Science for Communities

HEALTH RISK ASSESSMENT: PARABENS IN PERSONAL CARE PRODUCTS

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ACRONYMS AND ABBREVIATIONS

ADI	Acceptable daily intake
BP	Butyl paraben
bw	Body weight
EFSA	European Food Safety Authority
EMA	European Medicines Agency
EP	Ethyl paraben
ESR	Institute of Environmental Science and Research Limited
EU	European Union
FAO	Food and Agriculture Organization of the United Nations
GP	General practitioner
HBGV	Health-based guidance value
JECFA	Joint FAO/WHO Expert Committee on Food Additives
LD_{50}	Dose of a substance that is acutely lethal to 50% of a group of test animals
LOAEL	lowest observed adverse effect level
MOE	Margin of exposure
MP	Methyl paraben
NOAEL	no observed adverse effect level
PP	Propyl paraben
RIVM	Rijksinstituut voor Volksgezondheid en Milieu (Dutch National Institute for Public Health and the Environment)
RfD	Reference dose
SCCP	(European) Scientific Committee on Consumer Products
SCCS	(European) Scientific Committee on Consumer Safety
USEPA	United States Environmental Protection Agency

WHO World Health Organization

EXECUTIVE SUMMARY

The purpose of this report is to develop a generic health risk assessment for exposure to parabens from the use of personal care products. This report will only consider domestic, non-occupational, incidental exposure to parabens. Exposure scenarios will be considered for the most common or likely exposure events.

Personal care products are cosmetic products and may include “creams, emulsions, lotions, gels and oils for the skin, face masks, tinted bases (liquids, pastes, powders), make-up powders, after-bath powders, hygienic powders, toilet soaps, deodorant soaps, perfumes, toilet waters and eau de Cologne, bath and shower preparations (salts, foams, oils, gels), depilatories, deodorants and anti-perspirants, hair colorants, products for waving, straightening and fixing hair, hair-setting products, hair-cleansing products (lotions, powders, shampoos), hair-conditioning products (lotions, creams, oils), hairdressing products (lotions, lacquers, brilliantines), shaving products (creams, foams, lotions), make-up and products removing make-up, products intended for application to the lips, products for care of the teeth and the mouth, products for nail care and make-up, products for external intimate hygiene, sunbathing products, products for tanning without sun, skin-whitening products and anti-wrinkle products” (European Commission 2009).

Parabens are salts and esters of 4-hydroxybenzoic acid, that may be added to personal care products, singly or in combination, as preservatives. The most widely used paraben in cosmetic products is methyl paraben (MP), followed by propyl paraben (PP). Ethyl (EP) and butyl paraben (BP) are also used.

Animal studies suggest that the critical effects of parabens are effects associated with reproductive toxicity, particularly effects on male reproductive tissues. The potency of parabens with respect to these effects increases with increasing chain length, with BP having the greatest potency of the commonly used parabens. While the weak estrogenic potential of the parabens is in the same order as their potency as reproductive toxins, there is little evidence that their reproductive toxicity is due to their estrogenicity. More recent studies, following good laboratory practice, have generally shown parabens to be of lower chronic toxicity than earlier studies, particularly PP.

Human epidemiological studies have generally given weak and inconsistent evidence concerning effects on human health from paraben exposure. However, it should be noted that paraben exposure is usually determined in these studies from urinary paraben concentrations and, due to the rapid elimination of these compounds, this will not necessarily be a good indicator of chronic paraben exposure.

Exposure to parabens can be assessed by combining information on concentrations in personal care products, use rates of personal care products, skin retention and dermal absorption (forward method). Exposure can also be estimated from measurement of urinary paraben excretion and information on the proportion of dose that is excreted as the parent paraben (backward method). The latter approach will also include contributions from parabens in food and medicinal products but tends to give lower estimates than the former approach.

Risk characterisation, using margin of exposure (MOE) approaches, indicate that estimated exposure to MP and EP are of low toxicological concern. Similar conclusions can be drawn for PP when more recent toxicological studies are used to derive the toxicological point of

departure. Risk characterisation of BP exposure gives equivocal results, with estimates of exposure based on product use giving low MOEs, while estimates based on urinary output give acceptably high MOEs (>100).

The current weight of evidence suggests that exposure to parabens from use of personal care products is not an immediate cause for concern for reproductive toxicity, although developments on use levels and toxicology of BP may affect this conclusion.

1 INTRODUCTION

The purpose of this report is to develop a generic health risk assessment for exposure to parabens from the use of personal care products. This report will only consider domestic, non-occupational, incidental exposure to parabens. Exposure scenarios will be considered for the most common or likely exposure events.

1.1 CONSUMER PRODUCTS DESCRIPTION – PERSONAL CARE PRODUCTS

Personal care products are cosmetic products and may include “creams, emulsions, lotions, gels and oils for the skin, face masks, tinted bases (liquids, pastes, powders), make-up powders, after-bath powders, hygienic powders, toilet soaps, deodorant soaps, perfumes, toilet waters and eau de Cologne, bath and shower preparations (salts, foams, oils, gels), depilatories, deodorants and anti-perspirants, hair colorants, products for waving, straightening and fixing hair, hair-setting products, hair-cleansing products (lotions, powders, shampoos), hair-conditioning products (lotions, creams, oils), hairdressing products (lotions, lacquers, brilliantines), shaving products (creams, foams, lotions), make-up and products removing make-up, products intended for application to the lips, products for care of the teeth and the mouth, products for nail care and make-up, products for external intimate hygiene, sunbathing products, products for tanning without sun, skin-whitening products and anti-wrinkle products” (European Commission 2009).

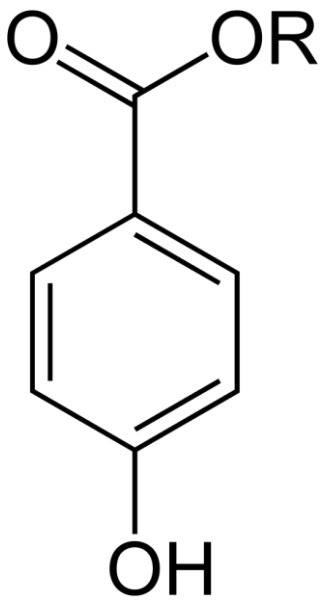
Personal care products may be classified as leave-on or rinse-off products.

In New Zealand, cosmetic products are regulated under an Environmental Protection Authority (EPA) Group Standard (NZEPA 2020). However, no definition of a cosmetic products is included in the group standard.

1.2 PARABENS

Parabens are salts and esters of 4-hydroxybenzoic acid, that may be added to personal care products, singly or in combination, as preservatives (SCCP 2005). The most widely used paraben in cosmetic products under the US Food and Drug Administration’s Voluntary Cosmetic Registration Program (VCRP) is methyl paraben (MP), followed by propyl paraben (PP) (CIR 2018). The other commonly used parabens are ethyl paraben (EP) and butyl paraben (BP). Figure 1 shows the core structure of the parabens and the substituent assignments for the major preservative parabens.

