Committee for Risk Assessment (RAC)

Committee for Socio-economic Analysis (SEAC)

Opinion

on an Annex XV dossier proposing restrictions on

Bisphenol A

ECHA/RAC/RES-O-0000001412-86-56/F

ECHA/SEAC/ RES-O-0000001412-86-82/F

Compiled version prepared by the ECHA Secretariat of RAC's opinion (adopted 5 June 2015) and SEAC's opinion (adopted 4 December 2015)

5 June 2015

ECHA/RAC/RES-O-0000001412-86-56/F

4 December 2015

ECHA/SEAC/ RES-O-0000001412-86-82/F

Opinion of the Committee for Risk Assessment

and

Opinion of the Committee for Socio-economic Analysis

on an Annex XV dossier proposing restrictions of the manufacture, placing on the market or use of a substance within the EU

Having regard to Regulation (EC) No 1907/2006 of the European Parliament and of the Council 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (the REACH Regulation), and in particular the definition of a restriction in Article 3(31) and Title VIII thereof, the Committee for Risk Assessment (RAC) has adopted an opinion in accordance with Article 70 of the REACH Regulation and the Committee for Socio-economic Analysis (SEAC) has adopted an opinion in accordance with Article 71 of the REACH Regulation on the proposal for restriction of

Chemical names:	**4,4'-isopropylidenediphenol (bisphenol A or BPA)**
EC No.:	201-245-8
CAS No.:	80-05-7

This document presents the opinion adopted by RAC. The Background Document (BD), as a supportive document to both RAC and SEAC opinions, gives the detailed ground for the opinions.

PROCESS FOR ADOPTION OF THE OPINIONS

France has submitted a proposal for a restriction together with the justification and background information documented in an Annex XV dossier. The Annex XV report conforming to the requirements of Annex XV of the REACH Regulation was made publicly available at: http://echa.europa.eu/web/guest/restrictions-under-consideration on **18 June 2014.** Interested parties were invited to submit comments and contributions by **18 December 2014.**

ADOPTION OF THE OPINION OF RAC

Rapporteur, appointed by RAC: ***Peter Hammer SORENSEN***

Co-rapporteur, appointed by RAC: ***Normunds KADIKIS***

The RAC opinion as to whether the suggested restrictions are appropriate in reducing the risk to human health and/or the environment has been reached in accordance with Article 70 of the REACH Regulation on ***5 June 2015***.

The opinion takes into account the comments of interested parties provided in accordance with Article 69(6) of the REACH Regulation.

The RAC opinion was adopted ***by consensus.***

ADOPTION OF THE OPINION OF SEAC

Rapporteur, appointed by RAC: ***Stavros GEORGIOU***

Co-rapporteur, appointed by RAC: ***Thea Marcelia SLETTEN***

The draft opinion of SEAC

The draft opinion of SEAC on the suggested restriction has been agreed in accordance with Article 71(1) of the REACH Regulation on ***11 September 2015.***

The draft opinion takes into account the comments of and contributions from the interested parties provided in accordance with Article 69(6) of the REACH Regulation.

The draft opinion was published at http://echa.europa.eu/web/guest/restrictions-under-consideration on ***16 September 2015.*** Interested parties were invited to submit comments on the draft opinion by ***16 November 2015.***

The opinion of SEAC

The opinion of SEAC on the suggested restriction was adopted in accordance with Article 71(1) and (2) of the REACH Regulation on ***4 December 2015.*** The opinion takes into account the comments of interested parties provided in accordance with Articles 69(6) and 71(1) of the REACH Regulation.

The opinion of SEAC was adopted by ***consensus***

OPINION

Original proposal by the Dossier Submitter:

Entry [#]. 4,4'-isopropylidenediphenol (Bisphenol-A) CAS No 80-05-7 EC No 201-245-8	"Shall not be placed on the market inthermal paper in concentration equal to or greater than 0.02% by weight, after [entry into force + 36 months]"

THE OPINION OF RAC

RAC has formulated its opinion on the proposed restriction based on information related to the identified risk and to the identified options to reduce the risk as documented in the Annex XV report and submitted by interested parties as well as other available information as recorded in the Background Document. RAC considers that the proposed restriction on **4,4'-isopropylidenediphenol *(bisphenol A, BPA)*** is the most appropriate EU wide measure to address the identified risks in terms of the effectiveness in reducing the risks.

The proposed restriction is as follows:

Entry [#]. 4,4'-isopropylidenediphenol (bisphenol A) CAS No 80-05-7 EC No 201-245-8	Shall not be placed on the market in thermal paper in concentration equal to or greater than 0.02% by weight. The Annex XVII entry should apply from [36] months after entry into force.

THE OPINION OF SEAC

SEAC has formulated its opinion on the proposed restriction based on information related to socio-economic benefits and costs documented in the Annex XV report and submitted by interested parties, the opinion of RAC, as well as other available information as recorded in the Background Document.

Comparing the socio-economic benefits to the socio-economic costs, the proposed restriction is considered unlikely to be proportionate. However, there may be favourable distributional and affordability considerations.

JUSTIFICATION FOR THE OPINION OF RAC AND SEAC

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JUSTIFICATION FOR THE OPINION OF RAC AND SEAC

1. IDENTIFIED HAZARD AND RISK

Justification for the opinion of RAC

This restriction proposal addresses the health risks identified for pregnant workers and consumers exposed to 4,4'-isopropylidenediphenol (further referred to in this opinion as BPA) contained in thermal paper they may handle. The population at risk is more precisely their unborn children which are exposed *in utero* via their mother.

The restriction proposal targets workers, such as cashiers, who are likely to handle thermal tickets and consumers who may receive a ticket or receipt after a purchase, an ATM withdrawal or a payment with credit card, in other words any consumer. The exposure route considered is the dermal route[1].

The risk is considered by the Dossier Submitter to be potentially severe and likely to concern every EU country. The evaluation of the effects reported throughout the scientific literature, including those arising at low doses allowed to demonstrate adverse effects for the health of the unborn child defined as 'at risk' for:

- The female reproductive system (increase in the occurrence of ovarian cysts, increase in the occurrence of endometriosis and disruption of ovarian cycles)

- The brain and the behaviour (alteration of spatial memory and learning functions)

- Vulnerability of the developing mammary gland (increase in the terminal end buds (TEB), terminal ducts (TD) and hyperplastic ducts (HD), considered as precursors to breast cancer with subsequent co-exposure to carcinogenic agents)

- Metabolism and obesity (increase in body weight (BW) and in cholesterol)

1.1. Hazard

The toxicity of BPA has been extensively reviewed in the recent past, amongst others in the EU by the European Chemicals Bureau resulting in the EU Risk Assessment Report (ECB 2007), by the European Food Safety Authority (EFSA 2015), by the Scientific Committee on Occupational Exposure Limits (SCOEL 2014) and by the Scientific Committee on Emerging and Newly-Identified Health Risks (SCENIHR 2015). RAC took these evaluations into account in its assessment of the proposed restriction, with a specific emphasis on the most recent evaluation of EFSA (EFSA 2015).

[1] The Dossier Submitter is aware that other routes of exposure to BPA such as hand-to-mouth contact are possible but was not able to evaluate them. It is conceivable, however, that hand-to-mouth contact could contribute to the exposure of workers and consumers to BPA from thermal paper. Due to the lack of information hand-to-mouth contact is not considered further in this opinion.

1.1.1. General toxicity

General toxicity was not specifically assessed by the Dossier Submitter. EFSA (2015) concluded the following regarding the general toxicity of BPA:

"In summary, BPA effects on the kidney and liver weight were reported both in rats and mice in the multi-generation studies by Tyl et al. in 2002 and 2008. In male mice the increased kidney weight was associated with nephropathy at the highest BPA dose, while the kidney weight changes were less marked in female mice and were not associated with nephropathy. Mild renal tubular degeneration was also observed in female rats at the highest dose. In contrast, Tyl et al. (2002) and the new subchronic rat study including prenatal exposure by US FDA/NCTR, showed reductions in kidney weight. EFSA noted that the mechanisms of the effects in the rodent kidney are not yet understood including whether these are due to the unconjugated or conjugated form of BPA. As it would not be possible to distinguish between effects of conjugated and unconjugated BPA, EFSA assumed that the effects in the kidney were caused by unconjugated BPA as a conservative approach. Liver weight was increased in rats (relative weight) and mice (both absolute and relative weight), the latter species also showing hepatocyte hypertrophy (Tyl et al., 2002; US FDA/NCTR, 2013 and Delclos et al., 2014). These observations support that changes in the kidney and liver are critical endpoints in BPA toxicity, and based on the EFSA evaluations of 2006 and 2010 EFSA considered that these effects were "likely" [2] *without performing a WoE* [Weight of Evidence]*. These endpoints were therefore taken forward for hazard characterisation.*

[…]

Based on the above mentioned robust studies on general toxicity, the reported effects on kidney and liver have been taken forward for hazard characterization. It should be noted that the US FDA/NCTR (2013) study is of shorter duration than the studies by Tyl and colleagues and effects indicative of general toxicity were only seen at doses higher than those in the Tyl studies, and therefore the latter studies have been selected as the basis for hazard characterisation for general toxicity."

EFSA (2015) calculated a BMDL10 (benchmark dose lower confidence limit of 10%) of 8960 µg/kg bw/day based on a 10% increase in the mean relative kidney weight in male mice of the F0 generation in Tyl et al. (2008). This increased kidney weight is an indication for systemic toxicity.

1.1.2. Brain and behaviour

The Dossier Submitter considered the oral study by Xu et al. (2010) in mice as the key study for neuro-developmental toxicity. The critical effects in this study were the alteration of memory and learning functions paralleled by a decrease in the expression of glutamate NMDA receptors.

