National Institute for Public Health
and the Environment
Ministry of Health, Welfare and Sport

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Synopsis

Aggregate exposure to isothiazolinones used as preservatives in consumer products.
Is the simultaneous presence of CMI, MI and BIT in personal care products, household cleaning products, toys, paints and glues of concern?

Isothiazolinones are preservatives. They are frequently used in, for example, personal care products like sunscreen and shampoo, as well as cleaning products, paint and aqueous toys like clay and toy slime. They ensure that a product does not spoil and that its shelf life is prolonged. If people come into contact with isothiazolinones, this could lead to allergic reactions of the skin.

Currently, consumers are advised to be cautious with these substances (see http://www.waarzitwatin.nl). In order to assess the risk of allergic reactions, the extent to which people are exposed to these substances should be determined. RIVM has investigated this by calculating the exposure to isothiazolinones.

This investigation was carried out by estimating to which extent various product groups contributed to the total exposure, as people can be exposed to isothiazolines via various different products every day. The total exposure in both adults and children has been investigated for three widely-used substances: methylisothiazolinone, chloromethylisothiazolinone and benzisothiazolinone.

The results of this investigation indicated that, in some cases, the total exposure is higher than the safe amount. More research is needed to know whether this is really the case. For example, for many products the exact amount of isothiazolinones they contain is unknown. In addition, it is not always determined how many people use such products and how often. It should also be investigated whether other types of isothiazolines, such as dichlorooctylisothiazolinone and octylisothiazolinone, contribute to the total exposure to isothiazolinones.

The NVWA has measured the amount of isothiazolinones in hundreds of different products. RIVM used these measurements to calculate the exposure using the PACEM and ConsExpo computer models. ConsExpo can provide a first estimation of the exposure that occurs when a person uses a single product. With PACEM, exposure to multiple products can be calculated. Furthermore, PACEM gives a more realistic estimation of the exposure, because it uses concrete data about the frequency of use.

Keywords: aggregate exposure, PACEM, ConsExpo, personal care products, cosmetics, household cleaning products, preservatives, isothiazolinones, MI, CMI, BIT

Publiekssamenvatting

Geaggregeerde blootstelling aan isothiazolinonen gebruikt als conserveermiddelen in consumentenproducten.
Is de gelijktijdige aanwezigheid van CMI, MI en BIT in persoonlijke verzorgingsproducten, huishoudelijke schoonmaakmiddelen, speelgoed, verf en lijm reden tot zorg?

Isothiazolinonen zijn conserveermiddelen. Ze worden vaak gebruikt in bijvoorbeeld persoonlijke verzorgingsproducten, zoals zonnebrand en shampoo. Maar ook in schoonmaakmiddelen, verf en 'waterig' speelgoed, zoals klei en slijm. Ze zorgen ervoor dat een product niet bederft en zo langer houdbaar blijft. Als mensen in contact komen met isothiazolinonen, kan dat allergische reacties van de huid veroorzaken.

Consumenten wordt nu aangeraden om voorzichtig te zijn met deze stoffen (zie http://www.waarzitwatin.nl). Om in te schatten hoe groot de kans op allergische reacties is, moet eerst worden bepaald in welke mate mensen met deze stoffen in aanraking komen. Het RIVM heeft dat onderzocht door de blootstelling aan isothiazolinonen te berekenen.

Het RIVM deed dat door in te schatten in welke mate verschillende productgroepen bijdragen aan de totale blootstelling. Mensen kunnen namelijk per dag via verschillende producten aan isothiazolinonen blootstaan. De totale blootstelling is voor volwassenen en kinderen uitgezocht voor drie veelgebruikte stoffen: methylisothiazolinon, chloormethylisothiazolinon en benzylisothiazolinon.

Dit onderzoek geeft aanwijzingen dat de totale blootstelling soms hoger is dan de veilige hoeveelheid. Meer onderzoek is nodig om te weten of dat echt zo is. Van veel producten is bijvoorbeeld niet bekend hoeveel isothiazolinonen erin zitten. Ook is niet altijd bekend hoe vaak en hoeveel mensen zulke producten gebruiken. Verder moet worden onderzocht of andere soorten isothiazolinonen, zoals dichlorooctylisothiazolinon of octylisothiazolinon, bijdragen aan de totale blootstelling aan isothiazolinonen.

De NVWA heeft van honderden verschillende producten gemeten hoeveel isothiazolinonen erin zitten. Het RIVM heeft deze gemeten hoeveelheden gebruikt om de blootstelling te berekenen met de computermodellen PACEM en ConsExpo. ConsExpo kan een eerste inschatting van de blootstelling geven als iemand één product gebruikt. Met PACEM kan de blootstelling aan meerdere producten worden berekend. PACEM geeft bovendien een realistischer schatting van de blootstelling, omdat het met concrete gegevens werkt hoe vaak mensen een product gebruiken.

Kernwoorden: geaggregeerde blootstelling, PACEM, ConsExpo, persoonlijke verzorgingsproducten, cosmetica, huishoudelijke producten, schoonmaakmiddelen, conserveermiddelen, isothiazolinonen, MI, CMI, BIT

Contents

Summary

Water-based consumer products may contain preservatives to slow down or prevent the growth of microorganisms, for example in personal care products, household cleaning products, do-it-yourself products and toys. An important group of preservatives are isothiazolinones (IT). This group of preservatives contains several substances, of which methylisothiazolinone (MI), chloromethylisothiazolinone (CMI) and benzisothiazolinone (BIT) are the most commonly used. Besides beneficial antimicrobial properties, MI, CMI and BIT have skin sensitising properties. The order of sensitising potency is suggested to be CMI>MI>BIT. Measures preventing skin sensitisation often depend on the legal framework under which the type of product is regulated. However, these specific legislations do not or hardly take into account exposure from multiple sources. As IT are often used in various products, estimated consumer exposure to IT from single products is an underestimation of the actual exposure. To determine whether there is a health risk from exposure to IT in various consumer products, an aggregate exposure is needed, i.e. the summed exposure from all IT containing products. The aim of this research is to get more insight in the aggregate dermal exposure of consumers to IT, and the contribution of the distinct products to this exposure, specifically personal care products (PCP), household cleaning products (HCP), (wall)paint, toys and glue.

Consumer exposure has been typically calculated per single product using ConsExpo. ConsExpo also allows the aggregation of exposure to a single substance present in multiple products. However, this aggregation can only be performed in a conservative manner without taking (differences in) use patterns within a population into account. Since PACEM, the Probabilistic Aggregate Consumer Exposure Model developed at RIVM, is a person-oriented model in which the exposure of a large population is simulated based on product use surveys, aggregate exposure can be calculated applying realistic use data of products. In addition, the magnitude of the contribution of different product groups to the total exposure to IT can be determined with this model. In this research, PACEM was used to estimate aggregate consumer exposure to IT in PCP and HCP in an adult population. However, for several product groups, subpopulations (children) and exposure scenarios, product use surveys are not available or not implemented in PACEM. For these cases, ConsExpo was used to estimate the exposure to IT. These cases included exposure to paint (adults) and laundry products (adults). Also, exposure of children to IT in PCP was estimated with ConsExpo. After cleaning, children are exposure to IT from washed fabrics and cleaned floors. This post-application exposure scenario was calculated with ConsExpo. For the estimation of exposure, measurement data from the Netherlands Food and Consumer Product Safety Authority (NVWA) of IT in various consumer products were used. These data were complemented with relevant data from available reports and literature on IT in consumer products.

In order to investigate the contribution of various sources to the IT exposure, comparison of the dermal load associated with each source

needs to be performed. However, the results of PACEM and ConsExpo differ in their level of conservatism, and may not be directly comparable. Also comparison of exposure estimates with ConsExpo should be performed with some caution due to different levels of uncertainty in each exposure scenario. Several factors within the exposure estimation affect the dermal exposure estimation, including: assumptions regarding the use frequency of products and the amount of product applied, the assumed concentration of IT in products, the occurrence of IT being present in products of a particular product group, and the estimation of the fraction of product that remains on the skin after application.

Keeping these considerations in mind, the aggregate exposure of adults to IT, expressed as MI-equivalents, seems to be primarily driven by either PCP or HCP. However, HCP likely lead to more skin sensitisation effects than PCP, due to the concurrent presence of other components with irritating properties in HCP. Regarding single products, the estimated dermal loads demonstrate that glues and wall paints may be major contributors to the IT exposure for adults. The IT exposure in children via shampoo was approximately two orders of magnitude higher than that via shower gel/foam/scrub, and comparable to that via putty and toy slime. The estimated post-application exposures from laundry product and floor cleaner are multiple orders of magnitude lower than the exposure to shampoo, putty and toy slime.

To estimate whether the calculated dermal exposure constitutes a potential health risk, the exposures were compared with Acceptable Exposure Limit (AEL) available in the literature. In case the exposure is below the AEL there is a sufficiently small risk on skin sensitisation induction in consumer. The AELs of MI, CMI and BIT were exceeded for a number of single product exposure estimates of MI, CMI, BIT and for MI-equivalents (ConsExpo). Specifically, for the dermal loads associated with exposure to laundry detergent when pouring with caps, wall paint, glue, the estimated 95th percentiles of MI, CMI, BIT and the MI-equivalents exceeded the AEL derived for the relevant IT. In addition, the MI-equivalent dermal load aggregated over PCP and HCP also exceeded the AEL of MI. For children shampoo, shower gel/foam/scrub, putty and toy-slime, the estimated 95th percentiles of the MI-equivalents exceeded the AEL derived for MI. For shampoo, putty and toy-slime also MI and CMI exceeded the AEL derived for the relevant IT. MI-equivalents are the summed exposures to MI, CMI and BIT corrected for their varying potency to cause sensibilisation.

Bearing the results of this research in mind, it is recommended to further investigate the exposure to IT, since the aggregate dermal loads were frequently in the same order of magnitude as the corresponding AELs. Furthermore, of the three studied IT, CMI is expected to be the IT with the highest contribution to the total IT exposure, while HCP are expected to have a higher skin sensitising effect than PCP. Acquiring additional information on CMI concentration in HCP, and product use of HCP is therefore recommended. Despite the high level of conservativity, the estimated dermal loads associated with exposure to putty and toy-slime call for investigations on the product use frequencies and amounts, in order to reduce the uncertainties around those exposure estimates.

1 Introduction

1.1 Consumer exposure to chemicals

Consumers are frequently exposed to chemical substances in or released from everyday consumer products like paint, cosmetics, clothing and cleaning products. The presence of chemical substances in these products should not give a concern for human health. To assess the risk of a chemical in a consumer product, it is necessary to determine the exposure to the chemicals in these products under normal use.

The assessment of aggregate exposure of chemical substances is important because consumers can be exposed to a chemical substance from different sources at the same time. When the same substance is present in various consumer products the exposure should be added up when calculating an (aggregate) exposure. This aggregate exposure is required to determine whether there is a risk from exposure to the substance from multiple products.

In previous calculations, exposure could only be calculated per product (ConsExpo). Since PACEM, the Probabilistic Aggregate Consumer Exposure Model developed at RIVM, is a person-oriented model in which the exposure distribution of a large population is simulated based on product use surveys, aggregate exposure can be calculated applying realistic use data of products. In addition, the model calculates with distributions instead of one (worst-case) value for the amount of product used, thus accounting for variations in product use by a person. Adding the different exposures in this way to an aggregate exposure distribution in the population gives a more realistic picture than the worst-case assumption that the entire population uses every day all products. Moreover, this method can be used to determine the relative contributions of individual product groups to the aggregate exposure to a specific substance in a population.

1.2 Preservatives

The term “preservatives” refers to the functional name for a wide variety of compounds that help to slow down or prevent the growth of microorganisms, such as bacteria, yeasts and fungi, in a wide range of products including foods, medicines, and personal care products. Also products like paints, glues, household cleaning products and toys can contain preservatives, especially water-based products. As these preservatives limit the growth of microorganisms, they help to prevent microbial contaminations that may cause irritation or infections. In addition, antioxidant preservatives can help in keeping personal care products from spoiling by suppressing reactions that can occur when ingredients in personal care products react with oxygen. As such, preservatives play an important role in many products that are used on a daily basis by prolonging the shelf life of the products.

The trend is that the list of allowed preservatives in Annex V of the Cosmetics Regulation in personal care products is shrinking as several preservatives have been banned and almost no new allowed

preservatives have been added to Annex V in recent years (NVWA, 2021). This results in a more limited selection of preservatives that a consumer is exposed to, which may lead to more frequent exposure to a particular preservative. An important group of preservatives are isothiazolinones (IT). This group of preservatives contains several substances, of which methylisothiazolinone (MI), chloromethylisothiazolinone (CMI) and benzisothiazolinone (BIT) are usually considered the most applied (Ducup de Saint Paul et al., 2021; Goodier et al., 2018; Goodier et al., 2019; Silva et al., 2020; Thomsen et al., 2018). IT are widely used in personal care products (MI and CMI/MI in EU only, no BIT), as well as in household cleaning products, toys, paints and glues. Where exposure to IT in one product poses a negligible or low risk, exposure to IT in multiple products may lead to a risk that is no longer negligible (NVWA, 2021).

1.3 Aim of the current research

The main aim of the current research is to get more insight in the aggregate dermal exposure of consumers to a group of widely used preservatives (namely IT), and the contribution of the different sources/ product groups to this exposure, specifically personal care products (PCP), household cleaning products (HCP), (wall)paint, toys and glue. This will be investigated for both adults and children. Given the focus on exposure in the current report, a full hazard assessment of IT, including the derivation of Acceptable Exposure Level (AEL), has not been performed. Instead, AELs of various IT, as determined in the literature, have been used to provide an indication of a potential health risk at estimated dermal exposure.

Measurement data from the Netherlands Food and Consumer Product Safety Authority (NVWA) of IT in various consumer products are used as a basis for the calculations. These data are complemented with relevant data from available reports and literature on IT in consumer products. For exposure calculations, the exposure models PACEM and ConsExpo are used. Preferably PACEM is used because this model provides a more realistic exposure estimate. However, for several products, subpopulations (children) and exposure scenarios, use surveys are not available or not implemented in PACEM. In such cases ConsExpo is applied to derive an exposure estimate. The results of both models differ in their level of conservatism, and may not be directly comparable. Comparisons are made as far as reasonably possible.

In the current report, background information on IT as preservatives including information on skin sensitisation and relevant legal frameworks for this research is described in Chapter 2. Chapter 3 describes the approach, the methods and the software models that are used for the exposure calculations. Also the product concentration data, the used exposure scenarios, as well as the associated assumptions are reported in this chapter. Results of the exposure calculations are reported in Chapter 4, followed by discussion in Chapter 5, and conclusions, knowledge gaps and recommendations in Chapter 6.

2 Background

2.1 Preservatives and health effects

2.1.1 Preservatives and sensitisation

Besides beneficial antimicrobial properties, many preservatives have skin sensitising properties, while being a common cause of allergic contact dermatitis in the general population (Ezendam et al., 2018; Schnuch et al., 2011; Schwensen et al., 2016; Wilkinson et al., 2002). If clinical evidence demonstrates that a preservative leads to a rise in the prevalence of contact allergy, measures preventing skin sensitisation often depend on the legal framework under which the type of product is regulated, for example restricting its use in certain products. An important cause of preservative contact allergy is exposure from personal care products (PCP) (Lundov et al., 2010). Therefore, preventive measures are often directed to restriction of their use in PCP, e.g. lowering the maximum concentration limit or banning its use. Consequently, new preservatives need to be developed to replace the ones that are not allowed anymore. Unfortunately, many of these new preservatives lead to a rise in contact allergy after market entry, which has been called the Dillarstone effect (Dillarstone, 1997; Ezendam et al., 2018).

