending on the level of detail needed for this purpose.

7.2 Basic starting points

Our basic point of departure for determining limit values for chemicals in toys is based on the same aspects that are important for safety evaluations of consumer products in general, but with specific attention to toys for children:

- The approach should provide a general framework that basically can be used for all chemicals.
- The approach should provide an adequate level of health protection for children.
- The approach is not based on health hazards only but is based on a quantitative health risk approach.
- Therefore, next to health hazards, exposure assessment will be a focal issue in the approach.
- The approach should be transparent.

- The approach should be applicable for the whole range of different toys and materials used to produce toys.
- The approach should include all potential routes of exposure.

When we take these aspects into account, our conceptual framework attaches great importance to the issue of exposure assessment. Exposure of children to chemicals from toys is not a one-dimensional issue involving only one type of exposure. Principally, all possible routes will have to be taken into account both for evaluating the safety of chemicals in toys and for setting safe limit values for these chemicals, although some routes of exposure will be quantitatively more important for certain chemicals or toys than others. As discussed in chapter 3, all the following routes of exposure are relevant for different types of toys and chemicals: oral route (e.g. mouthing, sucking and ingestion of matrix parts), dermal route (e.g. direct dermal contact, dermal loading of liquids), and inhalation (e.g. evaporation of substances, dusting). The significance of a certain exposure route is determined by both toy and chemical properties. This is depicted in the framework below, which shows that a range of factors determine the exposure of children to chemicals originating from toys. Contact scenarios (e.g. duration of contact, frequency of contact), routes of exposure, migration from the toy to a physiological matrix (e.g. saliva or skin), and uptake into the body all contribute to the total exposure to a chemical.

7.3 Proposed general methodology to derive limit values for chemicals in toys

With regard to chemical properties, the Toy Directive states that toys should not present health hazards by ingestion, inhalation or contact with the skin, mucous tissues or eyes, when used as intended or in a foreseeable way. The basic idea behind the proposed methodology is therefore to use health-based limit values as the core value from which other values such as migration limit values and product content limit values can be derived. In addition to this, one has to consider other potential routes of exposure next to toys. Some substances may occur naturally e.g. in the environment in food. Therefore, it is proposed to allocate only a fraction of the health-based limit value (e.g. 5, 10 or 20%). What this fraction should be can be scientifically advised but will eventually be a risk management decision. In practice, this can essentially be translated into the following statement:

The exposure of children to chemicals in toys may not exceed a certain fraction of a health based limit value (in mg/kg bw/day)

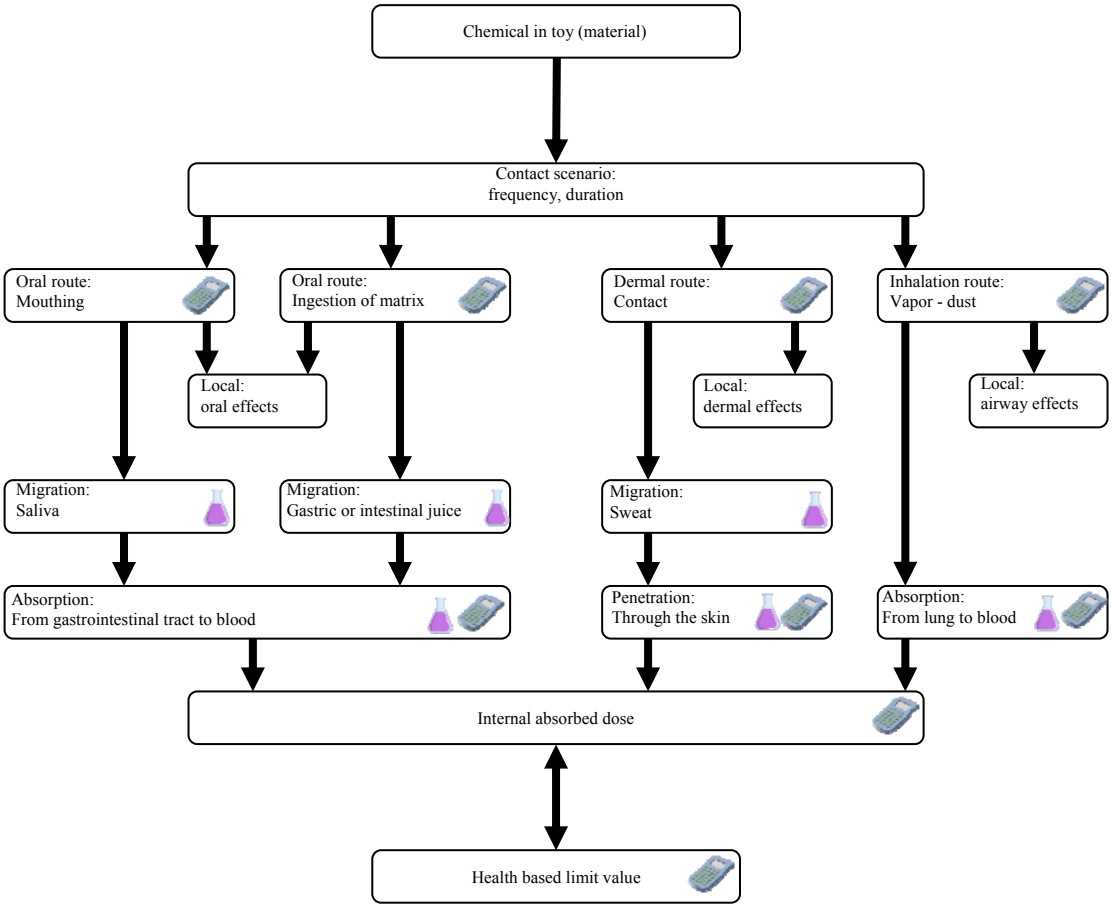

Figure 7-1 Risk based framework for chemicals in toys

7.3.1 Use of a risk based framework

The proposed methodology, based on a risk based framework, is illustrated by the scheme above (Figure 7-1) and can be used to serve two purposes:

1. to derive limit values that can be applicable for a whole range of toys covering a large number of exposure scenarios;
2. for an in-depth assessment of the risks associated with the use of chemicals in (specific) toys.

By working the scheme from *bottom to top*, it can be used for the first purpose: to derive safe limit values for chemicals in toy (materials), in terms of either migration limits or product content limits.

For the second purpose, the scheme should be followed from *top to bottom*, using all available information on the toy – chemical combination to determine whether the use of the toy may pose a health risk.
It is important to note that this approach takes all potential routes of exposure into account rather than considering a single route of exposure (e.g. mouthing toy). Another aspect that is included in this approach is the fact that also local effects due to dermal exposure or exposure via inhalation are considered relevant for setting limit values in toys.
We suggest this framework to provide the basic approach for the methodology to set limit values for chemicals in toys. As will be discussed in the next section, this does not imply that detailed exposure and migration data are always needed.

It should be stressed that this methodology is a risk based approach. This implies that policy issues, like e.g. phasing out CMRS substances from consumer products are not considered here. Of course hazard-based aspects can be added to this methodology although this should be carefully handled. However, it is up to the risk manager whether these hazard aspects should be incorporated in the methodology.

7.3.2 Necessary level of detail for setting limit values

The framework described above is an integral approach based on a quantitative risk based philosophy. Using such a framework, it is possible to derive safe and realistic limit values for chemicals in toys. From a scientific point of view this may be the most correct approach for setting limit values in toys. However, such a quantitative framework requires a substantial amount of (toy and exposure scenario) specific input data or the use of substantiated default values. Extensive experience in the field of consumer exposure and chemical migration reveals that such input data are generally absent or incomplete. Therefore, it is expected that this quantitative framework could only be used routinely if default values were adopted for the various factors for which input data are lacking. Although this might be a reasonable approach, it can be questioned whether such a procedure is necessary for all chemicals in all types of toys or toy materials.
For example, dermal exposure may provide a marginal contribution to the total exposure for a range of chemical-material combinations. In such a case, the dermal route can be set aside from the protocol. However, for some other chemical-toy or toy material combinations, dermal exposure may be very relevant (e.g. finger paint).
In a similar way, inhalation exposure is not quantitatively relevant for a large range of chemical-toy (material) combinations. For others, sucking and mouthing may be irrelevant (e.g when toys are unlikely to be accessible to children < 3 years of age, or when it is simply not possible to put the toy in the mouth). These examples show that it is not in all cases necessary to use all potential pathways in detail as depicted in the scheme above, but it is important to document if and why certain pathways are relevant or not.

From a scientific point of view, the most realistic limit values will be generated by using a quantitative risk based approach, including as much specific data on exposure and migration as possible. This can be directed not only towards systemic toxicity but also towards local route specific toxicity (e.g. dermal or respiratory irritation). However, it can be questioned whether a full quantitative risk assessment is always necessary. It may be in the interest of toy producers/importers to follow a simpler approach, using a number of worst case assumptions, with which they can demonstrate that their product is safe, without going into details.
The implementation of an approach for setting limit values for chemicals in toys also needs to look at practical aspects. Assessments and testing methods need to be easy and fast, and availability of (harmonized) testing methods or exposure assessment factors are important, especially with regard to the toy industry that is looking for transparent and simple testing strategies. So, the challenge is to provide a methodology that follows our conceptual framework but does not prescribe complex and unnecessary assessments. A methodology that includes different options may provide a pragmatic solution, as will be discussed in the next section.

7.3.3 Options within the proposed general methodology

Taking both the basic corner stones of our conceptual framework and the practical aspects into consideration, we propose to use a system providing three options for determining the appropriate limit values of chemicals in toys. Within each option, the relevant health-based limit value of the chemical under consideration is compared to the potential exposure. The relevant health-based limit value used for the comparison is the same for all options. The options differ in the way the exposure to the chemical is assessed, ranging from a very simple approach requiring little testing and worst case assessment data to a more complex quantitative risk based approach, which by means of considering data from migration tests and exposure assessments, may provide justification for the presence of higher levels of the chemical than was initially indicated for the simple approach.
The methodology is not designed as a sequential scheme in which the first option always has to be used first before entering into the next option. Each of the options can be used depending on the data available and the level of detail needed. The three options are discussed below.

7.3.3.1 Option 1: Use of migration data

This first option is comparable to what is currently used for elements in toys, i.e. using migration data to demonstrate that the amount of element migrating out of the toy stays below migration limit values, as described in EN 71-3. This can be depicted in the framework as follows:

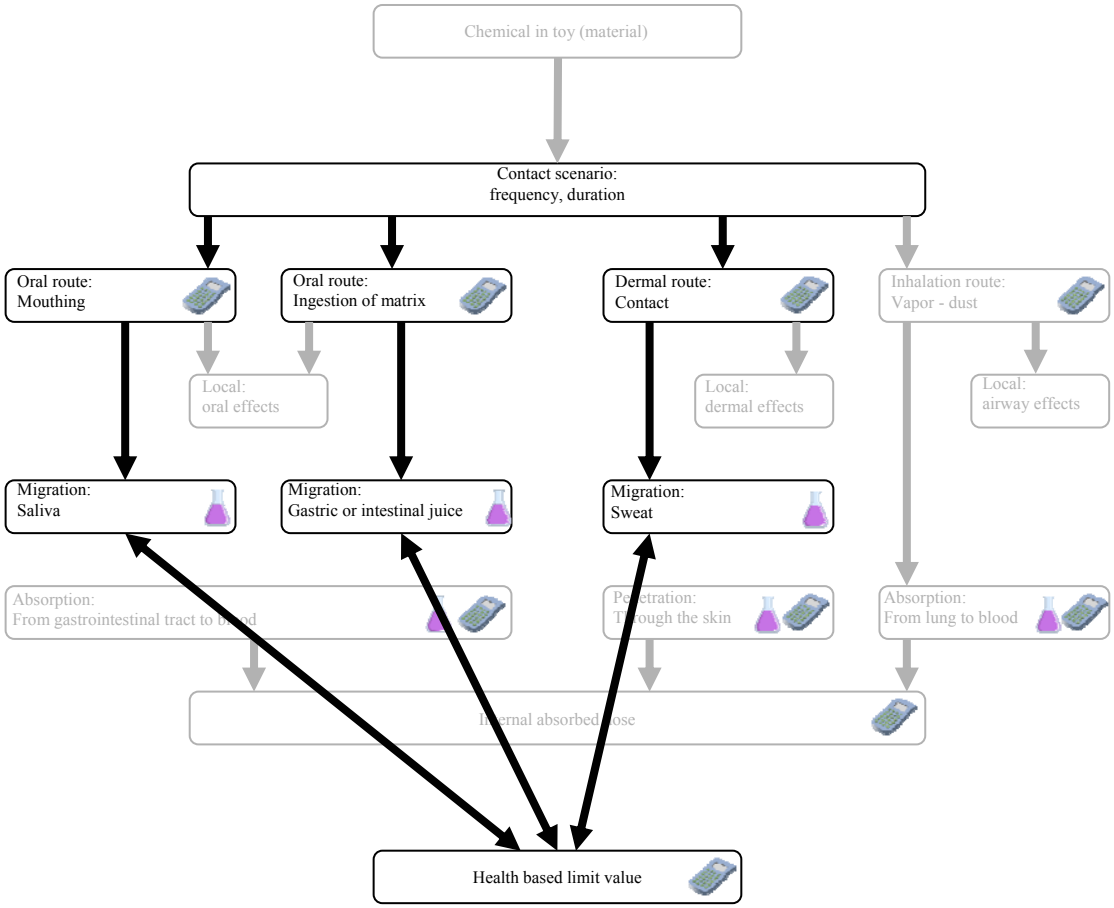

Figure 7-2 Part of the risk based framework used for option 1 of the methodology

Currently, for toys, migration limit values exist for elements only, but this approach could also be applied to chemicals in general. Data from migration testing can be used to demonstrate that the bioaccessibility of a chemical from the toy is sufficiently low that exposure will remain below the relevant health-based limit value.
By using (a fraction of) the health-based limit value as the basic assumption, we can generate maximum values for migration of chemicals from the toy to an adequate extraction fluid.

This option can only be used if one exposure route (normally oral) is dominant for systemic exposure.

This implies that either the contact scenario of the toy or the physico-chemical properties of the chemical under consideration justify that exposure via other routes will be negligible. It is

important to use the appropriate contact scenario and extraction fluid in the migration test, i.e. simulating the main route of systemic exposure. Some guidance can be given on this:

- For toys for children under 36 months and for toys intended to be put in the mouth, oral exposure is likely the main route of systemic exposure for all chemicals. Two types of oral exposure can be distinguished (see chapter 3): 1) mouthing and 2) ingestion of toy material. Depending on the properties of the toy and on the physico-chemical properties of the chemical under consideration, either mouthing or ingestion will contribute most to the systemic exposure:
    - Mouthing involves licking and sucking where the recipient fluid is saliva. For chemicals in toys for which mouthing is most contributing to systemic exposure, the relevant migration extraction fluid therefore simulates saliva. In addition, mouthing related exposure factors such as mouthing duration, amount and surface should be used to calculate bioavailability.
    - Ingestion involves, for example, scraping off small portions of toy material followed by swallowing where the recipient fluid is gastric or intestinal juice. For chemicals in toys for which ingestion contributes most to systemic exposure, the extraction fluid that will extract most of the chemical (based on its physico-chemical properties) should be used in the migration tests. In addition, defaults for ingestion related exposure factors such as amount ingested should be used to calculate bioavailability. For elements in the toys under consideration, as will be discussed later, ingestion probably contributes most to systemic exposure. For simple testing, the appropriate extraction fluid for elements simulates gastric acid, as described in EN 71-3. On the other hand, for most organic chemicals, a more complex extraction medium is required, simulating intestinal juice (for fed conditions).
- For other toys, the dermal or inhalation route may be the main route of systemic exposure. For inhalation it is assumed that chemicals present in the air that reaches the alveoli are all available for uptake, i.e. bioaccessible. Therefore, migration data are not relevant for the inhalation route. This option can therefore not be used for toys for which inhalation presents a major route of systemic exposure. If dermal exposure is the main route of systemic exposure, the relevant extraction fluid simulates sweat. If dermal and oral exposure likely contribute equally to systemic exposure of the chemical, this option should not be used. Instead, option 3 discussed below should be used.

Note: Currently, correction factors are included in the migration limit values to correct for analytical variation. We propose *not* to include correction factors, but to specify the magnitude of the analytical variation in the annex of the standard.

7.3.3.2 Option 2: Use of product composition data

As discussed earlier, it may not always be necessary to perform migration tests if information on the composition of the toy (material) is available. This option allows producers or sellers of toys to demonstrate that their product will not exceed the relevant health-based limit values with regard to chemical exposure using general statements and arguments only. This can be depicted in the framework as follows:

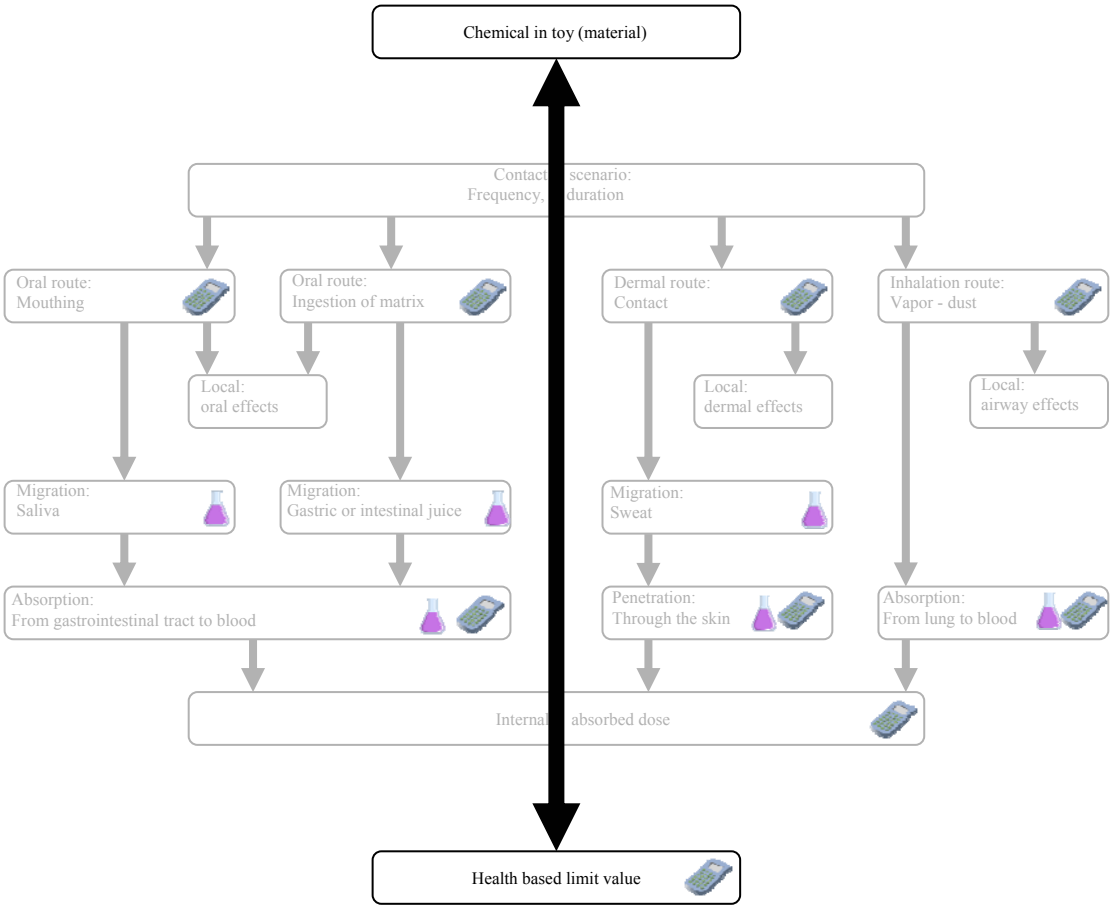

Figure 7-3 Part of the risk based framework used for option 2 of the proposed methodology

In this option the chemical safety of the toy is demonstrated by documentation on the amounts of chemicals present in the toy materials. This can be done using chemical analyses of the raw materials used for making the toy. If chemical analyses of the raw industrial materials are available and show only trace amounts of chemicals or such low levels are present that the total amount in toys is below (a fraction of) the relevant health-based limit value, then additional testing is not necessary. This documentation can then show the chemical safety of the product.

The following simplified and fictive example illustrates that, under certain conditions, such a simpler approach is sufficient. For a certain toy it is known that the total product only contains a limited amount of a certain chemical. The assumption can be made that all of this chemical is released at once resulting in an exposure on a single day. If this single exposure is

less than (a fraction of) the TDI (or another relevant health-based limit value) then this toy can never provide a health risk. A quantitative approach following all potential routes of exposure, or even migration tests are in that case rather superfluous.
It is important that the chemical analyses have to include all materials, not just the major raw industrial materials. For example, if raw material for plastics only demonstrates a trace of lead but the plastic will be mixed with a colouring mixture, an analysis of the raw material only is not sufficient because the colouring agent can introduce an amount of lead. Either an analysis (or an analysis certificate from the supplier) of the final coloured material is needed, or analyses of both the raw plastic material and the colouring mixture is needed.
This option can be viewed as a kind of 'waiver-opportunity' for further testing. Those producers that have data available to demonstrate the absence of chemicals in their material can use those data for compliance with the health-based limit value. Although we realize that currently such data may often not be available to the producers of toys, under the upcoming REACH regulations this may change.

7.3.3.3 Option 3: Use of risk based data

The use of this option is recommended in the following cases:

- Chemicals in toys for which exposure via inhalation may occur.
- Chemical in toys for which more than one exposure route contribute significantly to the systemic exposure.
- When the migration test results indicate that the bioaccessible amount may exceed the relevant health-based limit value for the chemical under consideration, and it can be demonstrated that default factors used for the derivation of these limit values are not relevant for the toy under consideration.

In essence, all the aspects of the framework as depicted in Figure 7-1 are taken into account in this option. The option provides the opportunity to demonstrate the chemical safety of a product by using a number of specific exposure scenarios and / or refined migration testing and therefore it can as such also be used as guidance for an EC type examination[6].
Within this option, it is possible to refine the exposure assessment in a number of ways.

1) Exposure scenarios and exposure factors that are more specific for the toy in question can be used instead of the defaults used in option 1. Some guidance on this is given in chapter 3. For example, for some toys the frequency of contact is not daily but instead only once a week.
2) Migration measurements can be refined in order to simulate the most realistic condition. Chapter 4 presents possibilities to refine migration testing, eg. by using more physiologically based migration tests.
3) A further step for refinement is the use of actual information on the absorption of the chemical via different exposure routes. In this way the internal (systemic) exposure

[6] EC type examination is the procedure by which an approved body, called 'Notified Body' ascertains and certifies that a model of a toy satisfies the essential requirements of the Directive Safety of Toy

can be calculated. One should realise then that also the TDI value should be transferred to an internal (systemic) value.

7.4 Chemicals with sensitising properties

The paragraphs above describe a methodology that can be used to assess the safety or set safe limit values for chemicals with toxicological endpoints for which a threshold can be set. This is mostly aimed at systemic exposure but local route specific toxicity (e.g. dermal irritation) can also be taken into account. However, for some chemicals, sensitisation may be the most critical effect upon dermal (or inhalation) contact. In this case, a limit value would have to be based on this endpoint.
However, a major shortcoming in the risk assessment of sensitising chemicals is the lack of a validated or harmonised method to use this endpoint in a quantitative risk assessment. Substantial efforts are made towards developing a method to determine the relative sensitising potency of a chemicals by several scientific groups (e.g. Ehling et al., 2005a,b; Griem et al., 2003; Jowsey et al., 2006) and in the scientific literature some proposals can be found for a quantitative risk assessment for sensitisation. There is however, at this point in time, no consensus on this aspect. It is currently therefore not possible to derive limit values for sensitizing chemicals. The only exception is when human response data (e.g. human patch testing) are available. In this case, a dermal limit value can be derived that will not lead to a significant response in the human population. Such an approach has been used for the regulations on nickel for example. However, such data are only available for some chemicals.

7.5 Hazard aspects

As described in the beginning of this chapter, in this risk based approach no hazard aspects are included. However, it can be proposed that some hazard characteristics of substances/products are considered undesired with respect to toys. Exclusion of substances with specific hazard characteristics is politically sensitive and we propose therefore, to leave such decisions with the risk managers. In addition to this, it should be emphasised to handle the hazard characteristics (classification and labelling) of single substances very carefully since this may not mean that the final product (toy) has the same level of concern (classification). For example, exclusion of an irritating substance (as classified by the response in the rabbit eye test with 100 mg of pure substance) has no real meaning if the substance only occurs in trace amounts in the final product.
Especially accessible liquid products may require some further consideration. In EN 71-9, additional exclusions have been formulated, such as accessible liquids classified as very toxic, toxic harmful, corrosive, irritant or sensitising. Although not all hazard aspects included in that regulation may require continuation, a careful re-evaluation of these aspects is proposed for addition to this methodology.

In the next chapter it is demonstrated how the proposed methodology can be used to derive migration or content limits for elements in toys by means of option 1 or 2 and which refinements can be made within option 3.

7.6 Conclusions

1) The proposed methodology is a risk based approach.
2) The cornerstone of the proposed methodology uses a maximal allowable level of exposure from toys expressed as a fraction of a chronic health-based limit value (TDI). This deviates from the current methodology on limit values for toys which are based on chosen percentages of background exposures in combination with limited toxicological evaluation, which represents a scientifically less rigorous approach than that proposed in the present report.
3) Migration limits or product limits are derived quantitatively but always represent values deduced from the fraction of the TDI.
4) To demonstrate that the exposure to chemicals from toys will remain below the set fraction of the TDI, three options are provided allowing maximal flexibility.

7.7 Recommendations

Currently no validated method exists to quantitatively assess sensitizing dermal or respiratory effects of chemicals. For the dermal route, developments for a quantitative method are ongoing, but no consensus exists. In time, when consensus has been reached and a method has been validated, dermal sensitising properties should be included in the derivation of safe limit values for chemicals in toys.
With respect to the inhalation route, research on the potency evaluation of respiratory sensitizers is still in its infancy. Further research in this area is needed before respiratory sensitisation can be included as an endpoint in the risk assessments or derivation of limit values of chemicals. Until then, chemicals with potential respiratory sensitising properties should be evaluated on a case by case basis.
An additional evaluation of various hazard aspects is recommended to decide which aspects should be placed on top of the proposed risk-based methodology. This discussion should be performed jointly by risk assessors and risk managers although the final decision is up to the latter group.

8 Application of the proposed methodology to derive limit values for elements in toys

The CSTEE is of the opinion that the current limit values listed for elements in Annex II of Directive 88/378/EEC need to be updated to take into account the latest scientific knowledge and associated revisions of tolerable daily intakes (TDI) and average daily intakes (ADI). In addition, the CSTEE suggests that limit values for other elements than those already listed might be needed.
In this chapter, the methodology proposed in chapter 7 will be used to derive limit values for elements in toys, that might be taken up in the Toy Directive. The focus of this part of the report is on inorganic substances (elements) specifically, with the exception of tin (Sn) compounds for which, as requested by DG Enterprise, also the organic substances were taken into account.

To derive the limit values the following steps need to be taken:

1) Determine relevant exposure routes.
2) Define a relevant toxicological health-based limit value.
3) Determine the relevant elements and the value of the health-based limit value for each element.
4) Determine the appropriate option of the methodology to derive limit values for elements in toys.
5) Compare exposure to health-based limit value and calculate migration and/or content limit values for elements in toys/toy material.

8.1 Determining the relevant exposure routes for elements in toys

Before a relevant health-based limit value can be selected, it needs to be determined what the relevant routes of exposure for elements in toys are. In chapter 3 an exposure scenario decision tree is presented that can be used to define relevant exposure scenarios.
As explained in this chapter in principal the contact scenarios for all three routes have to be considered to see whether they are relevant for the chemical-toy combination in question.

The contact scenarios for the oral route should be considered if the following questions are answered with yes:

- Can the toy be put in the mouth or is it intended to be put in the mouth?
- Can the toy or part of the toy be directly ingested (via hand-to-mouth contact e.g. finger paint or chalk, e.g. paint layer on the toy that might be scraped off with the teeth)?

In considering these contact scenarios for elements in particular, we can assume that both scenarios may be relevant for toys intended for children < 36 months or intended to be put in the mouth, as elements may migrate out of the toy to either saliva or digestive juices. For toys intended for children > 36 months that are not intended to be put in the mouth, the oral contact scenarios are not relevant.

The contact scenarios in the inhalation route should be considered if the following questions are answered with yes:

- Can the substance of interest be released from the toy by evaporation? (some toys may contain volatile substances that may be released during use).
- Can the toy release dust or spray? (e.g. while using crayons, chalk dust may be released and subsequently inhaled).

In considering these contact scenarios for elements in particular, we can assume that the first contact scenario, evaporation, is not relevant for elements because they are not volatile. On the other hand, elements may be present in dust or spray that may be inhaled. However, at present, this route is relevant probably only for a limited, very specific type of toys.

