European Commission

Scientific Committee on Consumer Safety

SCCS

OPINION ON

the safety of presence of Bisphenol A in clothing articles

Scientific Committees
on Consumer Safety
on Health, Environmental and Emerging Risks

The SCCS adopted this document
by written procedure on 16 October 2020

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1. ABSTRACT

The SCCS concludes the following:

1. *To review the available data on the presence and activity of Bisphenol A in clothing articles, taking into consideration the adopted opinions on tolerable intake limits and the legislative framework in other products (food contact materials, toys and printed paper)*

   Regarding potential health effects of BPA, this opinion is based on the information present in the most recent health risk assessments conducted by EFSA (2015) and ECHA (2017). SCCS is, however, aware of the fact that EFSA is currently re-evaluating the huge amount of data on BPA toxicity that came available since December 2012, *i.e.* the cut-off point for their latest assessment published in 2015. Hence, all outcomes and conclusions reported in this document with respect to human health might be subject of change in the near future. If this is the case, the opinion should be updated accordingly.

   Regarding exposure, a few studies have indicated BPA occurrence in clothing articles and provide dermal exposure estimates based on default values for substance migration. From these studies, it appears that the distributions of concentrations are similar for purchases all over the world with median concentrations ranging between 10.7 - 26.9 ng/g. However, only one study also provides experimental migration rates of BPA into artificial sweat, and on this basis provides dermal exposure estimates for dry and sweaty clothes (Wang *et al*. 2019). Based on these reported migration rates, exposure estimates were calculated under conservative assumptions, with an 8-hour chronic daily contact of the whole trunk to clothes fully soaked in sweat for men and women. As children only sweat marginally, only exposure to dry clothes was considered for this age group. Yet, for the latter, additional oral exposure due to sucking on clothes has been taken into consideration. From these calculations, it can be concluded that for adults the internal total BPA exposure due to clothing is ~0.5 ng/kg bw/d and ~3 ng/kg bw/d in case of average and high migration scenarios, respectively. For toddlers, exposure to total BPA *via* clothing is much less *i.e.* ~0.01 and ~0.15 ng/kg bw/d in case of average and high migration, respectively.

2. *To determine whether the exposure levels to BPA due to the use of clothing articles raises health concerns for consumers and, if possible, to provide indications on limit values for BPA content/release from clothing articles.*

   Currently, there is no legislation regulating restrictions for the presence or release of BPA in clothing or textile articles. Yet, BPA has been detected in clothing articles and taken into account its hazard profile, this might be of concern as clothing articles are in direct and prolonged contact with the skin. Moreover, in case of young children, oral exposure due to sucking on clothes can contribute to total BPA exposure.
   All clothing exposure scenarios analysed in this opinion result in an exposure level of BPA that is below the t-TDI of 4 µg/kg bw/d based on increased kidney weight in a 2-year generation study in mice as critical endpoint with a $BMDL_{10}$ of 8.96 mg/kg bw/d. However, regarding the dermal exposure *via* clothing, it is necessary to take into account the huge difference in dermal bioavailability of parent BPA when compared to the oral route. Therefore, the SCCS considered it appropriate to follow a MoS approach and to make the comparison using an internal HED (HEDi, 6.09 µg/kg bw/d when assuming 1 % free BPA after uptake by the oral route) rather than the external HED value. From a conservative point of view, SCCS further decided not to consider skin metabolism. For the average (~0.5 ng/kg bw/d) and high exposure (~3 ng/kg bw/d) scenarios considered, the MoS is >11500 and >1800, respectively. In case of toddlers who are significantly less exposed to BPA due to clothing, much higher MoS values are derived for both the average and high

exposure scenarios. Hence, there is no risk for adverse effects of the estimated exposure levels of BPA resulting from the use of clothes, independent of the age group of the consumer.

Furthermore, based on the estimated BPA exposure levels in clothing articles for the high exposure scenarios and assuming a surface weight of 0.2 kg/m^2 textile (Rovira *et al*. 2015, ECHA 2019), a maximum amount of BPA in textile of around 145 mg/kg could be established *via* back calculations.

3. *To identify whether vulnerable consumers such as infants and young children (who might put such articles in their mouth) or pregnant women are in particular risk. On the basis of the risk assessment, could it be indicated what level of exposure to BPA from textiles can be accepted in such groups.*

In view of the very low exposure levels of BPA from clothing, no particular population group is at risk. As indicated above, a concentration limit of around 145 mg BPA/kg textile could be proposed as a preventive measure to ensure the protection of consumers. This value is conservative and in line with the 130 mg/kg limit value that has recently been proposed to reduce the risk of sensitisation due to BPA in textiles (ECHA 2019).

Keywords: SCCS, scientific opinion, Bisphenol A, clothing, 2,2-bis(4-hydroxyphenyl)propane, CAS Number 80-05-7, Regulation 1223/2009

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Two independent non-food Scientific Committees provide the Commission with the scientific advice it needs when preparing policy and proposals relating to consumer safety, public health and the environment. The Committees also draw the Commission's attention to the new or emerging problems which may pose an actual or potential threat.
They are: the Scientific Committee on Consumer Safety (SCCS), the Scientific Committee on Health, Environmental and Emerging Risks (SCHEER) and are made up of independent experts.

In addition, the Commission relies upon the work of the European Food Safety Authority (EFSA), the European Medicines Agency (EMA), the European Centre for Disease prevention and Control (ECDC) and the European Chemicals Agency (ECHA).

SCCS

The Committee shall provide Opinions on questions concerning health and safety risks (notably chemical, biological, mechanical and other physical risks) of non-food consumer products (for example cosmetic products and their ingredients, toys, textiles, clothing, personal care and household products such as detergents, etc.) and services (for example: tattooing, artificial sun tanning, etc.).

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2. MANDATE FROM THE EUROPEAN COMMISSION

Background

Bisphenol A (BPA) or 2,2-bis(4-hydroxyphenyl)propane (CAS Number 80-05-7) is an organic compound consisting of two phenolic rings connected by a single carbon carrying two methyl groups. It is an industrial chemical, with a high production volume, widely used in the production of polycarbonate and epoxy resins and as an additive in polyvinyl chloride and thermal paper.

BPA can be found in a variety of common consumer goods, such as re-usable plastic tableware and bottles for drinks, sports equipment, CDs, and DVDs. It is also used in internal coatings of water pipes and cans for food and drink to increase the shelf life and maintain the organoleptic properties of the food and drinks. BPA is employed as a dye developer in thermal paper and common in shop sales receipts, and public transport and parking tickets.

BPA is classified as toxic for reproduction (category 1b) and as skin sensitiser (category 1). It can cause alterations in postnatal growth, reproductive organ development and function, and on behaviour. Recently, it has been suggested that it might also impair the development of the immune system. These effects seem derived from its chemical structure, which resembles that of estrogen. BPA can interfere with the endocrine system, leading to effects on the female reproductive system, the mammary gland, the metabolism and obesity. Consequently, it is listed as substance with endocrine disrupting activity.

1. Previous scientific opinions and existing restrictions

Because of the hazard profile of Bisphenol A, different Scientific Committees have evaluated its toxicity in the past. The European Food Safety Authority (EFSA) has regularly issued and updated scientific opinions on BPA since 2006. In 2015[1], the panel defined a temporary Tolerable Daily Intake (t-TDI) of 4 µg/kg bw per day and calculated the aggregated exposure based on diet, house dust, thermal paper and cosmetics. This value is temporary because there is uncertainty on the biological effects and the exposure levels through sources other than food. Furthermore, the results of an ongoing long-term toxicity study on BPA are also pending and might have an impact on the TDI calculation.

Various EFSA scientific opinions on BPA have led to the restriction of its use in the manufacture of different plastic food contact materials. The use of BPA in polycarbonate infant feeding bottles is prohibited since 1 March 2011[2]. Since 6 September 2018[3], its use in polycarbonate drinking bottles or cups for infants and young children is forbidden too. At the same time, its allowed migration from epoxy resins for varnishes and coatings for the interior of food cans has been limited to a maximum of 0,05 mg/kg.

Following the t-TDI defined in 2015 and the opinions of the subgroup “chemicals” of the Expert Group on Toys, the Commission has amended Appendix C to Annex II of the Toy Safety Directive (Directive 2009/48/EC). The new maximal migration value for BPA migration from toy material is reduced to 0,04 mg/l as of 26 November 2018[4].

In parallel to the evaluation by EFSA, the Committee for Risk Assessment (RAC) and the Committee for Socio-Economic Analysis (SEAC) of the European Chemicals Agency (ECHA) evaluated a restriction dossier on BPA in thermal paper. Their opinion lead the

[1] Scientific Opinion on the risks to public health related to the presence of bisphenol A (BPA) in foodstuffs. EFSA Journal 2015;13(1):3978. http://www.efsa.europa.eu/en/efsajournal/pub/3978.
[2] Commission Directive (EU) 2011/8 of 28 January 2011 amending Directive 2002/72/EC as regards the restriction of use of Bisphenol A in plastic infant feeding bottles
[3] Commission Regulation (EU) 2018/213 of 12 February 2018 on the use of bisphenol A in varnishes and coatings intended to come into contact with food and amending Regulation (EU) No 10/2011 as regards the use of that substance in plastic food contact materials
[4] Commission Directive (EU) 2017/898 of 24 May 2017 amending, for the purpose of adopting specific limit values for chemicals used in toys, Appendix C to Annex II to Directive 2009/48/EC of the European Parliament and of the Council on the safety of toys, as regards bisphenol A

Commission to amend the REACH regulation (Regulation (EC) No 1907/2006) by establishing a new entry in Annex XVII with a restriction on the use of BPA in thermal paper in concentrations equal or higher to 0,02% by weight as of 2 January 2020[5].

2. Presence in textile articles

There is no direct restriction on the use of BPA in textiles and its absence is only taken into consideration for the potential granting of the EU Ecolabel[6] for textiles. This is because BPA is included in the REACH list of Substances of Very High Concern (SVHC) whilst EU Ecolabel is only awarded to textiles not containing more than 0,1% in weight of SVHC[7].

The use of BPA has historically only been reported in polycarbonate, epoxy resins and thermal paper. Exposure scenarios or toxicity evaluations therefore never included textiles and clothing as potential source of BPA.

During the last two years, BPA has however been detected in clothing articles and some exposure studies were carried. In 2017 and 2018, two limited peer-reviewed articles identified BPA in infant socks[8] and women's pantyhose[9], on samples taken locally outside the European Union. Only recently, (April 2019) have the presence and endocrine disrupting activity of BPA being measured in samples of socks for infants and young children taken from the European market[10].