2.1.2 Sensitisation induced by individual IT

An example of a preservative that caused a rise in dermal contact allergy is methylisothiazolinone (MI) (Aerts et al., 2014; Gameiro et al., 2014; Hosteing et al., 2014; Lundov et al., 2011). The rise in prevalence of MI induced contact allergy caused a lot of concern and was an important trigger for a re-evaluation of the risk of MI for skin sensitisation.

Also other individual IT such as chloromethylisothiazolinone (CMI), benzisothiazolinone (BIT) and octylisothiazolinone (OIT) can cause sensitisation. There is some evidence that sensitisation by one IT may also trigger elicitation when exposed to another IT (e.g. Schwensen et al., 2017; Herman et al., 2019), a process which is termed cross-reaction. It should be noted that the evidence of cross-reaction is observed in the elicitation phase, this does not necessarily mean that simultaneous exposure to low levels (i.e. below sensitisation concentrations) of multiple IT can cause sensitisation due to dose-addition.

Sensitising potency of substances can be expressed in an EC3 value obtained from a local lymph node assay (LLNA). EC3 values are expressed as a percentage concentration of the substance required to elicit a sensitisation response. A low EC3 value indicates a strong sensitiser, because a very small amount of substance is needed to induce sensitisation, whereas a high EC3 value indicates a weak sensitiser. EC3 values can thus also be used as a measure of the relative potency of substances. Considering the individual IT, the order of sensitising potency is suggested CMI>MI>OIT>BIT (Schwensen et al., 2017; Herman et al., 2019; Alexander, 2002; Basketter et al., 1999).

The EC3s of these substances are 0.01%, 0.4%, 0.7% and 10.4%, respectively. The EC3 of OIT was not obtained experimentally, but estimated by Schwensen et al. (2017) based on the EC3 of MI corrected for molecular weight. Potency of MI was considered similar to that of OIT because of their similar chemical structure (see Figure 1).

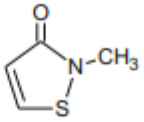
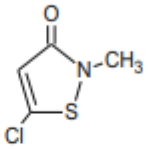
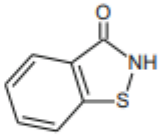
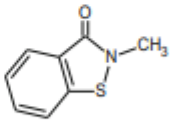
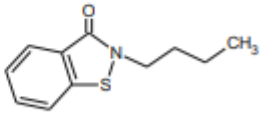
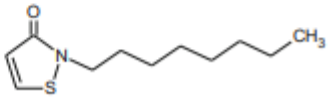
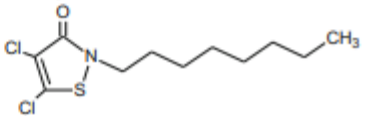
Isothiazolinones	CAS No.	Molecular Formula
MI	2682-20-4	
CMI	26172-55-4	
BIT	2634-33-5	
MBIT	2527-66-4	
BBIT	4299-07-4	
OIT	26530-20-1	
DCOIT	64359-81-5	

Figure 1 Chemical structures and CAS numbers of several isothiazolinones (IT): MI = 2-methyl-2H-isothiazol-3-one; CMI = 5-chloro-2-methyl-2H-isothiazol-3-one; BIT = 1,2-benzisothiazol-3(2H)-one; MBIT = 2-methyl-1,2-benzothiazol-3(2H)-one; BBIT = 2-Butyl-1,2-benzisothiazolin-3-one; OIT = 2-octyl-2H-isothiazol-3-one; DCOIT = 4,5-dichloro-2-octyl-2H-isothiazol-3-one (figure adapted from Ducup de Saint Paul et al. (2021)).

For the purpose of deriving the EC3, also the mixture of CMI and MI (CMI/MI; CAS 55965-84-9), in a 3:1 ratio (Kathon CG) has been tested. It seems that CMI/MI has an EC3 of 0.0082% (Basketter et al., 2003) where CMI alone has a very similar EC3 of 0.01% (Basketter et al., 1999; Botham et al., 1991). Comparison of the substances is hampered by the different vehicles used.

Other mixture experiments have not been performed to determine the sensitising potency of various mixture compositions, or to determine if dose addition can be applied when assessing the sensitizing risk of IT

mixtures. As a consequence it remains unclear whether or not dose addition applies to IT when considering the sensitizing properties of IT. In the current report both options will be assessed, i.e.:
1) Dose addition applies to IT. In this case relative potencies can be derived based on the available EC3s (see below). Subsequently, all concentrations of the individual IT can be transformed to equivalents of an index compound of which the (summed) exposure can be calculated, which may be compared to the Acceptable Exposure Level (AEL) of the index compound.
2) Dose-addition does not apply. In this case, all IT can be assessed individually.

2.1.3 Relative potencies based on EC3s

As mentioned, the EC3s of CMI, MI, OIT and BIT are 0.01%, 0.4%, 0.7% and 10.4%, respectively. Since previously a quantitative risk assessment (QRA) has been performed on MI (Ezendam et al., 2018), MI is chosen as the index compound with a relative potency of 1. Based on the EC3s, and assuming that the dose-responses from the LLNA studies are parallel, the relative potencies of CMI, MI, OIT and BIT are 40, 1, 0.6 and 0.04 respectively. In other words, CMI is 40 times more potent compared to MI. OIT and BIT are less potent than MI and therefore have a relative potency of less than 1, e.g. BIT is 26 times less potent compared to MI, and has a relative potency of 1/26=0.04 (=0.4/10.4).

2.1.4 Acceptable Exposure Levels of IT

To determine if a substance is safe to use at the intended product concentration, a quantitative risk assessment approach is needed that takes consumer exposure into account. For the use of sensitising substances in consumer products, a quantitative risk assessment (QRA) methodology for skin sensitisation is currently used by the fragrance industry to establish concentration levels that would not induce fragrance contact allergy (Api et al., 2008). In this QRA method, a No Expected Sensitisation Induction Level (NESIL) is derived, corresponding to the dermal load (amount per unit surface area of exposed skin) at which no induction of sensitisation is expected. The NESIL is the point of departure (PoD) of the hazard assessment and can be derived from (existing) human (Human Repeated Insult Patch Test (HRIPT)) or animal studies (Local Lymph Node Assay (LLNA)). The Acceptable Exposure Level (AEL) is the result of the NESIL divided by the total SAFs (Sensitisation Assessment Factors), which are applied to account for differences between experimental and real-life exposures and sensitivity among individuals. In the initial proposed QRA (Api et al., 2008) the risk was determined by comparing the AEL to the consumer exposure level (CEL), based on the use of a single product. When the CEL is equal to or lower than the AEL it is assumed that there is a sufficiently small risk on skin sensitisation induction in consumers (Api et al., 2008; WHO, 2012).

AELs derived for MI and BIT exposure have been reported in previous studies. Specifically, Ezendam et al. (2018) derived the AEL of MI using a NESIL of 100 µg/cm^2, which was originally derived using a LLNA. They included a default SAF of 10 to account for inter-individual variability (Basketter & Safford, 2016), a SAF of 15 to account for interspecies differences (i.e. LLNA to human) (Bil et al., 2017), and a SAF of 3 to

account for the frequency of product use (Basketter & Safford, 2016). However, they did not account for vehicle matrix effects, i.e. the fact that sensitisation potency of a substance may be increased by the presence of components with skin irritating properties. As the aim of the current report was not to perform a hazard assessment but to give an indication of the potential health risk, we chose to be conservative and added a matrix factor of 3, resulting in a total SAF of 1350. Dividing the NESIL by the total SAF gives an AEL of 7.4×10^{-2} µg/cm^2. It must be noted that an AEL for MI was also derived by the Scientific Committee on Consumer Safety (SCCS, 2015). However, this AEL of 0.15 µg/cm^2 is based on a NESIL that was provided by human studies that suffered from limitations in the study design and dose selection. Therefore, we decided to not use this AEL, and use the AEL derived by Ezendam et al. (2018) instead.

Although the AEL for CMI has not yet been directly derived, an AEL has been derived for the MI/CMI mixture (Wijnhoven et al., 2008). Since the potency of CMI is 40 times higher than that of MI, it is assumed that the AEL of the MI/CMI mixture is primarily driven by CMI, and thus also representing the AEL of CMI. The AEL of MI/CMI was derived using a NESIL of 1.25 µg/cm^2. A SAF of 10 was included to account for inter-individual variability, and a SAF of 10 was included to account differences in the site of contact, skin integrity and way of operating between the experimental setting and real life. In addition, Wijnhoven et al. (2008) applied a SAF of 3 for certain selected products to account for matrix. In the present research, this matrix factor of 3 was applied to all analysed product groups, as to derive a conservative AEL. This resulted in a total SAF of 300, giving an AEL of 4.2×10^{-3} µg/cm^2.

Garcia-Hidalgo et al. (2018) derived an AEL for BIT using a NESIL of 45 µg/cm^2 that was estimated by Novick et al. (2013). A total SAF of 300 was used, which consisted of a SAF of 10 to account for inter-individual differences, a SAF of 10 to account for use considerations and a SAF of 3 for the matrix. Since the NESIL was derived from human test studies, no inter-species SAF was applied. Given the NESIL of 45 µg/cm^2 and the total SAF of 300, an AEL of BIT was derived of 0.15 µg/cm^2. The AELs used in this current report are presented in Table 1.

Table 1 Overview of No Expected Sensitisation Induction Level (NESIL), Sensitisation Assessment Factors (SAF) and Acceptable Exposure Level (AEL) used in this current report.

IT	**NESIL (µg/cm^2)**	**SAF**	**AEL (µg/cm^2)**
MI	100	1350	7.4×10^{2}
MI/CMI	1.25	300	4.2×10^{3}
BIT	45	300	0.15

2.2 Legal frameworks

Depending on the type of product, different legislative frameworks are applicable with different attention to the presence of preservatives, IT or skin sensitisation (Smit & Schuur, 2014). The legislative aspects concerning IT relevant to the product groups considered in this document are briefly discussed below.

2.2.1 *REACH*

Under the European REACH (Registration, Evaluation, Authorisation and Restriction of Chemicals) Regulation (EC) 1907/2006, and the CLP (Classification, Labelling and Packaging) Regulation (EC) 1272/2008, the hazard classification and status of the IT in Figure 1 are as presented in Table 2. All IT have a hazard classification for skin sensitisation (Skin Sens 1A, H317 or Skin Sens 1), though the classification for CMI and BBIT is not harmonized but based on industry self-classification (notified). The 3:1 mixture of CMI with MI has a harmonized classification, which means that the decision on classification has been made at EU level. Of the product groups considered in this document, the labelling according to the CLP Regulation includes HCP, paints, glues and aqueous toys (but not PCP, which fall outside the scope of the CLP Regulation).

According to the CLP Regulation, a mixture (product) needs to be classified as skin sensitising when at least one ingredient has been classified as a skin sensitiser and is present at or above the generic concentration limit of 0.1% for substances classified as Skin Sens 1A and 1.0% for Skin Sens 1 or 1B. The label on the packaging of mixtures containing at least one substance classified as sensitising and present in a concentration equal to or higher than 0.1 %, or in a concentration equal to or higher than that specified under a specific note for the substance (in part 3 of Annex VI of the CLP regulations), shall bear the statement "EUH208 — 'Contains [name of sensitising substance]. May produce an allergic reaction'". This applies to all IT covered in this report, as they are all harmonized or self-classified as sensitising. However, the generic concentration limit is not applicable for MI, CMI/MI (3:1), MBIT, OIT and DCOIT as for these IT a specific concentration limit (SCL) is set at ≥ 0.0015% while for BIT this level is set at C ≥ 0.05% (Table 2).

Table 2 The isothiazolinones (IT) and their status under the REACH and CLP regulation. The CLP classification is depicted in italics when no harmonised (but notified) classification is present (November 2021). The hazard class on skin sensitisation (H317) is depicted in bold.

IT	**CAS No.**	**CLP classification for skin sensitisation, including applicable SCL**	**Harmonised *or notified***
MI	2682-20-4	Skin Sens. 1A (H317; C ≥ 0.0015%)	harmonised
CMI	26172-55-4	*Skin Sens. 1 (H317)*	*notified*
CMI/MI (3:1)	55965-84-9	Skin Sens 1A (H317; C ≥ 0.0015%)	harmonised
BIT	2634-33-5	Skin Sens. 1 (H317; C ≥ 0.05%)	harmonised
MBIT	2527-66-4	Skin Sens. 1A (H317; C ≥ 0.0015%)	harmonised

IT	CAS No.	CLP classification for skin sensitisation, including applicable SCL	Harmonised *or notified*
BBIT	4299-07-4	*Skin Sens. 1 (H317)*	*notified*
OIT	26530-20-1	Skin Sens. 1A (H317; C ≥ 0.0015%)	harmonised
DCOIT	64359-81-5	Skin Sens. 1A (H317; C ≥ 0.0015%)	harmonised

2.2.2 *Biocidal Product Regulation*

Preservatives in consumer products (excluding PCP) are often biocidal substances and subject to the Biocidal Product Regulation (BPR). Before the authorisation of such a biocidal product can be granted, the active biocidal substance needs to be approved (or under review) for the use in specific products (product types (PT)). Table 2 presents the status of the IT considered in this document under the BPR. The main group of preservatives consists of PT06 up to PT13.

*Table 3 The isothiazolinones (IT) and their status under the BPR with regard to the allowed product types (November 2021). X = approved; NA = applied for but not approved; * = Initial application for approval in progress.*

IT	Product Type (PT) [a]										
	disinfectants		*preservatives*								*other*
	02	**04**	**06**	**07**	**08**	**09**	**10**	**11**	**12**	**13**	**21**
MI			*					X	X	X	
CMI [b]			[b]								
CMI/MI (3:1)		X	X					X	X	X	
BIT	*		*			*	*	*	*	*	
MBIT			X							NA	
BBIT [c]			*	*		*	*			*	
OIT			*	*	X	*	*	*		*	
DCOIT				*	X	*	*	*			X

[a] PT02 = Disinfectants and algaecides not intended for direct application to humans or animals; PT04 = Food and feed area; PT06 = Preservatives for products during storage; PT07 = Film preservatives; PT08 = Wood preservatives; PT09 = Fibre, leather, rubber and polymerised materials preservatives; PT10 = Construction material preservatives; PT11 = Preservatives for liquid-cooling and processing systems ; PT12 = Slimicides; PT13 = Working or cutting fluid preservatives; PT21 = Antifouling products.
[b] CMI is authorized by National authorization in 10 EU Member States, including the Netherlands.
[c] BBIT concerns specifically 2-n-butyl-benzo[d]isothiazol-3-one (EC List no. 420-590-7).

Table 3 shows that, according to EU legislation, MI, CMI/MI, BIT, MBIT BBIT and OIT can be applied as preservatives for products during storage (PT06). In addition, CMI is also nationally authorized to be used as PT06 (Acticide C 1; NL-0026626-0000). DCOIT is not allowed to be used as preservatives for products during storage (PT06), but it can be present for instance in paint e.g. as film or wood preservative, or in

other products (e.g. as construction material preservative (PT10)) (Table 3).

