Health risk assessment of selected phthalates in children's toys

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by

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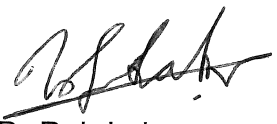

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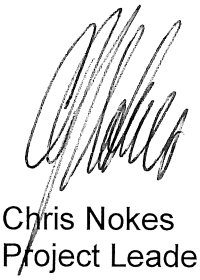

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GLOSSARY

Acute toxicity	1. *Adverse effects* of finite duration occurring within a short time (up to 14 d) after administration of a single *dose* (or *exposure* to a given *concentration*) of a test substance or after multiple doses (exposures), usually within 24 h of a starting point (which may be exposure to the *toxicant*, or loss of reserve capacity, or developmental change, etc.) 2. Ability of a substance to cause *adverse effects* within a short time of dosing or *exposure*
Adverse effect	A change in biochemistry, physiology, growth, development morphology, behaviour, or lifespan of an organism which results in impairment of functional capacity or impairment of capacity to compensate for additional stress or increase in susceptibility to other environmental influences
Ataxia	Unsteadiness or loss of coordination of movement
Bench mark dose	A dose or concentration which causes a predetermined change in response rate of an adverse effect compared to background
Chronic exposure	A continuous or intermittent long-term contact between an agent and a target. (Other terms, such as “long-term exposure,” are also used.)
Cilia	A hair-like appendage which is found in numbers on the surface of a cell
Critical effect	For deterministic effects, the first adverse effect that appears when the threshold (critical) concentration or dose is reached in the critical organ. Adverse effects with no defined threshold concentration are regarded as critical
Critical organ	Organ that first attains the critical concentration of a substance and exhibits the critical effect under specified circumstances of exposure and for a given population
Cytotoxicity	The property of causing damage to cell structure or function
Dermal	Cutaneous, pertaining to the skin
Deterministic effect	Phenomenon committed to a particular outcome determined by fundamental physical principles.
Dose	Total amount of a substance administered to, taken up, or absorbed by an organism, organ, or tissue
Dose response	Association between dose and the incidence of a defined biological effect in an exposed population
Dose response assessment	Analysis of the relationship between the total amount of an agent administered to, taken up by, or absorbed by an organism, system, or (sub)population and the changes developed in that organism, system, or (sub)population in reaction to that agent, and inferences derived from such an analysis with respect to the entire population. Dose–response assessment is the second of four steps in risk assessment

Exposure assessment	Evaluation of the exposure of an organism, system, or (sub)population to an agent (and its derivatives). Exposure assessment is the third step in the process of risk assessment.
Harm	An adverse effect. Damage or adverse effect to a population, species, individual organism, organ, tissue, or cell
Hazard identification	The identification of the type and nature of adverse effects that an agent has an inherent capacity to cause in an organism, system, or (sub)population. Hazard identification is the first stage in hazard assessment and the first of four steps in risk assessment
Hazard index (HI)	The sum of more than one hazard quotient for multiple substances and/or multiple exposure pathways. The HI is calculated separately for chronic, sub-chronic and shorter-duration exposures
Hazard quotient (HQ)	The ratio of a single substance exposure level over a specified time period (eg sub-chronic) to a reference dose for that substance derived from a similar exposure period. If the hazard quotient exceeds unity, the toxicant may produce an adverse effect, but normally this will require a hazard quotient of several times unity; a hazard quotient of less than 1.0 indicates that no adverse effects are likely over a lifetime of exposure
Hepatotoxic(ity)	Producing a toxic effect in the liver
Hyperplasia	Abnormal multiplication or increase in the number of normal cells in a tissue or organ
Incidence	Number of occurrences of illness commencing, injury, or of persons falling ill, during a given period in a specific population usually expressed as a rate
Injury	Any physical harm or damage serious enough to warrant medical treatment by a health professional either at the scene or in a hospital or primary care practice.
Ischemic necrosis	Cell or tissue death due to reduced blood supply
LC_{50}	Concentration of a substance in an environmental medium that causes death of 50% of test subjects following a certain period of exposure.
LD_{50}	Amount of a substance or physical agent that causes death of 50% of test subjects when taken into the body
Lowest observed adverse effect level (LOAEL)	Lowest concentration or amount of a substance (dose), found by experiment or observation, that causes an adverse effect on morphology, functional capacity, growth, development, or life span of a target organism distinguishable from normal (control) organisms of the same species and strain under defined conditions of exposure.
Margin of exposure (MOE)	Ratio of the no-observed-adverse-effect level (NOAEL) for the critical effect to the theoretical, predicted, or estimated exposure dose or concentration

Mode of action (MOA)	The understanding of how chemicals perturb normal biological function; the key steps in the toxic response after chemical interaction at the target site that are responsible for the physiological outcome or pathology of the chemical
Mucosal exposure	A dose received via a mucus membrane
New Zealand EPA	New Zealand Environment Protection Authority
No observed adverse effects level (NOAEL)	Greatest concentration or amount of a substance, found by experiment or observation, that causes no alterations of morphology, functional capacity, growth, development, or life span of target organisms distinguishable from those observed in normal (control) organisms of the same species and strain under the same defined conditions of exposure
Oedema	A fluid build-up in tissue
Oral	Pertaining to or via the mouth
Point of departure (POD)	A NOAEL or LOAEL for an observed incidence or change in level of response to a chemical toxicant.
Polarity	Pertaining to the separation of positive and negative charge between parts of a molecule
Qualitative	Relating to the presence
Quantitative	Relating to the amount
Reference dose	An estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. It can be derived from a NOAEL, LOAEL, or benchmark dose, with uncertainty factors generally applied to reflect limitations of the data used
Reference value	Quantity value, generally accepted as having a suitably small measurement uncertainty, to be used as a basis for comparison with values of quantities of the same kind.
Risk characterisation	The qualitative and, wherever possible, quantitative determination, including attendant uncertainties, of the probability of occurrence of known and potential adverse effects of an agent in a given organism, system, or (sub)population, under defined exposure conditions. Risk characterization is the fourth step in the risk assessment process.
Stricture	Abnormal narrowing of a duct or passage such as blood vessels or urethra
Stroma	Supportive tissue of an epithelial organ or tumour, consisting of connective tissue, blood vessels and other tissue
Toxicity	Inherent property of an agent to cause an adverse biological effect.
Threshold concentration	Dose or exposure concentration below which a defined effect will not occur

Toxicological endpoints	An observable or measurable biological event or chemical concentration (e.g., metabolite concentration in a target tissue) used as an index of an effect of a chemical exposure

EXECUTIVE SUMMARY

The purpose of this report is to develop a health risk assessment for selected phthalates in children's toys. This report considers domestic, non-occupational, routine and incidental exposure to phthalates, in particular, the ortho-dialkyl phthalates.

People, particularly infants and toddlers, are often exposed to a number of different phthalates through contact with the home environment and through diet. Additionally, infants and toddlers can also receive exposure whilst in out-of-home daycare facilities and through other activities such as transport in a vehicle.

We assessed the exposures and risks to two groups of phthalates, based on common toxicological properties: (1) Phthalates with reproductive or developmental toxicity concerns (including di-2-ethylhexyl phthalate (DEHP), dibutyl phthalate (DBP), benzylbutyl phthalate (BBP), and di-isobutylphthalate (DIBP)), and (2) phthalates with hepatoxicity concerns (including diisononyl phthalate (DINP), di-n-octyl phthalate (DNOP) and diisodecyl phthalate (DIDP)). Tolerable Daily Intakes (TDI) for five of these phthalates (DEHP, DBP, BBP, DINP, and DNOP) have been derived by the European Union and serve as the basis for the risks characterized in this report. TDIs were adopted for the two remaining phthalates (DIBP and DIDP), based on structural similarity to other compounds in these groups.

Because the toxicological effects of phthalates may be additive through common mechanisms of action, this report assesses the combined exposure and risks of these two groups of phthalates in children, using a hazard index approach for the two most relevant routes of exposure: ingestion and dermal absorption. Typical and worst-case exposure scenarios for these phthalates through contact with children's toys have been assessed and the estimated doses compared to the Europa Directorate General (DG) Health and Consumer Product TDI's for each phthalate, to form the hazard indices.

The phthalate concentration data used to calculate the exposures were taken from two sources. First, monitoring data collected in the EU from products which had notifications or product recalls issued due to exceeding permissible levels of specified phthalates in the composition, which provided an estimate of a reasonable worst case scenario. Second, the 0.1% w/w regulatory limit which appears to be frequently adopted by regional and national jurisdictions outside New Zealand, which provides an estimate of the health implications of exposure at that level. The data represented recent notifications from early 2013 to mid-2014 and, as such, are considered to represent recently manufactured products with high levels of phthalates in them.

Internationally the use of phthalates in children's toys is regulated with the majority of legislation directing a maximum permissible level of 0.1% by mass of phthalates as the statutory limit. The regulations enacted in other jurisdictions are generally broadly aimed at the two groups of phthalates which are characterised in this report.

Of the two exposure routes examined (ingestion and dermal), ingestion presented the greater contribution to overall dose for both groupings of phthalates; a cumulative dose of 64 µg/kg bw/day for the antiandrogenic group and 66 µg/kg bw/day for the hepatotoxic group under the worst case scenario. The greatest contribution to this dose was from DEHP and DINP; with DEHP being antiandrogenic and DINP hepatotoxic. In the absence of New Zealand specific data on the phthalate composition of children's toys it is not possible to determine if these phthalate levels are representative of typical or worst case exposures in New Zealand.