Figure 1. Structure of 4-hydroxybenzoic acid and the major parabens



R = H	4-hydroxybenzoic acid
R = CH_3	methyl paraben
R = CH_2CH_3	ethyl paraben
R = $CH_2CH_2CH_3$	propyl paraben
R = $CH_2CH_2CH_2CH_3$	butyl paraben

Under the New Zealand Cosmetic Products Group Standard, parabens are permitted preservatives up to a concentration of 0.4% for a single paraben or 0.8% for a mixture of parabens (NZEPA 2020).

1.2.1 Parabens in personal care products

Regulations in New Zealand and internationally define maximum concentrations for parabens in personal care products. While no information was found on surveillance of products available in New Zealand, surveys have been carried out in other countries. Results of some of these surveys are summarised in Table 1.

Table 1. Parabens in personal care products

Country	Product type	Number of samples	Concentration of paraben, mean (range), %[a]				Reference
			Methyl paraben	Ethyl paraben	Propyl paraben	Butyl paraben	
Brazil	Baby wipes	50	<0.001 (<0.001-0.03)[b]	<0.001 (<0.001-<0.001)	<0.001 (<0.001-<0.001)	<0.001 (<0.001-<0.001)	(Rocha et al 2020)
China	Toothpaste	28	0.006 (<0.001-0.043)	<0.001 (<0.001-0.002)	0.003 (<0.001-0.047)	0.015 (<0.001-0.39)	(Li et al 2021a)
	Shampoo	15	0.007 (<0.001-0.052)	<0.001 (<0.001-<0.001)	0.005 (<0.001-0.072)	<0.001 (<0.001-<0.001)	
	Face cleansers	18	0.036 (<0.001-0.12)	<0.001 (<0.001-0.005)	0.030 (<0.001-0.21)	<0.001 (<0.001-0.011)	
	Bath gels	21	0.005 (<0.001-0.022)	<0.001 (<0.001-0.016)	0.003 (<0.001-0.028)	<0.001 (<0.001-0.001)	
	Hand sanitisers	11	<0.001 (<0.001-<0.001)	<0.001 (<0.001-<0.001)	0.003 (<0.001-0.028)	<0.001 (<0.001-<0.001)	
	Sunscreens	12	0.043 (0.026-0.080)	0.026 (<0.001-0.10)	0.027 (0.005-0.049)	0.008 (<0.001-0.036)	
	Body lotions	8	0.028 (0.013-0.053)	0.006 (<0.001-0.012)	0.021 (0.004-0.057)	<0.001 (<0.001-0.002)	
	Lipstick	2	0.002 (0.001-0.003)	<0.001 (<0.001-<0.001)	<0.001 (<0.001-<0.001)	<0.001 (<0.001-<0.001)	
	Hand lotions	17	0.030 (0.010-0.064)	0.011 (<0.001-0.051)	0.034 (0.003-0.18)	0.001 (<0.001-0.006)	
	Hair gels	7	0.027 (0.003-0.088)	0.001 (<0.001-0.003)	0.003 (0.001-0.006)	<0.001 (<0.001-<0.001)	
	Masks	11	0.011 (0.001-0.026)	<0.001 (<0.001-0.004)	0.009 (<0.001-0.029)	<0.001 (<0.001-0.002)	
Iran	Sunscreens	30	0.11 (0.01-0.39)		0.16 (0.002-1.32)		(Vosough et al 2017)
Saudi Arabia	Face powder	9	<0.001 (ND-<0.001)	<0.001 (ND-<0.001)	<0.001 (<0.001-<0.001)	<0.001 (<0.001-<0.001)	(Ali et al 2020)
	Body powder	3	<0.001 (<0.001-<0.001)	<0.001 (ND-<0.001)	<0.001 (<0.001-<0.001)	<0.001 (<0.001-<0.001)	
	Wet wipe	9	<0.001 (ND-<0.001)	<0.001 (ND-<0.001)	<0.001 (ND-<0.001)	<0.001 (ND-<0.001)	
	Shampoo	3	ND	ND	ND	<0.001 (<0.001-<0.001)	
	Liquid hand soap	4	ND	ND	ND	<0.001 (<0.001-<0.001)	
	Shower gel	3	ND	ND	ND	<0.001 (<0.001-<0.001)	
Spain	Facial tonic	1	0.06				(Abad-Gil et al 2021)
	Hair spray	1	0.002				
	Mouthwash	2	0.17 (0.10-0.25)				
	Shampoo	1	0.16				
	Hair conditioner	3	0.14 (0.08-0.21)				
	Body cream	2	0.09 (0.07-0.10)				
Spain	Rinse-off products	5	<0.001 (<0.001-<0.001)	<0.001 (ND-<0.001)	<0.001 (ND-<0.001)	<0.001 (ND-<0.001)	(Celeiro et al 2014)
	Leave-on products	12	0.11 (<0.001-0.29)	0.05 (<0.001-0.23)	0.08 (<0.001-0.26)	<0.001 (<0.001-<0.001)	
Spain	Baby wipes	13	0.07 (<0.001-0.30)	0.03 (<0.001-0.07)	0.02 (<0.001-0.05)	0.02 (<0.001-0.06)	(Celeiro et al 2015)
	Wet toilet paper	7	0.07 (<0.001-0.14)	0.02 (<0.001-0.06)	0.02	-	
Spain	Various PCPs	9	0.09 (0.02-0.15)	0.04 (0.02-0.12)	0.03 (0.005-0.06)	0.01 (0.003-0.03)	(Márquez-Sillero et al 2010)