2.2.3 *Regulatory context of the different product groups*

Personal care products

The use of substances in personal care products (PCP) is regulated via the Cosmetics Regulation (1223/2009/EC). The use of MI and CMI/MI (3:1) is allowed to be used up to 0.0015% in rinse-off products. The restriction on MI and CMI came into effect at January 1st 2018. Before 2018, MI was allowed up to 0.01% in both rinse-off and leave-on products; CMI/MI (3:1) was already restricted to 0.0015% in rinse-off products.
Single CMI as well as other IT are not allowed to be used in PCP (as they are not on Annex V of the Cosmetics Regulation).

Household cleaning products

The safety of household cleaning products (HCP) is ensured via the General Product Safety Directive (2001/95/EC); with additional regulations such as the Detergents Regulation (648/2004/EC) without specific restrictions to the level of preservatives. The safety of the level of preservatives used has been assessed via the assessment of the safety of the preservative ingredients, i.e. as biocides. According to the Detergents Regulation, preservatives that are added need to be indicated on the packaging regardless of their concentration.

DIY products (paints and glues)

Similar to HCP, the safety of Do-It-Yourself (DIY) products such as paints and glues is ensured via the General Product Safety Directive with several additional directives, but with no specific restrictions to the level of preservatives. The safety of the level of preservatives used has been assessed via the assessment of the safety of the preservative ingredients, i.e. as biocides.

Toys

Toys must fulfil the requirements of the Toy Safety Directive (2009/48/EC), in addition to other legislations that are applicable. With respect to migration of certain elements (not including preservatives) from toys, the Toy Safety Directive distinguishes three classes of toys: I dry, brittle, powder-like or pliable toy material; II. liquid or sticky toy material; and III. scraped-off toy material. Based on viscosity and structure, usually putty can be considered a category I product, and toy-slime can be considered a category II product.

According to Commission Directive EU 2015/2116 (2015) and Commission Directive EU 2015/2117 (2015) amending the Toy Safety Directive, MI, CMI and BIT should not be present in aqueous toys as they are known skin sensitisers and their limits are based on achievable limits of quantification, i.e. 0.25 mg/kg for MI, 0.75 mg/kg for CMI, 1 mg/kg for CMI/MI (3:1), and 5 mg/kg for BIT. These legal limits for MI, CMI and BIT, only apply to aqueous (i.e. category II) toys intended for children under three years of age and therefore not for toy-slimes, as they are intended for children over 3 years of age. There are no restrictions to MI, CMI and BIT to be used in non-aqueous (i.e. category

I) toy products such as putty. There are no restrictions to other IT to be used in aqueous toys intended for children.

For finger paint there are additional restrictions, laid down in a harmonized standard EN71-7, that contains a list of preservatives allowed for use in finger paint, and is regularly updated. Since the publication of EN71-7:2014+A1:2017 in 2017, none of the IT (MI, CMI and BIT, or any other IT) are on this list. Earlier, CMI/MI (3:1) and MI were allowed to be used in finger paint. At present (after March 2018) IT may not be used anymore in finger paints.
In contrast to finger paint, it is not obligatory to declare all preservatives on the label of toy-slime and putty products.

Outside the EU
When searching for literature sources about the presence of IT in products, it is important to realize that outside the EU other legislations (less or more restricted) are applicable. For instance, in the USA MI is considered safe for use in rinse-off cosmetic products at concentrations up to 0.01% and safe in leave-on cosmetic products when present in low non-sensitising concentrations, which may be determined based on a quantitative risk assessment of single products (Burnett et al., 2019). This is in contrast with the EU where MI is only allowed in rinse-off cosmetic products at concentrations up to 0.0015%. In toys, in South Korea, the use of IT is prohibited. Contradictory, in many other Asian regions the use of IT in toys is less strict than in the EU (Lim et al., 2021). In South Korea, CMI and MI are also prohibited in HCP (Sardar et al., 2020).

2.3 Exposure models

Two consumer exposure models are used in the current research: ConsExpo (Delmaar & Schuur, 2017) and the Probabilistic Aggregate Consumer Exposure Model (PACEM) (Delmaar et al., 2014; Dudzina et al., 2015).

ConsExpo is a widely-used consumer exposure model which development started in 1994 (https://www.rivm.nl/consexpo). ConsExpo allows users to estimate consumer exposure to a wide variety of (single) products in a wide variety of circumstances. ConsExpo estimates chemical exposure from consumer products containing the substance. ConsExpo considers single products, possibly with different application or exposure scenarios. The exposure assessments tend to estimate high end exposure in screening situations. However, ConsExpo does not consider simultaneous exposure to multiple products. Combining various exposure sources or pathways may be done by summing separate consumer exposure evaluations from specific scenarios. However, the resulting aggregate exposure will tend to represent the upper limits of the exposure, rather than realistic population levels.

PACEM is consumer exposure model that incorporates information on product usage to calculate the aggregate exposure to a substance via multiple products (https://www.rivm.nl/en/consumer-exposure-to-

chemical-substances/exposure-models/PACEM). In PACEM, product usage information is incorporated for various products, all PCP and HCP.

Since PACEM allows for aggregate exposure estimations, calculations in the current research were preferably performed using PACEM. However, product use data concerning some product groups containing IT (e.g., paint, toys and glue), product use data of children, and indirect or post-application exposure scenarios are not incorporated in PACEM. For those products, subpopulations and scenarios, exposure calculations were performed with the ConsExpo Web tool (version 1.0.7) (www.consexpoweb.nl).

3 Materials and methods

3.1 Selection of relevant products

Information on IT concentrations in consumer products were obtained from measurements and published literature. Product data obtained through the below mentioned sources were only included in the aggregate exposure analyses if data were available on the concentration of at least one of the three IT (MI, CMI or BIT). In addition, PCP concentration data were only included in the analyses if the measurements took place after January 1st 2018. This is because a new restrictive measure on MI and CMI concentrations was enforced at that time. Since then, the use of MI in PCP is further limited to a maximum of 15 ppm in rinse-off products and is banned from leave-on PCP. Finally, due to differences in regulations between continents (see section 2.2.3), concentration data for PCP, HCP and toys were only included if the measured product was produced in Europe.

Specifically, the following data sources were screened:
Measurement data:

- PCP, HCP, paints and toys (n=808) (NVWA, Personal communication, 2021)
- Slime & putty (n=58) (NVWA, Personal communication, 2021)
- PCP (n=414) (NVWA, Personal communication, 2021)
- PCP (n=65) (NVWA, Personal communication, 2021)

Data from literature:

- HCP (n=34) (Marrero-Alemán et al., 2020)
- HCP (n=72) (Garcia-Hidalgo et al., 2017)
- HCP (n=7) (Ezendam et al., 2018)
- Paint (n=61) (Thomsen et al., 2018)
- Paint (n=35) (Schwensen et al., 2015)
- Paint (n=63) (Goodier et al., 2018)
- Glue (n=37) (Goodier et al., 2019)

Since the main goal of this research is to determine the relative contributions of individual product groups to the aggregate exposure to IT using PACEM, products were categorized into groups according to the product types supported by PACEM. See Tables 5, 6 and 7 for the product groups included in the PACEM analyses.

Note that not for all product groups concentration data were available. Product groups without concentration data were left out of the analysis with PACEM. Moreover, it must be noted that not all products with measured IT concentrations fit the in PACEM available product groups. These products were paint (n=180), laundry products (n=24) and glue (n=37). For these products, exposure estimations were conducted either by using ConsExpo (for wall paint and laundry products), or calculated otherwise in the case ConsExpo was considered not appropriate either (in case of toys). In general, product use data of children as a population are not incorporated in PACEM. Therefore, the exposure of

children to PCP and post-application exposure to washed fabrics and cleaned floor was estimated using ConsExpo.

Table 4 summarizes the different models used in the current report to estimate the exposure of adults and children to particular product groups and to compare the results of the different product groups in order to determine their contribution to the total exposure. Specifically, PACEM was used to estimate consumer exposure to IT in PCP and HCP in an adult population. ConsExpo was used to estimate the exposure to IT in paint (adults) and laundry products (adults). Also, post-application exposure of children to IT in PCP after cleaning, is estimated with ConsExpo. This post-application exposure scenario is relevant for washed fabrics and cleaned floors.

Table 4 Summary of the use of PACEM and ConsExpo to estimate consumer exposure to various product types

	PCP	**HCP**	**Laundry product**	**Wall Paint**	**Toys**	**Glue**
Adults	PACEM	PACEM	ConsExpo	Cons-Expo	-	Cons-Expo
Children	Cons-Expo	Post-application exposure ConsExpo (floor cleaner)	Post-application exposure ConsExpo	-	Other	-

3.2 Product concentration data

3.2.1 PACEM

In order to estimate the consumer exposure to the three separate IT, PACEM was employed. PACEM requires two input parameters: the *occurrence* in which the substance of interest (i.e., MI, CMI or BIT) is present in products of a certain product group (e.g. body lotions, shampoos), and the *concentration* of the substance in the products that contain the substance. In this project, the occurrence was simply calculated by dividing the number of products in a product group that contain the IT of interest by the total number of products in the product group. Important to note here is that this procedure was also performed for product groups containing only one single product. The concentration required in PACEM was provided as a lognormal distribution. The geometric mean and geometric standard deviation of the IT of interest were calculated per product group. It is acknowledged that, particularly at low sample sizes, the sample mean may be a poor proxy of the true mean. However, since the aim of PACEM is to provide an estimate of the true exposure (rather than a conservative estimate) it was decided not to use a worst case mean (upper confidence limit of the mean). The upper confidence limit of the sample standard deviation (on log scale) was used to characterize the SD of the lognormal distribution. Small sample sizes result in larger SDs, i.e. wider concentration distributions. The upper confidence limit (on log-scale) was derived by:

$$\sqrt{\frac{(n-1)\times sd^2}{\chi^2_{1-p,n-1}}}$$

where *n* is the sample size, *sd* is the sample standard deviation on log scale and χ^2 is the quantile of the χ^2 distribution with *n-1* degrees of freedom, p is the required percentile of the upper confidence limit, which is set to 0.95 here. The upper confidence limit of the GSD was used for further exposure assessment (Ezendam et al., 2018). If a product group comprised only a single product containing an IT, a uniform distribution was used instead of a lognormal distribution. The upper and lower bounds of the uniform distribution were ten times higher or lower than the measured IT of interest in that product.

For HCP, IT concentrations were summarized as lognormal of uniform distributions as described above, but calculated based on combined product groups. Specifically, product groups representing products with the same type of use and exposure were combined, i.e., liquids, sprays and wipes. The IT concentration and occurrence calculated for these three groups were subsequently used in PACEM for all product groups that contain products with the same type of use and exposure. For example, the same IT concentration and occurrence for liquids were used as input values for all-purpose cleaner liquids, bathroom cleaner liquids, kitchen cleaner liquids, etc. Products with the same use type are likely to contain similar IT concentrations. The advantage of combining IT concentrations of products with the same use type is therefore that more data is available to estimate the IT concentration in those products. Tables 5, 6 and 7 show the data used to specify the product characteristics in PACEM for MI, CMI and BIT, respectively.

Table 5 Number of MI concentration measurements per product group (n) and input data used to calculate the aggregate exposure to MI in PACEM. The occurrence represents the percentage of measurements with a concentration >0. The geometric mean and geometric standard deviation of the lognormal distribution were calculated if more than one concentration measurement was available for a product group. If only a single measurement was available, a uniform distribution was taken with lower and upper boundaries that were are 10 times lower, or 10 times higher than the measured concentration, respectively.

			MI concentration per product group			
	n	**Occurrence (%)**	**Geometric mean* (µg/g)**	**Geometric standard deviation*** [†] **(µg/g)**	**Lower boundary* (µg/g)**	**Upper boundary* (µg/g)**
PCP						
Conditioner	13	15	1.6	1.2	n.a.	n.a.
Shower gel /foam/scrub	244	4	2.9	3.2	n.a.	n.a.
Eye pencil	1	100	n.a.	n.a.	0.05	5
Face cream day	30	3	n.a.	n.a.	9.0	900
Hand cream	49	27	1.5	2.5	n.a.	n.a.
Makeup remover	20	25	1.2	3.7	n.a.	n.a.
Mascara	3	33	n.a.	n.a.	0.32	32
Shampoo	226	8	4.0	4.0	n.a.	n.a.
Shaving gel	1	100	n.a.	n.a.	0.16	16

			MI concentration per product group			
	n	**Occurrence (%)**	**Geometric mean* (µg/g)**	**Geometric standard deviation*† (µg/g)**	**Lower boundary* (µg/g)**	**Upper boundary* (µg/g)**
HCP						
Liquids	71	55	13	5.5	n.a.	n.a.
Sprays	46	48	9.5	8.1	n.a.	n.a.
Wipes	6	33	91	4.9	n.a.	n.a.

n.a.: Not applicable; either the lognormal (i.e. geometric mean and geometric standard deviation) or the uniform distribution (i.e. lower bound and upper bound) is chosen.
* rounded to two significant digits
† Upper limit of the confidence interval

Table 6 Number of CMI concentration measurements per product group (n) and input data used to calculate the aggregate exposure to CMI in PACEM. The occurrence represents the percentage of measurements with a concentration >0. The geometric mean and geometric standard deviation of the lognormal distribution were calculated if more than one concentration measurement was available for a product group. If only a single measurement was available, a uniform distribution was taken with lower and upper boundaries that were are 10 times lower, or 10 times higher than the measured concentration, respectively.

			CMI concentration per product group			
	n	**Occurrence (%)**	**Geometric mean* (µg/g)**	**Geometric standard deviation*† (µg/g)**	**Lower boundary* (µg/g)**	**Upper boundary* (µg/g)**
PCP						
Conditioner	14	14	4.1	1.5	n.a.	n.a.
Shower gel /foam/scrub	249	4	4.3	1.7	n.a.	n.a.
Eye pencil	1	100	n.a.	n.a.	0.02	2.0
Face cream day	30	0	n.a.	n.a.	n.a.	n.a.
Hand cream	49	16	4.6	1.9	n.a.	n.a.
Makeup remover	20	10	4.2	3.9	n.a.	n.a.
Mascara	3	0	n.a.	n.a.	n.a.	n.a.
Shampoo	226	4	5.9	1.3	n.a.	n.a.
Shaving gel	1	0	n.a.	n.a.	n.a.	n.a.
HCP						
Liquids	71	15	2.5	6.2	n.a.	n.a.
Sprays	46	5	0.30	8.5	n.a.	n.a.
Wipes	6	14	n.a.	n.a.	0.01	1.0

n.a.: Not applicable; either the lognormal (i.e. geometric mean and geometric standard deviation) or the uniform distribution (i.e. lower bound and upper bound) is chosen.
* rounded to two significant digits
† Upper limit of the confidence interval

Table 7 Number of BIT concentration measurements per product group (n) and input data used to calculate the aggregate exposure to BIT in PACEM. The occurrence represents the percentage of measurements with a concentration >0. The geometric mean and geometric standard deviation of the lognormal distribution were calculated if more than one concentration measurement was available for a product group. If only a single measurement was available, a uniform distribution was taken with lower and upper boundaries that were are 10 times lower, or 10 times higher than the measured concentration, respectively.