For toys, the dermal route is involved in almost all cases, because most if not all toys will at least be contacted with the hands. However, for elements in particular, the dermal route is unlikely to contribute significantly to systemic exposure, as the uptake of elements through the skin is generally very low except for some organo-metal complexes (chapter 4). For organic substances on the other hand, the dermal route may be quantitatively important and should be included in the methodology. However, deriving limit values for organic substances is outside the scope of the current assignment.
Dermal exposure to elements is relevant in case the element has sensitizing properties (nickel, chromium and organic tin). As discussed earlier, there is currently no validated method to quantify the sensitizing potential of a chemical and it is recommended to evaluate the safety of using of sensitizing chemicals in toys separately, on a case by case basis, until such a validated method exists. In addition, we recommend that the provisions of the EU legislation on Nickel (Commission Directive 2004/96/EC, amendment to Commission Directive 1994/27/EEC) be adopted for toy material. Therefore, for the purpose of deriving safe limit values for elements in toys in general, the dermal route will not be further worked out.

In conclusion, to derive limit values for elements in toys, only the oral route will be included. As this route is of no relevance for toys intended for children > 36 months that are not intended to be put in the mouth, limit values for elements will only be derived for toys intended for children < 36 months and for toys intended for children > 36 months that are intended to be placed in the mouth.

8.2 Defining a relevant health-based limit value

A fundamental aspect for setting limit values for chemicals in products (such as toys) is to decide what level of exposure is maximally acceptable for an individual from a perspective of health risks. This value ultimately determines the migration rate or product limit that can be considered acceptable. Various factors play a role in determining such a maximal acceptable exposure. These factors include duration of the exposure, frequency of the exposure, route of exposure, availability of toxicological data and their reliability, the availability of harmonized health-based limit values, and the margin of 'safety' that policy makers would like to include. Although exposure to various toys covers a wide range of products and exposures, a general characterization can be given. Exposure to chemicals from toys (e.g. when mouthed) is characterized by daily exposure during a period of maximum 1-2 years. In toxicological terms this represents subchronic exposure. However, subchronic limit values are not routinely available for all chemical substances. Chronic health-based limit values on the other hand are routinely available for most chemical substances, at least for the oral route. Using a chronic limit value also assures an adequate level of protection because such values will be lower than subchronic limit values, and the exposure duration is longer than in practice (daily during lifetime vs. frequently in the first years of life). Because of these arguments we propose to use the concept of the Tolerable Daily Intake (TDI) for setting limit values for elements in toys.

For local effects such as skin sensitisation and irritation, a different approach is needed. A safe exposure level which prevents sensitisation effects cannot be given, as there is no validated method to quantify such exposure levels. For chemicals with sensitising effects, its safety of use in toys is best considered on a case by case basis. Some sensitizing chemicals have been regulated in separate directives, such as nickel (Commission Directive 2004/96/EC, amendment to Commission Directive 1994/27/EEC). We recommend that the provisions of this directive be adopted for toy material.

In chapter 2, the concept of the TDI is explained. Although the TDI should provide a safe level of (oral) intake for the general population, special attention was paid to children as a sensitive group. Where appropriate the latest insights in the derivation of the TDI were addressed in the values that are proposed in chapter 2.
Most – if not all – substances do not exclusively occur in toys, but are used in various products. People are thus exposed to these substances through various products and routes. These may include food, drinking water, ambient air, consumer products etc. Some of these exposures are difficult to control, especially when dealing with widespread environmental occurring agents such as elements. It is not acceptable therefore that the (daily) systemic exposure from toys would fill up the total TDI. Background exposure through the environment and through food and drinking water should be taken into account in order to prevent a total exposure that exceeds the TDI. In our proposed methodology, only a fraction of the TDI should be allocated to exposure from toys. What this fraction would be is in

principle a decision that should be made by policy makers. However, some recommendations with respect to elements can be given.

General background exposure to most elements through other routes (in particular food and indirect environmental exposure through air and drinking water), may already account for a substantial fraction of the TDI. For example, daily maximum background exposure to elements (as reported in the toxicological profiles in Appendix II) ranges from only a few percent of the TDI to about 100% of the TDI. The majority of background exposures are in the order of 20 – 70%. This indicates that from the perspective of health protection, systemic exposure to elements from toys (if occurring daily for some continued period of time) may at least not be allowed to any more of about 30% of the TDI in order to avoid any exposure that will exceed this value. Again, this decision should be made by policy makers.

As a comparison it should be noted that in other regulatory frameworks, limit values for elements are also related to a fraction of the TDI. The most prominent example is the setting of limit values for drinking water as used by WHO for their drinking water guidelines. Limit values for drinking water are derived by allocating a maximum of 10% of the TDI for drinking water and an intake of 2 litres of water. This strategy is also adopted by individual countries like the Netherlands. Although again, this is a policy decision, it is proposed that systemic exposure to toys may not contribute to a higher fraction than is considered for drinking water.

Based on relevant background exposures, the aspects from other regulatory frameworks, and the aim of an adequate level of protection for children, the risk managers should decide on the actual fraction of the TDI that will be allocated to toys. When a fully risk based approach is followed, the fraction of the TDI used should be allocated for each element separately based on the level of the background exposure. Another option is to allocate a default fraction of the TDI for all elements (e.g. 5 or 30% for all elements). This is also a decision for the risk manager. For illustration purposes we will calculate the limit values for elements with 5, 10 and 20% of the TDI.

If the general framework will also be applied to other chemicals than elements, the issue of the fraction of the TDI has to be considered for different chemicals (or chemical classes) again.

8.3 Relevant elements and their health-based limit values

In chapter 2 toxicological profiles for a wide range of elements are described. These profiles take into account the most recent scientific knowledge also for the elements already present in the Toy Directive 88/378/EEC.

It was very difficult to get information on the presence of specific elements in different toy material. As far as the information was received, no conclusions can be drawn about which elements occur most frequently and/or whether some elements are specific for particular toys/toy materials. A general answer from the persons that were consulted was that the elements on the present list are in the majority of cases not present in significant levels in toys.
Therefore we used the following strategy: in addition to the present list of 8 elements, we used the list for Food Contact Materials and a list that contains elements that are found in the waste phase of plastics. We ended up with a list of 18 elements, for which we derived TDIs. Given their low toxicity potency, zirconium and titanium are not relevant to be included in the Directive and therefore no limit value will be derived for these two elements.
Since at present the main research on elements in toys considered the elements already included in the Directive, we recommend further research on which elements are present in toys by means of chemical analysis of a representative sample of toy (materials), so that irrelevant elements may be removed from the list, while others may be added.
For the time being we propose that Industry provides information to decide which elements are relevant for which type of toy material. Testing is then only needed for those elements (but at the same time, the limit values for the other elements should not be exceeded).

Table 8-1 TDIs and sensitising potential for the different elements

Element	TDI		Background exposure child (µg/kg bw/day)	Skin irritation and sensitisation contact risk (qualitative indication)
	Value (µg/kg bw/day)	Source or Reference		
Aluminum	750	Newly derived	300	Low
Antimony	6	WHO, 2003	0.53	Unknown
Arsenic	1.0	RIVM, 2001	0.4-0.7	Low
Barium	600	ATSDR, 2005	9	Unknown
Boron	160	EFSA, 2004a	80	Low
Cadmium	0.5	RIVM, 2001	0.45	Low
Chromium trivalent	5	RIVM, 2001	1	Low
Chromium hexavalent	5[a]	RIVM, 2001	0.1[c]	High
Chromium hexavalent	0.0053[b]	OEHHA, 1999	0.1	High
Cobalt	1.4	RIVM, 2001	0.6	Medium
Copper	83	SCF, 2003a	60	Low
Lead	3.6	JECFA, 1993; RIVM, 2001	2.0	Low
Manganese	30 (160)[d]	OEHHA, 2004	130	Unknown
Mercury	2	IPCS, 2003	0.1	Medium
Nickel	10	Newly derived	8	High
Selenium	5	SCF, 2000; RIVM 1998	2	Low
Silver	5	US-EPA, 1996a	1.3	Low
Strontium	600	US-EPA, 1996b	18	Unknown
Tin inorganic	2000	JECFA, 2001	290	Unknown
Tin organic	0.25	EFSA, 2004b	0.083	High
Zinc	500	SCF, 2003b	350	Low

a This value only takes into account non-carcinogenic effects by hexavalent chromium;

b This value takes into account carcinogenic effects by hexavalent chromium. It should be noted that for the carcinogenic effect a highly uncertain Virtually Safe Dose of 0.0053 µg/kg bw/day has been proposed by OEHHA (1999). A new drinking-water cancer bioassay with hexavalent chromium is being conducted within the US-NTP.

c Estimate for a child playing on CCA-treated timber as given in EU-RAR (2005).

d The value of 30 µg/kg bw/day applies to exposures **above** normal dietary intake. For the current method of calculation of the allowable toy-related exposure level (10% of the TDI) this TDI was converted to a value usable for evaluating total daily exposure (inclusive of normal dietary intake). Thus for manganese a figure of 160 µg/kg bw/day was used for calculation (estimated background added to 'non-dietary' TDI).

8.4 Determining the appropriate option for deriving limit values of elements in toys

As explained in the former paragraphs, the ultimate limit value for assessing the safety of elements in toys is the fraction of the TDI that can be allowed as exposure from toys. So any option of the methodology that will demonstrate that exposure to an element from a toy is below the fraction of the TDI of that particular element will suffice.

For inspection purposes, it would be convenient to translate this health-based limit value (TDI) into limit values for toy (material) that can be tested. With the proposed methodology, there are two possibilities for this by calculating back from the fraction of the TDI. Firstly, migration limit values can be generated which can be used in a comparable manner as those listed in EN 71-3. Secondly, maximum content of the element in the toy (material) can be derived. Both these limit values that can be used in practice for screening and inspection purposes. As demonstrated below, generation of these limit values can be accomplished by using options 1 and 2 of the proposed methodology. The third option can be used for an in depth assessment on an ad-hoc basis for specific purposes (e.g. to assess the safety of toys for which the current default factors used in the calculations are deemed too conservative). The next paragraphs will focus on generating migration and content limit values for elements by means of the proposed methodology.

8.5 Comparing exposure to health-based limit values

The next paragraphs will demonstrate how the options described in chapter 7 can be applied to elements in toys. As explained in section 8.1, limit values for elements will only be derived for toys intended for children < 36 months and for toys intended for children > 36 months that are intended to be placed in the mouth. Limit values for elements in other toys are not relevant.

8.5.1 Option 1: Use of migration data

As discussed earlier, the oral route is the most relevant systemic exposure route for the toys under consideration in this report and therefore, the extraction fluid used in the migration test needs to simulate saliva, gastric or intestinal fluid. The present migration testing guideline for toys, EN 71-3, uses a strong acidic extraction fluid representing the gastric compartment (see chapter 4). For elements specifically, EN 71-3 represents a worst case situation for mouthing and a more realistic but still conservative approach for ingestion. Therefore, we propose to use the EN 71-3 migration test for the oral ingestion route without additional testing for mouthing. If the results of the EN 71-3 migration test, i.e. the bioaccessible amount of element does not result in exceeding X% of the TDI, the toy material can be considered safe with respect to the oral route. This can be expressed as follows:

$$\frac{\textit{Bioaccessible amount of element (mg/mg toy)} \times \textit{amount of toy ingested (mg/day)}}{\textit{Body weight (kg)}} < \textit{X\% TDI}$$

Based on information in chapter 3, the following exposure scenarios and assumptions are proposed:

Toys intended to be put in the mouth for children aged over 3 years

Body weight:	15 kg (based on 3-4 years of age)
Duration:	1 hour/day (worst case estimation)
Amount ingested:	8 mg/day
Absorption:	100% over the intestinal tract of the amount of element migrated out of the toy

Toys intended for children aged 0-3 years

Body weight:	7.5 kg (based on 6-9 months of age)
Duration:	3 hours/day (worst case based on literature)
Amount ingested:	Toys consisting of liquid or sticky material: 400 mg/day Toys consisting of dry, brittle, powder-like or pliable material: 100 mg/day Toy material scraped off: 8 mg/day
Absorption:	100% over the intestinal tract of the amount of element migrated out of the toy

The justification for these defaults is explained in more detail in chapter 3.

The bioaccessibility testing as measured by the EN 71-3 migration test involves an extraction for 1 hour with and 1 hour without shaking (total 2 hour extraction). Normally the extraction period should be continued for the desired period of contact which is 1 or 3 hours according to the scenarios above. Since the EN 71-3 migration test is a rough and worst case simulation of reality the 2 hours testing can be regarded as being sufficient for longer periods up to 3 hours. In this sense, the difference between the 1 and 3 hour period is not really relevant.

> Note: The literature does not indicate any substantial difference between mouthing durations for objects intended or unintended to be put in the mouth by young children (chapter 3). Therefore, no distinction is made for toys intended or not intended to be put in the mouth for toys intended for children aged 0-3 years.

As explained, this option of the proposed methodology can also be used to deduce migration limit values for chemicals. By reversing the formula, migration limit values for elements can be derived:

Bioaccessible amount of element (mg/mg toy), i.e. migration limit value =

$$\frac{\textit{X \% TDI (mg/kg bw/day) x Body weight (kg)}}{\textit{Amount of toy ingested (mg/day)}}$$

This results in:

For toys intended for children 0-3 years: X% TDI x 7.5 kg / 8, 100 or 400 mg
For toys intended for children > 3 years: X% x TDI x 15 kg / 8 mg

To illustrate, the following example can be given. The proposed TDI for cobalt is 1.4 µg/kg bw/day. For the purpose of this illustration we assume that 10% of the TDI is used as the health-based limit value. It is assumed that a small child ingests 8 mg of scraped off toy material per day. The migration limit for cobalt in this material is:

10% x 1.4 x 10^{-3} mg/kg bw/day x 7.5 kg / 8 mg = 0.0001313 mg/mg toy or 131.3 mg/kg toy.

Analogously, migration limit values have been derived for all elements. These can be found in paragraph 2.6. For illustrative purposes, the limits have been calculated based on three different fractions of the TDI: 5, 10 and 20%. The ultimate fraction of the TDI that may be allocated to exposure from toys should be decided by risk managers.

Note: In the current Directive, correction factors are included in the migration limit values derived for elements in toys to account for variation in migration measurements. We propose *not* to include correction factors in the migration limit values. Instead, we propose to specify the variation in the migration measurements in the annex of the standard. In our view (consumer protection) it is best to substract the correction factor from the migration limit. This is however a risk management decision. On the other hand, from the standpoint of enforcement purposes one has to prove the incompliance with the migration limit. Then the correction factor should be used the other way around.

8.5.2 Option 2: Use of product composition data

Within this option, the safety of a toy (material) with a certain element content as derived from composition data of the material can be demonstrated by the following calculation:

$$\frac{\textit{Element in toy (mg/kg toy material) x weight of toy material present in toy (kg)}}{\textit{Body weight child (kg)}} < \textit{X\% TDI}$$

It is assumed that all of the element is released at once from the product and available for (oral) exposure. The bioaccessibility is thus 100%.

To illustrate the following (fictive) example is given.

The proposed TDI for cobalt is 1.4 µg/kg bw/day. For the purpose of this illustration we assume that 10% of the TDI is used as the health-based limit value. Available data for the toy material show that cobalt cannot be detected. The detection limit is reported to be < 0.02 ng/kg product (fictive example). The toy material as present in the toy is 200 gram.

$$\frac{0.02 \text{ ng/kg toy material} \times 0.2 \text{ kg}}{7.5 \text{ kg}} = 5.3 \times 10^{-4} \text{ ng/kg bw}$$

It is clear that the calculated amount is much lower than 10% of the TDI (0.1 x 1400 ng/kg bw/day = 140 ng/kg bw/day). Therefore, this toy material will not be able to provide an exposure level above 10% TDI and is therefore considered to be chemically safe with respect to cobalt. No migration testing for this element in this toy is required.

Using the same principles, a content limit value for cobalt in the toy for this example can be calculated by reversing the calculation:

$$\textit{Limit of element in toy (mg/kg toy material)} = \frac{\textit{10\% TDI x Body weight child (kg)}}{\textit{weight of toy material present in toy (kg)}}$$

So: 10% x 1400 ng/kg bw/day x 7.5 kg / 0.2 kg = 5250 ng/kg toy material

8.5.3 Option 3: Use of risk based data

In option 1 it is assumed that the measured migration will occur daily. In reality this will not be true since the EN 71-3 migration test uses an acidic test system which is worst case in the sense that most of the element present in the tested matrix will be released in the first test. A second extraction (e.g. day 2 of mouthing) will never release the same amount of elements. Another worst case assumption is that all toy-related exposures occur with a daily frequency. For some toys (e.g. finger paint) it is not necessary to use a daily frequency because normally this product will be used with larger intervals.
Option 3 provides the opportunity to demonstrate the safety of a certain amount of element in a toy by using a number of specific exposure factors and / or refined migration testing. The health-based limit value to compare the exposure assessment to is still a fraction of the TDI, being the maximal allowable oral exposure.
The exposure factors used for option 2 and other factors that can be used for the safety assessment (such as frequency of exposure) are explained in chapter 3. This chapter also gives guidance on how to evaluate other routes of exposure, which may be relevant for a small group of specific toys (e.g. inhalation via sprays) or for certain elements (e.g. dermal sensitisation of Ni).

The possibilities for migration testing are explained in more detail in chapter 4. This chapter discusses in detail which type of migration tests are relevant for oral exposure routes (mouthing and ingestion of toys).
As discussed for elements, the EN 71-3 test can be used as a worst case extraction system for the ingestion scenario. If desired, further refinement regarding the estimation of the bioavailability of substances from toys can be achieved by using a physiological based test system e.g. as developed by RIVM.
If it can be demonstrated that no toy material will be ingested, a migration test with water can be used as a representative test system for mouthing. In principle, the test system with simulant A as used in the FCM framework can be used given that relevant temperatures and test durations are used (chapter 4).
Other test systems used in the FCM framework cannot be used for toys because irrelevant recipient fluids (e.g. oil), and conditions (static extraction versus dynamic extraction for toys) are used. Such measurements provide data that cannot be used as representative for the physiological condition of mouthing or ingestion.

8.6 Migration limits for elements in toys

In the tables below, migration limits for elements in toys are presented, as derived by the methodology proposed in chapter 7. Further explanation and a calculation example can be found in section 8.5.1.

Table 8-2 For intake of 8 mg (scraped off material) for children < 3 years of age

* ***Age*** ***< 3 years***
* ***Body Weight*** ***7.5 kg***
* ***Material*** ***8 mg (scraped off)***

Element		**TDI (µg/kg bw/day)**	**Migration Limit value (mg/kg product)**			**Current Migration Limit (mg/kg product)**
			5% TDI	**10% TDI**	**20% TDI**	
Aluminum		750	35156.3	70312.5	140625.0	
Antimony		6	281.3	562.5	1125.0	60
Arsenic		1	46.9	93.8	187.5	25
Barium		600	28125.0	56250.0	112500.0	1000
Boron		160	7500.0	15000.0	30000.0	
Cadmium		0.5	23.4	46.9	93.8	75
Chromium[a,d]	Cr^{3+} ws	5	234.4	468.8	937.5	60
	Cr^{3+} wis	5000	234375.0	468750.0	937500.0	
	(Cr^{6+})[b]	5	234.4	468.8	937.5	60
	(Cr^{6+})[c]	0.0053	0.2	0.5	1.0	60
Cobalt		1.4	65.6	131.3	262.5	
Copper		83	3890.6	7781.3	15562.5	
Lead		3.6	168.8	337.5	675.0	90
Manganese		160	7500.0	15000.0	30000.0	
Mercury		2	93.8	187.5	375.0	60
Nickel		10	468.8	937.5	1875.0	
Selenium		5	234.4	468.8	937.5	500
Silver		5	234.4	468.8	937.5	
Strontium		600	28125.0	56250.0	112500.0	
Tin	Inorganic	2000	92750.0	187500.0	375000,0	
	Organic	0.25	11.7	23.4	46,9	
Zinc		500	23437.5	46875.0	93750.0	

[a] ws = water soluble, wis = water insoluble

[b] Based on a TDI of 5 µg/kg bw derived for non-carcinogenic effects by hexavalent chromium

[c] Based on a Virtually Safe Dose (VSD) of 0.0053 µg/kg bw/day derived for the genotoxic and carcinogenic action by hexavalent chromium. As explained in the appended toxicological profile on chromium, this VSD is based on a limited bioassay in mice and is fraught with additional uncertainty compared to the usual bioassay-derived VSDs. Results of NTP studies now in progress should allow more a reliable oral cancer risk estimation in the near future.

[d] Measurement of Cr^{6+} is difficult. Further research is needed to derive safe migration limit values for this element

Table 8-3 For intake of 100 mg (dry, brittle, powder-like or pliable material) for children < 3 years of age

* ***Age*** ***< 3 yrs***
* ***Body Weight*** ***7.5 kg***
* ***Material*** ***100 mg (dry, powder like or pliable)***

Element		**TDI (µg/kg bw/day)**	**Migration Limit value (mg/kg product)**			**Current Migration Limit (mg/kg product)***
			5% TDI	**10% TDI**	**20% TDI**	
Aluminum		750	2812.5	5625.0	11250.0	
Antimony		6	22.5	45.0	90.0	60
Arsenic		1	3.8	7.5	15.0	25
Barium		600	2250.0	4500.0	9000.0	250
Boron		160	600.0	1200.0	2400.0	
Cadmium		0.5	1.9	3.8	7.5	50
Chromium[a,d]	Cr^{3+} ws	5	18.8	37.5	75.0	25
	Cr^{3+} wis	5000	18750.0	37500.0	75000.0	
	(Cr^{6+})[b]	5	18.8	37.5	75.0	25
	(Cr^{6+})[c]	0.0053	0.020	0.040	0.080	25
Cobalt		1.4	5.3	10.5	21.0	
Copper		83	311.3	622.5	1245.0	
Lead		3.6	13.5	27.0	54.0	90
Manganese		160	600.0	1200.0	2400.0	
Mercury		2	7.5	15.0	30.0	25
Nickel		10	37.5	75.0	150.0	
Selenium		5	18.8	37.5	75.0	500
Silver		5	18.8	37.5	75.0	
Strontium		600	2250.0	4500.0	9000.0	
Tin	Inorganic	2000	7500.0	15000.0	30000.0	
	Organic	0.25	0.9	1.9	3.8	
Zinc		500	1875.0	3750.0	7500.0	

* Migration limits according EN 71-3 for modelling clay and finger paint

[a] ws = water soluble, wis = water insoluble

[b] Based on a TDI of 5 µg/kg bw derived for non-carcinogenic effects by hexavalent chromium

[c] Based on a Virtually Safe Dose (VSD) of 0.0053 µg/kg bw/day derived for the genotoxic and carcinogenic action by hexavalent chromium. As explained in the appended toxicological profile on chromium, this VSD is based on a limited bioassay in mice and is fraught with additional uncertainty compared to the usual bioassay-derived VSDs. Results of NTP studies now in progress should allow more a reliable oral cancer risk estimation in the near future.

[d] Measurement of Cr^{6+} is difficult. Further research is needed to derive safe migration limit values for this element

Table 8-4 For intake of 400 mg (liquid or sticky material) for children < 3 years of age

* ***Age*** ***< 3 yrs***
* ***Body Weight*** ***7.5 kg***
* ***Material*** ***400 mg (liquid & sticky)***

Element		**TDI (µg/kg bw/day)**	**Migration Limit value (mg/kg product)**			**Current Migration Limit (mg/kg product)***
			5% TDI	**10% TDI**	**20% TDI**	
Aluminum		750	703.1	1406.3	2812.5	
Antimony		6	5.6	11.3	22.5	60
Arsenic		1	0.9	1.9	3.8	25
Barium		600	562.5	1125.0	2250.0	250
Boron		160	150.0	300.0	600.0	
Cadmium		0.5	0.5	0.9	1.9	50
Chromium[a,d]	Cr^{3+} ws	5	4.7	9.4	18.8	25
	Cr^{3+} wis	5000	4687.5	9375.0	18750.0	
	(Cr^{6+})[b]	5	4.7	9.4	18.8	25
	(Cr^{6+})[c]	0.0053	0.005	0.010	0.020	25
Cobalt		1.4	1.3	2.6	5.3	
Copper		83	77.8	155.6	311.3	
Lead		3.6	3.4	6.8	13.5	90
Manganese		160	150.0	300.0	600.0	
Mercury		2	1.9	3.8	7.5	25
Nickel		10	9.4	18.8	37.5	
Selenium		5	4.7	9.4	18.8	500
Silver		5	4.7	9.4	18.8	
Strontium		600	562.5	1125.0	2250.0	
Tin	Inorganic	2000	1875.0	3750.0	7500.0	
	Organic	0.25	0.2	0.5	0.9	
Zinc		500	468.8	937.5	1875.0	

* Migration limits according EN 71-3 for modelling clay and finger paint

[a] ws = water soluble, wis = water insoluble

[b] Based on a TDI of 5 µg/kg bw derived for non-carcinogenic effects by hexavalent chromium

[c] Based on a Virtually Safe Dose (VSD) of 0.0053 µg/kg bw/day derived for the genotoxic and carcinogenic action by hexavalent chromium. As explained in the appended toxicological profile on chromium, this VSD is based on a limited bioassay in mice and is fraught with additional uncertainty compared to the usual bioassay-derived VSDs. Results of NTP studies now in progress should allow more a reliable oral cancer risk estimation in the near future.

[d] Measurement of Cr^{6+} is difficult. Further research is needed to derive safe migration limit values for this element

Table 8-5 For intake of 8 mg (scraped off material) for toys intended to be mouthed by children > 3 years of age

* ***Age*** ***> 3 yrs***
* ***Body Weight*** ***15 kg***
* ***Material*** ***8 mg (scraped off)***

Element		**TDI (µg/kg bw/day)**	**Migration Limit value (mg/kg product)**			**Current Migration Limit (mg/kg product)**
			5% TDI	**10% TDI**	**20% TDI**	
Aluminum		750	70312.5	140625.0	281250.0	
Antimony		6	562.5	1125.0	2250.0	60
Arsenic		1	93.8	187.5	375.0	25
Barium		600	56250.0	112500.0	225000.0	1000
Boron		160	15000.0	30000.0	60000.0	
Cadmium		0.5	46.9	93.8	187.5	75
Chromium[a,d]	Cr^{3+} ws	5	468.8	937.5	1875.0	60
	Cr^{3+} wis	5000	468750.0	937500.0	1875000.0	
	(Cr^{6+})[b]	5	468.8	937.5	1875.0	60
	(Cr^{6+})[c]	0.0053	0.5	1.0	2.0	60
Cobalt		1.4	131.3	262.5	525.0	
Copper		83	7781.3	15562.5	31125.0	
Lead		3.6	337.5	675.0	1350.0	90
Manganese		160	15000.0	30000.0	60000.0	
Mercury		2	187.5	375.0	750.0	60
Nickel		10	937.5	1875.0	3750.0	
Selenium		5	468.8	937.5	1875.0	500
Silver		5	468.8	937.5	1875.0	
Strontium		600	56250.0	112500.0	225000.0	
Tin	Inorganic	2000	187500.0	375000.0	750000	
	Organic	0.25	23.4	23.4	93.8	
Zinc		500	46875.0	93750.0	187500.0	

[a] ws = water soluble, wis = water insoluble

[b] Based on a TDI of 5 µg/kg bw derived for non-carcinogenic effects by hexavalent chromium

[c] Based on a Virtually Safe Dose (VSD) of 0.0053 µg/kg bw/day derived for the genotoxic and carcinogenic action by hexavalent chromium. As explained in the appended toxicological profile on chromium, this VSD is based on a limited bioassay in mice and is fraught with additional uncertainty compared to the usual bioassay-derived VSDs. Results of NTP studies now in progress should allow more a reliable oral cancer risk estimation in the near future.

[d] Measurement of Cr^{6+} is difficult. Further research is needed to derive safe migration limit values for this element

For a number of elements, the newly derived migration limit values may be lower than those currently listed in the Toy Directive 88/378/EEC, depending on which fraction of the TDI will be used. On the other hand, for some other elements, the newly derived migration limit values are substantially higher and in some cases so high that it may be considered removing these elements from the list of restricted elements.

8.7 Hazard aspects

Our methodology is a risk based approach in which no hazard aspects have been included. As described in chapter 7, some hazard aspects may be included after careful re-evaluation. This holds true also for elements.

8.8 Conclusions

- The proposed methodology can be used to derive migration and content limit values for elements in toys and to perform safety assessments of elements in toys.
- For elements in toys, oral exposure is the main route contributing to systemic exposure.
- The choice of relevant elements is based on the list of elements currently included in the Toy Directive, information on Food Contact Materials and information on elements present in Plastic Waste. Despite repeated requests, information from the toy industry on which elements are relevant for toy material was not received.
- New migration limit values have been derived for 16 elements, for toys intended for children under 3 years of age and for toys intended to be mouthed by children over 3 years of age.
- For these toys, migration studies can be performed with an acid extraction fluid, as described in the current EN 71-3 method.
- For toys intended for children under 3 years of age, three different toy categories have been distinguished for which separate migration limit values have been derived, depending on type of toy material
- The migration limit values derived have been calculated based on 5, 10 and 20% of the TDI. The ultimate migration limit values need to be adjusted based on the decision by risk managers on which fraction of the TDI is allocated for toys.
- Some newly derived migration limit values are lower than those currently listed in the Toy Directive, others are much higher.