These recent results are of concern as clothing articles are in direct and prolonged contact with the skin: This concern is strengthened, due to not only the high content levels of BPA measured and the estrogenic and anti-androgenic activities detected, but because young and vulnerable children usually put clothes in their mouth and suck it. The latter potentially increases exposure though ingestion and not only through dermal contact. Similarly, the risk on pregnant women is worrying due to the potential effect on the unborn child.

Furthermore, the study of Freire *et al*. also detected the presence of several parabens, which are suspected to have a potential endocrine disrupting activity and thus may contribute to further increase the effect of BPA alone.

Thereby and in the absence of any legislation regulating the presence of BPA in clothing articles intended for infants and young children, as well as, for pregnant women, it is critical to evaluate the potential risk derived from such presence.

3. Legal obligations

The presence of BPA's is regulated only under the following legal instruments, i) the Cosmetic Products, ii) the Plastic Food Contact Materials and iii) REACH Regulations, as well as, iv) the Toy safety Directive. None of these instruments defines restrictions for the presence or release of BPA in clothing or textile articles. Consequently, the safety and

[5] Commission Regulation (EU) 2016/2235 of 12 December 2016 amending Annex XVII to Regulation (EC) No 1907/2006 of the European Parliament and of the Council concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) as regards bisphenol A

[6] Commission Decision (EU) 2014/350 of 5 June 2014 establishing the ecological criteria for the award of the EU Ecolabel for textile products (notified under document

[7] Commission Decision (EU) 2017/1392 of 25 July 2017 amending Decision 2014/350/EU establishing the ecological criteria for the award of the EU Ecolabel for textile products

[8] Xue, J., Liu, W., Kannan, K., 2017. Bisphenols, benzophenones, and bisphenol A diglycidylv ethers in textiles and infant clothing. Environ. Sci. Technol. 51 (9), 5279–5286. PMID: 28368574. https://doi.org/10.1021/acs.est.7b00701.

[9] Li, A.J., Kannan, K., 2018. Elevated concentrations of bisphenols, benzophenones, and antimicrobials in pantyhose collected from six countries. Environ. Sci. Technol. 52, 10812–10819. PMID: 30137966. https://doi.org/10.1021/acs.est.8b03129.

[10] Freire, C., Molina-Molina, J.M., Iribarne-Durán L.M., Jiménez-Díaz, I., Vela-Soria, F., Mustieles V., Arrebola, J.P., Fernández, M.F., Artacho-Cordón. F.,Olea, N. Concentrations of bisphenol A and parabens in socks for infants and young children in Spain and their hormone-like activities. Environ Int. 127, 592–600. PMID: 30986741. https://doi.org/10.1016/j.envint.2019.04.013.

protection of the health of consumers against such a potential risk is covered by the General Product Safety Directive (GPSD, 2001/95/EC).

Under article 13, paragraph 1 of the GPSD the Commission is entitled to request the Member States to take measures against a product for which the Commission becomes aware that it poses a serious risk to the health and safety of consumers. To do, the Commission has to consult the Member States as well as the competent Community Scientific Committee. Such an opinion would additionally support the Commission in developing potential preventive measures ensuring the protection EU consumers.

Terms of reference

The Scientific Committee on Consumer Safety is kindly requested to provide a scientific opinion on “The safety of the presence of BPA in clothing articles”. The main purpose of the scientific opinion is to provide scientific support to assist the Commission in assessing the risk of the presence of BPA in clothing articles and the potential need for legislative amendments in the chemicals legislation and/or enforcement measures under the General Product Safety Directive.

In particular, the SCCS is asked to:

1. To review the available data on the presence and activity of Bisphenol A in clothing articles, taking into consideration the adopted opinions on tolerable intake limits and the legislative framework in other products (food contact materials, toys and printed paper)
2. To determine whether the exposure levels to BPA due to the use of clothing articles raises health concerns for consumers and, if possible, to provide indications on limit values for BPA content/release from clothing articles
3. To identify whether vulnerable consumers such as infants and young children (who might put such articles in their mouth) or pregnant women are in particular risk. On the basis of the risk assessment, could it be indicated what level of exposure to BPA from textiles can be accepted in such groups.

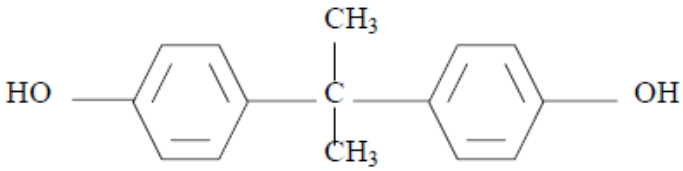
3. OPINION

3.1 Chemical and Physical Specifications

IUPAC name: 2,2-bis(4-hydroxyphenyl)propane

CAS / EC number:
CAS: 80-05-7
EC: 201-245-8

Structural formula:



Physical form: white solid flakes or powder

Molecular weight: 228,29 g/mol

Purity: 99 - 99.8 % with impurities typically including phenol (< 0.06 %), other isomers of bisphenol-A (< 0.2 %) and water (< 0.2 %) (ECB 2003)

Solubility: 300 mg/l in water at 25°C

Partition coefficient: Log Kow 3.3 - 3.5

Additional physico-chemical specifications:
- pK_a: 9.6 - 11.3
- melting point: 155 – 157 °C
- boiling point: 360 °C at 1013 kPa
- vapour pressure: 5.3 x 10^{-9} kPa at 25 °C

Ref: SCENHIR 2015

3.2 Function and uses

Bisphenol A (BPA) is a high-production volume industrial organic chemical that is widely used to manufacture polycarbonate (PC) plastics (75 % of its production volume *i.e.* ~1.1 Mt/year) and monomers of epoxy resins (~17 % of its production volume *i.e.* ~0.2 Mt/year) and other polymeric materials (WHO/FAO 2010, RIVM 2015, EFSA 2015). Both PC plastics and BPA-based resins are widely used for manufacturing food packaging and liquid containers. Hence, the primary route of exposure to BPA is oral, *via* leaching of BPA into food and beverages. Non-food related applications of PC include toys, pacifiers and medical devices (*e.g.* implants, catheters, tubing). Various dental materials are also fabricated from BPA-derived monomers. BPA has also been used in the production of thermal paper (*e.g.* cash receipts) but is subject to restriction under REACH (EU 2016/2235). BPA-based resins are used in the manufacturing

of paints, medical devices, surface coatings, printing inks and flame retardants (RIVM 2015, EFSA 2015, SCENHIR 2015).
Lately, the occurrence of BPA in clothes, mainly those made of polyester and Spandex, has been reported (Xue *et al*. 2017, Li and Kannan 2018, Freire *et al*. 2019, Wang *et al*. 2019). BPA is used as an intermediate chemical in the manufacturing of dyes and antioxidants present in finishes. The latter are used to obtain the desired properties of finished fabrics such as wrinkle-, stain-, soil- and UV-resistance; anti-fading; waterproofing; softening; and microbiological, fungal and antistatic protection (Li and Kannan 2018, Freire *et al*. 2019). For example, BPA derivatives are employed in the production of polyester fabrics to give a hygroscopic, antistatic fabric with good wash fastness (Xue *et al*. 2017). Due to direct and prolonged contact with the skin, clothing articles can thus be a potential source of dermal exposure to BPA. In addition, for young children, oral exposure due to sucking on clothes can contribute to total BPA exposure.

3.3 Exposure to BPA from clothing articles

3.3.1 Occurrence and concentrations

BPA occurrence and concentrations in clothes have been reported in four analytical studies (Xue *et al*. 2017, Li and Kannan 2018, Freire *et al*. 2019, Wang *et al*. 2019) that also provide dermal exposure estimates based on default values for substance migration. One study not only reports concentrations, but also provides experimental migration rates into artificial sweat, and on this basis provides dermal exposure estimates for dry and sweaty clothes (Wang *et al*. 2019). The studies are summarised in Table 1. In clothing samples purchased from outside the EU, the Danish EPA detected BPA in concentrations of 17 – 252 ng/g (personal communication to SCCS).

3.3.2 Migration experiments

Substances in textiles are mainly transferred to the human body by migration into body fluids such as sweat (dermal exposure) or saliva (oral exposure). In the absence of migration experiments, ECHA (2019) proposed a default migration fraction of 0.1 in its restriction dossier on sensitisers. The BfR used a default migration fraction of 0.005 (BfR 2012) which was subsequently used for the estimation of exposure to BPA from dry clothes by the groups cited in Table 1.

For BPA, migration rates into sweat have experimentally been assessed by Wang *et al*. 2019. They conducted an experiment where migration *via* sweat to skin was simulated by contact of sweat-soaked textiles with solid phase extraction cartridges for 2 hours (Table 2).

Table 1: Concentrations of BPA in clothes.

Study	Purchase of samples	No of samples	Type of samples	BPA Occurrence (%)	Median concentration (ng/g)	Mean ± SD (ng/g)	Range (ng/g)
Xue *et al*. 2017	US	77	Infant clothing	82	10.7	366 ± 1690	<2.2–13300
Li and Kannan 2018	Divers, including Portugal	36	Pantyhose	96	14.3	40.8 ± 75.3	<1.3–504
Freire *et al*. 2019	Spain	32	Children socks	91	20.5	n.a.	<0.7-3736
Wang *et al*. 2019	China	93	Divers	99	26.9	72.1 ± 209	<3.3-1823

Table 2: Experimentally determined migration rates of BPA from sweaty clothes ($EXP_{sweaty\ cloth}$) and the estimated daily dermal exposure from clothes (EXP_{daily}) by Wang *et al*. 2019. Skin contact was simulated for 2 hours.

		$EXP_{sweaty\ cloth}$ (ng/kg bw/d)				**EXP_{daily} (ng/kg bw/d)**		
BPA in clothes[a]	**MR ($ng/cm^2/d$)[b]**	**toddlers** high/low	**children** high/low	**adults** high/low		**toddlers** high/low	**children** high/low	**adults** high/low
Median (34.2 ng/g)	0.049	9.34/2.03	8.27/1.80	6.07/1.32		0.009	0.008	0.006
High (123 ng/g)	0.136	25.9/5.64	23.0/4.99	16.9/3.67		0.033	0.029	0.022
High (199 ng/g)	0.308	58.8/12.8	52.1/11.3	38.3/8.32		0.137	0.121	0.089

[a] The clothes with initial BPA concentrations of the median and 95th levels in the used clothes was selected. [b] MR= $mass_{BPA}$/cloth area, where $mass_{BPA}$ (ng/d) was the mass of detected BPA per day leached form the used clothes; cloth area was 16 cm^2 in this experiment. $EXP_{sweaty\ cloth}$ was calculated using bw values of 16.3 kg (for toddlers of 3 years old), 25.7 kg (for children of 7 years old), and 60.5 kg (for adults of 20-24 years old) from the Chinese National Physique Monitoring Communique (2014). The absorption rates of 46 % and 10 % were applied respectively in the calculation of $EXP_{sweaty\ cloth}$ for high and low dermal penetration rates.