Country	Product type	Number of samples	Concentration of paraben, mean (range), %[a]				Reference
			Methyl paraben	Ethyl paraben	Propyl paraben	Butyl paraben	
Spain	Shower gel	1	0.08	0.02	0.03	-	(Rodas et al 2015)
	Cleansing wipes	1	0.04	0.008	0.02	-	
	Baby wipes	1	0.13	-	0.06	-	
	Anti-age pearl	1	0.01	0.005	0.003	0.007	
	Hand cream	1	0.24	-	0.12	-	
Thailand	Mouthwash	4	0.007 (<0.001-0.014)	ND	0.002 (<0.001-0.003)	ND	(Makkliang et al 2018)
	Foam hand wash	2	<0.001 (<0.001-<0.001)	<0.001 (<0.001-<0.001)	<0.001 (<0.001-<0.001)	<0.001 (<0.001-<0.001)	
	Toner	3	0.01 (<0.001-0.03)	ND	<0.001 (<0.001-<0.001)	ND	
USA	Deodorant	1	1.6	0.35	0.00	0.00	(Myers et al 2015)
	Foundation	2	0.28 (0.0-0.55)	0.54 (0.04-1.04)	0.26 (0.00-0.51)	0.00	
	Toothpaste	1	0.14	0.04	0.00	0.00	
	Hand sanitiser	1	0.00	0.00	0.00	0.00	
	Lipstick	1	0.03	0.00	0.00	0.00	
	Hand lotion	1	0.05	0.03	0.00	0.00	
USA	Feminine hygiene products						(Gao and Kannan 2020)
	Pads	18	<0.001 (<0.001-<0.001)	<0.001 (<0.001-<0.001)	<0.001 (<0.001-<0.001)	<0.001 (<0.001-<0.001)	
	Panty liners	13	<0.001 (<0.001-<0.001)	<0.001 (<0.001-<0.001)	<0.001 (<0.001-<0.001)	<0.001 (<0.001-<0.001)	
	Tampons	12	<0.001 (<0.001-<0.001)	<0.001 (<0.001-<0.001)	<0.001 (<0.001-<0.001)	<0.001 (<0.001-<0.001)	
	Wipes	12	<0.001 (<0.001-<0.001)	0.001 (<0.001-0.002)	<0.001 (<0.001-<0.001)	<0.001 (<0.001-<0.001)	
	Bactericidal creams	14	0.007 (<0.001-0.03)	0.007 (<0.001-0.06)	0.003 (<0.001-0.014)	<0.001 (<0.001-<0.001)	
	Deodorant sprays	4	<0.001 (<0.001-<0.001)	<0.001 (<0.001-<0.001)	<0.001 (<0.001-<0.001)	<0.001 (<0.001-<0.001)	
	Powders	4	<0.001 (<0.001-<0.001)	<0.001 (<0.001-<0.001)	<0.001 (<0.001-<0.001)	<0.001 (<0.001-<0.001)	
Vietnam	Hair treatments	4	0.23 (0.12-0.30)	0.03 (0.001-0.09)	0.05 (0.002-0.10)		(Tran et al 2021)
	Face treatments	2	0.32 (0.27-0.36)	0.09 (0.01-0.17)	0.07 (0.07-0.08)		
	Body treatments	6	0.18 (0.07-0.34)	0.02 (0.01-0.03)	0.04 (0.002-0.09)		

[a] Due to the very wide range of paraben concentrations reported, a 'limit of reporting' of 0.001% has been adopted for the current table

[b] This study reported results in ng/g, with a median MP concentration of 3709 ng/g. The authors stated that this exceeded the Brazilian standard maximum of 0.4%. This is incorrect as the median concentration equates to 0.0003%. However, this calls into question whether the units reported in this study are correct.

The information summarised in Table 1 suggests that paraben concentrations in excess of the limits in the New Zealand group standard and elsewhere (0.4% for a single paraben and 0.8% for parabens combined) are quite rare. The summarised data also suggest that many personal care products may contain very low concentrations of parabens, possible due to their use as preservatives in an ingredient incorporated into the final product.

1.2.2 Incident surveillance and reporting

Parabens will usually be one or several of a large number of ingredients in personal care products. Additionally, when identified, adverse health effects due to paraben exposure are due to chronic exposure, rather than incident-based exposure. For these reasons, case or incident reporting due to paraben exposure was not expected and was not found in the literature or in any of the numerous assessments performed.

2 HAZARD IDENTIFICATION

2.1 HEALTH EFFECTS - PARABENS

No previous health impact assessments for parabens were found for New Zealand. However, several risk assessments of parabens are available internationally. For personal care products, risk assessments considering dermal exposure and, to a much lesser extent, oral exposure are of most relevance.

2.1.1 Toxicological assessments

MP, EP and PP are of low acute toxicity following oral exposure, with LD_{50} (mouse, guinea pig, rabbit, dog) ≥2000 mg/kg bw (JECFA 1974). BP exhibits low acute toxicity following oral (mouse, LD_{50} >5000 mg/kg bw) and dermal (rabbit, LD_{50} >2000 mg/kg bw) exposure (Hessel et al 2019).

Long-term studies in rats reported depression of growth rate when MP, EP or PP were incorporated into the diet at a rate of 8%, but not when incorporated at 2% (20,000 mg/kg of diet or 1000 mg/kg bw) (JECFA 1974). There were no significant pathological findings at autopsy. The Joint FAO/WHO Expert Committee on Food Additives (JECFA) used this NOAEL and an uncertainty factor of 100 to derive an acceptable daily intake (ADI) of 0-10 mg/kg bw. The ADI was considered to be applicable to MP, EP and PP. BP was considered at the same meeting, but the absence of any long-term toxicological study meant no evaluation could be made.

However, PP was subsequently excluded from the group ADI as PP had shown adverse effects on tissues of the reproductive organs of male rats at doses down to 10 mg/kg bw, with no NOAEL identified (JECFA 2007).

The European Food Safety Authority (EFSA) reviewed the available information and reached similar conclusions to JECFA; supporting a group ADI for MP and EP, but concluding that no ADI could be derived for PP (EFSA 2004).

The European Commission Scientific Committee on Consumer Products (SCCP) considered the safety of parabens when used in cosmetic products (SCCP 2005). SCCP noted the previous assessments carried out by JECFA and EFSA and concluded that MP and EP can be safely used up to the maximum authorised concentration as actually established (0.4%). SCCP noted that a study on oral BP exposure in mice showed clear effects on male reproductive parameters, with a NOAEL of 2 mg/kg bw per day. The study on PP did not show a clear NOAEL, but the lowest dose administered was 10 mg/kg bw per day. SCCP concluded that BP was the most potent of the main four parabens with respect to effects on the male reproductive system. It was further noted that the parabens are weakly estrogenic, with estrogenic activities in the order BP>PP>EP>MP. It is uncertain whether the impact of parabens on the male reproductive system is due to their estrogenic activity, however, a detailed development toxicity study of BP in rats (doses up to 1000 mg/kg per day) did not show any impact on embryo/foetal viability, foetal weight, malformations or variations. Strongly estrogenic substances are known to interfere with developmental parameters and SCCP concluded that the lack of effects in this study argued against an estrogenic basis for the impact of parabens on the male reproductive system.

SCCP was subsequently renamed the Scientific Committee on Consumer Safety (SCCS). SCCS reconsidered the safety of PP and BP in 2010 (SCCS 2010). SCCS concluded that *in*

vitro and *in vivo* data indicated that the estrogenic activity of parabens appears to increase with increasing chain length, but that estrogenic potency of these compounds was still 3 to 6 orders of magnitude less than the positive control (17β-estradiol). Industry presented data demonstrating the complete metabolism of parabens to non-estrogenic and non-reproductively toxic *p*-hydroxybenzoic acid in rat skin. SCCS noted apparent differences between metabolism in rat and human skin and derived a conservative value of 3.7% for dermal absorption of BP. Using a daily dermal exposure to preservatives of 17.4 g/day, a body weight of 60 kg, a NOAEL of 2 mg/kg bw per day and a margin of exposure (MOE) approach, SCCS estimated that to achieve an acceptable MOE of 100, the maximum concentration of the sum of PP and BP in cosmetic products should not exceed 0.19%.

The European Medicines Agency (EMA) considered the toxicity of MP and PP, due to their use as excipients in medicinal products (EMA 2015). EMA reiterated the finding of other reviews, that MP has no effect on the male reproductive organs in rats. In contrast to the earlier study reporting effects of PP on the male reproductive system at a dose of about 10 mg/kg bw per day (Oishi 2002), EMA summarised two more recent Good Laboratory Practice (GLP)-compliant studies that found no such effects at doses up to 1000 mg/kg bw per day (Gazin et al 2013).[1] EMA noted that in developmental toxicity studies in female rats, significantly accelerated onset of puberty and increased uterine weights were seen in the 1000 mg/kg bw per day dose group and the NOAEL for these effects was 100 mg/kg bw per day.

