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ESTIMATING MOUTHING EXPOSURE IN CHILDREN – COMPILATION OF CASE STUDIES

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or contact:

OECD Environment Directorate,
Environment, Health and Safety Division
2 rue André-Pascal
75775 Paris Cedex 16
France

Fax: (33-1) 44 30 61 80

E-mail: ehscont@oecd.org

Foreword

Children can be more vulnerable than adults to environmental hazards, such as those presented by chemicals, due to their physiological differences and unique behaviours. Considering global concern for children's health, the OECD has been working to bring together knowledge and experiences to reduce risks to children's health from chemicals.

The goal of this document is to review and update available information with a focus on direct object mouthing to ensure that potential risks for children are addressed.

Canada led the development of this document and the Working Party on Exposure Assessment (WPEA) reviewed the document. This document was published under the responsibility of the Joint Meeting of the Chemicals Committee and the Working Party on Chemicals, Pesticides and Biotechnology of the OECD.

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Abbreviations and acronyms

ANSES	Agency for Food, Environmental and Occupational Health and Safety
BfR	Federal Institute for Risk Assessment
BPA	bisphenol A
DBP	dibutyl phthalate
DEHT	bis(2-ethylhexyl)terephthalate
DIBP	diisobutyl phthalate
DIDP	di(isodecyl) phthalate
DINCH	diisononylcyclohexanoate
DINP	di(isononyl) phthalate
ECHA	European Chemicals Agency
EPTAC	2,3-epoxypropyltrimethylammonium chloride
INERIS	National Institute for Industrial Environment and Risks
NICNAS	National Industrial Chemicals Notification and Assessment Scheme
NIES	National Institute for Environmental Studies
RIVM	National Institute for Public Health and the Environment
SOP	Standard Operating Procedures
TCEP	tris(2-chloroethyl) phosphate
TCPP	tricresyl phosphate
TDCPP	tris(dichloropropyl) phosphate
TMPDB, TXIB	2,2,4- trimethyl-1,3-pentanediol diisobutyrate
US EPA	United States Environmental Protection Agency

Executive Summary

This considerations document presents a comprehensive analysis of children's exposure to chemicals through mouthing, sucking and chewing on toys, books, textiles, etc. for addressing potential risks to children's health from chemicals.

Based on fifteen case studies, the document discusses key considerations from these case studies for target age groups, mouthing materials, algorithms and parameters, exposure values, hazard endpoints, default values and uncertainties. The overall considerations are summarised in the final chapter. The document also provides an overview of the fifteen case studies individually, allowing interested stakeholders to review the details of each case study.

The information and key considerations provided in this document is expected to assist risk assessors in conducting exposure assessments of children exposed to chemicals through mouthing of objects. The considerations are not presented as strict guidance but provide important elements and good practices from the fifteen case studies.

1. Introduction

Children exhibit specific habits and practices that may result in exposure scenarios not considered for other population groups. Behaviours such as mouthing, sucking and chewing on articles such as toys, children's books and textiles may result in oral exposure to substances that migrate out of the article. Over time, many mathematical approaches have been used to estimate exposure to children as a result of mouthing objects, hand-to-mouth contact and ingesting articles.

In November 2011, the OECD Secretariat performed a survey to gather information on available methodologies and tools to assess the risks from chemicals to children's health and to identify the needs of countries regarding the development of additional methodologies or tools [ENV/JM/MONO(2013)20]. Also, a Workshop on Children's Exposure to Chemicals was held in Utrecht, the Netherlands, on 7-8 October 2013 [ENV/JM/MONO(2014)29]. The survey and the Workshop revealed a relatively high need for improved exposure assessment methodologies for children.

In order to review and update available information with a focus on direct object mouthing, the WPEA agreed to form a sub-group as part of the OECD Children's Health Project with the following delegates:

- Gerlienke Schuur, National Institute for Public Health and the Environment (RIVM) (the Netherlands);
- Cathy Fehrenbacher/Charles Bevington/Eva Wong, the United States Environmental Protection Agency (US EPA);
- Junko Kawahara, National Institute for Environmental Studies (NIES) (Japan);
- Yasmin Sommer, Federal Institute for Risk Assessment (BfR) (Germany);
- Anna Cruz, National Industrial Chemicals Notification and Assessment Scheme (NICNAS) (Australia);
- Lode Pottie (Belgium);
- Jérémy De Saint-Jores/Vincent Grammont, Agency for Food, Environmental and Occupational Health and Safety (ANSES) & National Institute for Industrial Environment and Risks (INERIS) (France);
- Angelika Zidek/Cathy Campbell, Health Canada (Canada);
- Rosemary Zaleski, BIAC/ExxonMobil Biomedical Sciences, Inc.; and
- Takaaki Ito, OECD Secretariat.

Health Canada (via an external contractor) gathered a compilation of mathematical approaches for conducting exposure assessments involving the direct mouthing of objects by young children, through a targeted search of the scientific literature as well as various government sources.

In an effort to identify the most useful and commonly used approaches to estimate exposure associated with mouthing activities, this considerations document was developed with a focus on mouthing of objects by infants and children, based on fifteen case studies submitted by sub-group members. The document provides information on the fifteen case studies and, based on these case studies, discusses key considerations regarding approaches, parameters and default values used to estimate children's exposure as a result of mouthing articles.

2. Discussion of Case Studies

A total of fifteen case studies estimating children's exposure to various chemical substances due to mouthing objects were submitted by sub-group members (Table 1). In some cases, there were considerable similarities among the case studies (e.g. phthalates and plastic toys). However, all case studies were included to demonstrate commonly used approaches as well as to highlight differences when similar approaches are used.

Table 1. Summary of Case Studies

Case Study	Chemical	Material / Product
1	DINP	Plastic toys
2	DBP	Plastic toys
3	DINCH, DEHT, TMPDB (TXIB)	Plastic toys
4	Lead	Jewellery
5	DINP, DIDP	Plastic toys, childcare articles
6	BPA	Plastic toys, pacifiers
7	2,4-Toluenediamine	Textile toys
8	EPTAC	Paper Books
9	DINP	Plastic toys
10	DEHT	Plastic toys, childcare articles, art or school supplies
11	DIBP	Plastic toys
12	TCPP, TDCPP	Children's products containing foam
13	TCEP	Products containing polyurethane foam
14	Triclosan	Plastic toys
15	DINP	Plastic toys

Note: See "Abbreviations and acronyms" for the full name of chemicals.

2.1. Target Age Groups

The majority of case studies included a separate exposure estimate for children <1 year (e.g. 6 months, 6-12 months, 10 months). No case studies examined the exposure to children over 4 years of age.

In most of the case studies, age categories were limited to age spans of 12 months or less (e.g. age groups <1 year, 1-2 years and 2-3 years). In four of the case studies, age categories spanned more than 12 months, specifically, case studies 6 (1-3 years), 11 (6-18 months), 12 and 13 (6 months to 4 years). Given the differences in mouthing activities as well as differences in body weight in children <3 years, it is considered relevant to consider the <1 year old age category separately as well as examining children >1 year in one year age categories (e.g. for children aged 1-3 years, examine 1-2 year olds separate from 2-3 year olds).

In almost every case study where the exposure was estimated for children >1 year and <1 year, the younger age category (i.e. <1 year) resulted in the highest exposure estimate. The two exceptions were for case studies 4 (metal jewellery) and 15 (soft plastic toys). In both cases, higher exposure estimates for children >1 year were due to higher values for the duration of exposure compared to children <1 year. In addition, children between the ages

of 0 and 18 months were found to mouth objects for different durations compared to 19 to 36 months (pacifiers (108 vs. 126 minutes), plastic toys (17 vs. 2 minutes), teethers (6 vs. 0 minutes) and other objects (9 vs. 2 minutes)) with a statistically significant difference for non-pacifier objects.

Key considerations:

- Age plays a key role for exposure considerations via mouthing.
- Consider the <1 year old (e.g. 6 months, 6-12 months, or 10 months) age category separate from toddlers/children >1 year of age. This is especially important for objects that are designed for infants.
- When separate age categories are identified, the selection of parameters such as mouthing duration may be specifically applied by age and type of object (e.g. as demonstrated in case study 15, plastic toys not specifically designed for teething may have higher exposure durations in older age groups (e.g. >1 year) compared to 3-11 months).
- Consider limiting age categories to a maximum of 12 months in duration for children <3 years (e.g. 1-2 years, 2-3 years) to account for differences in mouthing behaviour and body weights. This will also require a consideration of the sample size and whether the sample size of the mouthing observation supports this approach.
- Other considerations, not included in the examination of these case studies, are to note differences in mobility for children in different age groups; this may result in mobile children having access to a wider range of products (but also perhaps less time per day with a single product).

2.2. Materials

In most of the case studies, the objects and materials are specifically intended for small children (e.g. infants and toddlers). The type of material and/or object plays a key role in the identification of specific parameters considered in the algorithm (e.g. age group, duration of exposure). In addition, the type of object may also play a role in factors such as the type of hazard endpoint (e.g. textiles or certain toys that may be used daily by a child for several years versus a toy or object that is used less frequently (e.g. textile book, ball)).

The case studies address the following materials/types of objects:

- Plastic items intended for children (including polycarbonate) (ten case studies):
  - Plastic objects make up the majority of examples.
  - Plastic objects intended for mouthing or sucking (e.g. pacifiers) should be identified separately from products intended for children but not necessarily intended for sucking or mouthing (e.g. toy balls).
  - Migration data was often available for substances in plastic items, particularly in the case of well-studied plasticizers. Although standardised techniques to measure migration rates for oral exposures have become established over time, the case studies represent a variety of approaches (including *in vivo* methods, a

range of *in vitro* methods and application of data from dermal migration methods).

- Textiles (one case study):
  - The type of object may be a significant determinant of the likelihood of mouthing and influence parameters related to mouthing behaviours (e.g. duration of mouthing activity and age of child).
  - Although the type of textile (e.g. cotton) was not a parameter that was specifically identified for special consideration in this case study, it is anticipated that the type of textile may have an impact on migration.
  - Migration data appear to be less prevalent for substances in textiles. In the case study, an approach to estimate exposure considering the total substance in the product and the fraction available for extraction due to mouthing is outlined (this approach is similar to the approach used for the paper book).
- Jewellery/metal items (one case study):
  - This case study was different from all others included in this document as it is most relevant for an older age group (i.e. children 2-3 years of age) with higher exposure estimates than for the younger age group (i.e. children 6-12 months). This result is driven by "duration of exposure" values which were higher for children aged 2-3 years compared to the younger age group. In most of other case studies, the duration of mouthing is highest for children <1 year.
  - Migration data was available for the jewellery case study; this approach may be considered when dealing with similar substances in metal products.
- Polyurethane foam (two case studies):
  - One case study had migration data, whereas the other did not. When migration data is available, a standard algorithm with migration rate, surface area and duration of exposure may be used.
  - The other case study with no available migration data outlines an approach that incorporates the water solubility of the substance, a saliva extraction factor and the duration of exposure.
  - As an alternative approach, the total substance in the product and the fraction available for extraction due to mouthing may also be considered (similar to the textile and paper book approach).
- Paper book (one case study):
  - The availability of migration data is anticipated to be less common for these types of objects compared to other types of objects (e.g. plastic toys).
  - In the absence of migration data, the case study used an approach that considers the total substance in the product and the fraction available for extraction due to mouthing (similar to the textile approach).

A key limitation of these case studies is that they do not include other commonly mouthed objects such as arts and crafts, markers and crayons. These objects may have different mouthing exposure scenarios due to different mouthing behaviour for different age groups (e.g. duration may be higher for older age groups).

Key Considerations:

- The type of material and/or whether the object is intended for mouthing by infants (and/or children) may affect the duration and frequency of mouthing. For example, an infant is more likely to mouth a textile toy that is soft and pliable more frequently and for a longer duration of time than a paper book.
- Consideration should be given to the potential for the substance to be present in toys as well as non-toy objects; consideration of these types of objects separately allows application of specific values for parameters such as mouthing frequency and duration (e.g. specific to toys vs. non-toy objects).
- The type of material mouthed may result in a different migration rate (e.g. a substance may migrate out of foam at a different rate than plastic).
- The type of material may affect where the substance is found within the object (i.e. treated surface vs. impregnated vs. dispersed throughout), subsequently having an impact on migration and possible depletion of the substance from the object.
- The type of material and its subsequent density may play a role in assumptions made regarding total surface area mouthed (e.g. 10 cm^2 vs. 20 cm^2).

2.3. Algorithms

Table 2 provides an overview of the algorithms and parameters used in the case studies. Many algorithms (nine of the fifteen case studies, specifically case studies: 1-5 and 9--12) use very similar approaches that incorporate the following parameters:

- migration rate (µg/cm^2/hr) (M);
- surface area (cm^2) (SA);
- mouthing time (hr/day) (T); and
- body weight (BW).

Two of the fifteen algorithms present similar approaches to what is outlined above, but with slight variations:

- In case study 6, migration is presented in terms of the amount of substance leached (mass/product/day) and combined with a time factor (described as the fraction of a day spent mouthing the object) and a surface area factor (fraction of the surface of object mouthed).
- In case study 15, the migration rate (µg/min) is multiplied by time (duration of exposure). The surface area of the object used to derive the migration value is reported to be 10 cm^2, therefore the migration rate value represents a 10 cm^2 surface area.

In the remaining four case studies, migration data was not available and alternative approaches were used:

- In case studies 7 and 8, the total amount of substance in the object (µg/g-product) is derived and combined with factors (e.g. probability of toy containing substance (7) or fraction of ingestion (8)) to determine the amount of substance available to be digested through mouthing activities;
- Case study 13 uses the water solubility of the substance (mg/L), salivary flow rate (mL/min), extraction fraction (%) and duration of exposure (min/day) to estimate the amount of substance ingested; and
- Case study 14 (toy impregnated with substance as a material preservative) calculates the surface concentration of the substance using the weight of the toy (g), the surface area of the toy (cm^2), the concentration of substance in the toy (%) and the percent availability of substance on the surface of the toy.

Table 2. Summary of mouthing algorithms in the case studies

Case Study	Equation to estimate exposure (µg/kg bw per day)	Parameter					
1, 2	M * SA * T * n * B /100 / BW	M = Migration rate	SA = Surface area of mouth (10 cm^2)	T =Mouthing time (hr/day)	n = Mouthing frequency	BW = Body weight	B = Bioavailability (% or absorption factor)
3, 4, 5, 9, 10, 11, 12	M * SA * T / BW	M = Migration rate	SA = Surface area of mouth (10 cm^2)	T = Mouthing time (hr/day)	---	BW = Body weight	---
6	$\frac{q_{product} \times f_{time} \times f_{surface}}{BW}$	$q_{product}$= amount leaching from product in 24 hr (ng/24 hr)	$f_{surface}$ = Fraction of toy surface mouthed (0.25-0.5)	f_{time} = Fraction of day spent mouthing (0.0014 – 0.32)	---	BW = Body weight	---
7	Product amount * concentration * oral absorption * probability/BW	Product amount (g)	Concentration (µg/g product)	Probability of a toy containing substance		BW = body weight	Oral absorption (fraction)
8	Residue * Amt of starch * SA pages * fraction of ingestion * oral absorption/BW	Surface area of pages (m^2)	fraction of ingestion (5-10%)	Amount of cationic starch (0.3 g/m^2)	Residue of substance in starch (µg/g)	BW = Body weight	Oral absorption (fraction)
13	WS * Vs * CF * FR * AF_o * EF_{mouth} * 1/ BW [CF = Conversion Factor (0.001 L/mL)]	WS = Water solubility (mg/L)	Vs = Salivary flow rate (0.22 mL/min)	FR = Fractional rate extraction by saliva (0.0038)	EF_{mouth} = Exp Freq (min/day)	BW = Body weight	AF_o = Oral Absorption factor (0.5)
14	Wt. / SA toy * % substance in toy * % substance available on surface * CF = SR Dose = SR × SE × SA toy / BW [CF = conversion factor 1000 mg/g]	Wt.= Weight of toy (g)	SA toy = Surface area of toy (cm^2)	SE = Saliva extraction efficiency (50%)	Substance in toy (%)	BW = Body weight	Substance available on surface (0.5%)
		SR = Surface residue (mg substance/cm^2) SR = (Wt./SA toy) * (% substance/100) * (% substance available on surface) * conversion factor (1000 mg/g) = 0.0025					
15	Mp * Mh / Ml *Th * Td / BW (A Monte Carlo modelling (bootstrap) method was used to estimate exposure; this reflected prevalence of DINP in soft plastic toys (42%))	M_p = Migration rate of product (µg/min)	M_h = Migration rate (µg/min) (with human subject)	M_l = Lab Migration rate (by JRC method)	(T_h*T_d) = Daily mouthing Time (min/day)	BW = Body weight	
		Migration rates from the *in vitro* studies were adjusted for application to *in vivo* estimation (*in vivo* migration rate derived from adults chewing 10 cm^2 disks)					

Key Considerations:

- When migration data is available, algorithms/approaches for estimating mouthing exposure are relatively consistent. If the migration data is considered of adequate quality and representative of the substance/object being examined, the parameter with the most variability and uncertainty may be "duration of exposure".
- In the absence of migration data, various approaches were used. A straightforward approach noted in some case studies is to use the total amount of substance in the object and apply factors (e.g. probability that the object contains the substance, fraction of the substance on surface of the object) to describe the amount that would be available to be ingested through mouthing activities. These factors have a large amount of uncertainty and several considerations should be taken into account when determining such factors, including:
  - What type of the toxicological endpoint (i.e. acute, intermittent or chronic) is assessed? E.g. in an assessment of a short-term endpoint, a probability factor for the presence in the object may not be appropriate to estimate exposure.;
  - Replenishment of the substance may also be considered in chronic exposure scenarios. If the object may be replenished with the substance (e.g. by reapplication), this may be appropriate. If the substance is not likely to be replenished (i.e. only a finite amount is available), considerations of mass balance may be appropriate to determine when the substance in an object may be depleted;
  - Is the substance water-soluble? If so this may make the substance more likely to migrate out of the object;
  - Consider the use of the substance. Is it chemically bound inside the object, not tightly bound, or is it a surface application? In each of these cases, the likelihood of availability for uptake may be different and may be considered in the application of abovementioned factors; and
  - Application of the abovementioned factors in the absence of data should be done cautiously. If several factors with high levels of uncertainty are applied in a single algorithm, one may wish to consider a range of values to capture the range of possible outcomes. Sensitivity/uncertainty analyses may be useful to determine the impact of various factors with high uncertainty.