The EFSA (2015) opinion concluded on neurological, neurodevelopmental and neuroendocrine effects as follows: "[…] *In summary, there are indications from prospective studies in humans that prenatal BPA exposure (BPA exposure during pregnancy) may be associated with altered child behaviour in a sex-dependent*

[2] EFSA (2015) defined "likely" as having a likelihood of 66-100%.

manner. However, the associations were not consistent across the studies and it cannot be ruled out that the results are confounded by diet or concurrent exposure factors. The associations reported do not provide sufficient evidence to infer a causal link between BPA exposure during pregnancy or childhood and neurodevelopmental effects in humans.

A number of new studies report 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.). Whether such changes are mechanistically related to the neurobehavioral responses reported following exposure is attempted addressed by some studies but with inconsistent results.

Several new animal studies investigated anxiety-like behaviour, learning and memory, social behaviour and sensory-motor function. Some studies report changes in anxiety-like behaviour after BPA exposure. Some, but not all, studies reported significant impairment of either learning and/or memory capacities. A few studies also report effects on social behaviour and sensory-motor function. However, the studies present methodological shortcomings, such as small sample size, lack of consideration of the litter effect, not properly controlled variability of exposure through diet and inadequate statistics. Using a WoE approach, the CEF Panel assigned a likelihood level of "as likely as not" to neurological, neurodevelopmental and neuroendocrine effects of BPA[. Since the likelihood][3] *level for this endpoint is less than "likely" (see Appendix A), this endpoint was not taken forward for assessing the toxicological reference point, but was taken into account in the evaluation of uncertainty for hazard characterisation and risk characterisation".*

See sections 3.4 and 4.3 of the EFSA (2015) opinion for more details.

RAC considers that the results from the Xu et al. (2010) study suggest that developmental exposure to BPA can interfere with learning and memory capacities in different learning tasks in rodents, including spatial learning and passive avoidance learning together with down-regulation of the NMDA receptors. However, the effects of BPA on learning and memory abilities of laboratory rodents are not fully consistent, as both positive and negative effects are reported in different studies.

Two studies that were not included in the restriction report or in EFSA (2015) were submitted during public consultation (Elsworth et al. 2013 and Ferguson et al. 2014). Elsworth et al. (2013) showed effects on brain development (loss of midbrain TH-immunoreactive neurons and loss of hippocampal spine synapses) in non-human primates at low BPA doses. No alterations in sexually dimorphic behaviors in male and female Sprague-Dawley rats were observed by Ferguson et al. (2014).

Conclusion

RAC in principle agrees with EFSA's conclusion on effects on brain and behaviour. Since effects on brain and behaviour have been observed at and below the range where kidney effects occur, RAC considers it prudent to

[3] Included by RAC for clarification.

take them into account in hazard and risk assessment and in health impact assessment. RAC however acknowledges that the available information does not allow a quantification of the dose-response relationship, therefore this endpoint will be accounted for in the setting of Assessment Factors.

1.1.3. Effects on the female reproductive system

In animals with pre- and/or post-natal exposure the Dossier Submitter observed the following effects which were considered sufficiently of concern and relevant to be taken into account: increase in the occurrence of ovarian cysts, increase in the frequency of endometrial hyperplasia's and disruption of ovarian cycles. The key study ultimately chosen by the Dossier Submitter for the risk assessment was the study by Rubin et al. (2001) which showed a disruption of the ovarian cycle with lengthening of the oestrous cycle. This study used oral exposure and gave a NOAEL of 100 µg/kg bw/day and a LOAEL of 1200 µg/kg bw/day after treatment from GD6 until weaning in Sprague-Dawley rats.

The EFSA (2015) opinion concluded: *"In relation to reproductive and developmental effects in humans, the CEF Panel concluded that there are indications from prospective studies that BPA exposure during pregnancy may be associated with disturbed fetal growth, and weak indications that BPA exposure during pregnancy may be associated with maternal and infant decreased thyroid function, but it cannot be ruled out that the results are confounded by diet or concurrent exposure factors. The associations found in the human studies are not sufficient to infer a causal link between BPA exposure and reproductive effects in humans. Potential effects are considered to be as likely as not.*

Overall, the better powered, better conducted studies in animals found few consistent effects of in-utero exposure to BPA on reproductive development at dose levels at or below 3.6 mg BPA/kg/day HED [Human Equivalent Dose]*. On balance, the evidence remains contradictory and highly variable between studies. The CEF Panel noted that there is some evidence for effects of BPA exposure on several parameters indicative for changes in the reproductive system in adult male animals at dose levels below 3.6 mg/kg bw per day, although these effects were modest. It is not possible to conclude that these changes are reflective of changes in reproductive performance, since the studies rarely included a forced/continuous breeding phase in adulthood to establish reduced fertility. However, in several multigenerational studies no effects were observed at dose levels as low as 3 µg/kg bw per day up to at least 50 mg/kg bw per day.*

Using a WoE approach, the CEF Panel assigned a likelihood level of "as likely as not" [4] *to reproductive and developmental effects of BPA at low doses (below the HED of 3.6 mg/kg bw per day). Since the likelihood level for this endpoint is less than "likely" (see Appendix A), this endpoint was not taken forward for assessing the toxicological reference point, but was taken into account in the evaluation of uncertainty for hazard characterisation and risk characterisation."*

See sections 3.3 and 4.3 of the EFSA (2015) opinion for more details.

4 EFSA (2015) defined "as likely as not" as having a likelihood of 33-66%.

Based on the available studies, RAC considers that there is evidence of effects of BPA exposure on several parameters indicative of changes in the reproductive system. The multi-generation studies (Tyl et al. 2008 and 2002, NTP 1985, EMA et al. 2001) and a subchronic study (Delclos et al. 2014, also referred to as US FDA/NCTR 2013) were the basis of the CLP classification for fertility by RAC (2014). RAC's opinion (RAC 2014) was based on adverse effects, such as disturbances in the oestrous cycle, at a dose of 600 mg/kg bw/day (Tyl et al. 2008) and at a dose of 100 mg/kg bw/day (Delclos et al. 2014). The ovarian toxicity reported in Tyl et al. (2002) included reduced absolute and relative ovarian weight at the two highest doses of 50 and 500 mg/kg bw/day and in Delclos et al. (2014) an increase in ovarian follicular cysts was observed at 300 mg/kg bw/day. In Delclos et al. (2014), an increase in cystic endometrial hyperplasia was observed in the uterus at the highest dose of 300 mg/kg bw/day.

No adverse effects were observed at dose levels from 3 µg/kg bw/day up to 50 mg/kg bw/day in the aforementioned multi-generation studies and in Delclos et al. (2014), whereas several other studies do report effects at doses below 50 mg/kg bw/day. It is not possible to conclude that the changes seen in the latter studies reflect changes in reproductive performance. Due to the inconsistency in the study results, the low reproducibility of studies indicating reproductive effects at lower doses, and the uncertain adversity of the effects reported, the uncertainty of the results from studies reporting effects below dose levels of 50 mg/kg bw/day is consequently large.

Conclusion

RAC in principle agrees with EFSA's conclusion on effects on the female reproductive system. Since effects on the reproductive system have been observed at and below the range where kidney effects occur, RAC considers it prudent to take them into account in hazard and risk assessment and in health impact assessment. RAC however acknowledges that the available information does not allow a quantification of the dose-response relationship and therefore this endpoint will be accounted for in the setting of Assessment Factors.

1.1.4. Metabolism and obesity

The Dossier Submitter derived a LOAEL of 0.26 mg/kg bw/day based on increased body weight and increased cholesterolemia in female mice in Miyawaki et al. (2007).

The EFSA (2015) opinion concluded: *"Of the reviewed human studies on metabolic effects only two were prospective while 22 were cross-sectional and thus not suitable on their own to study exposure-disease associations. Inconsistent with the results of cross-sectional studies one prospective study found that a higher BPA concentration in maternal urine during pregnancy was associated with a lower level of obesity in daughters. A causal link between BPA exposure and metabolic effects in humans cannot be established.*

A number of studies in pre- and postnatally exposed rats and mice indicate that BPA exposure could have an effect on metabolic function as evidenced by effects on

glucose or insulin regulation or lipogenesis, and body weight gain (short-term studies). Based on the results from other studies with a longer duration (e.g. 90 days) there is no convincing evidence that BPA is obesogenic after intrauterine exposure or in longer-term studies.

Using a WoE approach, the CEF Panel assigned a likelihood level of "as likely as not" to metabolic effects of BPA. Since the likelihood level for this endpoint is less than "likely", this endpoint was not taken forward for assessing the toxicological reference point, but was taken into account in the evaluation of uncertainty for hazard characterisation and risk characterisation."

See sections 3.7 and 4.3 of the EFSA (2015) opinion for more details.

Conclusion

RAC in principle agrees with EFSA's conclusion on metabolism and obesity. Although RAC is of the opinion that the studies described are not sufficiently convincing for quantifying the dose-response, RAC considers it prudent to take the metabolic effects into account in hazard and risk assessment (by accounting for them in the setting of Assessment Factors) and in health impact assessment.

1.1.5. Immunotoxicity

The Dossier Submitter included no assessment of this endpoint in the restriction proposal. Thus, the public consultation did not cover immunotoxicity. Nevertheless, during the public consultation two new studies (Menard et al. 2014a,b) regarding this endpoint were submitted.

Menard et al. (2014a) reported that juvenile rats perinatally exposed to BPA failed to induce a proper cellular immune response after systemic immunisation. Perinatal exposure to BPA at 5 µg/kg bw/day increased susceptibility to *N. brasiliensis* parasitic infection by deregulating TH1/Th2 cytokines profile in infected intestinal mucosa.

In the other study, Menard et al. (2014b) investigated the consequences of low-dose exposure to BPA during the perinatal period on mucosal (i.e. GALT, gut-associated lymphoid tissue) and systemic immune responses to the food antigen ovalbumin in rats at adulthood. The authors concluded that perinatal BPA exposure impaired oral tolerance and sensitization to dietary antigens in adulthood. BPA not only affected local GALT function but also systematically activated the T-cell population and increased immune response to immunisation.