When taken in isolation of other contributory exposure sources, under reasonable worst case scenarios these data indicate that estimated doses received solely from exposure to phthalate-containing children's toys exceed a combined hazard index of 1.0 using TDI values set by the EU, and thus present potential for risk of adverse health effects due to phthalate exposure. However, it should also be noted that the exposure scenario represented by mouthing and handling of children's toys is only one of a number of contributory sources of phthalate exposure; with a recent report showing that at most the exposure to a single phthalate, DINP, from toys is not greater than 20% of the total dose, and the remaining phthalates being significantly lower, if not zero (Chronic Hazard Advisory Panel 2014). Of most significance is the dose contribution which is predicted for the antiandrogenic, reproductive/developmental toxicity phthalate group (DEHP, DBP, BBP and DINP) where, in the worst case scenario, a hazard index of 1.5 was found, based on the European TDI values from ingestion and dermal exposure combined. This HI indicates that phthalate exposure at the levels used for this scenario may give rise to adverse health effects.

For the typical case which was estimated using the 0.1% w/w European Union regulatory limit which is frequently cited by national and regional jurisdictions outside of New Zealand the HI were 0.02 for the antiandrogenic phthalates and less than 0.01 for the hepatotoxic phthalates. These values indicate that it would be considered unlikely that exposure to these phthalates at these doses would induce adverse effects.

1. INTRODUCTION

The purpose of this report is to develop a generic health risk assessment for selected phthalates in children's toys. The phthalates detailed in this report have been selected due to their toxicity and the international recognition which is accorded to them in many jurisdictions' legislation. This report only considers domestic, non-occupational, routine and incidental exposure to phthalates. Exposure scenarios are developed for the most common or likely exposure events to assess the health risk for children, who are considered a vulnerable population.

Phthalates are chemicals which are added as plasticisers to plastics to impart or improve flexibility to the polymer matrix. They are frequently added to polyvinyl chloride plastics (PVC). As an additive to PVC plastics, phthalates are found in many everyday household objects, of which recreational and children's toys are included (ATSDR 2001; 2002). Phthalates are not chemically bound into the polymer of the plastic in which they are additives; therefore they can be released from the matrix into the surrounding environment by a number of physical and chemical mechanisms throughout the life of the object (Ambrogi et al 2012; Audic et al 2003; Bouma and Schakel 2002; Braun et al 2013; Butte and Heinzow 2002; Carlstedt et al 2013; Fayz et al 1977; Gong et al 2014; Graham et al 1991; Green 2002; Liang and Xu 2014; Loff et al 2008; Maas et al 2004; Messadi et al 1983; Sioen et al 2012; Steiner et al 1998).

People, particularly infants and toddlers, can be exposed to a number of different phthalates through contact with the home environment and through diet. Additionally, infants and toddlers can also receive exposure whilst in cars, and at out-of-home daycare facilities (Bailey 2008; Braun et al 2013; Fromme et al 2004; Gevao et al 2013; Grandjean and Toppari 2006; Grynkiewicz-Bylina 2011; Kim et al 2011; Kim et al 2013; Koch et al 2004; Kolarik et al 2008; Koo and Lee 2005; Kubwabo et al 2013; Langer et al 2014; Xu et al 2009). Exposure is either through direct contact with objects or products containing phthalates; or through uptake of phthalates which have been shed from products and become a constituent of house dust (Bamai et al 2014; Beko et al 2013; Butte and Heinzow 2002; Kang et al 2012; Kolarik et al 2008; Kubwabo et al 2013; Langer et al 2014).

A range of specific toxicological effects have been attributed to individual phthalates. Di-2-ethylhexyl phthalate (DEHP), dibutyl phthalate (DBP), benzylbutyl phthalate (BBP) and diisobutyl phthalate (DIBP), have been identified as potentially producing developmental effects such as reduced weight of testes, reduced anogenital distance, nipple retention and decreased testosterone production. Diisononyl phthalate (DINP), di-n-octyl phthalate (DNOP) and diisodecyl phthalate (DIDP) are all noted to produce hepatotoxic effects in rat models, although the significance of the peroxisome proliferator activated receptor mechanism is considered to be less relevant to human health than in rats (Chronic Hazard Advisory Panel 2014).

Internationally, the use of phthalates in children's toys is regulated with the majority of legislation directing a maximum permissible level of 0.1% by mass of phthalates as the statutory limit. The phthalates covered in the various legislations are DEHP, DBP, BBP, DINP, DNOP and DIDP. Indicative information regarding the permissible concentrations in children's toys and childcare products is shown in Table 1.

Table 1: International regulatory conditions of restriction for use of selected phthalates in children's toys and childcare products

Country or Region	**Conditions of restriction (w/w%)** [1]
European Union	Applicable for all children's toys and childcare articles for children under 3 years of age: DEHP + DBP + BBP ≤ 0.1% Applicable for all children's toys and childcare articles that can be placed in children's mouth: DINP + DIDP + DNOP ≤ 0.1%
United States of America	Applicable for toys that cannot be placed in the mouth of children under 12 years of age: DEHP, DBP and BBP ≤ 0.1% Applicable for toys that can be placed in the mouth of children under 12 years of age: DEHP, DBP, BBP, DINP, DIDP, DNOP ≤ 0.1%
Canada	Applicable to ethylvinyl toys and childcare articles: DEHP, DBP, BBP ≤ 0.1% Applicable for soft ethylvinyl toys and childcare products that can be placed in mouth for children under 4 years of age: DINP, DIDP, DNOP ≤ 0.1%
Argentina	Applicable for all children's toys and childcare articles for children under 3 years of age: DEHP + DBP + BBP ≤ 0.1% Applicable for all children's toys and childcare articles that can be placed in children's mouth: DEHP + DBP + BBP + DINP + DNOP ≤ 0.1%
Brazil	Applicable to ethylvinyl toys and childcare articles: DEHP, DBP, BBP ≤ 0.1% Applicable for ethylvinyl toys and childcare products that can be placed in mouth for children under 3 years of age: DEHP, DBP, BBP, DINP, DNOP ≤ 0.1%

[1] http://www.cirs-reach.com/Testing/Phthalates_Testing.html for all countries or regions in this table except Australia, accessed 26/08/14.

Country or Region	Conditions of restriction (w/w%) [1]
Japan	Applicable for all synthetic resin toys: the use of DEHP is prohibited Applicable for mouth contact synthetic resin toys for children under 6 years of age: the uses of DEHP and DINP are prohibited.
Australia [2]	Applicable to children's toys and childcare articles for children under 3 years of age: DEHP ≤ 1%

The derivation of the 0.1% limit for either individual phthalates or the grouped phthalates identified in regional legislation appears to be based on delivering a total prohibition of the deliberate use of phthalates in (PVC) plastics. The functional use of phthalates for softening plastics requires that greater than 10% by mass be used in the matrix. By setting the regulatory limits at 0.1%, or 1% in the case of Australia, the regional authorities have effectively prevented the use of phthalates for their mechanical properties whilst accepting that there may be a small amount present as accidental contamination of a manufactured product, hence these limits do not necessarily represent a health risk-based regulatory limit (Chronic Hazard Advisory Panel 2014).

The ISO8124 – Part 6:2014 standard is the international standard for analytical determination of content of DBP, BBP, DEHP, DNOP, DINP, and DIDP in toys and children's products. Regulatory control of safety of children's toys for New Zealand is detailed on the MBIE Consumer Affairs website[3].

The regulatory control of phthalates in children's toys and childcare products has led to the undertaking of routine monitoring for compliance of these products by a number of territories. Transgressions of the regulations lead to either notification or issuing of recall notices for affected products. The European Union (EU) maintains a region-wide rapid alert system for non-food dangerous products called RAPEX[4]. The system contains details of current and historic notifications and recall notices and the results of chemical or physical analyses of notified products. Many other jurisdictions have similar systems; however the RAPEX system offers a high level search function which allows use of key words and time frames to deliver data for the whole of the EU. In a recently performed search (14/08/14) of the RAPEX system using the search terms 'phthalates' and 'toys' 778 recall notices were recovered for the time period 2009 – 2014. A sub-sample of these records (n = 50) were further examined to determine country of origin. China (including Hong Kong) was the source of 82% of recalled products; with the USA and the Ukraine in next position with 4% each of the recalled products. The range of phthalate concentrations represented in these data was 0.11% to 39.5% by mass. Further analysis of these data showed DEHP to

[2] http://www.comlaw.gov.au/Details/F2011L00192 accessed 05/09/14
[3] Children's toy standard | Consumer Affairs
[4] http://ec.europa.eu/consumers/consumers_safety/safety_products/rapex/index_en.htm

be the most frequently notified compound and also that it represented the highest concentration (w/w%) level in articles. These data are shown in Table 2.

Table 2: Phthalate compound occurrence and concentration range reported in a sample taken from the RAPEX system

Phthalate compound	**Occurrence frequency (%)**	**Concentration range (w/w%)**
DEHP	60.8	0.11 – 39.5
DINP	16.2	0.19 – 38.0
DBP	14.9	0.11 – 1.5
DIDP	4.1	0.32 – 5.5
DIBP*	2.7	1.1 – 29.0
DNOP	1.4	29.0**

* Diisobutyl phthalate

**A single DNOP sample was reported, hence there is no concentration range associated with this compound

It appears from the data reviewed from the RAPEX search performed on 14th August 2014 that, although there are strict guidelines on the composition of children's toys and childcare products in the EU there remains a significant number of transgressions occurring. Additionally, the transgressions which do occur are frequently at phthalate concentrations many times greater than the regulatory limits given in the regional guidelines.