PP was re-evaluated by SCCS (SCCS 2020) following publication of a further GLP-compliant study on the reproductive toxicity of PP (Sivaraman et al 2018). The study considered reproductive development and function in male and female rats administered PP on post-natal days 4-90. No treatment-related effects were observed across a large number of indices and a NOAEL of 1000 mg/kg bw per day was indicated by the study. A second good quality unpublished study was also reported with similarly negative results. SCCS considered that these results were of sufficient quality to overturn the finding of the earlier study (Oishi 2002) and support a NOAEL of 1000 mg/kg bw per day. SCCS concluded that, while the available data on propylparaben provide some indications for potential endocrine effects, the current level of evidence is not sufficient to conclusively regard it as an endocrine disrupting substance. SCCS examined a range of personal care product-related exposure scenarios using maximum reported PP use levels, a NOAEL of 1000 mg/kg bw per day and a MOE approach. The aggregate MOE was greater than 10,000.[2]

The Dutch National Institute for Public Health and the Environment (RIVM) reviewed the toxicity of BP, with particular reference to studies published since the SCCS evaluation (Hessel et al 2019). It was concluded that the most investigated endpoint was testicular toxicity, with several studies showing LOAELs of 10 mg/kg bw per day for testicular effects, such as reduced spermatogenesis and increases in defective spermatozoa. It was further concluded that the 'conservative' NOAEL of 2 mg/kg bw per day, used by SCCS, was not very conservative. RIVM further concluded that, based on EU criteria, although BP demonstrates a clear endocrine disrupting (ED) mode of action *in vitro*, it is still unclear whether there is a biologically plausible link between the adverse effects due to BP and its ED mode of action.

[1] The second study was not published in the open literature: Pouliot L (2013). Propylparaben: Three-month oral developmental study in juvenile rats. Unpublished, confidential data provided by Bristol-Myers Squibb Company. This study was not able to be reviewed but a summary was available in EMA (2015).

[2] For non-genotoxic compounds MOEs greater than 100 are usually considered acceptable.

2.1.2 Epidemiological studies

Epidemiological studies have focused on potential endocrine-disrupting effects of parabens.

In a recent screening assessment of parabens, Health Canada and Environment and Climate Change Canada reviewed epidemiological studies considering associations between urinary paraben concentrations and a range of health endpoints (Health Canada/Environment and Climate Change Canada 2020). The finding of this review are summarised below.

Urinary concentrations of MP, EP, PP and BP have been assessed in epidemiology studies addressing fertility, reproductive health, hormone levels, child and adolescent growth and development, allergic sensitisation, respiratory health and body weight.

The majority of studies considered did not find an association between urinary MP concentrations and the endpoints of interest in epidemiological studies addressing fertility, reproductive health, hormone levels, child and adolescent growth and development, allergic sensitisation and body weight. Weak positive associations with urinary MP concentrations were identified in single studies for increased time-to-pregnancy, lower odds of live birth in intrauterine insemination, selected hormone levels in pregnant females, growth rates in male neonates and toddlers, and allergic sensitisation. A weak inverse association with body mass index (BMI) and body weight was detected in adolescents, pregnant women, and adults, and a weak inverse association was found between MP levels in cord blood and foetal testosterone levels. Other than growth rates in neonates and toddlers and foetal testosterone levels, different studies gave conflicting results for these or similar endpoints.

The majority of studies did not find an association between urinary EP concentrations and endpoint of interest in epidemiological studies addressing fertility, reproductive health, serum hormone levels, child and adolescent growth and development, allergic sensitization, body weight, and respiratory health. Weak positive associations were identified in single studies between urinary EP concentrations and abnormal sperm morphology among patients of a fertility clinic, birth weight and height in male neonates, and allergic sensitisation. A weak inverse association was identified between EP concentration and serum thyroid hormone levels in adult females and BMI in pregnant women. Other than growth rates in neonates and toddlers and serum thyroid hormone levels, different studies gave conflicting results for these or similar endpoints.

The majority of studies did not find an association between urinary PP concentrations and the endpoint of interest in epidemiological studies addressing fertility, reproductive health, serum hormone levels, child growth and development, allergic sensitization, and respiratory health. Positive associations were reported between urinary PP concentrations in single studies and decreased odds of live birth in intrauterine insemination, birth weight in males, and allergic sensitisation. An inverse association was identified between PP concentrations and serum thyroid hormone levels in adult females (pregnant and general population), BMI in a general population and pregnant women, and between PP levels in cord blood and foetal testosterone levels. For all endpoints with an identified association, other than foetal testosterone levels, different studies gave conflicting results for these or similar endpoints.

The majority of studies did not report an association between urinary BP concentrations and the endpoint of interest in epidemiological studies addressing fertility, reproductive health, serum hormone levels, child and adolescent growth and development, allergic sensitization, body weight, and respiratory health. Positive associations were reported between urinary BP concentrations in single studies and reduced sperm motility, abnormal sperm morphology,

select hormones in pregnant women (decreased estradiol and increased thyroid hormone, T_4), male birth weight, and allergic sensitisation. An inverse association was identified between BP concentration and menstrual cycle length in young women, and serum thyroid hormone (T_3) level in adult females (pregnant and general population), and BMI in pregnant women. For all endpoints with an identified association, different studies gave conflicting results for these or similar endpoints.

In general, epidemiological studies have not shown consistent or strong associations with endpoints of interest, either across different studies or across different parabens. While the findings summarised above are from a single review of the epidemiological evidence, the conclusions reached are consistent with those of other recent systematic reviews (Hipwell et al 2019; Jamal et al 2019; Zhong et al 2020). It should be noted that urinary paraben concentrations are indicative of recent exposure and may not be a good indicator of chronic paraben exposure.

3 DOSE-RESPONSE INFORMATION

In the current context, concerns associated with dermal exposure to parabens will be related to chronic exposure.

Section 2 has summarised the history of toxicological evaluations of the four main parabens. In earlier assessments of parabens an ADI was derived, but in more recent evaluations the NOAEL has been used as the toxicological point of departure with risks characterised by a margin of exposure (MOE) approach. Table 2 summarises NOAELs for MP, EP, PP and BP.