			BIT concentration per product group			
	n	**Occurrence (%)**	**Geometric mean* (µg/g)**	**Geometric standard deviation*† (µg/g)**	**Lower boundary* (µg/g)**	**Upper boundary* (µg/g)**
PCP						
Conditioner	7	0	n.a.	n.a.	n.a.	n.a.
Shower gel/foam/scrub	222	0	n.a.	n.a.	n.a.	n.a.
Eye pencil	0	0	n.a.	n.a.	n.a.	n.a.
Face cream day	7	0	n.a.	n.a.	n.a.	n.a.
Hand cream	12	0	n.a.	n.a.	n.a.	n.a.
Makeup remover	1	0	n.a.	n.a.	n.a.	n.a.
Mascara	0	0	n.a.	n.a.	n.a.	n.a.
Shampoo	206	0	n.a.	n.a.	n.a.	n.a.
Shaving gel	1	0	n.a.	n.a.	n.a.	n.a.
HCP						
Liquids	68	35	30	4.7	n.a.	n.a.
Sprays	44	43	19	3.2	n.a.	n.a.
Wipes	6	33	120	1.8	n.a.	n.a.

n.a.: Not applicable; either the lognormal (i.e. geometric mean and geometric standard deviation) or the uniform distribution (i.e. lower bound and upper bound) is chosen.
* rounded to two significant digits
† Upper limit of the confidence interval

3.2.2 Aggregation of IT exposure

The aforementioned procedure and product data were used to estimate consumer exposures separately for each IT. In order to estimate the aggregate consumer exposure to the three IT (MI, CMI, BIT), the potency of the different IT needs to be considered. As described in section 2.1.1, the potency of each IT was calculated relative to MI. These relative potency factors were as follows (see section 2.1.3):

- MI: 1
- CMI: 40
- BIT: 0.04

The relative potency factors were used to perform a weighted summation of all measured IT concentrations per product. This weighted sum represented the total MI equivalent concentration in the product. If information on any of the three IT concentrations in a product was missing, it was assumed that those IT were not present in the product.

After deriving the MI equivalent concentrations in all consumer products, the PACEM procedure to estimate consumer exposure was repeated, but now for MI equivalents in consumer products instead of separate IT. The occurrence required in PACEM was calculated by dividing the products in a product group that contain one or more IT by the total number of products in the product group. The geometric mean and geometric standard deviation of the lognormal distribution were calculated based on the MI equivalent concentration per product group. If a product group comprised only a single product containing IT, a uniform distribution was used instead of a lognormal distribution. The upper and lower bounds of the uniform distribution were taken ten times higher or lower than the measured MI equivalent in that product. Finally, the aforementioned workflow for HPC was also employed to calculate the consumer exposure to MI equivalent. The resulting MI equivalent concentration characteristics used for the PACEM calculations are shown in Table 8.

Table 8 Number of measured MI-equivalent concentrations per product group (n) and input data used to calculate the aggregate exposure to MI-equivalents in PACEM. The occurrence represents the percentage of measurements with an MI-equivalent concentration >0. The geometric mean and geometric standard deviation of the lognormal distribution were calculated if more than one concentration measurement was available for a product group. If only a single measurement was available, a uniform distribution was taken with lower and upper boundaries that were are 10 times lower, or 10 times higher than the measured concentration, respectively

	n	**Occurrence (%)**	**Geometric mean* (µg/g)**	**Geometric standard deviation*† (µg/g)**	**Lower boundary* (µg/g)**	**Upper boundary* (µg/g)**
PCP						
Conditioner	14	14	160	1.5	n.a.	n.a.
Shower gel/foam/scrub	253	6	58	8.0	n.a.	n.a.
Eye pencil	1	100	n.a.	n.a.	0.85	85
Face cream day	30	3	n.a.	n.a.	9.0	900
Hand cream	49	27	24	17	n.a.	n.a.
Makeup remover	20	25	7.2	25	n.a.	n.a.
Mascara	1	100	n.a.	n.a.	0.32	32
Shampoo	226	8	50	9.0	n.a.	n.a.
Shaving gel	1	100	n.a.	n.a.	0.16	16
HCP						
Liquids	72	63	26	5.6	n.a.	n.a.
Sprays	46	57	8.2	8.0	n.a.	n.a.
Wipes	7	38	40	6.4	n.a.	n.a.

n.a.: Not applicable; either the lognormal (i.e. geometric mean and geometric standard deviation) or the uniform distribution (i.e. lower bound and upper bound) is chosen.
* rounded to two significant digits
† Upper limit of the confidence interval

3.2.3 ConsExpo

IT concentrations in PCP relevant for children

To estimate children's dermal exposure to IT from PCP, first the relevant products used by children were selected. Ficheux et al. (2015) have reported that the fraction of baby girls and boys (0-3 years old) using shampoo is 100% and 98%, respectively. They further reported that 90% of the baby girls and 88% of the baby boys use shower gel/foam/scrub (Ficheux et al. 2015). As shampoo and shower gel/foam/scrub were used by a high fraction of babies (0-3 years), these product were identified as relevant. The measured IT concentration data from the NVWA in shampoo and shower gel/foam/scrub were used although these products are not specifically intended for children. We assume that children use specific PCP for children with the same concentration of IT as products for adults. Therefore the IT concentrations in products for adults are used for the calculation for children. A small percentage of the measured shampoos and shower gel/foam/scrubs were preserved with at least one IT (see detailed information in Annex I, Table A1 and A2). Shampoo had a slightly higher percentage of IT (8.0%) than shower gel/foam/scrub (5.5%). In both shampoo and shower gel/foam/scrub, CMI was found most frequent in combination with MI. For the exposure estimation with ConsExpo the median concentration (and arithmetic coefficient of variation (CV)) is required to estimate the log normal distribution of the dermal load per event (Table 9).

IT concentrations in laundry products and floor cleaners

Data on IT concentration in laundry products and floor cleaners were obtained from NVWA measurements, Marrero-Aleman et al. (2020), Garcia-Hidalgo et al. (2017) and Ezendam et al. (2018). The IT concentration in floor cleaners is based on IT concentrations of all liquid cleaning products. BIT was most frequently found in laundry products (71%) with a median concentration (arithmetic CV) of 24 (±1.5) mg/kg. BIT was less frequently found in floor cleaners (35%) with a relatively higher median concentration (arithmetic CV) (35 (±0.91) mg/kg) (see detailed information in Annex I, Table A3 and A4). The occurrence of MI (58%) and CMI (21%) in laundry products was comparable with the occurrence in floor cleaners (55% and 15% respectively). MI was found more often and at higher median concentration then CMI in laundry products: 15 (±0.94) and 11 (±0.81) mg/kg, respectively. In floor cleaner the concentrations found were 24 (±1.2) mg/kg for MI and 6.3 (±0.57) mg/kg for CMI. For the exposure estimation with ConsExpo the median concentration (arithmetic CV) are required to estimate the log normal distribution of the dermal load (Table 9).

IT concentrations in wall paints

In earlier reports of Thomsen et al. (2018) and Schwensen et al. (2015) concentrations of IT in wall paints were described that were bought in five different EU countries (Denmark, France, Germany, Sweden, and the UK) in the years 2016 and 2013/2014, respectively. Goodier et al. (2018) reported IT concentrations in wall paints bought in 2017 in Minnesota, USA. These data were combined with the NVWA measurements in 4 different products (7 samples) (see detailed information in Annex I, Table A5).

Over 90% of the wall paints contained BIT and/or MI, at relatively high concentrations up to 1111 and 940 mg/kg, respectively. On average, concentrations of 116 mg/kg BIT and 83.8 mg/kg MI were found. A smaller number of wall paints (18%) contained CMI, with an average of 2.92 mg/kg CMI and a maximum of 13.1 mg/kg CMI. In all wall paints containing CMI also MI was present.

Besides MI, CMI and BIT, Thomsen et al. (2018) also analysed other isothiazolinones, i.e. OIT and DCOIT. OIT was present in 27% of the wall paints, at levels of 0.03-16 mg/kg. DCOIT was present in 50% of the wall paints, at levels of 0.01-160 mg/kg. Goodier et al. (2018) also analysed OIT, but only detected OIT in 1 out of 47 (2.1%) wall paints analysed, at a concentration of 43 mg/kg. However, OIT and DCOIT are not included in the current exposure calculations.

For the calculation of the overall exposure from products, the MI-equivalent median (and arithmetic CV) concentration from wall paint was determined at 76.5 mg/kg (±1.18) (Table 9).

IT concentrations in glues
To assess the dermal exposure from DIY glue, data from an American study by Goodier et al. (2019) were used. IT concentrations in 37 different types of glues bought in Minnesota, USA in 2017 were analysed including one product with two components which were analysed separately. Different application purposes of the products were reported: all-purpose glue (n=12), glue for school (n=10), wood (n=5), craft (n=5), fabric (n=4), eyelash (n=1) and shoe (n=1) (Goodier et al., 2019). The product intended to be used on eyelashes was excluded, as it was not considered a DIY product but a cosmetic, and is intendedly applied to the skin (this product does not contain the IT analysed).

Over 51% of the glues contained BIT and/or MI, at concentrations up to 87 and 133 mg/kg, respectively. On average, concentrations of 56 mg/kg BIT and 25 mg/kg MI were found. Of the glues analysed 32% contained CMI, up to a concentration of 28 mg/kg and an average of 17 mg/kg CMI. In all glues containing CMI, also MI was present (see detailed information in Annex I, Table A6).

Apart from MI, CMI and BIT, Goodier et al. (2019) analysed other isothiazolinones, i.e. OIT and BBIT. OIT was present in one sample with a concentration of 1.5 mg/kg; BBIT was not present in any glue sample.

For the calculation of the overall exposure from products, the calculated MI-equivalent median (and arithmetic CV) value from glue was determined at 365 mg/kg (±0.88) (Table 9).

Table 9 Concentration data used to calculate the exposure to IT from various products with ConsExpo.

Products	**Median (mg/kg) (±arithmetic CV)**			
	MI-equivalent	**MI**	**CMI**	**BIT**
Shampoo	170 (±0.80)	2.8 (±2.2)	5.8 (±0.23)	**-**
Shower gel/foam/scrub	130 (±0.78)	2.6 (±2.3)	4.1 (±0.47)	-
Laundry product	20 (±2.0)	15 (±0.94)	11 (±0.81)	24 (±1.5)
Floor cleaner	34 (±1.3)	24 (±1.2)	6.3 (±0.57)	35 (±0.91)
Wall paint	76.5 (±1.18)	55.5 (±1.22)	1.4 (±1.2)	85.6 (±1.07)
Glue	365 (±0.88)	12.8 (±1.19)	18.6 (±0.43)	68.8 (±0.53)

3.2.4 Additional calculations (without PACEM or ConsExpo)

IT concentrations in toys

IT can be found as preservatives in toys, such as toy-slime and putty (den Braver et al., 2021; O'Hern et al., 2021). The data on toy-slime and putty were derived from a specific sampling in 2019 which was performed at 14 different Dutch toy and department stores by the NVWA. These data were also used in an earlier assessment on boron in toy-slime and NDELA in putty (den Braver et al., 2021). This data set consisted of in total 23 toy-slimes and 16 putties, which came from 19 different producers, importers or distributers. These samples were taken from all brands and producers and are therefore are a good representation of the Dutch market. Some toy packages contained more than one sample (i.e. several colours); these subsamples were also analysed. A total of 29 samples for toy-slime and 22 samples for putty were analysed. Some of the products were labelled as toy-slime, but appeared to be a putty and vice versa. Therefore, the samples were categorized as category I (dry, brittle, powder-like or pliable toy material) and category II (liquid or sticky toy material) according to the explanatory guidance document of the Toy Safety Directive (2009/48/EC), based on the viscosity and structure which was analysed. The category I toy-slime and putty products were considered putty, the category II toy-slime and putty products were considered toy-slime. This differentiation is important as for the exposure calculation performed different skin adhesion rates are used for putty and toy-slime.

To acquire a larger data set, additional measurements from sampling on the Dutch market during 2016-2020 were added. This yielded seven additional putty samples and eight additional toy-slime samples, which were added to the other sets based on their description (i.e. name), as their viscosity and structure were not analysed. A recent data set by Lim et al. (2021) with toy-slime from different Asian regions was excluded, as the legislation regarding the use of IT in toys in Asia is different from the EU.

Data on finger paint was acquired on the Dutch market during 2015 (29 products), before the prohibition of the use of MI and CMI/MI in finger

paint. Some additional samples of finger paint acquired during 2016-2020 did not contain MI, CMI or BIT. Therefore, finger paint was not considered a source of exposure to IT from toys in the present document.

In none of the putty and toy-slime samples, BIT was found (see detailed information in Annex I, Table A7 and A8). Roughly a third of all toy samples analysed contained MI in concentrations, ranging from 0.50 up to 27 mg/kg. A smaller number of samples contained CMI, in concentrations ranging from 2.4 up to 38 mg/kg. All CMI containing samples also contained MI, except one (a putty).

The concentration data used for the exposure calculations from putty and toy-slime are summarized in Table 10. More details calculated from the measured concentrations of MI, CMI and BIT in the different putty and toy-slimes can be found in Annex I, Table A7 and A8, respectively.

Table 10 Concentration data used for the additional calculations (without PACEM or ConsExpo).

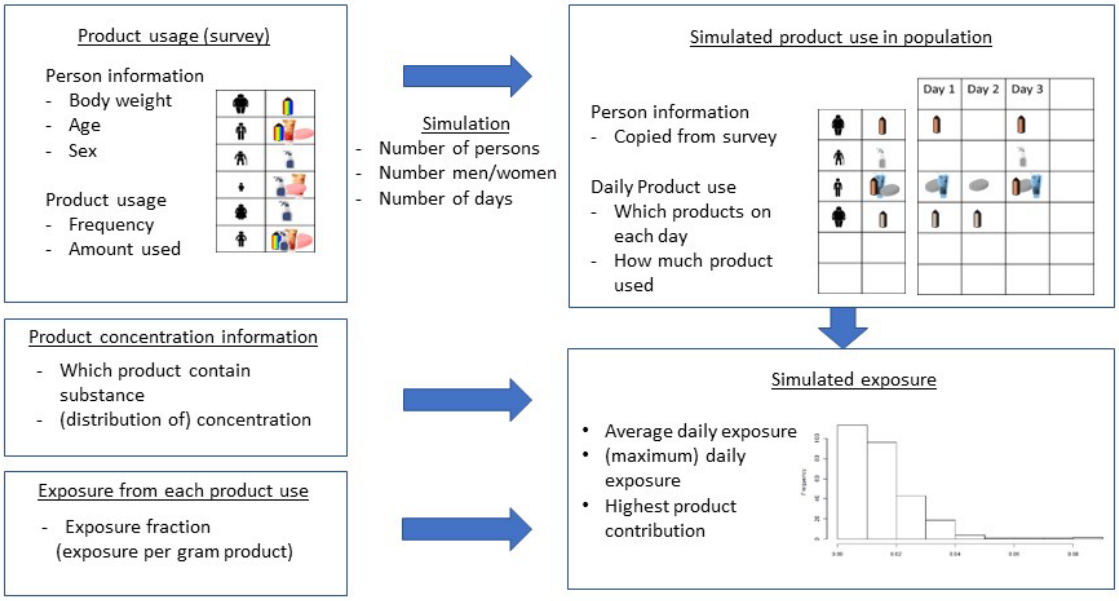
Product	**Median (mg/kg)**				**95th percentile (mg/kg)**			
	MI-equivalent	**MI**	**CMI**	**BIT**	**MI-equivalent**	**MI**	**CMI**	**BIT**
Putty	268	8.1	13.9	0	1157	25.0	28.6	0
Toy-slime	6.9	4.0	4.6	0	1114	25.6	33.8	0

3.3 Exposure calculations and parameters

3.3.1 PACEM

PACEM uses previously acquired product use data obtained from surveys in order to probabilistically estimate exposure to individuals of a population. Currently, product use information is available in PACEM from five different countries, i.e. France, Germany, Spain, United Kingdom and the Netherlands. Since this report focusses on dermal exposure to IT of the Dutch population, the Dutch survey data set was selected to perform the aggregate exposure calculations. In addition, the dermal load was chosen as exposure metric.