2. HAZARD IDENTIFICATION

The literature on the health effects of phthalates is extensive. In this report we rely on recent reviews by regulatory agencies, the most recent of which is the 2014 report by the US Chronic Hazard Advisory Panel (CHAP) (2014). Another major resource was the series of hazard assessments of phthalates published in 2008 by the National Industrial Chemicals Notification And Assessment Scheme (NICNAS) in Australia.[5] NICNAS has assessed all six phthalates included in the current assessment and an additional 18 phthalate compounds. A compendium of the hazard assessments has also been published (NICNAS 2008e). NICNAS categorised the 24 phthalates assessed into three categories, based on use patterns, physicochemical properties and toxicological properties. The three categories were:

- Low molecular weight phthalates, with ester substituents with straight-chain carbon backbones of three carbons or less (≤C3).
- High molecular weight phthalates, with ester substituents with straight-chain carbon backbones of ≥C7 or ring structure.
- Transitional phthalates, with ester substituents with straight-chain carbon backbones of C4-6. Phthalates of this backbone length have been associated previously with reproductive and developmental toxicity.

Phthalates included in the current assessment are either transitional (DEHP, DBP, BBP, DIBP) or high molecular weight (DINP, DNOP, DIDP).

This material was supplemented by searches via PubMed (MeSH keywords: phthalate and toxicology, phthalate and risk, phthalate and toy) back to 2009. The retrieved references were considered by title for relevance; with an emphasis on recent review articles.

2.1 Toxicokinetics of phthalates

Phthalates are rapidly metabolised, mainly to the relevant monoester, and are excreted in urine and faeces. Phthalates are rapidly absorbed from the gastrointestinal tract, following oral exposure, with up to 80% of the ingested dose absorbed for doses up to 200 mg/kg bw/day in rats (NICNAS 2008e). At higher doses the proportion absorbed is lower and a higher proportion of the ingested dose is excreted in the faeces. In human studies, phthalates have been shown to be excreted rapidly (to below detectable levels) in urine after 24 hours in adults, and do not bioaccumulate (Anderson et al 2001; Kay et al 2014).

Studies suggest decreased dermal absorption with increasing side-chain length (NICNAS 2008e). Dermal absorption of phthalates appears to be generally less than 15%, although a greater proportion of the applied dose may be retained in the skin. For high molecular weight phthalates, dermal absorption appears to be substantially less than 10% of the applied dose.

[5] Available from: http://www.nicnas.gov.au/chemical-information/other-assessment-reports/phthalates-hazard-assessment-reports accessed 1 October 2014

While there is evidence that phthalates are able to be absorbed from the respiratory tract, few quantitative data were available. A study with aerosols of DIDP reported that absorption from the lung was 73% (NICNAS 2008c).

2.2 Hazard identification for individual phthalates

The following sections summarise hazard information for the seven phthalates covered in the current report.

2.2.1 Diethylhexyl phthalate (DEHP)

DEHP (CAS 117-81-7; dioctyl phthalate, *bis*(2-ethylhexyl) phthalate) is a common component of plastics and may be present in vinyl materials at concentrations up to 40% (ATSDR 2002). At least 95% of DEHP produced is used in the manufacture of polyvinyl chloride (PVC).

The US Agency for Toxic Substances and Disease Registry (ATSDR) assessed DEHP and concluded that it was of low acute oral toxicity (ATSDR 2002). Repeat dose rodent studies identified the liver and testes as the primary target organs, but non-human primates appear to be relatively insensitive to these effects. Testicular toxicity results in loss of spermatogenesis and decreased fertility, while there is more limited evidence for reproductive toxicity in female rodents. DEHP is foetotoxic and teratogenic, inducing a range of developmental abnormality in the male reproductive tract. Hepatic effects include hypertrophy and hyperplasia, probably related to increases in peroxisome proliferation.

Some chemicals have the ability to mimic or block the action of endogenous hormones, through binding to hormone receptors and, either activating the receptor (agonist) or blocking the receptor, so that it cannot be activated by the endogenous hormone (antagonist). Such chemicals are referred to as endocrine disruptors. While DEHP is able to produce changes in androgen-sensitive tissues, it does not bind strongly to either the estrogen or androgen receptors and is not considered to be an endocrine disrupting substance. See section 3.1 for a discussion of the potential mechanism of action for the effect of phthalates on androgen-sensitive tissues.

Substantial evidence in animal studies suggests DEHP is not genotoxic, but long-term exposure may result in liver cancer, probably through epigenetic mechanisms. These mechanisms do not appear to be operative in humans (ATSDR 2002).

There is limited information on the toxicity of DEHP by inhalation and dermal routes of exposure. Changes to the lungs following inhalation exposure appear to be reversible. Reproductive and developmental toxic effects do not occur following inhalation exposure (ATSDR 2002).

DEHP does not appear to be a skin or eye irritant or a skin sensitiser (ATSDR 2002).

The European Chemicals Bureau (ECB) carried out a risk assessment of DEHP, reaching similar conclusions to ATSDR (European Chemical Bureau 2008). ECB concluded that carcinogenic effects on rodent livers were not relevant to humans, but noted toxic effects on the kidneys and testes. The most sensitive endpoint was

considered to be testicular toxicity. DEHP is classified in the European Union (EU) as toxic to reproduction, Category 2; R60 (may impair fertility) – 61(may cause harm to the unborn child). The category refers to the strength of evidence. Category 2 equates to the descriptor “Substance which should be regarded as if they impair fertility in humans/cause developmental toxicity in humans”. Category 1 is used for substances that are known to cause these adverse effects in humans.

Very similar conclusions were reached by NICNAS (2010) and the World Health Organization (International Programme on Chemical Safety 1992).
A Canadian joint agency assessment reviewed toxicological information on DEHP and concluded that, while liver carcinogenicity appeared to be the most sensitive endpoint in rodents, the mechanisms underlying this effect were unlikely to be relevant in humans (Government of Canada/Environment Canada/Health Canada 1994).

The California Environmental Protection Agency (CEPA) have also reviewed the carcinogenicity of DEHP and arrived at similar conclusions, that humans are likely to be less sensitive to the carcinogenic effects of DEHP, due to lower expression levels of the peroxisome proliferator activated receptor-alpha (PPAR-α) (California Environmental Protection Agency 2001). CEPA have also considered non-cancer toxicological endpoints for DEHP following oral exposure and concluded that the most sensitive endpoint relates to male reproductive effects (California Environmental Protection Agency 2005).

The US National Toxicology Program Center for the Evaluation of Risks to Human Reproduction (CERHR) reviewed information on DEHP and identified concern that DEHP exposure may adversely affect the development of the male reproductive tract for infants less than one year (NTP-CERHR 2006). Minimal concerns were identified for reproductive effects following adult male exposure to DEHP. This report identified release of DEHP from medical devices during medical procedures as a particular risk activity. The US Food and Drug Administration has also assessed risks associated with this route of exposure (USFDA 2000).

The US Consumer Product Safety Commission (CPSC) convened a Chronic Hazard Advisory Panel (CHAP) to “study the effects of all phthalates and phthalate alternatives as used in children’s toys and child care articles”. The review of toxicological information related to DEHP by the CHAP (Chronic Hazard Advisory Panel 2014) stated: *”A complete dataset suggests that exposure to DEHP in utero can induce adverse developmental changes to the male reproductive tract. Exposure to DEHP can also adversely affect many other organs such as the liver and thyroid.”*

It should be noted that, while other assessments have noted effects on thyroid hormone levels in some studies, the clinical significance of these findings is uncertain (ATSDR 2002).

2.2.2 Dibutyl phthalate (DBP)

DBP (CAS 84-74-2; 1,2-Benzenedicarboxylic acid, dibutyl ester) is used as a plasticiser in polyvinyl chloride (PVC) and nitrocellulose lacquers (ATSDR 2001).

DBP has been assessed by ATSDR and it was concluded that the main toxic effects were those on the developing male reproductive tract (ATSDR 2001). DBP is of low acute oral toxicity. Toxicological effects in animals are similar to those seen for DEHP, with effects mainly on the development of the male reproductive tract, foetotoxicity (increases in post-implantation losses, decreases in the number of live foetuses per litter, decreases in foetal and pup body weights) and teratogenicity (increases in incidences of external, skeletal, and internal malformations). Reproductive effects are seen in adult male and female animals. Minor liver, renal and haematological effects have been seen, but the liver and renal effects appear to be less serious than seen in animals exposed to DEHP. No human data are available on any of these toxic effects due to DBP exposure.

As noted for DEHP, DBP is able to produce changes in androgen-sensitive tissues, but does not bind strongly to either the estrogen or androgen receptors and is not considered to be an endocrine disrupting substance (ATSDR 2001).

DBP was assessed by ECB and it was concluded that DBP was of low acute toxicity by the oral and dermal routes of exposure and of low to moderate toxicity by the inhalation route (European Chemical Bureau 2004). Inhalation studies showed pronounced irritation of the mucous membranes. DBP is a very mild skin irritant and is not considered irritating to eyes. DBP is not a skin sensitiser in laboratory animals. *In vitro* and *in vivo* studies indicate that DBP is not genotoxic. No adequate long-term carcinogenicity studies were available for DBP, but it was noted that DBP is capable of inducing increases in peroxisome proliferation and chemicals with this activity have been shown to induce liver cancer. DBP exhibits developmental and reproductive toxicity in rodent species. DBP is classified in the European Union (EU) as R61 (may cause harm to the unborn child), category 2 (Substance which should be regarded as if they cause developmental toxicity in humans) and R62 (Possible risk of impaired fertility), category 3 (Substances which cause concern for human fertility).

CERHR concluded that there were some concerns for DBP causing adverse effects on the development of the male reproductive tract, but negligible concerns for reproductive toxicity in exposed adults (NTP-CERHR 2003b).

NICNAS have reviewed DBP and come to largely similar conclusions to other assessments summarised here; that the main toxicological concerns associated with DBP are due to its developmental and reproductive toxicity (NICNAS 2013). Similar conclusions were reached by the World Health Organization (International Programme on Chemical Safety 1997).