Table 2. NOAELs for the major parabens

Paraben	NOAEL (mg/kg bw per day)	Species, effect	Reference
MP	1000	Rat, dog, mouse, no effect at highest dose	(JECFA 1974)
MP	1000	Rat, dog, mouse, no effect at highest dose	(SCCP 2005)
MP	250	Rat, systemic toxicity	(Health Canada/Environment and Climate Change Canada 2020)
EP	1000	Rat, dog, mouse, no effect at highest dose	(JECFA 1974)
EP	1000	Rat, dog, mouse, no effect at highest dose	(SCCP 2005)
EP	900 517	Rat, depression and decreased motor activity Rat, effects on developing foetus	(Health Canada/Environment and Climate Change Canada 2020)
PP	1000	Rat, dog, mouse, no effect at highest dose	(JECFA 1974)
PP	No NOAEL identified	Rat, effects on tissues of male reproductive organs	(JECFA 2007)
PP	<10	Rat, effects on tissues of male reproductive organs	(SCCP 2005)
PP	100	Rat, early onset of puberty and increased uterine weight in females	(EMA 2015)
PP	1000	Rat, no effect at highest dose	(SCCS 2020)
PP	1000	Rat, no effect at highest dose	(Health Canada/Environment and Climate Change Canada 2020)
BP	2	Rat, effects on tissues of male reproductive organs	(SCCP 2005)
BP	100 (LOAEL)	Rat, developmental effects	(Health Canada/Environment and Climate Change Canada 2020)

NOAEL: no observed adverse effect level, LOAEL: lowest observed adverse effect level, MP: methyl paraben, EP: ethyl paraben, PP: propyl paraben, BP: butyl paraben

4 EXPOSURE ASSESSMENT

People may be exposed to parabens from several sources, including food, medicines, and personal care products. For food and medicines, exposure will generally be by the oral route, while personal care products will generally result in dermal exposure. In order to compare exposures from different routes or the aggregate exposures, external exposure doses need to be converted in internal exposure doses. Calculation of an internal dose requires knowledge of or assumption of the rate of absorption of the compounds from the gastrointestinal tract (oral) and through the skin (dermal).

Parabens are readily absorbed from the gastrointestinal tract (Health Canada/Environment and Climate Change Canada 2020) and for the purposes of exposure assessment absorption is generally assumed to be 100% (Gosens et al 2014; Hessel et al 2019).

Estimates of dermal absorption are more variable. Dermal absorption figures of 80% (Cowan-Ellsberry and Robison 2009), 36-55% (Gosens et al 2014; Rocha et al 2020; Tokumura et al 2020), and 45% (Zhu and Kannan 2020) have been used in exposure assessment of parabens. Dermal absorption estimates are often obtained from rodent studies and the relevance of rat data to humans has been questioned (SCCS 2010). SCCS used a much lower dermal absorption value (3.7%) for an assessment of BP (SCCS 2010).[3]

4.1 LITERATURE ESTIMATES OF EXPOSURE TO PARABENS FROM USE OF PERSONAL CARE PRODUCTS

Several estimates of exposure to parabens from the use of personal care products have been carried out and are reviewed in the following sections.

4.1.1 Cowan-Ellsberry (2009)

This study involved assessment of aggregate dermal exposure to parabens from the use of personal care products (Cowan-Ellsberry and Robison 2009). Estimates were initially made as the simple sum of exposures from use of 23 types of personal care product. It was assumed that all products were used on a daily basis and that all products contained parabens at the highest reported content. Estimates were progressively refined, taking into account:

- Patterns of product co-use and non-use
- Extent of use, and
- Dermal absorption and metabolism.

The various estimates of paraben exposure are shown in Table 3. Daily exposures for each personal care product were calculated from:

DE (mg/kg bw per day) = C_p x AMT x F x MF/BW

Where DE is the daily exposure, C_p is the fractional concentration of the paraben in the product, AMT is the amount of product used at each usage, F is the daily frequency of product use, MF is the fractional retention of the product on skin and BW is body weight.

[3] The figure of 3.7% is derived from studies using split-thickness human skin. The studies showed 37% absorption of BP. SCCS applied a 10-fold factor for metabolism of BP, although they recognise this factor as conservative as other studies suggest far greater metabolism of BP to inactive *p*-hydroxy benzoic acid.

Table 3. Estimates of exposure to parabens from use of personal care products (Cowan-Ellsberry and Robison, 2009)

Model	Exposure (mg/kg bw per day)			
	Methyl paraben	Ethyl paraben	Propyl paraben	Butyl paraben
Simple aggregate exposure (SAE)	1.61	1.70	0.80	0.02
Co-use (5)[a]	1.29	1.39	0.64	0.02
Co-use (9)[a]	0.99	1.03	0.51	0.01
Extent of use[b]	0.99	0.16	0.42	<0.01
Dermal absorption[c]	0.79	0.13	0.34	<0.01

[a] In detail analysis of use/non-use patterns were carried out for 5 or 9 products, with exposure estimates weighted accordingly. It was assumed that the remaining products were used daily by everyone
[b] Estimates weighted by proportion of products on the market that use the particular paraben
[c] Allowance made for 80% dermal absorption

4.1.2 Gosens *et al*. (2014)

The study determined aggregate exposure to parabens from use of personal care products by children 0-3 years (Gosens et al 2014). Deterministic exposure calculations were carried out using the ConsExpo software.[4] The external dose was calculated using the formula outlined above. Internal doses were calculated by adding a factor F_{dermal} for the fractional dermal absorption. Estimated doses are summarised in Table 4.

Table 4. Estimates of exposure to parabens from use of personal care products by children 0-3 years (Gosens *et al*., 2014)

Model	Methyl paraben	Ethyl paraben	Propyl paraben	Butyl paraben
External exposure (mg/kg bw per day)	2.32	0.36	1.05	0.47
Dermal absorption (%)	36	55	37	42
Internal exposure (mg/kg bw per day)	1.01	0.20	0.41	0.20

With the exception of the estimate for BP, the internal exposure estimates of Gosen *et al*. (2014) are similar to the most refined estimates of Cowan-Ellsberry and Robison (2009).

In addition, results of a small consumer survey were used to provide information on:

- The type of personal care product used
- The amount of product used
- The frequency of use within the last 6 months
- The age and gender of the child

These data and actual data on the concentrations of parabens in different products were used to construct a stochastic exposure model. Dermal absorption was treated as a uniform distribution between 1 and 55%. All iterations of the stochastic model gave estimates of internal exposure below the deterministic estimates. Exposure estimates were also compared to a putative health-based guidance value, calculated as the NOAEL from animal studies divided by 100. The NOAELs used for this exercise were 1000, 1000, 3.3 and 2 mg/kg bw per day, respectively for MP, EP, PP and BP. None of the exposure iterations

[4] http://www.rivm.nl/en/Topics/C/ConsExpo Accessed 14 April 2021

exceed NOAEL/100 for MP or EP. For PP and BP, NOAEL/100 was exceeded in 13 and 7% of iterations, respectively.

4.1.3 Csiszar *et al.* (2017)

This study used product and chemical specific parameters to calculate product intake fractions (PiF), which appear to be equivalent to the absorbed proportion of an applied personal care product dose (Csiszar et al 2017). The PiF was calculated from:

$$PiF^{\,derm,aq} = \frac{k_{ps}}{k_{ps} + k_{pa}} (1 - e^{-(k_{ps} + k_{pa})t})$$

Where $Pif^{derm,\,aq}$ is the PiF for an aqueous product applied to the skin, k_{ps} and k_{pa} are product-skin and product-air transfer rates,[5] and t is the time the product stays on the skin. Internal exposure was then calculated as:

$$I = \frac{\sum PiF \; x \; M_p \; x \; f_p}{BW}$$

Where I is the aggregate paraben exposure, M_p is the daily mass of product applied, f_p is the fraction of paraben in the product and BW is body weight.