8.9 Recommendations

- Risk managers need to decide which fraction of the TDI may be allocated for toys.

- The proposed migration limit value for Cr^{6+} is uncertain and needs to be investigated further.
- The provisions of the EU legislation on Nickel (Commission Directive 2004/96/EC, amendment to Commission Directive 1994/27/EEC) should be adopted for toys.
- The list of restricted elements may be shortened by removing those elements for which very high migration limit values have been derived.
- If the toy industry can provide actual data indicating many elements never occur in toys or do not migrate at all, then these data are highly relevant and should be submitted and considered.

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APPENDIX

I Answers to issues raised by CSTEE in their opinion and DG Enterprise in their call

The opinion of the CSTEE on "Assessment of the bioavailability of certain elements in toys" (opinion adopted on June 22, 2004) distinguished two main topics, i.e. 1) suitability of the proposed limit values and 2) the necessity of updating the standard EN 71-3:1994.

Issue: Choice of elements
Background: Directive 88/3/378 focuses on an-organic compounds, i.e. elements as the compounds of interest. Therefore organic compounds will in principle not be taken into account in this report. The toxicological profile of the elements presently taken up in the Directive has been reviewed. It was suggested by CSTEE that limit values for other elements than those already listed might be needed.
Answer: *Since the majority of testing for enforcement and quality assurance only consider the eight elements listed at present in the Toy Directive, it was very difficult to obtain information on the presence of additional elements (to the current list) for different toy material. Therefore, as a basis for the selection of additional elements the Synoptic Document (EU, 2005) from the food contact material framework and a study on the use and waste-disposal of synthetic materials was consulted.*
The following elements were selected for review:

Table I-1 Elements selected for review

Aluminium	Lead
Antimony	Manganese
Arsenic	Mercury
Barium	Nickel
Boron	Selenium
Cadmium	Silver
Chromium	Strontium
Cobalt	Tin (organic and inorganic)
Copper	Zinc

Molybdeen, Titanium, and Zirkonium were excluded from the list on the basis of their toxicological profile

Issue: Use of Health-based limit values
Background: CSTEE asked to include the latest scientific knowledge and associated revisions of tolerable daily intakes (TDI) and average daily intakes (ADI) into the newly proposed limit values. In this respect it was necessary that the ADI's and TDI's of the involved elements set by various organizations were compared and reviewed for the latest

updates. In addition, an additional literature search from the date of the latest update found can be used to identify potential new data published. Special focus was paid to the setting of TDI's with respect to the potential sensitivity of children.
Answer: *The toxicity of the elements presently in the Toy Directive and the above listed additional elements have been reviewed. The strategy for the derivation of health-based limit values (TDI/ADI) is presented in chapter 2, the toxicological profiles of the individual elements are presented in Appendix 2.*

Issue: Intake of toy-material
Background: The CSTEE considers the presumption that an average daily intake of 8 mg of toy material could be expected as incorrect. It might be more realistic that children may ingest much more than 8 mg in one day, for instance through ingestion of some liquid toy material. Although for some forms of toys this may be true, for other forms 8 mg per day may be an overestimation.
Answer: *This issue is discussed in chapter 3. It is concluded that for a risk-based safety assessment classification of toys based on exposure categories is most appropriate. For toys for children <3 of age default intake values are proposed for solid (easily to break or bit), liquid or sticky material and for material to be scraped off. For mouthing, default values are proposed for mouthing times for children <3 and for children >3y of age*.

Issue: Definition for bioavailability
Background: The CSTEE recommends to change the definition for bioavailability from "the soluble extract having toxicological significance" into "the amount of each element in the toy which could be absorbed into the systemic circulation of a child".
Answer: *It is important to note that these definitions point at different entities in the process of (oral) bioavailability. The way in which oral bioavailability is presently defined is conform the definition applied in pharmaceutical/pharmacokinetic sciences "the fraction of a substance present in toy material that reaches the systemic circulation (of a child)". RIVM interprets the present definition as stated in Council Directive 88/378/EEC as in compliance with bioavailability (F). However, the newly proposed definition by CSTEE is in agreement with the factor F_b, i.e. the bio-accessible fraction, which is a sub-process of oral bioavailability. In chapter 4 the pro's and con's of applying either F or F_b , and relationship between F and F_b are discussed.*

Issue: Use of an analytical correction factor
Background: To derive the final limit values, the CEN in their previous attempt made use of some kind of analytical correction factor. Just as CSTEE recognized it is not clear where this additional factor is based on.
Answer: *In EN 71-3 the analytical variation (correction values) is used to increase the limits. The limits for elements that are proposed in the present report are based on toxicological concepts, which means safety limits to ensure the health of children. It is therefore suggested to include the precision data of EN 71-3 in an Annex of this standard and*

not to prescribe how the obtained results must be corrected or interpreted, as this depends on the perspective of the test laboratory.
In our opinion analytical variation should be dealt with from different perspectives:
When a test laboratory wants to certify a test sample, they have to demonstrate compliance by proving that the migration value is below the legal limit. Therefore the found migration value including analytical variation may not exceed the migration limit.
When an enforcement laboratory analyses a sample, they must demonstrate that the sample exceeds the legal limit, before they can take an official measure. The migration value is corrected by subtracting the analytical variation.
As the analytical correction values used in EN 71-3 (30-60%) are high, and there are probably possibilities to improve the interlaboratory variability of the test, part of the problem may be solved by improvement of the method and re-evaluation of the analytical by a new ring trial.
Further details on this issue can be found in chapter 6.

Issue: A single representative or not ?
Background: The CSTEE does not accept that it is possible to take a single representative from many toys because of their heterogeneous nature. Sampling is a critical step in the enforcement and testing for compliance, that is often overlooked.
Answer: *In our opinion a single sample could be used for compliance testing. For enforcement laboratories measures can be taken based on the results of a single sample. Toy producers or importers must ensure that the sample used for compliance testing is representative for what they place on the market. Periodic testing is required if there are relevant changes in production circumstances, raw materials or in the standards. We propose that this test certificate may not be older than 5 year before the date of marketing of the toy. Moreover, all accessible parts of a toy must comply with EN 71-3. If a toy consists of different materials, subsamples should be made of each material. (see chapter 6).*

Issue: Limit values and maximum bioavailability
Background: The present limit values for concentrations in toy materials are more or less based on the maximum bioavailability. In the methodology used by the CEN conversion factors were applied to some metals to derive limit values, but not to others. CSTEE stated these factors to be unclear. The methodology used by CEN is evaluated in order to clarify the use of the conversion factors.
Answer: *Bioavailability of elements from toy is mainly focussed on oral bioavailability. Limit values for the bioavailability of several elements from toy are listed in Council Directive* 88/378/EEC. *The scientific background of these values are given in a report of the Scientific Advisory Committee (Report EUR 12964). Bioavailability values are used in this EUR 12964 report as it is stated that "bioavailability values are used as the bioavailability of toxic or harmful substances is more important than the total content of potentially dangerous substances in the toy". The bioavailability may be investigated by the extraction rate with media similar to saliva or gastric juice, thereby assuming that the exposure occurs via the*

oral route. Furthermore, report EUR 12964 gives a toxicological evaluation of the elements, with particular attention paid to the gastrointestinal absorption and to data on toxicokinetics in children. Furthermore, it is stated that the intake of the elements from toys should not exceed 10% of the total intake of these metals by children.
The thus obtained bioavailability limits are translated in EN 71-3 to migration limits in which the migration is determined in a hydrochloric acid solution (pH 1-1.5), thereby simulating the acid environment of the human stomach (for fasting conditions). For the conversion of bioavailability limits in Council Directive 88/378/EEC to migration limits in EN 71-3, it is assumed that a child daily ingests 8 mg toy. In addition, for barium and selenium a lower migration limit was derived to minimise exposure of children, and for antimony, arsenic and chromium a higher migration limit was derived to ensure analytical feasibility. Further details can be found in chapter 4.

Issue: Bioavailability or migration
Background: One of the purposes of the report is to examine whether the limit values for elements should be expressed in terms of bioavailability or in terms of migration.
In line with this discussion is the discussion on what type of extraction methods the limit values should be based. Currently, migration is assessed on the basis of chemical extraction procedures. Especially for elements released from toy parts which are ingested, this type of test might overestimate the release substantially. In addition to chemically extraction methods now also physiologically based extraction procedures are available, also for toys (Oomen et al., 2004).
Answer: *It was evaluated whether chemically (migration) or physiologically (bioavailability) based methods would be preferred taking into account both scientific credibility and analytical ease (chapter 4). The general methodology proposed offers the application of physiologically based methods, but at this moment chemically based methods are preferred. It is recognized that the potential of physiologically based methods is high, but these methods require further validation before they can be applied on a larger scale.*

Issue: Toys intended for different ages
Background: One of the discussion points identified by CSTEE is whether the age limit of 6 years of age as used in the current EN71-3 standard is appropriate, as it is “foreseeable that children under 6 will have access to toys intended for children over 6. In addition, the CSTEE noted that the age limit of 6 years is in contradiction with the Toy Directive 88/378/EEC.
Answer: *In chapter 3, the issue of age related exposure has been discussed extensively. In summary, we agree with the CSTEE that toys intended for older children may be accessible to younger children. In the current Toy Directive, a distinction is made between toys intended for children under three years of age and other toys with regard to safety aspects. These safety aspects relate mostly to labelling toys that may pose choking and strangulation hazards, due to small parts and long cords, respectively. With regard to toys containing these physical or mechanical hazards, some degree of carer responsibility may be assumed, as it is more or less common knowledge that such toys should be kept out of reach from young*

children displaying mouthing behaviour. On the other hand, for invisible hazards such chemical hazards, this is not always clear. We therefore recommend to include exposure scenarios specific for young children (mouthing, ingestion, crawling) in the exposure assessment for chemicals in all toys that can be placed in the mouth or crawled on, regardless of intended age group, unless toys are clearly unsuitable for young children based on physical or mechanical hazards.

Issue: Food Contact Materials
Background: It was proposed to examine whether the food contact materials (FCM) framework could provide a basis for setting limit values in toys.
Answer: *It may be possible that substances with low migration in the FCM framework (< 0.05 mg/kg food or fluid) may be directly allowable in toys without further testing because rough calculations indicate migration values in the same order of magnitude as calculated for toys when expressed in mg/kg toy material. However, this can only be allowed when it is assured that the finished toy material / matrix is similar to that tested in the FCM framework and when the testing conditions are relevant for toy exposure. There are however some uncertainties because FMC involves passive migration while mouthing involves active migration. Furthermore, the FCM concept allows exposure that may be higher than the fraction of TDI that is allowable for toys (at least for elements, see chapter 8). Therefore, this approach should only be used after sufficient experimental validation data become available showing that such an approach is indeed safe. For the time being, we recommend not to extrapolate FCM migration limits to toys.*

Issue: Analytical test methods
Background: It is stated that corresponding analytical test methods should be available. In our point of view it is necessary to have a closer look at the available European Standard (EN71-3: 1994, BS 5665-3: 1995 Specification for Migration) and the ISO Standard (ISO 8124-3: 1997 Migration of Certain Elements) for toys. Additionally the complementary Standards for food contact materials have to be taken into account.
Answer: *In chapter 6 several analytical issues are addressed, such as analysis of chromium^{3+} /chromium^{6+} and organic tin compounds, repetitive versus single testing, the use of reference materials etc. It appears that in the migration test (EN 71-3) chromium^{6+} cannot be detected as the acidic solution reduces it to chromium^{3+}. Further validation for the measurement of organic tin is required. Conform testing of childcare articles it is adviced to take the results of the first migration test in to account for compliance testing. Further validation of methods of analysis of the newly suggested elements will be required.*

II Toxicological Profiles

II.1 Aluminium

Aluminium and aluminium compounds have been evaluated within the scope of the WHO Drinking-water guidelines in 1996 and 1998. WHO/IPCS has published an Environmental Health Criteria on aluminium in 1997 (IPCS 1997). Further reviews are those by US-ATSDR (1999) and OEHHA (2000).

II.1.1 Normal exposure

Aluminium is the most prevalent metal in the earth's crust, of which it constitutes no less than 8%. It occurs as silicates, oxides and hydroxides, combined with other elements such as sodium and fluoride or as a complex with organic material. Aluminium is present in drinking-water at concentrations of up to 0.2 mg/L. In many countries non-occupational exposure for adults is between 2.5 and 13 mg aluminium/day from air, water and food (equal to 0.08-0.18 mg/kg body weight per day for a 60-kg individual). However, large variations in daily intake can occur as a consequence of differing intakes of foods containing commonly encountered food additives. Adults taking antacid medication in which aluminium is present, may have very high intakes (up to 5000 mg/day). Infant intakes from nutritional formulas as determined in the USA, Canada and the UK range from 0.03 to 0.7 mg/day. Formulas based on cow's milk are lower in aluminium content than those based on soy. When infant formulas contain aluminium as a food additive, higher intakes are possible (IPCS, 1997; WHO, 1998). A study carried out in Canada in 1999-2001 showed a decline in aluminium concentrations in infant formulas compared to levels found in 1992 (Health Canada, 2003). For older infants a 1995 German study found a daily intake of 0.78 mg (5-8 years old) whereas a US study from the same year reports 6.5 mg/day for 6 year-olds (IPCS, 1997).

Based on these data background maximum daily intake by young children is estimated at 0.3 mg/kg bw/day.

II.1.2 Toxicology

The primary target organs for aluminium toxicity are the central nervous system and the skeleton. In animals encephalopathy was observed including histopathological effects in brain cells. These findings have added relevance to suggestions that the presence of aluminium in drinking-water constitutes a risk factor for the development of Alzheimer's disease in humans. In a large number of epidemiological studies this possible connection has been studied. From this body of data WHO (1998) in its programme for drinking-water

guidelines concluded that a causal link is unlikely but nevertheless cannot be ruled out entirely. Within medical practice aluminium is regarded as a causative factor in encephalopathy as observed in certain hemodialysis patients ('dialysis encephalopathy'). Some non-dialysed cases with the same condition were children with renal failure. Neurotoxicity has also been observed in premature infants receiving intravenous feeding-solutions (for further discussion on this see below). As already remarked, neurotoxicity has also been observed in experimental animals. In rats and mice neurobehavioural effects in adult and developing animals have been observed after oral application. ATSDR concludes neurotoxicity is the critical end point of concern for aluminium with an overall NOAEL of 62 mg/kg bw/day from a 6-week mouse study.

Osteomalacia (softening of the bones) has been observed in both animals and humans. This effect occurs at concentrations of 100 to 200 mg Al/kg bone tissue. Further dose-response information for this effect is lacking.

II.1.3 Children as a sensitive subgroup

Limited data are available on aluminium toxicity in children. These data are summarised by ATSDR (1999). Neurological and skeletal effects have been reported in children with impaired renal function with high exposures to aluminium compounds (medical use). Adverse effects have also occurred due to binding of phosphate to aluminium in the gut (leading to decreased phoshate absorption) in infants given oral antacids against colic. As already mentioned above prematurely born infants appear to be very sensitive for aluminium neurotoxicity. Bishop et al. (1997) found impaired neurologic development after parenteral administration of standard feeding solutions resulting in Al intake of 45 μg/kg bw/day compared to Al-depleted solutions giving only 4.0–5.0 μg/kg bw/day. Feeding durations ranged from 6-16 days and for 157 infants on study. The exposure to the standard feeding solutions was associated with a reduction in the Bayley Mental Development Index ($p = 0.03$) of one point per day of aluminium exposure.

Animal studies generally do not indicate higher sensitivity of young animals for the neurotoxic potency of aluminium. One rat study even indicates lower sensitivity of young animals. In rabbits results are inconclusive. Interference by aluminium with absorption of calcium, zinc and magnesium, however, was found to be greater in young animals in a single rat study (ATSDR, 1999).

II.1.4 Local effects upon dermal contact

Human data are scarce. Aluminium compounds are widely used in cosmetic anti-perspirants, which application has not led to known adverse effects. Some individuals, however, are allergic for these products and possibly the reddening of the skin they experience is related to exposure to aluminium. Some aluminium salts (chloride, nitrate) have been shown to damage skin of animals at high concentrations (10%). Several other salts (sulfate, acetate,

chlorohydrate), however, did not show this effect. Further animal data are lacking (ASTDR, 1999).

II.1.5 Absorption

Studies in humans indicate that aluminium is absorbed in the GI-tract to a very limited extent only. In most studies percentages of 0.1 to 0.3% were found. From the more available chemical forms such as aluminium citrate absorption may be somewhat higher, i.e. up to 1% (ATSDR, 1999). Chedid et al. (1991) studied uptake of aluminium from antacids in infants and, based on increased blood aluminium concentration following antacid administration, estimated intestinal intake was about 0.08-0.16% (OEHHA, 2000).

II.1.6 Toxicological limit values for ingestion of aluminium

For aluminium a Provisional Tolerable Weekly Intake (PTWI) was established by JECFA (1989). Based on a NOAEL of 3% acidic sodium aluminium phosphate in the feed of dogs (equivalent to 110 mg Al/kg bw day) in a 27 week-study, the committee derived a PTWI of 7 mg/kg body weight/week. In the study in question, an unpublished study submitted to JECFA referenced as Katz (1981), no toxic effects were seen (NOAEL >110 mg/kg bw/day). On a daily basis the PTWI equals 1 mg/kg bw/day.

The US ATSDR derived an oral Minimal Risk Level for intermediate exposure duration of up to 1 year, of 2 mg/kg bw/day based on a NOAEL of 62 mg/kg bw from a 6-week neurotoxicity study in adult mice by Golub et al. (1989) with decreased motor activity as the critical effect. (ATSDR, 1999).

In its evaluation OEHHA (2000) concludes human data are the preferred basis for a limit value for aluminium in drinking-water. Two options are explored, one based on an LOAEL for increased aluminium in blood from a 20-day study in adults and the other based on a intravenous LOAEL from the study in premature infants by Bishop et al. (1997) in which neurotoxicity was observed after an exposure period of 6-16 days. Using an oral absorption factor of 0.002 the intravenous LOAEL was converted to an oral LOAEL of 22.5 mg/kg bw/day. To this level OEHHA applied a high uncertainty factor of 300, including a factor of 10 for extrapolation to a NOAEL, 3 for limited duration of the study and 10 for sensitive subpopulations. The latter factor however seems excessive given the fact that the study was done in a sensitive subpopulation. Omitting this factor leads to a TDI of 0.75 mg/kg bw/day.

II.1.7 Conclusion

Human data are considered the most suitable basis for deriving a TDI for aluminium with neurotoxicity as the preferred endpoint. The study by Bishop et al. (1997) dealt with

aluminium neurotoxicity in the sensitive subpopulation of premature infants and is considered the best available basis for a TDI. Using the LOAEL of 22.5 mg/kg bw/day from this study and applying a an uncertainty factor of 30 leads to a TDI of 0.75 mg/kg bw/day.

As to possible adverse direct dermal effects, aluminium is not expected to pose a risk. This is based on the apparent scarcity of adverse side effects attendant to aluminium's use in anti-perspirants and the fact that, as concluded from limited animal data, its skin-irritating potential is low.

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II.2 Antimony

Antimony and antimony compounds have been evaluated within the scope of the WHO Drinking-water guidelines in 1996 and 2003. Antimony trioxide has been evaluated by EFSA for its use as an additive and initiator in food contact materials in 2003 (EFSA, 2004). Antimony trioxide currently is also under evaluation within the EU Existing Substances programme (first draft 2004). A previous evaluation by RIVM is that from 1994 within the project for soil intervention values (RIVM, 1995). Further reviews were published by US-ATSDR (1992) and OEHHA (1997).

II.2.1 Normal exposure

Antimony is a non-essential element that resembles arsenic both chemically and biologically. Like arsenic it occurs mainly in a trivalent or pentavalent state. Natural levels in the environment (soil, water) are low (ppm or ppb). Antimony trioxide (Sb_2O_3; Sb^{3+}), a white powder, is the single most important economic form. It is used as a fire retardant in plastics, textiles, rubber, adhesives, pigments and paper and also as a stabilizer in plastics, vulcanization, ammunition primers and fireworks. Antimony tartrates are used medically in the treatment of bilharziasis (a tropical flatworm infection) (ATSDR, 1992; US-EPA, 1995). Antimony levels in both food and drinking-water are low. The available data are reviewed in EU-RAR (2004). Dietary data from the UK, Sweden, Germany, France, Brazil, Turkey and the USA showed average daily intakes for adults ranging from 1.1 to 29 μg/day. In infant foods in the UK an overall average concentration of 1.7 μg/kg food was found (data from 2003). Based on all available data, the daily intake via the diet for a child was estimated at 0.5 μg/kg bw/day. Children's intake via drinking-water was estimated at 0.03 μg/kg bw/day. Air exposure was evaluated as being very much lower (EU-RAR, 2004).

The estimates made in EU-RAR (2004) are accepted here. Thus background daily intake of antimony for a child is estimated at 0.53 μg/kg bw/day.

II.2.2 Toxicology

Human data are limited to occupational studies with inhalation exposure. Relevant animal data are relatively limited as well. Subchronic oral studies were carried in rats out with potassium antimony tartrate and antimony trioxide. Results show that the latter compound has lower toxicity, which may be explained by its lower bioavailability due to lower solubility. With potassium antimony tartrate Poon et al. (1998) reported subtle thyroid changes in rats after 90-days exposure via drinking-water at concentrations of ≥ 5 mg Sb/litre but in a subsequent evaluation Lynch et al. (1999) concluded that the reported effects were physiological rather that toxicological in nature and proposed a NOAEL of 50 mg Sb/litre (corresponding to 6.0 mg/kg bw/day) based on reduced growth and food and water consumption at the highest dose level of 500 mg Sb/litre. A 90-day study in rats with dietary

dosing of antimony trioxide showed biochemical changes and liver weight increase, suggesting liver toxicity at the highest dose level of 20,000 mg/kg (1407 mg Sb/kg bw/day). An NOAEL for this study of 421 mg/kg bw/day has been proposed (WHO, 2003; EU-RAR, 2004). The only chronic studies are those by Schroeder et al. (1970) and Kanisawa and Schroeder (1969) who administered a single concentration of 5 ppm potassium antimony tartrate in drinking-water of rats and mice during their entire lifetime. Effects observed were shortened lifespan, changes in blood biochemistry and decreased heart weight. In their evaluation of these studies Lynch et al. (1999) noted several crucial shortcomings and concluded that they were unsuitable for use in risk assessment.

An important issue in the toxicological evaluation of antimony has been its potential to cause genotoxicity and carcinogenicity. Results of several in vitro assays with antimony trioxide indicated a clastogenic potential. Several in vivo studies have been conducted with the compound, from which it has been concluded that the in vitro potential is not expressed in vivo (WHO, 2003; EFSA, 2004; RIVM, 2005). For soluble antimony compounds (trichloride, acetate, pentachloride, potassium tartrate) positive results were found in some in vitro studies and also in some in vivo studies (WHO, 2003). Carcinogenicity data for the oral route are limited to the two studies in rats and mice respectively carried out by Schroeder et al. (1970) and Kanisawa and Schroeder (1969). As indicated above, these studies were limited in design therefore not much weight should be given to their negative result for carcinogenicity. For the inhalation route increased incidence of lung tumours have been observed in female rats after chronic exposure to trioxide. This carcinogenic response was in combination with direct lung damage due to chronic overload with the insoluble antimony trioxide particulates and its relevance for antinomy trioxide risk assessment can not be ascertained as of yet. The data available indicate a non-genotoxic mechanism for the formation of these tumours (RIVM, 2005).

As to reproductive and developmental endpoints there is a paucity of data. The studies that were conducted suggest absence of significant toxic potential for producing adverse effects.

II.2.3 Children as a sensitive subgroup

No data are available on antimony toxicity in children or young animals.

II.2.4 Local effects upon dermal contact

Only limited data are available. Human data indicate that antimony trioxide may produce dermal irritation on skin damp with perspiration (occupational data). An NOAEL for this effect is not known. The sensitizing potential of antimony compounds cannot be assessed due to lack of adequate data (ASTDR, 1991; EU-RAR, 2004).

II.2.5 Absorption

Antimony absorption from the gastrointestinal system is relatively low, the available animal studies indicate. Absorption percentages found in studies in mice, hamster and cows ranged from 7 to 20% (OEHHA, 1997).

II.2.6 Toxicological limit values for ingestion of antimony

RIVM (1995) proposed a TDI for antimony of 0.86 µg/kg bw/day based on an LOAEL of 5 ppm from the rat study by Schroeder et al. (1970). This was the same derivation as earlier proposed for antimony by the WHO within the scope of its drinking-water guidelines programme (WHO, 1996).

In its 2003 update of the drinking-water guideline for antimony WHO used the NOAEL from the 90-day oral study with potassium antimony tartrate in rats by Poon et al. (1998). Following the proposal by Lynch et al. (1999) the NOAEL was put at 6.0 mg/kg bw/day and using an uncertainty factor of 1000 (100 for intra- and interspecies variation and 10 for the use of a subchronic study) a TDI was derived of 0.006 mg Sb/kg bw/day. EFSA (2004) in its evaluation for use of antimony trioxide in food contact materials adopted this TDI.

Other toxicological limit values are those of US-EPA (1991) and OEHHA (1997). Both these evaluations used the LOAEL from the Schroeder et al. (1970) chronic rat study. US-EPA applied an uncertainty factor of 1000 to an LOAEL of 0.35 mg/kg bw/day, resulting in an RfD of 0.0004 mg/kg bw/day (breakdown of this factor: 10 for interspecies conversion, 10 to protect sensitive individuals, and 10 because the effect level was a LOAEL and no NOEL was established). OEHHA in its proposal for a drinking-water guideline for antimony applied a factor of 300 (3-fold for LOAEL to NOAEL conversion and a non-severe endpoint, 10-fold for inter-species variation and 10-fold for variation in the human population) to the LOAEL (this LOAEL was put at 0.43 mg/kg bw/day). This implies a TDI of 0.0014 mg Sb/kg bw/day.

II.2.7 Conclusion

The updated TDI of 0.006 mg/kg bw/day as derived by WHO (2003) is chosen as the most appropriate value.

As to possible adverse direct dermal effects, available data are too limited for drawing conclusions. Antimony trioxide may produce irritation on damp skin but the relevance of this occupational finding for toy-related exposures is uncertain.

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II.3 Arsenic

Arsenic and arsenic compounds have been evaluated within the scope of the WHO Drinking-water guidelines in 1996. More recently, in a UN-wide initiative, WHO published a draft version of an expert synthesis report on arsenic in drinking-water (WHO, 2001). EFSA recently reviewed arsenic as an animal feed contaminant (EFSA, 2005). The most recent evaluation of arsenic toxicity by RIVM is from 2001 (RIVM, 2001). Further comprehensive reviews are those by IPCS (2001) and ATSDR (2005).

II.3.1 Normal exposure

Arsenic is a metalloid naturally occurring the earth's crust at an average concentration of about 2 mg/kg. Some minerals however contain much higher concentrations. Arsenic displays different valences (-3, 0, +3, +5) and occurs in cationic and anionic forms. It occurs in inorganic and numerous organic forms that differ not only in their physical and chemical properties but also in their occurrence and toxicity. Anthropogenic activity (mining, waste incineration, wood preservation) is the major source for arsenic in the environment. In some areas (Taiwan, Chile, Argentina, Mexico, China, West-Bengal, Bangladesh) levels in drinking-water are high as a result of high natural concentrations in groundwater. In other regions of the world food is the major source for daily exposure to arsenic. Much of ingested arsenic in food, however, is in organic forms which are known to be much less toxic than the inorganic forms. As *total arsenic* seafood contains by far the highest concentrations but this practically wholly consists of organic arsenic. On the basis of limited data, it has been estimated that in meat about 25% of total arsenic is organic arsenic, 35% in poultry, 25% in dairy products, and 35% in cereals. Based on diet studies from different countries daily intake of total arsenic for adults was estimated to be 1 μg/kg bw/day, of which 25% was presumed to be present as inorganic arsenic (0.3 μg/kg bw/day) (RIVM, 2001). In its review IPCS (2001) presents results for different age groups, including a USA market basket study that reported a total arsenic intake of 28 μg/day for children aged 0.2-2 years, an Australian market basket study reporting 17 μg/day for 2 year-olds and a Canadian total diet study carried out in 4 cities study reporting 15 μg/day for age 1-4 years. Assuming a child body weight of 10 kg and 25% inorganic arsenic these values lead to an estimated daily intakes via diet of 0.4-0.7 μg/kg bw/day for children. It should be noted that locally (near point sources) the contribution of soil and drinking-water may be as high as or even exceed that of food.

Based on the above information background daily intake of inorganic arsenic for a child is estimated to be between 0.4 and 0.7 μg/kg bw/day.