3.3.3 Dermal exposure calculation

3.3.3.1 Exposure models

Dermal exposure to substances in clothes is different for dry and sweaty clothes, since the sweat acts as a solvent, whereas for contact with dry clothes only mechanical transfer is possible. Exposure to dry clothes can be calculated according to equation (1) (Wang *et al*. 2019, citing Xue *et al*. 2017):

$$E_{derm-dry\ clothes} = \frac{C*D*SA_{dry}*f_{mig}*f_{uptake}}{BW} \qquad (1)$$

With C: concentration of substance in clothes; D: density of fabric per surface area; SA: surface area in contact with the skin; f_{mig}: substance fraction migrating from the clothes to the skin, f_{uptake}: substance fraction taken up into the body

Exposure to sweaty clothes can be calculated according to equation (2) by using experimentally determined migration rates MR (Wang *et al*. 2019, Xue *et al*. 2017, Liu *et al*. 2017, Rovira *et al*. 2015):

$$E_{derm-sweaty\ clothes} = \frac{MR*SA_{sweaty}*f_{uptake}}{BW} \qquad (2)$$

With MR: experimental migration rate; SA_{sweat}: sweaty surface area in contact with skin

Exposure to dry clothes will be for 24 hours. Sweating, however, will occur sporadically over the day. Therefore, in order to construct a chronic exposure estimate, the two contributions need to be weighed by the exposure duration T to dry and sweaty clothes, respectively. The overall dermal exposure to clothes $E_{derm\text{-}clothes}$ can then be calculated according to:

$$E_{derm-clothes} = \frac{T_{dry}}{T_{total}} * E_{derm-dry} + \frac{T_{sweaty}}{T_{total}} * E_{derm-sweaty} \qquad (3)$$

With T_{dry}: exposure duration dry clothes; T_{sweaty}: exposure duration to sweaty clothes; T_{total}: total exposure duration

3.3.3.2 Parameterization and exposure estimates

The comparison between concentration ranges of all four studies shows that the distributions of concentrations are similar for purchases all over the world (see Table 1), in particular also for China and Spain, probably because most clothes on the European market are made in China. Therefore, both the concentration ranges and the migration rates were taken from the most comprehensive study that reports the highest concentrations, covers most garments and provides in addition a migration experiment (Wang *et al*. 2019).

Since the density of clothes D was not given by Wang *et al*. 2019, a full recalculation of $E_{derm-dry}$ with European reference values was not possible. Additionally, $E_{derm-dry}$ is very small compared to $E_{derm-sweaty}$. Therefore, $E_{derm-dry}$ for 24 hours was taken over directly from the publication.

$E_{derm-sweaty}$ was calculated based on the migration rates (MR) from clothes determined by Wang *et al*. 2019 for three different clothes, by using the median (34.2 ng/g) and the P95 (199 ng/g) of the concentration distribution of used clothes (which showed slightly higher concentrations than new clothes) in the scenarios "conservative average" and "high", respectively. The exposure estimates take into account the SCCS NoG (SCCS/1602/18) default bodyweight for adults of 60 kg. The surface area for contact with sweaty clothes was assumed to be the whole trunk, *i.e.* 6370 cm^2 being 36.4% of 17500 cm^2, with the latter being the default surface area recommended in the SCCS NoG for calculating sunscreen exposure. The fraction for trunk is based on considerations by Bremmer *et al*. 2006. Children sweat only marginally. Therefore, for toddlers the sweating surface area is zero and no $E_{derm-sweaty}$ is calculated.

Taking into account the climatic and societal conditions in Europe, chronic daily exposure to clothes fully soaked in sweat will not be longer than 8 hours (corresponding *e.g.* to a working day), so that for adults T_{sweaty} is assumed to be 8 h. In all scenarios, f_{uptake} was considered to be 0.3 (30% uptake), as suggested in this dossier (see section 3.4.2.1). Note, that in the below calculations the estimates always refer to total BPA, including the toxicologically active form "free BPA" and the metabolised forms (see 3.4.1.1). Table 3 shows the estimates for the internal exposure to total BPA *via* dermal contact with clothing articles.

3.3.4 Oral exposure calculation

Oral exposure to BPA in textiles can be relevant for young children sucking on sleeves or socks. To date, no migration rates from textiles into saliva have been experimentally determined. However, saliva is quite similar to sweat, so that the migration rates from Wang *et al*. 2019 were also used for migration into saliva. To account for the uncertainty of the analogy, only the high migration rate (0.308 ng/cm^2/d) was used to assure a conservative calculation.
For the area mouthed $A_{mouthed}$ it was assumed that at maximum a piece of 5 cm x 5 cm is mouthed, *i.e.* 25 cm^2. The fraction of mouthing time was taken from Bremmer and van Veen (2002), who refer to a study by Groot *et al*. (1998) on mouthing behaviour of 42 children. Here, mouthing of textiles was found to be 7.2 min/d for toddlers of 12-18 months. The average sucking times plus twice the standard deviation were used to determine upper bound parameters for $f_{mouthing}$ for the high scenario. 100% uptake was assumed (*i.e.* f_{uptake} is 1).

$$E_{oral-clothes} = \frac{A_{mouthed} * MR * f_{mouthing} * f_{uptake}}{BW}$$

Table 4 shows the estimates for the internal exposure to total BPA for toddlers *via* sucking on clothing articles.

SCCS overall conclusion on exposure

Table 5 summarises the aggregate exposure estimates for total BPA due to release from clothing articles. From these conservative calculations, it can be concluded that adults are more highly exposed than children are. For adults, the internal exposure to total BPA due to

clothing is around 0.5 ng/kg bw/d and around 3 ng/kg bw/d in the average and high migration scenarios, respectively.

Table 3: Exposure scenarios and resulting daily internal exposure to total BPA *via* dermal contact with clothing articles, comparison with dermal exposure to cosmetics estimated by EFSA (2015).

Scenario	C* (ng/g)	$E_{derm\text{-}dry}$* (ng/kg bw/d)	MR* (ng/cm²/d)	$SA_{sweaty}$$ (cm²)	$E_{derm\text{-}clothes\_8h}$** (ng/kg bw/d)	EFSA, 2015 dermal cosmetics§ (ng/kg bw/d)
Adults, average migration	34.2	0.006	0.049	6370	**0.524**	1.0 (women)
Adults, high migration	199	0.089	0.308	6370	**3.329**	2.0 (women)
Toddlers, average migration	34.2	0.009	n.a.	n.a.	**0.009****	1.4
Toddlers, high migration	199	0.137	n.a.	n.a.	**0.137****	2.8

*from Wang *et al.* 2019; $assumption by SCCS; §absorption fraction 0.5; n.a. not available
**corresponding to 8 h fully sweaty clothes
***no sweating was assumed

Table 4: Internal exposure to total BPA for toddlers *via* sucking on clothing articles, comparison with average and high oral exposure *via* mouthing of toys and diet estimated by EFSA (2015). Bodyweights according to EFSA (2012).

Scenario	BW (kg)	MR* (ng/cm²/d)	Mouthing time (SD) (min/d)	$f_{mouthing}$	$E_{oral\_clothes}$ (ng/kg bw/d)	EFSA, 2015 oral toys§ Average/high (ng/kg bw/d)	EFSA, 2015 oral diet Average /high (ng/kg bw /d)
Toddlers, average migration	12	0.049	7.2 (14.2)	0.025	**0.003**	**0.01 (average)**	**375 (average)**
Toddlers, high migration	12	0.308	7.2 (14.2)	0.025	**0.016**	**0.01 / 0.01**	**375 / 857**

*from Wang *et al*. 2019
§absorption fraction of 1

Table 5: Internal exposure to total BPA from clothing articles estimated for various scenarios.

	Exposure estimation for total BPA in ng/kg bw/d		
	Clothing		
Scenario	**Dermal**	**Oral**	**Aggregate exposure to total BPA**
Adults, average migration	0.524*	-	**0.524**
Adults, high migration	3.329*	-	**3.329**
Toddlers, average migration	0.009**	0.003	**0.012**
Toddlers, high migration	0.137**	0.016	**0.153**

*corresponding to 8 h contact with fully sweaty clothes
**no sweating was assumed

3.4 Toxicokinetics and metabolism

3.4.1 Toxicokinetics and metabolism after oral uptake

3.4.1.1 Information from previous assessments

From previous assessments (ANSES 2013, EFSA 2015, SCENHIR 2015, ECHA 2015), following conclusions can be drawn:

- Major inter-species differences exist in the toxicokinetic profile of BPA after oral exposure. In rodents, enterohepatic recirculation and extensive fecal excretion of unconjugated BPA is observed whilst in primates there is an extensive urinary excretion of conjugated BPA, making the BPA half-life shorter in primates than in rats.

- Oral absorption of BPA can be considered complete (> 90 %). The systemic bioavailability of free BPA is, however, reduced by a very high first pass effect in the liver. Modelled data as well as biomonitoring studies indicate that the oral bioavailability in humans of unchanged parent BPA is very low (1 – 10 %). BPA conjugates that do not retain the biological activity of the parent BPA are readily excreted in urine; hence the half-life of BPA in humans is very short, ranging from 1 to 3.5 h.

- The major BPA metabolite in humans (as well as in non-human primates and rodents) is BPA-glucuronide (80 – 100 %). BPA-sulphate has also been detected as a minor metabolite (0 – 15 %). In humans, both BPA-conjugating enzymes *i.e.* UDP-glucuronyl-transferases (mainly UGT2B15) and sulfotransferases (mainly SULT1A1) are polymorphic. A variability in BPA concentrations by approximately a factor of 4 due to inter-individual variability in BPA metabolic disposition has also been observed in biomonitoring studies.

- Pregnant women show a slight induction of the glucuronidation pathway when compared to non-pregnant women. Thus, pregnant women are characterised by a higher metabolic clearance of BPA and thus a lower systemic availability of free BPA. As the *in utero* exposure depends on maternal blood concentrations, foetal/embryonal exposure to parent BPA is limited.