2.4. Parameters

2.4.1. Primary Parameters (common to most algorithms)

1) Migration rate (amount of substance extracted during mouthing)

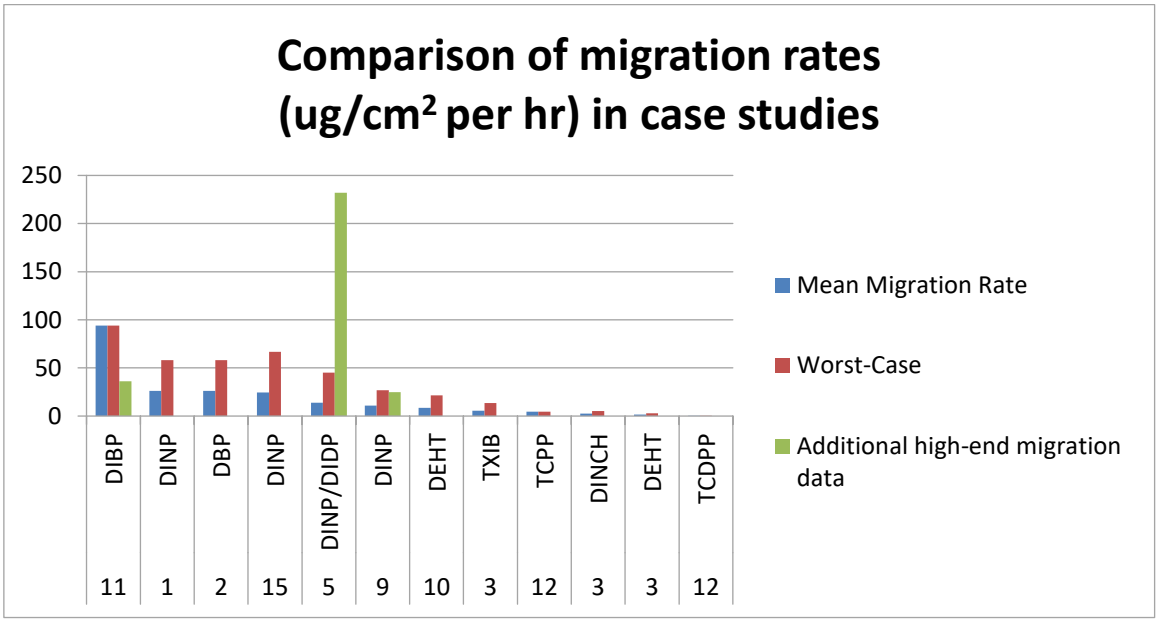
Migration rates with comparable units (i.e. µg/cm^2/hr) are used in eleven of the fifteen case studies. There was a wide range of values reported for typical/mean as well as "worst-case" migration rates. The difference between the highest typical value used to estimate exposure (i.e. 94 µg/cm^2/hr) and the lowest typical value (0.0056 µg/cm^2/hr) is large (more than four orders of magnitude). Although there was a significant difference between the highest and the lowest values used to describe typical migration rates, the majority of mean/typical migration rates were within a 10-fold range (e.g. between 1 and 30 µg/cm^2/hr). The consistency in migration rate values within these case studies may, in part, be due to the

similarity of substances (e.g. DINP was examined in four case studies; many others were also based on phthalates or similar substances).

Migration rates were also used in case studies 4 and 6, however, due to differences in approaches to derive these rates they were not included in the comparison with other case studies (Figure 1). In case study 4 (lead in jewellery), the migration rate is corrected based on reported concentration of lead in the object (migration rate was 0.7 µg/cm^2/hr/% lead). In case study 6 (BPA), the migration rate represented the total amount of substance migrating from an object over 24 hours. Although these values were not included in the graph below, they both appear to be significantly lower (e.g. migration rate of BPA was reported in the ng range for total product over 24 hours).

In the case studies, a wide variety of methodologies was used to derive the migration rates, including an *in vivo* method (e.g. collection of saliva after chewing on a disc), adoption of dermal migration approaches, as well as a variety of *in vitro* migration rate methods. In some case studies, details on the methodology used to derive the migration rate was not available.

Figure 1. Comparison of migration rates in case studies



When migration data was not available, various options were used to estimate the amount of substance available for uptake by mouthing, including considerations of the concentration of a substance in the object combined with a fraction considered available for ingestion.

Key Considerations:

- Careful consideration should be given to the selection of the mean, reasonable worst-case or maximum value for the migration rate to be used in the algorithm.

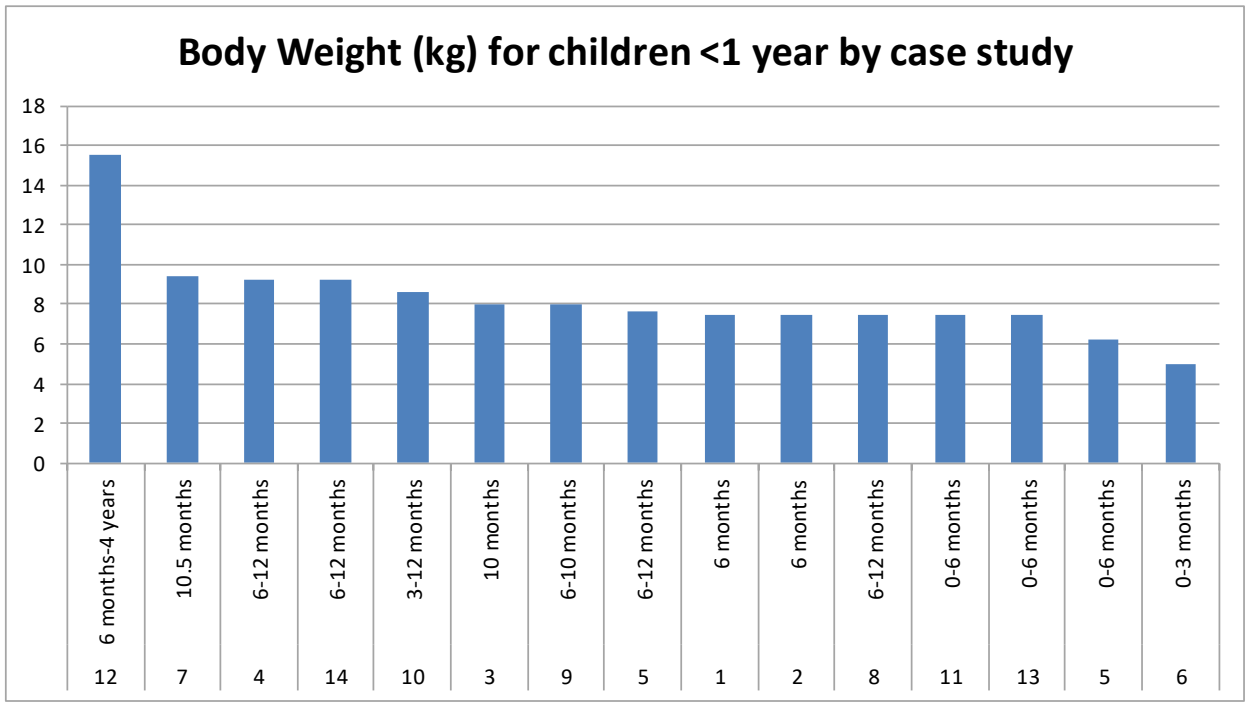
- The strength and relevance of the migration rate study should be carefully considered, including the protocol and the range of product concentrations (e.g. the substance concentrations used in the study should be relevant/able to be extrapolated to the exposure scenario). Migration study protocols (e.g. (Simoneau et al., 2001[1]), (US EPA, 2017[2])) can be used to evaluate the strengths and limitations of a given study.
- Further work may be done to examine a wider range of migration rates across a variety of substances to identify potential maximum or high-end values that could potentially be applied in situations where data is lacking.

2) Body weight of a child (kg)

Although various age categories were examined in the case studies, this analysis has focused on the age categories that included children <1 year. When comparing body weight values used in the case studies for children <1 year, the body weight values were found to be relatively consistent.

The range of body weights for the age categories used to characterise the <1 year age groups are shown in Figure 2. The body weights used in assessments examining only children <1 year varied between 5 kg to 9.9 kg (a 2-fold range). Case studies that included a wider age category (e.g. 6 months to 4 years) had notably higher values. When the <1 year age category is grouped with an older age category, a body weight greater than 10 kg was used; this may underestimate exposure to children <1 year of age.

Figure 2. Comparison of body weights (and age categories) in case studies



Key considerations:

- Consider children <1 year separate from other age categories.
- Consider restricting age categories to less than a one-- year span for mouthing scenarios for children <3 years.
- Separation of age categories by less than 12 months may be considered on a case-by-case basis; this level of refinement may not always be warranted.
- When a large age category is used to derive body weight (e.g. spanning >3 years), the resulting exposure estimate may be less conservative for the youngest age group represented in the range (e.g. an estimate for an age group of 6 months to 4 years may underestimate exposure for children <1 year).

3) Area of object in contact with the mouth (cm^2)

This parameter is commonly described either as the surface area of a child's open mouth or as the area of object mouthed by a child. In most of the case studies using a surface area parameter in the algorithms (eight of ten case studies), 10 cm^2 was used. The two other case studies assumed:

- 20 cm^2: representing two times the surface area of a child's open mouth (case study 12); and
- 50 cm^2: based on the maximum surface area of a toy (case study 14).

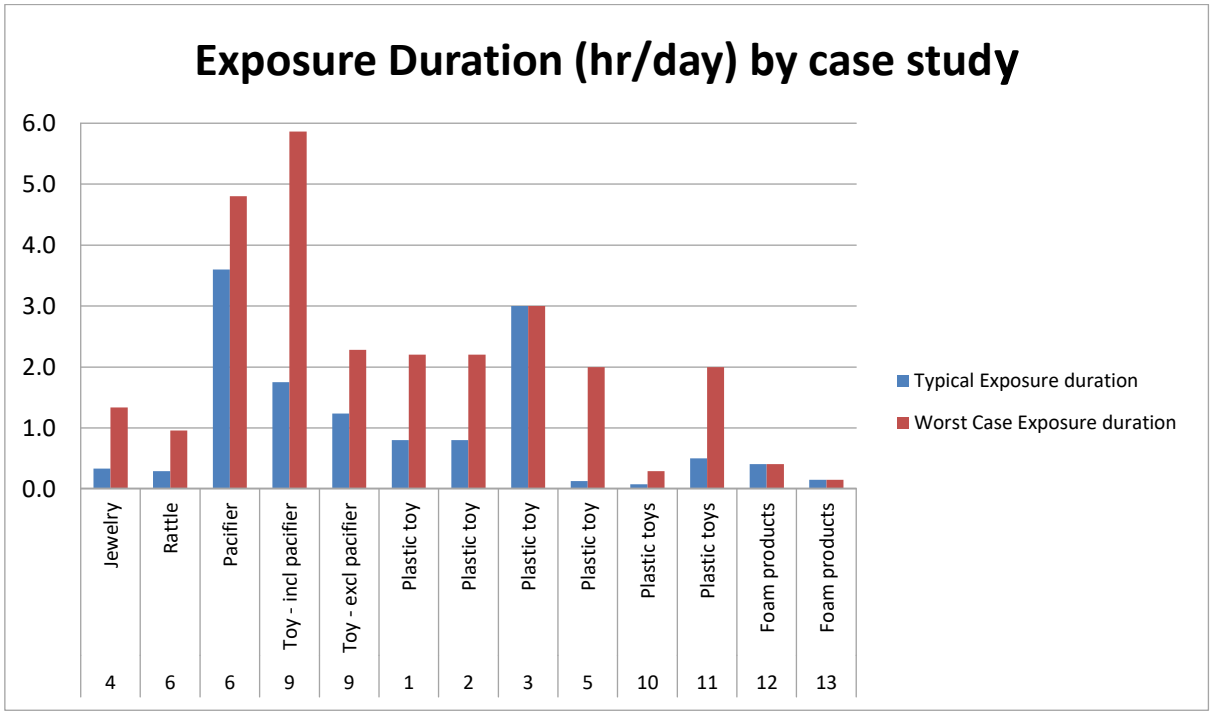
Key considerations:

- The use of 10 cm^2 is a commonly accepted surface area for mouthing activities.
- Migration studies typically use 10 cm^2; the units to describe the migration rate (e.g. $\mu g/cm^2/hr$ or $\mu g/hr$) and area of object should be considered when calculating exposure.
- The type and density of the material may be another consideration in the surface area mouthed (i.e. the surface area of paper or textile may be less than for an object made out of foam).

4) Exposure duration/time spent for mouthing product

In several of the case studies, typical and "worst-case" exposure durations were presented and a considerable amount of variability was noted (Figure 3). The maximum exposure duration was 7.7 hr/day (based on pacifiers). The highest typical exposure duration was 3.6 hr/day (also based on pacifiers) whereas the lowest typical value was 0.07 hr/day (4.2 minutes/day).

Figure 3. Comparison of exposure duration values in case studies



The exposure durations based on pacifiers are noted to be higher than exposure durations for other types of objects and may be considered a unique scenario, warranting higher exposure duration values.

For most case studies, typical durations ranged from 0.3 to 1.5 hours; 2 hours was often used as a worst-case value for plastic toys. A few case studies used very short durations of exposure as typical values (e.g. 0.07-0.15 hr/day). Standard references are provided for these values in the US Exposure Factors Handbook (US EPA, 2011[3]). The mean values for duration of contact for children <1 year range from 9 min/hr (6-12 months) to 11 min/hr (3-6 months) based on data from Juberg et al. (2001[4]), Greene (2002[5]) and Beamer et al. (2008[6]).

In case study 15, the daily mouthing time was not provided separately but was presented as two separate factors: total exposure time (hr/day) and hourly mouthing duration (min/hr). The total exposure time represented the time awake and not eating and was related to the child's age. The hourly mouthing duration was based on Greene (2002[5]) for selected objects in three age ranges (3-11, 12-23 and 24-36 months). In case study 15, mouthing of soft plastic toys resulted in higher exposure duration estimates for the 12-23 month age group than the 3-11 month age group.

These case studies provide useful sources of information and references for exposure duration.

Key considerations:

- Exposure duration is considered a KEY PARAMETER that is highly variable (typical duration values range from 0.07 to > 3 hr/day) based on the case studies.
- Consideration should be given as to whether the object is likely to be with the child often (e.g. toy vs. non-toy) as well as the potential for multiple objects to be available to a child that may contain the substance when selecting a duration of exposure.
- Specific objects may require the use of a unique exposure duration value (e.g. pacifiers).
- Different objects may result in the use of higher or lower exposure duration values.
- The case studies in Annex A provide references for selecting values for exposure durations of a specific situation. Considerations should be given to the sample size, duration of observation, age groups examined, categorization of objects and consideration of non-mouthing behaviour in selecting values from these references. A guidance document from the European Chemicals Agency ((ECHA, 2016[7]), section R.15.2.5) also provides references to information on realistic and reasonable worst case mouthing durations for specific articles. Examples such as these may be consulted for parameter values such as exposure duration if mouthed articles are considered similar.

2.4.2. Secondary parameters (sometimes present in algorithms)

1) Oral absorption

Oral absorption or oral bioavailability was considered in seven of the fifteen case studies. In most of these cases when oral bioavailability was noted (four of seven case studies), an oral absorption factor of 100% was used. In the three remaining case studies where an oral absorption factor of less than 100% was used, values ranged from 50% to 80%.

Key considerations:

- When oral absorption or oral bioavailability factors are integrated into exposure estimates, careful consideration should be given to the corresponding value used in the toxicological study (e.g. does this value also reflect a systemic dose?). In some cases, application of an oral bioavailability fraction may not be appropriate

2) Fraction of object mouthed

Only one case study (case study 6) incorporated the parameter of "fraction of object mouthed". In this case study, the fraction of object mouthed was multiplied by the amount of substance that leaches from an entire product; the derivation of the total leaching value was based on toys completely submersed in saliva for 7.75 or 24 hours. In addition, the fraction of toy surface mouthed was relatively large, in particular for rattles: 0.5 for rattles and 0.25 for pacifiers.

Key considerations

- The application of the fraction of object mouthed may be considered more appropriate when leaching rates are based on the whole object.
- When applying this factor, consideration may be given to surface area mouthed (i.e. surface area of object * fraction of object surface mouthed) compared to the 10 cm^2 commonly used in other algorithms/approaches.

3) Fraction of extraction by saliva

This parameter is described in the US EPA's Standard Operating Procedures (SOP) for Residential Pesticide Exposure Assessments (US EPA, 2012[8]). The US EPA's SOP provides background information on the derivation of recommended values for this parameter.

This parameter has been incorporated in some case studies (case studies 13 and 14) to estimate the fraction of substance transferred to saliva. In the US EPA's SOP, the saliva extraction factor is considered with parameters such the frequency of object-to-mouth contacts and the number of replenishment intervals per hour. When a saliva extraction factor is incorporated in the manner outlined in the US EPA (2012[8]), it may have a smaller impact on the exposure value.

Key considerations

- When considering the use of a saliva extraction factor, it may be beneficial to refer to the US EPA's SOP as an example of a method to integrate this factor into a mouthing algorithm.
- Careful consideration should be given when incorporating this factor to avoid duplication (e.g. incorporating this factor with a migration rate value may be considered inappropriate).

4) Percentage of the substance on surface of the object

This parameter was applied in a case study (case study 14) where the object was impregnated with a substance, however, only the amount available on the surface was considered available for ingestion.

Key considerations

- The treatment of a surface with a substance (e.g. treated surface) vs. impregnation throughout can play a role in both the amount of substance available for uptake and the rate of migration. Consideration should be given to the role of the substance in the material and whether it is expected to be evenly distributed throughout a given object or only at the surface.

5) Probability that the object contains the substance

Factors describing the probability that the object contains the substance were infrequently applied in the case studies. Two of the fifteen case studies applied such probability factor.

Case study 7 included a probability of presence of the substance in textile and a probability of textile used in the object. In this case study, a factor of 15-25% was applied to describe the probability of a textile containing the substance and a 20% probability factor for the toy being made from this textile. This case study is unique as it estimates lifetime exposure and compares to a negligible risk level (i.e. one in a million additional cancer risk).

Case study 15 used a probabilistic analysis, incorporating migration rates of zero with the migration rates measured in products to preserve the ratio of products containing/not containing DINP for articles in the soft plastic toys category as reported in Chen (2002[9]). The authors of the published article (Babich et al., 2004[10]) evaluated the impact of this assumption. They reported that if DINP was assumed to be present in all soft plastic toys, the estimated exposure would increase by about a factor of two which did not affect the assessment's conclusion.

Key considerations:

- Consideration should be given regarding the toxicological endpoint being assessed (e.g. non-cancer vs. cancer) and whether it is appropriate to use a probability factor for estimating mouthing exposures. The exposure estimate, when using a probability factor, will no longer represent the estimated exposure 'on the day of exposure'.

2.5. Exposure Values

Comparison of exposure values between the case studies should be viewed with caution as the exposure estimates are based on different chemicals, different matrices and, in some cases, for different purposes (e.g. acute vs. chronic risk). However, a general comparison of the exposure values was performed to examine the range of exposure values as well as to examine the influence of some parameters in these approaches. Typical exposure values for the case studies ranged from 0.0025 to 78.5 (µg/kg bw per day) for children in the <1 year age category, including case studies 12 and 13, that did not present a separate value for <1 year old. Approximately 2/3 of the case studies showed exposure values >1 µg/kg bw per day, and over one half of those case studies showed >10 µg/kg bw per day. Estimated exposure values based on worst-case parameters ranged up to 250 µg/kg bw per day.

Figure 4 presents exposure values calculated from the parameters presented in the case studies. "Typical" values represent exposure estimates based on typical exposure durations and/or mean migration rates. Worst-case values were calculated based on maximum (or high-end) migration values and/or high-end exposure duration values as presented in the case studies.

The highest typical exposure estimate was derived in a case study (case study 13) with the algorithm using the salivary flow rate and water solubility of the substance (TCEP) with various factors (e.g. saliva extraction factors). TCEP is reported to have relatively high water solubility, so extractability by saliva is considered to be an appropriate approach.

The next highest exposure estimate was the case study for DIBP in plastic toys (case study 11). In this case, the migration rate was much higher than typical migration rates used in other case studies. In this case study, migration rates ranging from 3.7 to 94 µg/cm^2/hr were cited, and the highest value was used in the exposure estimate (94 µg/cm^2/hr). Although a very high migration rate value was used, it is noted that the overall exposure estimate was not out of the range of exposure estimates for other phthalate and related substances in similar materials (e.g. plastic toys).

For most case studies with very low exposure estimates (i.e. below 0.03 µg/kg bw per day), specific characteristics were noted:

- very low migration rates (TCDPP, BPA); or
- low concentrations of substances in the objects (EPTAC).