EFSA´s review of immunotoxicological effects of BPA did not include the recent studies by Menard et al. (2014a,b) as they were published by the time EFSA was finalising their opinion. In the absence of this new information EFSA (2015) concluded: "*Based on recent human studies, there are indications that BPA may be linked to immunological outcomes in humans, although these studies had limitations and confounding factors may have been present. A causal link between BPA exposure during pregnancy or in childhood and immune effects in humans cannot be established.*

Studies in animals lend support to the possibility of immunological effects of BPA. Most of these studies suffered from shortcomings in experimental design and reporting. Although dose-responses could not be confidently established in most studies, a dose-related effect was observed in allergic lung inflammation.

Using a WoE approach, the CEF Panel assigned a likelihood level of "-as likely as not- to likely" to immunotoxic effects of BPA. Since the likelihood level for this endpoint is less than "likely" (see Appendix A), this endpoint was not taken forward for assessing the toxicological reference point, but was taken into account in the evaluation of uncertainty for hazard characterisation and risk characterisation".

See sections 3.5 and 4.3 of the EFSA (2015) opinion for more details.

Discussion

The two studies by Menard et al. (2014a,b) are the first studies reporting effects on food allergies and on resistance to infections. Earlier reports available on immunotoxicity are related to increased risk of respiratory allergies. In Menard (2014b) increases in anti-OVA IgG-levels were seen after BPA exposure in a dose range of 0.5-50 µg/kg bw/day. For other endpoints only one dose level (5 µg/kg bw/day) was used. Although the studies do not allow a quantification of the dose-response relationship, RAC is of the view that they add to the overall likelihood of immune effects, thereby reinforcing the conclusion by EFSA (2015) to apply an assessment factor of 6 to take into account the uncertainty regarding mammary gland, and reproductive, neurobehavioural, immune and metabolic systems (see section 1.1.8.3).

Conclusion

RAC took note of the information submitted through public consultation indicating effects of BPA on the immune system (food allergies and reduced resistance to infections) at 5 and possibly even 0.5 µg/kg bw/day (Menard et al. 2014a,b). RAC stressed that no assessment of this endpoint was included in the restriction proposal. Nevertheless, RAC considers it prudent to take the effects on the immune system into account in hazard and risk assessment (by accounting for them in the setting of Assessment Factors) and in health impact assessment.

1.1.6. Mammary Gland

The Dossier Submitter considered that the effects of BPA on the mammary gland were "recognised" effects in animals and should be taken into account to assess the risk to human health. The Dossier Submitter observed that EFSA's draft opinion also considered that the effects of BPA on mammary gland development are "likely" and that these effects are relevant to humans.

The Dossier Submitter considered that it is important to take into account the possibility of increased cancer risk in the children of women who have a high level of endogenous oestrogens or xeno-oestrogens during pregnancy and are then exposed to tumour initiating agents. Based on the studies described later in this

opinion, the Dossier Submitter considered ductal hyperplasia and effects on the architecture of the mammary gland, including effects on Terminal End Buds (TEB) as critical effects for the human risk assessment. For effects on these undifferentiated epithelial structures (Terminal Ducts (TB) and TEB), an oral NOAEL of 25 µg/kg bw/day and a LOAEL of 250 µg/kg bw/day were proposed by the DS based on Moral et al. (2008).

The EFSA (2015) opinion concluded: *"The proliferative responses and possibly enhanced sensitivity to mammary gland carcinogens seen in animal studies might be of relevance for human health and are therefore included in the risk assessment."* and *"the CEF Panel concluded that BPA-induced effects on the mammary gland of rats, mice or monkeys exposed pre- or perinatally were "likely" effects".*

However, EFSA considered none of the available studies to be sufficiently robust in terms of methodology, or a consistent dose-response for deriving a health-based guidance value based on mammary gland effects was absent.

See sections 3.9 and 4.3 of the EFSA (2015) opinion for more details.

1.1.6.1. Studies in humans

The associations between BPA exposure and breast cancer have been investigated in one case-control study in Korean women (Yang et al. 2009). The study does not allow for a conclusion on the link between BPA exposure and breast cancer.

1.1.6.2. Effects on mammary glands in animals

Several in vivo studies investigating the effects on the mammary gland in female offspring after oral / subcutaneous exposure to pregnant and/or lactating mothers were identified and have been summarized in Annex 1 and Annex 2. The studies are summarised and ordered by oral and subcutaneous administration. For further details, see also the Background Document.

The criteria used in Delclos et al. (2014) to evaluate changes in the mammary gland were as follows:

- *Alveolar hyperplasia* – density of lobules of alveoli in a lobuloalveolar (male) or tubuloalveolar (female) growth pattern per unit area of mammary fat pad present in the tissue section.
- *Terminal end bud hyperplasia* - The terminal end bud is the developmental immature precursor of the alveolar bud (Greaves, 2012). The term "terminal end bud" hyperplasia was used only by the pathologist form the Delclos 2014 study conducting the female PND 21 mammary gland evaluation. In the PND 90 evaluations, alveolar hyperplasia was used for both males and females.
- *Duct / ductal hyperplasia* – relative density (number) of branching ducts per unit area of unit mammary fat pad present in the tissue section.
- *Intraductal hyperplasia* – relative number of ducts lined by three or more layers of stratified epithelial cells.

The definitions used in the literature to evaluate changes in the mammary gland

are not always consistent. For example the term "intraductal hyperplasia", is used by the pathologist from the Delclos team to address intraductal epithelia proliferation but in the human literature is synonymous with "duct hyperplasia" (Murray et al. 2007).

Discussion

Reported changes in mammary tissue include intraductal and ductal hyperplasia; increased terminal end buds (TEBs), terminal ducts (TB) and alveolar buds (AB); accelerated differentiation; increased proliferation and reduced apoptosis, accompanied by changes in gene and protein expression related to the proliferative process. The majority of these studies were conducted in rodent species, however, accelerated mammary gland development and increased epithelial density in terminal end buds have also been reported in a recent study in monkeys.

The changes in proliferative / developmental advancement induced by BPA in mammary tissue may lead to enhanced susceptibility to mammary tumours in later life.

Two studies with subcutaneous, pre- or perinatal BPA exposure (Murray et al. 2007 and Vandenberg et al. 2008) report on intraductal hyperplasia (i.e., an increase in the relative number of ducts lined by three or more layers of epithelial cells), while no intraductal hyperplasia was observed in Delclos et al. (2014). Intraductal hyperplasia is observed in humans and is considered as a precursor of ductal carcinoma both in rodents and in humans. Therefore this lesion is of high relevance to predict cancer in the human and animal mammary gland and is considered as adverse.

An increase in the number of terminal end buds as well as ductal hyperplasia was reported at low doses (e.g., 250 µg/kg bw/day in Moral et al. 2008). Delclos et al. (2014) reported overall increases of duct and alveolar density (hyperplasia), but at higher doses (2700 µg/kg bw/day). The TEBs in rodent mammary tissue or the terminal ductal lobular unit in the human breast are considered to be the sites of breast cancer initiation. An increase in TEBs, or more specifically stem cells within TEBs, appears to increase the incidence of mammary tumours, related to the high cell proliferation activity in these structures. Ductal hyperplasia and an increase of the number of TEBs may be regarded as supporting evidence for tumour formation along with an increase in the proliferation of epithelial cells. These effects in experimental animals are dependent on the study design (e.g., the type of the diet, the administration and doses of the substances, the exposure time and the sampling time point). Ductal hyperplasia and increased TEB may not progress to neoplastic lesions and may be reversible. Therefore, the relevance of these hyperplastic lesions – in the absence of intraductal hyperplasia – and the level of adversity of these findings for humans is not clear.

The overall qualitative conclusion of RAC regarding the mammary gland changes is that BPA caused an acceleration of mammary gland maturation in experimental animals. There are slight indications of relevant intraductal hyperplasia from two studies with subcutaneous exposure (Murray et al. 2007 and Vandenberg et al. 2008).

Conclusion

RAC agrees that BPA has been shown to have a proliferative effect on mammary tissue at doses below the doses causing general toxicity (such as kidney weight changes).

RAC in principle agrees with EFSA's conclusion on mammary gland effects. The effects on mammary gland development should be taken into account in hazard and risk assessment and in health impact assessment. In line with EFSA (2015), no individual study is however considered robust enough by RAC to serve as critical study for the identification of a starting point for DNEL derivation. Therefore the effects will be accounted for in the setting of Assessment Factors.

1.1.7. Overall conclusion on hazard identification

In addition to effects on the liver and kidney, BPA may induce several other effects. RAC agrees with the Dossier Submitter that effects on the mammary gland, as well as reproductive, metabolic and neuro-behavioural effects need to be accounted for in the hazard, risk and health impact assessments. In addition, and in line with EFSA (2015), effects on the immune system were considered by RAC.

RAC does not agree with the starting points chosen by the Dossier Submitter to derive DNELs. RAC is of the view that the available data on these effects does not allow a quantification of the dose-response relationships. In line with EFSA (2015), these effects will be accounted for through the setting of Assessment Factors in DNEL derivation.

1.1.8. DNEL derivation

1.1.8.1. The Dossier Submitter's proposal

The Dossier Submitter derived DNELs for the effects of BPA on brain and behaviour, on female reproductive system, on metabolism and obesity and on mammary gland effects. The latter effects, based on a NOAEL of 25 µg/kg bw/day from Moral et al. (2008) and applied default assessment factors for inter/intraspecies differences (10 x 10 or 10 x 5) and an additional factor 3 for uncertainty (described below), resulted in the lowest DNEL. Results are presented in Table 2.

The Dossier Submitter proposed to use an assessment factor of 300 if the starting point was a NOAEL and an assessment factor of 900 if the starting point was a LOAEL. The following assessment factors were then used by the Dossier Submitter:

- Use of a LOAEL: a factor of 3 was applied.
- Inter-species variability: a factor of 10 was applied.
- Intra-species or inter-individual variability: This factor takes into account the variability within the human population. For consumer/the general population the default factor of 10 was applied.