In PACEM, the product use data obtained from surveys are used to simulate daily exposure to a product of interest (Figure 2). Specifically, a 14-day period is simulated during which individuals may or may not use a certain product. For each day in this period, and for each individual in the population, the use of a product is randomly sampled with a probability p. This probability is equal to the use frequency reported in the survey.



$$\text{Exposure} = \frac{\text{Amount x Frequency x Weight fr. x Exposure fraction (x Absorption)}}{\text{Body weight}}$$

Figure 2 General overview of the workflow in PACEM. From the use survey(s) (top left box) the product use of a population is simulated (top right box). For each individual, day, and product, the exposure is calculated from the use amount, use frequency, product concentration (middle left box), retention factor (bottom left box) and skin surface area. For each individual and day the results are aggregated and summarized in a fashion that suits the research question. In the current report a distribution is provided of the individual's highest daily dermal load of the highest exposed body part (bottom right box).

This sampling step results in a set of simulated product uses for each individual in the population. The exposure of an individual to the substance of interest is estimated by taking into account the frequency in which the substance was present in the product (i.e., the occurrence) and the concentration in which the substance is found in the products containing the substance. The occurrences and concentrations used to perform the calculation were estimated using the measured data and literature available, which is described in section 3.2.1, Tables 5, 6 and 7.

Besides the occurrence and the concentration, PACEM also requires a retention factor when estimating the dermal load. The retention factor indicates the fraction of the substance that remains on the skin after an exposure event. In this report, default retention factors were used as provided by PACEM. The retention factors for eye pencils and mascara, for which no default values are provided in PACEM, were set to 1 for the head area and 0 for other body areas. A retention factor of 1 indicates that the substance is retained on the skin for the entire day, which in principle translates to a worst case scenario. Nevertheless, given the typical use of eye pencils and mascara, this assumption seems probable.

After calculating the exposure to a substance following an exposure event, the exposures are aggregated. It is important to note that the time frame of aggregation is one calendar day, which means that all exposures that take place on the same calendar day are aggregated, whereas the exposures are treated as distinct when they occur on different days. Since the simulation duration in PACEM is always 14 days, 14 different aggregate exposures are estimated for each individual in the population.

PACEM provides two ways of expressing the dermal load based on the aggregate daily exposures. The first is the average dermal load, which means that the 14 daily exposures are averaged for each individual. The second is to show the peak dermal load, which is the highest dermal load obtained on a single day, within the simulation period. Since this report focuses on skin sensitisation following exposure to IT, the peak dermal load has been chosen. The dermal load of the entire simulated (adult) population is derived including individuals who may not use any IT containing products.

3.3.2 ConsExpo exposure scenarios

Children's exposure to IT in PCP

ConsExpo was used to assess the potential dermal exposure of children to IT in PCP. As mentioned before, only shampoo and shower gel/foam/scrub are relevant IT containing PCP for children. The *direct contact model – instant application* is used to assess the dermal exposure as suggested as default model in Cosmetics Fact Sheet (Bremmer et al., 2006). The Cosmetics Fact Sheet presents specific (default) estimations for shampoo and shower gel/foam/scrub during showering regarding the amount of product used for adults.
For children, different input parameters were used:

- amount of shampoo and shower gel/foam/scrub applied is 13 g and 2.3 g, respectively, obtained from Gosens et al. (2014).
- applied surface area for shampoo is 430 cm^2, based on both hands and half of the head surface area of a child of 1-2 years old = 230 cm^2 for hands and 400 cm^2 for head as described in the ConsExpo General Fact Sheet (te Biesebeek et al., 2014).
- applied surface area for shower gel/foam/scrub is 4800 cm^2 based on total body surface area of a child 1-2 years old as described in the ConsExpo General Fact Sheet (te Biesebeek et al., 2014).

For all default values used in the exposure scenario, see Annex II, Table A9 and A10. In this scenario a lognormal distribution for weight fraction is used by using 100,000 iterative calculations.

Adult's and children's exposure to IT in laundry product

Liquid laundry detergent is a concentrated product that is typically used in washing machines where it is diluted during the washing cycle. Dermal exposures for the scenarios mixing and loading and hanging of machine-washed laundry were evaluated. Default parameters used for this typical liquid laundry detergent scenario were obtained from the Cleaning Products Fact Sheet (Meesters et al., 2016) (for default values see Annex II, Table A11 and A12).

In addition, regular liquid laundry detergents were used for hand washing of clothing. Dermal exposures associated with hand-washed laundry during mixing and loading, hand-washing, and hanging of hand-washed laundry were evaluated based the default values provided in the Cleaning Products Fact Sheet (Meesters et al., 2016) (for default values see Annex II, Table A11, A13 and A14).

Also, post-application exposure is expected for adults and children through wearing washed clothes with laundry product residues that migrate from the fabric to the skin. Dermal exposure was evaluated for the machine-washed and hand-washed scenarios for both an adult and a child. For the post-application migration from washed fabrics, the leachable fraction of concentrated machine-washing laundry detergent and of regular hand-wash laundry detergent was calculated with the following equations: 0.000045 x W_f and 0.00088 X W_f, respectively (as described in the Cleaning Products Fact Sheet). For the weight fraction, the median concentration as shown in Table 9 is used. Table 11 shows the calculated leachable fraction of regular liquid and concentrated liquid detergents. For all default values used in the exposure scenario, see Annex II, Table A15 and A16.

Table 11 Leachable fraction (-) used to calculate the exposure to IT from laundry products in ConsExpo.

	MI-eq	**MI**	**CMI**	**BIT**
Leachable fraction regular liquid	$1.7x10^{-8}$	$1.4x10^{-8}$	$9.8x10^{-9}$	$2.1x10^{-8}$
Leachable fraction concentrated liquid	$8.9x10^{-10}$	$6.9x10^{-10}$	$5.0x10^{-10}$	$1.1x10^{-9}$

Children's post-application exposure to IT in liquid floor cleaner
A post-application exposure to liquid floor cleaners is expected, since a treated floor is accessible to small children. This form of post-application exposure is estimated using the *dermal–direct product contact–rubbing off* model of ConsExpo as described in the Cleaning Products Fact Sheet (Meesters et al., 2016). The values for the relevant parameters are described in this fact sheet as well (see Annex II, Table A17). Also in this scenario a lognormal distribution for weight fraction is used by using 100,000 iterative calculations.
Adults are assumed not to have close dermal contact with recently cleaned floors, and consequently their dermal post-application exposure is not calculated.

Adult's exposure to IT in wall paint
The dermal exposure of adults through the application of wall paint was calculated using the *brush and roller painting, water borne wall paint application* scenario in the ConsExpo Paint products Fact Sheet (Bremmer & van Engelen, 2007). The values for the relevant parameters are described in this fact sheet as well (see Annex II, Table A18). For the IT concentration data, the lognormal distribution is chosen as appropriate, using the median and the covariance of variation. For

loading the *constant rate* mode is used. In order to calculate the dermal load, a conservative skin surface area of both hands (adults), i.e. 860 cm^2 (te Biesebeek et al., 2014) is chosen as appropriate. Children are assumed not to paint walls and consequently their dermal exposure due to painting walls is not calculated. In addition, it is assumed that dermal post-application exposure to IT from paint is not relevant for children nor adults .

Adult's exposure to IT in glue
Dermal exposure of adults to IT through the application of glue was calculated using the *glues, bottled glue – universal/wood glue application* scenario in the ConsExpo Do-It-Yourself Fact Sheet (Ter Burg et al., 2007). The values for the relevant parameters are described in this fact sheet as well (see Annex II, Table A19). For the IT concentration data the lognormal distribution is chosen as appropriate, using the median and the covariance of variation. For loading the *instant application* mode, with an exposed area of 2 cm^2 and a product amount of 0.08 gram as input parameters (Ter Burg et al., 2007) is chosen as appropriate.
Children are assumed not to use glue for adults (unintended use) and consequently their dermal exposure due to gluing is not calculated. In addition, it is assumed that dermal post-application to IT from glue is not relevant for children nor adults. Children can also use specific glue intended for children, however, that scenario has not been calculated in the present exposure estimation.

3.3.3 Additional calculations (without PACEM or ConsExpo)

Toys
We acquired data from putty and toy slime. Putty and toy-slime are toys intended for children >3 years.

As the dermal exposure from toys is highly dependent on the migration of substances from toys and the possible adhesion of toy material to the skin, the current ConsExpo Children's toys Fact Sheet only provides general guidance to calculate exposure from toy products such as putty (Bremmer & van Veen, 2002). Therefore, dermal exposure from toy-slime and putty is calculated in the current report similarly to an exposure estimation from slime and putty as performed recently (den Braver et al., 2021). In this method skin adhesion factors as reported by Guak et al. (2018) were used. Based on this Korean behavioural study, the following values were selected for the skin adhesion rate: 1.3×10^{-6} kg/min/cm^2 for toy-slime (highest value out of four slimes) and 5.4×10^{-7} kg/min/cm^2 (PVA soft clay) for putty (Guak et al., 2018).

The dermal load was calculated according to the following formula (Guak et al., 2018):

Dermal load: $L_D = [N] \times t \times H_t$

with:

L_D	dermal load (mg/cm^2)
[N]	concentration of substance (mg/kg)
t	exposure time (min/playing event)
H_t	skin adhesion rate (kg/min/cm^2)

According to a Korean behavioural study consisting of 1000 children in the age of 3-12 years, children play with toy-slime on average once a week with a median duration of the playing activity of 15 to 20 min (Park et al., 2018). For frequency and exposure time, the highest 75th percentiles for this age group are 3 times a week and 30 min per playing event; therefore 30 minutes is taken as exposure time. For the exposure estimation, it is assumed that the playing behaviour is comparable for putty. The median and 95th percentile value of the concentrations of the different IT are used for the exposure calculation for putty and toy-slime.

4 Results

4.1 Exposure assessment for IT exposure in adults

4.1.1 Aggregate exposure assessment

Table 12 shows the aggregate exposure to IT in adults expressed as dermal load (µg/cm^2). The dermal load was estimated for MI equivalents as well as for the three separate IT (i.e. MI, CMI and BIT). Note that the dermal loads are estimated for a population, and the presented dermal loads correspond with the 50th (i.e. median) and 95th percentile of the population. A person that falls in the 95th percentile of MI exposure does not necessarily also fall in the 95th percentile of CMI and BIT exposure. The total MI-equivalent dermal load is thus not necessarily equal to the sum of the separate exposures to MI, CMI and BIT. The results presented in Table 12 demonstrate that the aggregate adult exposure to IT, expressed as MI-equivalents, is comparable for personal care products (PCP) and household cleaning products (HCP) when considering the 95th percentiles of the population. This indicates that exposure to IT is not primarily driven by either PCP nor HCP. Nevertheless, there are differences in the number of exposed people in the population between the two product groups. As the estimated median exposure to MI-equivalent through HCP was zero, it can be concluded that more than half of the population was **not** exposed to IT via HCP. This is in contrast to PCP where the estimated median exposure was higher than zero, indicating that more than half of the population is estimated to be exposed to IT via PCP. The reason for this is probably related to an intrinsic model assumption of PACEM. In fact, PACEM assumes that HCP are only used by one of two adults in a household, resulting in at least half of the population not being exposed to IT via HCP.

Despite the similarities in the MI-equivalent exposure, substantial differences were found when assessing the estimated exposure to the separate IT. As BIT is not allowed to be used in PCP, exposure to BIT through PCP was estimated to be zero. In addition, the estimated exposure to CMI was lower than the estimated exposure to MI, for both the HCP and the PCP. However, despite the lower exposure to CMI, it is expected that the contribution of CMI to the MI-equivalent exposure is similar or higher than that of MI, due to the higher relative potency of CMI.

4.1.2 Exposure assessment for single products

Besides the aggregate exposure to IT via PCP and HCP, Table 13 also presents a summary of IT exposure estimates in adults via laundry products, wall paint and glue. The estimated dermal loads demonstrate that glues and wall paints may be major contributors to the IT exposure for adults when considering such single products. In particular glue seems to be an important contributor with an estimated 95th percentile of the MI-equivalent exposure that is approximately 30 times higher than that estimated for wall paint, assuming a similar level of conservatism in both exposure calculations. This finding may be partially explained by the fact that the MI-equivalent concentration in glue is about five times higher than that in wall paint (Table 13).

Besides glues and wall paints, exposure to IT through laundry detergents also results in a relatively high dermal load when considering certain scenarios. In fact, the 'pouring with cap' scenario resulted in dermal loads that were comparable to those estimated for wall paints and are substantially higher than those estimated for the 'handwashing' scenario. This finding can be explained by the description of the scenarios. In the 'pouring with cap' scenario, a high concentration of the detergent is assumed to be spilled on a relatively small area of the hand, resulting in a high dermal load. In contrast, during hand washing, the detergent is diluted in water and exposure is assumed to occur over a larger skin area, i.e. the surface of the entire hands and forearms, subsequently resulting in lower dermal loads.

4.2 Exposure assessment for IT exposure in children

4.2.1 Exposure assessment for single products

Table 13 shows the dermal exposure estimates for IT exposure in children via shampoo, shower gel/foam/scrub, putty and toy-slime as well as post-application exposures via washed fabric and cleaned floor. The dermal exposure via shampoo was approximately two orders of magnitude higher than that via shower gel/foam/scrub, as more shampoo is used per event on a smaller area. The estimated dermal exposure via shampoo is comparable to that via putty and toy slime, which indicates that toys can also be potentially relevant contributors to the total IT exposure, assuming a similar level of conservatism in the exposure calculations. The estimated post-application exposures from laundry product and floor cleaner are multiple orders of magnitude lower than the exposure to shampoo, putty and toy slime.

4.3 Summary of exposure estimations

Table 12 Summary of exposure estimations for adults (including non-consumers) expressed as dermal load (µg/cm²) via various sources; product groups in case calculated with PACEM and single products in case calculated with ConsExpo. The dermal load derived with PACEM is based on survey information of use amount, use frequency and body weight, and a lognormal distribution for weight fraction. For other inputs (e.g. retention factors) point values are applied. The dermal load derived with PACEM represents the dermal load of the general population including non-consumers. The distribution reflects the variability and uncertainty of the dermal load in the general population. The dermal load derived with ConsExpo is based on a lognormal distribution for weight fraction. For all other inputs point values are applied. Due to the (reasonable) worst-case values used for most inputs the dermal load obtained from ConsExpo is considered representative for a high exposed individual. The distribution reflects the uncertainty of the dermal load of the highly exposed individual due to variation in IT concentration. The estimated MI-equivalent dermal load was compared to the AEL of MI (7.4 × 10^{-2} µg/cm²). The dermal loads associated with exposure to MI, CMI and BIT were compared to the AEL of MI (7.4 × 10^{-2} µg/cm²), AEL of MI/CMI mixture (4.2 × 10^{-3} µg/cm²), and the AEL of BIT (0.15 µg/cm²). Values matching or exceeding the AEL are marked in red. Additional exposure percentiles are reported in Annex III.