Exposure estimates between 1 and 10 µg/kg bw per day, appear to be influenced by the use of lower values to estimate exposure duration (e.g. case study 10 (DEHT), case study 12 (TCPP) and case study 5 (DINP/DIDP))

Figure 4. Comparison of exposure values in case studies

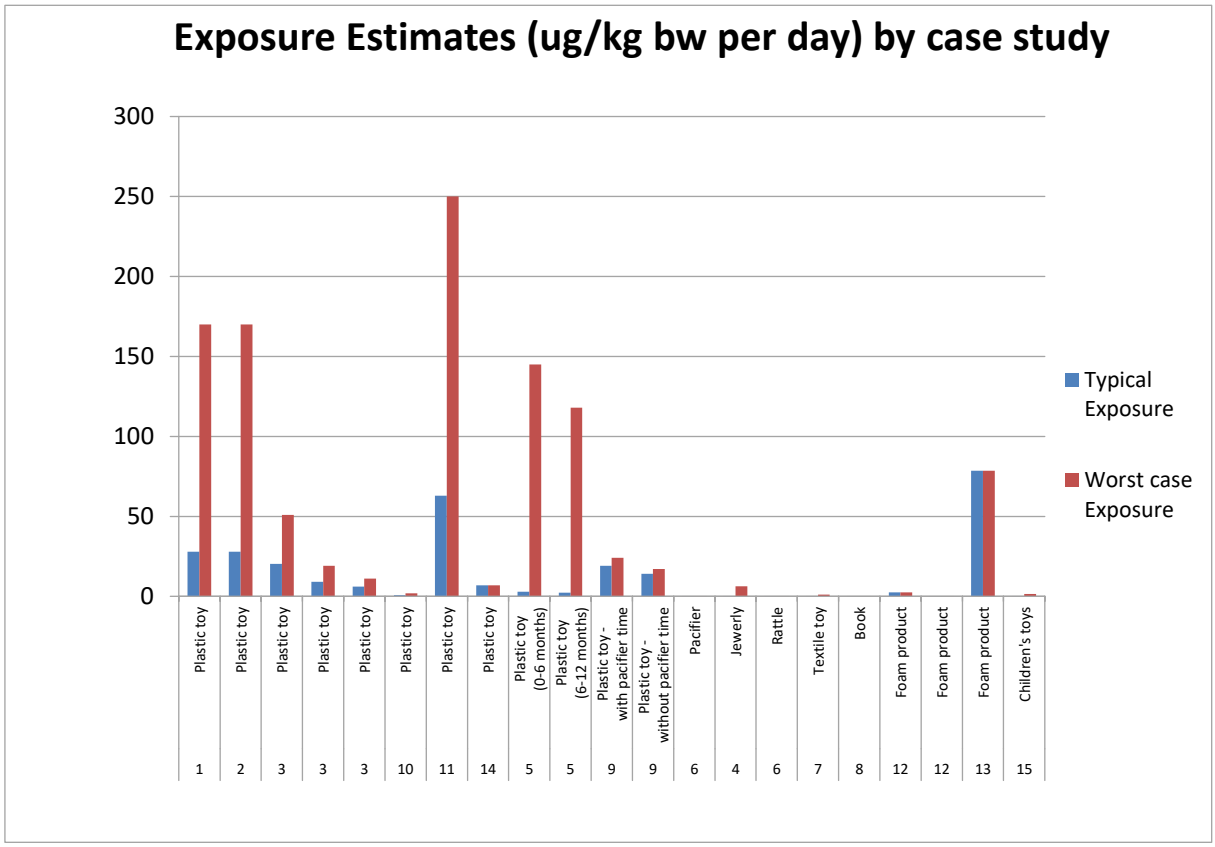


Table 3 compares the ranking of two key parameters (i.e. migration rate and exposure duration) with typical values for each of the case studies. Based on this comparison, it is noted that although case study 13 has the highest typical exposure value, migration rate and exposure duration do not appear to be significant factors in this estimate. In case studies 11, 1 and 2, relatively high migration rates appeared to have influenced exposure whereas

for case studies 3 and 9, relatively high exposure durations appeared to be an important parameter.

Table 3. Ranking by primary parameters (migration rates and exposure durations)

Case Study	13	11	1	2	3	9	9	3	14	3	5	12	5	10	15	7	12	4	6	8	6
Rank: Migration Rate (typical)	n/a	1	2	3	8	6	6	10	n/a	11	5	9	5	7	4	n/a	12	n/a	n/a	n/a	n/a
Rank: Duration (typical)	11	7	5	6	2	3	4	2	n/a	2	12	8	12	13	n/a	n/a	8	9	1	n/a	10

Key considerations:

- Consideration should be given as to whether the exposure estimate is for acute, intermittent or chronic exposure scenarios based on parameters and assumptions used.
- Consideration should be given as to whether the exposure estimate from mouthing will be aggregated with other exposures for the infant/child (e.g. exposures from dust ingestion, indoor air, food, nursing and cosmetics such as diaper creams).
- Consideration should be given to the full range of concentrations a substance could be present in as well as the range of materials available to children containing the substance when deriving exposure estimates.
- In the absence of data, conservative assumptions should be used to ensure that exposure estimates do not underestimate exposure.

2.6. Hazard Endpoints

The hazard endpoints used in each case study are summarised in Table 4. A variety of endpoints has been used in case studies, representing short-term and chronic exposure scenarios. This information has been included to demonstrate the types of endpoints that have been selected in the risk characterisations for various scenarios identified in the case studies.

Table 4. Hazard endpoints identified in case studies

Case Study	Substance	Endpoint
1	DINP	Oral NOAEL = 88 mg/kg/day (liver and kidney weights); 50 mg/kg bw per day (fertility-related effect: reduced testosterone); 50 mg/kg bw per day (developmental effect – reduced pup weight)
2	DBP	Oral NOAEL = 10 mg/kg bw per day (developmental effect – reduced fetal testosterone)
3	DINCH	NOAEL: 100 mg/kg bw per day based on a complete toxicological dataset available, including a chronic rat bioassay and a 2-generation reproduction study in rats (EFSA, 2008).
3	DEHT	NOAEL: 79 mg/kg bw per day based on a complete toxicological dataset available, including a chronic rat bioassay and a 2-generation reproduction study in rats (EFSA, 2008).
3	TMPDB	NOAEL: 30 mg/kg bw per day on a toxicological dataset with limited data on toxicokinetics in rats, acute and subacute toxicity in rats, skin/eye irritation and dermal sensitisation studies, semichronic toxicity in rats and dogs, genotoxicity, reproduction toxicity and developmental toxicity (EFSA, 2006).
4	Lead	Bench Mark Dose Level (BMDL): 0.5 µg/kg bw per day, equivalent to a blood level increase of 1.2 µg/L and an IQ reduction of 0.1 point (EFSA, 2013)
5	DINP	*Repeated dose toxicity:* oral NOAEL: 15 mg/kg bw per day (2-year study; significant increases of incidence of spongiosis hepatis together with other signs of hepatotoxicity), Oral DNEL for children 0.075 mg/kg bw per day, *Reproductive toxicity* NOAEL: 50 mg/kg bw per day (targeted developmental toxicity study; decreases foetal testicular testosterone concentration during critical time window of sexual differentiation and increased incidence of multinucleated gonocytes and Leydig cell aggregates)
5	DIDP	*Repeated dose toxicity:* oral NOAEL: 15-60 mg/kg bw per day (90-day rat and dog 2-year study rat; liver effects), oral DNEL 0.075 mg/kg bw per day *Reproductive toxicity* NOAEL: 33-52 mg/kg bw per day (reduced body weight in F2 pups in two generation reproductive toxicity study), Oral DNEL for children: 0.26 mg/kg bw per day
6	BPA	Based on literature review the hazard endpoint was based on studies in which BPA was found to affect kidney and liver weight in parental animals and in all the generations of rats. Toxicokinetic modeling (PROAST) simulated a 95% confidence interval (95% CI) for a benchmark response (BMR_{10}) at which kidney and liver size are increased with at least 10% (Tyl et al. 2008). The lower end of the 95%CI represents a Bench Mark Dose Level ($BMDL_{10}$) which was simulated to be 8960 µg/kg bw per day. The $BMDL_{10}$ is considered to be the endpoint for "general toxicity" in hazard characterisation. Using data on toxicokinetics, this BMDL10 was converted to an HED of 609 µg/kg bw per day. The CEF Panel applied a total uncertainty factor of 150 (for inter- and intra-species differences and uncertainty in mammary gland, reproductive, neurobehavioural, immune and metabolic system effects) to establish a temporary Tolerable Daily Intake (t-TDI) of 4 µg/kg bw per day.
7	2,4-toluenediamine	The negligible risk level (NRL), corresponding to one in a million additional cancer risk, derived for benzidine using human data is 0.004 ng/kg bw per day, which is also used for 2,4-toluenediamine. However, when using animal data, the NRLs would amount 3.2 and 5.6 ng/kg bw per day for benzidine and 2,4-TDA, respectively.
8	EPTAC	Summary of risk characterisation (included repeat dose toxicity, carcinogenicity and reproductive toxicity) concluded that the lowest MOS, derived for the cosmetic scenarios, may be applied to all scenarios
9	DINP	Oral NOAEL = 150µg/kg/day; weight loss and increase in relative organ weight of liver and kidney at 15 mg/kg bw per day (2 years), F344 male rat; long-term; uncertainty factor: 100.
10	DEHT	The reproductive NOAEL was 158 mg/kg-d in a two-generation study in SD rats, based on parental effects (Faber et al. 2007b). The developmental NOAEL was 458 mg/kg-d in rats, based on increased incidence of 14th rudimentary ribs (Faber et al. 2007a). DEHT did not produce antiandrogenic effects in rats at 750 mg/kg-d (Gray et al. 2000). No developmental effects were observed in mice (Faber et al. 2007a).
11	DIBP	Oral NOAEL = 300 mg/kg/day; Testicular pathology at 500 mg/kg bw per day (7 d)
12	TCPP	Based on the overall data available on health effects of TCPP, the critical effects for characterisation of risk to human health associated with exposure to TCPP are reproductive and developmental toxicity. In a two-generation reproductive toxicity study in rats, a LOAEL of 99 mg/kg bw per day, the lowest dose level tested, was identified for both reproductive and developmental effects (TNO Quality of Life 2007 cited in EU RAR 2008a). In a 13-week dietary study (Stauffer Chemical Co. 1981c cited in EU RAR 2008a and likely published by Freudenthal and Henrich 1999), a significant increase in liver weights in male rats was reported starting from the lowest dose tested of 52 mg/kg bw per day.
12	TDCPP	The critical effect for characterisation of risk to human health associated with exposure to TDCPP is carcinogenicity. A dose-response analysis of each tumour site by BMDS shows that the testis (interstitial cell tumour in male rats) is the most sensitive organ with a $BMDL_{10}$ of 6.74 mg/kg bw per day. For non-cancer effects, a chronic critical LOAEL of 5 mg/kg bw was identified, where hyperplasia of the epithelium of the convoluted tubule in the kidneys, and histological abnormalities in the testes, were observed in males at the lowest dose tested in a two-year chronic toxicity study in rats

Case Study	Substance	Endpoint
13	TCEP	With respect to non-cancer effects, the lowest LO(A)EL for short-term and subchronic exposures was 44 mg/kg-bw per day based on increased relative liver and kidney weights in a 16-week oral rat study. Renal tubular hyperplasia along with renal tubule and thyroid tumours were also observed at 44 mg/kg/day, the lowest dose tested in the 2-year rat study.
14	Triclosan	Database NOAEL of 25 mg/kg bw per day from sub-chronic 90-day oral toxicity study in the mouse (target MOE of 300); protective for potential liver effects, if any, that could occur in humans as well as effects in other organs and systems
15	DINP	ADI of 120 µg/kg/-day Authors indicate: liver is the most sensitive organ site. Lington et al. 197 study of liver effects in the rate NOAEL of 15 mg/kg-day (lower than that of the study of Moore 1998) used for basis of the ADI value. The CHAP applied a benchmark dose approach to estimate an ADI by fitting incidence data for spongiosis hepatis to a polynomial model (CPSC 2001). The maximum likelihood estimate (MLE) of the dose at 5% extra risk (D05) is 12 mg/kg/day. Applying an uncertainty factor of 100-fold results in an ADI of 120 µg/kg-day"

Key considerations:

- A wide variety of endpoints was considered in the case studies including short-term, reproductive, developmental and chronic endpoints.
- The type of product, prevalence of substance in other products (or other sources of exposure) and the timing of the exposure period (e.g. product used by infants, children or teens) may also play a role in the consideration of the endpoint.

2.7. Conservatism and Uncertainties

Table 5 summarises details provided within each case study regarding the level of conservatism and/or uncertainties associated with the mouthing scenario. Seven of the fifteen case studies used '**typical/reasonable and worst case**' and five of the fifteen case studies used '**worst-case**' or '**conservative or highly conservative**' scenarios. The remaining three case studies did not provide sufficient details regarding the level of conservatism used.

Table 5. Summary of the Level of Conservatism and Uncertainty across 15 Case Studies

Case Study	Level of Conservatism	Uncertainty or Limitations
1	Based on **typical and worst case** scenarios. A range of migration rate studies was considered, and the most conservative assumption was applied in the exposure scenarios.	Uncertainties in characterising the risk arise mainly from inadequate data, assumptions made during the process and variability in experimental conditions. They include absence of Australian specific data on children's mouthing behaviours, absence of specific information on migration rate (as a secondary plasticizer) from plastic matrices through the skin.
2	Exposure parameters and estimated daily internal doses were calculated based on **typical and worst case** scenarios.	Uncertainties in characterising the risk arise mainly from inadequate data, assumptions made during the process and variability in experimental conditions. They include absence of Australian specific data on children's mouthing behaviours and absence of specific information on migration rate (as a secondary plasticizer) from plastic matrices through the skin.
3	This scenario should be viewed as a **worst-case** default for mouthing by a young child. The starting point is a child with a body weight of 8 kg (age: about 10 months), who mouths a toy 3 hours per day. Children of this age show the most frequent mouthing-behaviour and have a low body weight. The exposure due to mouthing by children of this age will be the highest.	Uncertainties are not discussed in detail, because calculated margins of safety are very high, leading to the conclusion that these compounds are not expected to pose any health risk for toy-users at the migrated levels.

Case Study	Level of Conservatism	Uncertainty or Limitations
4	**Realistic and reasonable worst-case** scenarios are included. Mouthing times are based on information from mouthing of items/objects considered most representative for the articles intended to be restricted, i.e. items not including pacifiers, teethers, toys and fingers.	Very limited data is available on migration and the relationship between the migration rate and the lead content of materials. The 120 min of mouthing per day for 24-36 months old children are likely to be overestimates because only data from one study were used and these data were rather skewed.
5	**Typical and reasonable worst case** estimates for mouthing duration and migration rates.	The reasonable worst case mouthing time integrated data from several observational studies. There are uncertainties attached to this estimate as a consequence of the limitations and discrepancies in the data, as well as the skewness and difficulties to determine appropriate article categories. The possible mouthing of items during sleeping time was not taken into account in any of the estimates.
6	An **average scenario** is described with average values for all parameters, including sucking times (Juberg et al., 2001[4]). A **high-exposure scenario is considered as well,** with the same average parameters, but with P75 sucking times.	Data on occurrence, migration and transfer from non-food sources are scarce. An absorption percentage of 100% was used for ingestion in the calculation from external to internal exposure. The impact of uncertainty of each parameter on the exposure estimate is within ±20% for sucking times, about a factor of 0.5-2 for the fraction of surface and about a factor of 0.5-0.8 for the body weight.
7	The oral exposure was based on the assumption that all present azo dye is eventually ingested by the infant. The underlying assumption is that an infant is often very attached to its toys. In addition, the oral exposure was calculated based on mouthing of one toy.	For the exposure assessment, it was assumed that the prevalence was the same in toys as was for textile, with an additional correction for toys that do not contain textile.
8	Measurement of how EPTAC migrates from a booklet, when exposed to a child's saliva and mouthing activity, have not been made. Therefore, this estimate is based **on worst-case** assumptions.	Not noted.
9	Not provided.	Migration rate was based on adult data.
10	Exposure duration: mean and 95th percentile values (use of mouthing durations for the category "all soft plastic articles except pacifiers" provides a **reasonable upper bound estimate** for children's exposure from mouthing PVC children's products), migration rate: mean and 95th percentile.	The scenario-based exposure assessment presented in this example of phthalate exposure was made for individual sources such as toys, personal care products, and household products. However, the charge to the CPSC's CHAP was to conduct a cumulative risk analysis. This led to additional uncertainties because data on the exposures associated with all routes of entry into the body were not consistent for each potential source of one or more compounds. In addition, the toxicological data were normally obtained via oral exposure, whereas human exposure occurs by multiple routes.
11	Time parameters (0.5 to 2 hr/day): **typical and worst case scenarios,** respectively.	A range of migration rate studies was available reducing uncertainty for this parameter. Conservatisms were incorporated into the selection of migration rate values.
12	Estimates considered to be based on **conservative assumptions.**	The use of a passive migration rate may underestimate oral exposure from mouthing or sucking a foam object, an activity which is expected to be associated with a more active migration of the substance.
13	Exposures of infants and toddlers from mouthing of foam are **considered overestimates**, as the assumptions incorporated are **conservative** (of note: some of the factors may not necessarily be conservative, e.g. the 0.22 mL/min salivary flow rate is an unstimulated flow rate and a higher flow rate may be possible if stimulated by mouthing. In addition, 50% was used for the oral absorption factor).	Low confidence in the modelled estimates of exposure from consumer products, as there is a lack of data on specific types of products containing TCEP found in Canada and on the various chemical-specific parameters needed to estimate exposures to consumer products.
14	Aggregate exposure was calculated for infants. This was considered **highly conservative** (i.e. the combination of object-to-mouth, hand-to-mouth and nursing/breastfeeding exposures).	There is an uncertainty regarding the potential co-occurrence of all identified scenarios in practice. An assumption that a child will be exposed daily to high residues as identified for each scenario is considered conservative. The assumption that all potential exposure scenarios will co-occur also represents conservatism in the aggregate assessment for infants 6–12 months of age. Further, assumptions used in incidental oral exposure assessments (i.e. hand-to-mouth and object-to-mouth) are considered conservative, since it is unlikely that all plastic toys and carpets will be made with treated materials.
15	Probabilistic analysis performed based upon distributional data for each endpoint in equation. Detailed studies were done to provide data on DINP migration and mouthing time specific to soft toys.	Similar conclusions result if mean or 99th percentile exposure values are used for each age group. However, further analyses were also done to estimate the impact of several of the assumptions in this approach. For example, if DINP was assumed to be present in all soft plastic toys rather than 42%, exposures accordingly increased by about a factor of 2 which did not impact the conclusion.

3. Overall Considerations

Age group and mouthing material:

The case studies demonstrated that consideration should be given to the age group selected (e.g. exposures may be higher in a certain age group) as well as the choice of material mouthed (e.g. toy vs. non-toy objects). Juberg et al. (2001[4]) also found that mouthing behaviour is dependent on age and the types of items that are mouthed. In addition, children between the ages of 0 and 18 months were found to mouth objects for different durations compared to 19 to 36 months. The case studies also revealed a wide variability in the types of objects mouthed, including many non-toy objects.

Algorithms:

When migration data is available, algorithms/approaches for estimating mouthing exposure are relatively consistent. If the migration data is considered of adequate quality and representative of the substance/object being examined, the parameter with the most variability and uncertainty may be "duration of exposure".

In the absence of migration data, various approaches were used. A straightforward approach noted in some case studies is to use the total amount of substance in the object and apply factors to describe the amount that would be available to be ingested through mouthing activities. These factors have a large amount of uncertainty and several considerations should be taken into account when determining such factors.