II.3.2 Toxicology

On the toxic effects of arsenic a large literature exists. As already indicated, organic arsenic compounds have only very low toxicity, these compounds being excreted rapidly in urine in

unchanged form (ATSDR, 2005). Inorganic arsenic health effects have been studied in a large number of human studies. Chronic skin effects of arsenic, including pigmentation changes, hyperkeratosis and skin cancer, from medicinal use but also from drinking-water, were reported as early as the 19th century. An endemic peripheral vascular disease (PVD), known as blackfoot disease (BFD), leading to progressive gangrene of the legs, has been known in Taiwan since the 1920s. Important dose-response information on health effects of ingestion of inorganic arsenic comes from a series of epidemiological studies concerning exposure via drinking-water, performed in Taiwan. In one large scale study by Teng et al. (1968) and Tseng (1977) of the prevalence of BFD and dermal lesions (hyperkeratosis and hyperpigmentation) among villagers exposed to different levels of inorganic arsenic, an NOAEL of 0.8 μg/kg bw/day was found. Schoof et al. (1998) proposed a correction for simultaneous ingestion of inorganic arsenic via the diet in this study, thus suggesting an NOAEL of 1.6 μg/kg bw/day. Other NOAELs from similar epidemiological studies range from 0.4 to 20 μg/kg bw/day; LOAELs from these studies range from 2-22 μg/kg bw/day (ATSDR, 2005).

An important issue in the toxicological evaluation of arsenic has been its potential to cause genotoxicity and carcinogenicity. Studies in Taiwan, Chile and Argentina show consistently high mortality risks from lung, bladder and kidney cancer among populations exposed to arsenic via drinking-water. Where exposure–response relations have been studied, the risk of cancer for these sites increases with increasing exposure. Even when tobacco smoking has been considered, the exposure–response relationship remains. Studies on populations occupationally exposed to arsenic, such as smelter workers, pesticide manufacturers and miners in many different countries, consistently demonstrate an excess lung cancer risk among the arsenic-exposed. As is pointed out in RIVM (2001), the mechanism of tumour formation by inorganic arsenic is as of yet unknown. Genotoxicity data suggest a genotoxic potential that is limited to the induction of chromosome breaks (clastogenic activity). The weight of evidence, RIVM concluded, indicates that most likely a toxic threshold exists in the tumorigenic action of inorganic arsenic (RIVM, 2001).

Many other toxicological endpoints have been examined for arsenic but from the data base as a whole the above effects appear as critical.

II.3.3 Children as a sensitive subgroup

Available data are limited, so the review by ATSDR (2005) indicates. Medical surveys show children exposed to toxic levels of arsenic having similar symptoms than adults, including respiratory, cardiovascular dermal and neurological effects and vomiting when arsenic is ingested. Three epidemiological studies on children exposed to arsenic via drinking-water reported a negative impact on neurobehavioural parameters at low exposure levels (≥ 50 μg As/litre in drinking-water in one study, ≥ 1.7 μg/kg bw/day in another study, unspecified in a third) (ATSDR, 2005). Note, however, that the neurological effects,

especially at this low exposure range, do not represent a well-established effect by inorganic arsenic at the current level of knowledge.

II.3.4 Local effects upon dermal contact

Occupational studies reported contact dermatitis after dermal exposure to inorganic arsenic dust. Studies in guinea pigs, however, are reported as negative (no effect). Limited animal data (a study in mice and one in guinea pigs) indicate that dermal irritation occurs at very high concentrations only (ATSDR, 2005).

II.3.5 Absorption

The degree of absorption of inorganic arsenic in the gastro-intestinal system depends on the chemical form. Water-soluble salts are absorbed almost wholly (up to 95%) whereas insoluble salts absorbed considerably less (25%). Absorption of oral arsenic as part of soil matrices like soil frequently is even lower (3-50%) (ATSDR, 2005).

II.3.6 Toxicological limit values for ingestion of arsenic

JECFA (1989) proposed a Provisional Tolerable Weekly Intake (PTWI) of 15 μg/kg bw based on a chronic LOAEL of 100 μg As/litre in drinking-water of humans and using a daily water consumption of 1.5 litres. This value, expressed as a TDI of 2.1 μg/kg bw/day was adopted by RIVM (1991). In its 2001 evaluation RIVM proposed dividing this TDI by a factor of 2 because some epidemiological studies indicate this TDI is insufficiently protective. Thus a TDI of 1.0 μg/kg bw/day resulted (RIVM, 2001).

The US ATSDR derived an oral Minimal Risk Level for chronic exposure to arsenic of 0.3 μg/kg bw/day based on an NOAEL of 0.8 μg/kg bw/day from the epidemiological study by Tseng et al. (1968) and Tseng (1977) among Taiwanese farmers with the prevalence of Blackfoot Disease and dermal hyperkeratosis and hyperpigmentation as the critical effect. To this NOAEL a uncertainty factor of 3 was applied to cover intrahuman variability (ATSDR, 2005).

Other organisations have developed proposals for limit values, especially for drinking-water, based on quantitative cancer risk estimation. WHO (1996) for instance proposed a drinking-water guideline of 10 μg/litre which was estimated to represent a lifetime skin cancer risk of $6x10^{-4}$. The US National Research Council estimated a comparable cancer risk for arsenic in drinking-water (NRC, 2001).

II.3.7 Conclusion

The weight of evidence indicates a threshold in the carcinogenic action by arsenic. Thus a TDI value is chosen for risk assessment. The value of 1.0 μg/kg bw/day as proposed by RIVM (2001) is chosen as the most appropriate value for toy-related exposures.

As to possible adverse direct dermal effects, available data overall suggest a low risk. Dermal contact with arsenic as contained in dust has been reported to produce dermatitis under occupational conditions. The relevance of this finding for toy-related exposures, however, is uncertain. A sensitisation study in guinea pigs was negative (no effect). The dermal irritation potential of arsenic seems low, based on limited animal data.

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II.4 Barium

The toxicity of barium and barium compounds has been evaluated by IPCS (2001) and US-EPA (2005). RIVM has evaluated the group in 1991 and again in 2001 (scope: derivation of soil intervention values). Further reviews are those by WHO (1996) and ATSDR (2005).

II.4.1 Normal exposure

Barium is present in the earth's crust at a mean concentration of about 0.05%, mostly as barium sulfate and barium carbonate. These forms are insoluble in water. Other barium salts such as barium chloride en barium nitrate, however, readily dissolve in water. Barium is present surface water and drinking-water (natural occurrence). The barium content in drinking-water depends on regional geochemical conditions. For drinking-water in the Netherlands average concentrations of 230 μg/litre have been reported (measurements from 1989) but in specific regions of the world much higher levels have occasionally been reported (WHO, 1996; IPCS, 2001). Food also contains barium. Data for the year 1994 indicate a total daily intake via the diet in the Netherlands of on average 480 μg/person (maximum 1260 μg/person) (RIVM, 1998). This is in line with an estimate given in WHO (1996) for daily dietary intake of barium for adults for the period 1970–1991 of 180 μg (minimum), 300 μg (median), and 720 μg (maximum) mg/person. How much of the barium present in the diet is in insoluble form is unknown. RIVM (2001) cited UK data showing total barium intake of 650 to 1330 μg/ day for adults and estimated the intake of water-soluble barium as the lower bound of this range, i.e. 650 μg /person (9 μg/kg bw/day). No specific data for normal intake by children are available

Based on these data background daily intake by young children is estimated at 9 μg/kg bw/day (estimate for adults adopted).

II.4.2 Toxicology

Insoluble forms of barium have very low toxicity. The insoluble salt barium sulfate is used in medicinal diagnostics as an opaque contrast medium for röntgenographic studies of the gastrointestinal tract. For soluble barium available animal and human data indicate hypertension and renal toxicity as the health end-points of concern. Humans who ingested high single doses of soluble barium compounds and workers who inhaled dusts of barium ores and barium carbonate have shown hypertensive effects. Similar effects occurred in experimental animals given barium intravenously, and in rats exposed to soluble barium in drinking-water while on restricted diets. Based on these findings, lower-dose human studies were conducted to examine the potential effects on blood pressure in humans and on both blood pressure and kidney function in animals. Although the experimental study by Wones et al. (1990), together with the epidemiological study by Brenniman and Levy (1984), did not report any significant effects on blood pressure, they establish a NOAEL in humans of

0.21 mg barium/kg bw/day. The animal data suggest that the kidney may also be a sensitive target for ingested soluble barium from low-level exposure. In chronic studies in rats and mice, carried out within the US National Toxicology Program, increased kidney weight was the critical effect. The NOAEL from these studies was 60 mg/kg bw/day (Dallas and Williams, 2001).

II.4.3 Children as a sensitive subgroup

US-EPA (1998/2005) provides a review of the data, which turned out to be very limited. Two animal studies indicate that young animals may have higher absorption of barium in the gastrointestinal tract compared to adults. The mechanism behind this apparent increase in absorption efficiency among younger animals, EPA adds, is not known, and it is not known if similar findings would be observed in humans (US-EPA, 1998). No further information is available.

II.4.4 Local effects upon dermal contact

Only very limited information is available. A dermal study with barium carbonate in rats and rabbits suggests a skin irritative potential for this salt but the study had serious flaws. Data on sensitization are lacking (ATSDR, 2005).

II.4.5 Absorption

US-EPA (1998/2005) and ATSDR (2005) provide reviews of the data. The absorption of barium from the gastrointestinal tract is compound dependent. Barium sulfate is insoluble and very little, if any, ingested barium sulfate is absorbed. Acid-soluble barium compounds, such as barium chloride and barium carbonate, are absorbed in the gastrointestinal tract, although the amount of barium absorbed is highly variable. Older human studies estimated that barium was poorly absorbed with absorption percentages ranging from 1 to 15%. In animal studies absorption showed a very large variation from less than 1% to more than 85%. Apart from solubility, the matrix in which barium is present is an important variable (from complex food matrices absorption is lower), animal age (young animals absorb more) and nutritional status. For poorly soluble compounds the ingested dose is a major factor. In the acid gastric environment a slight proportion of the poorly soluble compounds present may be dissolved in a saturable process, leading to increased absorption of these compounds at low dose levels.

II.4.6 Toxicological limit values for ingestion of barium

For water-insoluble barium compounds RIVM (2001) derived no TDI because these compounds were concluded to be non-toxic. For soluble barium compounds a TDI of 0.02 mg/kg bw/day was proposed based on a human NOAEL of 0.21 mg/kg bw/day from the Wones et al. (1990) study, to which an uncertainty factor of 10 was applied for intrahuman variability and study limitations. IPCS (2001) proposed the same derivation.

US-EPA (2005) used nephropathy in a chronic NTP drinking-water study in mice as the critical effect. Based on a benchmark dose for 5% effect (BMD) of 84 mg/kg bw/day and a corresponding $BMDL_{05}$ of 63 mg/kg bw/day, and using an uncertainty factor of 300 a RfD of 0.2 mg/kg bw/day was obtained. The factor 300 included 10 for interspecies variation, 10 for intraspecies variation and 3 for deficiencies in the database.
ATSDR (2005) derived oral MRLs for intermediate and chronic durations. The chronic MRL was based on the mouse NTP drinking-water study (also used by US-EPA) from which a $BMDL_{05}$ for nephropathy was derived of 61 mg/kg bw/day for male mice, to which an uncertainty factor of 100 was applied (10 for interspecies variation, 10 for intraspecies variation). Thus a chronic MRL of 0.6 mg/kg bw/day resulted. An intermediate MRL of 0.7 mg/kg bw/day was proposed based on a semichronic NOAEL of 65 mg/kg/day for increased kidney weight from a rat 90-day drinking-water study carried out within the NTP (ATSDR, 2005).

II.4.7 Conclusion

Although human data are considered a more suitable basis for deriving a TDI, the pivotal study as used by IPCS (2001) and RIVM (2001) had important flaws (Dallas and Williams 2001). The chronic drinking-water study in mice represents a more reliable basis for a TDI. Following the approach developed by ATSDR for its chronic MRL, in which a benchmark approach was chosen, a TDI of 0.6 mg/kg bw/day is proposed as the most appropriate value.

As to possible adverse direct dermal effects, available data for barium are too limited for drawing conclusions.

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II.5 Boron

The toxicity of boron and boron compounds has been evaluated by WHO (1996), IPCS (1998) and US-EPA (2004). RIVM evaluated boron in 1995 (scope: derivation of soil intervention values). EFSA has derived a Tolerable Upper Intake Level for boron in 2004 (EFSA 2004). Sodium perborate is under evaluation within the EU Existing substances Programme EU-RAR (2005).

II.5.1 Normal exposure

Boron is a naturally occurring non-metal element that is found in the form of borates in the oceans, sedimentary rocks, coal, shale, and some soils. In water at neutral pH boric acid is the dominant form. In food boron occurs as borate or boric acid. The concentration of boron in the earth's crust is 10 mg B/kg (range 5 mg/kg in basalts to 100 mg/kg in shales) whereas in oceans 4.5 mg B/litre in the ocean is present. Boron, as boric acid, borax and other borates, are found in a wide range of consumer products, including boron-silicate glass, soaps, detergents, preservatives, adhesives, porcelain, cosmetics, enamel, leathers, carpets, artificial gemstones, high-contrast photographic material, wicks, electric condensers, fertilisers, insecticides, and herbicides (EFSA, 2004).

Boron has not been established to be an essential nutrient for humans. Food is the main source of exposure for most populations but exposure via water, especially bottled mineral water can be substantial as well. Data on dietary intakes of boron are limited. Foods rich in boron include fruits, leafy vegetables, mushrooms, nuts and legumes as well as wine, cider and beer. Meat, fish and dairy products are poor sources. For the UK total dietary intake for adults has been estimated at 1.5 mg/day (mean) and 2.6 mg/day (97.5 percentile) for the year 1994. Also for the UK a 2003 estimate for adults indicates a mean intake via water of 0.2-0.6 mg/day, via supplements up to 2.0 mg/day, and via cosmetics and consumer products of up to 0.47 mg/day. Maximum total daily intake was estimated at 5.67 mg/day. As stated intake via bottled water may be high. EFSA (2005) indicates concentrations as high as 4.3 mg B/litre have been measured in bottled mineral water. Specific data for total daily boron intake for children are not available.

Based on these data normal maximum daily intake is estimated to be 5 mg/day which equals 0.08 mg/kg bw for a 70 kg adult. In absence of specific data for children this estimate is adopted for this group.

II.5.2 Toxicology

EFSA (2004) reviewed boron toxicity. Human data, the panel concluded, are sparse and not suitable for dose-response assessment. Animal studies comprised several short-term and long-term toxicity studies in a number of animal species (mouse, rat, dog, pig). From these

studies developmental and reproductive effects appear as the critical adverse effects. Reproductive effects were observed both in repeated dose toxicity studies and reproduction studies. In a 2-year toxicity study in rats by Weir and Fisher (1972) reproductive effects (atrophy of seminiferous epithelium and decreased size of testicular tubules) were observed at 58.5 mg B/kg bw/day but not at the lower dose level of 17.5 mg B/kg bw/day (NOAEL). Developmental effects produced by boron included short ribs, variation in the number of ribs and decrease in foetal body weight. The NOAEL for decreased foetal body weight in a rat study by Price et al. (1996) was 9.6 mg B/kg bw/day (LOAEL 13.3 mg B/kg bw/day (EFSA, 2004).

II.5.3 Children as a sensitive subgroup

US-EPA (2004) provides a review of the data. As they point out, effects for boron on the fetus are well established based on animal studies. Data on the possible differential susceptibility of young children however are lacking.

II.5.4 Local effects upon dermal contact

Limited data indicate that 5 or 10% aqueous solutions of boric acid and borates are mild skin irritants. An NOAEL for this effect is unknown (IPCS, 1998). No data on sensitization are available.

II.5.5 Absorption

Both borates and boric acid are well absorbed from the gastrointestinal tract. In several studies in human volunteers absorption percentages of 84% and higher were found (US-EPA, 2004).

II.5.6 Toxicological limit values for ingestion of boron

RIVM (1995) proposed a TDI for boron of 0.09 mg/kg bw/day based on an NOAEL of 8.8 mg/kg bw/day from a 2-year diet study in dogs with testicular toxicity as the critical effect. An uncertainty factor of 100 was applied to this level (10 for intraspecies variation, 10 for intraspecies variation).

IPCS (1998) derived a TDI of 0.4 mg/kg bw/day based on NOAEL for developmental toxicity of 9.6 mg/kg bw/day from the rat study by Price et al. (1996). The applied uncertainty factor comprised subfactors for interspecies and intraspecies differences in toxicokinetics and toxicodynamics. For interspecies differences in kinetics a compound-specific subfactor of 1 was applied, for interspecies differences in toxicodynamics a default of $10^{0.4}$, for intraspecies differences in toxicokinetics a compound-specific factor of $10^{0.4}$ and for intraspecies differences in toxicodynamics a default factor of $10^{0.5}$.

EFSA (2004) in its derivation of an Tolerable Upper Intake Level used an approach similar to that chosen by IPCS (1998). Based on the NOAEL of 9.6 mg/kg bw/day for developmental effects a tolerable intake of 0.16 mg/kg bw/day was calculated, providing for an Upper Level (UL) for an adult of 10 mg B/day. For intraspecies differences in toxicokinetics a compound-specific extrapolation factor of 1.8 was applied (based on interindividual differences among humans in renal glomerular filtration rate, which is the critical physiological process in boron clearance). For interspecies differences in toxicokinetics and inter- and intraspecies differences in toxicodynamics default subfactors of 3.2 were applied. EFSA (2004) derived ULs for different age groups. Pointing out that multigeneration studies in animals did not indicate young animals to be more susceptible than adults, the Panel chose to extrapolate the UL from adults to children on a surface area (body weight$^{0.75}$) basis. For the age group 1-3 years (bw 12-13 kg) an UL of 3 mg/day was proposed and for age group 4-6 years (bw 19-20 kg) an UL of 4 mg/day (EFSA, 2004).

US-EPA (2004) used a similar approach based a $BMDL_{05}$ for decreased fetal weight calculated from the rat developmental study by Price et al. (1996) in conjunction with another similar study by Heindel et al. (1992). Compound-specific subfactors were applied for both interspecies and intraspecies differences in toxicokinetics whereas for differences in toxicodynamics default subfactors were applied. Thus an RfD of 0.2 mg /kg bw/day was established

II.5.7 Conclusion

The UL for 1-3 years of 3 mg/day (0.16 mg/kg bw/day) is chosen as the most appropriate value for toy-related exposures.

As to possible adverse direct dermal effects, no conclusion is possible on sensitization due to lack of data. Concentrations of 5 or 10% of boric acid and borates are known mild to be mildly skin irritating but whether toy-related exposures could be this high is uncertain. Overall the risk seems low.

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II.6 Cadmium

Cadmium and cadmium compounds have been evaluated within the scope of the WHO Drinking-water guidelines in 1996. JECFA evaluated the compound as a food contaminant on several occasions (JECFA, 1989; 2001). EFSA recently reviewed cadmium as an animal feed contaminant (EFSA, 2004). The most recent evaluation by RIVM is from 2001 (RIVM, 2001). Cadmium and cadmium oxide are under evaluation within the EU Existing Substances Programme (EU-RAR, 2003). A further comprehensive review is that by ATSDR (1999).

II.6.1 Normal exposure

Cadmium is a metal occurring in the earth's crust at concentrations of 0.1 to 1 ppm, primarily associated with zinc ores. Small amounts of cadmium enter the environment from the natural weathering of minerals, forest fires, and volcanic emissions, but most is released by human activities such as mining and smelting operations, fuel combustion, disposal of metal-containing products, and application of phosphate fertilizer or sewage. The principal chemical species in air is cadmium oxide, although some cadmium salts, such as cadmium chloride, can enter the air, especially during incineration. In surface water and groundwater, cadmium can exist as the hydrated ion, or as ionic complexes with other inorganic or organic substances.

For non-smokers diet is the major route of exposure to cadmium. A wealth of data is available on cadmium levels in foods and diets in various countries across the world (JECFA, 2001). In a recent SCOOP report thirteen Member States of the EU submitted data based on some of the 16 food categories, relevant for the estimation of cadmium intake. The resulting mean intake was around 100 µg/week (range 2.7 - 176 µg/week) or 1.6 µg/kg bw/week for a 60 kg adult (EFSA, 2004). Children's exposure per kg body weight will generally be larger than that for adults, EFSA adds, because children have a lower body mass. JECFA (2001) report a study from Australia in which average daily intakes for adults ranged from 0.07 to 0.24 µg/kg bw/day and for children of age 2 years from 0.18 to 0.57 µg/kg bw/day. This indicates an intake for young children twice that of adults.

Smoking contributes significantly to the cadmium body burden (1-3 µg/package of cigarettes as internal dose).

Based on the above information background daily intake of cadmium for a child is estimated to be 0.45 µg/kg bw/day (twice the mean intake for an adult as reported by EFSA, 2004).

II.6.2 Toxicology

De toxicity of cadmium has been examined in a vast number of studies in animals and humans. The crucial dose response information comes from the numerous epidemiological

studies among populations with increased exposure. A variety of toxic effects has been described including nephrotoxicity, osteoporosis, neurotoxicity, carcinogenicity and genotoxicity, teratogenicity, and endocrine and reproductive effects. The most sensitive effect is renal toxicity consisting of the induction of irreversible tubular nephropathy that may lead to renal insuffiency. Any cadmium in blood is bound to proteins, especially albumine. In the liver complexation to metallothioneïn (MT) takes place. The Cd-MT-complex is then redistributed to several organs and tissues, predominantly to the kidneys, where part of the cadmium is released, finding its way to sensitive cellular membranes in the tubuli. Damage of these leads, if exposure is sufficiently high and long-lasting, to the characteristic tubular nephropathy. In de kidneys cadmium has a very long half life, viz. of 10 to 30 years, which explains the continuous accumulation in this organ up to the age of 50 to 60 years.

Based on all data pertaining to the renal toxicity of cadmium as arising from the numerous human studies, Järup et al. (1998) concluded that at 50 mg cadmium/kg (ww) in the renal cortex (corresponding to a cadmium excretion in urine of about 2.5 μg/g creatinine) renal effects are present in low percentage of the population (estimated at 4%). At 125 mg/kg in the renal cortex 10% of the population is thought to experience such effects. In line with evaluations by JECFA, Järup et al. (1998) concluded that in order to prevent renal tubular damage developing into clinical disease cadmium concentrations in the renal cortex should remain below 50 mg/kg (cadmium in urine below 2.5 μg/g creatinine). Based on a critical analysis of all available studies and model calculations they conclude that the critical level of 50 mg/kg in the renal cortex is reached after about 45 years of exposure to 50 μg/day (about 1 μg/kg bw/day). As explained in JECFA (2001) these model calculations are based on plausible assumptions regarding cadmium absorption and cadmium excretion. Different assumptions within the plausible range will lead to somewhat different intake levels as needed for reaching the critical renal level.

As already indicated above, cadmium exposure has been linked to a wide range of other toxicological endpoints but the level of evidence for these possible associations is lower than for renal toxicity. Accordingly renal toxicity has been the effect chosen as critical in cadmium risk assessment.

II.6.3 Children as a sensitive subgroup

Cadmium is a cumulative toxicant, and the human exposure conditions of most concern are long-term. Average cadmium concentrations in the kidney are near zero at birth, and rise roughly linearly with age to a peak (typically around 40-50 μg/g wet weight) between ages 50 and 60, after which kidney concentrations plateau or decline. It is not known whether children have a higher toxicodynamic susceptibility for renal toxicity of cadmium. Toxicokinetically, however, children may have increased sensitivity due to higher absorption in the gastro-intestinal system; so at least several animal studies indicate (ATSDR, 1999).

II.6.4 Local effects upon dermal contact

Dermal contact with cadmium does not produce allergic reactions, the available limited data indicate. In patients suffering from dermatitis or eczema skin irritation occurred at 2% cadmiumchloride with no effect at 1%. A test in guinea pigs with the same compound at a concentration of concentration of 0.5% showed no effect (ATSDR, 1999).

II.6.5 Absorption

After oral intake cadmium is absorbed to a limited extent only. The matrix in which it is present is an important factor. From food uptake into the body is lower that from drinking-water. Fysiological status also is an important variable. The iron status strongly influences the degree of absorption. Generally more than 90% of the ingested amount passes through the gastro-intestinal system without absorption (ATSDR, 1999). WHO (1992) concluded that on average, 5% of the total oral intake of cadmium is absorbed, but individual values range from less than 1% to more than 20%. As already stated above, young animals have higher absorption than older animals.

II.6.6 Toxicological limit values for ingestion of cadmium

JECFA (1989) proposed a Provisional Tolerable Weekly Intake (PTWI) of 7 μg/kg bw. This was based on the proviso that levels of cadmium should not exceed 50 μg/g in renal cortex and assuming an absorption rate of 5% and a daily excretion of 0.005% of body burden. It was added that since the PTWI was derived from estimated accumulation of cadmium over a period of 50 years at an exposure rate equivalent to 1 μ/kg bw/day for adults, excursions above this figure may be tolerated provided that they are not sustained for a long period of time and do not produce a significant increase in integrated lifetime dose. The PTWI of 7 μg/kg bw/week has been confirmed in JECFA (2001).

RIVM (2001) followed a recommendation by Järup et al. (1998) who estimated that for maintaining the risk level as intended by JECFA (50 mg/kg in the renal cortex) the lifetime daily intake of cadmium should be lowered from 50 μg/day to 30 μg/day. Thus, using a safety factor of 2 on the existing PTWI previously derived by JECFA, a new value of 3.5 μg/kg bw/week was derived, equivalent to 0.5 μg/kg bw/day.

The US ATSDR derived an oral Minimal Risk Level for chronic exposure to cadmium of 0.2 μg/kg bw/day based on an NOAEL of 2.1 μg/kg bw/day for renal damage (proteinuria) as the critical effect, selected from the human study by Nogawa et al. (1989). In this derivation an uncertainty factor of 10 was applied for human variability (ATSDR, 1999).

II.6.7 Conclusion

The value of 0.5 μg/kg bw/day as proposed by RIVM (2001) is chosen as the appropriate value for toy-related exposures.

As to possible adverse direct dermal effects, the data indicate a low risk only. No sensitization has been observed and no skin-irritation occurred at concentrations as high as 0.5 and 1.0%.

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II.7 Chromium

Chromium and chromium compounds have been evaluated within the scope of the WHO Drinking-water guidelines in 1996. RIVM reviewed chromium in 1991 and 2001. Comprehensive reviews are those by US-EPA (1998a, 1998b, 1998c, 1998d), OEHHA (1999), ATSDR (2000) and EU-RAR (2005).

II.7.1 Normal exposure

Chromium is ubiquitous in nature. The chromium content of rocks varies from an average of around 20 mg/kg for granitic rocks up to 1,800 mg/kg in ultra basic and serpentine rocks. Chromium can exist in oxidation states of +2 to +6 but the three environmentally stable forms are the 0, +3 and +6 states. Naturally occurring chromium is almost always present as trivalent chromium. Hexavalent chromium in the environment almost totally derives from human activities. Hexavalent chromium as chromates and dichromates are used for various industrial applications in metal processing and also as pigment and dye. Under most environmental conditions hexavalent chromium wil be reduced to the trivalent form but nevertheless hexavalent may sometimes persist over long periods, especially at higher pH (around 7-8 and above) and when no oxygen, iron and organic matter are present (ATSDR, 2000; EU-RAR, 2005).

The major route for exposure of the general population to chromium is food, in which it is exclusively present as trivalent chromium. Total adult daily intake ranges from 25 to 224 µg/day with a reported average of 60 µg/day (data from the US) (ATSDR, 2000). Based on these data RIVM (2001) estimated adult background exposure at 1 µg/kg bw/day. Exposure to hexavalent chromium via food is negligible. There is suggestive evidence that a small part of the total chromium present in drinking-water (which is mostly below 2 µg/litre) may be present as hexavalent chromium. Contact with copper chrome arsenate (CCA)-treated wood may lead to low exposure of consumers to hexavalent chromium. A body burden of 1.63 µg/kg bw has been calculated, based on the inhalation and dermal exposure values for a typical consumer handling and sawing dry CCA treated timber. For a child playing on CCA treated timber, a body burden of 0.1 µg/kg bw has been estimated for oral ingestion and dermal exposure (EU-RAR, 2005). Exposure of the general population to hexavalent chromium via air has been estimated at 0.0057 to 0.43 ng/kg bw/day (RIVM, 2001).

Based on the above information background daily intake of trivalent chromium for a child is estimated to be 1 µg/kg bw/day (estimate for adults as given in RIVM 2001 adopted in the absence of data more specifically for children). The background daily intake to hexavalent chromium probably is very low. Using the estimate for a child playing on CCA-treated timber as given in EU-RAR (2005), would lead to an estimate of 0.1 µg/kg bw/day.

II.7.2 Toxicology

There is a marked difference in toxicity between trivalent and hexavalent chromium, the latter having a much higher potency for all toxic endpoints studied.

II.7.3 Trivalent chromium

Trivalent chromium is considered an essential element for humans with a daily requirement for adults estimated to be 0.5-2 µg of absorbable trivalent chromium (WHO, 1996).

Results of chronic animal studies with trivalent chromium indicate that water solubility of the compound tested is an important factor. For the insoluble compound Cr_2O_3 (chromic oxide) a chronic NOAEL in rats is known of 2040 mg/kg bw/day, for the slightly soluble $CrCl_3$ (chromium chloride) a value of 3.6 mg/kg bw/day and for the readily soluble compound $Cr(CH_3COO)_3$ (triacetate) a value of 0.46 mg/kg bw/day. Demonstrating the low toxic potential of trivalent chromium, in none of these studies toxic effects were seen (RIVM, 2001; ATSDR, 2000). In contrast with the clear genotoxic and carcinogenic potential of hexavalent chromium, trivalent chromium has shown little activity for these endpoints (US-EPA, 1998a).