- Age-dependent differences in BPA metabolism and disposition have been reported. Due to potential immature BPA metabolism, newborns and babies up to 6 months represent a

potentially susceptible subpopulation. There is no indication that the elderly are at risk, since their metabolic capacity associated with phase II enzymes is not affected.

3.4.1.2 New relevant information in humans

Thayer *et al*. (2015) investigated the pharmacokinetics of deuterated BPA (d6-BPA) in humans following a single administration (n=14). After fasting, subjects were fed a cookie containing a dose of 100 µg/kg bw of d6-BPA. Blood and urine analysis were conducted over a 3-day period. A mean serum total (unconjugated and conjugated) d6-BPA C_{max} of 1711 nM (390 ng/ml) was observed at T_{max} of 1.1 ± 0.50 h. Unconjugated (free) d6-BPA appeared in serum within 5–20 min of dosing with a mean C_{max} of 6.5 nM (1.5 ng/ml) observed at T_{max} of 1.3 ± 0.52 h. Detectable blood levels of unconjugated or total d6-BPA were observed at 48 h in some subjects at concentrations near the LOD (0.001 – 0.002 ng/ml). The half-lives for elimination of total d6-BPA and unconjugated d6-BPA were 6.4 ± 2.0 h and 6.2 ± 2.6 h, respectively. Recovery of total administered d6-BPA in urine was 84 – 109 %. Most subjects (10 of 14) excreted > 90 % as metabolites within 24 h. This study confirms previous findings that conjugation reactions of BPA are rapid and nearly complete after oral intake (< 1 % of the total d6-BPA in blood is unconjugated BPA at all times). Elimination of conjugates into urine largely occurs within 24 h.

Table 6: Pharmacokinetic parameters in human subjects following ingestion of 100 µg/kg bw deuterated BPA (d6-BPA).

	Serum						Urine
	T_{max} (h)	C_{max} (nM)	% free C_{max}	AUC (nM x h)	% free AUC	$t_{1/2}$ (h)	%
Total d6-BPA	1.1 ± 0.50	1711 ± 495	0.39 ± 0.17	4263 ± 1008	0.56 ± 0.16	6.4 ± 2.0	95 ± 7.1 (of dose administered)
Free d6-BPA	1.3 ± 0.52	6.5 ± 3.2	-	23 ± 6.2	-	5.6 ± 1.2	0.11 ± 0.19 (of total d6-BPA)

3.4.2 Toxicokinetics and metabolism after dermal uptake

3.4.2.1 Dermal/percutaneous absorption

1) In vitro human data

Several *in vitro* studies have previously measured dermal penetration of BPA in human skin (Demierre *et al*. 2012, Marquet *et al*. 2011, Mørck *et al*. 2010, Zalko *et al*. 2011), but show highly variable results due to differences in the skin samples (*e.g.* thickness, viable *vs.* non-viable skin) and experimental conditions such as vehicle, exposure duration and concentration of BPA used (ANSES 2014, ECHA 2015).Based on the *in vitro* OECD TG428 study performed by Demierre *et al*. (2012) using BPA in an aqueous solution on non-viable human skin samples, EFSA estimated that the dermal bioavailability of BPA was around 10% of the applied dose over a period of 24 h. This value is based on 8.6% of the applied dose absorbed in the receptor fluid and 0.6% present in the skin, but excludes 35.5% of the applied dose for

systemic uptake that was deposited in the *stratum corneum* (EFSA 2015). Not taking into account this skin reservoir effect could be an underestimation of the daily dose of absorbed BPA (ANSES 2014). Also, in the EU Risk Assessment Report (EU RAR) a dermal absorption of 10% was assumed, based on default considerations with respect to lipophilicity and molecular mass (ECB 2003, EC 2008). However, considering that BPA has a moderate water solubility, a log Pow of 2.2 and a relatively low molecular weight, a dermal penetration higher than 10% was suggested by SCENHIR. In their Opinion, a worst--case dermal absorption in the range of 25 – 30% instead of 10% of the applied dose was proposed (SCENHIR 2015).

As part of the Community Rolling Action Plan (CoRAP) by ECHA, a new *in vitro* dermal penetration study for BPA according to OECD TG428 was more recently conducted using fresh, metabolically active human skin, also intended to investigate potential BPA metabolism (Toner *et al*. 2018):

Guideline:	OECD 428 (2004), SCCS 1358/10
Test system:	Fresh split-thickness human abdominal skin 350-400 µm from 4 donors (3 females, 1 male) aged 33 to 46 years
Membrane integrity:	Checked by measuring electrical resistance; samples exhibiting a resistance < 10.9 kΩ were considered to have intact skin barriers
Replicates:	12 skin samples from 4 different donors
Method:	Dermatomed fresh skin mounted on Scott-Dick diffusion cells with automated flow-through system
Test substance:	[^{14}C]-BPA
Purity:	99.9% (non-labelled material) 99.8% (labelled material; radiochemical purity)
Test item:	[^{14}C]-BPA diluted in phosphate buffered saline (PBS) at 300, 60, 12 and 2.4 mg/l
Exposure area:	0.64 cm^2
Dose applied:	10 µl/cm^2
Exposure period:	24 h
Sampling period:	24 h (at 0 and 1 h, and then every 2 h)
Receptor fluid:	Tissue culture medium (DMEM) containing ca 1 % (v/v) ethanol, UGT cofactor uridine 5'-diphosphoglucuronic acid (UDPGA, 2 mM) and SULT cofactor 3'-phosphoadenosine-5'-phosphosulfate (PAPS, 40 µM)
Solubility in receptor fluid:	Not provided
Mass balance analysis:	Provided
Tape stripping:	Yes (20)
Method of Analysis:	Liquid Scintillation Counting (LSC)
GLP:	Yes
Study period:	2018

The *in vitro* percutaneous absorption of [^{14}C]-BPA by using 4 test preparations prepared in PBS at 300, 60, 12 and 2.4 mg/l was determined in fresh human dermatomed skin. Split-thickness human skin samples exhibiting a resistance higher than 10.9 kΩ were considered to have intact skin barriers. Human dermatomed skin samples were mounted onto diffusion cells. Tissue culture medium (DMEM) containing ca 1 % (v/v) ethanol, UGT cofactor uridine 5'-diphosphoglucuronic acid (UDPGA, 2 mM) and SULT cofactor 3'-phosphoadenosine-5'-phosphosulfate (PAPS, 40µM) was used as receptor fluid, pumped underneath the skin at a flow rate of 0.75 ± 0.10 ml/h. The skin surface temperature was maintained at 32 ± 1 °C throughout the experiment. A quantity of 10 µl/cm^2 of the test preparations was applied to the skin surface. Receptor fluid was collected for Donor 1 at 0.5, 1, 2, 4, 6, 8, 10, 12 and 24 h post dose. Receptor fluid was collected for Donors 2-4, at 0 and 1 h post dose and then in two-hourly fractions from 2 to 24 h post dose. After 24 h of exposure, the skin surface was rinsed-off using a concentrated commercial soap for hand washing, rubbed in with a tissue swab, followed by rinsing with a dilute 2% (v/v) soap solution of the same soap and drying

the skin surface with tissue paper. This process was repeated. The skin was subsequently removed from the cells and the *stratum corneum* was removed by 20 consecutive tape strips. The unexposed skin was cut away from the exposed skin. The exposed epidermis was separated from the dermis using a scalpel. To determine percutaneous absorption, each test concentration was applied to a total of 12 skin samples from 4 donors (*i.e.* 3 skin samples/donor). The penetration, mass balance and distribution of [^{14}C]-BPA were determined by measuring its concentration in the relevant compartments using LSC.

Results

Two samples from the same donor showed an electrical resistance below 10.9 kΩ. The samples were, however, not excluded from the study because no more skin samples were available from this donor. The lower electrical resistance indicates poorer barrier integrity, and therefore potential for greater absorption and thus a more conservative approach.

Mean recovery rates were 98.5% (3200 ng equiv/cm²), 96.4 % (620 ng equiv/cm²), 98.6% (120 g equiv/cm²) and 99.4% (25 ng equiv/cm²) of the applied dose, for the tested concentrations of 300, 60, 12 and 2.4 mg/l, respectively. Apart from one cell of the lowest concentration, the recovery (= mass balance) fell within the acceptable range (*i.e.* between 85 and 115%) (BAuA 2018). Table 7 shows a summary of the test results.

The mean absorbed doses (receptor fluid + receptor chamber wash + receptor rinse) were 2.0% (63 ng equiv/cm^2), 1.7 % (11 ng equiv/cm^2), 2.7 % (3.4 ng equiv/cm^2) and 3.6 % (0.91 ng equiv/cm^2) of the applied BPA concentrations, respectively. The mean dermal deliveries of BPA (epidermis + dermis + absorbed dose) were 15.9% (511 ng equiv/cm^2), 16.1% (103 ng equiv/cm^2), 19.3% (24.1 ng equiv/cm^2) and 20.0 % (5.07 ng equiv/cm^2) of the applied doses, respectively; with the majority of the radioactivity associated with the epidermis (11.9 - 10.4%) compared to the dermis (6.2 - 3.3%) and the receptor fluid (3.6 - 1.7%).

Table 7: Distribution of dose recovered after 24 h incubation (% of dose applied and ng equiv./cm^2). Each test preparation was applied to a total of 12 samples of skin from 4 donors (3 skin samples per donor) and values are expressed as mean results ± SD.