Parameters:

Careful consideration should be given to the selection of the mean, reasonable worst-case or maximum value for the migration rate to be used in the algorithm. The strength and relevance of the migration rate study should be carefully considered, including the protocol and the range of product concentrations including examining a wider range of migration rates across a variety of substances to identify potential maximum or high-end values that could potentially be applied in situations where data is lacking.

The use of 10 cm^2 is a commonly accepted surface area for mouthing activities. The type and density of the material is an important consideration in the surface area mouthed (i.e. the surface area of paper or textile may be less than for an object made out of foam).

Exposure duration is considered a KEY PARAMETER that is highly variable (typical duration values range from 0.07 to > 3 hr/day) based on the case studies. Consideration should be given as to whether the object is likely to be with the child often (e.g. toy vs. non-toy) as well as the potential for multiple objects to be available to a child that may contain the substance when selecting a duration of exposure. Specific objects may require the use of a unique exposure duration value (e.g. pacifiers). Different objects may result in the use of higher or lower exposure duration values.

When oral absorption or oral bioavailability factors are integrated into exposure estimates, careful consideration should be given to the corresponding value used in the toxicological study. In some cases, application of an oral bioavailability fraction may not be appropriate.

The application of the fraction of object mouthed may be considered more appropriate when leaching rates are based on the whole object.

When considering the use of a saliva extraction factor, it may be beneficial to refer to the US EPA's SOP as an example of a method to integrate this factor into a mouthing algorithm. Careful consideration should be given when incorporating this factor to avoid duplication (e.g. incorporating this factor with a migration rate value may be considered inappropriate).

The treatment of a surface with a substance (e.g. treated surface) vs. impregnation throughout can play a role in both the amount of substance available for uptake and the rate of migration. Consideration should be given to the role of the substance in the material, whether it is expected to be evenly distributed throughout a given object or only at the surface.

Exposure values:

Consideration should be given as to whether the exposure estimate from mouthing will be aggregated with other exposures for the infant/child. Consideration should be given to the full range of concentrations a substance could be present in as well as the range of materials available to children containing the substance when deriving exposure estimates. In the absence of data, conservative assumptions should be used to ensure that exposure estimates do not underestimate exposure.

Hazard Endpoints:

Hazard endpoint information may be kept in mind when reflecting upon approaches to estimate exposure. For example, if the toxicological endpoint is considered relevant for short term or intermittent exposures, it may be important to reflect this in the exposure approach. In such cases, approaches using factors such as a probability factor may not represent exposure 'on the day of exposure' for an individual exposed to the product.

Conservatism and Uncertainty:

Overall, when there is a considerable amount of uncertainty, conservative values are often recommended. In particular when considering children <1 year, it has been noted that this age group is often teething and generally has demonstrated high frequency of mouthing events.

References

Babich, M. et al. (2004), "Risk assessment of oral exposure to diisononyl phthalate from children's products", *Regulatory Toxicology and Pharmacology*, Vol. 40/2, pp. 151-167, http://dx.doi.org/10.1016/j.yrtph.2004.06.005. [10]

Beamer, P. et al. (2008), "Quantified activity pattern data from 6 to 27-month-old farmworker children for use in exposure assessment", *Environmental Research*, Vol. 108/2, pp. 239-246, http://dx.doi.org/10.1016/j.envres.2008.07.007. [6]

Chen, S. (2002), *Screening of Toys for PVC and Phthalates Migration*, US Consumer Product Safety Commission, Bethesda, MD. [9]

ECHA (2016), *Guidance on Information Requirements and Chemical Safety Assessment. Chapter R.15: Consumer exposure assessment Version 3.0*, ECHA-16-G-07-EN, http://echa.europa.eu/documents/10162/13559/mb_63_2013_consultation_procedure_for_gui. [7]

Greene, M. (2002), *Mouthing times among young children from observational data*, US Consumer Product Safety Commission, Bethesda, Maryland. [5]

Juberg, D. et al. (2001), "An observational study of object mouthing behavior by young children", *Pediatrics*, Vol. 107/1, pp. 135-142, http://www.ncbi.nlm.nih.gov/pubmed/11134447. [4]

Simoneau, C. et al. (2001), *Validation of methodologies for the release of di-isononylphthalate (DINP) in saliva simulant from toys*, European Commission DG-Joint Research Center, Food Products Unit, Institute for health and Consumer Protection, I-21020, https://ec.europa.eu/jrc/sites/jrcsh/files/Simoneau%20EUR%2019826%20EN%20toys%20DINP.pdf. [1]

US EPA (2017), *Indoor Exposure Product Testing Protocols Version 2.0*, Office of Chemical Safety and Pollution Prevention – Document #740-S1-7002, Washington DC, https://www.epa.gov/sites/production/files/2018-01/documents/indoor_exposure_testing_protocols_version_2.pdf. [2]

US EPA (2012), *Standard Operating Procedures for Residential Pesticide Exposure Assessment*, http://www.epa.gov/oppfead1/trac/science/. [8]

US EPA (2011), *Exposure Factors Handbook 2011 Edition*, EPA/600/R-09/052F, Washington DC, https://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=236252. [3]

Annex A. Case Studies

EXAMPLE 1: Mouthing of toys containing phthalates – DINP used as a primary

<table>
<tr><th colspan="4">EXAMPLE 1: Mouthing of toys containing phthalates – DINP used as a primary plasticizer in children's toys and childcare articles (submitted by Australia)</th></tr>
<tr><td colspan="4">Information on identity of substance</td></tr>
<tr><td>CAS RN:
68515-48-0; 28553-12-0 (DINP)</td><td>Common Names:
Diisononyl phthalate (DINP)

(High molecular weight phthalate)</td><td>Product/material type reported in Australia:
toys; play and exercise balls; hoppers</td><td>Notes: DINP can be found in plasticine, in several categories of toys (plastic books, balls, dolls and cartoon characters) and in baby products (changing mats/ cushions) that could be placed in the mouth, although this is not the purpose for which they were designed. DINP was also found in other articles for/or in contact with children (clothes, mittens, covers for pacifiers, PVC-containing soap packaging and shower mats).</td></tr>
<tr><td colspan="4">Description of chemical specific information available/necessary for the exposure scenario</td></tr>
</table>

<table>
<tr><td>Concentration of substance in a given product or matrix:

Concentration range of 0.005% to 35% DINP in Australian imported PVC toys

A concentration of 43% DINP as a primary plasticizer was used based on in vivo studies measuring the migration of plasticizer in toys that are likely to be mouthed by children, into the saliva as a function of time (migration rate) (Chen 1998; Meuling and Rijk 1998)</td><td colspan="2">Migration rate:(µg/cm^2/hr)

Typical exposure = 26.03 (Chen 1998)
Worst case exposure = 57.93 (Chen 1998)</td><td>Physiochemical properties (e.g. water solubility):
Not used in the quantitative assessment of exposure from mouthing in this approach</td><td>Notes:
Oral exposure was modelled by: estimation of highest plausible concentrations of DINP as a primary plasticizer in toys and childcare articles in Australia; and estimation of children’s mouthing time of toys and childcare articles based on overseas data which is assumed to be similar to Australian children’s mouthing activities and behaviours estimation of the migration rate of DINP from PVC matrix into saliva based on experimental studies on the extractability of phthalate under various mouthing conditions</td></tr>
<tr><td colspan="5">Type of hazard endpoint: Oral NOAEL = 88 mg/kg/day (liver and kidney weights); 50 mg/kg bw per day (fertility-related effect: reduced testosterone); 50 mg/kg bw per day (developmental effect – reduced pup weight)</td></tr>
<tr><td colspan="5">Description of exposure scenario: Not provided</td></tr>
<tr><td>Population(s)/age group:
6-month-old infant</td><td colspan="2">Exposure frequency:
Daily</td><td colspan="2">Duration of exposure:
0.8 hr/day (typical); 2.2 hr/day (worst-case)</td></tr>
<tr><td rowspan="3">Algorithm Used

Internal dose via the oral dose ($D_{int,oral}$ µg/kg bw per day)

$$D_{int,oral} = \frac{M \bullet S_{mouth} \bullet t \bullet n \bullet \frac{B_{oral}}{100}}{BW}$$</td><td>Parameter Definitions:</td><td>Source/Reference for Parameters</td><td colspan="2" rowspan="3">Justification for Algorithm:
The values used in the parameters were derived from peer-reviewed studies. Where possible the most conservative values were used in the calculations of risk estimates and margins of exposure from mouthing toys and childcare articles.

The exposure estimates were made for</td></tr>
<tr><td>M = migration rate (26.03 µg/cm^2/hr for typical exposure; 57.93 µg/cm^2/hr for worst case exposure)</td><td>Chen 1998</td></tr>
<tr><td>S_{mouth} = surface area of a child’s open mouth (10 cm^2)</td><td>LGC 1998</td></tr>
</table>

	t x n = mouthing time (hr/day) x frequency (0.8 hr (typical); 2.2 hr/day (worst-case)	Greene 2002 (typical) Groot el al 1998; Juberg et al. 2001(worst-case)	six-month-old infants who demonstrate the maximum mouthing behaviour. The bioavailability of DINP via the oral route was estimated to be 100% based on animal studies.
	BW = child body weight (7.5 kg based on 6-month-old child) B_{oral} = bioavailability via the oral route (100%)	US EPA 2006	
Exposure Estimate based on algorithm and parameters: Estimated daily internal dose from oral exposure for 6-month-old infant mouthing toys and childcare articles are: **27.8 µg/kg bw per day** (typical exposure) and **169.9 µg/kg bw per day** (worst case exposure)			
Qualification in terms of the level of conservatism: Exposure parameters and estimated daily internal doses were calculated based on typical and worst case scenarios.			
Uncertainties or limitations associated with the scenario: Uncertainties in characterising the risk for DINP arise mainly from inadequate data, absence of Australian specific data on DINP content in toys and childcare articles, absence of Australian specific data on children's mouthing behaviours, and specific information on migration rate of DINP from plastic matrices through the skin. A range of migration rate studies was considered, and the most conservative assumption was applied in the exposure scenarios.			
Links to the Publication: Priority Existing Chemical Assessment Report No.35 Diisononyl phthalate: https://www.nicnas.gov.au/chemical-information/pec-assessments Phthalates – Final hazard assessments and compendium: https://www.nicnas.gov.au/chemical-information/other-assessment-reports/phthalates-hazard-assessment-reports NICNAS Inventory Multi-tiered Assessment and Prioritisation (IMAP) Tier II – Human Health (C4–6 side chain transitional phthalates), https://www.nicnas.gov.au/chemical-information/imap-assessments/imap-group-assessment-report?assessment_id=1126#cas-A_84-74-2			

References:

Chen SB (1998), Migration of DINP from polyvinyl chloride (PVC) children's products. Annex A to 'The risk of chronic toxicity associated with exposure to diisononyl phthalate (DINP) in children's products' by Babich MA (1998), US Consumer Product Safety Commission.

ECB (European Chemicals Bureau) (2003), European Union Risk Assessment Report on 1,2-benzenedicarboxylic acid, di-C8-10-branched alkyl esters, C9-rich and di-'isononyl' phthalate (DINP).

Greene MA (2002), Mouthing times among young children from observational data. Bethesda, MD, US Consumer Product Safety Commission.

Juberg DR, Alfano K, Coughlin RJ, Thompson KM (2001), An observational study of object mouthing behavior by young children, Pediatrics, Vol. 107/1, pp. 135-142.

LGC (Laboratory of the Government Chemist) (1998), Laboratory-based agitation methods for the determination of phthalate plasticizer migration from PVC toy and child-care articles: LGC Technical Report No.: LGC/1998/DTI/009. Teddington, Middlesex, UK.

US EPA (2006), Child-specific exposure factors handbook (External Review Draft). http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=56747

EXAMPLE 2: Mouthing of toys containing phthalates – DBP used as a secondary plasticizer

<table>
<tr><th colspan="4">EXAMPLE 2: Mouthing of toys containing phthalates – Dibutyl phthalate (DBP) used as a secondary plasticizer in children's toys and childcare articles (submitted by Australia)</th></tr>
<tr><td colspan="4">Information on identity of substance</td></tr>
<tr><td>CAS RN: 84-74-2 (DBP)</td><td>Common Names: Dibutyl phthalate (DBP)
(Transitional phthalate)</td><td>Product/material type reported in Australia: play and exercise balls, children's toys and childcare articles.</td><td>Notes: DBP can be found in plasticizer for rubber and PVC consumer products that could be placed in the mouth by children, although this is not the purpose for which they were designed.</td></tr>
<tr><td colspan="4">Description of chemical specific information available/necessary for the exposure scenario</td></tr>
<tr><td>Concentration of substance in a given product or matrix:
Concentration range of 0.45% DBP to 40% of phthalate composites in imported PVC toys in Australia.

A concentration of 0.5% DBP as secondary plasticizer is used based on literature review of analytical studies of toys as well as the reported maximum DBP level of 0.45% in children's toys by the Australian industry.</td><td>Migration rate:(µg/cm^2/hr)

26.03 µg/cm^2/hr for a mouthing time of 0.8 hr/day (i.e. typical exposure scenario);

57.93 µg/cm^2/hr for a mouthing time of 2.2 hr/day (i.e. worst-case exposure scenario) (Chen 1998), based on the assumption that the mixed phthalate (0.5% DBP + 42.5% DINP) has the same migration rate as for 43% DINP.</td><td>Physiochemical properties (e.g. water solubility): Not used in the quantitative assessment of exposure from mouthing in this approach</td><td></td></tr>
<tr><td colspan="4">Type of hazard endpoint: Oral NOAEL = 10 mg/kg bw per day (developmental effect – reduced fetal testosterone)</td></tr>
<tr><td colspan="4">Description of exposure scenario</td></tr>
</table>

<table>
<tr><td colspan="2">Population(s)/age group:
6-month-old infant</td><td colspan="2">Exposure frequency: Daily</td><td colspan="2">Duration of exposure:
0.8 hr/day (typical); 2.2 hr/day (worst-case)</td></tr>
<tr><td colspan="2" rowspan="5">Algorithm Used

Internal dose via the oral dose
($D_{int,oral}$ µg/kg bw per day)

$D_{int,oral} = \frac{M \times S_{mouth} \times t \times n \times B_{oral}}{BW}$</td><td>Parameter Definitions:</td><td>Source/Reference for Parameters</td><td>Justification for Algorithm:</td></tr>
<tr><td>M = migration rate (26.03 µg/cm^2/hr for typical exposure; 57.93 µg/cm^2/hr for worst case exposure)</td><td>Chen 1998</td><td rowspan="4">The values were derived from peer-reviewed studies. Where possible the most conservative values were used in the estimation of exposure from mouthing toys and childcare articles.

The exposure estimates are the maximum mouthing behaviour.

The bioavailability of DBP via the oral route was estimated to be 100% based on animal studies</td></tr>
<tr><td>S_{mouth} = surface area of a child's open mouth (10 cm^2)</td><td>LGC 1998</td></tr>
<tr><td>t x n = mouthing time x frequency (0.8 hr/day for typical exposure; 2.2 hr/day for worst-case exposure)</td><td>Greene 2002 (typical)
Groot el al 1998; Juberg et al. 2001(worst-case)</td></tr>
<tr><td>BW = child body weight (7.5 kg based on 6 month-old child)

B_{oral} = bioavailability via the oral route (100%)</td><td>US EPA 2006</td></tr>
<tr><td colspan="6">Exposure Estimate based on algorithm and parameters:
Estimated daily internal dose from oral exposure for 6-month-old infant mouthing toys and childcare articles are:
27.8 µg/kg bw per day (typical exposure) and 169.9 µg/kg bw per day (worst case exposure)</td></tr>
</table>

Qualification in terms of the level of conservatism: Exposure parameters and estimated daily internal doses were calculated based on typical and worst case scenarios.

Uncertainties or limitations associated with the scenario: Uncertainties in characterising the risk for DBP arise mainly from inadequate data, assumptions made during the process and variability in experimental conditions. They include absence of Australian specific data on children's mouthing behaviours and absence of specific information on migration rate of DBP (as a secondary plasticizer) from plastic matrices through the skin.

Links to the Publication:

NICNAS 2013. Priority Existing Chemical Assessment (PEC) assessment report No.36 Dibutyl phthalate, https://www.nicnas.gov.au/chemical-information/pec-assessments/priority-existing-chemical-assessments

NICNAS Inventory Multi-tiered Assessment and Prioritisation (IMAP) Tier II – Human Health (C4–6 side chain transitional phthalates), https://www.nicnas.gov.au/chemical-information/imap-assessments/imap-group-assessment-report?assessment_id=1126#cas-A_84-74-2

References:

Chen SB (1998), Migration of DINP from polyvinyl chloride (PVC) children's products. Annex A to 'The risk of chronic toxicity associated with exposure to diisononyl phthalate (DINP) in children's products' by Babich MA (1998), US Consumer Product Safety Commission.

ECB (European Chemicals Bureau) (2004), European Union Risk Assessment Report on dibutyl phthalate (DBP).

Greene MA (2002), Mouthing times among young children from observational data. Bethesda, MD, US Consumer Product Safety Commission.

Juberg DR, Alfano K, Coughlin RJ, Thompson KM (2001), An observational study of object mouthing behavior by young children, Pediatrics, Vol. 107/1, pp. 135-142.

LGC (Laboratory of the Government Chemist) (1998), Laboratory-based agitation methods for the determination of phthalate plasticizer migration from PVC toy and child-care articles: LGC Technical Report No.: LGC/1998/DTI/009. Teddington, Middlesex, UK.