Median PiF during the personal care product usage stage were in the range 2 to 88%, with the highest for EP in body lotion and the lowest for EP in conditioner. After consideration of product usage, paraben occurrence and PiF, mean population exposure estimates were 0.2, 0.03, 0.06 and 0.02 mg/kg bw per day for MP, EP, PP and BP, respectively. The major contributors to exposure were:

- MP: body wash, body lotion and conditioner
- EP: body wash and body lotion
- PP: shampoo, body wash, body lotion and conditioner
- BP: shampoo, body wash, body conditioner and facial cleanser

4.1.4 Li *et al.* (2021)

This study estimated exposure to parabens from use of 11 personal care products (Li et al 2021a). Exposure was estimated using the equation:

$$EDI = \frac{C_i \times DC_i}{BW} f_1 f_2$$

Where EDI is the estimated daily internal exposure, C_i is the concentration of paraben in the products, DC_i is the daily use rate for the product, BW is body weight, f_1 is the skin retention factor and f_2 is the fraction of the dermal dose that is absorbed. A dermal absorption figure of 40% was used for all parabens.

Using mean concentrations of parabens and summing across all products, the EDIs were 37, 11, 28 and 2.5 μg/kg bw per day (0.037, 0.011, 0.028 and 0.0025 mg/kg bw per day) for MP, EP, PP and BP, respectively. These estimated exposures are substantially lower than those reported for the studies summarised in sections 4.1.1 to 4.1.3. These differences

[5] The base data for calculating these transfer rates and references to original studies are included in the supplementary information to this study

appear to be due to the use of measured paraben concentrations in products, rather than the assumption of maximum or typical use levels.

4.1.5 Tokumura *et al*. (2020)

This study took a similar approach to that of Cowan-Ellsberry and Robison (2009), but represented all variables by statistical distributions and estimated exposure by simulation analysis (Tokumura et al 2020). Dermal absorption was included as triangular distributions with a minimum of 1% and a maximum of 55% and medians of 36, 55, 37 and 42% for MP, EP, PP and BP, respectively.

Separate estimates were derived for women and children, as these population groups were expected to have higher exposures to parabens than other population groups. Study results are summarised in Table 5.

Table 5. Estimates of exposure to parabens from use of personal care products by Japanese women and children (Tokumura *et al*., 2020)

Population/parameter	Estimated paraben exposure (mg/kg bw per day)			
	Methyl paraben	Ethyl paraben	Propyl paraben	Butyl paraben
Females (>20 years)				
- Median	1.2	0.43	0.35	0.25
- 95th percentile	6.9	3.0	1.9	1.2
Children (1-3 years)				
- Median	0.47	0.11	0.13	0.13
- 95th percentile	2.2	0.60	0.78	0.85

While the estimates of exposure to parabens summarised in the previous section differ, estimates for a particular paraben are generally within an order of magnitude of one another. The studies of Cowan-Ellsberry and Robison (2009), Gosens et al (2014) and Tokumura et al (2020) derived quite similar estimate of exposure, with central estimates for MP, EP, PP and BP in the range 0.47-1.2, 0.11-0.43, 0.13-0.41 and <0.01-0.25 mg/kg bw per day, respectively. The studies of Csiszar et al (2017) and Li et al (2021a) derived somewhat lower exposure estimates, mainly due to their more detailed consideration of dermal absorption and product paraben concentrations, respectively.

4.2 BIOMARKERS OF EXPOSURE

There is good evidence that the majority of paraben exposure is due to the use of personal care products (Aylward et al 2020; Csiszar et al 2017; Hajizadeh et al 2020; Harley et al 2016). For example, a small study reported mean urinary excretion of EP of 1.90 μg/kg bw per day in users of EP-containing personal care products and 0.17 μg/kg bw per day in those who did not use any EP-containing personal care products (Aylward et al 2020). Similarly, when users of high paraben personal care products switched to low paraben products for a period of six days, mean 24-hour urinary excretion of MP, EP, PP and BP decreased from 75, 0.64, 14 and 0.40 μg to 13, 0.11, 3.9 and 0.06 μg, respectively (Huang et al 2021). These changes represent decreases of 72-85% in urinary paraben excretion.

The HERMOSA study recruited 100 adolescent girls from a predominantly Latino community in northern California (Harley et al 2016). An intervention was carried out, during which participants were requested to use provided low-preservative personal care products. Table 6 summarises urinary concentrations of parabens in this cohort pre- and post-intervention

and compares their urinary paraben concentrations to the general US population of the same demographic (female, 14-18 years).

Table 6. Summary of urinary paraben concentrations from the HERMOSA study

Cohort	Units	Urinary paraben concentration, geometric mean (95th percentile)			
		Methyl paraben	Ethyl paraben	Propyl paraben	Butyl paraben
General US population (female, 14-18 years, *n* = 108)	mg/kg, creatinine adjusted	11.0 (490)	0.9 (20.1)	1.4 (89)	0.1 (0.6)
HERMOSA cohort (*n* = 100), pre-intervention	mg/kg, creatinine adjusted	43.4 (1,010)	1.6 (62)	12.7 (270)	0.5 (20.2)
HERMOSA cohort (*n* = 100), pre-intervention	μg/L, specific gravity adjusted	77.4	2.9	22.6	0.8
HERMOSA cohort (*n* = 100), post-intervention	μg/L, specific gravity adjusted	43.2	4.2	12.3	1.7

Source: Harley et al (2016)

It should be noted that the intervention period in the HERMOSA study was quite short (3 days) and only a proportion of personal care products were replaced by low-preservative alternatives. Nevertheless, clear decreases in urinary paraben concentrations are apparent for MP and PP. It should be noted that urinary elimination half-lives for parabens are quite short, with estimates in the range of 3-7 hours (Health Canada/Environment and Climate Change Canada 2020).

The authors of this study noted that urinary concentrations of EP and BP increased post-intervention. They speculated that this may have been due to the unlabelled presence of these compounds in the replacement products, but were unable to carry out analysis to confirm this speculation.

Further detailed analysis of urinary MP and PP concentrations for the HERMOSA cohort were carried out based on frequency of use of personal care products (Berger et al 2019). For those reporting daily use of makeup, urinary MP and PP geometric mean concentrations were 120 and 60 μg/L (specific gravity adjusted), respectively, while for those who used makeup rarely or never the equivalent concentrations were 13 and 2.9 μg/L.

Biomonitoring studies have determined paraben concentrations in bodily fluids, usually urine. Table 7 summarises results of some studies involving biomonitoring for parabens. It should be noted that there are a huge number of studies that have determined urinary paraben concentrations and the studies in Table 7 are representative, rather than exhaustive.