II.7.4 Hexavalent chromium

For this form of chromium there is a large occupational database showing that upon inhalation (as aerosol or mist) it produces lung cancer. Based on these findings IARC classified hexavalent chromium as a proven human carcinogen (Group I). In vitro and in vivo genotoxicity for a wide variety of endpoints showed positive results as well. Data on the occurrence of cancer after oral exposure to hexavalent chromium, however, are scarce. No adequate human data are available and only very limited animal data, i.e. a mouse study in which potassium chromate was given in drinking-water at 9 mg Cr(VI)/litre for three generations (study by Borneff et al., 1968). Neoplastic findings in this study were limited to 2/66 carcinomas (versus 0/79 controls) and 10/66 papillomas (vs. 2/97 in controls) (ATSDR, 2000; RIVM, 2001).

Hexavalent chromium has also shown high toxic potential for non-carcinogenic endpoints after oral administration. It produced liver and kidney toxicity and in some studies also adverse effects on the haematopoeietic system. Developmental and reproductive effects were found in mice and rats at oral dose levels of $\geq$ 20 mg/kg bw/day. No adequate chronic toxicity studies for the oral route are available. In a study by MacKenzie et al. (1958) in which rats received potassium chromate in their drinking-water for 1 year, no toxic effects were observed (NOAEL > 2.4 mg Cr(VI)/kg bw/day). This study has been used as the basis for deriving chronic limit values (see below).

II.7.5 Children as a sensitive subgroup

No specific data are available on the susceptibility of young children or young animals to oral trivalent or hexavalent chromium. An absorption study in rats, however, showed ten times higher absorption of trivalent chromium from the gastrointestinal tract in 2-day-old rats compared to adult ones (ATSDR, 2000).

II.7.6 Local effects upon dermal contact

Hexavalent chromium is an extremely potent inducer of contact dermatitis. It is also a potent respiratory allergen. Both human experience and animal studies indicate it to be a strong skin and eye irritant as well. Based on numerous reports in the literature, the prevalence of hexavalent chromium sensitivity in the general population has been estimated at 0.08% (ATSDR, 2000). The dose-response relation for hexavalent chromium contact dermatitis has been studied in humans. Analysis of these data led to an estimate that at a concentration of 10 mg Cr(VI)/litre a proportion of 10% of chromium sensitised persons would show a sensitisation reaction. This exposure concentration would then protect more that 99.5% of the population. In several studies the threshold for induction of allergic contact dermatitis was expressed as amount per cm^2 of skin, which is a more exact dose measure. Nethercott et al. (1994) examined 54 individuals known to be sensitive to chromium-induced allergic contact dermatitis. For hexavalent chromium they found that 10% of these already sensitised subjects reacted at 0.09 µg Cr(VI)/cm^2 (ATSDR, 2000).

Trivalent chromium has much lower potency for producing and skin irritation and skin sensitization. In hexavalent chromium-individuals trivalent chromium was more than 300 times less potent in producing a dermal reaction compared to hexavalent chromium (RIVM, 1998).

II.7.7 Absorption

Trivalent chromium has low absorption after oral intake. Absorption percentages in experiments in human volunteers ranged from 0.13 to 2.8%. In these experiments chromium was mostly given in water. The degree of absorption correlated reciprocally with dosage level (higher at low dosages) (ATSDR, 2000).

Hexavalent consistently shows higher absorption across mucous membranes than does trivalent chromium. In the gastrointestinal tract, however, reduction of the hexavalent chromium to trivalent chromium, especially in the stomach, reduces the amount available of absorption. An early experiment in human volunteers showed 10% absorption of the dose after application of hexavalent chromium into the duodenum (versus 0.5% for trivalent chromium). After normal oral intake absorption for hexavalent chromium in this study was only 2.1%. Several more recent volunteer experiments with hexavalent chromium are available in which absorption percentages of 0.5% to 18% were found (ATSDR, 2000).

II.7.8 Toxicological limit values for ingestion of chromium

I.1.1.1 Trivalent chromium

RIVM (2001) noted that toxicity data indicate that solubility is an important determining factor in trivalent chromium toxicity. Insoluble forms appear to have very low toxicity, most likely due to poor absorption. Based on NOAELs it was estimated that insoluble trivalent chromium is 1000 times less toxic than soluble trivalent chromium. For water-soluble trivalent a TDI of 5 μg/kg bw/day was derived from a rat NOAEL of 2.5 mg/kg bw/day derived for 1-year drinking-water study. To this NOAEL an overall uncertainty factor of 500 was applied (incorporating 10 for intraspecies variation, 10 for interspecies variation, and an extra factor of 5 for limited study duration). Based on this value a TDI for water-insoluble trivalent chromium was estimated at 5 mg/kg bw/day (1000 times higher).

ATSDR (2000) established no oral limit values for trivalent chromium because the available data were deemed to be insufficient. US-EPA (1998c) derived a TDI of 1.5 mg/kg bw/day for insoluble trivalent chromium based on a chronic NOAEL of 1468 mg Cr(III)/kg bw day from a rat feeding study with chromic oxide by Ivankovic and Preussman (1975). In this derivation a total uncertainty factor of 1000 was applied (10 for intraspecies variation, 10 for interspecies variation and an additional factor of 10 for database deficiencies). For soluble trivalent chromium no TDI was proposed.

I.1.1.2 Hexavalent chromium

Hexavalent chromium is a genotoxic carcinogen, for which effect, it is generally assumed, no threshold exists. For the inhalation route quantitative cancer risk assessments (QCRAs) are available. For the oral route, however, due to a lack of relevant data, QCRAs have not been developed by most evaluating bodies. Hexavalent chromium upon oral intake will be partly converted to trivalent chromium, for which reduction the stomach juices possess considerable capacity. Despite this, a residual cancer risk may remain, especially locally in the gastrointestinal system. The only QCRA for the oral route is that by the California Environmental Protection Agency (OEHHA, 1999) based on the Bornef et al. (1968) study in mice in which fore-stomach tumours were observed. This led to a cancer slope factor of 0.19 per mg/kg bw/day. Based on this slope factor it can be calculated that extra lifetime cancer risks of 10^{-5} and 10^{-6} are reached at daily intakes of 53 and 5.3 ng Cr(VI)/kg bw, respectively (daily exposure throughout a lifetime of 70 years). Given the study limitations, however, this estimate must be considered as highly uncertain. Following the evaluation by OEHHA (1999) hexavalent chromium has been included in the US-NTP working programme and an oral bioassay in rats and mice with application in drinking-water is now being conducted. The result of this study should make a more reliable QCRA for the oral route feasible.

Given the lack of adequate chronic data on which an oral QCRA could be based, RIVM (2001) derived a *provisional* TDI for hexavalent chromium based on non-carcinogenic effects. A 1-year NOAEL of 2.5 mg/kg bw/day deriving from the rat drinking-water study by

MacKenzie et al. (1958), was divided by a total uncertainty factor of 500 (10 for intraspecies variation, 10 for interspecies variation and an additional factor of 10 limited study duration). Thus a provisional TDI of 5 μg/kg bw/day was derived.

US-EPA (1998d) used the same NOAEL of 2.5 mg/kg bw/day to derive an RfD of 3 μg/kg bw/day. Here a total uncertainty factor of 900 was applied (10 for intraspecies variation, 10 for interspecies variation and an additional factor of 3 for limited study duration and a modifying factor of 3 because of concern over a human study by Zhang and Li (1987) in which increased incidences of gastrointestinal disease was reported in subjects whose drinking-water contained 20 ppm hexavalent chromium).

ATSDR (2000) established no oral limit values for hexavalent chromium due to lack of appropriate data.

II.7.9 Conclusion

For water-soluble trivalent chromium the TDI of 5 μg/kg bw/day as proposed by RIVM (2001) can be used for toy-related exposures. For water-insoluble trivalent chromium the TDI of 5 mg/kg bw/day as proposed by RIVM (2001) can be used for toy-related exposures. Hexavalent chromium should be regarded as a genotoxic carcinogen for the oral route. A highly uncertain estimate of the size of this cancer risk indicates extra cancer risk levels of 10^{-5} and 10^{-6} at 53 and 5.3 ng Cr(VI)/kg bw/day, respectively (lifetime exposure, 70 years). For non-carcinogenic effects by hexavalent chromium a provisional TDI of 5 μg/kg bw/day is available.

As to possible adverse direct dermal effects, hexavalent chromium is a potent inducer of skin irritation and skin sensitisation. Levels as low as 0.09 μg Cr(VI)/cm^2 of 10 mg Cr(VI)/litre have been reported as the estimated 10% response dose in popuations of hexavalent chromium-sensitised subjects. Trivalent chromium is much less potent in inducing direct skin effects (no risk).

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II.8 Cobalt

Cobalt and cobalt compounds have been evaluated by RIVM in 1991 and 2001. A comprehensive review is that by ATSDR (2004).

II.8.1 Normal exposure

Cobalt occurs in the earth's crust at average concentrations of 20-25 mg/kg. Low levels may be present in surface water and groundwater (range < 1 to 10 µg/litre). Food is the dominant source of general population exposure. Data on daily intake in Europe are limited. A total diet study from Canada indicated mean daily intakes for adults of 8-15 µg/day. In France the average daily intake via food was 29 µg/day (ATSDR, 2004). In RIVM (2001) average adult background exposure was estimated at 0.3 µg/kg bw/day. In the Canadian total diet study already mentioned, the average intake for age 1-4 years was 7 µg/day and for 4-11 years 10 µg/day (ATSDR 2004). On a body weight basis this indicates an intake for young children twice that of adults.

Based on the above information background daily intake of cobalt for a child is estimated to be 0.6 µg/kg bw/day (twice the mean intake for adults as estimated by RIVM, 2001).

II.8.2 Toxicology

As a component of cyanocobalmin (vitamin B_{12}), cobalt is essential in the body. The US Recommended Dietary Allowance of vitamin B_{12} is 2.4 µg/day, which contains 0.1 µg of cobalt ATSDR 2004).

Cobalt toxicity has been examined to a limited extent only. Adequate chronic studies for the oral route in humans and animals are not available. From limited human data an increase in erythrocyte numbers (polycythemia) appears as the most sensitive endpoint following oral exposure. This effect has been observed at 1 mg Co/kg bw/day in a subacute study in human volunteers (LOAEL) (study by Davis and Fields,1958). In a 8-week study in rats (study by Stanley et al. 1947) this effect was also found at this dose level; the NOAEL in this study was 0.6 mg Co/kg bw/day (ATSDR, 2004). Humans who regularly consumed beer that contained cobalt sulphate as a foam stabiliser and who ingested an average of 0.04 mg to 0.14 Co/kg bw/day over a period of years, showed severe cardiomyopathy. This effect has been reported in several studies but, as is pointed out in ATSDR (2004), in its development chronic alcohol abuse may have contributed significantly.

II.8.3 Children as a sensitive subgroup

No toxicity data are available on the susceptibility of young children or young animals to oral cobalt. An absorption study in rats and guinea pigs, however, showed increased absorption from the gastrointestinal tract in younger animals (3- to 15-fold higher) (ATSDR, 2004).

II.8.4 Local effects upon dermal contact

The potential of cobalt to induce dermatitis has been demonstrated in a large number of human studies. Using patch tests and intradermal injections, it has been demonstrated that the dermatitis is probably caused by an allergic reaction to cobalt, with the cobalt ion functioning as a hapten. Exposure levels in these studies, however, mostly were not reported. A NOAEL for induction of dermatitis has not been established. In two Polish occupational studies 10 or 20% of the study populations of nurses and dentists reacted positively to a patch test 1.0% cobalt chloride. Another study in patients known to have cobalt allergy (Nielsen et al., 2000), suggests that the allergic reactions to cobalt are primarily linked to cobalt metal and not to cobalt salts. Interrelationships exist between nickel and cobalt sensitization but the extent of this (potential) interaction on immunologic endpoints is not well understood. No data on the potential of cobalt compounds to induce skin irritation are available (ATSDR, 20004).

II.8.5 Absorption

Gastrointestinal absorption of cobalt and its compounds shows wide variation (18-97% of the dose), depending on dosing level and its type and the nutritional status. The iron status influences the degree of absorption. Humans deficient in iron absorbed 31-71% of a dose compared to 18-44% in controls. Animal studies show that soluble cobalt chloride is better absorbed than insoluble cobalt oxide (13-34% versus 1-3%). In one study in rats and guinea pigs absorption in younger animals (age 1-60 days) was 3- to 15-fold higher than in adult animals (200 days old) (ATSDR, 2004).

II.8.6 Toxicological limit values for ingestion of cadmium

RIVM (2001) proposed a TDI of 1.4 μg/kg bw/day based on a human LOAEL of 0.04 mg/kg bw/day derived from the studies on beer drinkers ingesting cobalt sulphate as a foam stabiliser. To this LOAEL an uncertainty factor of 3 was applied for intra-human variability and factor of 10 for extrapolation of an LOAEL to an NOAEL.

ATSDR (2004) derived an oral Minimal Risk Level (MRL) for intermediate exposure duration of up to 1 year, of 10 μg/kg bw/day based on a LOAEL for polycythemia of 1 mg/kg bw from a 22-day study in humans (Davis and Fields, 1958). The LOAEL was divided by an uncertainty factor of 100 (10 for the use of an LOAEL and 10 for human variability). No chronic oral MRL was derived due to lack of appropriate data.

II.8.7 Conclusion

The value of 1.4 μg/kg bw/day as proposed by RIVM (2001) is chosen as the appropriate value for toy-related exposures.

As to possible adverse direct dermal effects, cobalt is a skin sensitiser. The dose-response relation for this effect however is poorly understood. Possibly only cobalt as a metal has sensitising potential with cobalt salts having none. The skin-irritating potential of cobalt is unknown.

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II.9 Copper

Copper and copper compounds have been evaluated within the scope of the WHO Drinking-water guidelines in 1996 and 1998. The EU Scientific Committee Food recently derived a Tolerable Upper Intake Level for Copper (SCF, 2003). A previous evaluation by RIVM is that from 2001. Comprehensive reviews are those by IPCS (1998), US-NRC (2000) and US-ATSDR (2002).

II.9.1 Normal exposure

Copper occurs in the environment in three major valence states: copper metal Cu^0, Cu^+ and Cu^{2+}. The mean concentration of copper in soil ranges from 5 to 70 mg/kg and is higher in soils near smelters, mining operations, and combustion sources. The median concentration of copper in rivers, lakes, and oceans is 4–10 ppb. It is predominantly in the Cu^{2+} state, most of it complexed or tightly bound to organic matter. The combined processes of complexation adsorption and precipitation control the level of free Cu^{2+}. The chemical conditions in most natural water are such that, even at relatively high copper concentrations, these processes will reduce the free Cu^{2+} concentration to extremely low values. Sediment is an important sink and reservoir for copper (ATSDR, 2004).

Food and drinking-water are the major sources for general population exposure to copper. In drinking-water relatively high concentrations may be present due to migration from distribution systems (both from the water treatment plant and in the home), especially after a period in which the system has not been flushed. Mean daily intake from foods in different EU countries ranges from 1.1 to 2.2 mg/day (97.5-percentiles 1.2 to 4.2) (SCF 2003). Drinking-water may contribute up to 1 mg/day according to RIVM (2001).Total background exposure from food and drinking water has been estimated at 0.03 mg/kg bw/day for an adult (RIVM 2001). Data for intake by children are limited. In one US study intake by children aged 2 years was about half that of adults expressed as mg/day (0.48 mg/day versus about 1 mg/day). Per kg body weight infant intake thus would be about twice that of adults.

Copper is essential element for biological organisms, being an essential component of many enzymes (cuproenzymes) and proteins. Recommended daily allowances for human adults as given in the UK and USA range from 0.9 to 1.2 mg/day (SCF, 2003).

Based on the estimate for adults of 0.03 mg/kg bw/day as given by RIVM (2001), children's normal exposure is estimated at 0.06 mg/kg bw/day (twice the adult value, as suggested by US data).

II.9.2 Toxicology

Animal data on copper toxicity are relatively limited. Human data indicate that chronic copper toxicity has its most pronounced effects on liver function whilst acute effects of copper toxicity are primarily observed in the gastrointestinal tract, as a local intestinal irritation effect. Acute copper toxicity in drinking water appears to have a threshold of approximately 6 mg/L. For longer exposures SCF (2003) considered liver damage the critical endpoint. After long-term copper intake at 30 mg/day or 60 mg/day for several years acute liver failure developed, so O'Donohue et al. (1993) report for a single case. Several other human studies indicated absence of adverse liver effects after prolonged intake of 7 to 10 mg/day. From a 12-weeks supplementation study by Pratt et al. (1985) an overall NOAEL of 10 mg/day for liver effects was selected.

For other toxicity endpoints the available data are limited. Poor quality studies of copper compounds in rats and mice suggest absence of carcinogenic activity. Genotoxicity data are inconclusive. In developmental and reproduction studies testicular degeneration and reduced neonatal body and organ weights were seen in rats at dose levels in excess of 30 mg Cu/kg body weight per day over extended time periods, and fetotoxic effects and malformations were seen at high dose levels (>80 mg Cu/kg body weight per day) (IPCS,1998; SCF, 2003).

II.9.3 Children as a sensitive subgroup

Copper is an essential element required for normal growth and development. Signs of copper deficiency in infants and children include anemia that is unresponsive to iron supplementation, neutropenia, bone abnormalities, and hypopigmentation of the hair. Indian childhood cirrhosis and idiopathic copper toxicosis are two syndromes associated with high intake of copper. Both are characterized by severe liver damage in infants and children (< 5 years of age). The syndromes have been linked to genetic defects, due to which copper metabolic capacity is exceeded in certain individuals, leading to excessive copper concentrations in the liver. Several reports indicate that children may be more sensitive to the gastro-intestinal effects produced by copper but the evidence on this issue is inconclusive as of yet (ATSDR, 2004).

II.9.4 Local effects upon dermal contact

Some medical case studies show that copper may produce dermal contact dermatitis. No dose response information for this supposed effect is available. Data on skin-irritating potential are lacking (ASTDR, 2004).

II.9.5 Absorption

The percentage absorption of dietary copper depends on the amount of copper ingested, with the percentage absorption decreasing with increasing intakes. A series of studies in humans demonstrated that a 10-fold increase in dietary copper resulted in only twice as much copper

being absorbed. A theoretical maximum absorptive capacity of 63-67% has been estimated from aggregate results of human copper absorption studies at various copper daily intakes. With typical diets in developed countries the average copper absorption has been estimated to be in the 30-40% range (SCF, 2003). Limited evidence in humans and animals suggests that the process of absorption is less easily saturated in young humans and animals than in older ones, which effect could lead to higher absorption rates in the former, of which however no quantitative estimate is available (ATSDR, 2004).

II.9.6 Toxicological limit values for ingestion of copper

RIVM (2001) proposed a TDI for copper of 0.14 mg/kg bw/day, which was loosely based on an LOAEL of 4.2 mg/kg bw/day for chronic oral exposure in mice (study by Massie and Aiello 1984), taking into account minimum nutritional requirement for copper in humans of 0.02 to 0.08 mg/kg bw/day.

The US ATSDR derived an oral Minimal Risk Level for intermediate exposure duration of up to 0.01 mg/kg bw/day based on a study by Araya et al. (2003) in which gastrointestinal effects were observed. This study identified NOAEL and LOAEL values of 0.042 and 0.091 mg Cu/kg/day, respectively; these copper doses were in excess of normal dietary intake. The NOAEL was divided by an uncertainty factor of 3 (to account for human variability) to yield an intermediate-duration oral MRL of 0.01 mg Cu/kg/day. The intermediate-duration MRL is intended to protect against exposure to excess copper in drinking water and assumes a normal copper dietary intake (ATSDR, 2004).

SCF (2003) established a Tolerable Upper Intake Level (UL) for copper based on a NOAEL of 10 mg/day for adverse effects on liver function as the critical endpoint, derived from a study by Pratt et al. (1985) in which seven adult human volunteers had their diets supplemented with 10 mg Cu/day over a period of 12 weeks. Noting the homeostatic nature of copper uptake into the body (lower absorption rates as higher amounts are ingested), the Committee decided that an UF of 2 is adequate to allow for potential variability within the normal population. Thus a UL of 5 mg/day was established for adults (0.083 mg/kg bw/day for 60 kg adult). For the age group 1-3 years (bw 12-13 kg) a corresponding UL of 1 mg/day was proposed and for age group 4-6 years (bw 19-20 kg) an UL of 2 mg/day (SCF, 2003).

II.9.7 Conclusion

The UL of 5 mg/day corresponding with 0.083 mg/kg bw/day, as derived by SCF (2003), is chosen as the most appropriate value.

As to possible adverse direct dermal effects, no conclusion is possible due to lack of data. However, given the wide use of copper in various applications (water transport, electricity wires) without this leading to frequent reports of adverse skin effects, the potential to induce these effects probably is very low.

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II.10 Lead

The toxicity of lead and inorganic lead compounds has been studied extensively in both animals and humans. On numerous occasions these data have been evaluated by expert committees. The contaminants panel of the EFSA has recently evaluated lead in the food chain (EFSA, 2004). Other major reviews are those by JECFA (2000) and ATSDR (2005). RIVM reviewed lead in 1997 and 2001. Further evaluations are OEHHA (1997) and IPCS (1995).

II.10.1 Normal exposure

Lead occurs naturally in the environment with an overall level in the earth's crust of 20 mg Pb/kg dry matter. Background levels in the topsoil vary between 10 and 70 mg/kg whereas levels in surface water are generally below 0.01 mg/l; levels up to 1 mg/l can be expected in polluted areas with soft waters. Lead occurs naturally mainly in its inorganic form as oxide or sulfide, but also as carbonate, sulfate and chromate. Technical use of lead, for instance as anti-knocking agent in petrol, has resulted in increased levels in soil, water and air. Use in solders and alloys for water pipes (drinking water supplies) has been another major source of environmental pollution, and human and animal exposure. Both the use in petrol and in water pipes has been abandoned in most countries. Further uses of lead are in mining, smelting and processing, pigments, batteries and ceramics and glassware (EFSA, 2004).

General population exposure is predominantly via food and water. For infants exposure via dust, however, can be a major additional source. JECFA (2000) summarises data on lead intake from food and water from all seven continents. A wealth of data was available both for adults and children. From this body of data the estimated range of intake levels from food for children was 0.6-30 µg/kg bw per week. This was generally two to three times the adult intake in the same country when evaluated on the basis of body weight (JECFA, 2000). This estimate is exclusive of tapwater for which there were insufficient data to make a reliable estimate. As already indicated non-food sources may contribute significantly in specific situations. Use of ceramic drinking-vessels may sometimes even lead to intoxications. Intake from soil is important especially in industrialized areas where children play in dusty environments. The latter intakes tend to be highly location-specific. The Health Council of the Netherlands (1997) estimated lead intake in the Netherlands from all sources, including soil, at 2.0 µg/kg bw/day (14.0 µg/kg bw/week) for children aged 1-4 years. For higher ages this was estimated to be 0.64 µg/kg bw/day (4.5 µg/kg bw/week).

Based on the above data normal exposure for children is estimated to be 2.0 µg/kg bw/day which is the estimate for the Netherlands as adopted in RIVM (2001). As indicated above in specific regions exposure may well be either higher or lower than this level.

II.10.2 Toxicology

The dose response for lead toxicity has been examined in numerous epidemiological studies. This research has provided fairly detailed knowledge of the toxic effects occurring at different concentrations of lead in the blood. At higher Pb-levels haemsynthesis is affected. In children this is seen at about 400 μg Pb/litre and higher and in adults at 800 μg Pb/litre and higher. But already at lower concentrations neurological functioning is impaired. This is measurable as a decrease in IQ. JECFA (2000) presents results of statistical dose-response assessment of neurobehavioural effects of lead in children. The best analysis that could be developed showed a decrease of one IQ point for every 20-40 μg/litre increase in blood lead concentration, with a greater effect at higher concentrations than at lower ones. A meta-analysis of seven studies showed that an increase in the blood lead concentration from 100 to 200 μg/litre would result in a decrease of approximately 2.5 IQ points. A conclusion as to the existence of a threshold for these effects (a blood PB-concentration below which no adverse effect occurs) cannot be drawn at the present stage. In experimental animals adverse effects on cognitive function have been demonstrated at concentrations of 110-150 μg Pb/litre. Severe damage such as brain damage occurs only at ≥1000 μg Pb/litre.

II.10.3 Children as a sensitive subgroup

A large body of data is available on the effects of lead in children. As already stated children are a well-identified sensitive group for lead neurotoxicity and the dose response for this effect has been studied widely, leading to fairly detailed insight into the relation of blood Pb-levels in children and cognitive function. The TDI for lead is based on these data.

II.10.4 Local effects upon dermal contact

With lead no dermal irritation and en sensitization studies have been carried out.

II.10.5 Absorption

ATSDR (2005) provides a review of the data. Important modulating factors for absorption of ingested inorganic lead are physiological status (e.g., age, fasting, nutritional calcium and iron status, pregnancy) and physicochemical characteristics of the medium ingested (e.g., particle size, mineralogy, solubility, and lead species). Lead absorption may also vary with the amount of lead ingested. Both animal data and human data indicate that absorption in the young is higher. Estimates derived from dietary balance studies conducted in infants and children (ages 2 weeks to 8 years) indicate that 40–50% of ingested lead is absorbed. In adults the estimated absorption ingested water-soluble lead compounds ranged from 3 to 10% in fed subjects. Absorption under fasted conditions will be higher than these levels. Animal and human data indicate that absorption from soil is low compared to absorption from soluble lead salts (ATSDR, 2005).

II.10.6 Toxicological limit values for ingestion of lead

JECFA (1986) concluded that no effect on cognitive function is expected below 50 µg Pb/litre in blood. A *provisional tolerable weekly intake* (PTWI) was proposed of 25 µg/kg bw for children. This was based on the condition that any increase in lead concentration in blood should be avoided. This approach was chosen because in many urban areas no margin of safety exists between lead concentrations in blood and the level of 50 µg/litre (this level even is exceeded in many situations). The derivation of this PTWI was based on metabolism studies in infants and children in which mean daily intakes of 3-4 µg/kg bw of lead by infants and children were not associated with an increase in blood lead levels. At the slightly higher intake level of 5 µg/kg bw/day children are in positive balance for lead retention, JECFA points out, also noting that the net absorption of dietary lead at this level averages 40% of the lead intake, with the net retention estimated to be about 30% of intake. Metabolic studies indicate a negative balance when lead intake is less than 4 µg/kg bw/day. By cumulating the mean daily intake of 3-4 µg/kg bw over a week the PTWI was obtained specifically for children (JECFA, 1986). In 1993 JECFA extended this PTWI to adults because of the sensitivity of the developing fetus (JECFA, 1993). RIVM (1997, 2001) has adopted the JECFA approach. Expressed as a daily dose the PTWI equals 3.6 µg/kg bw (RIVM, 2001).

ATSDR (2005) has not derived limit values for lead due to lack of a clear threshold for the critical effect and considered a case by case approach more appropriate (site-specific risk assessment for lead as soil contaminant).

OEHHA (1997) derived a ‘level of concern’ for lead neurotoxicity in children aged 1-2 years, using a blood level of 100 µg/litre as the point of departure. This blood level was calculated to be associated with an intake of 28.6 µg/day and subsequently an uncertainty factor of 3 was applied. For a 10 kg child this approach implies a tolerable level of about 0.9 µg/kg bw/day.

II.10.7 Conclusion

The value of 3.6 µg/kg bw/day as proposed by JECFA (1986, 1993) and RIVM (2001) is chosen as the appropriate value for toy-related exposures.

As to possible adverse direct dermal effects, no conclusion is possible due to lack of data. However, lead’s former wide use in water transport without attendant of adverse skin effects, suggests the potential to induce these effects is low.

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II.11 Manganese

The oral toxicity of manganese and its compounds was reviewed by WHO (1996), US-EPA (1996), IPCS (1999) and ATSDR (2000). The former Scientific Committee of the EU evaluated manganese as a food mineral (derivation of Upper Intake Level) in 2000.

II.11.1 Normal exposure

Manganese is ubiquitous in the environment, occurring in soil, air, water, and food. Thus, all humans are exposed to manganese and manganese is a normal component of the human body. Food is usually the most important route of exposure for humans. The dietary intake of adults has been estimated to range from 0.9 to 9.4 mg Mn/day in various countries (SCF, 2000). The intake can be higher for vegetarians because higher levels of manganese occur in food of plant origin. The consumption of tea may contribute substantially.

Children are exposed to manganese in the same manner as adults, the main source of exposure being food. Specific data for intake by this group, however, are not available (ATSDR, 2000).

Based on the above information background daily intake of manganese for a child is estimated to be 130 μg/kg bw/day. This is the adult intake calculated from the maximum of the reported range of food intakes (9.4 mg/day), assuming a body weight of 70 kg.