US EPA (2006), Child-specific exposure factors handbook (External Review Draft). http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=56747

EXAMPLE 3: Non-phthalate plasticizers in toys

<table>
<tr><th colspan="4">EXAMPLE 3: Non-phthalate plasticizers in toys (Janssen and Bremmer, 2009) (submitted by RIVM)</th></tr>
<tr><td colspan="4">Information on identity of substance</td></tr>
<tr><td>CAS RN:
166412-78-8
6422-86-2
6846-50-0</td><td>Common Names:
Diisononylcyclohexanoate (DINCH)
bis(2-ethylhexyl)terephthalate (DEHT)
2,2,4- trimethyl-1,3-pentanediol diisobutyrate (TMPDB)</td><td>Product/material type:
Non-phthalate plasticizers in toys</td><td>Notes:</td></tr>
<tr><td colspan="4">Description of chemical specific information available/necessary for the exposure scenario</td></tr>
<tr><td>Concentration of substance in a given product or matrix:</td><td>Migration rate or fraction information:
Migration rate µg/(min x 10 cm^2)
DINCH 0.41 (mean), 0.86 (max)
DEHT 0.27 (mean), 0.48 (max)
TXIB: 0.87 (mean), 2.25 (max)
Oral absorption fraction (%)
DINCH 50, DEHT 60, TMPDB 80</td><td>Physiochemical properties (e.g. water solubility):
Not used in the quantitative assessment of exposure from mouthing in this approach</td><td>Notes:</td></tr>
<tr><td colspan="4">Type of hazard endpoint: Overall No Observed Adverse Effect Level (Overall-NOAEL):
DINCH 100 mg/kg bw per day based on a complete toxicological dataset available, including a chronic rat bioassay and a 2-generation reproduction study in rats (EFSA, 2008).
DEHT 79 mg/kg bw per day based on a complete toxicological dataset available, including a chronic rat bioassay and a 2-generation reproduction study in rats (EFSA, 2008).
TMPDB 30 mg/kg bw per day on a toxicological dataset with limited data on toxicokinetics in rats, acute and subacute toxicity in rats, skin/eye irritation and dermal sensitisation studies, semichronic toxicity in rats and dogs, genotoxicity, reproduction toxicity and developmental toxicity (EFSA, 2006).</td></tr>
<tr><td colspan="4">Description of exposure scenario: “A child of 8 kg mouths a surface of 10 cm^2 of the toy during 3 hours per day“</td></tr>
<tr><td>Population(s)/age group:
Toddlers (10 months)</td><td>Exposure frequency: Per day</td><td>Duration of exposure: 180 min</td><td></td></tr>
<tr><td rowspan="2">Algorithms Used
EE = (MR × SA × T) / BW</td><td>Parameter Definitions:</td><td>Source/Reference for Parameters:</td><td rowspan="2">Justification for Algorithm:
This particular scenario proposed by the CSTEE (1998a,b) is frequently used in</td></tr>
<tr><td>EE: external exposure(µg/kg bw per day)</td><td>See algorithms used</td></tr>
</table>

Internal Exposure (µg/kg bw per day) = EE × OA **Source/reference for algorithm:** CSTEE, 1998a,b	OA: oral absorption fraction (see 2) DINCH (50%) DEHT (60%) TMPDB (80%)	 NICNAS, 2008 ECC, 2007 ECC, 2007	the EU (Janssen and Bremmer, 2009). This scenario should be viewed as a worst-case default for mouthing by a young child.
	MR: migration rate (see 2)	VWA 2009	
	SA: surface area (10 cm^2)	CSTEE, 1998a,b	
	T: Mouthing Time (180 min)	CSTEE, 1998a,b	
	BW: Body Weight (8 kg)	CSTEE, 1998a,b	
Estimation result: external and internal oral exposure The exposure values presented below are based on maximum migration values. For the purpose of comparing with other case studies, "typical" exposure values were calculated using the mean migration values from section 2 of this table. The "typical" and worst case exposure estimates are presented Figure 4 of this document. TXIB: external oral exposure: 2.25 µg/(min*10 cm^2) = 2.25 * 180/8 kg = **51 µg/kg bw per day**; internal: 41 µg/kg bw per day (based on 0.8 absorption factor) DEHT: external oral exposure: 0.48 µg/(min*10 cm^2) = 0.48 * 180/8 kg = **11 µg/kg bw per day**; internal: 6.6 µg/kg bw per day (based on 0.6 absorption factor) DINCH: external oral exposure: 0.86 µg/(min*10 cm^2) = 0.86 * 180/8 kg **= 19 µg/kg bw per day**; internal: 9.5 µg/kg bw per day (based on 0.5 absorption factor)			
Qualification in terms of the level of conservatism: This scenario should be viewed as a worst-case default for mouthing by a young child. The starting point is a child with a body weight of 8 kg (age: about 10 months), who mouths a toy 3 hours per day. Children of this age show the most frequent mouthing-behaviour and have a low body weight. The exposure due to mouthing by children of this age will be the highest, expressed in mg/ kg bw (CSTEE (1998a,b).			
Uncertainties or limitations associated with the scenario: Uncertainties are not discussed in detail, because calculated margins of safety for DEHT and DINCH are very high, leading to the conclusion that these compounds are not expected to pose any health risk for toy-users at the migrated levels. For TMPDB the margin of safety was considerably lower but still above 100, which is the margin usually taken into account in deriving safe levels.			
Links to the Publication: Janssen and Bremmer. 2009. Risk assessment non-phthalate plasticizers in toys. RIVM Report dated: 9 November 2009. Report to the Dutch Food and Consumer Product Safety Authority (VWA)			

References:

CSTEE (EU Scientific Committee on Toxicity, Ecotoxicity and the Environment) (1998a), Phthalate migration from soft PVC toys and child-care articles. Opinion expressed at the CSTEE third plenary meeting Brussels, 24 April 1998.

CSTEE (1998b), Opinion on Phthalate migration from soft PVC toys and child-care articles - Data made available since the 16th of June 1998, opinion expressed at the 6th CSTEE plenary meeting, Brussels, 26/27 November 1998.

ECC (Eastman Chemical Company) (2007) Toxicity summary for Eastman® 168 plasticizer. Prepared by Product Safety & Stewardship Eastman Chemical Company Kingsport, Tennessee 37662, US. Data supplied by Eastman Kodak.

EFSA (2008), Opinion of the Scientific Panel on food additives, flavourings, processing aids and materials in contact with food (AFC) on a request related to the 18th list of substances for food contact materials Question N° EFSA-Q-2007-167, EFSA-Q-2006-177, EFSA-Q-2005-152, EFSA-Q-2007-022, EFSA-Q-2007-004, EFSA-Q-2007-024, Adopted on 31 January 2008. The EFSA Journal (2008) 628- 633, 1-19

Janssen and Bremmer (2009), Risk assessment non-phthalate plasticizers in toys. RIVM Report dated: 9 November 2009. Report to the Dutch Food and Consumer Product Safety Authority (VWA)

NICNAS (2008), Full Public Report 1,2-Cyclohexanedicarboxylic Acid, 1,2-Diisononyl Ester ('Hexamoll Dinch'). File No: STD/1259 August 2008.

VWA (Dutch Food and Consumer Product Safety Authority) (2009), Toepassing alternatieve weekmakers in speelgoed- en kinderverzorgingartikelen. Inventarisatie en migratieonderzoek [The Application of alternative plasticizers in toys and health care articles]. Ir. M.P.Y. van Vondel, Voedsel en Waren Autoriteit Regio Noord. (Deel)projectnummer: ND082211. Report dated October 2009.

EXAMPLE 4: Lead and its compounds in articles intended for consumer use

EXAMPLE 4: Lead and its compounds in articles intended for consumer use (ECHA, 2014a) (submitted by RIVM)			
Information on identity of substance			
CAS NR: 7439-92-1	**Common Names**: Lead	**Product/material type:** Coating and lead-containing articles intended for consumer use	**Notes:** A previous Risk Assessment Committee (RAC) opinion on lead and lead compounds in jewelry established a maximum exposure value of 0.05 µg/kg bw per day for lead (ECHA, 2011).
Description of chemical specific information available/necessary for the exposure scenario			
Concentration of substance in a given product or matrix: Alloy M57: 0.1-0.2% Alloy Z45: 1.7-2.2% Alloy Z33: 3.1-3.5% Alloy (average): 1.6-2.0%	**Migration rate or fraction information:** µg/cm^2/hr 0.041 (ECHA, 2014a,b) 0.173 (ECHA, 2014a,b) 0.243 (ECHA, 2014a,b) 0.152 (ECHA, 2014a,b) The migration rate used in this restriction dossier (0.7 µg/hr/cm^2) is taken from the migration data presented by the Danish EPA survey (2008) and re-evaluated by RAC for the background document to RAC and SEAC opinions on lead and its compounds in jewelry (ECHA, 2011).	**Physiochemical properties (e.g. water solubility):** Not used in the quantitative assessment of exposure from mouthing in this approach.	**Notes:** Migration rate studies (ECHA, 2014a,b) confirm that there is a migration of lead ions from both metallic (i.e. brass alloys) and polymeric materials. A migration limit would is considered an appropriate measure to cover the potential for exposure to the consumer articles (ECHA, 2014a,b). The 'migration rate' referred to in the algorithm is actually a migration limit in order to derive concentration limits for lead in consumer articles.
Type of hazard endpoint: Bench Mark Dose Level (BMDL): 0.5 µg/kg bw per day, equivalent to a blood level increase of 1.2 µg/L and an IQ reduction of 0.1 point (EFSA, 2013)			
Description of exposure scenario: Not provided			
Population(s)/age group: Toddlers (6-12 months old) Toddlers (12-24 months old) Toddlers (24-36 months old)	**Exposure frequency:** Daily	**Duration of exposure:** Realistic: 20 min, Reasonable worst case: 80 min Realistic: 20 min, Reasonable worst case: 65 min Realistic: 15 min, Reasonable worst case: 120 min	

Algorithm Used Source/reference for algorithm	**Parameter Definitions:**	**Source/Reference for Parameters:**	**Justification for Algorithm:**
Lead exposure (µg/kg bw per day) = Surface (cm^2) × mouthing time (hr) × migration rate (µg/cm^2/hr/% lead) / body weight (kg)	migration rate: 0.7 µg/cm^2/hr/% lead	ECHA, 2011	Mouthing time, surface area exposed and frequency of mouthing have been evaluated and summarised in numerous publications (Babich et al. 2004; Greene 2002; Juberg et al. 2001; RIVM, 1998). ECHA also recently evaluated these parameters for phthalates in a recent DINP and DIDP risk assessment (ECHA, 2013).
	Surface: surface area (10 cm^2)	RIVM, 2002 and 2008	
	Mouthing Time: see duration of exposure	ECHA, 2014b	
	Body Weight: 9.2 kg (6-12 months), 11.4 (12-24 months), and 13.8 (24-36 months)	Norden, 2011	

Estimation result: external and internal oral exposure

For the purposes of comparison of exposures in Figure 4, the values for the 0.05% were used to represent "typical" exposures and the values based on 6% lead were used to represent "worst-case"

6-12 months: 0.05% lead**: 0.01 µg/kg bw per day** – 6% lead: **6.2 µg/kg bw per day**

12-24 months: 0.05% lead: **0.01 µg/kg bw per day** – 6% lead: **4 µg/kg bw per day**

24-36 months: 0.05% lead: **0.05 µg/kg bw per day** – 6% lead: **9 µg/kg bw per day**

Qualification in terms of the level of conservatism: Realistic and reasonable worst case scenarios are included. Mouthing times are based on information from mouthing of items/objects considered most representative for the articles intended to be restricted, i.e. items not including pacifiers, teethers, toys and fingers.

Uncertainties or limitations associated with the scenario: Very limited data is available on migration and the relationship between the migration rate and the lead content of materials. The 120 min for 24-36 months old children are likely to be overestimates because only data from one study were used and these data were rather skewed.

Links to the Publication ECHA 2014b: https://echa.europa.eu/documents/10162/10a7006f-1342-40ad-8aa3-c28365d0faca

References

Babich MA, Chen SB, Greene MA, Kiss CT, Porter WK, Smith TP, Wind ML, Zamula WW (2004), Risk assessment of oral exposure to diisononyl phthalate from children's products. Regul Toxicol Pharmacol 40:151-67.

ECHA (2011), Background Document to the opinions on the Annex XV dossier proposing restrictions on Lead and its compounds in jewelry http://echa.europa.eu/documents/10162/c9388bba-2660-4c0e-946b-c3bbe5539940

ECHA (2012), Agency Annex XV restriction report proposal for a restriction lead and its compounds in articles intended for consumer use https://echa.europa.eu/documents/10162/80f7edca-b6c1-4433-8734-854594530db2

ECHA (2013), Evaluation of new scientific evidence concerning DINP (Diisononyl' phthalate) and DIDP (Diisodecyl' phthalate) in relation to entry 52 of Annex XVII to REACH Regulation (EC) No 1907/2006
http://echa.europa.eu/documents/10162/13579/201308_echa_review_dinp_didp_final_report_en.pdf

ECHA (2014a), Opinion on an Annex XV dossier proposing restrictions on lead and its compounds in articles intended for consumer use ECHA/RAC/RES-O-0000003487-67-04/F (compiled version) https://echa.europa.eu/documents/10162/f5a59251-8ef0-4f44-bfd4-95bffca7f807

ECHA (2014b), Background document to the Opinion on the Annex XV dossier proposing restrictions on Lead and its compounds in articles intended for consumer use
https://echa.europa.eu/documents/10162/10a7006f-1342-40ad-8aa3-c28365d0faca

EFSA (European Food Safety Agency) (2013), Scientific Opinion on Lead in Food. EFSA Journal 8 (4). 1570

Greene MA (2002), Mouthing times among young children from observational data. US Consumer Product Safety Commission, Bethesda, MD.

Juberg DR, Alfano K, Coughlin RJ, Thompson KM (2001), An Observational Study of Object Mouthing by Young Children, Pediatrics, Vol. 107/1, pp.135-142 .

RIVM (1998), Phthalate release from soft PVC baby toys, Report from the Dutch Consensus Group, Bilthoven, The Netherlands. RIVM Report 31 3320 002. http://www.rivm.nl/bibliotheek/rapporten/613320002.pdf

EXAMPLE 5: Estimated exposure to DINP and DIDP in 0-6 months, 6-12 months and 12-18 months old children associated with mouthing articles

EXAMPLE 5: Estimated exposure to DINP and DIDP in 0-6 months, 6-12 months and 12-18 months old children associated with mouthing articles (submitted by RIVM)			
Information on identity of substance			
CAS RN: 68515-48-0 (DINP) and 68515-49-1 (DIDP)	Common Names: di-"isononyl" phthalate (DINP) 1,2-benzenedicarboxylic acid, di-C8-10-branched alkyl esters, C9-rich di-"isodecyl" phthalate (DIDP) 1,2- benzenedicarboxylic acid, di-C9-11-branched alkyl esters, C10-rich	Product/material type: Toys and childcare articles	Notes: It is assumed that the oral and daily exposure estimates from mouthing of articles by newborns and infants (0-3 years old) are equal for both DINP and DIDP.
Description of chemical specific information available/necessary for the exposure scenario			
Concentration of substance in a given product or matrix: 19-50% (Teether) 38% (Rattle) 53.8 -58.3% (Pacifier) 16-29% (Soft doll) 46.2-48.8% (Plate) 25.5-25.6% (Ball) 12.9-58% (Toys) 15.2-52.5% (Plastic Discs)	Migration rate or fraction information: µg/cm^2/hr 0.1-232 (Fiala et al. 2000; Rastogi et al. 1997) 22.4-112.5 (Niino et al. 2002a,b) 20-117.3 (Niino et al. 2002a,b) 3.8 -85.2 (Niino et al. 2002b,a) 32.4-124.8 (Niino et al. 2002a,b) 7.8-33.6 (Niino et al. 2002b,a) 1-35 (Axford et al. 1999) 0.9-44 (CSTEE 1997d; TNO 2010)	Physiochemical properties (e.g. water solubility): Not used in the quantitative assessment of exposure from mouthing in this approach	Notes: Exposure to DINP and DIDP from mouthing of toys and childcare articles was estimated with typical migration rates based on *in vivo* migration rates and worst case on *in vitro* migration rates of DINP and DIDP. Oral exposure estimates for infants aged 0 to 18 months ranged from 2 to 145 µg/kg bw per day.

<table>
<tr><td colspan="4">Type of hazard endpoint (DINP): Repeated dose toxicity oral NOAEL: 15 mg/kg bw per day (2-year study; significant increases of incidence of spongiosis hepatis together with other signs of hepatotoxicity), oral DNEL for children 0.075 mg/kg bw per day, Reproductive toxicity NOAEL: 50 mg/kg bw per day (targeted developmental toxicity study; decreases foetal testicular testosterone concentration during critical time window of sexual differentiation and increased incidence of multinucleated gonocytes and Leydig cell aggregates),
Type of hazard endpoint (DIDP): Repeated dose toxicity oral NOAEL: 15-60 mg/kg bw per day (90-day rat and dog 2-year study rat; liver effects), oral DNEL 0.075 mg/kg bw per day , Reproductive toxicity NOAEL: 33-52 mg/kg bw per day (reduced body weight in F2 pups in two generation reproductive toxicity study), oral DNEL for children 0.26 mg/kg bw per day</td></tr>
<tr><td colspan="4">Description of exposure scenario: Not provided</td></tr>
<tr><td>Population(s)/age group:
Children (0-6 months; 6-12 months; 12 to 18 months)</td><td>Exposure frequency:
Daily</td><td colspan="2">Duration of exposure: mouthing times
7.5 min/day (typical) * mean mouthing time of 30 min/day might be assumed for mouthing of the relevant articles. It is estimated that half of those articles would be made of plastic (Smith and Norris 2002). An arbitrary assumption could be made that half of these articles would contain DINP or DIDP if the current restriction on toys and childcare articles would be lifted. This would lead to a rough exposure estimate of 7.5 min/day for the average child of 0-18 months to DINP or DIDP containing articles.
120 min/day (reasonable worst case)</td></tr>
<tr><td rowspan="4">Algorithm Used
Exposure (µg/kg bw per day) =
(MR x SA x T)/BW

Source/reference for algorithm:
ECHA, 2013</td><td>Parameter Definitions:</td><td>Source/Reference for Parameters:</td><td rowspan="4">Justification for Algorithm:
Mouthing time, surface area exposed and frequency of mouthing have been evaluated and summarised in numerous publications (Juberg et al. 2001; Smith and Norris, 2003; Greene, 2002; RIVM, 1998; Sugita et al. 2003; Beamer et al. 2008). Health Canada also recently evaluated these parameters for phthalates in a recent DIBP risk assessment (Health Canada, 2015)</td></tr>
<tr><td>MR= Migration Rate
Typical 14 µg/cm^2/hr
Reasonable worst case 45 µg/cm^2/hr</td><td>Typical: Mean of all the mean in vivo samples (ECHA, 2013)
Worst case: in vitro measured for a plate (TNO, 2010)</td></tr>
<tr><td>SA = Surface area mouthed (10 cm^2)</td><td>ECHA, 2013, reference to Bremmer and van Veen (2002)</td></tr>
<tr><td>T = time (min/day);
7.5 (typical); 120 (reasonable worst case)</td><td>ECHA, 2013 (see notes)</td></tr>
</table>

	BW = body weight; 6.21 kg for 0-6 months, 7.62 kg for 6-12 months, and 9.47 kg for 12-18 months	ECHA, 2013, based on Bremmer and van Veen (2002)	

Estimation of oral exposure
Oral exposure estimates for infants aged 0 to 18 months ranged from 2 to 145 µg/kg bw per day.

Oral exposure estimates for infants
- 0-6 months: 2.8 – 145 µg/kg bw per day.
- 6-12 months: 2.3 – 118 µg/kg bw per day.
- 12-18 months: 1.8 – 95 µg/kg bw per day

Qualification in terms of the level of conservatism: Typical and reasonable worst case estimates for mouthing duration and migration rates.

Uncertainties or limitations associated with the scenario: There are substantial differences amongst the reported mouthing times and migration rates in the literature.
The reasonable worst case mouthing time integrated data from several observational studies. There are uncertainties attached to this estimate as a consequence of the limitations and discrepancies in the data, as well as the skewness and difficulties to determine appropriate article categories. The possible mouthing of items during sleeping time was not taken into account in any of the estimates (ECHA, 2013).

Links to the Publication: Evaluation of new scientific evidence concerning DINP and DIDP (https://echa.europa.eu/documents/10162/31b4067e-de40-4044-93e8-9c9ff1960715)

References:

Axford IP, Earls AO, Scott RP and Braybrook JH (1999). Interlaboratory validation of laboratory-based agitation methods for the determination of phthalate plasticizer migration from PVC toys and childcare articles laboratory of the government chemist. Teddington, Middlesex, UK. (as cited in US CPCS 2010).

Beamer P, Key ME, Ferguson AC, Canales RA, Auyeung W and Leckie JO (2008), Quantified activity pattern data from 6 to 27-month-old farmworker children for use in exposure assessment. Environ Res 108(2): 239-246.

Bremmer HJ and van Veen MP (2002), Children's Toys Fact Sheet. To assess the risk for the consumer. RIVM report 612810012/2002. http://www.rivm.nl/bibliotheek/rapporten/612810012.pdf

ECHA (2013), Evaluation of new scientific evidence concerning DINP and DIDP. Final Review Report. Available from: http://echa.europa.eu/documents/10162/31b4067e-de40-4044-93e8-9c9ff1960715

Fiala F, Steiner I and Kubesch K (2000), Migration of di-(2-ethylhexyl)phthalate (DEHP) and diisononyl phthalate (DINP) from PVC articles. Deutsche Lebensmittel-Rundschau 96(2): 51-57.

Greene MA (2002). Mouthing times among young children from observational data. US Consumer Product Safety Commission , Bethesda, MD.

Health Canada (2015), State of the Science Report Phthalate Substance Grouping Medium-Chain Phthalate Esters. Available from: http://www.ec.gc.ca/ese-ees/4D845198-761D-428B-A519-75481B25B3E5/SoS_Phthalates%20%28Medium-chain%29_EN.pdf
Juberg DR, Alfano K, Coughlin RJ and Thompson KM (2001). An observational study of object mouthing behavior by young children. *Pediatrics* 107(1):135–142.