The review of toxicological information related to DBP by the CHAP (2014) stated: "*A relatively complete dataset suggests that exposure to DBP can cause reproductive or (nonreproductive) developmental effects. DBP can also induce other target organ effects, such as changes in body weight and liver weight.*"

2.2.3 Butylbenzyl phthalate (BBP)

BBP (CAS No 85-68-7) is used mainly as a plasticiser in PVC.

BBP was assessed by ECB (European Chemical Bureau 2007). It was concluded that BBP was of low acute toxicity by the oral and dermal routes of exposure, but no information was available on its acute toxicity by the inhalation route of exposure. BBP is not irritating or corrosive to skin or eyes and does not appear to be a skin senitiser. No information was available on irritation by the inhalation route of exposure.

BBP is not considered to be genotoxic or carcinogenic. BBP appears to be less effective in inducing peroxisome proliferation than DEHP (European Chemical Bureau 2007).

While repeated dose studies in animals showed effects on the liver, kidneys and pancreas, the most significant effects are considered to be those on the development of the male reproductive tract. There is evidence that BBP has anti-androgenic activity (European Chemical Bureau 2007).

BBP is able to produce changes in androgen-sensitive tissues. In *in vitro* receptor-based assays BBP was only weakly estrogenic and not androgenic, but was strongly anti-androgenic. That is, it is able to bind to the androgen receptor and prevent androgens, such as dihydrotestosterone, exerting their androgenic activity (European Chemical Bureau 2007).

BBP is classified in the European Union (EU) as R61 (may cause harm to the unborn child), category 2 (substances which should be regarded as if they cause developmental toxicity in humans) and R62 (Possible risk of impaired fertility), category 3 (substances which cause concern for human fertility).

NICNAS reviewed BBP and came to the same conclusions as those reached by ECB (NICNAS 2008d).

The review of toxicological information related to BBP by the Chronic Hazard Advisory Panel (2014) stated: "*A relatively complete dataset suggests that exposure to BBP can cause reproductive or (nonreproductive) developmental effects. BBP can also induce other target organ effects, such as changes in body weight and liver weight.*"

2.2.4 Diisobutyl phthalate (DIBP)

DIBP **(**CAS No 84-69-5) is a specialist plasticiser often used in combination with other high molecular weight phthalates as a gelling agent. DIBP has very similar application properties to DBP and may be substituted for DBP in many of its applications. These range from the plasticising of PVC to the production of paints, printing inks and adhesives.

DIBP has not been assessed by ATSDR. While DIBP has been classified in the EU, no risk assessment has been published by ECB.

DIBP has been assessed by NICNAS and concluded to be of very low acute toxicity by the oral and intraperitoneal exposure routes (NICNAS 2008a).No information is available on its acute toxicity following dermal or inhalation exposure. DIBP is

considered to be non-irritant or mildly irritant to the skin and non-irritant to the eyes. However, it should be noted that there is little available information and the studies these conclusions are based on are not well documented. There is no evidence that DIBP is a skin sensitiser.

There is limited evidence that DIBP is estrogenic, but not anti-estrogenic in receptor binding studies (Takeuchi et al 2005). DIBP is also able to bind to the human androgen receptor and exert anti-androgenic activity. DIBP has been shown to down-regulate genes involved in male reproductive tract development in a dose-dependent manner (Hannas et al 2011).

There is insufficient information to determine the genotoxic potential of DIBP and no long-term carcinogenicity studies have been carried out. Effects on the liver and testes were noted in a four-month repeated dose study. In rodent studies, DIBP caused skeletal abnormalities and impaired development of the male reproductive tract in progeny of treated females. Spermatogenesis was impaired in treated adult male rats.

DIBP is classified in the European Union (EU) as R61 (may cause harm to the unborn child), category 2 (Substance which should be regarded as if they cause developmental toxicity in humans) and R62 (Possible risk of impaired fertility), category 3 (Substances which cause concern for human fertility).

The review of toxicological information related to DIBP by the CHAP (2014) stated: "*Animal and human studies suggest that exposure to DIBP can cause reproductive and developmental effects*."

2.2.5 Diisononyl phthalate (DINP)

DINP refers to two sets of mixed phthalates **(**CAS No 28553-12-0 and CAS No 68515-48-0); made up of predominantly 8 and 9 carbon branched-chain esters. The vast majority of DINP (approximately 95%) is used in PVC applications.

DINP has been assessed by ECB and concluded to be of low acute toxicity by all exposure routes and is not considered to be irritant to the skin, eyes or respiratory system (European Chemical Bureau 2003b).

DINP is not considered to be genotoxic and liver neoplasms and leukaemias seen in rodent studies are considered to occur by mechanisms that are not relevant to humans (European Chemical Bureau 2003b).

DINP is only weakly toxic in developmental and reproductive studies and the most sensitive chronic toxicological endpoints relate to effects on the liver and kidney. However, effects on the liver and kidney appear to be mediated by rodent-specific mechanisms (European Chemical Bureau 2003b).

While some of the experimental information is equivocal, DINP does not appear to have significant binding affinity for the estrogen receptor and does not appear to be significantly estrogenic or a strong estrogen antagonist (European Chemical Bureau 2003b).

DINP is not classified as hazardous in the European Union (EU).

An assessment by NICNAS arrived at similar conclusions (NICNAS 2008b).

The review of toxicological information related to DINP by the Chronic Hazard Advisory Panel (2014) stated: "*A relatively complete dataset suggests that exposure to DINP can cause reproductive or (nonreproductive) developmental effects, although it is less potent than other active phthalates, for example, DEHP*."

2.2.6 Diisodecyl phthalate (DIDP)

DIDP **(**CAS No 26761-40-0 and CAS 68515-49-1) refers to a group of mixed phthalates made up of predominantly 10 carbon chain esters, but may also include a mixture of 9, 10 and 11 carbon esters, where 10 carbon chains dominate. The vast majority of DINP (approximately 95%) is used in PVC applications.

DIDP has been assessed by ECB and concluded to be of low acute toxicity by all exposure routes and is not considered to be irritant to the skin, eyes or respiratory system (European Chemical Bureau 2003a). There is no evidence that DIDP is a skin or respiratory sensitiser.

The toxicology of DIDP appears to be very similar to DINP, with inconsistent developmental and reproductive effects. DIDP is not estrogenic or anti-estrogenic (European Chemical Bureau 2003a).

DIDP is not genotoxic and, although no long-term carcinogenicity studies have been carried out, it is expected that any effects will be related to DIDP ability to induce peroxisome proliferation – a mechanism not relevant to humans. The most sensitive chronic effects were seen on the liver and kidneys (European Chemical Bureau 2003a).

DIDP is not classified as hazardous in the European Union (EU).

An assessment by NICNACS reached similar conclusions (NICNAS 2008c).

The review of toxicological information related to DIDP by the Chronic Hazard Advisory Panel (2014) stated: "*CPSC staff has previously concluded that DIDP may be considered a "probable toxicant" in humans by the oral route, based on sufficient evidence of systemic, reproductive, and developmental effects in animals."*

"DIDP does not appear to possess anti-androgenic potential; nonetheless, the CHAP is aware that DIDP is a potential developmental toxicant, causing supernumerary ribs, and a potential systemic toxicant, causing adverse effects on the liver and kidney."

2.2.7 Di-n-octyl phthalate (DNOP)

DNOP (CAS No 117-84-0, di-n-octylphthalate) may be used as a plasticiser in carpetback coating, packaging films, medical tubing and blood storage bags, floor

tile, wire, cables, and adhesives. DNOP is also used in cosmetics and pesticides (ATSDR 1997). When used as a plasticizer, DNOP can represent 5-60% of the total weight of the plastics and resins.

ATSDR assessed DNOP and found there was very little information on health effects from inhalation, ingestion or skin contact (ATSDR 1997). DNOP had caused death in some rats and mice given very high doses by mouth. Mildly harmful effects have been seen in the livers of some rats and mice given very high oral doses of DNOP for short or intermediate durations of time. Brief oral exposures to lower doses of DNOP generally caused no harmful effects.

Unlike other phthalates such as DEHP, DNOP does not appear to affect male fertility in experimental animals. An increased incidence of gross foetal malformations were observed in offspring of rats receiving high doses (approximately 5 g/kg bw) of DNOP by injection during pregnancy. However, humans are not exposed to DNOP this way, and no harmful effects on developing foetuses were seen when mice received DNOP by the oral route of exposure (ATSDR 1997).

The ATSDR review from 1997 did not make a statement about whether DNOP caused cancer in humans or animals and did not comment on endocrine mediated toxicity due to DNOP.

The most recent review of toxicological information related to DNOP is by CHAP (Chronic Hazard Advisory Panel 2014). Only animal studies were available, and were presumed to be applicable to humans. The review stated that a limited developmental toxicity dataset did not identify DNOP as an antiandrogen. However, with the exception of one study, the developmental toxicity studies making up the dataset all had major limitations. Although DNOP was not antiandrogenic in the single relevant study, exposure to this phthalate was associated with developmental toxicity, i.e., supernumerary ribs, although developmental toxicologists were divided over whether this effect is a malformation or a minor variation. On the other hand, a systemic toxicity dataset, although incomplete, suggests that exposure to DNOP can induce adverse effects in the liver, thyroid, immune system, and kidney.

2.3 Mechanism of phthalate developmental toxicity

CHAP reviewed the mechanism by which phthalates induce changes in the male reproductive tract (Chronic Hazard Advisory Panel 2014). It was concluded that although some studies have shown phthalates to have some hormone receptor (estrogen, androgen, peroxisome proliferator activated) binding activity, there is little evidence that these effects are responsible for the structural changes induced in the male reproductive tract.