According to the Dossier Submitter, the default factor of 5 for workers implicitly considers a population with less variability and does not include the unborn child. The unborn child is part of the general population and the default intra-species assessment factor for the general population is proposed to be taken forward for (prenatal) developmental effects[5].

- An additional assessment factor of 3 was applied in connection with the body of data available and the severity of the effect. The assessment factor was used to cover the uncertainties relating to the effects of BPA in:

  - lower doses than those used for DNEL derivation;

  - for the existence of a non-monotonic dose-response relationship;

  - and for the existence of data in vitro and ex vitro showing a greatly increased sensitivity (above a factor of 3, already considered in the inter-species variability factor) of human tissue to BPA compared to animal tissue.

1.1.8.2. Human Equivalent Dose (HED) approach as used by EFSA

Area under the curve values[6] for unconjugated BPA in serum (AUC in what follows) can be used to compare exposure resulting from experimental doses. AUC values were obtained from toxicokinetic experiments with oral administration, IV injection or subcutaneous injection in adult CD-1 mouse, Sprague-Dawley rats and rhesus monkeys (Doerge et al. 2010 a,b, 2011a,b, 2012). These studies provide unconjugated BPA serum measurements obtained using identical experimental protocols in the species studied. The AUC values for oral dosing of human adults were predicted by PBPK modelling using a monkey-based PBPK model (Yang et al. 2013).

In considering the inter-species variability related to the effects of BPA, EFSA (2015) used this chemical-specific data to derive the ratio AUC_{animal} / AUC_{human}. The dosimetric Human Equivalent Dose adjustment Factor (HEDF) is defined by a common relationship between the external dose given to an animal and the resultant AUC, and the external dose given to a human and its AUC. HEDF is defined as AUC animal / AUC human.

The HED represents the multiples of the dose (D) in an animal species by a specified route and life-stage that a human would require to obtain an equivalent AUC from oral administration (D x HEDF = HED).

These AUC ratios are chemical-specific adjustment factors that replace the default uncertainty factor for inter-species extrapolation of toxicokinetics. Then the remaining 2.5 (out of 10) for toxicodynamics will remain. The standard AF for

[5] Note: this interpretation is not in line with the current ECHA guidance and is not agreed with by RAC.

[6] An area under the curve (AUC) value for unconjugated BPA in serum is the area under the curve of concentration of unconjugated BPA in serum plotted against time. The AUC is a measure of exposure to BPA.

toxikokinetics for rats (4) or for mouse (7) will be replaced with 1, as the the HEDF will take their place.

Table 1 Determination of Human-Equivalent dosimetric Factors (HEDF) for BPA in human adults (EFSA 2015)

Species-Route	**AUC-Adult (nmol x h x L-1)**	**HEDF – Adult** *(calculation shown in red)*
Mouse – oral **Mouse – IV injection**	**0.244** **54**	**0.068** (0.244/3.6) **15** (54/3.6)
Rat - Oral **Rat - IV injection**	**2.6** **95**	**0.72** (2.6/3.6) **26** (95/3.6)
Monkey – Oral **Monkey – IV injection**	**1.5** **180**	**0.42** (1.5/3.6) **50** (180/3.6)
Human-Oral PBPK simulation (Yang et al. 2013)	**3.6** (Reference value)	**-**

HEDF values were calculated from experimentally determined serum AUCs of unconjugated BPA from adult animals for a common gavage or injection dose of 100 µg/kg bw/day and from AUCs for human adults that were simulated for the same oral dose using a human PBPK mode. A HEDF value above 1 illustrates that the animal has a higher uptake than the human. A HEDF value below 1 means the human has a higher uptake than the animal.

RAC's opinion on the use of the Human Equivalent Dose approach

The HED approach used by EFSA (2015) for calculating the HED and the temporary Tolerable Daily Intake (t-TDI) seems reasonable. The use of a HEDF for adult mouse following oral administration of 0.068 results in a relatively low HED and therefore the DNEL derived from the mouse study will be low as well. It is noted that EFSA (2015) calculated a lower-bound HEDF of 0.030 and an upper-bound HEDF of 0.349 for adult mice with oral administration.

The HED approach can only be used when reliable data is available and all PBPK modeling assessments are valid. Toxicokinetic data are available for animals, however not for humans. PBPK models were used by EFSA to derive (simulate) the human AUC, in order to derive the ratio AUC_{animal} / AUC_{human} and thereby the HEDF. Using the HED approach is considered to provide a better estimate of the toxicokinetics than the default uncertainty factor for interspecies extrapolation for toxicokinetics (AF of 4 for rats, equivalent to a factor of 0.25). Therefore, **RAC agrees to use the HED approach in the risk assessment for BPA**.

1.1.8.3. EFSA's derivation of the t-TDI

EFSA (2015) derived a t-TDI by using the HEDF of 0.068 based on the adult mouse. Multiplying the HEDF by the point of departure (i.e. a NOAEL or BMDL10) of a toxicity study yields a human-equivalent oral dose that can be used for risk assessment. EFSA (2015) derived a BMDL10 of 8960 µg/kg bw/day based on changes in relative kidney weights in the Tyl et al. (2008) study on mice. To obtain the equivalent dose in humans, the HEDF of 0.068 is multiplied by the BMDL10 of 8960 µg/kg bw/day resulting in a human equivalent dose of **609 µg/kg bw /day.**

The overall uncertainty evaluation by EFSA (2015) included the effects on mammary gland as well as reproductive, metabolic, neuro-behavioural and immune systems. EFSA concluded that the health-based guidance value should cover the lowest dose in the dose range for which the likelihood approaches "likely" from the overall uncertainty evaluation, taking into account uncertainty of all the evaluated endpoints as well as their relevance and adversity to humans. The uncertainty evaluation approached "likely" in the (HED) dose range of 100-1000 µg/kg bw/day. EFSA (2015) therefore concluded that the uncertainty regarding the abovementioned effects at the HED of 100 µg/kg bw/day and higher should be taken into account when establishing a health-based guidance value by including an extra factor in establishing the t-TDI. Thus, as the reference point was 609 µg/kg bw/day based on the mean relative kidney weight and the lower end of the dose-range for which the uncertainty evaluation for other endpoints approached "likely" is 100 µg/kg bw/day, a **factor of 6** was applied. Applying the remaining assessment factor of 25 (remaining factor of 2.5 for interspecies differences, and factor 10 for intraspecies differences), the resulting t-TDI was 4 µg/kg bw/day.

1.1.8.4. Oral DNEL derivation by RAC

Taking into account the overall data set, RAC supports the EFSA value of 4 µg/kg bw/day as a DNEL for oral exposure in the general public. RAC recognizes that for kidney effects, the HED of approximately 600 µg/kg bw/day would allow a DNEL of 24 µg/kg bw/day (600 divided by 2.5*10). However, the available data indicate that kidney effects are not the most critical effects of BPA. Whereas the data on other adverse effects do not allow to identify a sufficiently robust starting point, the WoE analysis by EFSA (2015) indicates that they could occur starting from a HED of 100 µg/kg bw/day, i.e. at a 6-fold lower level than the HED for kidney effects. Consequently, a DNEL accounting for these effects would be 6-fold lower than a DNEL based on kidney effects alone. This results in an oral DNEL of 4 µg/kg bw/day for the general population. The corresponding oral DNEL for workers is 8 µg/kg bw/day workers (given their 2-fold lower AF for intraspecies differences).

Table 2 Summary of the derivation of oral DNELs by the Dossier Submitter and by RAC.

Table 2 Derivation of oral DNELs

Starting point	NOAEL/ BMDL10 µg/kg bw/day	Assessment factor or HEDF	DNEL oral general population. µg/kg bw/day	DNEL oral worker µg/kg bw/day
DNELs based on mammary gland effects (DS proposal)	**NOAEL = 25**	**AF general population = 300 (10x10x3)** **AF worker = 150 (10x5x3)**	**0.0833**	**0.167**
DNELs based on kidney effects	**BMDL10 = 8960** **(kidney effects in mice)**	**HEDF = 0.068** **AF general population = 25** **AF worker = 12.5**	**24**	**48**
DNELs accounting for effects on mammary gland, reproductive, neurobehavioural, immune and metabolic systems	**BMDL10 = 8960 (kidney effects in mice)**	**HEDF = 0.068** **Extra AF = 6** **AF general population = 25 x 6 = 150** **AF worker = 12.5 x 6 =75**	**4**	**8**

1.1.8.5. Non Monotonic Dose Response (NMDR)

RAC noted the following conclusion from EFSA (2015): "*In summary, none of the studies fulfill the criteria for a NMDR established by the CEF Panel. Overall the CEF Panel concluded that the available data do not provide evidence that BPA exhibits a NMDR for the endpoints considered (reproductive and developmental toxicity, neurotoxicity/behavioural effects, metabolic effects, proliferative changes in mammary gland).*"

1.1.8.6. DNEL for the dermally absorbed dose

As this restriction proposal concerns the dermal route of exposure due to handling

thermal paper, a DNEL for the dermally absorbed dose needs to be determined. To derive such a DNEL, it is necessary to have information that allows the fraction of an external dermal dose reaching the systemic circulation to be determined and that allows to quantify how the external dermal dose translates into the AUC for unconjugated BPA.

No toxicokinetic study in humans involving dermal exposure has been referenced in the background document, but a study in humans was submitted during the public consultation on this restriction dossier (Thayer et al. 2014a; NB, not peer reviewed). Furthermore, several in vitro studies on cutaneous penetration using pig skin and human skin samples are available and described in EFSA (2015). The information of these in vitro studies can be used in PBPK modelling to simulate the fate of BPA taken up dermally. EFSA did this by using the Fisher/Yang model (for oral exposure; used for species to species extrapolation) and the Mielke model (for dermal exposure, enabling predictions of serum concentration time profiles and estimations of internal dose metrics for unconjugated BPA by dermal route).

In Table 3AUC predictions from PBPK-models are presented, for doses of 100 µg/kg bw.