Niino T, Asakura T, Ishibashi T, Itoh T, Sakai S, Ishiwata H, Yamada T and Onodera S (2002a), A simple and reproducible testing method for dialkyl phthalate migration from polyvinyl chloride products into saliva simulant, J Food Hyg Soc Japan 44(1): 13-18.

Niino T, Ishibashi T, Itoh T, Sakai S, Ishiwata H, Yamada T and Onodera S (2002b), Comparison of diisononyl phthalate migration from polyvinyl chloride products into human saliva *in vivo* and into saliva simulant *in vitro*, Journal of Health Science 48(3): 277-281.

Niino T, Asakura T, Ishibashi T, Itoh T, Sakai S, Ishiwata H, Yamada T, Onodera S. (2003), A simple and reproducible testing method for dialkyl phthalate migration from polyvinyl chloride products into saliva simulant, J Food Hyg Soc Japan 44:13–8.
RIVM (1998), Phthalate release from soft PVC baby toys. Report from the Dutch Consensus Group, Bilthoven, The Netherlands. RIVM Report 31 3320 002http://www.rivm.nl/bibliotheek/rapporten/613320002.pdf

Smith S and Norris B (2002). *Research into the mouthing behaviour of children up to 5 years old*. Consumer and Competition Policy Directorate, Department of Trade and Industry (DTI), London

Sugita et al. (2003), Contents of phthalate in polyvinyl chloride toys. Food Hygiene and Safety Science (*Shokuhin Eiseigaku Zasshi*) vol. 44.22 pp.96-102. [in Japanese]

EXAMPLE 6: BPA in toy rattles and pacifiers with polycarbonate shields

<table>
<tr><th colspan="4">EXAMPLE 6: BPA in toy rattles and pacifiers with polycarbonate shields (EFSA, 2015) (submitted by RIVM)</th></tr>
<tr><td colspan="4">Information on identity of substance</td></tr>
<tr><td>CAS RN:
80-05-7</td><td>Common Names:
Bisphenol A (BPA)</td><td>Product/material type:
An organic chemical used in the manufacture of polycarbonate (PC) plastics, epoxy resins and other polymeric materials.</td><td>Notes:</td></tr>
<tr><td colspan="4">Description of chemical specific information available/necessary for the exposure scenario</td></tr>
<tr><td>Concentration of substance in a given product or matrix:
The matrix is represented by rattles and pacifiers with PC shields.</td><td>Migration rate or fraction information:
Amount of substance that leaches over 24 hours from a product: 141 ng/product per 24 h for rattles 987 ng/product per 24 h for pacifiers</td><td>Physiochemical properties (e.g. water solubility):
Not used in the quantitative assessment of exposure from mouthing in this approach</td><td>Notes:
The presence of BPA is identified in the products, but concentration levels are not given. Instead exposure is calculated from migration experiments in which the rattles and pacifiers are submersed in saliva.</td></tr>
<tr><td colspan="4">Type of hazard endpoint: Based on literature review the hazard endpoint was based on studies in which BPA was found to affect kidney and liver weight in parental animals and in all the generations of rats. Toxicokinetic modeling (PROAST) simulated a 95% confidence interval (95% CI) for a benchmark response (BMR_{10}) at which kidney and liver size are increased with at least 10% (Tyl et al. 2008). The lower end of the 95%CI represents a Bench Mark Dose Level ($BMDL_{10}$) which was simulated to be 8960 µg/kg bw per day. The $BMDL_{10}$ is considered to be the endpoint for “general toxicity” in hazard characterisation. Using data on toxicokinetics, this BMDL10 was converted to an HED of 609 µg/kg bw per day. The CEF Panel applied a total uncertainty factor of 150 (for inter- and intra-species differences and uncertainty in mammary gland, reproductive, neurobehavioural, immune and metabolic system effects) to establish a temporary Tolerable Daily Intake (t-TDI) of 4 µg/kg bw per day.</td></tr>
<tr><td colspan="4">Description of exposure scenario
High and average exposure scenarios for infants (5 kg) and toddlers (12 kg) mouthing a rattle, and for mouthing a pacifier. For the average scenarios, average values for all parameters were chosen. For the high scenarios, the mouthing time parameter was modified to account approximately for the P75 (Bremmer and van Veen, 2002).</td></tr>
<tr><td>Population(s)/age group:</td><td>Exposure frequency:</td><td colspan="2">Duration of exposure:</td></tr>
</table>

<table>
<tr><td>Infants (0-3 months) and toddlers (1-3 years)</td><td></td><td colspan="2">Sucking time is not mentioned in the report. Based on average sucking times (Juberg et al. 2001) and P75 (Bremmer and van Veen, 2002) per minute, a fraction of the 24 hr migration experiment is calculated for infants and toddlers.</td></tr>
<tr><td rowspan="5">Algorithm Used

$E_{toy} = \frac{q_{product} \times f_{time} \times f_{surface}}{bw}$

Source/reference for algorithm:
EFSA, 2015</td><td>Parameter Definitions:</td><td>Source/Reference for Parameters:</td><td rowspan="5">Justification for Algorithm:
Calculation of daily exposure using the results of migration experiments in which toys were completely submersed in saliva for 7.75 h (pacifiers, extrapolated to 24 h) or 24 h (rattles).</td></tr>
<tr><td>$q_{product}$ = amount of substance that leaches over 24 hours from a product
141 ng/product per 24 h for rattles
987 ng/product per 24 h for pacifiers</td><td>KEMI, 2012
Lassen et al. 2011</td></tr>
<tr><td>f_{time}= fraction of the day that the rattle or pacifier is mouthed (based on sucking times)
rattles (average) 0.012 infants / 0.0014 toddlers
rattles (high) 0.04 infants / 0.0021 toddlers
pacifiers (average) 0.15 infants / 0.32 toddlers
pacifiers (high) 0.20 infants / 1 toddlers</td><td>Juberg et al. 2001
Bremmer and Van Veen, 2002
Juberg et al. 2001
Bremmer and Van Veen, 2002/Juberg et al. 2001</td></tr>
<tr><td>$f_{surface}$= fraction of the toy surface that is mouthed
0.5 for rattles
0.25 for pacifiers</td><td>Lassen et al. 2011</td></tr>
<tr><td>bw = body weight (5 kg for infants, 12 kg for toddlers)</td><td>EFSA, 2012</td></tr>
<tr><td colspan="4">Estimation of oral exposure
Oral exposure estimates for infants
- Rattles/infants: 0.000169 µg/kg bw per day (average); reported value: infants (toys) average: 0.0002 µg/kg bw per day: high: 0.0006 µg/kg bw per day
- Pacifiers/infants: 0.0074 µg/kg bw per day (average); reported value (pg. 57): Infants (pacifier) average: 0.0066 µg/kg bw per day; high: 0.01 µg/kg bw per day</td></tr>
<tr><td colspan="4">Qualification in terms of the level of conservatism: An average scenario is described with average values for all parameters, including sucking times (from</td></tr>
</table>

Juberg et al. 2001). A high-exposure scenario is considered as well, with the same average parameters , but with P75 sucking times (Bremmer and van Veen, 2002)
Uncertainties or limitations associated with the scenario: Data on occurrence, migration and transfer of BPA from non-food sources are scarce. An absorption percentage of 100% was used for ingestion in the calculation from external to internal exposure. An uncertainty table is included in the opinion with relative qualifications on the uncertainty on the exposure estimate, as well as if it points to a lower or higher exposure estimate. The estimated migration amount was estimated to result within ±20% for uncertainty in sucking times, within a range from half to two times for uncertainty in the fraction of surface and within a range from 0.5 times to 0.8 times for uncertainty in body weight.
Links to the Publication: [EFSA] European Food Safety Authority. 2015. http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2015.3978/epdf
References: Bremmer HJ and van Veen MP (2002), Children's toys fact sheet. To assess the risk for the consumer. RIVM report 612810012/2002. EFSA (European Food Safety Authority) (2012), Guidance on selected default values to be used by the EFSA Scientific Committee, Scientific Panels and Units in the absence of actual measured data. EFSA Journal 2012; 10(3):2579, 32 pp. doi:10.2903/j.efsa.2012.2579 EFSA (2015), Scientific Opinion on the risks to public health related to the presence of bisphenol A (BPA) in foodstuffs: Executive summary. EFSA Journal 2015;13(1):3978 Juberg DR, Alfano K, Coughlin RJ and Thomson KM (2001), An observational study of object mouthing behavior by young children. Pediatrics, 107, 135–142. KEMI (Swedish Chemicals Agency) (2012), Bisfenol A i leksaker och barnartiklar. 6/12. KEMI, Sundbyberg, Sweden, 55 pp. Lassen C, Mikkelsen SH and Brandt (2011), Migration of bisphenol A from cash register receipts and baby dummies. Survey of Chemical Substances in Consumer Products. Danish Ministry of the Environment, No. 110. PROAST http://www.rivm.nl/en/Documents_and_publications/Scientific/Models/PROAST Tyl RW, Myers CB, Marr MC, Sloan CS, Castillo NP, Veselica MM, Seely JC, Dimond SS, Van Miller JP, Shiotsuka RN, Beyer D, Hentges SG, Waechter JM (2008), Two-generation reproductive toxicity study of dietary bisphenol a in CD-1 (Swiss) mice. Toxicological Sciences, 104, 362-384.

EXAMPLE 7: Mouthing of textiles on toys containing 2,4-toluenediamine (azo dye) by children (10.5 months old)

<table>
<tr><th colspan="4">EXAMPLE 7: Mouthing of textiles on toys containing 2,4-toluenediamine (azo dye) by children (10.5 months old) (submitted by RIVM)</th></tr>
<tr><td colspan="4">Information on identity of substance</td></tr>
<tr><td>CAS RN: 95-80-7
2,4-toluenediamine</td><td>Common Names:
2,4-toluenediamine</td><td>Product/material type:
Textile toys</td><td>Notes: Children often have a favorite toy which is kept close to them; therefore a reasonable assumption would be that children will only mouth a few toys. Furthermore, for this scenario it is assumed that a children’s toy is bought for a life time and that children will not mouth toys longer than two years (in general, because children will grow out of this mouthing habit)</td></tr>
<tr><td colspan="4">Description of chemical specific information available/necessary for the exposure scenario</td></tr>
<tr><td>Concentration of substance in a given product or matrix:
Zeilmaker et al. (2000): amount of 2,4-toluenediamine in textile toy; seven toys investigated for presence of carcinogenic aromatic amines (concentration range of 30 to 359 µg/g product).

Mensink et al. (1997) reported a range of 50 to 480 µg/g.

Product concentration of 200 µg/g is used in this case.</td><td>Migration rate or fraction information:
Total amount of 2,4-toluenediamine in a toy was was calculated (200 µg/g * 10 g = 2000 µg).

It was assumed that 2000 µg represented lifetime exposure to 2,4-toluenediamine via textile toy over a lifetime (along with probability factors, see Notes section</td><td>Physiochemical properties (e.g. water solubility):
Not used in the quantitative assessment of exposure from mouthing in this approach.</td><td>Notes:
Assumed that the probability of textile containing azo is:
- Scenario 1: 25% and
- Scenario 2: 15%

Probability of toys with textile fabrics assumed to be 20%

- Scenario 1 (25%*20%) = 0.05
- Scenario 2 (15%*20%) = 0.03</td></tr>
<tr><td colspan="4">Type of hazard endpoint: The negligible risk level (NRL), corresponding to one in a million additional cancer risk, derived for benzidine using human data is 0.004 ng/kg bw per day, which is also used for 2,4-toluenediamine. However, when using animal data, the NRLs would amount 3.2 and 5.6 ng/kg bw per day for benzidine and 2,4-TDA, respectively.</td></tr>
<tr><td colspan="4">Description of exposure scenario: Not provided</td></tr>
<tr><td>Population(s)/age group:</td><td>Exposure frequency:</td><td colspan="2">Duration of exposure:</td></tr>
</table>

<table>
<tr><td>10.5 months</td><td></td><td></td><td></td></tr>
<tr><td rowspan="6">Algorithm Used
Estimated Daily Exposure (µg/kg bw per day) =
Product amount (g product) * total concentration of aromatic amine (µg/g product) * oral absorption * probability of a toy containing aromatic amines/ BW

Source/reference for algorithm:
None provided</td><td>Parameter Definitions:</td><td>Source/Reference for Parameters</td><td rowspan="6">Justification for Algorithm:</td></tr>
<tr><td>Product amount = 10 g product</td><td></td></tr>
<tr><td>Total conc. of aromatic amine = 200 µg/g product</td><td>Zeilmaker et al. (2000); Mensink et al. (1997)</td></tr>
<tr><td>Oral absorption = 100%</td><td>EC 2005</td></tr>
<tr><td>Probability of a toy containing aromatic amines:
Scenario 1: 25%*20%*10% = 0.005
Scenario 2: 15%*20%*10% = 0.003</td><td></td></tr>
<tr><td>Body weight = 9.45 kg</td><td>Bremmer and Van Veen 2002</td></tr>
<tr><td colspan="4">Estimation of oral exposure
Daily Oral Exposure:
- Scenario 1: 1.05 µg/kg bw per day (0.04 ng/kg bw per day over lifetime)
- Scenario 2: 0.63 µg/kg bw per day (0.025 ng/kg bw per day over lifetime)</td></tr>
<tr><td colspan="4">Qualification in terms of the level of conservatism
The oral exposure was based on the assumption that all present azo dye is eventually ingested by the infant. The underlying assumption is that an infant is often very attached to its toys. In addition, the oral exposure was calculated based on mouthing of one toy.</td></tr>
<tr><td colspan="4">Uncertainties or limitations associated with the scenario:
For the exposure assessment it was assumed that the prevalence was the same in toys as was for textile, with an additional correction for toys that do not contain textile</td></tr>
<tr><td colspan="4">Links to the Publication:
http://www.rivm.nl/dsresource?objectid=38f6d08a-eee3-424b-89f4-77981732e2cc&type=org&disposition=inline</td></tr>
<tr><td colspan="4">References:
Mensink JS et al. (1997), Voorkomen van kankerverwekkende azo-kleurstoffen in Nederland. Amsterdam. CREM.

Zeilmaker MJ et al. (2000), Cancer risk assessment of azo dyes and aromatic amines from tattoo bands, folders of paper, toys, bed clothes, watch straps and ink. RIVM 601503019.</td></tr>
</table>

EXAMPLE 8: Mouthing of children's books containing EPTAC (residue in products prepared with cationic starches used in paper and board industry)

<table>
<tr><th colspan="4">EXAMPLE 8 Mouthing of children's books containing EPTAC (residue in products prepared with cationic starches used in paper and board industry) - RIVM</th></tr>
<tr><td colspan="4">Information on identity of substance</td></tr>
<tr><td>CAS RN: 3303-77-0
2,3-Epoxypropyltrimethylammonium Chloride</td><td>Common Names:
EPTAC</td><td>Product/material type:
Books for small children</td><td>Notes: Cationic starch may be used in thin laminated paper outer layer of children cover book to enhance their printing properties. Quantity is typically 0.3 g cationic starch/m^2 laminated paper (ranging from 0.1 g/m^2 to 0.5 g/m^2); cationic starch cover book (60-100g/m2, typically 80 g/m^2).</td></tr>
<tr><td colspan="4">Description of chemical specific information available/necessary for the exposure scenario</td></tr>
<tr><td>Concentration of substance in a given product or matrix:
Quantity is typically 0.3 g cationic starch/m^2 laminated paper (ranging from 0.1 g/m^2 to 0.5 g/m^2).

95th%ile of residues in starch is 24 ppm</td><td>Migration rate or fraction information:
It is estimated that in the worst case, during one day, about 5-10% of the EPTAC residues in the surface of the book could either be ingested by the child or becomes into contact with the skin. This would represent the worst case scenario.</td><td>Physiochemical properties (e.g. water solubility):
Not used in the quantitative assessment of exposure from mouthing in this approach.</td><td>Notes:</td></tr>
<tr><td colspan="4">Type of hazard endpoint: Section 4.1.3.3.8: Summary of risk characterisation (including repeat dose toxicity, carcinogenicity and reproductive toxicity, concluded that the lowest MOS, derived for the cosmetic scenarios, may be applied to all scenarios.</td></tr>
<tr><td colspan="4">Description of exposure scenario: Not provided</td></tr>
<tr><td>Population(s)/age group:
6-12 months</td><td>Exposure frequency:
n/a</td><td colspan="2">Duration of exposure:
n/a</td></tr>
<tr><td rowspan="2">Algorithm Used
Estimated Daily Oral Exposure (µg/kg bw per day) =</td><td>Parameter Definitions:</td><td>Source/Reference for Parameters</td><td rowspan="2">Justification for Algorithm:</td></tr>
<tr><td>Surface area of two pages = 0.066 m^2</td><td>Assumed to only be in cover pages</td></tr>
</table>

<table>
<tr><td rowspan="4">Total amount of EPTAC in book (µg) * fraction of ingestion/bw (kg)

50% oral absorption assumed to derive Daily Internal Dose (µg/kg bw per day)

Source/reference for algorithm:
None provided</td><td>Total amount of cationic starch = 0.3 g/m^2 * 0.066 m^2 = 0.02 g</td><td></td><td rowspan="4"></td></tr>
<tr><td>Residues of EPTAC in starch = 24 ppm * 0.02 g starch = 0.5 µg EPTAC</td><td>24 mg/kg from Quaternisation of Starch Producers Association 10 June 2003</td></tr>
<tr><td>Fraction of EPTAC residues in surface of book that could be ingested during one day = 5-10%</td><td></td></tr>
<tr><td>bw (body weight) = 7.5-9.9 kg</td><td></td></tr>
<tr><td colspan="4">Estimation of oral exposure
Daily Oral Exposure: 0.0025 -0.006 µg/kg bw per day
Daily Internal Dose: 0.003 µg/kg bw per day</td></tr>
<tr><td colspan="4">Qualification in terms of the level of conservatism</td></tr>
<tr><td colspan="4">Uncertainties or limitations associated with the scenario:
Measurement of how EPTAC migrates from a booklet, when exposed to a child's saliva and mouthing activity, have not been made and therefore, this estimate is based on worst case assumptions.</td></tr>
<tr><td colspan="4">Links to the Publication:
https://echa.europa.eu/documents/10162/ad2b9958-d74b-42cf-9cb1-521f017737e1</td></tr>
<tr><td colspan="4">References: N/A</td></tr>
</table>

EXAMPLE 9: DINP in toys - Exposure estimates based on direct object mouthing scenario