II.11.2 Toxicology

In humans manganese is an essential nutrient that plays a role in bone mineralization, protein and energy metabolism, metabolic regulation, cellular protection from damaging free radical species, and the formation of glycosaminoglycans. As is pointed in SCF (2000), no formal Recommended Dietary Allowance (RDA) for manganese is available. However, 2-5 mg/day for adults has been derived as an ‘estimated safe and adequate dietary intake’ by the US National Research Council. In 1993 the EU Scientific Committee for Food estimated 1-10 mg/day as an acceptable range of intakes.

Occupational studies have shown neurological effects after inhalation exposure to manganese. These neurological effects have been observed following exposure durations that span from 1 to 35 years. The characteristic syndrome is known as “manganism”. Symptoms are weakness, anorexia, muscle pain, apathy, slow speech without inflection, emotionless “mask-like” facial expression, and slow clumsy movement of the limbs. In general, these effects are irreversible. The minimal exposure level producing neurological effects is not certain but is probably in the range of 0.1-1 mg/m^3 (WHO, 1996). Several human studies with exposure via drinking-water suggest that ingestion of manganese can also lead to neurological effects. A study by Kondakis et al. (1989) carried out in Northern Greece, found

higher prevalences of neurological signs of chronic manganese poisoning and increased manganese concentration in the hair of older persons. In this study however there was simultaneous exposure to manganese via food, which was presumably high but the exact magnitude is unknown. Overall no oral NOAEL of LOAEL could be derived for manganese neurotoxicity in humans. Oral animal data are also insufficient for an NOAEL or LOAEL. The latter was the conclusion reached by SCF (2000).

II.11.3 Children as a sensitive subgroup

Children as a group have not been studied for the adverse effects of overexposure to inorganic manganese. Thus no estimation of the quantitative susceptibility of children to the preclinical effects of excess manganese exposure is possible (ATSDR, 2000).

II.11.4 Local effects upon dermal contact

No toxicity data are available for the dermal exposure route (ATSDR, 2000).

II.11.5 Absorption

According to ATSDR (2000) the amount of manganese absorbed across the gastrointestinal tract in humans is variable but typically averages about 3–5%. Limited human and animal data suggest that children/young animals may have a somewhat higher absorption of manganese than adults. Quantification of this potential difference is however not possible.

II.11.6 Toxicological limit values for ingestion of manganese

SCF (2000) concluded that the available data indicate manganese is neurotoxic after oral intake despite its poor absorption in the gastrointestinal tract. However, the limitations of the human data and the non-availability of NOAELs for critical endpoints from animal studies preclude derivation of an upper level (UL).

US-EPA (1996) noted the limited data set for the oral route. Rodents were concluded not to provide a good experimental model for manganese toxicity. In its derivation of an RfD US-EPA therefore focussed on what is known to be a safe oral intake of manganese for the general human population. Based on estimates of ‘safe and adequate manganese intake levels’ by US organisations and measured levels of normal dietary intake US-EPA concluded that 10 mg/day (0.14 mg/kg bw/day) is an appropriate Reference Dose for manganese. Similarly ATSDR (2000) adopted a US estimate of 5 mg/day (0.07 mg/kg bw/day) as the ‘safe and adequate daily dietary intake’ as its provisional chronic oral MRL for manganese.

OEHHA (2004) in its draft derivation of a Reference Dose for manganese specifically for children (ChRD) developed several approaches. Using an estimate by the US Food and Nutrition Board of an NOAEL for manganese of 11 mg/day for an adult and subtracting from this level a normal mid-range dietary intake of 5 mg/day led to non-dietary NOAEL of

6 mg/day or 0.086 mg/kg bw/day (assumed body weight 70 kg). To this NOAEL then an uncertainty factor of 3 was applied for the protection of infants and children yielding a ChRD of 0.03 mg/kg bw/day. Alternative calculations were based on neurotoxic endpoints as determined in two studies in neonatal rats (increased acoustic startle response; righting, homing, and passive avoidance tests). This involved using a LOAEL of 11 mg/kg bw/day, based on which a possible ChRD of 0.01 mg/kg bw/day was calculated (uncertainty factor 1000) and an NOAEL of 8.3 mg/kg bw/day, based on which a possible ChRD of 0.08 mg/kg bw/day was calculated (uncertainty factor 100). In conclusion OEHHA proposed a value of 0.03 mg/kg bw/day. Given its derivation this ChRD refers to exposures above normal dietary intake.

II.11.7 Conclusion

The ChRD as proposed by OEHHA (2004) of 0.03 mg/kg bw/day is chosen as the best available value for toy-related exposures. Given its derivation this ChRD refers to exposures **above** normal dietary intake.

As to possible adverse direct dermal effects, no conclusion is possible due to lack of data.

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II.12 Mercury

On the toxicity of mercury and mercury compounds a large literature exists. Mercury occurs as a metal (element), as inorganic salt or as organic mercury (methylmercury). For toy-related exposures only inorganic forms are considered relevant. Inorganic mercury was evaluated within the scope of the WHO Drinking-water guidelines in 1996. RIVM (2001) and ATSDR (1999) also carried out evaluations, as did more recently IPCS (2003).

II.12.1 Normal exposure

Mercury is a naturally occurring element (around 80 µg/kg) in the Earth's crust. Elemental mercury may occur in both liquid and gaseous states. Inorganic mercury compounds include mercurous chloride, mercuric chloride, mercuric acetate, and mercuric sulfide. Major anthropogenic sources of mercury in the environment have been mining operations, industrial processes, combustion of fossil fuels (especially charcoal), production of cement, and incineration of municipal, chemical, and medical wastes. Dental amalgam fillings are the primary source of inorganic mercury exposure for the general population. Estimates of daily intake from amalgam restorations range from 1 to 27 µg/day, with the majority of dental amalgam holders being exposed to less than 5 µg Hg/day. Average additional daily intake of inorganic mercury was estimated at 4.3 µg/day (IPCS, 2003). In RIVM (2001) total background exposure to elemental mercury and inorganic mercury was estimated to be 0.1 µg/kg bw/day.

Based on the above information background daily intake of elemental mercury and inorganic mercury for a child is estimated to be 0.1 µg/kg bw/day (adult intake as presented by RIVM (2001) adopted).

II.12.2 Toxicology

As is pointed out in ATSDR (1999) the kidney is the primary site for mercuric ion toxicity because in fulfilling its major role of filtering and purifying the blood, the kidney is continually exposed to ionic mercury. For both elemental mercury and inorganic mercury renal toxicity has been observed in humans. Oral dose response data for humans however, are scarce, for which reason the risk assessment for this route has been based on animal data. For elemental mercury no oral data are available. Within the US-NTP mercuric chloride was tested in rats. In a 26-week study in rats renal toxicity was seen at ≥ 46 mg Hg/kg bw/day with an NOAEL of 0.23 mg Hg/kg bw/day. In a 2-year study in rats 1.9 mg Hg/kg bw/day was the LOAEL for renal toxicity (IPCS, 2003).

II.12.3 Children as a sensitive subgroup

On the effect of inorganic mercury in children or young animals no data are available (ATSDR, 1999).

II.12.4 Local effects upon dermal contact

Human case studies suggest that dermal contact with elemental mercury and mercuric salts may produce dermatitis. Dose response information for this possible effect, however, is lacking. No animal data are available for this endpoint. The skin-irritating potential of inorganic or metallic mercury is known insufficiently. Use of ointments in which the compounds were present has led to adverse, irritative skin reactions in some instances but the dose response for these effects remains unclarified (ATSDR, 1999).

II.12.5 Absorption

Absorption of inorganic mercuric salts may range from 2 to 38% depending upon the form and test conditions. Oral absorption of elemental mercury is negligible. Human data on absorption are scarce. In older animal studies only low absorption percentages were found for inorganic mercury (1-8.5%) but in more recent ones percentages were higher (25-40%). A study in mice indicated that young animals absorb considerably more (38% compared to 7% in adult animals) (ATSDR, 1999).

II.12.6 Toxicological limit values for ingestion of inorganic mercury

ATSDR (1999) derived an intermediate duration MRL of 0.002 mg Hg/kg bw/day oral exposure to inorganic mercury. No chronic MRL was derived due to lack of appropriate data. The intermediate MRL was based on the NOAEL of 0.23 mg Hg/kg bw/day for renal effects in rats from the NTP study already mentioned above. This dose was duration-adjusted for a 5 day/week exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

RIVM (2001) proposed a TDI of 0.002 mg Hg/kg bw/day, like ATSDR using the NOAEL of 0.23 mg Hg/kg bw/day for renal effects from the NTP study and also applying an uncertainty factor of 100. IPCS (2003) proposed the identical derivation as a tolerable intake.

II.12.7 Conclusion

The TDI of 0.002 mg Hg/kg bw/day as proposed by RIVM (2001) and IPCS (2003), is chosen as the appropriate value for toy-related exposures.

As to possible adverse direct dermal effects, qualitatively it is known that elemental mercury and mercury as salt may produce skin irritation and sensitization under certain conditions. Quantitative data on this effect are however lacking.

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II.13 Nickel

The toxicology of nickel and nickel compounds has been evaluated by WHO within its drinking-water programme (WHO, 1996). RIVM reviewed nickel as a soil contaminant in 2001. Comprehensive reviews are those by TERA (1999), ATSDR (2005) and by the EU (EU-RAR, 2005). US-EPA (1996), OEHHA (2001) and EFSA (2005) are further reviews specifically focussed on oral toxicity.

II.13.1 Normal exposure

Nickel and its compounds are naturally present in the Earth's crust, and releases to the atmosphere occur from natural discharges such as windblown dust and volcanic eruptions, as well as from anthropogenic activities. The latter are the dominant source for environmental release. The general population is exposed to low levels of nickel in ambient air, water, and food. Food is the most important source with drinking-water on average being ten times lower. Specific foods high in nickel content are cocoa and soybeans. EU-RAR (2005) gives an estimate for the total intake of nickel via food and drinking-water of 250 µg/day, based on UK data from 2003. Also mentioned is an estimate by the Council of Europe of 400 µg/day. Canadian data for children and adults indicate that nickel intake for children (3-12 years old) is twice that for adults on a body weight basis (EU-RAR, 2005). RIVM (2001) estimated an average adult intake of 4 µg/kg bw/day. This figure is in line with the estimates as presented in EU-RAR (2005).

An important consumer exposure to nickel is through skin contact with objects such as earrings, medallions, buttons, metal wires in clothing, wrist watches, rings etc. These exposures may lead to nickel dermatitis. The prevalence of nickel sensitivity in the population is about 8-14.5% for adult women and about 1% for men (WHO, 1996).

Based on the above information background daily intake of nickel for a child is estimated to be 8 µg/kg bw/day, which is twice the adult intake as presented by RIVM (2001).

II.13.2 Toxicology

Nickel is essential for the catalytic activity of some plant and bacterial enzymes but biochemical functions in humans and higher animals have not been demonstrated. Nickel compounds are recognized human carcinogens via the inhalation route (IARC Group I). For the oral route, however, such evidence is lacking. A recent 2-year study with nickel sulfate in rats (CRL, 2005) showed no carcinogenic response after oral (gavage) application. Genotoxicity data have shown effects at the chromosome level (aberrations, SCEs) occurring at high, toxic doses, most likely due to indirect mechanisms. In view of these data a threshold approach is warranted for the oral route, which conclusion is in line with RIVM (2001), EFSA (2005) and EU-RAR (2005)

In studies on subchronic toxicity, the main targets for the toxicity of orally ingested nickel salts are kidneys, spleen, lungs, and the myeloid system. These studies mostly were limited in design. In a 90-day study in rats by ABC (1988) with gavage administration of nickel chloride, clinical signs of toxicity were seen, body weights and weights of kidney, liver and spleen were reduced and mortality increased. The NOAEL in this study was 5 mg/kg bw/day. In a 2-year feeding study in rats by Ambrose et al. (1976) with elemental nickel decreased body weight was the critical effect with an NOAEL of 5 mg Ni/kg bw/day. This study, however, was flawed because of high mortality in all groups, including the control. In the new 2-year study in rats with nickel sulphate by CRL (2005), decreased body weight and increased mortality were the critical effects. The NOAEL in this study was 2.2. mg Ni/kg bw/day, it is concluded in EU-RAR (2005), while adding that uncertainty remains because the effects were present to a statistically non-significant degree at this level as well. EFSA (2005) notes that in a reproduction study in rats (Smith et al., 1993) with nickel chloride administration via drinking-water, peri-natal mortality was increased, even at the lowest administered dose of 1.3 mg Ni/kg bw/day. In the EU-RAR (2005) a similar effect is reported at 2.2 mg/kg bw/day in a 2-generation study in rats referred to as SLI (2000b) with gavage application of nickel sulphate. The NOAEL in this study was 1.1 mg Ni/kg bw/day.

In individuals suffering from dermal nickel allergy, oral intake of low doses can provoke eczema. This has been examined in a several oral challenge studies, in which single oral doses of a few mg nickel provoked dermal reactions in nickel-sensitised subjects. EFSA (2005) cites studies by Nielsen et al. (1990, 1999) who report lowest oral doses, given to nickel sensitive subjects and reported to exacerbate hand eczema, of 0.49 mg/day in a high nickel diet (equivalent to about 8 µg Ni/kg bw/day), and 12 µg/kg bw/day given in drinking water on an empty stomach.

II.13.3 Children as a sensitive subgroup

Only limited data are available. Some epidemiological surveys suggest young girls are more sensitive to nickel-induced dermatitis but most likely this just reflects increased exposure by this group. Further data are lacking (ATSDR, 2005).

II.13.4 Local effects upon dermal contact

A large literature exists on nickel induced dermatitis. The dose response for this effect has been examined in human experiments. Human studies on the threshold for *induction* of nickel dermatitis are not available. Indeed, such studies are contra-indicated for ethical reasons. Menné et al. (1987) found high elicitation percentages (56-81%) among a group of 173 nickel-sensitive subjects after exposure to alloys with release levels of 10 to 80 µg/cm^2/week. Studies with nickel sulfate have shown that even a very low patch exposure for 48 hours to 0.05 µg Ni/cm^2 may elicit a response in nickel-sensitive subjects (study by Uter et al. 1995). As is concluded in the EU-RAR for nickel, on the basis of the available

data it is not possible to set a scientifically based threshold for elicitation (NOEL) in nickel-sensitised subjects. The EU-RAR notes that Danish regulation limiting nickel release from objects in direct contact with skin to less than 0.5 μg Ni/cm^2/week, has resulted in a significant reduction of prevalence of nickel sensitisation. In addition data suggest that this release level is sufficient to prevent reactions in a significant proportion of nickel-sensitised subjects. But complete protection, the EU-RAR adds, for the most sensitive subjects may only be achieved at levels an order of magnitude lower than the limit of 0.5 μg Ni/cm^2/week (EU-RAR, 2005).

II.13.5 Absorption

The available evidence is reviewed in the EU-RAR (2005). Nickel absorption from the gastro-intestinal tract depends in part on the solubility of the nickel compound ingested, with insoluble forms having lower absorption. Poorly soluble compounds, however, may be more soluble in gastric juice and thus still be absorbed. More specific data on the latter point, however, are lacking. Another important factor is the matrix in which the compound is present. Uptake from water is higher than from food, especially under fasted conditions. Nickel absorption following administration in drinking-water to fasting subjects may be as high as 25-27% whereas it was 1-6% in non-fasted subjects and/or in close proximity with a meal. For fasting-conditions the EU-RAR concluded to an absorption percentage of 30% and for other exposure scenarios to a percentage 5% (EU-RAR, 2005).

II.13.6 Toxicological limit values for ingestion of nickel

US-EPA (1996) derived an RfD for soluble nickel compounds of 20 μg Ni/kg bw/day based on an NOAEL of 5 mg Ni/kg bw/day from the study by Ambrose et al. (1976). An uncertainty factor of 300 was applied, consisting of a factor of 10 for interspecies extrapolation, 10 to protect sensitive populations and an additional factor of 3 to account for inadequacies in the reproductive studies.

ATSDR (2005) derived no oral MRLs for nickel due to lack of appropriate data. EFSA (2005) derived no Tolerable Upper Intake Level for nickel because adequate dose response data on the effect of oral nickel in nickel-sensitised subjects was lacking. The Panel noted that oral intakes of nickel as low as about 8 μg/kg body weight/day have been reported to aggravate hand eczema in nickel-sensitised subjects.

RIVM (2001) proposed a TDI of 50 μg Ni/kg bw/day based on an NOAEL of 5 mg/kg bw/day from both a 90-day study in rats by ABC (1988) and the 2-year study by Ambrose et al. (1976). This NOAEL was divided by an uncertainty factor of 100 (10 for interspecies extrapolation and 10 for intraspecies extrapolation).

OEHHA (2001) identified the oral dose of 1.12 mg Ni/kg bw/day as the appropriate NOAEL for deriving its guideline value for drinking-water. This NOAEL was obtained from a

reproduction study by SLI (2000b). A total uncertainty factor of 1000 was used, including a factor of 10 for interspecies extrapolation, 10 for intra-species variability, and an additional 10 to account for the potential carcinogenicity of soluble nickel by the oral route. This derivation implies an oral limit value of 1.1 μg Ni/kg bw/day.

As already stated, a new 2-year study is available and its NOAEL is recommended in the EU-RAR (2005) for assessing repeated dose toxicity. This NOAEL was 2.2 mg Ni/kg bw/day. For developmental toxicity the EU-RAR (2005) concludes to an overall NOAEL of 1.1 mg/kg bw/day (LOAEL 2.2. mg/kg bw/day) derived from the rat 2-generation study by SLI (2000b). Using an uncertainty factor of 100 (10 for interspecies extrapolation and 10 for intra-species extrapolation), from the latter NOAEL a TDI of 10 μg Ni/kg bw/day can be derived.

II.13.7 Conclusion

For nickel a TDI of 10 μg Ni/kg bw/day is proposed based on the NOAEL of a recent 2-generation study in rats, as evaluated in the EU-RAR (2005).

As to possible adverse direct dermal effects, nickel is notorious for its potency to induce dermal contact allergy. For persons already sensitised very low doses may suffice for producing symptoms. Danish regulation limits nickel release from objects in direct contact with skin to less than 0.5 μg Ni/cm^2/week. This regulation has resulted in a significant reduction of prevalence of nickel sensitisation. The data suggest that this release level is sufficient to prevent reactions in a significant proportion of nickel-sensitised subjects. But for complete protection for the most sensitive subjects the limit may have to be an order of magnitude lower than the limit of 0.5 μg Ni/cm^2/week.

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II.14 Selenium

Selenium and selenium compounds have been evaluated within the scope of the WHO Drinking-water guidelines in 1996. Another evaluation is by SCF (2000), which committee derived a Tolerable Upper Intake Level for selenium. RIVM, within the project for soil intervention values, evaluated selenium in 1998 (RIVM, 1998). Further reviews were published by US-EPA (1991) and US-ATSDR (2003).

II.14.1 Normal exposure

Selenium is present in the earth's crust often in association with sulfur-containing minerals. It can assume four oxidation states (-2, 0, +4, +6) and occurs in many forms, including elemental selenium, selenites and selenates. The principal releases of selenium into the environment as a consequence of human activities result from the combustion of coal. For the general population food is the primary exposure route followed by water and air. The greatest portion of dietary intake occurs from organic forms of selenium, mainly the amino acids selenomethionine and selencysteine, in grains, cereals, and forage crops. The main inorganic sources of selenium in the diet are selenate and selenite, which are less absorbed than the organic forms (ATSDR, 2003).

EFSA (2000) gives an overview of daily intake levels in European countries. The mean intakes of non-vegetarian adults in different studies were: Belgium 28-61 µg/day, Denmark 41-57 µg/day, Finland 100-110 µg/day, France 29-43 µg/day, United Kingdom 63 µg/day, The Netherlands 40-54 µg/day, Norway 28-89, and µg/day, Spain 79 µg/day, and Sweden 24-35 µg/day (SCF 2000). These data indicate daily intake levels up to about 1 µg/kg bw/day. Results from a dietary intake study carried out in the USA indicate that children up to age 6 years have almost twice the intake of adults on a body weight basis (ATSDR, 2003). Levels of selenium in tap water samples from public water supplies around the world are usually much less than 10 µg/litre. Drinking-water from a high-selenium area in China was reported to contain 50-160 µg/litre. In air the level of selenium (mostly bound to particles) in most urban areas ranges from 0.1 to 10 ng/m^3, but higher levels may be found in certain areas, e.g. in the vicinity of copper smelters (WHO, 1996).

European data as summarised by SCF (2000) indicate a mean adult daily intake of 1 µg/kg bw/day. For children twice this figure should be a reasonable estimate, i.e. 2 µg/kg bw/day.

II.15 Toxicology

Being part of several enzymes, selenium is an essential element in humans and animals. Estimated daily requirements as summarised in SCF (2000) range from 40 to about 50 µg/day for adults with a lower limit of 20 µg/day.

Acute oral exposure to extremely high levels of selenium (e.g., several thousand times more than normal daily intake) produces nausea, vomiting, and diarrhea in both humans and laboratory animals. Acute oral exposure of humans to selenium has occasionally caused cardiovascular symptoms, such as tachycardia, but no electrocardiographic abnormalities were found in individuals from a human population chronically exposed to selenium. In laboratory animals, acute- and intermediate-duration oral exposure to very large amounts of selenium (approximately 100 times normal human intake) has produced myocardial degeneration in laboratory animals. In certain areas with high natural levels of selenium (selenoferous areas) chronic oral intake of very high levels (10–20 times more than normal) via food and water occurs, leading to selenosis, the major effects of which are dermal and neurological. As shown by affected populations in China, chronic dietary exposure to these excess levels of selenium has caused diseased nails and skin and hair loss, as well neurological problems, including unsteady gait and paralysis. Dose response information for this effect comes form several Chinese studies published from 1989 through 1994. The minimum daily dietary intake sufficient to cause symptoms of selenosis (i.e., hair or nail loss, nail abnormalities, mottled teeth, skin lesions and changes in peripheral nerves) was about 1200 µg Se (range: 913-1907 µg Se). No clinical signs of selenosis were recorded in individuals with blood selenium below 1000 µg/l, corresponding to an intake of about 850 µg/day, which has been taken as a NOAEL for clinical selenosis. Slight increases in prothrombin-time and in the liver enzyme ALAT, indicating liver damage, have also been observed in some selenium exposed populations but the clinical significance of these findings remains unclear (SCF, 2000).

As to its carcinogenic potential IARC concluded there was inadequate evidence for classification. Evidence suggests that some forms of selunium exert a anti-tumorigenic action in animals and humans. Selenium sulfide however appears an exception, producing increased tumor incidences after oral administration. The relevance of this compound for toy-related exposures seems limited. In genotoxicity tests selenium compounds have shown both genotoxic and anti-genotoxic effects. Generally the genotoxic effects were observed at high dosages and the anti-genotoxic at low dosages (RIVM, 1998).

II.15.1 Children as a sensitive subgroup

Limited data in humans suggest than children may be less sensitive for selenium toxicity than adults (ATSDR, 2003).

II.15.2 Local effects upon dermal contact

Limited data suggest that selenium and compounds have only low potential for inducing irritation and sensitisation (ATSDR, 2003).

II.15.3 Absorption

Selenium compounds are generally readily absorbed from the human gastrointestinal tract. The physical state of the compound (e.g., solid or solution) the chemical form of selenium (e.g., organic, inorganic), and the dosing regimen are factors influencing absorption. Generally absorption percentages of 80% and higher have been observed in human volunteers (ATSDR, 2003).

II.15.4 Toxicological limit values for ingestion of selenium

US-EPA (1991) used a Chinese epidemiological study by Yang et al. (1989) for deriving a human NOAEL for selenosis. The LOAEL derived from this study was 1.26 mg Se/day and the NOAEL 0.85 mg/day (0.015 mg/kg bw/day). An uncertainty factor of 3 to account for sensitive individuals was applied, leading to an RfD of 5 μg/kg bw/day.

RIVM (1998) concurred with the approach developed by US-EPA. Thus a TDI of 5 μg/kg bw/day was proposed. ATSDR (2003), like US-EPA, concluded to an NOAEL from the Chinese studies of 0.015 mg/kg bw/day. With an uncertainty factor of 3 a chronic MRL of 0.005 mg/kg bw/day was proposed (ATSDR, 2003).

SCF (2000) also used an NOAEL of 0.85 mg/day as derived from the Chinese epidemiology studies. It was pointed out that other studies from the USA and Venezuela supported this NOAEL. Application of an uncertainty factor of 3 to allow for the remaining uncertainties of the studies used led to Tolerable Upper Intake Level (UL) of 300 μg/day. No specific UL for children was derived because of lack of appropriate data.

II.15.5 Conclusion

The limit values as reviewed are in agreement. Thus a value of 5 μg/kg bw/day is chosen as the most appropriate value for toy-related exposures.

As to possible adverse direct dermal effects, the limited data available suggest that selenium and compounds have only low potential for inducing irritation and sensitisation

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II.16 Silver

The oral toxicity of silver and its compounds has been reviewed by ATSDR (1990), RIVM (1995), and WHO (1996).

II.16.1 Normal exposure

Silver is a rare element, which occurs naturally in its pure form as a white, ductile metal, and in ores. It has an average abundance of about 0.1 ppm in the earth's crust and about 0.3 ppm in soils.
US data indicate that food and drinking-water are the major sources of exposure, totalling an estimated 0.06-1.3 μg/kg bw/day (RIVM, 1995). Data specifically for children are lacking.

Based on the above information background daily intake of silver for a child is estimated to be 1.3 μg/kg bw/day. This the maximum of the adult range as estimated by RIVM (1995).

II.16.2 Toxicology

In animal studies toxic effects were seen at high dose levels only (> 90 mg/kg bw/day). In humans the critical effect is argyria, a medically benign but permanent bluish-gray discoloration of the skin. Argyria results from the deposition of silver in the dermis and also from silver-induced production of melanin. Although silver has been shown to be uniformly deposited in exposed and unexposed areas, the increased pigmentation becomes more pronounced in areas exposed to sunlight due to photoactivated reduction of the metal. Although the deposition of silver is permanent, it is not associated with any adverse health effects. No pathologic changes or inflammatory reactions have been shown to result from silver deposition.

Silver compounds have been employed for medical uses for centuries. In the nineteenth and early twentieth centuries, silver arsphenamine was used in the treatment of syphillis; more recently it has been used as an astringent in topical preparations. From a case review concerning intravenous use of silver arsphenamine in syphilis patients US-EPA (1995) concluded to a LOAEL for mild argyria of 0.014 mg/kg bw/day[7] for this sensitive subpopulation.

[7] This derivation was based on:
- the body accumulates silver throughout life
- a total intravenous dose of 1 g silver (4 g silver arsphenamine) will cause mild argyria in the most sensitive individuals
- an oral absorption factor of 4% to calculate the oral dose equivalent to the i.v. dose of 1 g
- the total dose is averaged over a lifetime of 70 years

II.16.3 Children as a sensitive subgroup

No data are available.

II.16.4 Local effects upon dermal contact

Medical case histories describe mild allergic responses attributed to dermal contact with silver and silver compounds. The exposure concentrations involved in these cases are unknown. Dermal contact with silver compounds may lead to local argyria; quantitative data on this effect (dose response relation) are lacking (ATSDR, 1990).

II.16.5 Absorption

Absorption of silver was examined in four animal species and was found to be very low. From this study 4.4% was derived as a conservative estimate for absorption of silver in human after ingestion (US-EPA, 1996).

II.16.6 Toxicological limit values for ingestion of zinc

US-EPA (1996) derived an RfD of 0.005 mg/kg bw/day by dividing the LOAEL for mild argyria of 0.014 mg/kg bw/day by a factor of 3 (modifying factor). A higher factor was considered unwarranted given the non-adverse nature of the critical effect and the fact that the study was done in a sensitive subpopulation. This approach was adopted by RIVM (1995), leading to a TDI of 0.005 mg/kg bw/day.

II.16.7 Conclusion

The RfD 0.005 mg/kg bw/day as proposed by US-EPA (1996) is chosen as the appropriate value for toy-related exposures.

As to possible adverse direct dermal effects, case reports indicate silver may produce allergic reactions and local argyria. The dose response relation for these effects is unknown. Despite these reports of adverse effects, the fact that humans are widely exposed to silver in jewelry without this leading to a high prevalence of medical complaints, suggests that the risk for dermal effects is low.

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II.17 Strontium

The oral toxicity of strontium and its compounds has been reviewed by RIVM (1989), US-EPA (1996) and ATSDR (2004).

II.17.1 Normal exposure

Strontium is ubiquitous in the environment and is present in nearly all rocks and soils. Chemically it resembles calcium. Food and drinking-water are the main sources of background exposure. Dutch data indicate a mean total daily intake of 1.3 mg/person (maximum 3.6 mg/person) (RIVM, 1998). Similar levels were reported for the USA and Australia. Data specifically for children are lacking.

Based on the above information background daily intake of strontium for a child is estimated to be 18 μg/kg bw/day. This the maximum of the mean adult range as reported in RIVM (1998).