Table 3 PBPK model-based predictions of the area under the curve (AUC) for unconjugated BPA in serum in adults for an oral dose of 100 µg/kg bw or a dermally absorbed dose of 100 µg/kg bw (see Table 5 of PART II in EFSA 2015)

PBPK Models	**Oral AUC (nmol x h x L-1)**	**Dermally absorbed AUC (nmol x h x L-1)**
Mouse	**0.244**	
Human-Oral PBPK simulation (Fisher/Yang model)	**3.6** (Reference value)	**329.5*** **
Human-oral PBPK simulation (Mielke model)	**29.2***	**350.6****

* *An oral dose of 0.336 µg/kg/d corresponds to $AUC_{oral,Mielke}$ of 0.098 nMol x h/L. Thus an oral dose of 100 µg/kg/d corresponds to $AUC_{oral,Mielke}$ of 29.2 nMol x h/L.*

** *An external dermal dose of 0.542 corresponds to and absorbed dose of 0.0542 µg/kg/d when assuming 10% absorption. This dose corresponds to $AUC_{dermal,Mielke}$ of 0.19. Thus a dermally absorbed dose of 100 µg/kg/d corresponds to $AUC_{dermal,Mielke}$ 350.6 nMol x h/L (0.19x100/0.0542).*

*** *The relationship between the two PBPK models for dermal AUCs is: $AUC_{dermal,Fisher/Yang} = 0.94 \times AUC_{dermal,Mielke}$ (see p. 585 of PART II in EFSA 2015). Thus dermal $AUC_{dermal,Fisher/Yang} = 329.5$.*

The DNEL for dermally absorbed dose can be calculated as follows:

- for workers

$$\text{DNEL dermally abs.} = \left(\frac{BMDL_{10/Mouse/Tyl}}{\frac{\text{AUC dermal abs. Human}}{\text{AUC Oral abs. Mouse}}} \right) / \text{AF (2.5 x 5 x 6)}$$

- for general population

$$\text{DNEL dermally abs.} = \left(\frac{BMDL_{10/Mouse/Tyl}}{\frac{\text{AUC dermal abs. Human}}{\text{AUC Oral abs. Mouse}}} \right) / \text{AF (2.5 x 10 x 6)}$$

Table 4 Derivation of DNELs for the dose dermally absorbed using the Fisher/Yang (FY) and Mielke (M) model.

Species **Route**	**Mouse** **Oral**	**Human** **Dermally absorbed (FY)** (calculations shown in red)	**Human** **Dermally absorbed (M)** (calculations shown in red)
AUC for 100 µg/kg bw/day **(nmol x h x L-1)**	**0.244**	**329.5**	**350.6**
Conversion factors		**1350.4 (oral mouse to dermal human)** (329.5 / 0.244)	**1436.9 (oral mouse to dermal human)** (350.6 / 0.244)

Conversion to HED **(µg/kg bw/day)**	**8960**	**6.64** (8960 / 1350.4)	**6.24** (8960 / 1436.9)
Assessment factors **Worker** **General population**		**75** (2.5 x 5 X 6) **150** (2.5 x 10 X 6)	**75** (2.5 x 5 X 6) **150** (2.5 x 10 X 6)
DNELs for the dose dermally absorbed **(µg/kg/d)** **Worker** **General population**		**0.089** (6.64 / 75) **0.044** (6.64 / 150)	**0.083** (6.24 / 75) **0.042** (6.24 / 150)

Both models result in roughly the same DNELs for the dermally absorbed dose, i.e. approximately 0.1 µg/kg bw/day for workers and 0.05 µg/kg bw/day for the general population. It is to be noted however that skin metabolism is not accounted for in these DNEL values. The restriction dossier and EFSA (2015) considered that the available information does not enable derivation of a reliable estimate of the extent of skin metabolism and decided not to correct for skin metabolism. This decision results in a conservative estimate of the fraction of an external dermal dose of unconjugated BPA reaching the systemic circulation.

It is known that conjugation enzymes are present in the skin, making skin metabolism plausible. There are some preliminary data from a pilot study by Thayer et al. (2014a) (unpublished, with limited reporting) that suggest that bioactive BPA comprises only 11-15 % of the AUC for total BPA following dermal administration. Zalko et al. (2011) showed a biotransformation of a minimum 27% of the dose administrated and this could be higher *in vivo*. The study shows that at low concentrations applied to human skin, approximately 40% of the dose which diffuses into the liquid receiver is as glucuronide and sulfate.

Based on the above, there is reason to believe that the calculated DNELs for workers and general population of 0.1 and 0.05 µg/kg bw/day, respectively, should be increased.

As a compromise RAC agreed to take a biotransformation rate of 50% into account. That means 50% systemic bioavailability for the unconjugated BPA. The resulting

DNEL for dermally absorbed BPA is presented in Table 5.

Table 5 Resulting DNEL for the total BPA dose dermally absorbed (corrected for skin metabolism and rounded up)

DNEL for the dermally absorbed total BPA dose, µg/kg bw/day	General population	Workers
DNELs accounting for effects on mammary gland, reproductive, neurobehavioural, immune and metabolic systems.	**0.1**	**0.2**

1.1.8.7. Likelihood for effects that might be expected when the DNEL is exceeded

EFSA experts were asked to make judgements about the overall likelihood, in each HED dose interval, that BPA has the inherent ability to cause one or more type of effects in animals and that it is relevant and adverse in humans.

Between 6 and 13 individual experts responded to the following question for each dose interval for a particular endpoint (using the example of reproductive toxicity):

"What is the likelihood that BPA has the capability to cause reproductive effects (of one or more of the types listed in the summary graph) in this dose interval, for one or more combinations of the animal species tested, exposure period and measurement time. In other words, if large, well-conducted experiments were done for the same species with a range of combinations of exposure period and time, what is the likelihood that one or more of the types of reproductive effect listed in the summary graph would be found in this dose interval?", *"What is the likelihood of this effect being relevant in humans, if it occurred in animals?",* and *"What is the likelihood of this effect being adverse in humans, if it occurred in humans?"*

Terms and abbreviations used to express likelihood in the uncertainty evaluation for hazard characterisation (from Mastrandrea et al. 2010).

Virtually certain (VC)	99-100 % probability
Very likely (VL)	90-100 % probability
Likely (L)	66-100 % probability
As likely as not (ALAN)	33-66 % probability
Unlikely (U)	0-33 % probability
Very unlikely (VU)	0-10 % probability
Exceptionally unlikely (EU)	0-1 % probability

The outcome of the evaluation for individual effects is presented in Table 6. The expert judgement of the overall likelihood in each HED dose interval that BPA has the ability to cause one or more type of effect in animals and that it is relevant and adverse in humans is presented in Table 7.

EFSA concluded that, overall, 100-1000 µg/kg bw/day is the lowest HED dose interval where the likelihood of BPA causing one or more type of effects approaches "likely" (5 of 10 experts in Table 7 considered the overall likelihood could be above 66%).

Table 6 Summary of EFSA expert judgements of the likelihood that BPA has the inherent ability to cause effects in animals in different dose intervals and their human relevance (if they occur in animals) and adversity (if they occur in humans). Sexes were differentiated only for neurobehavioural effects (Table 18 in EFSA 2015)

Effect type	Human relevance	Adversity in humans	Likelihood that BPA causes the effect in animals in different dose intervals Human equivalent dose (HED), µg BPA/kg bw per day									
			10^{-4}-10^{-3}	10^{-3}-10^{-2}	10^{-2}-10^{-1}	10^{-1}-10^{0}	10^{0}-10^{1}	10^{1}-10^{2}	10^{2}-10^{3}	10^{3}-10^{4}	10^{4}-10^{5}	10^{5}-10^{6}
Mammary proliferation	ALAN-L	ALAN-L	VU	VU	VU	VU	U-ALAN	U-ALAN	ALAN-L	ALAN-L	ALAN-L	ALAN-L
Reproductive system	ALAN-L	ALAN-L	-	-	VU-U	VU-U	VU-U	VU-ALAN	VU-ALAN	VU-ALAN	VU-L	L-VL
Metabolic	ALAN-L	U-L	VU-ALAN	VU-ALAN	VU-ALAN	VU-ALAN	VU-U	VU-ALAN	VU-ALAN	VU-ALAN	VU-L	VU-L
Immune system	U-L	ALAN-L	-	-	VU-U	VU-U	U-ALAN	U-L	U-L	U-L	U-L	-
Neurobehaviour (males)	U-L	U-L	-	VU-U	VU-U	U-ALAN	ALAN	ALAN	ALAN	ALAN-L	-	-
Neurobehaviour (females)			-	VU-U	VU-U	U	U	U-ALAN	ALAN	U-L	-	-

- no data available

Table 7 EFSA expert judgement of the overall likelihood, in each HED dose interval, that BPA has the inherent ability to cause one or more type of effect in animals *and that it is relevant and adverse in humans* (Table 19 in EFSA 2015)

Expert	HED Dose interval (µg BPA/kg bw/day)									
	10^{-4}-10^{-3}	10^{-3}-10^{-2}	10^{-2}-10^{-1}	10^{-1}-10^{0}	10^{0}-10^{1}	10^{1}-10^{2}	10^{2}-10^{3}	10^{3}-10^{4}	10^{4}-10^{5}	10^{5}-10^{6}
1			U	U	U-ALAN	U-ALAN	ALAN	ALAN		
2			VU	VU-U	U-ALAN	ALAN	ALAN-L	ALAN-L		
3			U	U	U	ALAN	ALAN	ALAN-L	L	L
4	VU	VU	VU	VU	U	U-ALAN	ALAN	ALAN-L	ALAN-L	L
5	VU	U	U	U	U	ALAN	L	L	L	VL
6			VU-U	VU-U	U	U-ALAN	U-ALAN	ALAN		
7			U	U	ALAN	ALAN	L	L	L	
8	VU	VU-U	U	U	ALAN	ALAN	ALAN-L	L	L	L
9			U	U	ALAN	ALAN	ALAN-L	ALAN-L	ALAN	ALAN
10	EU	EU	VU	VU	U	U	U-ALAN	ALAN	ALAN	L
GROUP EVALUATION	**(EU - VU)***	**(EU - U)***	**VU - U**	**VU - U**	**U- ALAN**	**U- ALAN**	**U-L**	**ALAN- L**	**(ALAN-L)***	**(ALAN-VL)***

* For these ranges of doses the experts did not provide a full evaluation because there were not data available for all the endpoints.