<table>
<tr><th colspan="4">EXAMPLE 9: DINP in toys - Exposure estimates (µg/kg bw per day) based on direct object mouthing scenario (submitted by Japan)</th></tr>
<tr><td colspan="4">Information on identity of substance</td></tr>
<tr><td>CAS RN: 68515-48-0, 28553-12-0 (DINP)</td><td>Common Names:
Diisononyl phthalate</td><td>Product/material type:
Toy/plastic</td><td>Notes: Di-isononyl phthalate (DINP) is a commonly used plasticizer in PVC applications. DINP has been frequently detected in PVC toys and floor dust in Japan (Sugita et al. 2001, Ait Bamai et al. 2014).</td></tr>
<tr><td colspan="4">Description of chemical specific information available/necessary for the exposure scenario</td></tr>
<tr><td>Concentration of substance in a given product or matrix:
39% (teething toy)
58% (pacifier)
38% (rattle)</td><td>Migration rate or fraction information: (µg/cm^2/hr)
Teething toy: 9.24 (Sugita et al.2003)
Pacifier: 10.70 (Sugita et al.2003)
Rattle:8.68 (Sugita et al.2003)</td><td>Physiochemical properties (e.g. water solubility):
Average amount migrated in saliva (µg/10 cm^2/hr, Adult human); Teething toy: 92.4 (range: 13.2 - 240.4), Pacifier: 107.0 (28.4-267.3); Rattle: 86.8 (10.5-248.7)</td><td>Notes: Exposures to DINP from three different types of toys were estimated for toddlers aged 6 to 10 months under two scenarios.
-Point estimate, Mean oral exposure (µg/kg/day):
Scenario 1; 14.3 to 16.6,
Scenario 2; 19.1 to 23.6
-Probabilistic estimate (µg/kg/day, for teething toy only)
Mean: Scenario 1; 14.8, Scenario 2; 21.4 95th percentile: Scenario 1; 35.7, Scenario 2; 65.8</td></tr>
<tr><td colspan="4">Type of hazard endpoint: Oral NOAEL = 150µg/kg/day; weight loss and increase in relative organ weight of liver and kidney at 15 mg/kg bw per day (2 years), F344 male rat; long-term; uncertainty factor:100.</td></tr>
<tr><td colspan="4">Description of exposure scenario: Not provided</td></tr>
<tr><td>Population(s)/age group:
Toddlers (6 to 10 months)</td><td>Exposure frequency:
Daily</td><td colspan="2">Duration of exposure:
Scenario 1; mouthing time excluding time pacifier were in her/his mouth: 73.9 min. (11.4-136.5min)
Scenario 2; mouthing time including time pacifier were in her/his mouth: 105.3 min. (11.4 -351.8min)</td></tr>
<tr><td colspan="4">Algorithm Used</td></tr>
</table>

Algorithm: Exposure (µg/kg bw per day) = (MR x SA x T)/BW	Definitions: MR = migration rate (µg/cm^2/hr) SA = Surface area mouthed (10 cm^2) T = time (hr/day) BW = body weight (7.96 kg based on 3-10 months, Japanese)	Source/reference: Surface area mouthed was based on the reports by Könemann et al. (1998) and Chen et al. (1998)	Justification: Mouthing time in toddlers (6 to 10 months) was based on the study by Sugita et al. (2003) Body weight was based on the national survey in 1990
Estimation of oral exposure Oral exposure estimates for infants - Without pacifier (time): 14.2 (rattle toy) µg/kg bw per day - 16.5 (pacifier) µg/kg bw per day (reported to be 14.3-16.6 µg/kg bw per day) - With pacifier (time): 19.2 (rattle toy) µg/kg bw per day - 23.7 (pacifier) µg/kg bw per day (reported to be 19.1-23.6 µg/kg bw per day)			
Qualification in terms of the level of conservatism: Time parameters			
Uncertainties or limitations associated with the scenario: Migration rate was based on adult data.			
References Chen SB (1998), Migration of DINP from polyvinyl chloride (PVC) children's products. Annex A to 'The risk of chronic toxicity associated with exposure to diisononyl phthalate (DINP) in children's products' by Babich MA (1998), US Consumer Product Safety Commission. Könemann et al. (1998), Phthalate release from soft PVC baby toys. Report from the Dutch Consensus Group, Bilthoven, The Netherlands. RIVM Report 31 3320 002. Sugita et al. (2003), Contents of phthalate in polyvinyl chloride toys. Food Hygiene and Safety Science (*Shokuhin Eiseigaku Zasshi*) vol. 44.22 pp.96-102. [in Japanese]			

EXAMPLE 10: Mouthing of toys containing phthalates (specifically DEHT, used as plasticizer) by children under 3 years of age

<table>
<tr><th colspan="4">EXAMPLE 10: Mouthing of toys containing phthalates (specifically DEHT, used as plasticizer) by children under 3 years of age (submitted by the US)</th></tr>
<tr><td colspan="4">Information on identity of substance</td></tr>
<tr><td>CAS RN: 6422-86-2 (DEHT)
1,4-benzenedicarboxylic acid, 1,4-bis(2-ethylhexyl) ester</td><td>Common Names:
bis(2-ethylhexyl)terephthalate (DEHT)</td><td>Product/material type: children’s toys and childcare articles; art or school supplies</td><td>Notes: DEHT may be present in a variety of items (e.g. child care articles, including toys such as baby dolls and doll accessories, action figures, balls). DEHT was found to be present in 37.8% of articles tested, with a majority of the samples containing a combination of two or more plasticizers.</td></tr>
<tr><td colspan="4">Description of chemical specific information available/necessary for the exposure scenario</td></tr>
<tr><td>Concentration of substance in a given product or matrix:
3-60 mass percent in children’s toys made with PVC or children’s products (from Dreyfus 2010)</td><td>Migration rate or fraction information:
(µg/10 cm^2-min), from Dreyfus 2010
1.4 (mean and median)
0.14 (minimum)
3.6 (maximum)
2.7 (95th percentile)</td><td>Physiochemical properties (e.g. water solubility):
Not used in the quantitative assessment of exposure from mouthing in this approach.</td><td>Notes: Exposure to DEHT from mouthing of toys and childcare articles was estimated as a range based on in vitro migration rates of DEHT from PVC</td></tr>
<tr><td colspan="4">Type of hazard endpoint: The reproductive NOAEL was 158 mg/kg-d in a two-generation study in SD rats, based on parental effects (Faber et al. 2007b). The developmental NOAEL was 458 mg/kg-d in rats, based on increased incidence of 14th rudimentary ribs (Faber et al. 2007a). DEHT did not produce antiandrogenic effects in rats at 750 mg/kg-d (Gray et al. 2000). No developmental effects were observed in mice (Faber et al. 2007a).</td></tr>
<tr><td colspan="4">Description of exposure scenario: Not provided</td></tr>
<tr><td>Population(s)/age group:
3 to < 12 months
12 to < 24 months</td><td>Exposure frequency:
Daily (minutes/day), based on “all soft plastic except pacifiers“ category</td><td colspan="2">Duration of exposure:
Duration of exposure depends on age grouping and type of object mouthed. The mean migration rate and mouthing duration were</td></tr>
</table>

<table>
<tr><td>24 to <36 months</td><td>3 to < 12 mon: 4.4 (mean), 17.5 (95th percentile)
12 to < 24 mon: 3.8 (mean), 13 (95th percentile)
24 to <36 mon: 4.2 (mean), 18.5 (95th percentile)</td><td colspan="2">used to estimate the mean oral exposure. The 95th percentile exposure was estimated in two ways, using either the 95th percentile migration rate or 95th percentile mouthing duration.</td></tr>
<tr><td rowspan="5">Algorithm Used
Estimated Daily Exposure (µg/kg bw per day),
E = (R x T)/ W

Source/reference for algorithm:
CPSC 2014</td><td>Parameter Definitions:</td><td>Source/Reference for Parameters</td><td rowspan="5">Justification for Algorithm: Mouthing time, surface area exposed and frequency of mouthing have been evaluated and summarised in CPSC 2014</td></tr>
<tr><td>R = migration rate for a 10 cm^2 disk (see item 2 above)</td><td>Dreyfus 2010</td></tr>
<tr><td>Surface area mouthed (10 cm^2)</td><td>Dreyfus 2010</td></tr>
<tr><td>T = time (min/day) (see item 4 above)</td><td>Greene 2002</td></tr>
<tr><td>W = body weight (8.6 kg for 3 to <12 months; 11.4 kg for 12 to <24 months; 13.8 kg for 24<36 months)</td><td>EPA 2011 (Table 8-1)</td></tr>
<tr><td colspan="4">Estimation of oral exposure
- <12 months: 0.69 µg/kg bw per day (mean) - 1.8 µg/kg bw per day (95th %ile)
- 12-23 months: 0.45 µg/kg bw per day (mean) - 1.2 µg/kg bw per day (95th %ile)
- 24-36 months: 0.41 µg/kg bw per day (mean) - 1.1 µg/kg bw per day (95th %ile)</td></tr>
<tr><td colspan="4">Qualification in terms of the level of conservatism: Exposure duration: mean and 95th percentile values (use of mouthing durations for the category “all soft plastic articles except pacifiers” provides a reasonable upper bound estimate for children’s exposure from mouthing PVC children’s products), migration rate: mean and 95th percentile.</td></tr>
<tr><td colspan="4">Uncertainties or limitations associated with the scenario: The scenario-based exposure assessment presented in this example estimates of phthalate exposure were made for individual sources such as toys, personal care products, and household products however the charge to the CPSC’s CHAP was to conduct a cumulative risk analysis. This led to additional uncertainties because data on the exposures associated with all routes of entry into the body were not consistent for each potential source of one or more compounds. In addition, the toxicological data were normally obtained via oral exposure, whereas human exposure occurs by multiple routes.</td></tr>
<tr><td colspan="4">Links to the Publication: https://www.cpsc.gov/en/Regulations-Laws--Standards/Statutes/The-Consumer-Product-Safety-Improvement-Act/Phthalates/Chronic-Hazard-Advisory-Panel-CHAP-on-Phthalates/</td></tr>
<tr><td colspan="4">References:
Dreyfus, M. (2010), Phthalates and Phthalate Substitutes in Children’s Toys. US Consumer Product Safety Commission, Bethesda, MD. March 2010. http://www.cpsc.gov/PageFiles/126545/phthallab.pdf</td></tr>
</table>

Faber, W.D., Deyo, J.A., Stump, D.G., Navarro, L., Ruble, K., Knapp, J., (2007a), Developmental toxicity and uterotrophic studies with di-2-ethylhexyl terephthalate. Birth Defects Res B Dev Reprod Toxicol 80, 396–405.

Faber, W.D., Deyo, J.A., Stump, D.G., Ruble, K., (2007b), Two-generation reproduction study of di-2-ethylhexyl terephthalate in Crl:CD rats. Birth Defects Res B Dev Reprod Toxicol 80, 69–81.

Gray, L.E., Jr., Ostby, J., Furr, J., Price, M., Veeramachaneni, D.N., Parks, L., (2000), Perinatal exposure to the phthalates DEHP, BBP, and DINP, but not DEP, DMP, or DOTP, alters sexual differentiation of the male rat. ToxSci 58, 350–365.

Greene MA (2002), Mouthing times from the observational study. US Consumer Product Safety Commission, Bethesda, MD.

US CPSC (Consumer Product Safety Commission) (2014). Report to the US CPSC by the Chronic Hazard Advisory Panel on Phthalates and Phthalate Alternatives, July 2014, Directorate for Health Sciences, Bethesda, MD 20814 https://www.cpsc.gov/en/Regulations-Laws--Standards/Statutes/The-Consumer-Product-Safety-Improvement-Act/Phthalates/Chronic-Hazard-Advisory-Panel-CHAP-on-Phthalates/

US EPA (2011), Exposure Factors Handbook: 2011 Edition. US EPA, Office of Research and Development, Washington, DC 20460. EPA/600/R-090/052F. http://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=236252

EXAMPLE 11: Mouthing of toys containing phthalates (specifically DIBP, used as plasticizer) by children under 18 months of age

EXAMPLE 11: Mouthing of toys containing phthalates (specifically DIBP, used as plasticizer) by children under 18 months of age (submitted by Canada)			
Information on identity of substance			
CAS RN: 84-69-5 (DIBP)	**Common Names**: Diisobutyl phthalate (DIBP) (Medium-chain Phthalate Esters)	**Product/material type:** Balance ball Toy balls	**Notes:** DIBP may be present in a variety of items (e.g. plastic sandals, balance balls, furniture, and decorative articles). Canadian use was identified in toys and exercise equipment (e.g. yoga mats, balance balls). DIBP was found to be present at a low market penetration rate in children's articles, such as bibs, handbags, slippers and balls.
Description of chemical specific information available/necessary for the exposure scenario			
Concentration of substance in a given product or matrix: 35.4% (balance ball, DIBP) 1–10% (toy ball, DBP) 10-15% (toy ball, DBP) > 20% (toy ball, DBP)	**Migration rate or fraction information:** (µg/cm^2/hr) 3.70 (Danish EPA 2010a) 5.31 (RIVM 2001; Niino et al. 2001, 2003) 36.0 (Niino et al. 2003) 94.1 (Niino et al. 2003)	**Physiochemical properties (e.g. water solubility):** Not used in the quantitative assessment of exposure from mouthing in this approach	**Notes:** Exposure to DIBP from mouthing of toys and childcare articles was estimated as a range based on *in vitro* migration rates of DIBP and DBP. Oral exposure estimates for infants aged 0 to 18 months ranged from 2.47 to 251.0 µg/kg/day.
Type of hazard endpoint: Oral NOAEL = 300 mg/kg/day; Testicular pathology at 500 mg/kg bw per day (7 d)			
Description of exposure scenario: Not provided			
Population(s)/age group: Infants (0-6 months) Toddlers (6 to 18 months) were also considered however, intake estimates were lower (all parameters except bw were the same)	**Exposure frequency:** Daily	**Duration of exposure:** 0.5 hr/day (typical) 2 hr/day (worst-case)	

<table>
<tr><td rowspan="5">Algorithm Used
Exposure (µg/kg bw per day) = (MR x SA x T)/BW
Source/reference for algorithm:
ECHA, 2013</td><td>Parameter Definitions:</td><td>Source/Reference for Parameters</td><td rowspan="5">Justification for Algorithm: Mouthing time, surface area exposed and frequency of mouthing have been evaluated and summarised in numerous publications (Babich et al. 2004; US EPA 2011; Greene 2002; Juberg et al. 2001; Xue et al. 2010). ECHA also recently evaluated these parameters for phthalates in a recent DINP and DIDP risk assessment.</td></tr>
<tr><td>MR = migration rate (in this case 94.1 µg/cm^2/hr)</td><td>Niino et al. 2003</td></tr>
<tr><td>SA = Surface area mouthed (10 cm^2)</td><td>ECHA, 2013</td></tr>
<tr><td>T = time (hr/day);
0.5 hr (typical); 2 h/day (worst-case)</td><td>ECHA, 2013</td></tr>
<tr><td>BW = body weight (7.5 kg) W = body weight (7.5 kg based on 0-6 months)</td><td>Health Canada, 1998</td></tr>
<tr><td colspan="4">Estimation of oral exposure
- 0-6 months: 62.7 - 250 µg/kg bw per day (based on typical and worst case times, using highest migration rate)

(From section 2: Oral exposure estimates for infants aged 0 to 18 months ranged from 2.47 to 251.0 µg/kg/day.)</td></tr>
<tr><td colspan="4">Qualification in terms of the level of conservatism: Time parameters (0.5 to 2 hr/day): typical and worst case scenarios, respectively.</td></tr>
<tr><td colspan="4">Uncertainties or limitations associated with the scenario: A range of migration rate studies were available reducing uncertainty for this parameter. Conservatisms were incorporated into the selection of migration rate values.</td></tr>
<tr><td colspan="4">Links to the Publication: State of the Science Report Phthalate Substance Grouping Medium-Chain Phthalate Esters (http://www.ec.gc.ca/ese-ees/4D845198-761D-428B-A519-75481B25B3E5/SoS_Phthalates%20%28Medium-chain%29_EN.pdf)</td></tr>
<tr><td colspan="4">References:
Babich MA, Chen SB, Greene MA, Kiss CT, Porter WK, Smith TP, Wind ML, Zamula WW (2004), Risk assessment of oral exposure to diisononyl phthalate from children's products. Regul Toxicol Pharmacol 40:151-67.

ECHA. (2013), Evaluation of new scientific evidence concerning DINP and DIDP. Final Review Report. Available from: http://echa.europa.eu/documents/10162/31b4067e-de40-4044-93e8-9c9ff1960715

Greene MA (2002), Mouthing times among young children from observational data. Bethesda, MD, US Consumer Product Safety Commission.

Health Canada (1998), Exposure factors for assessing total daily intake of priority substances by the general population of Canada. Unpublished report. Ottawa (ON): Health Canada, Environmental Health Directorate.

Juberg DR, Alfano K, Coughlin RJ, Thompson KM (2001), An observational study of object mouthing behavior by young children, Pediatrics, Vol. 107/1, pp. 135-142.</td></tr>
</table>

Niino T, Asakura T, Ishibashi T, Itoh T, Sakai S, Ishiwata H, Yamada T, Onodera S. (2003), A simple and reproducible testing method for dialkyl phthalate migration from polyvinyl chloride products into saliva simulant. J Food Hyg Soc Japan 44:13–8.

US EPA (2011), Exposure Factors Handbook: 2011 Edition. US EPA, Office of Research and Development, Washington, DC 20460. EPA/600/R-090/052F. http://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=236252

EXAMPLE 12: Mouthing of children's products containing flexible foam (containing TCPP and TDCPP) by children (6 months to 4 years old)

<table>
<tr><th colspan="4">EXAMPLE 12: Mouthing of children's products containing flexible foam (containing TCPP and TDCPP) by children (6 months to 4 years old) (submitted by Canada)</th></tr>
<tr><td colspan="4">Information on identity of substance</td></tr>
<tr><td>CAS RN:
1330-78-5 (TCPP)
13674-87-8 (TDCPP)</td><td>Common Names:
2-propanol, 1chloro-, phosphate (TCPP)
2-propanol, 1,3dichloro-, phosphate (TDCPP)</td><td>Product/material type: children's products containing flexible foam (e.g. toys containing foam)</td><td>Notes: TCPP and TDCPP have been measured in several children's products containing foam in the US, including nap mats (CEH 2013b), foam chairs (CEH 2013a), car seats, changing table pads, portable mattresses and rocking chairs, ranging from 0.11 to 1.4% for TCPP and 0.24 to 12.4% for TDCPP in concentration (reported as 1.11 to 14.4 mg/g and 2.4 to 124 mg/g, respectively) (Stapleton et al. 2011)</td></tr>
<tr><td colspan="4">Description of chemical specific information available/necessary for the exposure scenario</td></tr>
<tr><td>Concentration of substance in a given product or matrix:
- measured in nap mats, foam chair, car seats, changing table pads, portable mattresses and rocking chairs:
- 0.11 to 1.4% (TCPP); reported as 1.11 to 14.4 mg/g)
- 0.24 to 12.4% (TDCPP) (reported as 2.4 to 124 mg/g

Product testing by Health Canada (2014) detected TDCPP at mean concentration of approximately 7%; TCPP was not detected above LOQ (0.3%) (based on 23 children's</td><td>Migration rate or fraction information: (µg/cm^2/hr)
TCPP: 4.6 (EU RAR 2008a, US CPSC 2005)
TCDPP: 0.056 (EU RAR 2008a, US CPSC 2005)</td><td>Physiochemical properties (e.g. water solubility):
Not used in the quantitative assessment of exposure from mouthing in this approach</td><td>Notes: Dermal exposure intakes were estimated for children and adults in contact with foam mattresses as a representative upper bounding scenario of potential exposure; in addition exposure from mouthing a foam object was determined based on the same migration rates.</td></tr>
</table>

<table>
<tr><td>products purchased in retail stores in Ottawa) > 20% (toy ball, DBP)</td><td></td><td></td><td></td></tr>
<tr><td colspan="4">Type of hazard endpoint:
TDCPP: the critical effect for characterisation of risk to human health associated with exposure to TDCPP is carcinogenicity. A dose-response analysis of each tumour site by BMDS shows that the testis (interstitial cell tumour in male rats) is the most sensitive organ with a $BMDL_{10}$ of 6.74 mg/kg bw per day. For noncancer effects, a chronic critical LOAEL of 5 mg/kg bw was identified, where hyperplasia of the epithelium of the convoluted tubule in the kidneys, and histological abnormalities in the testes, were observed in males at the lowest dose tested in a two-year chronic toxicity study in rats

TCPP: In a two-generation reproductive toxicity study in rats, a LOAEL of 99 mg/kg bw per day, the lowest dose level tested, was identified for both reproductive and developmental effects (TNO Quality of Life 2007 cited in EU RAR 2008a). In a 13-week dietary study (Stauffer Chemical Co. 1981c cited in EU RAR 2008a and likely published by Freudenthal and Henrich 1999), a significant increase in liver weights in male rats was reported starting from the lowest dose tested of 52 mg/kg bw per day.</td></tr>
<tr><td colspan="4">Description of exposure scenario: Not provided</td></tr>
<tr><td>Population(s)/age group:
Toddler (6 months to 4 years)</td><td>Exposure frequency:
Daily</td><td colspan="2">Duration of exposure:
24.5 min/day</td></tr>
<tr><td rowspan="5">Algorithm Used
Exposure (µg/kg bw per day) =
(MR x SA x T)/BW

Source/reference for algorithm:</td><td>Parameter Definitions:</td><td>Source/Reference for Parameters</td><td rowspan="5">Justification for Algorithm:</td></tr>
<tr><td>MR = migration rate (µg/cm^2/hr)
4.6 (TCPP) and 0.056 (TDCPP)</td><td>See section 2 for references for migration</td></tr>
<tr><td>SA = Surface area mouthed (20 cm^2)</td><td>Prof judgement (2 times the SA area of open toddler’s mouth)</td></tr>
<tr><td>T = time (hr/day);
24.5 min/day</td><td>Smith and Norris (2002) cited in US EPA 2011)</td></tr>
<tr><td>BW = body weight (15.5 kg)</td><td>Health Canada 1998</td></tr>
<tr><td colspan="4">Estimation of oral exposure
Toddler (6 months – 4 years): TCPP: 2.4 µg/kg bw per day; TDCPP: 0.03 µg/kg bw per day</td></tr>
<tr><td colspan="4">Qualification in terms of the level of conservatism: Estimates considered to be based on conservative assumptions</td></tr>
<tr><td colspan="4">Uncertainties or limitations associated with the scenario:
The use of a passive migration rate may underestimate oral exposure from mouthing or sucking a foam object, an activity which is expected to be associated with a more active migration of the substance.</td></tr>
<tr><td colspan="4">Links to the Publication:</td></tr>
</table>

http://www.ec.gc.ca/ese-ees/default.asp?lang=En&n=B4374491-1#toc93

References:

CEH Center for Environmental Health (2013a), Playing on poisons: harmful flame retardants in children's furniture.