Source	**Product use stage**								
		MI-equivalent		**MI**		**CMI**		**BIT**	
		Median	**P95**	**median**	**P95**	**median**	**P95**	**median**	**P95**
Aggregate exposure assessment		*Dermal load (µg/cm²) of general population*							
PCP	-	1.0 × 10^{-4}	0.16	5.3 × 10^{-7}	6.7 × 10^{-3}	0	3.4 × 10^{-3}	0	0
HCP	-	0	0.15	0	8.4 × 10^{-2}	0	9.1 × 10^{-4}	0	0.37
Total of PCP and HCP		7.3 × 10^{-4}	0.47	1.2 × 10^{-4}	8.8 × 10^{-2}	0	7.6 × 10^{-3}	0	0.37
Exposure assessment to single products		*Dermal load (µg/cm²) of high exposed individuals*							
Hand washing liquid, regular	Mixing & Loading, pouring with cap	0.20	1.7	0.15	0.59	0.11	0.39	0.24	1.4
	Hand washing	1.7 × 10^{-3}	1.4 × 10^{-2}	1.4 × 10^{-3}	5.4 × 10^{-3}	9.9 × 10^{-4}	3.4 × 10^{-3}	2.1 × 10^{-3}	1.2 × 10^{-2}

Source	Product use stage	MI-equivalent		MI		CMI		BIT	
		Median	**P95**	**median**	**P95**	**median**	**P95**	**median**	**P95**
	Hanging hand-washed laundry	1.7×10^{-3}	3.5×10^{-2}	1.3×10^{-3}	5.3×10^{-3}	9.7×10^{-4}	3.5×10^{-3}	2.1×10^{-3}	1.2×10^{-2}
Machine-washing liquid, concentrated	Mixing & Loading, pouring with caps	0.20	1.7	0.16	0.60	0.11	0.41	0.24	1.4
	Hanging machine-washed laundry	9.1×10^{-5}	7.6×10^{-4}	7.2×10^{-5}	2.8×10^{-4}	5.2×10^{-5}	1.9×10^{-4}	1.1×10^{-4}	6.7×10^{-4}
Wall paint		0.32	1.4	0.23	1.1	5.7×10^{-3}	2.7×10^{-2}	0.36	1.5
Glue		14	50	0.51	2.4	0.75	1.5	2.8	6.5
Post-application exposure		*Realistic worst-case estimate of the dermal load (µg/cm²)*							
Hand washing liquid, regular	Post-application hand washed laundry*	8.2×10^{-4}		6.4×10^{-4}		4.6×10^{-4}		9.8×10^{-4}	
Machine-washing liquid, concentrated	Post-application machine washed laundry*	4.2×10^{-5}		3.2×10^{-5}		2.4×10^{-5}		5.2×10^{-5}	

* Leachable fraction is calculated with median concentration

Table 13 Summary of exposure estimations for children expressed as dermal load (µg/cm²) via various sources; all single products calculated with ConsExpo. The dermal load derived with ConsExpo is based on a lognormal distribution for weight fraction. For all other inputs point values are applied. Due to the (reasonable) worst-case values used for most inputs the dermal load obtained from ConsExpo is considered representative for a high exposed individual. The distribution reflects the uncertainty of the dermal load of the high exposed individual due to variation in IT concentration. The estimated MI-equivalent dermal load was compared to the AEL of MI (7.4×10^{-2} µg/cm²). The dermal loads associated with exposure to MI, CMI and BIT were compared to the AEL of MI (7.4×10^{-2} µg/cm²), AEL of MI/CMI mixture (4.2×10^{-3} µg/cm²), and the AEL of BIT (0.15 µg/cm²). Values matching or exceeding the AEL are marked in red. Additional exposure percentiles are reported in Annex III.

Source								
	MI-equivalent		**MI**		**CMI**		**BIT**	
	median	**P95**	**median**	**P95**	**median**	**P95**	**median**	**P95**
Exposure assessment to single products	*Dermal load (µg/cm²) of high exposed individuals*							
Shampoo	5.3	17	8.4×10^{-2}	0.75	0.18	0.26	-	-
Shower gel/foam/scrub	6.2×10^{-2}	0.20	1.2×10^{-3}	1.2×10^{-2}	2.0×10^{-3}	4.2×10^{-3}	-	-
Post-application of cleaned floor	4.5×10^{-4}	2.3×10^{-3}	3.3×10^{-4}	1.6×10^{-3}	8.3×10^{-5}	2.1×10^{-4}	4.6×10^{-4}	1.6×10^{-3}
Putty	4.3	19	0.13	0.41	0.23	0.46	-	-
Toy-slime	0.27	43	0.16	1.0	0.18	1.3	-	-
Post-application exposure	*Realistic worst-case estimate of the dermal load (µg/cm²)*							
Post-application migration of hand-washed textile	8.2×10^{-4}		6.4×10^{-4}		4.6×10^{-4}		9.8×10^{-4}	
Post-application migration of machine-washed textile	4.2×10^{-5}		3.2×10^{-5}		2.4×10^{-5}		5.2×10^{-5}	

5 Discussion

IT are commonly added to consumer products as preservatives to prolong the shelf lives of the products. IT have skin sensitising properties. To assess the health risks associated with exposure to IT, the magnitude of the aggregate exposure needs to be determined for each consumer product group containing IT. In an effort to improve our understanding of the aggregate consumer exposure to IT, this research aimed to estimate the exposure to a group of widely used IT, i.e., MI, CMI and BIT, and provide a better insight into the contribution of various sources of exposure.

5.1 Contribution of various sources to IT exposure

In order to investigate the contribution of various sources to the IT exposure, comparison of the dermal load associated with each source needs to be performed. However, although tempting, it must be noted that comparison and/or summation of the exposures estimated for adults for the aggregate products (PCP and HCP) with the single exposures to other product groups (washing liquids, wall paint and glue) is not justified. This is because there are intrinsic differences between the models used (PACEM and ConsExpo), which makes it impossible to accurately compare the resulting exposures. The aggregate exposure assessment was performed with PACEM, which means that the estimation was performed to be as realistic as possible. The resulting exposure distributions obtained from PACEM are assumed to reflect the actual exposure in the entire (adult) population ranging from low or zero exposed people, e.g. individuals who do not use PCPs or HCPs containing IT, to highly exposed people who use multiple IT containing products with relatively high concentrations on a single day. In contrast, ConsExpo is designed to provide an initial, worst case assessment of the exposure, to be used in preventive risk assessment. The obtained exposure from ConsExpo reflects a (very) high exposure, due to the use of a 75^{th} percentile for the use amount and for other input parameters. In addition, ConsExpo estimates dermal exposure based on a single exposure event, without taking the use of multiple products nor the use pattern within a population. These model differences should be considered when interpreting the results.

Despite the difficulties in comparing results from PACEM and ConsExpo, it should be emphasized that comparison between the contributions of HCP and PCP is possible as they are both estimated using PACEM. In addition, comparison between the dermal loads resulting from single products (performed with ConsExpo) can also be performed. However, it is important to note here that each ConsExpo scenario is subject to different levels of uncertainty. Comparison of the results should therefore be performed with caution.

Keeping these considerations in mind, the calculations performed with PACEM regarding the aggregate exposure to IT show that the estimated aggregate MI-equivalent dermal load (i.e. assuming dose-addition applies) is similar for PCP and HCP. The aggregate MI-equivalent dermal

load therefore does not seem to be driven by either PCP or HCP. It must be noted that less than half of the population is estimated to be exposed to MI-equivalents through HCP. This is likely due to the intrinsic assumption in PACEM that only one of two adults in a household uses HCP. When estimating the dermal load separately for each IT (i.e. assuming dose-addition does not apply), it was found that the dermal loads associated with exposure to MI were approximately an order of magnitude higher than the dermal loads associated with exposure to CMI. However, despite the lower estimated dermal load when exposed to CMI, the skin sensitisation effect of CMI is expected to be similar or higher compared to that of MI, due to the high relative potency of CMI with respect to MI. Similarly, the dermal load resulting from exposure to BIT via HCP was estimated to be substantially higher than those resulting from exposure to MI and CMI. However, due to the low relative potency of BIT, the skin sensitising effect is expected to be comparable as or lower than that of MI and CMI.

Regarding the calculation performed regarding single products, it was observed that glues, wall paints, and laundry detergents (hand- and machine washing; mixing & loading, pouring with caps) were estimated to be major contributors to the total dermal load of adults. In fact, the dermal loads of these products groups were substantially higher than the aggregate dermal load associated with exposure to PCP and HCP, both for the MI-equivalents as for the separate IT. However, it must be emphasized that, as mentioned before, these differences are likely caused by the varying levels of conservativity used in calculations with PACEM and ConsExpo. Interestingly, the post-application exposure to laundry detergents did not lead to dermal loads that exceeded the AEL of any of the IT.

Concerning the children's exposure to IT, it seems that exposure to toy-slime and putty is a relevant contributor to the dermal load. The dermal load associated with exposure to toy-slime and putty is comparable to that of shampoo, while being multiple orders of magnitude larger than that of shower gel/foam/scrub and post-application exposure to laundry detergents. Considering that skin sensitisation after contact with liquid children's toys has been reported in numerous cases (O'Hern et al., 2021), liquid children's toys should not be overlooked when estimating the exposure to IT.

5.2 Uncertainty analysis with regard to exposure

To provide some insight into the uncertainties that may have affected the dermal exposure estimations, potentially relevant uncertainties have been listed in Table 14. For each type of uncertainty, a brief description is given as well as their potential effect(s) on the estimated dermal load. An arrow upwards (↑) refers to an uncertainty that increased the estimated dermal load with respect to the actual dermal load, whereas an arrow downwards (↓) refers to an uncertainty that decreased estimated dermal load with respect to the actual dermal load.

Table 14 Overview of the main uncertainties faced when performing the exposure assessment and their potential effect on the estimated exposure (↑ = increases exposure estimate, ↓ = decreases exposure estimate).

Uncertainty	Description	Effect
Aggregate PCP and HCP (PACEM)		
Concentration data	Concentration of IT in the products.	↑ / ↓
Occurrence data	The occurrence of IT being present in products of a particular product group.	↑ / ↓
Retention factor	The fraction of a product that remains on the skin. Conservative (default) estimates were assumed. If no guidance was available, a worst case retention of 1 was assumed.	↑
Product use data	Frequency and amount of the product used is estimated through surveys, which might not be fully representative of the whole Dutch population	↑ / ↓
IT selection	IT exposure estimates are limited to MI, CMI and BIT.	↓
Product group selection	Product groups were only included in the analyses if IT measurements were available.	↓
Cross-sensitivity of IT	It is unclear whether simultaneous exposure to low levels (i.e. below sensitisation concentrations) of multiple IT can cause sensitisation due to dose-addition.	↑
Single products (ConsExpo)		
Concentration data	Concentration of IT in the products.	↑ / ↓
Default values	The defaults values used as input for the exposure parameters.	↑ / ↓
IT selection	IT exposure estimates are limited to MI, CMI and BIT.	↓
Product group selection	Product groups were only included in the analyses if IT measurements were available.	↓
Cross-sensitivity of IT	It is unclear whether simultaneous exposure to low levels (i.e. below sensitisation concentrations) of multiple IT can cause sensitisation due to dose-addition.	↑

One of the main sources of uncertainty faced in this research is the IT concentration and occurrence data of various product groups. Although relatively many IT measurements were available for product groups such as shower gels/scrub/foams (n=254) and shampoo (n=226), only few measurements were available for eye pencil (n=1), mascara (n=3), shaving gel (=1), and wipes (n=8). Due to the lack of data of those product groups, the corresponding IT concentration data may be subject to uncertainty that can lead to both an overestimation as well as an underestimation of the dermal exposure. Furthermore, when only a

single measurement was available for a product group, the occurrence was assumed to be either 100% or 0%, depending on the outcome of the measurement. These values are likely to be over- or underestimations of the actual occurrence. In order to assess the extent of overestimation of the exposure, an additional analysis was performed. In this analysis, the occurrence of the IT in the two PCP that initially was assumed to be 100%, has been changed to 0%. This resulted in a dermal load through PCP that was less than two times lower than the initial dermal load. This indicates that the overestimation of IT exposure via these two product groups was rather small.

Besides the concentration and occurrence data, the quality of the product use data can also affect the simulated dermal exposures. In PACEM, the product use data is obtained through surveys. PCP use data of the Dutch population were obtained through a survey containing product use data of approximately 500 people, while the HCP use data was based on a survey among 1774 people of the German population. Both surveys might not be fully representative for the Dutch population. In ConsExpo, the dermal exposure is calculated for a single (high exposure) individual instead of a population. The product use data is therefore provided as a conservative estimate of the actual product use, which might result in an overestimation of dermal exposure. Further, at this moment the Cosmetics Fact Sheet and Do-it-yourself Fact Sheet are being updated. This could result in an update of product use data resulting in different estimates of dermal load.

Another source of uncertainty is the retention factors chosen in PACEM. If available, default retention factors were chosen, which were originally proposed by the Scientific Committee on Consumer Safety in 2021 (SCCS, 2021). These retention factors are based on rough estimations, and might therefore differ from the actual retention factors. In addition, no default retention factors were available for eye pencils and mascara. Therefore, retention factors of 1 were assumed for these two product groups, which might have resulted in an overestimation of the dermal exposure.

To perform an exposure assessment in ConsExpo, an exposure scenario needs to be defined. To this end, we typically use the default values reported in the ConsExpo fact sheets for different product groups. Examples of default values are the amount of product used, or the exposed skin surface. As these default values may not always be fully representative of the Dutch population, they may lead to additional uncertainties in the estimated dermal load.

In this research, the (aggregate) exposure to IT was limited to three IT, as these three IT are most commonly found in consumer products. In reality, however, additional IT exist that can potentially be present and contribute to the total exposure to IT (and MI-equivalent exposure). In addition, with increasing restrictions on the use of certain IT in consumer products (e.g. banning or lowering the specific concentration limit of BIT and tightening up the regulations of MI/CMI in PCP), might induce a shift towards an increased use of other IT in consumer products, as far as allowed by current restrictions. In order to include other IT in the analyses, efforts should be made to perform additional

measurements of other IT. OIT and DCOIT have already been detected in HCP and DIY products such as paints and sealants (Ducup de Saint Paul et al., 2021; Goodier et al., 2018; Goodier et al., 2019; Thomsen et al., 2018). For instance, according to Thomsen et al. (2018) OIT was identified in 27% of the paints analysed (with a concentration up to 16 mg/kg), and DCOIT in 50% of the paints (up to 156 mg/kg). In addition, the sensitising effect of those IT should be investigated to assess potential health risks.

An important knowledge gap in the risk assessment of skin sensitisers is the period of time over which the exposure is aggregated. In PACEM, a time period of 24h is taken, in which exposures from different sources are aggregated. However, the exact timeframe for aggregation relevant to sensitisation is unknown, and may be different than 24h and different for various product groups. This might also affect the estimated aggregate dermal load estimated in the current research.

It may be possible that not all relevant sources of IT exposure have been included in this research. In PACEM, product groups were only included if at least a single measurement was available in which IT were measured. As a consequence, PACEM product groups such as hair spray, parfum and lipstick were excluded from the analyses. Furthermore, various PCP and HCP are not incorporated in PACEM, while they potentially also contain IT, such as sunscreens and moisturizers. IT in animal care products and medicines such as ointments have also not been included in the analyses. Since the contribution of these product groups to the total IT exposure is unknown, exclusion of these product groups may have led to an underestimation of the dermal load.