Table 7. Summary of biomonitoring of paraben exposure

Country	Year	Cohort	Units	Paraben concentrations, mean (high percentile)[a]				Reference
				Methyl paraben	Ethyl paraben	Propyl paraben	Butyl paraben	
Australia	2012-2013	De-identified urine samples, polled by age and gender (*n* = 24)	µg/L, no adjustments	230	34	61	4.3	(Heffernan et al 2015)
Brazil	NS	Children (*n* = 20)	µg/L, no adjustments	43	0.5	4.2	0.28	(Silveira et al 2020)
Canada		Females, 6-17 years (*n* = 382)	mg/kg creatinine	11 (157)[e]	0.84 (4.0)[e]	1.8 (25) [e]	0.23 (0.1)[e]	(Guth et al 2021)
Canada	2014-2015	All, 3-79 years (*n* = 2564) Males, 3-79 years (*n* = 1,275) Females, 3-79 years (*n* = 1,289)	µg/L, no adjustments	17 9.4 30		2.5 1.3 4.9		(Health Canada/Environment and Climate Change Canada 2020)
China, South	2018	Adults (*n* = 319)	µg/L, specific gravity adjusted	5.8[b]	0.39[b]	0.35[b]	0.01[b]	(Zhao et al 2021)
China (Guangzhou)	2018	General population (480) Urban Suburban	µg/L, no adjustments	 14[c] 15	 4.3[c] 4.8	 3.2[c] 3.3	 0.2[c] 0.5	(Li et al 2021b)
China	2015	Children, 3-11 years (*n* = 255)	µg/L, no adjustments	22 (63)[c]	8.7 (23)[c]	8.0 (31)[c]	0.16 (0.55)[c]	(Lu et al 2019)
China	2013-2015	Adults, 22-59 years (*n* = 562)	µg/L, no adjustments	43 (180)[c]	68 (340)[c]	35 (190)[c]	9.9 (48)[c]	(Yu et al 2019)
France	2014-2016	Adults (*n* = 600) Children (*n* = 398)	mg/kg creatinine	8.2 (220) 5.3 (311)	(36) (18)	(59) (45)	(2.4) (0.9)	(Fillol et al 2021)
Germany	2015-2017	Children 3.5 years (*n* = 93) 6-10 years (*n* = 155) 11-13 years (*n* = 97) 14-17 years (*n* = 145) All	µg/L, no adjustments	 11.3 (994) 7.3 (660) 5.2 (115) 8.4 (516) 7.7 (617)	 0.94 (12)	 0.56 (19)	 <LOQ (<LOQ)	(Murawski et al 2021)
Korea, Republic of	2015-2017	Preschoolers (*n* = 557) School children (*n* = 839) Adolescents (*n* = 807)	µg/L, specific gravity adjusted	51 30 32	16 12 24	4.8 1.9 3.9	0.6 0.5 0.5	(Lim 2020)

		Adults (*n* = 3759)		41	36	3.6	0.4	
Mexico	2008	Women, midlife (*n* = 73)	μg/L, creatinine adjusted	55[d]	370[d]	130[d]	2.6[d]	(Zamora et al 2021)
Netherlands	NS	Adults (*n* = 662)	μg/L, no adjustments	27[b]	1.7[b]	2.7[b]	0.16[b]	(van der Meer et al 2020)
Norway	2010	Very low birth weight infants (*n* = 36) - First week - Fifth week	μg/L, no adjustments	 396 187	 0.78 2.05	 24 12	 0.17 0.52	(Strømmen et al 2021)
Norway	2016-2017	Adults, 24-72 years (*n* = 144)	μg/L, specific gravity adjusted	12 (160)	1.8 (34)	0.55 (33)	0.16 (0.88)	(Husøy et al 2019)
Poland	2014-2019	Females, 25-39 years (*n* = 511)	μg/L, specific gravity adjusted	108 (730)	13 (260)	19 (360)	5.0 (37)	(Jurewicz et al 2020)
Slovenia	2016-2019	Children (*n* = 149) Adolescents (*n* = 97)	μg/L, specific gravity adjusted	5 (73) 5 (105)	2.7 (34) 4.4 (63)	0.21 (3.6) 0.22 (3.1)	0.15 (1.2) 0.15 (1.7)	(Tkalec et al 2021)
USA	2014-2016	Children 3-6 years (*n* = 180)	μg/L, specific gravity adjusted	57 (1800)[b]	1.4 (123)[b]	8.5 (270)[b]	ND (7)[b]	(Levasseur et al 2021)
USA	2013-2016	Women, 18-45 years (*n* = 895)	μg/L, no adjustments	84[b]	2.6[b]	15.7[b]	0.07[b]	(Arya et al 2020)
USA	2013-2014	Adults (*n* = 827)	μg/L, creatinine adjusted	57	2.5	6.5	-	(Pazos et al 2020)
USA	2017-2018	General population (*n* = 726)	μg/L, no adjustments	66 (270)[c]	9.5 (38)[c]	15 (60)[c]	-	(Dodson et al 2020)
USA	2005-2007	Women, 18-44 years (*n* = 143)	μg/L, no adjustments	59[b]	1.1[b]	15[b]	0.54[b]	(Pollack et al 2020)
USA	2010-2012	Women, 23-34 years (*n* = 766)	mg/kg creatinine	116[b]	2.4[b]	17[b]	0.1[b]	(Bethea et al 2020)

NS: not stated, ND: not detected, LOQ: limit of quantification
[a] High percentile is the 95th percentile unless otherwise specified, mean is geometric mean unless otherwise specified
[b] Median
[c] Not stated whether the mean is arithmetic or geometric
[d] Arithmetic mean
[e] High percentile is the 90th percentile

The studies summarised in Table 7 show a range of measured paraben concentrations but are largely consistent in showing that MP is the paraben that populations are most exposed to, while exposure to BP is often much lower than exposure to the other parabens. A recent Canadian evaluation of parabens included data on importation of parabens, which supported the observed levels in urine reported in Table 7 (Health Canada/Environment and Climate Change Canada 2020). MP was the paraben imported in the greatest volumes (563,190 kg), followed by PP (8,526 kg), EP (4,029 kg) and BP (100-1000 kg).

In order to assess the toxicological significance of urinary concentrations of parabens, some studies have used urinary concentrations to estimate exposure (Murawski et al 2021). The conversion is carried out using literature data for the fraction of urinary excretion (F_{ue}) for the parabens. This allows calculation of the internal paraben dose for comparison with ADIs. The ADIs are derived from oral administration studies and it is assumed that parabens are 100% absorbed by the oral route.

Murawski *et al*. (2021) estimated median (95th percentile) internal doses of MP, EP, PP and BP from urinary concentrations of 0.4 (35), 0.09 (1.2), 0.06 (2.6) and 0.07 (0.27) μg/kg bw per day, respectively. These estimates are 2-3 orders of magnitude lower than estimated from product concentrations and use patterns of personal care products.

Yu *et al.* (2019) used a similar approach to Murawski et al (2021) to estimate internal paraben exposure for an adult cohort. However, despite the median urinary MP concentrations being similar; 5.1 and 8.9 μg/L for Murawski and Yu, respectively, the median estimates of exposure were quite different; 0.4 for Murawski and 1.6 (male) or 25 μg/kg bw per day (female) for Yu. The two studies differed in that Murawski used creatinine excretion to convert urinary concentration to daily excretion, while Yu used a standard estimate of daily urine excretion (2 L).