Discussion

RAC supports EFSA's conclusion that from the HED dose of 100 µg/kg bw/day it becomes "likely" that one or more effects may occur. Thus, the likelihood that BPA has the capability to cause an effect in animals and that this effect is also relevant and adverse in humans approaches "likely" in the HED dose interval of 100-1000 µg/kg bw/day. This does not however provide information on the frequency at which such effects might be observed. The dermal exposure equivalent of this dose interval after applying assessment factors would be of 0.2 – 2 µg/kg bw/day for workers and 0.1 – 1 µg/kg bw/day for the general population.

Looking at the individual EFSA experts' evaluations for the dose range 100-1000 µg/kg bw/day, the occurrence of effects on the mammary gland and the immune system has been rated "likely" by more experts than the occurrence of reproductive, neurotoxic and metabolic effects. See Table 8 below. In fact, any of these effects may occur, as for each of these effects there is experimental evidence in this dose range.

Table 8 Mean probability score (and range) of EFSA experts for likelihood of effects in HED dose interval of 100-1000 µg/kg bw/day

EFFECT TYPE	Mean probability score of EFSA experts (range)
Mammary proliferation	66% (50-83)
Reproductive system	37% (18-56)
Metabolic	26% (4-49)
Immune system	65% (43-87)
Neurobehaviour (males)	54% (33-76)
Neurobehaviour (females)	45% (28-61)

1.2. Exposure assessment

The entire population is likely to be exposed to BPA regardless of age - infants, children and adults - through inhalation, ingestion and skin contact due to the wide disperse use of BPA. Polymers and resins containing BPA are used for the manufacture of everyday consumables. For example, polycarbonate plastic is used to make food containers, such as returnable beverage bottles, tableware (plates and mugs) and storage containers. BPA can migrate in small amounts into food and beverages stored in materials containing the substance.

In comparison with the use of BPA in the manufacture of polycarbonate and epoxy resins, the use in thermal papers is minor (about 0.2% of the total volume of BPA used in the EU). However, exposure to BPA from thermal papers is facilitated by the fact that BPA is present as a free monomer on the surface of the paper and can migrate easily to the skin upon contact. BPA is typically present in the paper in a concentration of 1-2% by weight.

Oral exposure through food intake is considered to be the main exposure route by EFSA (2015). EFSA (2015) considered that dermal exposure from thermal paper containing BPA is the second largest source of exposure.

The exposure assessment in the restriction proposal is based on modelling results as well as on biomonitoring data both with respect to the general population (consumers) and workers (e.g. shop cashiers).

1.2.1. Modelling

The Dossier Submitter estimated the exposure of workers using a percutaneous absorption flow model. Two models were used for exposure assessment of the general public, namely, the 'percutaneous absorption flow model' and an 'absorption rate model'.

The Dossier Submitter justified the additional use of the absorption rate model as follows: *"unlike the professionals, the consumer will touch relatively few receipts over the course of a day and it is likely that the quantity of bisphenol A on the fingers is not constant through time. It appeared therefore justified to use an approach based on the level of absorption (absorption rate) combined with contact with a thermal receipt with BPA."*.

EFSA (2015) also used an absorption rate model for consumers.

The Dossier Submitter chose to model exposure to BPA from thermal paper using a probabilistic approach[7].

[7] The probabilistic approach takes into account all of the possible modalities of an entry variable through the intermediary of its distribution of probabilities and incorporates variability of exposure. So any possible modality of an entry variable of a model can be combined with the modalities of the other entry variables depending on their probability of occurrence. Random samples using the Monte Carlo approach (10000 iterations) were taken for each of the entry parameters of the model to define an exposure distribution. The Dossier Submitter has confirmed that 10000 iterations were sufficient to reach the acceptable consistency of results.

Percutaneous absorption flow model

The percutaneous absorption flow model is based on the following formula:

IED = (F x D x S)/BW

IED: Internal (exposure) daily dose	[µg/kg_{BW}/day]
F: Absorption flow	[µg/cm^2/hour]
D: Duration of exposure	[hours/day]
S: Surface area	[cm^2]
BW: Body weight	[kg_{BW}]

Absorption rate model

The absorption rate model is based on the following formula:

IED = (Rabs x Qsubs x N)/BW

IED: Internal (exposure) daily dose	[µg/kg_{BW}/day]
R_{abs}: Level of absorption (absorption rate)	[%]
Q_{subs}: Quantity of the substance deposited by contact	[µg/finger]
N: Number of fingers in contact with the till receipt	[finger]
BW: Body weight	[kg_{BW}]

Note: the model implicitly assumes that the quantity of BPA deposited on the skin will be available throughout the whole day and that this quantity is replaced with a new quantity the next day.

Conclusion

RAC agrees with the use of both the percutaneous absorption flow model and an absorption rate model for consumers, and the use of the absorption flow model for workers. RAC used a corrected formula for the absorption rate model (omitting the parameter related to absorption duration). RAC also chose to complement the probabilistic modelling results with deterministic modelling.

1.2.1.1. Workers – Percutaneous absorption flow model

1.2.1.1.1. Discussion on absorption flow

The Dossier Submitter considered Marquet et al. (2011) as the key study and was of the view that the use of an aqueous solution in the study by Demierre et al. (2012) was not more realistic than acetone used in the Marquet et al. (2011) study, reasoning that as the acetone immediately evaporated, BPA in solid form was directly put into contact with the *stratum corneum*, which is similar to the case of BPA transferred from thermal paper to the *stratum corneum* of the finger. The Dossier Submitter therefore considered that although Marquet et al. (2011) did not adhere to the relevant guidelines (OECD 428, EHC235), it was still acceptable to use.

The permeability coefficient of BPA is independent of the concentration of BPA in the applied BPA solution but can be affected by the vehicle, skin thickness, etc. The

permeability coefficient (Kp) calculated from the experimental data reported by Zalko et al. (2011) is 0.9 10^{-4} cm/h. This Kp value is the same as the value obtained with Demierre et al. (2012) (kp=1.1 10^{-4} cm/h) who used a 194 µg/mL aqueous solution of BPA, and Morck et al. (2010) (kp=1.75 10^{-4} cm/hour) who used a 3995 µg/mL hydro-ethanol solution. Likewise, the fraction of BPA absorbed within 24 hrs. is comparable for Morck et al. (2010) (approximately 6.5 %= 13 X 24 hours/48 hours), Demierre et al. (2012) (8.6 %) and Zalko et al. (2011) (15.2 %= 45.6 % X 24 hours/72 hours).

EFSA (2015) considered that the use of acetone as a vehicle in Marquet et al. (2011) would have impacted the absorption flow: *"The disruption by acetone of skin lipid structure and the associated barrier function has been described previously (Zhai et al., 1998) so this exposure condition is a conservative model for the extent of human exposure from thermal paper."*.

Thus, the water based vehicle (physiological serum) used in the experiments of Demierre et al. (2012) could be more appropriate (See scenario III in Table 10). The guideline study by Demierre et al. (2012) is considered as the key study by EFSA (2015). EFSA (2015) reasoned that the use of water as a vehicle for BPA in the Demierre et al. (2012) study is more comparable to a scenario of consumer exposure to thermal paper than acetone (Marquet et al., 2011) or diluted hydro-ethanol solutions (Mork et al., 2010, Zalko et al., 2011), and the applied surface density of 1.83 µg/cm^2 is comparable to exposure estimates as derived for thermal paper (1.37-5.5 µg/cm^2 fingertip).

The studies performed by Marquet et al. (2011) and Demierre et al. (2012) as well as findings on dermal absorption flow are compared in the Table 9.

Table 9 Comparison of Marquet et al. (2011) and Demierre et al. (2012) in vitro studies on BPA percutaneous absorption flow in human explants

Design of the study	Marquet et al. (2011)	Demierre et al. (2012)
Number of specimens	15	7
Number of donors	6	2
Nature of the skin	Cold	Defrosted
Thickness of the skin	400 µm	200 µm
Anatomical region of the skin	Abdomen	Thigh
BPA dose/area	200 µg / cm^2	1.82 µg / cm^2
BPA concentration	4 mg/ml	0.193 mg/ml
Solvent	Acetone	Physiological serum
Number of points to evaluate the flow	NC*	4
Fmax	0.12µg/cm^2/hour **	0.022 µg/cm^2/hour

* *NC = not communicated*

** *Mean F_{max} or maximum absorption flux as reported in the study. Annex 4 lists the individual flux values (maximum of 0.331 µg/cm^2/hour), as obtained from the study authors.*

Demierre et al. (2012) determined a much lower max flow of BPA through skin explants (0.022 µg/cm^2/hour) in comparison to Marquet et al. (2011) (0.12 µg/cm^2/hour).

RAC considered the above arguments from EFSA (2015) and the Dossier Submitter, noting that it is unclear whether the exposure conditions are necessarily more realistic in Demierre et al. (2012) compared with Marquet et al. (2011). Conversely,

RAC considered that acetone might have influenced the skin permeability. RAC was of the opinion that the load on the skin is insufficient in Demierre et al. (2012) to reliably determine the flux, especially for workers. Thus, it is possible that in part the discrepancy of results is explained by the much lower load of the skin in Demierre et al. (2012) (1.82 µg/cm^2) compared with the Marquet et al. (2011) (200 µg/cm^2).

The draft OECD guidance notes on dermal absorption state *"Flux values are frequently reported, especially in the open literature, to describe dermal absorption under infinite dose testing conditions. However, this parameter is of limited value in evaluating risks arising from real-world exposure to finite amounts of dilute chemicals in a complex formulation".* Considering roughly 1 µg is deposited on one finger following contact with thermal paper (Biedermann et al. 2010), the load used in Demierre et al. (2012) might give a better reflection of the flux and absorption rate following dermal contact with BPA containing thermal paper for consumers. However, repeated contacts in workers might result in near to infinite dose conditions.