II.17.2 Toxicology

Strontium is able replace calcium in its physiological role and accordingly is incorporated in bone tissue. Abnormal skeletal development is the most important toxicological effect produced by strontium. Usable human toxicity data are lacking. Skeletal abnormalities were observed in weanling rats after 20 days of dosing with 550 mg Sr/kg bw/day (LOAEL). The NOAEL in weanling rats was 140 mg/kg bw/day. In adult rats the NOAEL was 690 mg/kg bw/day in the same study (ATSDR, 2004).

II.17.3 Children as a sensitive subgroup

Animal data clearly show young animals to be more sensitive to strontium toxicity than adult animals (see above). Human data on this point are very scarce. Because the immature skeleton has a high rate of bone remodeling, and strontium adversely affects bone development children must be expected to indeed be at increased risk.

II.17.4 Local effects upon dermal contact

No data are available (ATSDR, 2004).

II.17.5 Absorption

Absorption of strontium was examined in a number of human volunteer studies. The results of these studies indicate that approximately 20% (range 11–28%) of ingested strontium is absorbed from the gastrointestinal tract.

II.17.6 Toxicological limit values for ingestion of strontium

Based on an NOAEL of 140 mg/kg bw/day in weanling rats, ATSDR (2004) proposed an intermediate MRL of 2 mg/kg bw/day. In this derivation an uncertainty factor of 90 was applied (10 for extrapolation from animal to human and 3 for human variability, 3 for short study duration and limited endpoint examination). A partial uncertainty factor was used to account for human variability because the selected NOAEL was based on the response of juveniles, which is also the most sensitive human group. ATSDR derived no chronic MRL because appropriate data were lacking. Based on the same study US-EPA proposed an RfD of 0.6 mg/kg bw/day (US-EPA, 1996). They applied a total uncertainty factor of 300 (10 for interspecies extrapolation, 10 for an incomplete database, including a lack of developmental and reproductive data, 3 for for sensitive subpopulations). Again a low intra-species factor was used because the NOAEL was for a sensitive subgroup.

II.17.7 Conclusion

The RfD 0.6 mg/kg bw/day as proposed by US-EPA (1996) is chosen as an appropriate value for toy-related exposures.

As to possible adverse direct dermal effects, no conclusion is possible due to lack of data.

References

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II.18 Tin (inorganic)

The oral toxicity of inorganic tin and compounds has been reviewed by RIVM (1991), WHO/JECFA (1982, 1989, 2001), IPCS (2005), EFSA (2005) and ATSDR (2005).

II.18.1 Normal exposure

Tin occurs naturally in the earth's crust with a concentration of approximately 2–3 ppm. The major source of human exposure is through migration from tin cans to foods. Within the European Union $SnCl_2$ is a permitted food additive (E512) for bottled and canned white asparagus.

Data on mean inorganic tin intake from food for the populations of seven countries (Australia, France, Japan, Netherlands, New Zealand, the United Kingdom, and the USA) indicate intakes ranging from < 1 up to 15 mg/person per day. Certain individuals who routinely consume canned fruits, vegetables, and juices from unlacquered cans could ingest up to 50–60 mg of tin daily (IPCS, 2005). Specifically for children JECFA (2001) cites a UK study of 97 pre-school children (age 1.75–2.2 years) in which average daily intakes of 1.7-2.9 mg/day were found. Intake showed strong correlation with consumption of canned foods. An Australian study among two-year-olds showed a mean intake of 1.3 mg/day (JECFA, 2001).

Based on the above information background daily intake of inorganic tin for a child is estimated to be 290 μg/kg bw/day. This figure is calculated from the maximum mean of 2.9 mg/day of the range for young children as reported in JECFA (2001), assuming a child body weight of 10 kg.

II.18.2 Toxicology

Tin has not been shown to be essential for humans or animals, and there are no data on deficiency effects resulting from an inadequate intake of inorganic tin. Inorganic tin has a low systemic toxic potential due to its low absorption in the gastrointestinal tract. The only effect in humans is acute irritation of the mucosa of the gastrointestinal tract (no known chronic effects). This was seen in consumers drinking fruit juices containing high concentrations of tin (≥ about 200 mg/kg product). In experimental animals anemia, liver and kidney damage have been observed. In a sub-chronic feeding study in rats the NOAEL was 32 mg/kg bw/day. In a chronic feeding study in rats the NOAEL was 400 mg/kg diet (equivalent to 20 mg/kg bw/day).

II.18.3 Children as a sensitive subgroup

No data are available.

II.18.4 Local effects upon dermal contact

No data are available (ATSDR, 2005).

II.18.5 Absorption

The absorption of inorganic compounds of tin from the gastrointestinal tract in humans and animals is very low with as much as 98% being excreted directly in the faeces (EFSA, 2005).

II.18.6 Toxicological limit values for ingestion of strontium

Based on the level of 200 mg/kg in food as the approximate threshold for adverse gastrointestinal effects in humans JECFA (1982) proposed a TDI of 2 mg/kg bw/day, a value maintained in its later evaluations (JECFA, 1989, 2001). RIVM adopted this TDI in 1991.

Based on an NOAEL of 32 mg/kg bw/day from a subchronic feeding study in rats, ATSDR (2003) proposed an intermediate MRL of 0.3 mg/kg bw/day. In this derivation an uncertainty factor of 100 (10 for animal to human extrapolation and 10 for human variability) was applied. ATSDR derived no chronic MRL because appropriate data were lacking.

EFSA (2005) noted that because of their limited absorption, orally ingested inorganic tin compounds have low systemic toxicity in man and animals but concluded the available evidence was insufficient for deriving an Upper Level for inorganic tin.

II.18.7 Conclusion

The JECFA (2001) TDI of 2 mg/kg bw/day is chosen as the appropriate value for toy-related exposures.

As to possible adverse direct dermal effects, no conclusion is possible due to lack of data.

References

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II.19 Tin (organic)

The oral toxicity of organic tin compounds has been evaluated by EFSA recently (EFSA 2004). Other reviews are those by JMPR (1992), US-EPA (1997), IPCS (1999) and RIVM (1999).

II.19.1 Normal exposure

Organotin compounds are manmade chemicals used for several applications. The tri-substituted compounds tributyltin (TBT) and triphenyltin (TPT) have been used extensively as biocides in wood preservatives, in antifouling paints for boats and as pesticides. Mono-and di-substituted compounds like monomethyltin (MMT), dimethyltin (DMT), dibutyltin (DBT), mono-n-octyltin (MOT) and di-n-octyltin (DOT) are used in mixtures in various amounts as PVC stabilizers, which use includes food contact materials. Organotins are lipophilic contaminants sparingly soluble in water and easily adsorbed to particulate matter in the aquatic environment. Hence, they accumulate in sediments where they are relatively persistent and can be taken up by benthic organisms such as clams. Organotins tend to accumulate in fish and other aquatic organisms. Because of their adverse effects on the aquatic ecosystem the use of TBT and TPT as biocides in antifouling paints for boats has been restricted (EFSA, 2004).

Food is the major source of human exposure to organotins. EFSA (2004) summarizes data on dietary exposure from eight European Countries (Belgium, Denmark, Germany, France, Italy, Netherlands, Greek and Norway). Fish and seafood are the primary sources of exposure. Using the high mean fish/seafood consumption levels of 80 grams/day as prevalent in Norway as a conservative paradigm, in combination with the *median* international concentrations of TBT, DBT, and TPT, a total daily intake of 0.018 µg/kg bw/day was calculated. When *mean* international concentrations were used, the calculated intake was 0.083 µg/kg bw/day. For the 95 percentile for fish/seafood consumption by Norwegians of 165 grams/day combined with the *median* international concentrations of TBT, DBT, and TPT the total intake of organotins was 0.037 µg/kg bw/day. The same with the *mean* international concentrations of TBT, DBT, and TPT led to 0.17 µg/kg bw/day. For high fish/seafood consumers from Norway, consuming products in the high range of organotin concentrations (95-percentile), an intake of 0.30 µg/kg bw/day was calculated.

Based on the above information background daily intake of organic tin for a child is estimated to be 0.083 µg/kg bw/day. This is the mean calculated for adults in Norway as the EU country with highest fish consumption.

II.19.2 Toxicology

The toxicity of organotins has been studied in numerous animal studies. TBT and TPT have the largest data bases; DOT was also studied in a range of toxicity tests. Both tumorigenicity, developmental and reproductive toxicity and neurotoxicity were observed consistently in various studies but the critical endpoint for TBT, DBT, TPT and DOT was their immunotoxicity. These compounds produce thymus atrophy with lymphocyte depletion in the thymus, spleen and peripheral lymphoid tissues, decreases in immunoglobulin concentrations, lymphopenia and decrease in white blood cells in rodents. This results in depression of thymus dependent immunity. *In vitro* studies with human thymocytes indicate that these cells are sensitive to organotins. Mechanistic data indicate a similar mode of action for the different organotins. Based on this the effects of organotins can be considered additive. As to potency the available results indicate equipotency of the various organotins. An overall NOAEL of 0.025 mg/kg bw/day was derived from a chronic rat study with TBTO in which reduced resistance to *T. spiralis* infection was the critical effect. In this study weanling rats were dosed for 4-6 or 15-17 months. The same NOAEL was observed in a 2-year study in rats carried out by the same laboratory (EFSA, 2004).

II.19.3 Children as a sensitive subgroup

As is pointed out in US-EPA (1997), rat data indicate young animals are more susceptible to TBT immunotoxicity. The overall NOAEL, however, already includes this factor because it stems from a study using weanling rats.

II.19.4 Local effects upon dermal contact

TBTO is an irritant of the eyes and skin in experimental animals. These effects were observed at concentrations of ≥0.5% (skin) and 0.15% (eyes). A NOAEL for these endpoints is lacking. In human beings, TBTO may cause severe dermatitis after direct skin contact (conclusion based on *case studies*). This reaction has a delayed character, i.e. the symptoms develop only several hours after the start of contact. The dose-effect relation for this effect is unknown. The lowest effect concentration reported is 0.01 g/litre (value derived from a *case study*). A NOAEL for this endpoint is lacking. The observed dermatitis is probably not a hypersensitivity response. No effect was seen in a standard test for dermal sensitization in guinea pigs with tributyltinoxide. Triphenyltin was tested in guinea pigs as the hydroxide with a negative result but in a guinea pig study with the acetate a sensitising response occurred. In skin irritation tests triphenyltin showed only a mild response at high concentrations (RIVM, 2000).

II.19.5 Absorption

Human data are lacking. In rat studies with TBT, TPT and DOT absorption after oral administration ranged form 20 to 55% (EFSA, 2004).

II.19.6 Toxicological limit values for ingestion of organotins

Based on the overall NOAEL for organotins of 0.025 mg/kg bw/day EFSA (2005) proposed a group-TDI of 0.25 µg/kg bw/day. An uncertainty factor of 100 for interspecies and interindividual variation was used in this derivation. US-EPA (1997) calculated a Benchmark Dose (BMD) for 10% effect of 0.03 mg/kg bw/day from the same study as used by EFSA (2004). This level was divided by a factor of 100 (10 for extrapolation form animals to humans and 10 to protect sensitive humans) leading to RfD of 0.3 µg/kg bw/day.

II.19.7 Conclusion

The EFSA (2004) group-TDI for organotins of 0.25 µg/kg bw/day is chosen as the appropriate value for toy-related exposures.

As to possible adverse direct dermal effects, some organotins are known as powerful dermal irritants, producing dermatitis as a delayed reaction to dermal exposure (non-sensitizing reaction). The dose-effect relation for this effect however is insufficiently known. The lowest effect concentration reported is 0.01 g/litre (value derived from a *case study*). Other organotins may pose a sensitisation risk, animal bioassay data indicate. Again the dose-response relation for this effect has not been characterized.

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II.20 Zinc

The oral toxicity of zinc and its compounds has been reviewed by WHO (1996), IPCS (2001), US-EPA (2005) and ATSDR (2005). The former Scientific Committee of the EU evaluated zinc as a food mineral (derivation of Upper Intake Level) in 2003.

II.20.1 Normal exposure

Zinc is ubiquitous in the environment, constituting 20–200 ppm (by weight) of the earth's crust. Food is the most important route of exposure for humans. SCF (2003) summarizes available data on dietary intakes in European countries. Mean values ranged from 7.5 to 12.1 mg/day (97.5 percentiles 13.6-23.5 mg/day). US data as cited by ATSDR (2005) indicate that on a body weight basis children will ingest 2-3 times the adult amount.

Based on the above information background daily intake of zinc for a child is estimated to be 350 μg/kg bw/day. This is twice the adult intake as calculated from the maximum of the reported range of mean food intakes (12.1 mg/day), assuming a body weight of 70 kg.

II.20.2 Toxicology

Zinc is an essential element for humans, as co-factor in enzymes playing a role in general growth and development, in testicular maturation, neurological function, wound healing and immunocompetence. Well-known zinc containing enzymes include superoxide dismutase, alkaline phosphatase and alcohol dehydrogenase. Recommended dietary allowances as proposed by the SCF in 1993 is 9.5 mg/day for adult males and 7.0 mg/day for females. US guidelines recommend daily intakes of 11 mg/day and 8 mg/day for men and women respectively (SCF, 2003). On a body weight basis US guidelines are somewhat higher in young children (0.23 mg/kg bw/day versus 0.13-0.15 in adults) (US-EPA, 2005).

Zinc can be toxic when exposures exceed physiological needs. The effects of zinc supplementation have been studied in several human studies of longer duration. As is concluded by SCF (2003), chronic zinc toxicity is associated with symptoms of copper deficiency. Overt adverse effects (e.g. anaemia, neutropaenia, impaired immune responses) are evident only after feeding zinc in the form of dietary supplements in excess of 150 mg/day for long periods. At lower intake levels of 100-150 mg/day the picture is less clear. Short-term balance studies, SCF points out, would indicate adverse effects on copper retention at intakes as low as 18.2 mg/day but more recent longer-term balance studies indicate that positive copper balance can be maintained at 53 mg/day zinc in post-menopausal women for 90 days provided copper intakes are adequately high (3 mg/day). Overall the data indicate an NOAEL of 50 mg/day for adults, SCF concludes.

II.20.3 Children as a sensitive subgroup

Infants, more than adults, appear to be particularly sensitive to zinc deficiency, possibly the result of their higher zinc requirements on a per body weight basis. For toxic effects data are limited to a few animals studies indicating young animals are more susceptible to excess intake of zinc (no usable human data) (ATSDR, 2005).

II.20.4 Local effects upon dermal contact

At high concentrations inorganic zinc compounds are irritating to the skin. Zinc oxide however is used to promote the healing of burns and wounds and is a well-known anti-inflammatory agent used in creams for dermal care of babies and infants.

II.20.5 Absorption

Absorption of dietary zinc ranges from 15 to 60%. When zinc intake is increased, the fractional absorption decreases and intestinal excretion increases while urinary losses remain fairly constant. Under fasted conditions absorption was measured to be as high as 81%. When humans are under-supplied in zinc absorption may be higher still. Zinc appears to be absorbed by both passive diffusion and a saturable carrier-mediated process. The carrier-mediated mechanism appears to be most important at low zinc levels (SCF, 2003; US-EPA, 2005).

II.20.6 Toxicological limit values for ingestion of zinc

SCF (2003) concluded to an NOAEL of 50 mg/day based on the absence of any adverse effects on a wide range of relevant indicators of copper status (as the critical endpoint) in human studies. An UF of 2 was applied because of the small number of subjects included in relatively short-term studies but acknowledging the rigidly controlled metabolic experimental conditions employed. Thus an UL of 25 mg/day was recommended. Extrapolated to a 1-3 year old an UL of 7 mg/day was recommended. The later figure equals about 0.5 mg/kg bw/day (body weight 15 kg).

Similarly to SCF, US-EPA (2005) concluded that available data indicate that the most sensitive effects of zinc are alterations in copper status. Based on four human studies a mean NOAEL of 0.91 mg/kg bw/day was calculated. A threefold intraspecies uncertainty factor was applied to account for variability in susceptibility in human populations, giving an RfD for zinc of 0.3 mg/kg bw/day.

ATSDR (2005) presented a similar approach as US-EPA (2005). Thus a chronic MRL of 0.3 mg/kg bw/day was derived.

II.20.7 Conclusion

The UL of 0.5 mg/kg bw/day as proposed by SCF (2003) is chosen as the appropriate value for toy-related exposures.

As to possible adverse direct dermal effects, zinc compounds may irritating to skin at high concentrations but the wide use of zinc oxide as an anti-inflammatory agent in dermal care products for babies without side effects being reported, indicates a low risk for this endpoint.

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III Current definitions and EU legislations on toys

Within the EU, regulations on toys are harmonized, based on Council Directive 88/378/EEC on the approximation of the laws of Member States concerning the safety of toys.
According to these regulations, toys must not contain dangerous chemical substances or preparations within the meaning of EU Council Directive 67/548/EEC and 88/379/EEC in amounts which may harm the health of children using them. Furthermore, bioavailability limits have been set for 8 elements: antimony, arsenic, barium, cadmium, chromium, lead, mercury, selenium.
Additional restrictions on the use of substances in toys are specified in adaptations to Council Directive 76/769/EEC on the approximation of the laws, regulations and administrative provisions of the Member States relating to restrictions on the marketing and use of certain dangerous substances and preparations, such as the adaptations regulating the use of phthalates (2005/84/EC) and azo-colorants (2004/21/EC).

A definition of toy and toy material is needed to identify products for which limits for elements need to be established.
The definition for 'toy' used in Council Directive 88/378/EEC is as follows:

"Any product or material designed or clearly intended for use in play by children of less than 14 years of age"

Annex I of Directive 88/378/EEC provides a list of articles that are not regarded as toys:
1. Christmas decorations
2. Detailed scale models for adult collectors
3. Equipment intended to be used collectively in playgrounds
4. Sports equipment
5. Aquatic equipment intended to be used in deep water
6. Folk dolls and decorative dolls and other similar articles for adult collectors
7. 'Professional' toys installed in public places (shopping centres, stations, etc.)
8. Puzzles with more than 500 pieces or without picture, intended for specialists
9. Air guns and air pistols
10. Fireworks, including percussion caps ([1])
11. Slings and catapults
12. Sets of darts with metallic points
13. Electric ovens, irons or other functional products operated at a nominal voltage exceeding 24 volts
14. Products containing heating elements intended for use under the supervision of an adult in a teaching context
15. Vehicles with combustion engines
16. Toy steam engines

17. Bicycles designed for sport or for travel on the public highway
18. Video toys that can be connected to a video screen, operated at a nominal voltage exceeding 24 volts
19. Babies' dummies
20. Faithful reproductions of real fire arms
21. Fashion jewellery for children
([1]) With the exception of percussion caps specifically designed for use in toys without prejudice to more stringent provisions already existing in certain Member States.

NOTE: According to this list, jewellery for children is not considered a toy and as such does not need to comply with the European Standard for the Safety of Toys (EN 71). However, children's jewellery may be a relevant group of products for which exposure assessments for elements should be considered. Health Canada has recently proposed new Children's Jewellery Regulations under the Hazardous Products Acts because a large proportion of costume jewellery sold in North America today contains lead. Several cases of lead poisoning have been reported in the United States and Canada as a result of chewing or swallowing leaded pendants (Florin et al., 2005; VanArsdale et al., 2004). A recent study by Maas et al. (2005) found that many children's jewellery items sold in California retail stores contained high levels of lead, with an overall mean lead content of 27.4%.

IV Existing Toy Categories

IV.1 Basis of toy categories

To determine which categories are most appropriate for setting limits of substances such as elements in toys, the basis of a number of different toy categories used for international legislations and other purposes have been reviewed.

IV.2 Possible safety hazards

The Hazardous Products (Toys) Regulations of Health Canada employ toy categories that are based on specific toy types and their possible safety hazards. Specific product categories listed are: dolls and soft toys, pull and push toys, toy steam engines, finger paints, rattles, elastic and batteries.
This type of categorization is useful to determine which group of toys poses a possible toxic hazard, for example experimental chemistry sets. For elements in particular, however, very limited information is available on which toys contain which elements. No group of toys can therefore be identified as requiring special attention with regard to their potential toxic risk from the presence of elements.

IV.3 Toy material

The European Committee for Standardization (CEN) provides a European Standard for the Safety of toys (EN 71). In Part 3 of EN 71 (Migration of certain elements), toys are categorized according to the material they consist of, to determine the applicable test requirements for the migration of elements (European Committee for Standardization (CEN), 1994). The categories include:

- Coatings of paints, varnishes, lacquers, printing inks, polymers and similar coatings
- Polymeric and similar materials, including laminates, whether textile reinforced or not
- Paper and paper board
- Textiles (natural and synthetic)
- Other materials whether mass coloured or not (e.g. wood, leather and other porous substances)
- Materials intended to leave a trace (e.g. the graphite materials in pencils and liquid ink in pens)
- Pliable modelling materials, including modelling clays and gels
- Paints, including finger paints, varnishes, lacquers, glazing powders and similar materials in solid or in liquid form appearing as such in the toy.

Categorisation of toys based on material is useful if different materials need a different treatment with regard to the migration testing procedure. The tests required in the current standard are designed to simulate toy material remaining in contact with stomach acid for a period of time after swallowing. It should be noted that tests simulating exposure to elements via other routes than the oral route are not included in this standard. As will be discussed later, the dermal and the inhalation route may also be relevant routes of exposure to consider in the risk assessment of elements in toys, particularly with regard to sensitisation.

IV.4 Contact scenarios

The workgroup CEN/TC52/WG9 carried out a risk assessment of organic compounds in toys to ensure that the requirements for this standard were scientifically well-founded (European Committee for Standardization (CEN), 2003). For the risk assessment of organic compounds in toys, the following groups of toys were considered:

- Toys that might be sucked
- Toys or parts of toys that might be ingested
- Toys coming into contact with the skin
- Toys coming into contact with the mucous membranes
- Toys coming into contact with the eyes
- Toys containing volatile substances that could be inhaled

Based on these contact scenarios, it was concluded that the risks of organic chemicals in toys could be addressed by assessment of the following three contact routes: ingestion, skin contact and inhalation. The mucous membrane contact route was considered to be of minor significance. The eye contact route was considered not relevant, as any injury from toys would most likely be of a physical rather than a chemical nature.
The same contact scenario categories may apply to elements in toys, although elements are usually not in a volatile form. However, as explained in chapter 3 substances do not necessarily need to be in volatile form to be available for inhalation.

IV.5 Type of toy

In the final draft of Part 9 (Organic chemical compounds – requirements), the applicable migration or contact limits of organic chemical compounds depend on the type of toy and on the toy material. Types of toys distinguished are:

	SPECIFIC TOY/TOY COMPONENT	Toy material
1	Toys intended to be *mouthed* by children under 3 years of age	*POLYMERIC*[a]
2	Toys, or *accessible* toy components, with a mass of 150 g or less intended to be played with in the hands by children under 3 years of age	*POLYMERIC*[a]
3		*WOOD*
4		*PAPER*
5	Toys and *accessible* components of toys intended for children under 3 years of age	*TEXTILE*
6		LEATHER
7	Mouthpiece components of *mouth-actuated* toys	*POLYMERIC*[a]
8		*WOOD*
9		*PAPER*
10	Inflatable toys with a surface greater than 0,5 m^2 when fully inflated	*POLYMERIC*[a]
11	Toys worn over the mouth or nose	*POLYMERIC*[a]
12		*TEXTILE*
13		*PAPER*
14	Toys which the child can enter	*POLYMERIC*[a]
15		*TEXTILE*
16	Components of graphic instruments sold as toys or used in toys	*POLYMERIC*[a]
17	Toys and *accessible* components of toys for indoor use	WOOD
18	Toys and *accessible* components of toys for outdoor use	WOOD
19	Toys and components of toys which mimic food	*POLYMERIC*[a]
20	Solid toy materials intended to leave a trace	ALL
21	Coloured *accessible liquids* in toys	LIQUID
22	Non-coloured *accessible liquids* in toys	LIQUID
23	Modelling clay, play clay and similar, except those chemical toys addressed by EN 71-5	ALL
24	Balloon-making compounds	ALL
25	Imitation tattoos with adhesive	ALL
26	Imitation jewellery	*POLYMERIC*[a]

[a] excluding polymeric coatings with a thickness of less than 500 µm.

This type of categorization is useful to quickly look up the applicable contact limits in a certain type of toy made of a specific material. A similar table might be helpful for contact limits for elements. However, as is noted in the standard, the limits for organic compounds given in the limit tables have been calculated with the specific toy and toy material in mind. In the case of other toys and toy materials not specified, they may not be appropriate and should not be applied without further expert toxicological/exposure assessment. Similarly, it will be difficult to create a table with contact limits for every element (or other substance) in every single type of toy available on the market.

IV.6 Intended age groups

The US Code of Federal Regulations regulating the safety of toys (Child Protection Act and toy Safety Act of 1969, amendment to the Federal Hazardous Substances Act (16 CFR Ch2) describes test methods for articles intended for specified age groups of children:

- 18 months of age or less
- over 18 months but not over 36 months of age
- over 36 months but not over 96 months of age

The age of the intended user is determined by looking at the following factors: the manufacturer's stated intent (such as the age stated on a label) if it is reasonable; the advertising, marketing and promotion of the article; and whether the article is commonly recognized as being intended for children this age group.
To help determine the intended age group of a toy, the U.S. Consumer Product Safety Commission (CPSC) developed extensive *Age Determination Guidelines* (U.S. Consumer Product Safety Commission (CPSC), 2002). The primary content of the *Age Determination Guidelines* is organized into four levels, each representing an increasing level of detail. These levels are play categories, toy subcategories, age groups, and toy characteristics.
The following play categories (in approximate developmental order) and derived toy subcategories were defined:

A. Early exploratory/practice play
    a. Mirrors, mobiles, and manipulatives
    b. Push and pull toys
B. Construction play
    a. Blocks
    b. Interlocking building materials
C. Pretend and role play
    a. Dolls and stuffed toys
    b. Play scenes and puppets
    c. Dress-up materials
    d. Small vehicle toys
    e. Tools and props
D. Game and activity play
    a. Puzzles
    b. Card, floor, board, and table games
    c. Computer and video games
E. Sports and recreational play
    a. Ride-on toys
    b. Recreational equipment
    c. Sports equipment
F. Media play
    a. Arts and crafts
    b. Audiovisual equipment
    c. Musical instruments
G. Educational and academic play
    a. Books
    b. Learning toys
    c. Smart toys and educational software

The information presented in each subcategory is distributed among the following ten age groups:

- Birth through 3 months
- 4 Through 7 Months
- 8 Through 11 Months
- 12 Through 18 Months
- 19 Through 23 Months
- 2 Years
- 3 Years
- 4 Through 5 Years
- 6 Through 8 Years
- 9 Through 12 Years

Each toy subcategory describes appropriate and appealing toy characteristics based on the physical, cognitive, social, and emotional levels and abilities of children as they progress through the ten age groups. These toy characteristics include: size, shape, number of parts, interlocking versus loose parts, materials, motor skills required, color/contrast, cause and effect, sensory elements, level of realism/detail, licensing, classic, robotic/smart features, and educational.

Partly based the US Age Determination Guidelines, the CEN prepared a document that gives guidelines for deciding which toys are intended for children under 36 months of age and which toys are not intended for such children (European Committee for Standardization (CEN), 2002). 24 categories of toys have been selected:

A. Activity toys
B. Aquatic toys
C. Art and craft materials and related articles
D. Audio/visual equipment
E. Books with play value
F. Construction toys and puzzles
G. Costumes, disguises and masks (intended to imitate)
H. Dolls and soft filled toys
I. Experimental sets
J. Functional toys
K. Game sets
L. Mechanical and/or electrical driven vehicles
M. Play scenes and constructed models
N. Projectile toys with a launching device
O. Push-along toys, pull-along toys and walking aids
P. Role playing toys
Q. Sand-water toys
R. Skill development toys
S. Toy cosmetics
T. Toy musical instruments

U. Toy sports equipment and balls
V. Toys for babies for looking at, grasping and/or squeezing
W. Toys intended to bear the mass of a child
X. Toys intended to be entered by a child

The toy's suitability for children under or over 36 months is based on its functions and characteristics such as the overall dimensions of the toy, the number and size of the parts or components of the toy, the degree of detail and special functions a toy may have.

For risk assessment purposes, it is not necessary to base toy categories on ten different age groups. The main purpose for categorizing toys according to intended or suitable age group is to determine whether toys may pose a choking hazard for children under 36 months of age. The value for looking at intended age for the purpose of setting limits for elements and other substances in toys is further discussed in chapter 3.

IV.7 Exposure categories

The RIVM has created a fact sheet for children's toys to be used in combination with the computer program ConsExpo (Bremmer et al., 2002). The fact sheet defines 17 toy exposure categories with representative examples of toys for which default ConsExpo models and parameter values are given. These exposure categories are divided up in the five main categories: ingestion, mouthing, inhalation, skin contact and eye contact.