The Canadian evaluation also estimated exposure to parabens from urinary excretion, but only the 95th percentile exposure estimates were reported (Health Canada/Environment and Climate Change Canada 2020). Estimates for MP, EP, PP and BP were in the ranges 32-73, 0.7-28, 10-54 and 0.3-5.3 μg/kg bw per day, respectively.

4.3 EXPOSURE SUMMARY

Estimates of paraben exposure calculated from urinary excretion are typically an order of magnitude or more lower than estimates of exposure calculated from concentrations of parabens in personal care products, use levels and dermal absorption. For example, mean or median exposure estimates for MP based on product use range from 37 to approximately 1000 μg/kg bw per day, while estimates based on urinary excretion are typically less than 50 μg/kg bw per day and sometimes lower than 1 μg/kg bw per day. This suggests that one or more assumptions employed in these methods may not be robust.

Both approaches are critically dependent on parameter estimates from a small number of studies. Estimates from product use will generally be unable to capture the range and combinations of personal care products used and their actual paraben content, while estimates of dermal absorption are derived from a small number of studies, sometimes of questionable applicability (Cross and Roberts 2000; Jewell et al 2007). Similarly, derivation of exposure estimates from urinary excretion are dependent on estimates of the proportion of the exposure dose that is excreted as the parent compound, in either free or conjugated form (Moos et al 2016; Moos et al 2017; Shin et al 2019).

While it is not possible to say definitively which approach is likely to yield more accurate estimates of exposure, extrapolation from urinary excretion requires fewer assumptions and generalisations. Urinary excretion is also able to capture the variation in exposure between individuals, although a proportion of this variability may be due to differences in metabolism

and elimination of parabens. Conversely, estimates based on product use and product paraben concentrations appear likely to be more conservative and evaluations based on these estimates are more likely to be protective of public health.

5 RISK CHARACTERISATION

Recent evaluations of parabens have mostly characterised risks by a margin of exposure (MOE) approach. The margin of exposure (MOE) is the ratio between a defined point on the dose-response curve for the adverse effect and the estimated human intake or exposure (EFSA 2005). When the defined point on the dose-response curve is a NOAEL and the MOE is >100 the exposure is usually considered to be of low toxicological concern.

5.1 LITERATURE EVALUATIONS

5.1.1 Canada

Measured urinary excretion of parabens for 2564 Canadians aged 3 to 79 years were converted to daily exposures (Health Canada/Environment and Climate Change Canada 2020). NOAELs as outlined in Table 2 were divided by the 95th percentile estimate of exposure for age ranges 3-5, 6-11, 12-19, 20-59 and 60-79 years. For MP, EP, PP and BP MOEs were in the range 3,400-7,900, 20,900-1.3 million, 24,500-96,500, and 18,700-320,000, respectively.

The evaluation also calculated exposure to parabens based on use rates and paraben concentrations for products such as face paints, sunscreens and some medications. While most MOEs were well in excess of 100, some were not. For example, for a toddler (0.5-4 years) taking an oral anti-diarrhoeal medication containing 1.5% MP, systemic exposure was estimated to result in a MOE of 5.

5.1.2 Europe

SCCS determined MOEs for PP based on a NOAEL of 1000 mg/kg bw per day and exposure calculated from maximum use levels of PP in finished products, product use rates, a dermal absorption of 3.7% and an oral absorption of 100% (SCCS 2020). Aggregate MOEs across 17 personal care product types were in the range 12,000 to 30,000, depending on assumptions around concentrations of PP in products.

5.1.3 Japan

Aggregate internal exposure to parabens was assessed for women (10 products) and children (11 products) using a probabilistic approach (Tokumura et al 2020). NOAELs of 1000, 1000, 3.3 and 2 mg/kg bw per day were used to calculate MOEs for MP, EP, PP and BP, respectively. For women, median (95th percentile) MOEs for MP, EP, PP and BP were 850 (140), 2300 (340), 9.5 (1.8) and 7.9 (1.7), respectively. For children, the corresponding MOEs were 2100 (450), 9400 (1700), 25 (4.2) and 16 (2.3), respectively. It should be noted that the NOAEL for PP has subsequently been revised substantially upwards (see Table 2) and application of the revised NOAEL would have resulted in median MOEs for women and children of 2,900 and 7,500.

5.1.4 Netherlands

Internal exposures to MP, EP, PP and BP were estimated for infants and toddlers (0-3 years), as outlined in section 4.1.2 (Gosens et al 2014). NOAELs of 1000, 1000, 3.3 and 2.0 mg/kg bw per day were used to determine MOEs. MOEs for MP and EP were adequate; 990 and 5000, respectively. However, for PP and BP the MOEs were quite low; 8 and 10, respectively. It should be noted that the NOAEL for PP has subsequently been revised

substantially upwards (see Table 2) and application of the revised NOAEL would have resulted in a MOE of 2,400.

Exposure to MP was predominantly from the use of toothpaste and baby wipes. EP and BP exposure was almost solely (>60%) due to use of baby wipes. PP exposure was also predominantly due to use of baby wipes, but with substantial (>20%) contributions from body lotion and sunscreen use.

6 CONCLUSIONS

Parabens are used as preservatives in a wide range of personal care products. The majority of parabens used are the shorter chain, less toxic parabens, particularly MP (CIR 2018; Health Canada/Environment and Climate Change Canada 2020).

Animal studies suggest that the critical effects of parabens are effects associated with reproductive toxicity, particularly effects on male reproductive tissues. The potency of parabens with respect to these effects increases with increasing chain length, with BP having the greatest potency of the commonly used parabens. While the weak estrogenic potential of the parabens is in the same order as their potency as reproductive toxins, there is little evidence that their reproductive toxicity is due to their estrogenicity. More recent studies, following good laboratory practice, have generally shown parabens to be of lower chronic toxicity than earlier studies, particularly PP.

Human epidemiological studies have generally given weak and inconsistent evidence concerning effects on human health endpoints. However, it should be noted that paraben exposure is usually determined in these studies from urinary paraben concentration and, due to the rapid elimination of these compounds, this will not necessarily be a good indicator of chronic paraben exposure.

Exposure to parabens can be assessed by combining information on concentrations in personal care products, use rates of personal care products, skin retention and dermal absorption. Exposure can also be estimated from measurement of urinary paraben excretion and information on the proportion of dose that is excreted as the parent paraben. The latter approach will also include contributions from parabens in food and medicinal products but tend to give lower estimates than the former approach.

Risk characterisation, using MOE approaches, indicate that estimated exposure to MP and EP are of low toxicological concern. Similar conclusions can be drawn for PP when more recent toxicological studies are used to derive the toxicological point of departure. Risk characterisation of BP exposure gives equivocal results, with estimates of exposure based on product use giving low MOEs, while estimates based on urinary output give acceptably high MOEs.

The current weight of evidence suggests that exposure to parabens from use of personal care products is not an immediate cause for concern, although developments on use levels and toxicology of BP and PP may affect this conclusion.

7 REFERENCES

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