RAC sees the limited number of donors (2) as a disadvantage of the Demierre et al. study. This can underestimate the absorption flow variability being quite high in Marquet et al. (2011) (6 donors; see Annex 4). However the authors of Demierre et al. (2012) stress that the distribution of flow values was relatively similar in both donor skin samples.

RAC noted that although Demierre et al. (2012) used physiological serum resembling human sweat, the relatively low absorption flow obtained from this study is not supportive of a possibly enhanced permeability caused by wet/greasy skin conditions.

Conclusion

RAC considered the absorption flow range from the Marquet et al. (2011) study as relevant to the risk assessment of dermal contact with thermal paper by workers and consumers by means of percutaneous absorption flow model. In addition, modelling with the maximum absorption flow given by Demierre et al. (2012) is performed for the sake of comparison. RAC used the geometric mean and the 95th percentile from the individual flow values from Marquet et al. for additional (deterministic) modelling.

1.2.1.1.2. Discussion on duration of exposure and exposed surface area

RAC considers that it is impossible to adequately assess the duration of exposure to BPA from a till receipt, which might in some cases be considerably longer than 10 hours (the maximum duration proposed by the Dossier Submitter), taking into account the amount of BPA still left on the fingers after the working shift and the possible reservoir effect of BPA absorption. Therefore, RAC included additional scenarios with an exposure duration of 24 hours. On the other hand, part of the BPA is removed from the skin over the day by washing hands and by touching different surfaces and objects.

The Dossier Submitter proposed an exposed surface area of 12 cm^2, which is the cumulative surface area of the pads of the ten fingertips. RAC considers that the exposed surface area might be larger and therefore included additional exposure

scenarios with half a palm as exposed surface area, i.e., 111 cm^2 (default value according to US EPA 1986).

1.2.1.1.3. Conclusion on input parameters

Three worker exposure scenarios were modelled using probabilistic modelling as reflected in Table 10. Input parameters for deterministic modelling by means of the absorption flow model for workers are also reflected. Two alternatives for three parameters are proposed giving 4 scenarios for deterministic modelling of worker exposure.

Table 10 Input parameters for workers' exposure assessment using the absorption flow model

	Probabilistic			Deterministic	
Input parameter	**Scenario I** (proposed by the Dossier Submitter)	**Scenario II**	**Scenario III**	**Combination of values leads to 4 scenarios**	
F: Absorption flow	Uniform distribution within the range **0.026 – 0.331** µg/cm^2/hour Marquet et al. (2011) In vitro human skin explants, from 15 measurements, vehicle – acetone	Uniform distribution within the range **0.026 – 0.331** µg/cm^2/hour Marquet et al. (2011) In vitro human skin explants, from 15 measurements, vehicle – acetone	Single value **0.022** µg/cm^2/hour Demierre et al. (2012) In vitro human skin explants, the max value obtained, vehicle - physiological serum	**0.09** µg/cm^2/hour Marquet et al. (2011) Geometric average from 15 measurements	**0.258** µg/cm^2/hour Marquet et al. (2011) 95th percentile from 15 measurements
D: Duration of exposure	Triangular distribution with min, mean (mode) and max values **3, 6.5, 10** hours/day Assessment of ANSES experts based on the data from the collective agreement of the retail trade and the wholesale trade with dietary predominance	Triangular distribution with min, mean (mode) and max values **3, 5.5, 8** hours/day RAC expert judgement	Triangular distribution with min, mean (mode) and max values **3, 5.5, 8** hours/day RAC expert judgement	**10** hours/day	**24** hours/day

S: Surface area	**12** cm^2 Assessment of ANSES experts: the cumulated surface area of the pads of the ten fingers (last phalanxes). Based on the US EPA (1986) default surface area of 2 cm² for the thumb and 1 cm² for each of the other fingers.	**6** cm^2 RAC assessment - pads of the 5 fingers of one hand, based on the US EPA (1986) default surface area of 2 cm² for the thumb and 1 cm² for each of the other fingers.	**6** cm^2 RAC assessment - pads of the 5 fingers of one hand, based on the US EPA (1986) default surface area of 2 cm² for the thumb and 1 cm² for each of the other fingers.	**12** cm^2	**111** cm^2
BW: Body weight	Discrete distribution of probabilities illustrating the body weight for the pregnant woman The EDEN[8] study	Discrete distribution of probabilities illustrating the body weight for the pregnant woman The EDEN study	Discrete distribution of probabilities illustrating the body weight for the pregnant woman The EDEN study	**70** kg EFSA (2011) default assumption for adults	

[8] The EDEN study of pre- and post-natal determinants of development and health of the child gives the body weights of the pregnant women at different stages of the pregnancy and was used to document this parameter, with the similar exception of the weights measured taken into account in order to calculate the average weight of the women from the start of the pregnancy until the 7th month and a half. The EDEN study was initiated by several teams of epidemiologists from the Institut Fédératif de Recherche 69, as well as participating clinicians from the CHU *(University Hospitals)* of Poitiers and Nancy. Their aim was to better define the characteristics of foetal development and the first few months of life which influence the development and the subsequent health of the child. 2002 women agreed to participate. Among the very large amount of data available from this study, a distribution of discrete probabilities was simulated from the pairs "average weight/probability of occurrence".

1.2.1.2. Consumers – Percutaneous absorption flow model

1.2.1.2.1. Absorption flow

RAC notes that the above discussion concerning the selection of absorption flow values for the workers exposure assessment is pertinent as well for consumer exposure modelling.

1.2.1.2.2. Absorption duration

The Dossier Submitter assumed an absorption duration of up to 2 hours/day based on expert judgment and on a study by Danish EPA (2011). The value can be obtained by multiplying the duration of contact with the daily frequency of contact. The duration of contact is estimated to be 5 to 66 seconds per contact, and the daily frequency is assumed to be 1 to 5 contacts. These data are based on the number of credit card transactions in Denmark, on the distribution of payment methods, and the percentage of thermal paper receipts containing BPA (EU data). RAC notes, that the maximal absorption duration of 2 hours also takes into account possible contamination of the fingers after the receipt is thrown away.

1.2.1.2.3. Surface in contact with the till receipt

The surface in contact with the till receipt is assumed to be 12 cm^2, i.e., the cumulated surface area of the pads of the ten fingertips (the Dossier Submitter proposed a distribution ranging from 1 to 12 cm^2).

1.2.1.2.4. Conclusion on input parameters

Probabilistic modelling was used to generate three consumer exposure scenarios using the input parameters given in Table 11. Input parameters for deterministic modelling for consumers by means of the absorption flow model are also provided in Table 11.

Table 11 Input parameters for consumers' exposure assessment using the absorption flow model

	Probabilistic			Deterministic	
Input parameter	**Scenario I** (proposed by the Dossier Submitter)	**Scenario II**	**Scenario III**	**Combination of values leads to 2 scenarios**	
F: Absorption flow	Uniform distribution within the range **0.026 – 0.331** µg/cm^2/hours Marquet et al. (2011) In vitro human skin explants, from 15 measurements, vehicle – acetone	Uniform distribution within the range **0.026 – 0.331** µg/cm^2/hours Marquet et al. (2011) In vitro human skin explants, from 15 measurements, vehicle – acetone	**0.022** µg/cm^2/hours Demierre et al. (2012) In vitro human skin explants, the max value obtained, vehicle - physiological serum	**0.258** µg/cm^2/hours Marquet et al. (2011) 95th percentile from 15 measurements	**0.09** µg/cm^2/hours Marquet et al. (2011) Geometric average from 15 measurements
D: Duration of exposure	Uniform distribution up to **2** hours/day as a maximum Assessment of ANSES experts	Uniform distribution up to **2** hours/day as a maximum Assessment of ANSES experts	Uniform distribution up to **2** hours/day as a maximum Assessment of ANSES experts	**2** hours/day	
S: Surface area	Uniform distribution within the range **1-12** cm^2 Assessment of ANSES experts: the cumulated surface area of the pads of the ten fingers	Uniform distribution within the range **1-6** cm^2 RAC assessment- pads of the 5 fingers of one hand, based on the US EPA (1986) default	Uniform distribution within the range **1-6** cm^2 RAC assessment- pads of the 5 fingers of one hand, based on the US EPA (1986) default	**12** cm^2	

	(last phalanxes). Based on the US EPA (1986) default surface area of 2 cm² for the thumb and 1 cm² for each of the other fingers.	surface area of 2 cm² for the thumb and 1 cm² for each of the other fingers.	surface area of 2 cm² for the thumb and 1 cm² for each of the other fingers.	
BW: Body weight	Discrete distribution of probabilities illustrating the body weight for the pregnant woman The EDEN study	Discrete distribution of probabilities illustrating the body weight for the pregnant woman The EDEN study	Discrete distribution of probabilities illustrating the body weight for the pregnant woman The EDEN study	**70** kg EFSA (2011) default assumption for adults

1.2.1.3. Consumers – Absorption rate model

1.2.1.3.1. Absorption rate

RAC does not agree with the Dossier Submitter to derive a maximum absorption rate of 60% for thermal paper from Biedermann et al. (2010). RAC noted that the experiments by Biedermann et al. (2010) did not measure absorption but only penetration of the outer skin layers. The authors noted that either BPA remains in the skin until the stratum corneum is removed or migrates into and perhaps through the dermis. The results therefore give an indication of the upper boundary of absorption. Moreover, in the specific experiment that gave this high penetration result an ethanol solution with BPA was applied to the skin. Biedermann et al. (2010) stated that ethanol was a vector supporting penetration of the skin surface.

The same authors conducted another experiment where an amount of BPA was transferred onto the skin of fingers after 5 seconds of contact with thermal paper. They reported that two hours after contact, 27% of BPA could no longer be washed off by water, but was still extractable with ethanol. The amount extractable by ethanol had penetrated the skin sufficiently deeply not to be washed off by water but could still be extracted with ethanol. Thus, this amount of 27% was not absorbed, but might be available for absorption.