CEH Center for Environmental Health (2013b), Naptime nightmares: toxic flame retardants in child care nap mats.

EU RAR (2008a), European Union Risk Assessment Report.Tris(2chloro-1-methylethyl)phosphate (TCPP). Luxembourg: Office for Official Publications of the European Communities. [Internet]. [cited 2014 Jun 18]. https://echa.europa.eu/documents/10162/13630/trd_rar_ireland_tccp_en.pdf_

Health Canada (1998), Exposure factors for assessing total daily intake of priority substances by the general population of Canada. Unpublished report. Ottawa (ON): Health Canada, Environmental Health Directorate.

Smith S and Norris B (2002). Research into the mouthing behaviour of children up to 5 years old. Consumer and Competition Policy Directorate, Department of Trade and Industry (DTI), London US CPSC (Consumer Product Safety Commission) (2005), Migration of Flame Retardant Chemicals in Upholstered Furniture Foam. Washington (DC): Division of Chemistry (uhff2)

US EPA (2011), Exposure Factors Handbook: 2011 Edition. US EPA, Office of Research and Development, Washington, DC 20460. EPA/600/R-090/052F. http://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=236252

EXAMPLE 13: Mouthing of consumer products made with polyurethane foam containing certain flame retardants (specifically TCEP) by children under 4 years of age

<table>
<tr><th colspan="4">EXAMPLE 13: TCEP – Mouthing of consumer products made with polyurethane foam containing certain flame retardants (specifically TCEP) by children under 4 years of age (submitted by Canada)</th></tr>
<tr><td colspan="4">Information on identity of substance</td></tr>
<tr><td>CAS RN: 115-96-8 (TCEP)</td><td>Common Names: Ethanol, 2-chloro-, phosphate (3:1); (Tris(2-chloroethyl) phosphate)</td><td>Product/material type: Products containing polyurethane foam</td><td>Notes:</td></tr>
<tr><td colspan="4">Description of chemical specific information available/necessary for the exposure scenario</td></tr>
<tr><td>Concentration of substance in a given product or matrix:
- 8 toys produced from foam plastic; TCEP not detected (LOD was 50 mg/kg (Borling et al. 2006).
- Toys: 4/5 not above detection limit (not specified); (1 detection at 4900-6500 mg/kg in soft cube toy made of textile, plastic and foam rubber)
- Baby products: not detected above the detection limit of 1 µg/g in the six products samples (Tønning et al. 2008).</td><td>Migration rate or fraction information:
N/A</td><td>Physiochemical properties (e.g. water solubility):
Water solubility = 7820 mg/L</td><td>Notes: potential exposure from consumer products that contain polyurethane foam</td></tr>
<tr><td colspan="4">Type of hazard endpoint: With respect to non-cancer effects, the lowest LO(A)EL for short-term and subchronic exposures was 44 mg/kg-bw per day based on increased relative liver and kidney weights in a 16-week oral rat study. Renal tubular hyperplasia along with renal tubule and thyroid tumours were also observed at 44 mg/kg/day, the lowest dose tested in the 2-year rat study.</td></tr>
<tr><td colspan="4">Description of exposure scenario: Not provided</td></tr>
<tr><td>Population(s)/age group:
Infants (0 -6 months)
Toddlers (6 months – 4 years)</td><td>Exposure frequency:
Daily</td><td colspan="2">Duration of exposure:
9 minutes/day</td></tr>
<tr><td rowspan="2">Algorithm Used

Dose rate (mg/kg bw per day) =</td><td>Parameter Definitions:

WS = water solubility (7820 mg/L)</td><td>Source/Reference for Parameters
ECB 2000</td><td>Justification:</td></tr>
</table>

$WS \times Vs \times CF \times FR \times AF_o \times EF_{mouth} \times 1/BW$ **Source/reference:** Algorithm and default values (except bw) from ENVIRON Inter. Corp (2003)	Vs = salivary flow rate (0.22 mL/minute)	ENVIRON Inter. Corp (2003)	Methodology used by US EPA for another flame retardant (TCEP is also a flame retardant)
	CF = conversion factor (0.001 L/mL)	ENVIRON Inter. Corp (2003)	
	FR = fractional rate extraction by saliva (0.038)	ENVIRON Inter. Corp (2003)	
	AF_o = Absorption factor by oral route (0.5)	ENVIRON Inter. Corp (2003)	
	EF_{mouth} = exposure frequency (9 min/day)	ENVIRON Inter. Corp (2003)	
	BW = 7.5 kg (infant) or 15.5 kg (toddler)	Health Canada, 1998	
	1 = not defined (may represent one 9 minute exposure event/day)	ENVIRON Inter. Corp (2003)	

Estimation of oral exposure
- Without absorption factor: infant**: 78.5 µg/kg bw per day**
- With absorption factor: infant: 39 µg/kg bw per day

Qualification in terms of the level of conservatism: "Exposures of infants and toddlers to TCEP from mouthing of foam are considered overestimates, as the assumptions incorporated are conservative." (of note: some of the factors may not necessarily be conservative (e.g. the 0.22 mL/min salivary flow rate is unstimulated flow rate, a higher flow rate may be possible if stimulated by mouthing; a 50% oral absorption factor was also used)

Uncertainties or limitations associated with the scenario: Low confidence in the modelled estimates of exposure from consumer products, as there is a lack of data on specific types of products containing TCEP found in Canada and on the various chemical-specific parameters needed to estimate exposures to consumer products.

References and links to the publication:
Screening Assessment for the Challenge, Ethanol, 2-chloro-, phosphate (3:1) (Tris(2-chloroethyl) phosphate [TCEP]) Chemical Abstracts Service Registry Number 115-96-8 Environment Canada, Health Canada (August 2009) (http://www.ec.gc.ca/ese-ees/default.asp?lang=En&xml=C378778A-D834-54E0-7F69-E6E2944A74FC)

References:
ECB (European Chemicals Bureau) (2000), IUCLID dataset for tris (2-chloroethyl) phosphate (CAS No. 115-96-8). Available from: http://ecb.jrc.it/esis/

ENVIRON International Corporation (2003a), Voluntary Children's Chemical Evaluation Program Pilot (VCCEPP) - Tier 1 assessment of the potential health risks to children associated with exposure to the commercial PBDE. http://www.epa.gov/oppt/vccep/pubs/chem22a.html

ENVIRON International Corporation (2003b), Voluntary Children’s Chemical Evaluation Program Pilot (VCCEPP)—Tier 1 assessment of the potential health risks to children associated with exposure to the commercial octabromodiphenyl ether product and appendices [Internet]. Emerville (CA). http://www.epa.gov/oppt/vccep/pubs/chem23a.html

Health Canada (1998), Exposure factors for assessing total daily intake of priority substances by the general population of Canada. Unpublished report. Ottawa (ON): Health Canada, Environmental Health Directorate.

EXAMPLE 14: Mouthing of toys containing triclosan by children (6-12 months old)

<table>
<tr><th colspan="4">EXAMPLE 14: TRICLOSAN – Mouthing of toys containing triclosan (used as material preservative) by children (6-12 months old) (submitted by Canada)</th></tr>
<tr><td colspan="4">Information on identity of substance</td></tr>
<tr><td>CAS RN: 3380-34-5</td><td>Common Names: Triclosan</td><td>Product/material type:
Consumer products with triclosan (plastic toy - impregnated with triclosan as a material preservative)</td><td>Notes:</td></tr>
<tr><td colspan="4">Description of chemical specific information available/necessary for the exposure scenario</td></tr>
<tr><td>Concentration of substance in a given product or matrix:
The following assumptions were used:
- application rate of 0.5% triclosan,
- 0.5% triclosan available on the surface of the toy</td><td>Migration rate or fraction information:
N/A</td><td>Physiochemical properties (e.g. water solubility):
N/A</td><td>Notes: the approach is for a surface residue of a substance</td></tr>
<tr><td colspan="4">Type of hazard endpoint: Database NOAEL of 25 mg/kg bw per day from sub-chronic 90-day oral toxicity study in the mouse (target MOE of 300); protective for potential liver effects, if any, that could occur in humans as well as effects in other organs and systems.</td></tr>
<tr><td colspan="4">Description of exposure scenario: Mouthing of toys containing triclosan (used a material preservative) by children 6-12 months of age</td></tr>
<tr><td>Population(s)/age group:
Infants (6-12 months)</td><td>Exposure frequency:
Daily</td><td colspan="2">Duration of exposure:
No duration parameter in algorithm</td></tr>
<tr><td rowspan="6">Algorithm Used

- Surface residue (SR) (mg/cm^2) = Wt./SA toy × % substance in toy × % substance available on surface × conversion factor (1000 mg/g) = 0.0025 mg active ingredient/cm^2</td><td>Parameter Definitions:</td><td>Source/Reference for Parameters</td><td rowspan="6">Justification:</td></tr>
<tr><td>Wt. (Weight) of toy = 5 g</td><td rowspan="5">US EPA 2011</td></tr>
<tr><td>SA (surface area) of toy = 50 cm^2 (maximum)</td></tr>
<tr><td>% substance in toy = 0.5%</td></tr>
<tr><td>% sub. avail. on surface = 0.5%</td></tr>
<tr><td>SR = surface residue (mg/cm^2)</td></tr>
</table>

- Daily dose (mg/kg bw/day) = SR (mg a.i./cm^2) × SE × SA toy / BW	SE = saliva extraction efficiency (50%) BW = 9.2 kg		
Estimation of oral exposure (to toys) Infant: 6.8 µg/kg bw per day			
Qualification in terms of the level of conservatism: Aggregate exposure was calculated for infants. This was considered highly conservative (i.e. the combination of object-to-mouth, hand-to-mouth and nursing/breastfeeding exposures).			
Uncertainties or limitations associated with the scenario: There is an uncertainty regarding the potential co-occurrence of all identified scenarios in practice. An assumption that a child will be exposed daily to high triclosan residues as identified for each scenario is considered conservative. The assumption that all potential exposure scenarios will co-occur also represents conservatism in the aggregate assessment for infants 6–12 months of age. Further, assumptions used in incidental oral exposure assessments (i.e. hand-to-mouth and object-to-mouth) are considered conservative, since it is unlikely that all plastic toys and carpets will be made with material treated with triclosan.			
References and links to the publication: Assessment Report, Triclosan, Chemical Abstracts Service Registry Number 3380-34-5 Environment and Climate Change Canada, Health Canada, November 2016 (http://www.ec.gc.ca/ese-ees/65584A12-2B7D-4273-9F7A-38EDF916ECAF/EN%20FSAR%20Triclosan%20with%20ISBN.pdf)			
References: US EPA (2011), Exposure Factors Handbook: 2011 Edition. US EPA, Office of Research and Development, Washington, DC 20460. EPA/600/R-090/052F. http://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=236252			

EXAMPLE 15: DINP in toys

EXAMPLE 15: DINP in toys (Published study) – BIAC			
Information on identity of substance			
CAS RN: 28553-12-0	**Common Names**: **Di-isononyl phthalate (DINP)**	**Product/material type:** Children's toys	**Notes:** children's products represents soft plastic toys
Description of chemical specific information available/necessary for the exposure scenario			
Concentration of substance in a given product or matrix: From Chen, 2002: DINP concentrations were measured in 85 soft plastic articles. Of the 85, 36 contained DINP (42% of the articles). From Simoneau et al. 2001; DINP content in the toys tested for migration (24 of the 36) ranges from 13-39%, with 30% being both the mean and median, and SD of 6.2. For probabilistic analysis, Values by product tested can be found in Table 3 of Babich et al. 2004.	**Migration rate or fraction information:** Simoneau et al. 2001: Product specific migration rates were measured by the head over heels method for this study. This was a new method developed following an interlaboratory study to evaluate methods for measuring DINP migration from children's toys. Migration rates were measured for 24 of the 36 articles identified to contain DINP in Chen 2002 (14 products were not amenable to migration testing). Migration rate was not related to %DINP content. Values by product tested can be found in Table 3 of Babich et al. 2004. In units of µg/10 cm^2/min, mean =4.1, median =3.4, SD = 2.7, range – 1- 11.1, Expressing these values in units of µg/cm^2/hr [multiplied by (1/10 cm^2) X (60 min/hr)]: mean 24.6, median=20.4, range 6 – 66.6 .	**Physiochemical properties (e.g. water solubility):** Pchem parameters were not utilised in the exposure estimate, as measured migration rates were used (probabilistic analysis sampled from the distribution of measured rates).	**Notes:**

	For the probabilistic analysis, 33 articles with 0 migration were added to the 24 migration rates, to retain the ratio of Chen 2002 of 42% of articles having DINP. Migration rates from the *in vitro* studies were adjusted for application to *in vivo* estimation. The *in vivo* migration rate was taken from the RIVM 1998 study of adults chewing 10 cm^2 disks containing 40% DINP. Simoneau et al. (2001) tested standard disks using the head over heels methods to calibrate to enable calibration of *in vivo* to *in vitro* rates. The calibration factor used in the exposure equation is Mhuman/Mlab; each was sampled from a distribution but to give some sense of magnitude, it would be 0.3 based upon means (*in vitro* method yielded higher migration rates than *in vivo* one).		
Type of hazard endpoint: Acceptable Daily Intake based upon liver effects in rats as considered to be sensitive endpoint for assessing systemic effects.			
Description of exposure scenario			

Population(s)/age group: 3-11 months 12-23 months 24-36 months	**Exposure frequency:** Daily	**Duration of exposure:** Mouthing times taken from an observational study of 169 children aged 3-36 months, observed by trained observers for 12 observations of 20 minutes each over 2 days, in the child's home with the child's toys [summary results provided in Table 4 of Babich et al. 2004]. Objects mouthed were classified into 13 categories and subcategories, including soft plastic toys. The observational study results were reported as hourly mouthing duration. Parental observations for hours of time awake and not eating were used to develop an equation to estimate total daily exposure time by age (Tday = 9.46 + 0.0375 + Age). The hourly mouthing time was then multiplied by this factor to get total daily mouthing time. A distribution of daily mouthing time was estimated based upon the Tday equation and standard deviation of 1.26 hour assuming a normal distribution.	
Algorithm Used			
Algorithm: $E = \frac{\left[Mproduct \times \left(\frac{Mhuman}{Mlab}\right) \times Thour \times T\,day\right]}{B}$	**Definitions:** E = oral daily exposure (µg/kg bw per day) $M_{product}$ = migration rate of product as measured by JRC lab method (µg/min) M_{human} = migrate rate of the standard disk with human subject (µg/min) M_{lab} = migration rate of the standard disk by the JRC method (µg/min) T_{hour} = hourly mouthing time (min/hr) T_{day} = exposure duration (time awake and not eating) (hr/day) B= body weight Migration rates are for the surface of 10 cm^2	**Source/reference:** Babich et al. 2004	**Justification:** In 1998, CPSC multiplied migration rates estimated from the impaction method by a scaling factor to adjust for the difference between migration rates measured by impaction and human subjects. Adjusted for prevalence of DINP in products tested. Monte Carlo bootstrap method used to estimate exposure and develop CI for selected percentiles. The dependence of mouthing time, exposure time and body weight on age were preserved yet other

			variables were independent. Each factor was sampled from a distribution.

Algorithm in Mouthing tool

Equation 14 of the Mouthing Exposure In Silico Tool

Estimation of oral exposure

From Table 5 of Babich et al. 2004:

Estimated oral exposure to DINP from soft plastic toys – µg/kg-day. Values in parentheses are 95% confidence intervals

Age	3-11 months	12-23 months	24-36 months
Mean	0.07 (0.03 – 0.13)	0.08 (0.04 – 0.14)	0.03 (0.01 – 0.06)
Median	0.00 (0.00 – 0.00)	0.00 (0.00 – 0.00)	0.00 (0.00 – 0.00)
95th percentile	0.44 (0.15 – 0.82)	0.53 (0.24 – 0.89)	0.12 (0.04 – 0.23)
99th percentile	1.4 (0.74 – 2.4)	1.5 (0.89 – 2.3)	0.56 (0.17 – 1.6)

Note these results are based upon the approach described above, including the assumption that DINP was present in 42% of soft plastic toys. Table 6 of the same publication provides hypothetical oral exposures calculated for DINP for products in which it was not found, and also assuming in 100% of products (see discussion under the Uncertainties section below).

Qualification in terms of the level of conservatism:

Probabilistic analysis performed based upon distributional data for each endpoint in equation. Detailed studies were done to provide data on DINP migration and mouthing time specific to soft toys.

Uncertainties or limitations associated with the scenario:

Similar conclusions result if mean or 99th percentile exposure values are used for each age group. However, further analyses were also done to estimate the impact of several of the assumptions in this approach. For example, if DINP was assumed to be present in all soft plastic toys rather than 42%, exposures accordingly increased by about a factor of 2 which did not impact the conclusion.

References and links to the publication

Babich MA, Chen SB, Greene MA, Kiss CT, Porter WK, Smith TP, Wind ML, Zamula WW (2004), Risk assessment of oral exposure to diisononyl phthalate from children's products. Regul Toxicol Pharmacol 40:151-67.

Chen, SB, (2002), Screening of toys for PVC and phthalates migration. US Consumer Product Safety Commission. Bethesda, MD.

Simoneau, C. H. Geiss, A. Roncari, P, Zocchi, P. Hannaert. (2001), Validation of methodologies for the release of di-isononylphthalate (DINP) in saliva simulant from toys. European Commission, DG-Joint Research Center, Food Products Unit, Institute for Health and Consumer Protection, I-21020, EUR 19826 EN.