Test preparation	1	2	3	4
BPA concentration (mg/L)	300	60	12	2.4
(% applied dose)				
Dislodgeable dose	72 ± 5.7	70.9 ± 6.2	72 ± 8.0	72 ± 9.1
Stratum corneum tapes 1–2	2.5 ± 1.5	2.3 ± 1.3	1.8 ± 1.0	2.3 ± 1.9
Whole *stratum corneum*	10 ± 5.4	9.3 ± 4.3	7.3 ± 3.3	7.7 ± 4.9
Unabsorbed dose	83 ± 8.4	80 ± 6.9	79 ± 10	79 ± 10
Epidermis	11 ± 6.4	10 ± 5.7	10 ± 5.3	12 ± 4.9
Dermis	3.3 ± 2.4	4.0 ± 2.0	6.2 ± 4.3	4.5 ± 3.7
Absorbed dose	2.0 ± 1.4	1.7 ± 1.2	2.7 ± 2.0	3.6 ± 1.7
Dermal delivery	16 ± 8.14	16 ± 7	19 ± 8.5	20 ± 6.2
Mass balance	98.5 ± 1.99	96.4 ± 1.5	98.6 ± 2.2	99.4 ± 6.5
ng equiv./cm^2				
Dislodgeable dose	2300 ± 200	450 ± 36.0	90 ± 9.4	18 ± 1
Stratum corneum tapes 1–2	80 ± 48	15 ± 8.5	2.2 ± 1.3	0.60 ± 0.50
Whole *stratum corneum*	330 ± 180	59 ± 28	9.1 ± 4.3	2.0 ± 1.3
Unabsorbed dose	2700 ± 300	510 ± 42	99 ± 12	20 ± 2.3
Epidermis	340 ± 210	67 ± 38	13 ± 6.7	3.0 ± 1.4
Dermis	100 ± 76	26 ± 13	7.8 ± 5.4	1.1 ± 0.9
Absorbed dose	63 ± 45	11 ± 7.9	3.4 ± 2.5	0.9 ± 0.4
Dermal delivery[a]	510 ± 260	100 ± 47	24 ± 11	5.1 ± 1.7
Mass balance	3200 ± 120	620 ± 24	120 ± 2.9	25 ± 1.9

Terms used are derived from the glossary of OECD Guidance document No. 28.
Dislodgeable dose = skin wash + tissue swabs + pipette tips + donor chamber wash.
Unabsorbed dose = dislodgeable dose + whole *stratum corneum* (*all tape strips* + unexposed skin.
Absorbed dose = receptor fluid + receptor chamber wash + receptor rinse.
Dermal delivery = epidermis + dermis + absorbed dose.
Mass balance = dermal delivery + unabsorbed dose.
[a] Numerical values are rounded to two digits.

Conclusion

Under the experimental conditions of this study, the authors concluded that a dermal absorption of 16 - 20% of the applied doses could be established.

SCCS comment

Seen the high variability observed in this study between the dermal delivery values obtained for the different concentrations tested and the small deviation from the test protocol, the SCCS considers that the mean + 2 SD should be used, as indicated in Table 8. Based on these *in vitro* data, and in agreement with BAuA 2018, a rounded value of 30% for dermal absorption could be established.

Table 8: *In vitro* dermal absorption values.

BPA concentration (mg/l)	Mean dermal delivery + 2 SD (% of applied dose)	Mean dermal delivery + 2 SD (ng equiv/cm^2)
2.4	32	9
12	36	46
60	30	194
300	32	1030

Liu and Martin (2019) further compared the percutaneous absorption of a low (1.5 µg/cm^2) and high (7.7 µg/cm^2) dose of isotope-labelled BPA and bisphenol S (BPS) over a 25-hour period *in vitro* using the EpiDerm™ reconstructed human skin model. It was found that 43 - 46% of total BPA was recovered in receiver solutions and 13 - 14% in skin tissue. Although the EpiDerm™ skin model consists of normal human epidermal keratinocytes, permeation exceeds that of human epidermis (Schäfer-Korting *et al*. 2008). Therefore, permeation data from this *in vitro* study should be regarded with caution when extrapolating to *in vivo* conditions.

Recently, in an *in vitro* percutaneous absorption study conducted by Champmartin *et al*. (2020), it was shown that after 40 h topical exposure of human split-thickness skin sections (500 µm) to 20 µg/cm^2 of BPA, the absorption of BPA is vehicle dependent ranging from 3% of the applied dose in case of sebum to 6% with acetone and 41% with water. Except with water, the dislodgeable dose corresponded to the majority of the BPA applied. The proportion of BPA detected in the skin was very low with sebum (3%) compared to 24% and 27% for acetone and water, respectively. However, the distribution of BPA in the individual skin layers (*stratum corneum* – living epidermis – dermis) was not assessed, making it difficult to compare the data with the OECD TG428 study of Toner *et al*. (2018).

2) *In vivo* animal data

Marquet *et al*. (2011) studied dermal absorption of BPA in male Sprague Dawley rats upon 24 h topical administration (under occlusion) of a concentrated solution of ^{14}C-BPA in acetone (4 mg/ml, 500 µl total volume) in a surface density of 200 µg/cm^2 and a 72 h sample collection interval. Based on recovery form urine, faeces and the carcass, it was found that approximately 26% of the applied dose was absorbed.

3) *In vivo* human data

Biedermann *et al*. (2010) investigated dermal penetration of BPA by exposing human volunteers to solid BPA by pressing thermal paper or by directly applying ethanolic solutions of BPA to their finger pad. Recovery from the fingertips was determined for different exposure times by measuring BPA in the ethanolic extraction solution. It was found that 2 h after contacting thermal printer paper with dry skin, 27% of the BPA picked up could no longer be washed off by water, but was still extractable with ethanol. When 1 µl of a 10 mg/ml BPA solution in ethanol was directly applied to the fingertips, a recovery of 40% after 1.5 h and a maximal dermal absorption fraction of 0.6 was observed. When the same amount of BPA was applied in a larger volume of solvent (10 µl, 1 mg/ml), a recovery of < 5% was obtained, indicating that the maximal dermal absorption of BPA can reach 95 – 100% when it is topically applied in an ethanolic solution. As ethanol may act as penetration enhancer, it can be assumed that the dermal absorption fraction for BPA dissolved in ethanol may be used for BPA in formulations that have similar vehicle properties as ethanol (*e.g.* emulsions such as body lotions and creams) (EFSA 2015). Yet, for emulsions and creams where, apart from lipophilic substances, a high percentage of water is also present, the vehicle effect of ethanol will overestimate the vehicle effect of cosmetic formulations and thus the dermal absorption will be < 100%. Based on the study of Biedermann *et al*. (2010), ANSES' experts considered 27% to be the most likely value for skin penetration rate (ANSES 2013). However, in its opinion of 2015, EFSA considered a value of 10% dermal absorption for exposure scenarios with dermal contact to thermal paper (derived from the *in vitro* study of Demierre *et al*. 2012) and 50% for dermal absorption of BPA from cosmetics.

Thayer *et al*. 2016 investigated occupational exposure of cashiers (n=33) to BPA from handling thermal receipts. However, no significantly higher urinary BPA after the work shift compared to pre-shift urinary samples was observed.

Liu and Martin (2017 & 2019) conducted studies on 5 to 6 male volunteers whereby the participants handled thermal receipts containing 25 mg/g paper deuterated (d16-BPA) for 5 min, followed by hand washing 2 h later. Urine (0 - 48 h) and serum (0 - 7.5 h) were

monitored for free (unconjugated) and total d16-BPA. One week later, participants returned for a dietary administration (cookie containing 20 µg d16-BPA) and followed the same monitoring. One participant repeated the dermal administration with extended monitoring of urine (9 days) and serum (2 days). After dietary exposure, urine total d16-BPA peaked within 5 h and quickly cleared within 24 h. After dermal exposure, the cumulative excretion increased linearly for 2 days, and half the participants still had detectable urinary total d16-BPA after 1 week. The participant repeating the dermal exposure had detectable d16-BPA in urine for 9 days, showed linear cumulative excretion over 5 days, and had detectable free d16-BPA in serum. Proportions of free d16-BPA in urine following dermal exposure were 0.71 - 8.3% of total d16-BPA and were generally higher than following the dietary exposure (0.29 -1.4%). Thus, compared to dietary BPA exposure, dermal absorption of BPA leads to prolonged exposure and may lead to higher proportions of unconjugated BPA in systemic circulation. However, the participants had to wear a nitrile glove on the exposed hand for 2 h to prevent any incidental hand to-mouth exposure and to prevent contamination of urine samples during collection. These occlusive conditions may have influenced permeation of BPA.

Overall, a lot of variation is measured in human volunteer studies with handling BPA-containing thermal paper due to the many factors that play a role including handling time and frequency, concentration BPA in thermal paper, skin contact area, length of time between contact and hand washing.

Recently, Sasso *et al*. (2020) performed a toxicokinetic study in 10 volunteers (6 men and 4 women) following direct dermal administration of 100 µg/kg of deuterated BPA (d6-BPA) over a 12 h period, either in 0.3% carboxymethylcellulose suspension or 95% ethanol solution. Blood and urine concentrations were measured of free and conjugated d6-BPA (Table 9). There was no difference in total d6-BPA kinetics between the carboxymethylcellulose and ethanol vehicles. Total BPA was observed in serum approximately 1.4 h after application and unconjugated d6-BPA was measured in serum approximately 2.8 h after the start of the dermal administration. Total and free d6-BPA serum concentrations increased rapidly for 7 h. Recovery of total administered d6-BPA in urine was ~1% of the applied dose after 3 days, but a high inter-individual variability was observed. 71 – 99 % of the applied dermal dose remained unabsorbed over a 12 h period, indicating that 12 – 29 % of the applied dose penetrated the skin over a 12 h period. The mean C_{max} for total and free 6-BPA was 3.26 nM and 0.272 nM, respectively; the area under the curve (AUC) for total d6-BPA was 99.2 nM x h, and 7.35 nM x h for free d6-BPA. Free d6-BPA represented 10.9 ± 3.73 % of C_{max} and 8.95 ± 3.43% of AUC. Analysis of the AUC for dermal (this study) and oral administration (Thayer *et al*. 2015) revealed that 2.3% of the dermal dose became systemically available. Also a higher free:total d6-BPA ratio compared to oral administration is observed, likely due to less metabolism in the skin *versus* the extensive first pass metabolism in the liver following BPA ingestion. At cessation of the dermal application, elimination from the serum was slow with half-lives for free and total d6-BPA of 15 – 20 h (*i.e.* 2.5 times greater than after oral exposure), indicating a slow release of d6-BPA from a skin depot into the blood.

Table 9: Experimentally determined kinetic parameters in 10 human subjects following 12 h dermal application of 100 µg/kg deuterated BPA (d6-BPA).

	Serum					Urine
	C_{max} (nM)	% free C_{max}	AUC (nM x h)	% free AUC	$t_{1/2}$ (h)	Cumulative excreted (µg/kg bw)
Total d6-BPA	3.26 ± 2.31	10.9 ± 3.73	99.2 ± 56.7	8.95 ± 3.43	17.9 ± 4.88	0.998 ± 0.546
Free d6-BPA	0.272 ± 0.141	-	7.35 ± 2.95	-	14.8 ± 4.06	-

SCCS overall conclusion on dermal absorption

Based on the relevance and methodological soundness, SCCS regards the *in vitro* study of Toner *et al*. (2018) using viable human skin and the most recent kinetics study of Sasso *et al*. (2020) in humans as key studies. From both studies, it can be concluded that a rounded value of 30% dermal absorption has to be considered.