CHAP concluded that it was more plausible that the phthalates that exhibit development toxicity (DEHP, DBP, BBP and DIBP) exert their toxicity through epigenetic mechanism, down-regulating genes for cholesterol transport and steroidogenesis in Leydig cells. This results in decreased cholesterol transport and testosterone synthesis and adverse effects on androgen-dependent tissue differentiation.

2.4 Summary of key endocrine and reproductive toxicity studies

A recent systematic review considered the scientific literature for effects of phthalates on reproduction in males (Kay et al 2014). This review considered all phthalates, but most animal literature concerned DEHP, DBP and DIBP.

The conclusion stated that "*although the literature has been expanded with many new epidemiological studies in recent years, there is insufficient evidence to determine causal association between phthalate exposure and hypospadias or cryptorchidism in male humans. The current evidence also suggests no causal association between phthalate exposure and changes in the timing of puberty onset. Furthermore, associations found between with anogenital distance, and concentrations of reproductive hormones are weak due to conflicting results, although the evidence for reduced testosterone is more persuasive. There exists greater weight of evidence in terms of the consistency of the epidemiologic literature for a causal association between phthalate exposure and semen quality, although the clinical relevance remains to be determined.*"

2.5 Classification of phthalates in New Zealand

Table 3 summarises the hazard classifications for phthalates included in this report, assigned by the New Zealand Environmental Protection Agency.

Table 3: New Zealand Environmental Protection Agency (NZEPA) hazard codes

Chemical (CAS Number)	**EPA Classification (human toxicity)[1]**
DEHP (117-81-7)	6.8A (Known or presumed human reproductive or developmental toxicants 6.9B (oral) (Harmful to human target organs or systems)
DBP (84-74-2)	6.1E (oral) (acutely toxic) 6.4A (Irritating to the eye) 6.8A (Known or presumed human reproductive or developmental toxicants)
BBP (85-68-7)	6.1E (oral) (acutely toxic) 6.3B (Mildly irritating to the skin)
DIBP	6.8B (Suspected human reproductive or developmental toxicants)
DINP (28553-12-0) and Benzenedicarboxylic acid, di-C8-10-branched alkyl esters, C9-rich (68515-48-0)	28553-12-0 Not classified 68515-48-0 6.3A (irritating to the skin) 6.4A (irritating to the eye)
DIDP (and 1,2,Benzenedicarboxylic acid, diC9-11-branched alkyl esters, C-10 rich ()	26761-40-0 Not classified 68515-49-1 Not classified
DNOP (117-84-0)	Not classified

[1] NZEPA were accessed at http://www.epa.govt.nz/search-databases/Pages/HSNO-CCID.aspx using a CAS number search

2.6 Summary data

Information on acute toxicity, irritant and sensitization effects and genotoxicity for all seven phthalates is summarised in Table 4.

Table 4: Summary of acute toxicity data and genotoxicity (NICNAS 2008e)

Chemical (CAS Number)	Acute Toxicity (animal used in study)			Irritation			Skin sensitisation	Genotoxicity
	Oral LD_{50} (mg/kg bw)	Dermal LD_{50} (mg/kg bw)	Inhalation LC_{50} (mg/L)	Skin	Eye	Respiratory		
DEHP (117-81-7)	Rat: 30600 - >40000	Rabbit: >3160	ND	ME	ME	Insufficient data	Negative	Non-genotoxic
DBP (84-74-2)	Rat: 6300-8000	Rabbit >20000	Rat 4h ≥ 15.68	ME	ME	ME	Negative	Non-genotoxic
BBP (85-68-7)	Rat: 2330-20400	Rat: 6700	ND	ME	ME	ND	Negative	Non-genotoxic
DIBP (84-69-5)	Rat: 16000-60320	ND	ND	ME	Negative	ND	Negative	Insufficient data
DINP (28553-12-0) and Benzenedicarboxylic acid, di-C8-10-branched alkyl esters, C9-rich (68515-48-0)	Rat: >40000 (28553-12-0) >10000 (68515-48-0)	Rabbit: >3160 (68515-48-0)	Rat: 4h: >4.4	ME	ME	ND	Negative	Non-genotoxic
DIDP (26761-40-0 and 1,2,Benzenedicarboxylic acid, diC9-11-branched alkyl esters, C-10 rich (68515-49-1)	Rat: >29100	Rat: >2910	Rat, 4h: >12.54	ME	ME	ND	Negative	Non-genotoxic
DNOP (117-84-0)	Rat: 53700	Guinea pig: 75 mL/kg bw	ND	ME	ME	Insufficient data	Negative	Non-genotoxic

ND = Not determined ME = minimal effects

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3. DOSE RESPONSE

Tolerable daily intakes (TDI) for the suites of phthalates considered in this report are proposed by Europa DG Health and Consumer Product, Public Health Division[6]. The TDIs proposed are shown in Table 5.

Table 5: Europa DG Health and Consumer Product Public Health division tolerable daily intake for selected phthalates

Phthalate	Critical toxic effect	TDI (mg/kg BW/day
DEHP	Reproduction	0.05
BBP	Reproduction and development	0.5
DBP		0.01
DIBP		0.1[7]
DINP	Liver	0.15
DIDP		0.15
DNOP	Liver and thyroid	None available

The justifications provided by the Standing Committee on Health and Environmental Risk (SCHER) for each of the phthalates listed in Table 5 are given below. Additional data relating to limits identified by other public health organisations are also identified.

3.1 Di-ethylyhexyl phthalate

The critical toxic effects of DEHP relate to reproduction. A three-generation reproductive study in which DEHP was administered to rats in the diet gave a NOAEL of 4.8 mg/kg bw/day for testicular and developmental toxicity (European Chemical Bureau 2008). A TDI of 0.05 mg/kg bw/day is based on this NOAEL; the default uncertainty factor of 100, was established for DEHP by EFSA and is supported by SCHER.

USEPA has identified a reference dose (RfD) for DEHP of 0.02 mg/kg based on a LOAEL of 19 mg/kg bw/day in a study performed by Carpenter et al (1953). A conservative uncertainty of 1000 was applied to derive the RfD (US Environmental Protection Agency 1987a). DEHP was administered to Guinea pigs at two concentrations equivalent to 64 or 19 mg/kg bw/day in feed for one year. Statistically significant increase in relative liver weight were observed at both dosing levels for female subjects; there were no treatment related effects observed on mortality, body weight or kidney weight; and no gross pathology or histopathology of kidney, liver, lung spleen or testes.

[6] Phthalates: 5. What daily exposure levels to phthalates are considered safe? Accessed 17/10/14
[7] This is an ADI from CPSC (2011)

In this report the Europa DG Health and Consumer Product, Public Health Division TDI is preferred in the case of DEHP as it provides data on the reproductive effects of DEHP; there is no assessment of reproductive effects in the principal study cited in the USEPA report.

3.2 Benzylbutyl phthalate

A NOAEL for benzylbutyl phthalate (BBP) of 20 mg/kg bw/day for developmental effects was observed in a two-generation study in rats (Nagao et al 2000) based on a decreased body weight in offspring at the LOAEL of 100 mg/kg bw/day. The NOAEL for effects on reproductive organs was 100 mg/kg bw/day. A NOAEL of 50 mg/kg bw/day for developmental effects was also observed in a second two-generation study (Tyl et al 2004). Therefore, a TDI of 0.5 mg/kg bw/day based on a reduction of anogenital distance in the F1 and F2 generation with a LOAEL of 250 mg/kg bw/day was derived for BBP.

USEPA has identified an RfD for BBP of 0.2 mg/kg bw/day based on a reported NOAEL of 2800 ppm (159 mg/kg/day) (US Environmental Protection Agency 1988). An uncertainty factor of 1000 was applied to derive the RfD. BBP was administered in powdered food for 26 weeks to 15 males/group at six different concentrations from 0 – 1420 mg/kg bw/day. In the 1420 mg/kg bw/day dose group significant loss of body weight and reduction in size of testes was seen relative to the control group, no effects on reproductive organs were seen in groups at or below the 159 mg/kg bw/day dosing level.

In this report the Europa DG Health and Consumer Product, Public Health Division TDI is preferred in the case of BBP as it provides data on the reproductive effects of BBP; there is no assessment of reproductive effects in the principal study cited in the USEPA report.

3.3 Dibutyl phthalate

The male reproductive system is a main target of DBP toxicity with a NOAEL (50 mg/kg) and a LOAEL (100 mg/kg) for DNBP-effects on male reproductive development in the F1 generation (Mylchreest et al 2000). In a two–generation rat study, a LOAEL of 52 mg/kg for embryotoxicity in the F2–generation was observed. A developmental toxicity study in the rat (Lee et al 2004), with dietary exposure to DNBP during the period from late gestation (gestational day 15) to the end of lactation (Postnatal day 21), showed effects on the development of male and female offspring at lower doses than when examining the development of reproductive tissues at various postnatal ages in detail. Reduction of testicular spermatocyte development and mammary gland changes in both sexes of offspring were seen at PND 21 at doses of approximately. 1.5 – 3.0 mg/kg bw/day and above, with dose-dependent increased incidence and/or severity. Loss of germ cell development was no longer present at 1.5 – 3 mg/kg bw/day at postnatal week 11, but showed a dose-dependent increase in a dose range from 14 – 28 mg/kg bw/day to 712 – 1372 mg/kg bw/day (Lee et al 2004). Based on loss of germ cell development and mammary gland changes at 1.5 – 3 mg/kg bw/day in the diet (the lowest tested dose), a NOAEL could not be established. EFSA has

derived a TDI of 0.01 mg/kg bw/day from these data using a safety factor of 200 (European Food Standard Agency 2005).