Finally, an important uncertainty of the interpretation of the IT exposure is whether simultaneous exposure to various IT in low concentrations (i.e. below sensitisation concentrations) causes skin sensitisation due to addition of the different IT doses. Although some studies have shown that sensitisation by one IT can also result in elicitation when exposed to different IT (e.g. Schwensen et al., 2017; Herman et al., 2019), this does not necessarily hold when considering sensitisation. In this research, we therefore opted to investigate the dermal load both in the scenario where dose-addition would apply (calculated as MI-equivalent doses), as well as in the scenario where dose-addition would not apply (i.e. considering the dermal load from MI, CMI and BIT separately). The true dermal load is likely to be between the estimated dermal loads resulting from the two investigated scenarios.

5.3 Comparison with Acceptable Exposure Levels of IT

For a number of products, the dermal loads estimated in the current research exceed the Acceptable Exposure Level (AEL) of the various IT as determined in literature. Specifically, the 95th percentiles of the aggregate MI-equivalent dermal load from PCP and HCP, as well as the 95th percentiles of the MI-equivalent dermal loads associated with exposure to laundry detergent via pouring with caps, wall paint, glue, shampoo (children), shower gel/foam/scrub (children), putty and toy-slime exceeded the AEL derived for MI (7.4×10^{-2} µg/cm^2).

When considering exposure to MI only, the 95th percentiles of the dermal loads via exposure to wall paint, glue and laundry detergent by pouring with caps (Table 12) were higher than the AEL derived for MI (7.4×10^{-2} µg/cm^2). Similarly, for shampoo (children), toy slime and putty the 95th percentiles of the dermal loads associated with MI exposure were higher than the AEL of MI for (Table 13). The more realistic estimations of the aggregate exposure to MI via PCP resulted in a 95th percentile of the dermal load (Table 12) that is below the AEL of MI, whereas the estimated 95th percentile of the dermal load via HCP was higher than the AEL of MI. This finding is particularly interesting when considering the matrix SAF that was applied to derive the AEL. A matrix SAF of 3 was applied to all products. Although this value is accurate for HCP as these likely contain components with skin irritating properties, the matrix SAF is conservative for PCP as these are not expected to contain such irritants. Furthermore, the 95th percentile of the aggregate PCP and HCP dermal load exceeds the AEL for MI. This finding is different from that estimated by Ezendam et al. (2018), where only 0.7% of the population was exposed to levels of MI in PCP and HCP that exceeded the AEL. These differences may be explained by the differences in the product groups that were included by Ezendam et al. (2018), and the differences in occurrence and concentration data between the studies. For example, Ezendam et al.(2018), did not include eye pencils, mascara or shaving gel in their exposure assessment. Another difference is that the present research was performed based on PACEM survey data of the Dutch population, whereas Ezendam et al. (2018) based their calculations based on survey data of five European countries (the Netherlands, France, Germany, United Kingdom and Spain). Finally, the present research used an AEL that was rather conservative, since a matrix SAF was applied to both PCP and HCP, whereas Ezendam et al. (2018) applied this matrix SAF only to HCP.

In this research, an AEL for CMI (4.2×10^{-3} µg/cm^2) was used that was originally derived for MI/CMI mixtures (SCCS, 2015). The 95th percentiles of the aggregate dermal loads were below this AEL when considering PCP and HCP separately. However, the aggregate exposure to CMI in PCP and HCP exceed the AEL of MI/CMI, with the dermal load via PCP being approximately four times larger than that via HCP. Considering the single products, the 95th percentiles of the dermal loads associated with CMI exposure estimated for laundry detergent when pouring with caps, wall paint, glue, shampoo (children), shower gel/foam/scrub (children), putty and toy-slime exceeded the AEL of CMI.

The results of the present research show that the estimated 95th percentiles of the dermal load exceed the AEL of BIT (0.15 µg/cm^2) for aggregate exposure to HCP (0.37 µg/cm^2), and exposure to laundry detergent when pouring with caps (hand washing: 0.59 µg/cm^2; machine washing: 0.60 µg/cm^2), wall paint (1.5 µg/cm^2) and glue (6.5 µg/cm^2) (Table 12). The estimated dermal load associated with exposure to BIT in HCP (P95 = 0.37 µg/cm^2) is higher than the AEL of BIT, indicating that more than 5% of the population is exposed to BIT levels higher than the AEL. This result is different from that reported by Garcia-Hidalgo et al. (2018), who estimated that only 0.01% of the population exposed to BIT via HCP exceed the AEL of BIT. A possible

explanation for the difference is that Garcia-Hidalgo et al. (2018) analysed detergents based on a product use patterns of the Swiss population. Moreover, they included different HCP in the analyses. For example, carpet cleaners and fungicide spray were included, whereas cleaning wipes were excluded.

For all abovementioned comparisons with AELs, it must be emphasized that all AELs used in this research were derived using a matrix safety factor of 3 for all product groups. This matrix factor is used to account for an increased potency of IT due to the presence of components with skin irritating properties in a product. Although HCP commonly contain such irritants (e.g. alcohol, soap), PCP and children's toys are likely free of irritants. The matrix factor of 3 can therefore be considered to be a conservative choice, at least for certain product groups.

6 Conclusions and recommendations

Bearing the results and uncertainties of this research in mind, the following conclusions and recommendations have been formulated.

6.1 Conclusions

- The estimated dermal loads associated with exposure to PCP and HCP were comparable.
- Despite the comparable dermal loads, the contribution of HCP to skin sensitization is likely higher since HCP commonly contain components with skin irritating properties.
- Glues, wall paints and laundry detergent are potentially relevant contributors to the total IT exposure of adults, both when dose-addition of different IT applies, and when treating exposure to each IT separately.
- Aqueous toys, i.e. toy-slime and putty, cannot be overlooked as contributors to the dermal load of IT in children, as the dermal load associated with exposure to aqueous toys was similar to that of shampoo.
- In general, the dermal load associated with exposure to CMI is lower than those associated with exposures to MI and BIT.
- Due to the higher relative potency of CMI with respect to MI and BIT, the skin sensitising effect of CMI is expected to be comparable as or higher than that of MI and BIT.
- The 95th percentiles of the estimated dermal loads to MI-equivalent, MI, CMI and BIT were frequently of the same order of magnitude as the respective AELs derived for those IT.

6.2 Recommendations

Based on the results and uncertainties of the current research, and the conclusions formulated in the previous section, the following recommendations are made:

- In order to reduce the uncertainties regarding the estimated dermal loads, additional, representative data needs to be acquired concerning IT concentrations on the one hand and product use patterns of consumer products on the other. In particular, as glue and wall paints have been identified as potentially relevant contributors to the IT exposure of adults, IT concentrations measurement in various types of glue and wall paints would help to further refine the calculations for adults. Moreover, acquiring and incorporating product use patterns of glue and wall paint in PACEM would enable to include these product groups in the aggregate exposure estimations. This would give a more complete view on the total exposure of adults to IT.
- The results presented in this report demonstrate that aqueous children's toys may be relevant contributors to the dermal load of IT in children. It is therefore recommended to verify the quality of the IT concentration data in putty and slime and to further refine the exposure scenarios regarding the use of children's toys. In addition, product use data is lacking for

children's toys, it is recommended to conduct surveys to provide a better insight into the use patterns of children's toys. If the estimated dermal loads remain high after refinement of the exposure scenarios and elaboration of the concentration data in these toy products, IT restrictions in putty and toy-slime may need to be considered. Another option would be to reconsider the classification limits of the three categories of toy materials (Toy Safety Directive 2009/48/EC).

- Concentration measurements of IT other than MI, CMI and BIT need to be performed to determine whether other IT also contribute substantially to the aggregate dermal load. For example, DCOIT and OIT have already been found in wall paints (Thomsen et al., 2018). This might also help in identifying a potential shift towards the use of different IT if restrictions on a certain IT are imposed.
- In the current research, aggregation of IT exposure was performed over a timeframe of 24 hours. However, there is no evidence that this period is the most appropriate for skin sensitisation after exposure to various different consumer products. Further research on the aggregation time period relevant to skin sensitisation is needed in order to further reduce the uncertainty of the estimated dermal loads used in the QRA.
- Since the estimated dermal loads aggregated over PCP and HCP were in the same order of magnitude as the corresponding AELs for all three IT, further research may be necessary to verify the results. In particular, since HCP likely contributes more to the skin sensitization effect, it is recommended to focus on further refining and improving the exposure estimates for HCP. In addition, one could subsequently investigate the impact of potential IT restrictions on the dermal load by simulating the dermal loads for various HCP in which IT concentrations above a certain threshold are excluded.
- The current research estimated the (aggregate) dermal loads for IT following exposure to various product groups. Product groups were included in case measured IT concentration data were available. However, due to the lack of IT concentration data, various product groups had to be excluded. Additional IT concentration data are necessary of products groups that may potentially contain IT. Such products groups are for instance medicines (e.g. ointments and creams) and animal care products (e.g. shampoos, parfums, detanglers and grooming wipes). Similarly, product use patterns of these product groups should be investigated in order to allow incorporation of additional product groups in the aggregate exposure estimates performed in PACEM.
- In the interpretation of the comparison between dermal load values and AELs for the different IT, specific attention should be given to the applied safety assessment factors (SAF). Particularly, the matrix SAF is important in the current research. This SAF is (amongst others) used to account for the presence of irritating substances in the product that may increase the sensitising potency of IT in the product. Although in the current research, not all product groups are expected to contain irritating substances, a matrix SAF of 3 was

used for all product groups. A possible way of refining this matrix SAF would be to define and apply a matrix SAF per product group. For example, Ezendam et al. (2018) defined a matrix SAF of 3 for HCP, and a matrix SAF of 1 for PCP.

- The dermal load estimated for exposure to CMI was in the same order of magnitude of the corresponding AEL for numerous product groups. Further research is necessary to refine the estimated dermal loads concerning CMI exposure.

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Annex I Concentration data

Table A1 Overall measured concentrations of MI and CMI in shampoo derived from NVWA data, and the MI-equivalent concentration calculated from these data used for the exposure assessment for children.

	N	**occurrence**	**concentration *(mg/kg)***					
			Range	**Median (±C_v)**	**75th**	**90th**	**95th**	**99th**
MI-eq	226	8.0% (n=18)	0.6-360	170 (±0.80)	240	280	330	350
MI	226	8.0% (n=18)	0.6-110	2.8 (±2.2)	6.2	33	84	100
CMI	226	4.4% (n=10)	4.1-8.9	5.8 (±0.2)	6.6	8.0	8.5	8.8

Table A2 Overall measured concentrations of MI and CMI in shower gel/foam/scrub derived from NVWA data, and the MI-equivalent concentration calculated from these data used for the exposure assessment for children.

	N	**occurrence**	**concentration *(mg/kg)***					
			Range	**Median (±C_v)**	**75th**	**90th**	**95th**	**99th**
MI-eq	253	5.5% (n=14)	0.7-360	130 (±0.78)	220	310	330	350
MI	244	4.1% (n=10)	0.7-62	2.6 (±2.3)	3.2	9.2	35	56
CMI	249	4.0% (n=10)	1.5-8.9	4.1 (±0.47)	6.7	8.0	8.5	8.8

Table A3 Overall measured concentrations of MI and CMI in laundry product derived from NVWA data and Marrero-Alemán et al. (2020), Garcia-Hidalgo et al. (2017), and the MI-equivalent concentration calculated from these data.

	N	**occurrence**	**concentration *(mg/kg)***					
			Range	**Median (±C_v)**	**75th**	**90th**	**95th**	**99th**
MI-eq	24	83% (n=20)	0.002-610	20 (±2.0)	40	470	550	600
MI	24	58% (n=14)	0.3-66	15 (±0.94)	29	42	51	63
CMI	24	21% (n=5)	0.1-15	11 (±0.81)	13	15	15	15
BIT	24	71% (n=17)	0.06-250	24 (±1.5)	43	98	150	230

Table A4 Overall measured concentrations of MI and CMI in floor cleaner derived from NVWA data, Marrero-Alemán et al. (2020), Garcia-Hidalgo et al. (2017) and Ezendam et al. (2018), and the MI-equivalent concentration calculated from these data.

	N	**occurrence**	**concentration *(mg/kg)***					
			Range	**Median (±C_v)**	**75th**	**90th**	**95th**	**99th**
MI-eq	72	63% (n=45)	0.43-400	34 (±1.3)	57	250	280	400
MI	71	55% (n=39)	0.05-180	24 (±1.2)	43	52	71	160
CMI	66	15% (n=10)	0.08-10	6.3 (±0.57)	6.9	9.1	9.6	9.9
BIT	69	35% (n=24)	0.16-170	35 (±0.91)	76	140	160	170

Table A5 Overall measured concentrations of BIT, MI and CMI in wall paint derived from Thomsen et al. (2018), Schwensen et al. (2015), Goodier et al. (2018) and NVWA data, and the MI-equivalent concentration calculated from these data.

	N	**occurrence**	**concentration *(mg/kg)***						
			range	**mean (±SD)**	**Median (±C_v)**	**75th**	**90th**	**95th**	**99th**
MI-eq	180	(n=173)	0.004-945	105 (±124)	76.5 (±1.18)	119	223	337	572
MI	176	93.2% (n=164)	0.67-940	83.8 (±103)	55.5 (±1.22)	106	158	241	411
CMI	172	18.0% (n=31)	0.17-13.1	2.9 (±3.5)	1.4 (±1.2)	3.5	8.2	10.8	12.6
BIT	178	92.1% (n=164)	0.1-1111	116 (±124)	85.6 (±1.07)	168	259	309	432

Table A6 Goodier et al. (2019) data on DIY glues (glue for eyelash excluded), and the MI-equivalent concentration calculated from these data.

	N	**occurrence**	**concentration *(mg/kg)***						
			range	**mean (±SD)**	**Median (±C_v)**	**75th**	**90th**	**95th**	**99th**
MI-eq	37	51.4% (n=19)	0.43-1138	444 (±403)	365 (±0.88)	776	983	1113	1133
MI	37	45.9% (n=17)	4.3-133	24.6 (±30)	12.8 (±1.19)	32.5	36.1	57.1	118
CMI	37	32.4% (n=12)	7.3-27.6	16.7 (±7.4)	18.6 (±0.43)	21.4	26.6	27.2	27.5
BIT	37	16.2% (n=6)	10.8-87	56 (±33)	68.8 (±0.53)	80.9	84.9	85.7	86.3

Table A7 Measured concentrations of BIT, MI and CMI (reference to NVWA) in putty (mg/kg) and the MI-equivalent concentration calculated from these data.

	n	**occurrence**	**range**	**Mean (±SD)**	**Median (±Cv)**	**75th**	**90th**	**95th**	**99th**
MI-eq	29	31.0% (n=9)	1-1189	435 (±465)	268 (±1.01)	694	1125	1157	1183
MI	29	27.6% (n=8)	1-25	10.8 (±9.9)	8.1 (±0.85)	16.7	25.0	25.0	25.0
CMI	29	20.7% (n=6)	5.2-29.1	16.0 (±10.3)	13.9 (±0.59)	24.6	28.1	28.6	29.0
BIT	24	0% (n=0)	-	-	-	-	-	-	-

Table A8 Measured concentrations of BIT, MI and CMI (reference to NVWA) in toy-slime (mg/kg) and the MI-equivalent concentration calculated from these data.

	n	**occurrence**	**range**	**Mean (±SD)**	**Median (±Cv)**	**75th**	**90th**	**95th**	**99th**
MI-eq	37	32.4% (n=12)	0.5-1529	232 (±464)	6.9 (±1.91)	174	717	1114	1446
MI	37	32.4% (n=12)	0.5-27	7.6 (±8.9)	4.0 (±1.12)	7.9	22.9	25.6	26.7
CMI	37	13.5% (n=5)	2.4-37.6	13.5 (±15.0)	4.6 (±0.99)	18.7	30.0	33.8	36.8
BIT	33	0% (n=0)	-	-	-	-	-	-	-

Annex II Default values input parameters ConsExpo

Table A9 Default values for estimating dermal exposure to shampoo.