3.4.2.2 Dermal metabolism

Most of the major biotransformation enzymes found in the liver are present in the skin, but often at lower activity levels. In general, phase II reactions play a greater role in the skin compared to phase I reactions of which the metabolic capacity is considered very low (Gundert-Remy *et al*. 2014, SCCS/1602/18). Phase II glucuronidation and sulfation are the major metabolic processes for BPA in humans following oral exposure (Thayer *et al*. 2015, Oh *et al*. 2018). Since both UGT and/or SULT expression and/or activity have been measured in human skin samples (Gundert-Remy *et al*. 2014, Toner *et al*. 2018), BPA conjugation (*i.e.* inactivation) is plausible.

1) In vitro human data

The metabolism of BPA in the skin has been previously evaluated in a number of *in vitro* studies using human skin samples. Marquet *et al*. (2011) reported that absorbed BPA was nearly not biotransformed (*i.e.* < 3 % after 24 h exposure), whilst in the study of Zalko *et al*. 2011 27 % of the applied dose of BPA was metabolised into BPA mono-glucuronide and BPA mono-sulphate after 72 h of incubation. Yet, both studies show methodological shortcomings and did not permit to arrive at a reliable estimate of skin metabolism. From a conservative point of view, EFSA therefore did not consider skin metabolism in their risk assessment (EFSA 2015).

More recently, Toner *et al*. (2018) performed an *in vitro* study on fresh, metabolically active human skin to assess the rate and extent of absorption and metabolism of BPA. From this study it appears that after 24h exposure the overall metabolism ranges between 7.1 - 19.6 % of the applied dose of BPA (300 mg/l). No metabolism was observed in any of the epidermis samples; only in the dermis and receptor fluid samples BPA-glucuronide and BPA-sulphate (and some polar metabolites) were measured, but a large inter-donor variability of levels and distributions of metabolites was observed over the different skin compartments. However, the study setup was primarily intended to determine the dermal absorption of BPA. Hence, experimental conditions such as the concentrations of the UGT cofactor uridine 5'-diphosphoglucuronic acid (UDPGA) and SULT co-factor 3'-phosphoadenosine-5'-phosphosulfate (PAPS) in the receptor fluid would need further adaptation to be able to more accurately assess BPA skin metabolism. Nevertheless, based on the study of Toner *et al*. (2018), the evaluating Member State Competent Authority (eMSCA) suggested in its corrigendum to ECHA's Risk Assessment Committee (RAC) safety evaluation of BPA to use a value of around 10 % for skin metabolism (BAuA 2018).

Liu and Martin (2019) examined the extent of biotransformation of BPA (and BPS) in the EpiDerm™ keratinocyte model, displaying phase II enzymatic activity (including UGT) comparable to human skin (Götz *et al*. 2012). No significant difference was observed between free and total BPA in the skin tissue, suggesting limited biotransformation in skin. There was also little evidence for any BPA metabolites crossing into the receiver solutions; except at 3h where in the high-dose treatment (7.7 µg/cm^2), free BPA was significantly lower (71%) than total BPA.

Very recently, Champmartin *et al.* (2020) also reported that the absorbed dose of BPA measured in the receptor fluid of their human *in vitro* percutaneous absorption study was mostly composed of the non-metabolized form. However, the study authors indicate methodological shortcomings. Further experiments and analytical development are necessary to better characterise the skin's metabolic activity towards BPA.

2) In vivo human data

As described under section 3.4.2.1, the human kinetics study of Liu and Martin (2017) showed that proportions of free d16-BPA in urine following dermal exposure (*via* handling of thermal receipts) were 0.71 - 8.3% of total d16-BPA and were generally higher than following dietary exposure (0.29 - 1.4%). Thus, compared to dietary BPA exposure, dermal absorption of BPA may lead to higher proportions of unconjugated BPA in systemic circulation.

In the study of Sasso *et al*. (2020) it was reported that the mean C_{max} for total and free 6-BPA was 3.26 nM and 0.272 nM, respectively. The AUC for total d6-BPA was 99.2 nM x h, and 7.35 nM x h for free d6-BPA. Free d6-BPA represented 10.9 ± 3.73% of C_{max} and 8.95 ± 3.43% of AUC. Analysis of the AUC of dermal *versus* oral administration (Thayer *et al*. 2015) revealed that a higher free:total d6-BPA ratio compared to oral administration is observed, likely due to less metabolism in the skin *versus* the extensive first pass metabolism in the liver following BPA ingestion.

SCCS overall conclusion on dermal metabolism

Both *in vitro* and *in vivo* studies indicate dermal biotransformation of BPA, albeit much lower than after oral intake. Since biotransformation of BPA mainly represents a detoxification, SCCS considers that from a conservative point of view the lowest value measured of 7.1% in the *in vitro* study of Toner *et al*. (2018) has to be taken into account for skin metabolism.

3.4.3 PBPK modelling

3.4.3.1 Information from previous assessments

In its BPA opinion of 2015, EFSA summarised the PBPK models (Teeguarden *et al*. 2005, Mielke and Gundert-Remy 2009, Edginton and Ritter 2009, Fisher *et al*. 2011, Yang *et al*. 2013 & 2015) which have been developed for oral and dermal exposure in humans. These PBPK models were developed to predict the internal exposures in laboratory animals and humans in a route-specific manner.

Mielke *et al*. (2011) developed a PBPK model which enables predictions of serum concentration-time profiles and estimations of internal dose metrics for unconjugated BPA following oral and dermal exposure. For the uptake of BPA from cosmetics, a constant uptake rate was assumed, leading to 50% absorption of the external dermal dose within 24 h.

The PBPK models for BPA were further evaluated against published human pharmacokinetic studies with BPA (Völkel *et al*. 2002 & 2005, Thayer *et al*. 2015, Teeguarden *et al*. 2015).

Thayer *et al*. (2015) measured BPA and total BPA both in serum and urine. Teeguarden *et al*. (2015) measured BPA, BPA-glucuronide and BPA-sulfate in serum and urine. In the study of Thayer *et al*. (2015), BPA was applied to a cookie, whereas in the study of Teeguarden *et al*. (2015) BPA was added to tomato soup.

Since the EFSA opinion on BPA from 2015 (EFSA 2015), another PBPK model was published (Karrer *et al*. 2018).

The authors used the model developed by Yang *et al*. (2015) with a modification in the maximal velocity of the glucuronidation in the small intestine which was scaled up to the body weight for comparing the pharmacokinetics of BPA. For the oral route, the predicted AUC 0-24 h for a dose of 30 µg/kg bw (dose used Teeguarden *et al*. 2015), was 4.15 (2.91 - 5.15) nM x h, whereas the experimental value was 2.5 (1.4 – 5.7) nM x h.

For dermal absorption, the authors used 20% for thermal paper (Toner *et al*. 2018), and 60% for personal care products (Biedermann *et al*. 2010). The model was evaluated against data from 3 adults after handling BPA-containing receipts and eating French fries (Hormann *et al*. 2014). When comparing the measured and predicted serum concentration, the model estimated adequately (*e.g.* ratio between observed and predicted is less than 2) the serum concentration of BPA in female, but overestimated for the male.

SCCS comment

PBPK models for the aggregated oral and dermal exposure have been developed to estimate the internal concentration of unconjugated BPA. Using the most recently developed PBPK model of Karrer *et al*. (2018), a good prediction of the unconjugated BPA serum concentrations for 2 female volunteers was found, but the model failed for 1 male volunteer. It should be noted, however, that in the study of Hormann *et al*. (2014) to which the modelled data were compared, volunteers were exposed both *via* dermal and oral ways. It is not possible to discriminate between oral and dermal exposure in this study.

The SCCS considers that these PBPK models are only suitable to estimate the upper limits of the internal dose metric of BPA following skin contact. Additional human data are needed to calibrate and validate dermal absorption.

3.5 Toxicological evaluation

3.5.1 Summary of existing assessments on BPA

Information on adverse effects after exposure to BPA is solely based on the most recent health risk assessments conducted by EFSA (2015) and ECHA (2017). SCCS is, however, aware of the fact that EFSA is currently re-evaluating the huge amount of data on BPA toxicity that came available since December 2012, *i.e.* the cut-off point for their latest assessment published in 2015. Hence, this opinion should be updated accordingly when this information becomes available.

General toxicology

According to the harmonised classification and labelling approved by the EU, BPA is not a skin irritant, but it can lead to serious eye damage (Eye Dam. 1), is able to elicit skin sensitization (Skin Sens. 1) and may cause respiratory irritation (STOT SE 3) (ECHA 2017).

BPA has low acute toxicity for all routes of exposure relevant to human health (EFSA 2015).

BPA has been found to affect kidney and liver weight in parental animals and in all the generations of rats and mice examined in multi-generation studies. EFSA considered these effects as relevant systemic effects for the identification of a NOAEL in their risk assessment. In mice, the increased kidney weight was associated with nephropathy at the highest BPA dose. Liver weight was increased in rats (relative weight) and mice (both absolute and relative weight). The latter species also showed hepatocellular hypertrophy (EFSA 2015).

Reproductive and developmental effects

BPA is classified as toxic for reproduction (Repr. 1B) (ECHA 2017). Exposure to BPA at the adult stage alters the endocrine steroidogenic function of the ovary and more specifically the production of estrogens by the follicle, potentially leading to disturbance in the estrous cycle. Although most of the reported evidence relies on rodent studies, there are *in vitro* data showing the same negative effect of BPA on the estrogen production in the human follicle cells. Furthermore, an indication of a negative association between the ability of the follicle to produce estrogens and exposure to BPA was observed in women. Lastly, the role of estrogens in the maintenance of the cycle is similar in rodents and humans. ECHA's report concludes that it is quite likely that BPA may alter the ovarian cycle in humans through the disruption of the endocrine activity of the ovarian follicle (ECHA 2017).

Neurological, neurodevelopmental and neuroendocrine effects

In its opinion of 2015, EFSA stated that there are indications from prospective studies in humans that BPA exposure during pregnancy might be associated with altered child behaviour in a sex-dependent manner. However, the associations were not consistent across the studies and it could not be ruled out that the results were confounded by diet or concurrent exposure factors. Studies also reported changes that may indicate effects of BPA on brain development

(effect on neurogenesis and on gene expression, neuroendocrine effects, effects on the morphology of certain brain regions, etc.). ECHA, more recently concluded that on the basis of i) the significant amount of *in vivo* and *in vitro* animal data showing impairment of learning and memory by exposure to BPA and the potential alteration of cellular and molecular mechanisms underlying these processes through disturbance of the estrogenic pathway, ii) the similar types of signalling pathways underlying human cognition and iii) the numerous data showing sex steroid regulation of these behaviours, exposure to BPA could alter human cognitive abilities. At the neuroendocrine level, BPA can also act during the perinatal/postnatal organisation or adult activation of the hypothalamus-pituitary system in rodents or primates. Because of the similarities in sex-steroid-induced regulation of this axis between humans and rodents, it is possible that the changes in kisspeptin, GnRH expression, activity or liberation and sex steroid receptor expression induced by developmental or adult exposure to BPA occur also in humans and therefore impact estrous cyclicity (ECHA 2017).