USEPA has identified an RfD of 0.1 mg/kg/day based on a reported NOAEL of 125 mg/kg/day in rats based on increased mortality (Smith 1953; US Environmental Protection Agency 1987b). An uncertainty factor of 1000 was applied to derive the RfD. DBP was administered in food to groups of 10 rats at 0, 0.01, 0.05, 0.25 and 1.25% DBP by weight for one year. Half of the animals receiving the highest dose died within the first week of the trial. The remaining animals survived the trial with no apparent ill effects and there was no effect of treatment on gross pathology or haematology. Organs were reportedly sectioned and stained, but no histopathology was reported. The confidence in the RfD is stated as low due to low confidence in the study methodology and low confidence in the database quality.

In this report the Europa DG Health and Consumer Product, Public Health Division TDI is preferred in the case of DBP as it provides data on the reproductive effects of DBP; there is no assessment of reproductive effects in the principal study cited in the USEPA report and there is low confidence in the derived RfD.

3.4 Di-isononyl phthalate

Presently, two different DINP types are used (CAS 68515-48-0 and CAS 28553-12-0). These DINP mixtures are considered together. Previously, a group TDI for DINP and DIDP of 0.15 mg/kg bw/day, was based on peroxisome proliferation in rodent liver, but peroxisome proliferation in rodents is not relevant for human risk assessment. In a two–generation reproductive toxicity study with DINP, NOAELs of 500 mg/kg bw/day and 622 mg/kg bw/day were established for minor developmental effects and decreases in live birth and survival indices, respectively (European Chemical Bureau 2003b). The pivotal toxicological effects for DINP are hepatic changes. Using the NOAEL of 15 mg/kg bw/day for non-peroxisome proliferation-related chronic hepatic and renal effects and an uncertainty factor of 100, a TDI of 0.15 mg/kg bw/day was derived.

NICNAS (2012) derived an overall NOAEL for liver and kidney effects of 88 mg/kg bw/day (Lington et al 1997). The NOAEL for developmental and reproductive toxicity of 50 mg/kg bw/day is based on a number of studies, amongst which the principal studies were identified as Boberg et al (2011) and Hannas et al (2011).

In this report the Europa DG Health and Consumer Product, Public Health Division TDI is preferred in the case of DINP as it provides data on the reproductive and hepatotoxic effects of DINP; the assessment from NICNAS, although thorough, does not proceed to a point of deriving a TDI, only NOAELs.

3.5 Di-isodecyl phthalate

There are also two different di-isodecyl phthalate (DIDP) products with different CAS numbers (68515-49-1 and 26761-40-0). The two phthalates are considered fully interchangeable and are considered together. There is no indication of reproductive organ effects for DIDP evidenced in repeated dose toxicity studies. In a 13-week oral study in dogs, a NOAEL of 15 mg/kg bw/day could be derived

(NICNAS 2008c). Based on the liver effects in dogs, selected dogs were considered a non-sensitive species to peroxisome proliferation, with a NOAEL of 15 mg/kg bw/day, a lowest overall NOAEL of 15 mg/kg bw/day could be considered. No TDI for DIDP is available, but low concern can be derived when exposures are below 0.15 mg/kg bw/day (MOE > 100).

No other TDI's were found for DIDP, and hazard assessments which provided relevant points of departure also utilised the dog study summarised above, with caveats applied around the uncertainty of the data due to the low numbers of animals used.

3.6 Di-n-octyl phthalate

The results of several acute- and intermediate-duration oral studies in rodents indicate that the potential of di-*n*-octyl phthalate (DNOP) to cause adverse reproductive and developmental effects is low. Unlike other phthalate esters such as DEHP, DNOP does not appear to affect testicular function or morphology (Hardin et al 1987; Heindel et al 1989). Observed hepatic effects in intermediate duration studies consisted of a statistically significant increase in hepatic ethoxyresorufin-0-deethylase activity and histological changes in hepatic architecture. Thyroid toxicity was also noted at a concentration of 2000mg/kg/day (Hinton et al 1986; NTP-CERHR 2003a). No chronic oral TDI is available for DNOP.

The NICNAS hazard assessment of DNOP identifies a NOAEL of 37mg/kg bw/day (500 ppm) based on liver and thyroid effects observed at 370 mg/kg bw/day (5000 ppm) from data reported by Poon et al (Poon et al 1997).

For the purposes of this report a TDI of 0.15 mg/kg bw/day is used, this is consistent with other derived TDI's for compounds in the hepatotoxic group.

3.7 Di-isobutyl phthalate

DIBP, administration to rats at high doses of 600 mg/kg bw/day from gestational day (GD) 7 to either GD 19 or GD 20/21, induced testicular and developmental effects similar to DBP and DEHP (Borch et al 2006). However, since no dose response was assessed, further developmental and postnatal studies are needed to characterize the reproductive effects of DIBP and derive a NOAEL for risk assessment (Borch et al 2006). A TDI has not been defined by Europa DG Health and Consumer Product Public Health division. However, acceptable daily intakes (ADIs) have been identified by CPSC (2011) as 0.85 mg/kg/day for long term oral exposure; and 0.098 mg/kg/day for developmental effects. The ADI of 0.098 mg/kg/day is used for the purposes of this report.

4. EXPOSURE ASSESSMENT

Exposure assessments have been performed for a number of individual phthalates by various public health bodies and individual research centres. The approach to developing a cumulative risk assessment for exposure to phthalates was addressed by National Academy of Sciences (National Research Council of the National Academies 2008). The NAS document proposed the assumption of effect additivity for calculating a benchmark dose (BMD), additional assumptions which are made in the application of this model are around the percent composition ratio of individual phthalates in a mixture. The mathematical approach proposed by NAS has been adapted for this report to utilise the tolerable daily intake values identified in Table 5. For the purposes of this health risk assessment assumptions are made regarding the duration of mouthing behaviours by infants and toddlers, these data are drawn from the CHAP report appendix E1 and E2 (Chronic Hazard Advisory Panel 2014) and the NICNAS priority existing chemical reports on DBP, DINP and DEHP (NICNAS 2010; 2012; 2013).

4.1 Scenarios

Exposure scenarios have been developed to model both a worst case exposure via oral and dermal routes and exposure at the 0.1% w/w phthalate concentration level. The worst case scenario assumes that exposure to all the selected phthalates occurs at the maximal concentrations cited, from either a single product or multiple products. Evidence from the RAPEX database enquiry indicates that high concentrations of single phthalates in individual products and the presence of multiple phthalates in single product occurs frequently, hence supports the assumption of the worst case scenario described here. The 0.1% concentration level is identified in the majority of regulatory frameworks referenced in this report and might be appropriately considered as an upper limit for a typical phthalate exposure in the context of this report.

4.1.1 Oral exposure

Oral exposure of children to the selected phthalates from mouthing of toys was estimated from the USEPA (US Environmental Protection Agency 2011) mean and 5th percentile bodyweight of children, estimated mouthing duration and phthalate migration rate from toys (Babich 1998; Health Canada 1998; NICNAS 2008b). The estimates are for a six-month-old infant, based on the studies which demonstrate that six-month-old infants are within an age range showing maximum mouthing behaviour and have the lowest bodyweight in this age range. The following assumptions were also used:

- A child of six months weighs 7.4 kg (mean) or 5.7 kg (5th percentile). The use of the 5th percentile bodyweight provides a more conservative assessment as it is a smaller value. The bodyweight data are for combined sexes (US Environmental Protection Agency 2011).
- The surface area of a child's open mouth and the typical surface of an article available for mouthing at any one time is approximately 10 cm^2 (LGC 1998).

- The reasonable worst-case total time the child spends mouthing toys is 2.2 hours per day and a typical mouthing time is around 0.8 hours per day (Health Canada 1998; NICNAS 2008b).
- The migration rate of phthalates (M, in equation 1) is based on data from the study of Chen (1998), where 10 adult volunteers were asked to chew PVC discs of approximately 10.3 cm^2 surface area and a concentration of 43% DINP. The subjects chewed discs for 4 x 15 minutes intervals, saliva samples were collected after each chewing interval and analysed for DINP. A concentration range of 6.14 – 57.93 $\mu g/cm^2/h$ was reported from analysed samples, with an average of 26.03 $\mu g/cm^2/h$. The average migration rate value is used for calculation of the exposure dose in this report.
- Phthalate bioavailability via the oral route is assumed to be 100%.

4.1.1.1 Worst case oral exposure scenario

The internal dose for a specified phthalate received via the oral route is calculated as described in equation 1, a modifying factor (R_{phth}) is included to represent the percentage composition of each specific phthalate found in children's toys or child care products as shown in Table 6; the column shown as 'Selected mass' represents the values used for calculation of the dose contribution from each phthalate and represent the greatest reported value. The grouping of DEHP, DBP and BBP as phthalates with antiandrogenic mode of action; and DINP, DNOP and DIDP as phthalates with liver as the target organ means that effect additivity is an appropriate approach for assessment of cumulative dose for either groupings of phthalates (Meek et al 2011). For the purposes of this health risk assessment the individual products of each equation and the phthalate specific TDI are used to derive a hazard quotient (HQ) as shown in equation 2. Individual HQ are then summed to derive the hazard index (HI) for additive action of the mixture of phthalates as a whole. These data are used to estimate a worst case exposure scenario shown in Table 7.