Default value		**Source**
Model	Direct product contact	Cosmetics Fact Sheet
Loading	Instant application	Cosmetics Fact Sheet
Exposed area	430 cm^2	hands and ½ head surface area of a child of 1-2 years old (230 cm^2 for hands and 400 cm^2 for head based on Table 32 in reference General Fact Sheet (te Biesebeek et al., 2014)).
Weight fraction	MIeq: $1.7x10^{-4}$ (±0.8) MI: $2.8x10^{-6}$ (±2.2) CMI: $5.8x10^{-6}$ (±0.2)	NVWA data (from Table A1)
Product amount	13 g	Gosens et al., 2014

Table A10 Default values for estimating dermal exposure to shower gel/foam/scrub during showering.

Default value		**Source**
Model	Direct product contact	Cosmetics Fact Sheet
Loading	Instant application	Cosmetics Fact Sheet
Exposed area	4800 cm^2	total body surface area of a child 1-2 years old (Table 32 in reference General Fact Sheet (te Biesebeek et al., 2014)).
Weight fraction	MIeq: $1.3x10^{-4}$ (±0.8) MI: $2.6x10^{-6}$ (±2.3) CMI: $4.1x10^{-6}$ (±0.5)	NVWA data (from Table A2)
Product amount	2.3 g	Gosens et al., 2014

Table A11 Default values for estimating dermal exposure to regular hand-washing liquid and concentrated machine-washing liquid from mixing and loading – pouring via cap

Default value		**Source**
Model	Direct product contact	Cleaning Products Fact Sheet
Loading	Instant application	Cleaning Products Facts Sheet
Exposed area	53 cm^2	Cleaning Products Fact Sheet
Weight fraction	MIeq: $1.97x10^{-5}$ (±2.0) MI: $1.54x10^{-5}$ (±1.0) CMI: $1.11x10^{-5}$ (±0.9) BIT: $2.37x10^{-5}$ (±1.5)	Measurements and literature (see Table A3)
Product amount	0.53 g	Cleaning Products Fact Sheet

Table A12 Default values for estimating dermal exposure to concentrated machine-washing liquid during hanging-out of machine-washed laundry.

Default value		**Source**
Model	Direct product contact	Cleaning Products Fact Sheet
Loading	Instant application	Cleaning Products Fact Sheet
Exposed area	900 cm^2	Cleaning Products Sheet
Weight fraction	MIeq: $1.97x10^{-5}$ (±2.0) MI: $1.54x10^{-5}$ (±1.0) CMI: $1.11x10^{-5}$ (±0.9) BIT: $2.37x10^{-5}$ (±1.5)	Measurements and literature (see Table A3)
Product amount	0.0042 g	Cleaning Products Fact Sheet

Table A13 Default values for estimating dermal exposure to hand-washing detergents during application.

Default value		**Source**
Model	Direct product contact	Cleaning Products Fact Sheet
Loading	Instant application	Cleaning Products Fact Sheet
Exposed area	2200 cm^2	Cleaning Products Fact Sheet
Weight fraction	MIeq: $1.97x10^{-5}$ (±2.0) MI: $1.54x10^{-5}$ (±1.0) CMI: $1.11x10^{-5}$ (±0.9) BIT: $2.37x10^{-5}$ (±1.5)	Measurements and literature (see Table A3)
Product amount	0.194 g	Cleaning Products Fact Sheet

Table A14 Default values for estimating dermal exposure to regular hand-washing liquid during hanging-out of hand-washed laundry.

Default value		**Source**
Model	Direct product contact	Cleaning Products Fact Sheet
Loading	Instant application	Cleaning Products Fact Sheet
Exposed area	900 cm^2	Cleaning Products Fact Sheet
Weight fraction	MIeq: $1.97x10^{-5}$ (±2.0) MI: $1.54x10^{-5}$ (±1.0) CMI: $1.11x10^{-5}$ (±0.9) BIT: $2.37x10^{-5}$ (±1.5)	Measurements and literature (See Table A3)
Product amount	0.079 g	Cleaning Products Fact Sheet

Table A15 Default values for estimating dermal exposure to hand-washing laundry detergents from post-application migration of residues from fabric.

Default value		**Source**
Model	Direct product contact	Cleaning Products Fact Sheet
Loading	Migration	Cleaning Products Fact Sheet
Exposed area	1700 cm^2	Cleaning Products Fact Sheet
Leachable fraction	MIeq: $1.7x10^{-8}$ MI: $1.4x10^{-8}$ CMI: $9.8x10^{-9}$ BIT: $2.1x10^{-8}$	See Table 10
Product amount	1000 g	Cleaning Products Fact Sheet
Skin contact factor	0.8	Cleaning Products Fact Sheet

Table A16 Default values for estimating dermal exposure to machine-washing laundry detergents from post-application migration of residues from fabric.

Default value		**Source**
Model	Direct product contact	Cleaning Products Fact Sheet
Loading	Migration	Cleaning Products Fact Sheet
Exposed area	1700 cm^2	Cleaning Products Fact Sheet
Leachable fraction	MIeq: $8.9x10^{-10}$ MI: $6.9x10^{-10}$ CMI: $5.0x10^{-10}$ BIT: $1.1x10^{-9}$	See Table 10
Product amount	1000 g	Cleaning Products Fact Sheet
Skin contact factor	0.8	Cleaning Products Fact Sheet

Table A17 Default values for estimating dermal exposure to floor cleaning liquid by rubbing off.

Default value		**Source**
Model	Direct product contact	Cleaning Products Fact Sheet
Loading	Rubbing off	Cleaning Products Fact Sheet
Exposed area	3000 cm^2	Cleaning Products Fact Sheet
Weight fraction substance	MIeq: $3.37x10^{-5}$ (±1.3) MI: $2.44x10^{-5}$ (±1.2) CMI: $6.3x10^{-6}$ (±0.6) BIT: $3.48x10^{-5}$ (±0.9)	Measurements (see Table A4)
Transfer coefficient	0.2 m^2/hr	Cleaning Products Fact Sheet
Dislodgeable amount	0.2 g/m^2	Cleaning Products Fact Sheet
Contact time	60 min	Cleaning Products Fact Sheet
Contacted surface	22 m^2	Cleaning Products Fact Sheet

Table A18 Default values for estimating dermal exposure to wall-paint.

Default value		**Source**
Model	Direct product contact	Painting products Fact Sheet
Loading	Constant rate	Painting products Fact Sheet
Exposed area	860 cm^2	Both hands (adults) (te Biesebeek et al., 2014)
Weight fraction substance	MIeq: $7.65x10^{-5}$ (±1.18) MI: $5.55x10^{-5}$ (±1.22) CMI: $1.4x10^{-6}$ (±1.2) BIT: $8.56x10^{-5}$ (±1.07)	Measurements from literature data and NVWA data (see Table A5)
Contact rate	30 mg/ min	Painting products Fact Sheet
Release duration	120 min	Painting products Fact Sheet

Table A19 Default values for estimating dermal exposure to glue.

Default value		**Source**
Model	Direct product contact	Do-It-Yourself Fact Sheet
Loading	Instant application	Do-It-Yourself Fact Sheet
Exposed area	2 cm^2	Do-It-Yourself Fact Sheet
Product amount	0.08 g	Do-It-Yourself Fact Sheet
Weight fraction substance	MIeq: $3.65x10^{-4}$ (±0.88) MI: $1.28x10^{-5}$ (±1.19) CMI: $1.86x10^{-5}$ (±1.2) BIT: $6.88x10^{-5}$ (±0.53)	Measurements from literature data (see Table A6)

Annex III Output calculations

Adults

Table A20 Aggregated exposure expressed as maximum daily dermal load (µg/cm²) to PCP and HCP as calculated with PACEM for the Dutch population. The exposure is shown as a percentiles table, giving exposure at pre-defined percentiles of the population.

Percentile	**25th**	**50th**	**75th**	**90th**	**95th**	**99th**
MI equivalent						
PCP	0	1.0×10^{-4}	2.3×10^{-3}	3.0×10^{-2}	0.16	3.3
HCP	0	0	3.9×10^{-4}	4.5×10^{-2}	0.15	1.3
Total	0	7.3×10^{-4}	1.8×10^{-2}	0.15	0.47	6.1
MI						
PCP	0	5.3×10^{-7}	5.5×10^{-4}	3.3×10^{-3}	6.7×10^{-3}	2.6×10^{-2}
HCP	0	0	1.7×10^{-4}	2.3×10^{-2}	8.4×10^{-2}	1.1
Total	0	1.2×10^{-4}	4.0×10^{-3}	2.7×10^{-2}	8.8×10^{-2}	0.85
CMI						
PCP	0	0	5.8×10^{-7}	4.1×10^{-4}	3.4×10^{-3}	3.5×10^{-2}
HCP	0	0	0	0	9.1×10^{-4}	2.5×10^{-2}
Total	0	0	7.2×10^{-6}	1.9×10^{-3}	7.6×10^{-3}	7.4×10^{-2}
BIT						
PCP	0	0	0	0	0	0
HCP	0	0	0	4.4×10^{-2}	0.37	7.3
Total	0	0	0	4.4×10^{-2}	0.37	7.3

Table A21 Exposure expressed as dermal load (µg/cm²) of hand washing liquid, regular of a single exposure event as calculated with ConsExpo.

	Median	**95th perc**	**99th perc**	**Realistic worst-case estimate**
$MI_{equivalent}$				
Handwashing	1.7×10^{-3}	1.4×10^{-2}	3.6×10^{-2}	
Hanging hand-washed laundry	1.7×10^{-3}	1.4×10^{-2}	3.5×10^{-2}	
Pouring with caps	0.20	1.7	4.2	
Post-application migration of hand-washed textile (adult)*				8.2×10^{-4}
MI				
Handwashing	1.4×10^{-3}	5.4×10^{-3}	9.5×10^{-3}	
Hanging hand-washed laundry	1.3×10^{-3}	5.3×10^{-3}	9.5×10^{-3}	
Pouring with caps	0.15	0.59	1.1	
Post-application migration of hand-washed textile (adult)*				6.4×10^{-4}
CMI				
Handwashing	9.9×10^{-4}	3.4×10^{-3}	5.8×10^{-3}	
Hanging hand-washed laundry	9.7×10^{-4}	3.5×10^{-3}	6.0×10^{-3}	
Pouring with caps	0.11	0.39	0.67	
Post-application migration of hand-washed textile (adult)*				4.6×10^{-4}
BIT				
Handwashing	2.1×10^{-3}	1.2×10^{-2}	2.7×10^{-2}	

	Median	**95th perc**	**99th perc**	**Realistic worst-case estimate**
Hanging hand-washed laundry	2.1×10^{-3}	1.2×10^{-2}	2.7×10^{-2}	
Pouring with caps	0.24	1.4	3.1	
Post-application migration of hand-washed textile (adult)*				9.8×10^{-4}

* Leachable fraction is calculated with median concentration

Table A22 Exposure expressed as dermal load (µg/cm^2) of machine washing liquid, concentrated of a single exposure event as calculated with ConsExpo.

	Median	**95th perc**	**99th perc**	**Realistic worst-case estimate**
$MI_{equivalent}$				
Hanging hand-washed laundry	9.1×10^{-5}	7.6×10^{-4}	1.8×10^{-3}	
Pouring with caps	0.20	1.7	4.2	
Post-application migration of machine-washed textile (adult)*				4.2×10^{-5}
MI				
Hanging machine-washed laundry	7.2×10^{-5}	2.8×10^{-4}	4.8×10^{-4}	
Pouring with caps	0.16	0.60	1.1	
Post-application migration of machine-washed textile (adult)*				3.2×10^{-5}
CMI				
Hanging machine-washed laundry	5.2×10^{-5}	1.9×10^{-4}	3.2×10^{-4}	
Pouring with caps	0.11	0.41	0.67	
Post-application migration of machine-washed textile (adult)*				2.4×10^{-5}
BIT				
Hanging machine-washed laundry	1.1×10^{-4}	6.7×10^{-4}	1.5×10^{-3}	
Pouring with caps	0.24	1.4	2.7	
Post-application migration of machine-washed textile (adult)*				5.2×10^{-5}

* Leachable fraction is calculated with median concentration

Table A23 Exposure expressed as dermal load (µg/cm²) by different isothiazolinones through the application of wall paint as calculated with ConsExpo for a single exposure event.

	Median	**95th perc**	**99th perc**
$MI_{equivalent}$	0.32	1.4	2.6
MI	0.23	1.2	2.2
CMI	5.8×10^{-3}	2.7×10^{-2}	5.3×10^{-2}
BIT	0.36	1.5	2.7

Table A24 Exposure expressed as dermal load (µg/cm²) by different isothiazolinones through the application of DIY glue as calculated with ConsExpo for a single exposure event.

	Median	**95th perc**	**99th perc**
$MI_{equivalent}$	14	50	86
MI	0.51	2.4	4.7
CMI	0.75	1.5	2.0
BIT	2.8	6.5	8.9

Children

Table A25 Exposure expressed as dermal load (µg/cm²) of shampoo, child 1.5 years as calculated with ConsExpo for a single exposure event.

	Median	**95th perc**	**99th perc**
$MI_{equivalent}$	5.3	17	28
MI	8.4×10^{-2}	0.75	1.8
CMI	0.18	0.26	0.31

Table A26 Exposure expressed as dermal load (µg/cm²) of showering, child 1.5 years as calculated with ConsExpo for a single exposure event.

	Median	**95th perc**	**99th perc**
$MI_{equivalent}$	6.2×10^{-2}	0.20	0.33
MI	1.2×10^{-3}	1.2×10^{-2}	3.1×10^{-2}
CMI	2.0×10^{-3}	4.2×10^{-3}	5.8×10^{-3}

Table A27 Post-application exposure expressed as dermal load (µg/cm²) to child of 1.5 years old, wearing washed textile as calculated with ConsExpo for a single exposure event.

	Post-application migration of machine-washed textile*	**Post-application migration of hand-washed textile***
$MI_{equivalent}$	4.2×10^{-5}	8.2×10^{-4}
MI	3.2×10^{-5}	6.4×10^{-4}
CMI	2.4×10^{-5}	4.6×10^{-4}
BIT	5.2×10^{-5}	9.8×10^{-4}

* Leachable fraction is calculated with median concentration

Table A28 Post-application exposure expressed as dermal load (µg/cm²) to child of 1.5 years old, crawling over cleaned floor as calculated with ConsExpo for a single exposure event.

	Median	**95th perc**	**99th perc**
$MI_{equivalent}$	4.5×10^{-4}	2.3×10^{-3}	4.6×10^{-3}
MI	3.3×10^{-4}	1.6×10^{-3}	3.0×10^{-3}
CMI	8.3×10^{-5}	2.1×10^{-4}	3.1×10^{-4}
BIT	4.6×10^{-4}	1.6×10^{-3}	2.7×10^{-3}

Toys

Table A29 Exposure (dermal load) from different types of toys (µg/cm²).

	Putty		**Toy-slime**	
	Median	95th perc	Median	95th perc
MI	0.13	0.41	0.16	1.0
CMI	0.23	0.46	0.18	1.3
BIT	-	-	-	-
MI-eq	4.3	19	0.27	43

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