Immune effects

There is recently emerging evidence that BPA may have immunotoxic effects. The variability of the effects makes the interpretation and the transposition of these effects to humans uncertain. It is, however, noted that the role of estrogens has been often reported in immunocompetence and in the development of innate and adaptive immune response (ECHA 2017).

Cardiovascular effects

According to EFSA (2015), an overall causal link between BPA exposure and cardiovascular effects in humans could not be established. There were also insufficient animal data to suggest that BPA has an effect on cardiac function or causes cardiotoxicity. Yet, a recent review reports evidence suggesting an effect of BPA on the cardiovascular system that may involve estrogen receptor rapid signalling (ECHA 2017).

Metabolic effects

EFSA could not establish a causal link between BPA exposure and metabolic effects in humans (EFSA 2015). In its report of 2017, ECHA concludes that based on animal studies (rodents and non-rodents) after prenatal and/or perinatal or adult exposure, there is evidence that BPA may increase the incidence of type-2 diabetes *via* an ED MoA. In particular, BPA has been shown to alter insulin secretion and/or release by β-pancreatic cells, or insulin signalisation (signalling mechanisms) within insulin-sensitive organs (*i.e.* liver, muscle, adipose tissues). This resulted in variations in the expression levels of hepatic or adipose tissue markers, which are indicative of a state of insulin resistance. These effects were considered by the experts as hallmarks of endocrine disruption mechanisms, especially if there is a combination of effects each leading to insulin resistance within the different insulin-sensitive tissues. In addition, while most studies were performed on males, a few studies have also examined the impact of BPA either on both sexes or on females. However, more studies should be undertaken before one can conclude on a sex-specificity or not of the metabolic impact of BPA.

Recent experimental *in vivo* and *in vitro* studies indicate that these effects may involve ERα, ERβ or GPR30 pathways. Other hormones such as leptin and adiponectin, which are involved in resistance to insulin and lipogenesis, are also modified following BPA exposure. This shows that BPA could interfere in the balanced interplay between insulin secretion and insulin action that controls glycaemia.

Overall, it is suggested that the pancreas is targeted by BPA exposure and that mechanisms could differ depending on whether exposure occurs during the foetal life or in adulthood. Foetal differentiation of the pancreas appears highly sensitive to BPA exposure based on the outcomes surveyed *e.g.* β-cell proliferation and apoptosis. Limited data exist on the impact of BPA on α-cells and glucagon secretion. Conclusions indicate that BPA can elicit histopathological modifications during the foetal life, with consequences on insulin synthesis rate and/or release.

Moreover, most of the *in vitro* studies showing adverse effects of BPA on adipocyte differentiation and function point to alteration of endocrine mechanisms (*e.g.* adiponectin

release, insulin signalling cascade effectors). It is not clear whether BPA activates PPARγ and/or other nuclear receptors. Cross-talk between nuclear receptors may explain these uncertainties.
Even if available epidemiological studies are inconclusive, these effects are considered relevant for humans because similarities exist in homeostatic regulation of insulin production and sensitivity between animals and humans and because of *in vitro* experimental data using human cells or tissue.

Genotoxicity
The available data support that BPA is not mutagenic (in bacteria or mammalian cells), or aneuploidy *in vitro* was not expressed *in vivo.* The positive finding in the post-labelling assays *in vitro* and *in vivo* is unlikely to be of concern, given the lack of mutagenicity and clastogenicity of BPA *in vitro* and *in vivo* (EFSA 2015).

Carcinogenicity
There is evidence from rodents and non-human primate studies that prenatal and postnatal exposure to BPA causes endocrine modifications in the mammary tissue, ultimately increasing its susceptibility to chemical carcinogens. All data presented in the ECHA 2017 report support the possibility that BPA, through interaction with the nuclear ERs, or GPER, and indirectly with PR, modulates estrogenic- and progestin agonist activities. Emerging epigenetic studies have suggested changes related to estrogen-dependent genes (such as EZH2 and HOTAIR), as well as HOX genes (involved in embryogenesis and postnatal development) which could be associated with the BPA-induced abnormal development and cancer increased susceptibility of the mammary gland.
Mechanistic studies also support the conclusion that BPA affects a number of receptor-dependent and independent signalling pathways, resulting in effects on hormone homeostasis and gene expression as well as in cytogenetic and epigenetic effects (EFSA 2015). In this context, it has been shown that the induction of androgen receptors in foetal mice by estradiol or BPA is permanent, leading to dramatically increased prostatic androgen receptors. This increase may result in a marked increase in the sensitivity of the adult prostate to hormonal stimulation, which is associated with prostate enlargement and pre-cancerous cellular abnormalities (metaplasia) (ECHA 2017).
These effects were, however, not further investigated because the level of evidence is considered insufficient at this point, but it cannot be excluded that the range of effects related to the ED-properties of BPA may be wider than those described above. Recently, using a combined morphometric and statistical approach, non-monotonic effects of BPA on the developing rat mammary gland that differed from those of ethinyl estradiol have been reported (Montévil *et al*. 2020).

3.6 Risk assessment associated with BPA-containing clothing

3.6.1 Determination of the Human Equivalent Dose by EFSA

Several epidemiological studies suggest associations between exposure and a range of health effects and diseases, including metabolic syndrome, infertility, and severity of asthma (Rochester 2013, Rezg *et al*. 2014, Rancière *et al*. 2015). However, these studies have generally a cross-sectional design, which makes their interpretation difficult in regard to the causal nature of the link between measured BPA exposures and observed health events.. Moreover, most of these studies suffer from methodological weaknesses or oppose conflicting results. Consequently, existing risk assessments on BPA, as *e.g.* by EFSA (2015) or the French Agency for Food, Environmental and Occupational Health & Safety (ANSES 2013), have made use of epidemiological data only as supporting evidence for the selection of the BPA critical effect, which was determined from toxicological data. Thus, the calculation of the MoS for BPA

could not be based on any solid relationship between BPA exposure biomarker concentrations and an adverse health effect observed in human.

Allowable oral exposure guidance values for BPA were identified from the US EPA (1993), Health Canada (2008), EFSA (2015) and ECHA (2015). Values from Health Canada and the US EPA, are respectively 50 µg/kg bw/day (as provisional tolerable daily intake (p-TDI)) and 25 µg/kg bw/day (as reference dose), based on the reduction of the body weight of rodents as critical effect.

Considering available human and animal evidence prior to 2015, EFSA estimated "likely" the effects of BPA on liver and kidney weight and mammary gland proliferation as "likely" effects that could be used for dose-response analysis and for defining the Point of Departure (POD) for the TDI derivation. Thereby, the mean F0 relative kidney weight increase in the 2-generation study in mice by Tyl *et al*. (2008) was used as critical endpoint (Table 10). A Benchmark Dose 10 % Lower Confidence Limit ($BMDL_{10}$) of 8.96 mg/kg bw/day for changes in the kidney weight of mice in the Tyl *et al*. (2008) study was calculated. This dose in mice was extrapolated to an oral Human Equivalent Dose (HED), by application of a Human Equivalent Dose Factor (HEDF) of 0.068 equivalent to the ratio of BPA-specific area under the curve (AUC) values for free BPA in serum across mice and humans. While AUC values of unconjugated BPA in adult and newborn CD-1 mice serum after oral dosing were available from toxicokinetic experiments, AUC values after oral exposure of human adults were predicted using a human PBPK model by Yang *et al*. (2013). This model is built on a monkey-based PBPK model (Fisher *et al*. 2011), which was further evaluated against the results of a BPA toxicokinetic study in humans with gelatin-capsule administration of BPA (Völkel *et al*. 2002). Multiplying the mice $BMDL_{10}$ by the HEDF, a HED value of 609 µg/kg bw/day was calculated. The t-TDI value of 4 µg BPA/kg bw/day was finally obtained by dividing the HED by an overall assessment factor (AF) of 150 to account for intra-species differences (AF of 10), inter-species toxicodynamic differences (AF of 2.5) and for remaining uncertainties (AF of 6) about possible toxic effects below the dose at which effects on the kidney are observed, *i.e.* regarding mammary gland, reproductive, neurobehavioural, immune and metabolic systems.

Table 10: EFSA and ECHA's exposure guidance values derived for BPA in the general population.

Agency	Key study	Endpoint	Point of departure (µg/kg bw/day)	Assessment factors	Exposure guidance value
EFSA (2015)	Tyl *et al*. 2008 (mouse two-generation toxicity study)	Increased relative mean kidney weight in male F0 adult mice	$BMDL_{10}$=8960 HED=609 with HEDF=0.068	**150** - 2.5 for interspecies differences - 10 for intra-species differences - 6 for the uncertainty in the database	**t-TDI** **4 µg/kg bw/day**
ECHA (2015)	Tyl *et al*. 2008 (mouse two-generation toxicity study)	Increased relative mean kidney weight in	$BMDL_{10}$=8960 HED=609	**150**	**oral DNEL** **4 µg/kg bw/day**

		male F0 adult mice	with HEDF=0.068 $BMDL_{10}$=8960 HED=6.64 or 6.24 with conversion factor 'oral mouse' to 'dermal human' either 1350.4 or 1436.9 depending upon PBPK model used (Yang *et al*. 2013 or Mielke *et al*. 2011)	- 2.5 for interspecies differences - 10 for intra-species differences - 6 for the uncertainty in the database	**DNEL for dermally absorbed total BPA dose** **0.1 µg/kg bw/day** (with assumed skin biotransformation rate of 50 %)

BMDL = lower confidence limit of the benchmark dose level; DNEL= derived no effect level; HED = human equivalent dose; HEDF = human equivalent dose factor; t-TDI = temporary tolerable daily intake

3.6.2 Determination of the oral and dermal derived no effect level by ECHA

EFSA's derivation approach was supported by ECHA's Risk Assessment Committee (RAC) and the value of 4 µg BPA/kg bw/day was endorsed as derived no effect level (DNEL) for oral exposure in the general population (Table 10) (ECHA 2015). Based on the same HED approach, the RAC also derived a DNEL value of 0.1 µg/kg bw/day for a dermally absorbed total BPA dose in the general public. To this end, the human PBPK model from Mielke *et al*. (2011) that includes both the oral and dermal exposure routes, was used. The predictions of serum concentration-time profiles and estimations of internal dose metrics for free BPA following oral and dermal exposure enabled the RAC to calculate a conversion factor 'oral mouse' to 'dermal human', allowing thereby for converting the $BMDL_{10}$ for alteration of the kidney weight into a HED. The DNEL for a dermally absorbed dose of BPA was calculated by application of the same AFs than for the oral DNEL and by considering a BPA biotransformation rate in the skin of 50%, assuming thereby that only the half of an external dermal dose of BPA may reach the systemic circulation as free BPA.