Table 6 Phthalate concentrations identified as representing maximum concentrations in children's toys

	Phthalate concentration (% w/w)			
Phthalate	RAPEX[8]	CHAP	NICNAS[9]	Selected mass (% w/w)
DEHP	39.5	33	43	43
DBP	1.7	0	1.16	1.7
BBP	no reports	0	no value	0
DIBP	29	no value	no value	29
DINP	38	12.8	43	43
DNOP	29	0	no value	29
DIDP	5.5	0	no value	5.5

[8] Data taken by ESR from review of RAPEX system notifications of phthalate exceedances
[9] From PEC reports DBP, DINP and DEHP

Equation 1

$$D_{int,oral} = \left(\left(\frac{M \times S_{mouth} \times t \times n \times \frac{B_{oral}}{100}}{BW} \right) \times \frac{R_{phth}}{100} \right)$$

Where

$D_{int,oral}$	internal dose rate by oral route of specified phthalate (µg/kg bw/d)
M	migration rate of specified phthalate from matrix (µg/cm^2/h)
S_{mouth}	surface area of infants open mouth (cm^2)
t	mouthing time (h)
n	Frequency (d^{-1})
B_{oral}	bioavailability via oral route (%, 100% assumed)
BW	body weight (kg)
R_{phth}	mass ratio of specified phthalate in matrix relative to experimental level in literature (43% by mass)

The R_{phth} value is derived by dividing the % mass fraction of specified phthalate by the value provided in relevant literature, this process allows the migration of the phthalate % mass fraction value to be normalized against the experimentally derived migration rate.

Equation 2

$$HQ = \frac{D_{int,oral}}{TDI}$$

Where

HQ	hazard quotient (unitless)
TDI	tolerable daily intake (µg/kg bw/d)

Table 7 Daily dose and derived hazard quotient for worst case scenario concentrations of selected phthalates from ingestion exposure due to mouthing of children's toys

	DEHP	DBP	BBP	DIBP	DINP	DNOP	DIDP
M[10]	26.03	26.03	26.03	26.03	26.03	26.03	26.03
S_{mouth} (cm^2)	10	10	10	10	10	10	10
t x n (hours/day)	0.8	0.8	0.8	0.8	0.8	0.8	0.8
B_{oral}	1	1	1	1	1	1	1
BW_{mean} (kg)	7.4	7.4	7.4	7.4	7.4	7.4	7.4
$BW_{5th\ \%ile}$ (kg)	5.7	5.7	5.7	5.7	5.7	5.7	5.7
R_{phth}	1	0.04	0.04	0.67	1	0.67	0.14
$D_{int,oral\ BWmean}$ (µg/kg bw/d)	28.1	1.1	1.1	19.0	28.1	19.0	3.9
$D_{int,oralBW5\%ile}$ (µg/kg bw/d)	36.5	1.4	1.4	24.6	36.5	24.6	5.1
TDI (µg/kg bw/d)	50	10	500	98[11]	150	150[12]	150[11]
HQ $_{BWmean}$	0.56	0.11	0.002	0.19	0.19	0.13	0.03
HQ $_{BW5\%ile}$	0.73	0.14	0.003	0.25	0.24	0.16	0.03

4.1.1.2 European Union regulatory limit oral exposure scenario

This scenario uses the regulatory limits cited in Table 8 to derive a received dose for the antiandrogenic and hepatotoxic phthalate groups. The EU limits have been used as they appear to be representative of those adopted throughout other jurisdictions.

[10] Migration rates of the phthalates from PVC under mouthing conditions are poorly characterised and a value is only available for a single phthalate (DINP), this value has been used for all phthalates that do not have specific migration rate identified.

[11] This is an acceptable daily intake (ADI) identified by CPSC, see section 3.7.

[12] Assumed TDI value carried across from similarly structured DINP.

Table 8 Phthalate concentrations identified as representing European Union regulatory concentration limits in children's toys

Phthalate	Regulatory limit (% w/w)
DEHP	0.1
DBP	0.1
BBP	0.1
DIBP	0.1[13]
DINP	0.1
DNOP	0.1
DIDP	0.1

The scenario uses the same mathematical approach and data as section 4.1.1.1, but recalculates the R_{phth} value using a mass of 0.1% w/w for each individual phthalate. Hence the reported dose and subsequent HQ shown in Table 9 represent the dose received from articles containing 0.1% w/w of each phthalate.

Table 9 Daily dose and derived hazard quotient for regulatory limit concentrations of selected phthalates from ingestion exposure due to mouthing of children's toys

	DEHP	DBP	BBP	DIBP	DINP	DNOP	DIDP
R_{phth}	0.002	0.002	0.002	0.002	0.002	0.002	0.002
$D_{int,oral\ BWmean}$ (µg/kg bw/d)	0.1	0.1	0.1	0.1	0.1	0.1	0.1
$D_{int,oralBW5\%ile}$ (µg/kg bw/d)	0.1	0.1	0.1	0.1	0.1	0.1	0.1
TDI (µg/kg bw/d)	50	10	500	98	150	150	150
HQ_{BWmean}	<0.01	0.01	<0.01	<0.01	<0.01	<0.01	<0.01
$HQ_{BW5\%ile}$	<0.01	0.01	<0.01	<0.01	<0.01	<0.01	<0.01

4.1.2 Dermal exposure

Dermal exposure of children to phthalates is predominantly via contact with the hands and lips from holding or mouthing of toys and is proportional to the amount of time spent handling the item and the area of skin in contact with it. The dermal phthalate doses for the specified phthalates were estimated using the mean and 5th percentile bodyweight of infants aged six months, estimated dermal contact duration and phthalate migration rate from toys.

[13] DIBP is not cited in international regulations but is included in this list as it appeared in the information retrieved from the RAPEX system; the 0.1% w/w limit ascribed is an assumption based on the assignment of this level to all phthalates which are subject to regulatory control.

Limited quantitative absorption data are available for DEHP and less so for other phthalates considered in this report. Deisinger et al (1998) investigated the skin absorption of DEHP from PVC film in rats. Sheets of PVC film (15 cm^2, total of 40.4% DEHP w/w) were applied to shaved backs of eight male rats in two separate experiments. The mean dermal absorption of DEHP in rats was determined to be 0.24 µg/cm^2/h.

In *in vitro* tests, rat skin was determined to be four times more permeable to DEHP than human skin (Barber et al 1992; Scott et al 1987). Equivalent comparative *in vivo* data are not available. The rate of dermal absorption of 0.24 µg DEHP/cm^2/h, determined in the *in vivo* test in rats, is used for the exposure estimates in this report (NICNAS 2010). The following assumptions were also used:

- a child of six months weighs 7.4 kg (mean) or 5.7 kg (5^{th} percentile). The use of the 5^{th} percentile bodyweight provides a more conservative assessment as it is a smaller value. The bodyweight data are for combined sexes (Chronic Hazard Advisory Panel 2014; USEPA 2011).
- the reasonable worst-case total time the child spends handling toys is 2.2 hours per day and a typical contact time is around 0.8 hours per day; and
- the contact surface area is 100 cm^2 based on exposure to lips and hands (NICNAS 2008b).

4.1.2.1 Worst case dermal exposure scenario

For a six-month-old child, the internal dose from dermal exposure was calculated using equation 3 and the HQ derived for individual phthalate exposures as shown in **Table 10**.
:

Equation 3

$$D_{int,derm} = \left(\frac{R_{derm} \times S_{derm} \times t \times n}{BW}\right) \times \frac{R_{phth}}{100}$$

Where:

$D_{int,derm}$	internal dose via the dermal route (µg/kg bw/d)
R_{derm}	dermal absorption rate of specified phthalate in skin (µg/cm^2/h)
S_{derm}	surface area of child's lips and hands (cm^2)
t	contact time (h)
n	frequency (d^{-1})
BW	body weight (kg)
R_{phth}	mass ratio of specified phthalate in matrix relative to experimental level in literature (40.4% by mass)

Table 10 Daily dose and derived hazard quotient for worst case scenario concentrations of selected phthalates from dermal exposure due to handling and mouthing of children's toys

	DEHP	DBP	BBP	DIBP	DINP	DNOP	DIDP
R_{derm} (ug/cm^2/h)[14]	0.24	0.24	0.24	0.24	0.24	0.24	0.24
S_{derm} (cm^2)	100	100	100	100	100	100	100
t x n (h/d)	3	3	3	3	3	3	3
BW_{mean} (kg)	7.4	7.4	7.4	7.4	7.4	7.4	7.4
$BW_{5th\ \%ile}$ (kg)	5.7	5.7	5.7	5.7	5.7	5.7	5.7
R_{phth}	1.06	0.04	0.04	0.72	1.06	0.72	0.15
$D_{int,oralBWmean}$ (µg/kg bw/d)	10.4	0.4	0.4	7.0	10.4	7.0	1.4
$D_{int,oralBW5\%ile}$ (µg/kg bw/d)	13.4	0.5	0.5	9.1	13.4	9.1	1.9
TDI (µg/kg bw/d)	50	10	500	98	150	150	150
HQ_{BWmean}	0.21	0.04	<0.01	0.07	0.07	0.05	0.01
$HQ_{BW5\%ile}$	0.27	0.05	<0.01	0.09	0.09	0.06	0.01

4.1.2.2 European Union regulatory limit dermal exposure scenario

This scenario uses the regulatory limits cited in Table 8 to derive a received dose for the antiandrogenic and hepatotoxic phthalate groups.

The scenario uses the same mathematical approach and data as section 4.1.2.1 but recalculates the R_{phth} value using a mass of 0.1% w/w for each individual phthalate. Hence the reported dose and subsequent HQ shown in Table 11 represent the dose received from articles containing 0.1% w/w of each phthalate.

[14] Migration rates of the phthalates from PVC under mouthing conditions are poorly characterised and a value is only available for a single phthalate (DINP), this value has been used for all phthalates that do not have specific migration rate identified.