Exposure category	Examples
Mouthing	
Toys meant for mouthing	Teething ring
Other toys	Cuddly toy, plastic doll
Ingestion	
Direct ingestion	Modeling clay, paint from toy car, ball pen
Hand-mouth contact, direct	Finger paint, chalk
Hand-mouth contact, indirect	Face paint
Inhalation	
Evaporation from liquids	Felt pen
Evaporation from solid products	Tent
Dust	Chalk, cosmetics (blusher)

Exposure category	Examples
Skin contact	
Leaching from solid products	Cowboy suit, tent ground sheet, cuddly toy
Rubbing off	
Application on the skin	Tent canvas, preserved wood
Intensive hand contact	Cosmetics, face paint
Spillage	Modeling clay, finger paint Poster paint
Eye contact	
Leaching from solid products	Diving goggles
Application on the skin near eyes	Cosmetics (eye shadow), face paint
Evaporation from solid products	Diving goggles
Hand-eye contact	Finger paint, chalk

The exposure categories above are useful to obtain an approximation of the exposure levels to elements and other substances from toys by means of first or higher tier models in ConsExpo. For the purpose of setting limits for elements in toys, some examples in the table above may be too specific. A more pragmatic approach can be derived from this exposure based categorization of toys, as discussed in chapter 3.

V Migration Tests

V.1 Migration tests

The EU countries and majority of the non-EU countries use the CEN 71-3 migration test for the 8 different elements. However, some non-EU countries use different migration tests.

V.2 European Committee for Standardization (CEN)

The CEN 71-3 (safety of toys – part 3: migration of certain elements) standard is an European standard prepared by the CEN/TC 52 – safety of toys committee for the European Commission and the European Free Trade Association. This standard applies for Austria, Belgium, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, The Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, Switzerland, and United Kingdom. Albania, Bulgaria, Croatia, The Former Yugoslav Republic of Macedonia, and Turkey are affiliates of the CEN and participate in the General Assembly and technical bodies, but are not full members. Currently, they are implementing the CEN standards into their own national legislation. CEN 71-3 specifies requirements and migration tests for the elements: antimony (Sb), arsenic (As), barium (Ba), cadmium (Cd), chromium (Cr), lead (Pb), mercury (Hg), and selenium (Se) from toys and packaging material when they are part of the toy or have intended play value (European Committee for Standardization (CEN), 1994). There are different test methods for different toy materials:

- coatings of paints, varnishes, lacquers, printing inks, polymers and similar coatings.
  If 100 mg of coating can be removed from the toy then this fraction is sieved over 0.5 mm. Only if the coating can not be comminuted (e.g. plastic or elastic paint), a test portion is removed and used to measure the migration. For the migration test, a portion of the coating is mixed with 50 times 0.07 ± 0.005 M of HCl. After 1 min the pH is measured and if necessary set at 1.0-1.5 using 2 M HCl. Under the exclusion of light the mixture is agitated for 1 h at 37 ± 2 °C and then stand for another hour. The solution and coating are separated using a membrane filter (pore size of 0.45 μm) and if necessary centrifugation at 5000 g for as maximum of 10 min. Hydrochloric has to be added if the samples are not analysed within 24 h up to a concentration of 1 M. If only 10 to 100 mg of coating can be obtained then 5 ml of 0.07 ± 0.005 M HCl is added and the same migration test procedure is followed as described above.
- paints (including finger paint, varnishes, lacquers, glazing powders and similar materials in solid or in liquid form appearing as such in the toy).
  A test portion of 10-100 mg should be obtained and a dimension < 6 mm if the material is solid. If it contains grease oil, wax or similar material, the test portion should be enclosed

in hardened filter-paper and the ingredients should be removed with 1,1,1-trichloroethane or other suitable solvent using solvent extraction.

- samples not containing grease, oil wax or similar material.
  The test portion is incubated with 50 times its mass 0.07 ± 0.005M HCl. If only 10 to 100 mg of coating can be obtained then 5 ml of 0.07 ± 0.005 M HCl. After 1 min shaking, the pH is measured and if necessary set at 1.0-1.5 using 2 or 6 M HCl depending on the alkalinity of the sample. Under the exclusion of light the mixture is agitated for 1 h at 37 ± 2 °C and then stand for another hour. The solution and coating are separated and stored as described previously for coatings of paints, varnishes, lacquers, printing inks, polymers and similar coatings.
- samples containing grease, oil, wax, or similar material.
  An amount of water 25 times the mass of the original material is added to the hardened filter-paper and macerated. at 37 ± 2 °C until the mixture is homogeneous. Next, an amount of 25 times the mass of the test portion of 0.14 ± 0.01 M HCl is added. After 1 min, the pH is measured and if necessary set at 1.0-1.5 using 2 or 6 M HCl depending on the alkalinity of the sample. Under the exclusion of light the mixture is agitated for 1 h at 37 ± 2 °C and then stand for another hour. The solution and coating are separated and stored as described previously for coatings of paints, varnishes, lacquers, printing inks, polymers and similar coatings.

- materials to leave a trace (e.g. the graphite material in pencils and liquid ink in pens).
  A test portion of 10-100 mg should be obtained and a dimension < 6 mm if the material is solid. If it contains grease oil, wax or similar material, the test portion should be enclosed in hardened filter-paper and the ingredients should be removed with 1,1,1-trichloroethane or other suitable solvent using solvent extraction.
  - samples not containing grease, oil wax or similar material.
    The same procedure to determine the migration is followed as described for paints not containing grease, oil wax or similar material.
  - samples containing grease, oil, wax, or similar material.
    The same procedure to determine the migration is followed as described for paints containing grease, oil wax or similar material. Except if the original amount is between 10 and 100 mg then 2.5 ml water and 0.14 M HCl are used.
- paper and paper board with a maximum mass per unit area of 400 g/m^2.
  A test portion of 10 to 100 mg should be obtained and macerated in 25 times its mass of water at 37 ± 2 °C until the mixture is homogenous. Next, an amount of 25 times the mass of the test portion of 0.14 ± 0.01 M HCl is added. After 1 min the pH is measured and if necessary set at 1.0-1.5 using 2 M HCl. Under the exclusion of light the mixture is agitated for 1 h at 37 ± 2 °C and then stand for another hour. The solution and coating are separated using a membrane filter (pore size of 0.45 μm) and if necessary centrifugation at 5000 g for as maximum of 10 min. Hydrochloric has to be added if the samples are not analysed within 24 h up to a concentration of 1 M.
- glass, ceramic and metallic materials.

Small parts (fitting in the small parts cylinder described in standard CEN 71-1) will be tested entirely and if the material is larger a part is removed as described for coatings of paints, varnishes, lacquers, printing inks, polymers and similar coatings. Next, the toy or component is placed in a 50 ml glass container (height 60 mm and diameter of 40 mm) and 0.07 ± 0.05 M HCl is added to just cover the toy. The container is covered and under the exclusion of light is left to stand for 2 h at 37 ± 2 °C. The solution and coating are separated using a membrane filter (pore size of 0.45 μm) and if necessary centrifugation at 5000 g for as maximum of 10 min. Hydrochloric has to be added if the samples are not analysed within 24 h up to a concentration of 1 M.

- natural and synthetic textiles.
  A test portion of 100 mg should be obtained and cut out from the area representing the whole material and a dimension < 6 mm. The same procedure to determine the migration is followed as described for coatings of paints, varnishes, lacquers, printing inks, polymers and similar coatings.
- polymeric and similar materials, including laminates, whether textile reinforced or not, but excluding other textiles.
  A test portion of 10 to 100 mg should be obtained and cut out from the area having the thinnest material cross section and a dimension < 6 mm. The same procedure to determine the migration is followed as described for coatings of paints, varnishes, lacquers, printing inks, polymers and similar coatings.
- pliable modelling materials (including modelling clay and gel).
  A test portion of at least 100 mg should be obtained. If it contains grease oil, wax or similar material, the test portion should be enclosed in hardened filter-paper and the ingredients should be removed with 1,1,1-trichloroethane or other suitable solvent using solvent extraction.
  - samples not containing grease, oil wax or similar material.
    The same procedure to determine the migration is followed as described for paints not containing grease, oil wax or similar material.
  - samples containing grease, oil, wax, or similar material.
    The same procedure to determine the migration is followed as described for paints containing grease, oil wax or similar material
- other materials whether mass coloured or not (e.g. wood, fibre board, hard board, bone, leather and paper and paper board > 400 g/m^2).
  A test portion of 10 to 100 mg should be obtained and should be tested using the most appropriate method described for coatings of paints, varnishes, lacquers, printing inks, polymers and similar coatings, paper and paper board with a maximum mass per unit area of 400 g/m^2, natural and synthetic textiles, and glass, ceramic and metallic materials.

Not part of this legislation are toys and parts of toys which obviously exclude any hazard due to sucking, licking or swallowing due to their accessibility, function, mass, size or other characteristics, but bearing in mind the normal and foreseeable behaviour of children under the age of 7. The principle of the migration test is that the soluble element extracted represents the amount released in the stomach.

V.3 Health Canada

There are different test methods for different toy materials in Canada:

- Leachable cadmium, barium, antimony, selenium and arsenic in applied coatings
  This method is used by Health Canada to determine the migration from decorative and protective coatings. The coating is removed by using a scalpel or tetrahydrofuran or another suitable solvent without removing the underlying substrate material. If a solvent is used then evaporate the solvent in an air convection oven at 60 °C for 1 h. Next, grind the sample in a mortar and sieve to get a fraction 250 and 500 µm. Dry the sample again in an oven at 60 °C for 1 h. For the migration determination, an amount of 100 mg sample is incubated with 20 ml 5% HCl solution for 10 ± 1 min at 20 ± 2 °C under constant stirring. The solution is filtered using Whatman no. 40 filter paper and the filter is washed with deionised water. Add 1 ml of concentrated nitric acid to the filtrate and add deionised water until a volume of 50 ml. This solution is used to determine the migration.
- Leachable lead in metallic consumer products which pose a hazard from ingestion
  This method is used by Health Canada to determine the release of lead from metallic consumer product like jewellery and figurines which fit into the truncated right circular cylinder (small parts cylinder), because the pose an ingestion hazard. Acetone is used to prewash the sample. Next, the sample is covered with 0.07 M HCl and incubated for 2 h under the exclusion of light at 37 ± 2 °C. The solution is filtered using Whatman no. 40 filter paper. Add 2 ml of concentrated HCl to the filtrate and add 0.07 M HCl until a volume of 25 ml. This solution is used to determine the migration.
- *Leachable lead and cadmium from glazed ceramics and glassware*
  Health Canada uses this method to determine the release of lead and cadmium from toys containing glazed ceramics or glass, e.g. children's tea set. Cover the sample with 4% acetic acid and incubate for 24 h ± 10 min at 22 ± 2 °C. An aliquot is used to analyse for lead and cadmium.

V.4 Fowles et al. method

Fowles describes a method with several variables used to determine the leaching of cadmium from plastic toys (Fowles et al., 1977). Samples were taken using a rough file, a Stanley shaper, a Surform hand tool, and human teeth. All samples were sieved mechanically trough different sieves to obtain samples in different categories, namely < 0.106 mm, 0.106-0.5 mm, 0.5-1.0 mm and > 1.0 mm. For the extraction procedure, 1 g of sample was placed in 25 ml HCl (ranging from 0.046-0.47 M) solution and shaken (3 different speed settings) for 1 to 24 h in the absence and presence of light and air. Also the temperature was varied ranging from 19 to 42.5 °C. Fowles showed that the different methods to obtain a sample gave similar

fraction and that the leaching depended mainly on the sample size, acid strength and temperature (increased leaching with decreased particle size, increasing acid strength and temperature). Light had a dramatic effect on the leaching of cadmium from plastic toys, highly increased in the presence of light. Shaking speed had no effect on the leaching and air only a minor effect. The most physiological conditions are according to the author 0.1 M HCl, presence of air, absence of light, incubation of 4h and varying particle sizes (not the standard factory regrind that the industry tests).

V.5 Physiologically-based extraction tests

There are several other physiologically-based extraction test to simulate sucking than mentioned here. However, all these tests were developed and used to determine the release of phthalates from toys and other consumer products. Examples are the Joint Research Centre (JRC) model and a model developed by the U.S. Consumer Product Safety Commission (Simoneau et al. 2001; U.S. Consumer Product Safety Commission,).

V.6 RIVM method

The composition and preparation of non-stimulated (under fasted conditions and no stimuli for secretion like sucking) and stimulated (under fed conditions and stimulus like sucking) digestive fluids are described in detail in the publications by Oomen et al. (Oomen et al., 2003a) and Versantvoort et al. (Oomen et al., 2003c; Versantvoort et al., 2005). Stimulated and non-stimulated digestive juices differ in pH, salt concentrations, and enzyme concentrations. The mixtures are rotated head-over-heels at 55 rpm and the whole process is performed at 37°C. At the end of the digestion process the tubes are centrifuged for 5 min at 2750 g, yielding the chyme (the supernatant) and the digested matrix (the pellet), and sampled to obtain information on the bioaccessibility of the contaminant. Samples can be taken from the saliva, stomach and chyme phase to obtain information on the bioaccessibility of the contaminant and its behaviour in the different compartments of the digestive tract. The main differences between the suck, suck-swallow, and swallow *in vitro* digestion model are the stomach pH and the composition of the digestive juices. The matrix may affect the pH in the stomach. However, under fasting conditions, the pH in the stomach is usually low and set at 2.5 ± 0.1 in the suck and suck-swallow model and to 1.6 ± 0.1 in the swallow model under fasted conditions (see Figure V-1). The pH in the gastric compartment of the swallow model under fasted conditions is lower, because less saliva is entering the gastric compartment in the swallow model (6 ml saliva instead of 18 ml). These pHs were chosen because an *in vitro* digestion without matrix results in this pH and because this pH falls in the range of pH values for fasting conditions (Charman et al., 1997).

V.6.1 Suck model

The model is applied to simulate sucking by a child on a consumer product (Oomen et al., 2003c). The suck time depends on the age of the child (at the age of 0.5-2 years children have the longest suck time), but also on the product (Bremmer and Van Veen, 2002). The migration of a contaminant from its matrix into saliva simulant after a certain time based on mouthing duration can be measured with this model. It can either be assumed that all the contaminant that is released in the mouth is also available for absorption, in which case the model is terminated after the mouth phase, or that the contaminant can form aggregates that can not be absorbed in the stomach or intestinal compartment. With the suck model, the contaminant that is released in the mouth during sucking (one compartment model) or the fraction that is available for absorption in the small intestine (three compartment model) can be investigated. Different amounts of matrix are introduced to 21 ml stimulated saliva and rotated for a variable time periods. The time period applied can be either a default value (30 min) or a period considered to be specifically appropriate for a certain product which is based on the product and the input of the risk assessor. The digestion tubes are centrifuged to remove the matrix and 18 ml of supernatant used for further incubation (the other 3 ml are used for analysis of the bioaccessibility in saliva). For the one compartment model, the sucking model is terminated after the saliva incubation. For the three compartment model, a volume of 12 ml gastric juice (pH 1.07 ± 0.07) is added to the saliva supernatant. The mixture is rotated for 1 h and the pH of the mixture is determined and, if necessary, set to 2.5 ± 0.1. Then, the mixture is rotated for another hour. Finally, 12 ml of duodenal juice (pH 7.8 ± 0.2) and 6 ml bile (pH 8.0 ± 0.2) are added simultaneously, and the pH of the chyme is determined and if necessary set to 6.5 ± 0.5. Then, the mixture is rotated for another 2 h. The digestion tubes are centrifuged and the supernatant is suitable for analysis.

V.6.2 Suck and swallow model

This method is applied to simulate mouthing and then ingestion of a certain consumer product (Oomen et al., 2003c). Thus, contrary to the three compartment suck model the matrix is ingested after sucking. The only modification is that the digestion starts by introducing 18 ml stimulated saliva to different amounts of matrix. This mixture is rotated head-over-heels for 30 min and then gastric juice is directly added without centrifuging. The rest of the procedure is the same as described for the three compartment suck model.

V.6.3 Swallow model under fasted conditions

This model is applied to simulate ingestion of a certain consumer product under fasted conditions (Oomen et al., 2003c). It starts by introducing 6 ml saliva (pH 6.5 ± 0.2) to different amounts of matrix. This mixture is rotated for 5 min. Subsequently, 12 ml of gastric juice is added and the pH of the mixture of saliva and gastric juice is determined and, if necessary, directly set to 1.6 ± 0.1. The mixture is rotated for 2 h. Finally, 12 ml of duodenal

juice and 6 ml bile are added simultaneously and the pH is determined and if necessary set to 6.0 ± 0.5. The mixture is rotated for another 2 h. The digestion tubes are centrifuged and the supernatant is used for analysis.

V.6.4 Swallow model under fed conditions

The digestion starts by introducing different amounts of matrix to 6 ml stimulated saliva and 4.5 g infant food (product number 282, Olvarit (Nutricia®, the Netherlands), supplemented with 2 ml sunflower oil per 100 g). This infant food with sunflower oil represents the mean food intake for adults in the Netherlands for a cooked meal regarding macronutrients and caloric composition. It is based on the third Dutch National Food Consumption Survey from 1998 (Versantvoort et al. 2005). Immediately, 12 ml of stimulated gastric juice (pH 1.30 ± 0.02) is added and pH of the mixture is set to 2.5 ± 0.5. After 2 h of rotating, 12 ml of stimulated duodenal juice (pH 8.1 ± 0.2), 6 ml stimulated bile (pH 8.2 ± 0.2), and 2 ml sodium bicarbonate (84.7 g/l) are added simultaneously. The pH is set to 6.5 ± 0.5 and the mixture is rotated for another 2 h. Separation of chyme and pellet was obtained by centrifugation and the supernatant can be analysed to determine the bioaccessibility of the contaminant.

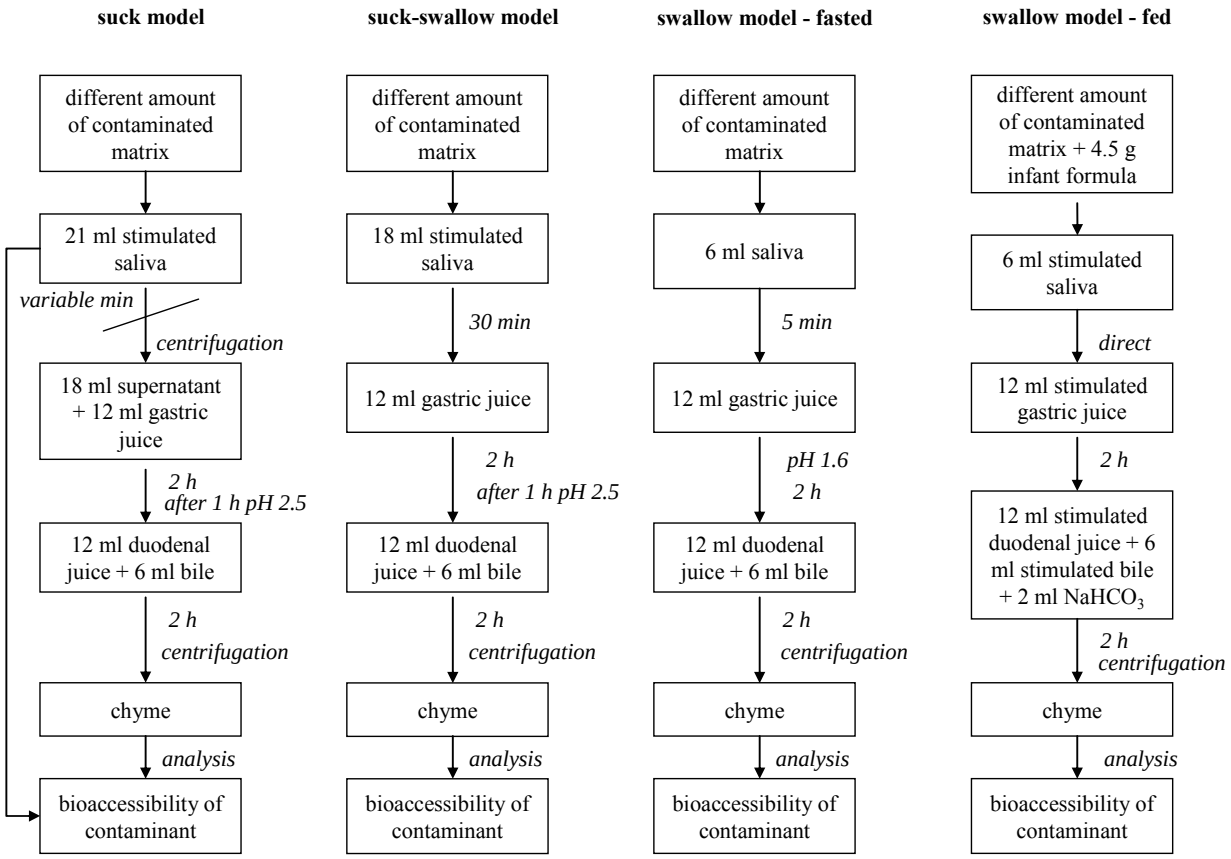

Figure V-1. Schematic representation of the RIVM suck, suck-swallow, and swallow under fasted and fed conditions in vitro digestion models.

V.6.5 Iliano et al. method

Iliano et al. describes a physiologically-based extraction method for antimony (Sb), arsenic (As), barium (Ba), cadmium (Cd), chromium (Cr), lead (Pb), mercury (Hg), and selenium (Se) from toys using saliva simulant (Iliano et al., 1988). The simulated saliva consist of 4.2 mg/ml $NaHCO_3$, 500 µg/ml NaCl and 200 µg/ml K_2CO_3 with a pH of 8.8. The toy or part of the toy is immersed in the simulated saliva for 2 h at 37 °C. After filtration the filtrate is analysed to determine the migration.

ERRATUM d.d. 26-01-2015
RIVM report 320003001
Chemicals in toys. A general methodology for assessment of chemical safety of toys with a focus on elements (2008)
Openbaar sinds: 02-04-2009
Auteur: van Engelen JGM, van der Zee Park M, Janssen PJCM, Oomen AG, Brandon EFA, Bouma K, Sips AJAM, van Raaij MTM
RIVM Rapport 320003001

The work described in this report report was carried out in 2006 on request of DG Enterprise in view of contract nr. SI2.ICNPROCE003918500. The Commission used content of this report as a starting point for the derivation of migration limits as included in Annex III of the Toys Safety Directive (2009/48/EC).
The following inconsistency in RIVM report 320003001 is identified:

In Chapter 3 of the RIVM Toys report, a choice is made regarding the ingested amount of toys material and the frequency of exposure. The ingested amount of toys material is chosen as 100 mg for dry, pliable or powder-like toy materials and 400 mg for liquid or sticky material. It is noted on page 41 that "The ingestion of 100 mg by children is considered reasonable, but may not occur daily. For exposure assessment refinement purposes, we propose to use a frequency of 1/week for this ingestion default when the exposure is compared to a chronic health-based limit value. This is a rough estimate and needs further research. "
And on page 42: " Similar to the ingestion default for dry, brittle, powder-like and pliable materials, an ingestion of 400 mg may occasionally occur, but not daily. For the purpose of an exposure assessment refinement, when comparing exposure to a chronic health-based limit value, we propose to use a frequency of 1/week as a default. This is a rough estimate and needs further research."
The proposed frequency of exposure is once a week.

In Chapter 8, the migration limits are derived and presented in Tables 8-3 and 8-4. In the calculation an ingested amount of 100 mg **per day** (dry, pliable or powder-like toy materials) and 400 mg (liquid or sticky material) **per day** were used. For explanation, the reader is referred to Chapter 3. The migration limits are derived base on a frequency of exposure of once a day. This should have been 100 mg per week and 400 mg per week.
The result is that the limit values presented in Tables 8-3 and 8-4 are incorrect.
In the Erratum, the inconsistency between Chapter 3 and Chapter 8 is corrected. In tables 8-3 and 8-4, the columns of the migration values, using 5, 10 or 20% of the TDI in the calculation have been corrected using the correct assumption of an ingestion frequency of once a week, in the Tables 8-3 and 8-4.

Adapted information:

8.6 Migration limits for elements in toys

In the tables below, migration limits for elements in toys are presented, as derived by the methodology proposed in chapter 7. Further explanation and a calculation example can be found in paragraph 8.5.1.

Table 8-2 For intake of 8 mg (scraped off material) for children < 3 years of age

* ***Age*** ***< 3 years***
* ***Body Weight*** ***7.5 kg***
* ***Material*** ***8 mg (scraped off) per day***

Not changed

Table 8-3 For intake of 100 mg (dry, brittle, powder-like or pliable material) for children < 3 years of age

* ***Age*** ***< 3 yrs***
* ***Body Weight*** ***7.5 kg***
* ***Material*** ***100 mg (dry, powder like or pliable) once a week***

Element		**TDI (µg/kg bw/day)**	**Migration Limit value (mg/kg product)**			**Current Migration Limit (mg/kg product)***
			5% TDI	**10% TDI**	**20% TDI**	
Aluminum		750	19687,5	39375,0	78750,0	
Antimony		6	157,5	315,0	630,0	60
Arsenic		1	26,3	52,5	105,0	25
Barium		600	15750,0	31500,0	63000,0	250
Boron		160	4200,0	8400,0	16800,0	
Cadmium		0.5	13,1	26,3	52,5	50
Chromium[a,d]	Cr3+ ws	5	131,3	262,5	525,0	25
	Cr3+ wis	5000	131250,0	262500,0	525000,0	
	(Cr 6+)[b]	5	131,3	262,5	525,0	25
	(Cr 6+)[c]	0.0053	0,1	0,3	0,6	25
Cobalt		1.4	36,8	73,5	147,0	
Copper		83	2178,8	4357,5	8715,0	
Lead		3.6	94,5	189,0	378,0	90
Manganese		160	4200,0	8400,0	16800,0	
Mercury		2	52,5	105,0	210,0	25
Nickel		10	262,5	525,0	1050,0	
Selenium		5	131,3	262,5	525,0	500
Silver		5	131,3	262,5	525,0	
Strontium		600	15750,0	31500,0	63000,0	
Tin	Inorganic	2000	52500,0	105000,0	210000,0	
	Organic	0.25	6,6	13,1	26,3	
Zinc		500	13125,0	26250,0	52500,0	

* Migration limits according EN 71-3 for modelling clay and finger paint

[a] ws = water soluble, wis = water insoluble

[b] Based on a TDI of 5 µg/kg bw derived for non-carcinogenic effects by hexavalent chromium

[c] Based on a Virtually Safe Dose (VSD) of 0.0053 µg/kg bw/day derived for the genotoxic and carcinogenic action by hexavalent chromium. As explained in the appended toxicological profile on chromium, this VSD is based on a limited bioassay in mice and is fraught with additional uncertainty compared to the usual bioassay-derived VSDs. Results of NTP studies now in progress should allow more a reliable oral cancer risk estimation in the near future.

[d] Measurement of Cr^{6+} is difficult. Further research is needed to derive safe migration limit values for this element

Table 8-4 For intake of 400 mg (liquid or sticky material) for children < 3 years of age

* ***Age*** ***< 3 yrs***
* ***Body Weight*** ***7.5 kg***
* ***Material*** ***400 mg (liquid & sticky, once per week)***

Element		**TDI (µg/kg bw/day)**	**Migration Limit value (mg/kg product)** 5% TDI	10% TDI	20% TDI	**Current Migration Limit (mg/kg product)***
Aluminum		750	4921,9	9843,8	19687,5	
Antimony		6	39,4	78,8	157,5	60
Arsenic		1	6,6	13,1	26,3	25
Barium		600	3937,5	7875,0	15750,0	250
Boron		160	1050,0	2100,0	4200,0	
Cadmium		0.5	3,3	6,6	13,1	50
Chromium[a,d]	Cr3+ ws	5	32,8	65,6	131,3	25
	Cr3+ wis	5000	32812,5	65625,0	131250,0	
	(Cr 6+)[b]	5	32,8	65,6	131,3	25
	(Cr 6+)[c]	0.0053	0,0	0,1	0,1	25
Cobalt		1.4	9,2	18,4	36,8	
Copper		83	544,7	1089,4	2178,8	
Lead		3.6	23,6	47,3	94,5	90
Manganese		160	1050,0	2100,0	4200,0	
Mercury		2	13,1	26,3	52,5	25
Nickel		10	65,6	131,3	262,5	
Selenium		5	32,8	65,6	131,3	500
Silver		5	32,8	65,6	131,3	
Strontium		600	3937,5	7875,0	15750,0	
Tin	Inorganic	2000	13125,0	26250,0	52500,0	
	Organic	0.25	1,6	3,3	6,6	
Zinc		500	3281,3	6562,5	13125,0	

* Migration limits according EN 71-3 for modelling clay and finger paint

[a] ws = water soluble, wis = water insoluble

[b] Based on a TDI of 5 µg/kg bw derived for non-carcinogenic effects by hexavalent chromium

[c] Based on a Virtually Safe Dose (VSD) of 0.0053 µg/kg bw/day derived for the genotoxic and carcinogenic action by hexavalent chromium. As explained in the appended toxicological profile on chromium, this VSD is based on a limited bioassay in mice and is fraught with additional uncertainty compared to the usual bioassay-derived VSDs. Results of NTP studies now in progress should allow more a reliable oral cancer risk estimation in the near future.

[d] Measurement of Cr^{6+} is difficult. Further research is needed to derive safe migration limit values for this element

Table 8-5 For intake of 8 mg (scraped off material) for toys intended to be mouthed by children > 3 years of age

*	***Age***	***> 3 yrs***
*	***Body Weight***	***15 kg***
*	***Material***	***8 mg (scraped off, per day)***

Not changed