In a corrigendum to the ECHA report of 2015 (BAuA 2018), the evaluating Member State Competent Authority (eMSCA) addressed discrepancies on the dermal DNEL derivation by the RAC related to dermal absorption and skin metabolism. In its report of 2015, ECHA calculated the DNEL for the dermally absorbed dose based on a dermal absorption value of 10%. Using the PBPK model of Mielke *et al*. (2011), a dermal absorption percentage of 30% instead of 10 % results in the same human dermal AUC value and, consequently, in the same value for the DNEL dermally absorbed. Furthermore, ECHA suggested that the dermal DNEL of roughly 0.05 µg/kg bw/d (based on the calculated value of 0.04 µg/kg bw/d) should be rounded to 0.1 µg/kg bw/d based on the assumption that 50% of the parent BPA is bio-transformed (inactivated) in the skin. Therefore, the eMSCA suggested to keep the DNEL for the dermally absorbed dose for the general population at 0.042 µg/kg bw/d (rounded: 0.05 µg/kg bw/d).

3.6.3 Risk assessment by SCCS

For risk assessment of BPA in textiles performed in this opinion, SCCS decided to use the Point of Departure (POD) that was selected for the derivation of t-TDI value or oral DNEL of 4 µg/kg bw/day (EFSA 2015, ECHA 2015). Therefore the HED value of 609 µg/kg bw/d was taken as a POD. SCCS is also aware that reports produced by national bodies such as ANSES, the Danish Environmental Protection Agency, the Swedish Chemicals Agency and the Dutch

National Institute for Public Health and the Environment all conclude that effects are observed consistently at doses well below those that were considered by EFSA to set the t-TDI value of 4 µg/kg bw/day (Danish EPA 2012, KEMI 2013, ANSES 2013, RIVM 2015). Several studies published after ECHA's and EFSA's assessments suggest that BPA causes developmental effects at exposure levels far below the EFSA critical dose (Beausoleil *et al*. 2018, Hessel *et al*. 2016, Lind *et al*. 2019). However, some of these studies have limitations in design and reporting and are not consistent with results obtained in other studies. This decision was taken, however, in the light of the upcoming EFSA re-assessment of the hazards of BPA. Indeed, EFSA's experts committed to re-evaluate the substance's toxicity by reviewing the data published since December 2012 (the cut-off point of EFSA's latest assessment), also taking into consideration the results of a large 2-year BPA rat study by the US Consortium Linking Academic and Regulatory Insights on BPA Toxicity (CLARITY-BPA) (Badding *et al*. 2019). The selected endpoint and critical dose to derive the 2015 t-TDI may change in light of the new available data. If this is the case, the risk assessment of BPA in textiles, based on the 2015 t-TDI should be updated accordingly.

For the MoS calculation *via* clothing, it is necessary to take into account the huge difference in metabolization of free BPA when comparing the dermal and the oral route. Therefore, the SCCS considered it appropriate to calculate the MoS by comparing the aggregate SED (dermal plus oral) to an internal HED (HEDi) rather than the external HED value. Assuming 1 % free BPA after uptake by the oral route, a HEDi of 6.09 µg/kg bw/d or 6090 ng/kg bw/d can be derived (SCENHIR 2015).

The same percentage of free BPA was applied to the calculated exposure estimates for total BPA to derive the SED_{oral} for free BPA. For the dermal route, although available experimental data indicates 7.1 % metabolism of BPA into non-toxic metabolites in the skin (see section 3.4.2.1.), SCCS decided from a conservative point of view to not consider skin metabolism, and assumed for the calculation of SED_{dermal} that 100 % free BPA is present after dermal uptake.

The following MoS calculations for the different BPA exposure scenarios *via* clothing can be made:

Table 11: Conservative MoS calculations for exposure to BPA due to the use of clothing articles.

	ng/kg bw/d			
Scenario	**SED_{dermal}**	**SED_{oral}**	**Aggregate SED**	**MoS**
Adults, average migration	0.524	-	0.524	11617
Adults, high migration	3.329	-	3.329	1829
Toddlers, average migration	0.009	0.003	0.012	507500
Toddlers, high migration	0.137	0.016	0.153	39804

Following this approach for the estimated average (~0.5 ng/kg bw/d) and high exposure (~3 ng/kg bw/d) levels of BPA resulting from clothing for adults, gives a MoS of >11500 and >1800, respectively. In case of toddlers that are significantly less exposed to BPA from clothing due to less sweating, much higher MoS values are derived for both the average and high exposure scenarios. From these calculations, it can be deduced that at the estimated BPA exposure levels due to the use of clothing articles there is no health concern for consumers.

From the HEDi, it can be derived that an aggregate daily internal exposure to total BPA of 60.9 µg/kg bw/d due to clothing ($E_{derm\text{-}clothes}$) would correspond to a MoS of 100. Conversion of equation (3) (see section 3.3.3.1) allows to back calculate $E_{derm\text{-}dry}$ and subsequently to determine a limit concentration C of BPA in clothes using equation (1). Assuming a surface weight of 0.2 kg/m^2 textile (Rovira *et al*. 2015, ECHA 2019), following concentration limits for BPA in clothing for the high exposure scenarios could be established (Table 12):

Table 12: Estimated conservative concentration limits for BPA in clothing articles for the high exposure scenarios.

Scenario	Estimated limit concentration of BPA in clothing (mg/kg textile)
Adults, high migration	296
Toddlers, high migration	145

From these calculations, a maximum of around 145 mg BPA/kg textile could be proposed to protect consumers. This value is in line with the 130 mg/kg limit value that has recently been proposed to reduce the risk of sensitization due to BPA in textile (ECHA 2019).

4. CONCLUSION

1. *To review the available data on the presence and activity of Bisphenol A in clothing articles, taking into consideration the adopted opinions on tolerable intake limits and the legislative framework in other products (food contact materials, toys and printed paper)*

Regarding potential health effects of BPA, this opinion is based on the information present in the most recent health risk assessments conducted by EFSA (2015) and ECHA (2017). SCCS is, however, aware of the fact that EFSA is currently re-evaluating the huge amount of data on BPA toxicity that came available since December 2012, *i.e.* the cut-off point for their latest assessment published in 2015. Hence, all outcomes and conclusions reported in this document with respect to human health might be subject of change in the near future. If this is the case, the opinion should be updated accordingly.

Regarding exposure, a few studies have indicated BPA occurrence in clothing articles and provide dermal exposure estimates based on default values for substance migration. From these studies, it appears that the distributions of concentrations are similar for purchases all over the world with median concentrations ranging between 10.7 - 26.9 ng/g. However, only one study also provides experimental migration rates of BPA into artificial sweat, and on this basis provides dermal exposure estimates for dry and sweaty clothes (Wang *et al*. 2019). Based on these reported migration rates, exposure estimates were calculated under conservative assumptions, with an 8-hour chronic daily contact of the whole trunk to clothes fully soaked in sweat for men and women. As children only sweat marginally, only exposure to dry clothes was considered for this age group. Yet, for the latter, additional oral exposure due to sucking on clothes has been taken into consideration. From these calculations, it can be concluded that for adults the internal total BPA exposure due to clothing is ~0.5 ng/kg bw/d and ~3 ng/kg bw/d in case of average and high migration scenarios, respectively. For toddlers, exposure to total BPA *via* clothing is much less *i.e.* ~0.01 and ~0.15 ng/kg bw/d in case of average and high migration, respectively.

2. *To determine whether the exposure levels to BPA due to the use of clothing articles raises health concerns for consumers and, if possible, to provide indications on limit values for BPA content/release from clothing articles.*

Currently, there is no legislation regulating restrictions for the presence or release of BPA in clothing or textile articles. Yet, BPA has been detected in clothing articles and taken into account its hazard profile, this might be of concern as clothing articles are in direct and prolonged contact with the skin. Moreover, in case of young children, oral exposure due to sucking on clothes can contribute to total BPA exposure.

All clothing exposure scenarios analysed in this opinion result in an exposure level of BPA that is below the t-TDI of 4 µg/kg bw/d based on increased kidney weight in a 2-year generation study in mice as critical endpoint with a $BMDL_{10}$ of 8.96 mg/kg bw/d. However, regarding the dermal exposure *via* clothing, it is necessary to take into account the huge difference in dermal bioavailability of parent BPA when compared to the oral route. Therefore, the SCCS considered it appropriate to follow a MoS approach and to make the comparison using an internal HED (HEDi, 6.09 µg/kg bw/d when assuming 1 % free BPA after uptake by the oral route) rather than the external HED value. From a conservative point of view, SCCS further decided not to consider skin metabolism. For the average (~0.5 ng/kg bw/d) and high exposure (~3 ng/kg bw/d) scenarios considered, the MoS is >11500 and >1800, respectively. In case of toddlers who are significantly less exposed to BPA due to clothing, much higher MoS values are derived for both the average and high exposure scenarios. Hence, there is no risk for

adverse effects of the estimated exposure levels of BPA resulting from the use of clothes, independent of the age group of the consumer.

Furthermore, based on the estimated BPA exposure levels in clothing articles for the high exposure scenarios and assuming a surface weight of 0.2 kg/m^2 textile (Rovira *et al*. 2015, ECHA 2019), a maximum amount of BPA in textile of around 145 mg/kg could be established *via* back calculations.

3. *To identify whether vulnerable consumers such as infants and young children (who might put such articles in their mouth) or pregnant women are in particular risk. On the basis of the risk assessment, could it be indicated what level of exposure to BPA from textiles can be accepted in such groups.*

   In view of the very low exposure levels of BPA from clothing, no particular population group is at risk. As indicated above, a concentration limit of around 145 mg BPA/kg textile could be proposed as a preventive measure to ensure the protection of consumers. This value is conservative and in line with the 130 mg/kg limit value that has recently been proposed to reduce the risk of sensitisation due to BPA in textiles (ECHA 2019).

5. MINORITY OPINION

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6. REFERENCES

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7. GLOSSARY OF TERMS

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8. LIST OF ABBREVIATIONS

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