Table 11 Daily dose and derived hazard quotient for regulatory limit concentrations of selected phthalates from dermal exposure due to mouthing and handling of children's toys

	DEHP	DBP	BBP	DIBP	DINP	DNOP	DIDP
R_{phth}	0.00	0.00	0.00	0.00	0.00	0.00	0.00
$D_{int,oralBWmean}$ (µg/kg bw/d)	0.0	0.0	0.0	0.0	0.0	0.0	0.0
$D_{int,oralBW5\%ile}$ (µg/kg bw/d)	0.0	0.0	0.0	0.0	0.0	0.0	0.0
TDI (µg/kg bw/d)	50	10	500	98	150	150	150
HQ BW_{mean}	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
HQ $BW_{5\%ile}$	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01

5. RISK CHARACTERISATION

5.1 DEHP, DBP BBP and DIBP hazard indices

The combination of three phthalates identified in international regulations for consideration together due to their reported reproductive and antiandrogenic activity and DIBP, were assessed and individual HQ values derived for each of the compounds under the conditions described in the exposure scenarios.

5.1.1 Oral exposure worst case scenario

The summed HQ values in Table 12 derive HI values that include both the ingestion and dermal exposure routes to DEHP, DBP, BBP and DIBP at worst case scenario concentrations.

Table 12 HI for reproductive/developmental effects from cumulative exposure to DEHP, DBP, BBP and DIBP via ingestion and dermal routes for worst case scenario

	DEHP	DBP	BBP	DIBP	Cumulative HI
HI_{BWmean}	0.77	0.15	<0.1	0.26	1.2
$HI_{BW5\%ile}$	1.0	0.20	<0.1	0.34	1.5

5.1.2 Oral exposure regulatory limit scenario

The summed HQ values in Table 13 derive HI values that include both the ingestion and dermal exposure routes to DEHP, DBP, BBP and DIBP at regulatory limit scenario concentrations.

Table 13 HI for reproductive/developmental effects from cumulative exposure to DEHP, DBP, BBP and DIBP via ingestion and dermal routes for regulatory limit scenario

	DEHP	DBP	BBP	DIBP	Cumulative HI
$HI\ BW_{mean}$	<0.01	0.01	<0.01	<0.01	0.01
$HI\ BW_{5\%ile}$	0.002	0.012	0.000	0.001	0.02

5.2 DINP, DIDP and DNOP hazard indices

The combination of three phthalates identified in international regulations for consideration together due to their reported hepatotoxic effect were assessed and individual HQ values derived for each of the compounds under the conditions described in the exposure scenarios.

5.2.1 Dermal exposure worst case scenario

The summed HQ values in Table 14 derive HI values that represent the worst case scenario used in this report and includes both ingestion and dermal exposure routes to DINP, DIDP and DNOP.

Table 14 HI for hepatotoxicity from cumulative exposure to DINP, DIDP and DNOP via ingestion and dermal routes for worst case scenario

	DINP	DNOP	DIDP	Cumulative HI
HI_{BWmean}	0.26	0.17	0.04	0.5
$HI_{BW5\%ile}$	0.33	0.23	0.05	0.6

5.2.2 Dermal exposure regulatory limit scenario

The summed HQ values in Table 14 derive HI values that represent the regulatory limit scenario used in this report and includes both ingestion and dermal exposure routes to DINP, DIDP and DNOP.

Table 15 HI for hepatotoxicity from cumulative exposure to DINP, DIDP and DNOP via ingestion and dermal routes for regulatory limit scenario

	DINP	DNOP	DIDP	Cumulative HI
HI_{BWmean}	<0.01	<0.01	<0.01	<0.01
$HI_{BW5\%ile}$	<0.01	<0.01	<0.01	<0.01

5.3 Risk characterization discussion

The HI shown in Table 12 and Table 14 represent the potential health impact of a reasonable worst case scenario for mouthing and dermal contact with children's toys. It should be recognised that the exposure source represented by toys is not considered the principal exposure source for any of the phthalates; for all of the phthalates identified in this report, with the exception of DNOP, the principal source of exposure is through diet. For DNOP the principal exposure source is through childcare products (Chronic Hazard Advisory Panel 2014). Rather, exposure through children's toys is a potentially significant and manageable contributor to the existing predominant sources of phthalate exposures in the household/domestic environment.

When considered in isolation of other phthalate exposure sources, the HI derived for the antiandrogenic phthalates group (Table 12) represents an exposure which may potentially produce adverse effects from chronic exposure. The HI values of 1.2 – 1.5 are based on the worst case scenario for infants of 6 months of age. Our report does not consider the further additivity from exposure to antiandrogenic phthalates from other sources such as diet, indoor environment or personal care products which are widely acknowledged to be of significance (Chronic Hazard Advisory Panel 2014).

When considered in isolation from other phthalate exposure sources, the HI derived for the hepatotoxic phthalate group represents an exposure which is unlikely to produce any adverse effects from a chronic exposure as it is significantly less than the current TDI. The maximum HI calculated for the scenario was 0.6, below the HI value of concern of 1.0. However, it may be appropriate to consider the significance which is attributed to this value, as it represents only a fraction of the total exposure which might occur in the household/domestic environment. The CHAP report on phthalates and phthalate alternatives has provided a recent assessment of the relative contributions of individual phthalates

to the total received dose, the data for infants are shown in Table 16 (Chronic Hazard Advisory Panel 2014). When considered in this context the worst case scenario which was used for this assessment produces a dose contribution with an HI in the range of 0.5 – 0.6.

Table 16 Source of phthalate exposure (percent of total exposure) for infants[15]

Phthalate	Weight percentile	Diet	Drugs	Toys	Child care	Personal care	Indoor	Outdoor
DBP	mean	39.1	0	0	0	0	60.9	0.1
	95	45.6	0	0	0	0	54.3	0.1
DIBP	mean	73.6	0	0	0	0	26.4	<0.1
	95	80.8	0	0	0	0	19.1	<0.1
BBP	mean	30.8	0	0	0	0	69.1	<0.1
	95	16.8	0	0	0	0	81.1	<0.1
DNOP	mean	8.5	0	0	91.5	0	<0.1	<0.1
	95	10.2	0	0	89.8	0	<0.1	<0.1
DEHP	mean	41.1	0	9.2	33	0	16.7	<0.1
	95	54.3	0	9.8	25.6	0	10.3	<0.1
DINP	mean	66.9	0	12.8	16.5	0	3.8	<0.1
	95	62.4	0	16.6	12.7	0	8.3	<0.1
DIDP	mean	93	0	0	5.7	0	1.3	<0.1
	95	93.8	0	0	4.6	0	1.6	0

The HI shown in Table 13 and Table 15 represent the potential health impact of an exposure of 0.1% w/w per phthalate in children's toys by mouthing and dermal contact. This level was identified in this report as a reasonable upper limit for a typical exposure to the seven phthalates assessed. The HI for both antiandrogenic and hepatotoxic phthalate groups are 0.02 and less than (<) 0.01 respectively; well below the value of 1.0, hence would indicate that exposure to these phthalates under the conditions identified in the risk assessment would be unlikely to cause adverse health effects.

[15] This table is a partial reproduction of data presented in the Table E1-21 of the CHAP report (2014).

6. CONCLUSION

The scenarios used in this report present a reasonable worst case for exposures to two groupings of phthalates in toys: Antiandrogenic/reproductive phthalates and those that are hepatotoxic, both of which have been subject to regulatory control in a number of international jurisdictions. Infants aged 6 months, were identified as a group to be at greatest risk of exposure from the sources represented by phthalate-containing toys. This is due to the exploratory mouthing behaviours of infants at this age; the contact time, both oral and dermal; their lower body weight, and the ready migration or loss of phthalates from plastics to receiving environments. Infants are also a high risk group for developmental effects due to their rapidly developing organs and tissues. The risk of exposure from contact with children's toys and related articles decreases with changes in behavioural patterns for exploration occurring and an increase in bodyweight meaning a smaller dose per unit bodyweight being received.

We found, using European notifications for violations of phthalate regulatory compliance in 2013-2014, as surrogate data for random monitoring of toys in New Zealand, that the hazard index for reproductive/developmental risks from combined phthalate exposures exceeded the level of concern of 1.0. Considering that the exposures from toys are not expected to constitute the majority of daily phthalate exposures, it appears that high levels of phthalates in toys represent a significant risk for endocrine mediated effects in young children. Monitoring of phthalate levels in toys in New Zealand would help inform the accuracy of this conclusion.

Using the regulatory limit of 0.1% w/w, which is frequently adopted in national and regional jurisdictions outside of New Zealand the maximum HI for both antiandrogenic and hepatotoxic effects were 0.02 and less < 0.01 respectively. This indicates that there is little likelihood of adverse effects being induced by these exposures.

Of the two exposure routes (ingestion and dermal) examined, ingestion presented the greater accumulated dose for both groupings of phthalates. The greatest contribution to this dose was jointly from DEHP and DINP; with DEHP being antiandrogenic and DINP hepatotoxic. The phthalate concentration data used to calculate the exposure and dose were taken from data collected in the EU from products that had notifications issued due to exceeding permissible levels of specified phthalates in the composition. The data represented recent notifications from early 2013 to mid-2014 and as such are considered to be a valid capture of the high end of expected phthalate concentrations in the current environment; these data are used to derive a reasonable worst case exposure scenario. In the absence of New Zealand specific data on the phthalate composition of children's toys it is not possible to produce a more precise New Zealand perspective.

When taken in isolation, these data indicate that exposure to children's toys alone may lead to a risk of potentially adverse endocrine or developmental effects due to phthalate exposure. However, if phthalate levels in toys were to be kept at or below the European regulatory limit of 0.1%, these risks would be avoided. It should also be noted that the exposure scenario represented by mouthing and

handling children's toys is only one of a number of contributory sources of exposure in a child's environment. Of most significance is the dose contribution which is predicted for the antiandrogenic phthalate group where, in the worst case scenario, an HI of 1.2 – 1.5 is derived from the combined ingestion and dermal exposures.

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