Using physiological serum (most resembling the conditions of human sweat) as a vehicle, the guideline and GLP compliant study by Demierre et al. (2012) reported a skin penetration of 8.6% and a total amount bioavailable after 24 hours of 9.2% (8.6% percent in the receptor fluid and 0.6% remained in the skin membrane after tape stripping). As a possible weakness of Demierre et al. (2012), the Dossier Submitter considered that the so-called 'reservoir effect' was not taken into account in the study, possibly giving underestimation of the absorbed BPA dose.

An absorption rate of 10% is used by default in the RAR of the European Commission (EC 2010) and in EFSA (2015).

RAC considers that an absorption rate of 10% can be applied for the estimation of a reasonable worst case of exposure in an additional deterministic scenario.

1.2.1.3.2. Quantity of the substance deposited

The quantity of BPA deposited by contact with thermal paper on the fingers was estimated to be 1.13 µg/finger in the Biedermann et al. (2010) study and 1.375 µg/finger in Lassen et al. (2011).

Biedermann et al. (2010) showed that the two sides of thermal paper transferred very different amounts of BPA to fingers and that the reverse side (as opposed to the thermally printed side) of the thermal paper probably only released a small amount of BPA due to contamination. So, it is taken into account that thermal paper releases BPA only from the printed side. In the consumer scenario it is assumed by the Dossier Submitter that the skin in contact with thermal paper ranges from a minimum of one thumb to a maximum of 10 fingers. Consumers in contact with the receipt may typically hold it with one or two thumbs on the printed surface and then store it, or curl it up and throw it away. However, since the curling up can involve a higher contact surface than one or two thumbs, RAC suggests that 10 fingers be used for the deterministic exposure modelling.

1.2.1.3.3. Conclusion on input parameters

Probabilistic modelling was used to generate three consumer exposure scenarios using the input parameters given in Annex 3. However, since RAC used a corrected formula for the absorption rate model (omitting the parameter related to absorption duration), the results from the probabilistic modelling were not considered to be valid (for more details, see Annex 3). Input parameters for deterministic modelling by means of absorption rate model for consumers are also provided in Annex 3 and in Table 15 below.

1.2.1.4. Probabilistic modelling results

The probabilistic modelling results from the percutaneous absorption flow model are summarized in the Table 12 below. The 95th percentile values were considered to represent a reasonable worst case exposure estimate.

Table 12 Probabilistic modelling results for worker and consumers using the percutaneous absorption flow model (dermally absorbed total BPA expressed as µg/kg bw/day)

Population	Exposure scenario	Range	Median	AM	GM	95th perc.
Workers	I	0.014 - 0.71	0.20	0.21	0.172	0.43
	II	0.006-0.311	0.084	0.09	0.073	0.181
	III	0.003-0.023	0.011	0.011	0.011	0.016
Consumers	I	2.90 x 10^{-5} - 0.14	0.01	0.02	0.01	0.05
	II	0-0.067	0.006	0.009	0.005	0.028
	III	0-0.0048	0.0009	0.0012	0.0008	0.0029

Note: AM= arithmetic mean; GM= geometric mean

By comparison, for consumer exposure to thermal paper, EFSA (2015) modelled an average internal exposure of 9.4 ng/kg bw/day and a high internal exposure of 86.3 ng/kg bw/day for adolescents (10-18 years) as the highest exposed age group, and for women (18-45 years) an average internal exposure of 5.9 ng/kg bw/day and a high internal exposure of 54.2 ng/kg bw/day (see Tables 31 and 32 of EFSA 2015). The latter value corresponds well to the 95th percentile of 50 ng/kg bw/day in Scenario I in Table 15.

1.2.1.5. Deterministic modelling results

The deterministic modelling results for workers and consumers are reflected in Table 13 to Table 15.

Table 13 Workers' exposure assessment with different exposure determinants using the absorption flow model and deterministic modelling

	Absorption flow (µg/cm²/hour)	Duration of exposure (hours)	Surface area (cm²)	Body weight (kg)	Total BPA dose dermally absorbed (µg/kg bw/day)
Realistic case	0.09	10	12	70	0.154
Reasonable worst case	0.258	10	12	70	0.442
	0.09	24	12	70	0.370
	0.09	10	111	70	1.427*

* The scenario using a surface area of 111 cm^2 might also be considered to be a worst case exposure scenario.

Table 14 Consumer exposure assessment with different exposure determinants using the absorption flow model and deterministic modelling

	Absorption flow (µg/cm²/hour)	Duration of exposure (hours)	Surface area (cm²)	Body weight (kg)	Total BPA dose dermally absorbed (µg/kg bw/day)
Reasonable worst case	0.258	2	12	70	0.088
	0.09	2	12	70	0.031

Table 15 Consumer exposure assessment using the absorption rate model and deterministic modelling

	Absorption rate (%)	Quantity of the substance deposited by contact (µg/finger)	Number of fingers in contact with the till receipt	Body weight (kg)	Total BPA dose dermally absorbed (µg/kg bw/day)
Reasonable worst case	10	3.56	10	70	0.05

1.2.2. Biomonitoring

In a number of biomonitoring investigations, an estimate of the daily dose absorbed is given, allowing comparisons with modelled values and DNELs. All urinary biomonitoring was performed for the general population apart from a few biomonitoring investigations for workers that have been carried out recently. The majority of the studies reported total urinary BPA (unconjugated BPA + conjugated BPA). Urinary biomonitoring results reflect all possible exposure routes, including dermal exposure to BPA in thermal paper.

The reported urinary biomonitoring results show a large variability both on the population level and on the level of the individual. Indeed, due to the particularly rapid kinetics of elimination of BPA, the urinary concentration does not reflect the average level of exposure but only the recent exposure. The rapid elimination of BPA is in principle responsible for the high variations in urinary concentration observed intra- and inter-individually over the course of one day.

Therefore the following general conclusions can be drawn: 1) a single sample of urine taken at random over the course of a day does not account for the average exposure level of an individual; 2) the collection of urine over 24 hours does not account for the average level of exposure for a longer period (weeks or months); and 3) the concentration in the first morning urination is not representative of the average concentration over the course of the day.

1.2.2.1. General population

Figure 1 gives an overview of the results from urinary biomonitoring studies published between 2001 and 2012. As shown in the figure, the geometric means are quite similar across the different studies and are mostly in the range of **1** to **5 µg total BPA/l**.

This range of values is supported by the more recent Porras et al. (2014) study dedicated to estimation of background urinary BPA excretion among non-occupationally exposed Finnish working-age people (n=121, GM of **2.6 µg/l)**. The 95th percentile of the non-occupationally exposed people was **8 µg/l**.

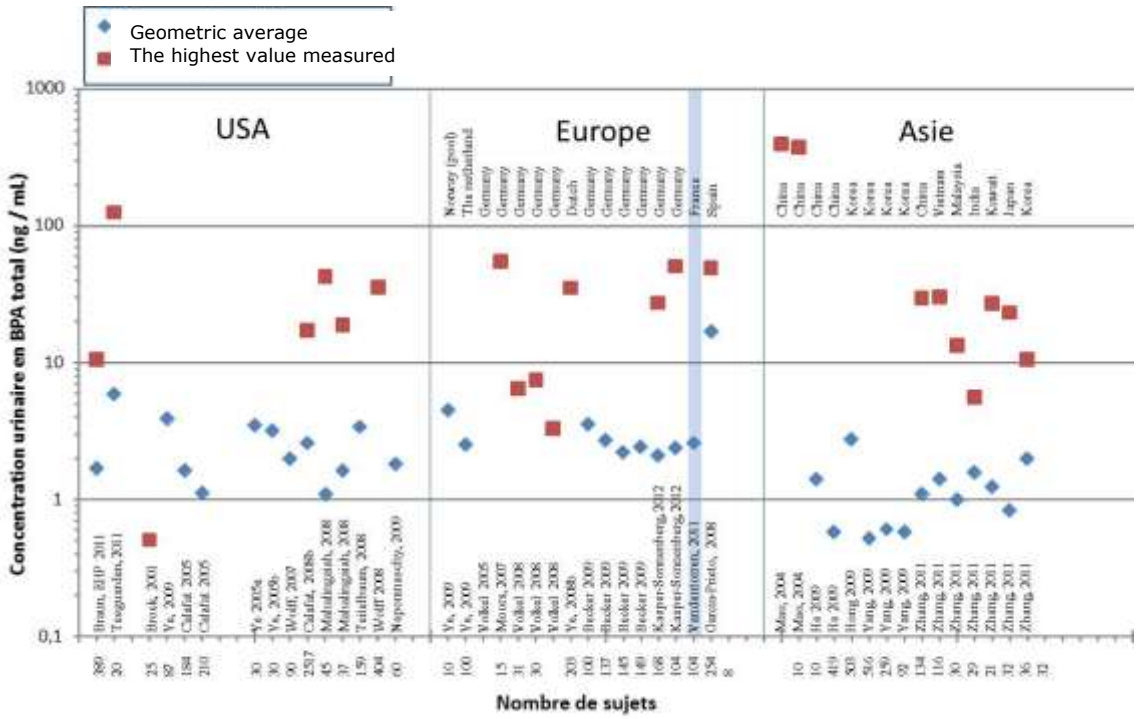

Figure 1: Urinary concentrations (ng total BPA/ml) reported in the literature for studies published between 2001 and 2012

Based on the urinary BPA concentration, an estimate of the daily dose absorbed may be made by comparing the concentration measured to the volume of urine produced, considering that the totality of BPA absorbed is eliminated in the urine. The results in Figure 2 show that the daily exposure to BPA expressed as geometric average is in the range from **10** to **100 ng/kg bw/day**. A number of studies (e.g., Morgan et al. 2011 and Teeguarden et al. 2011) show that dietary exposure may account for more than 95% of the total exposure.

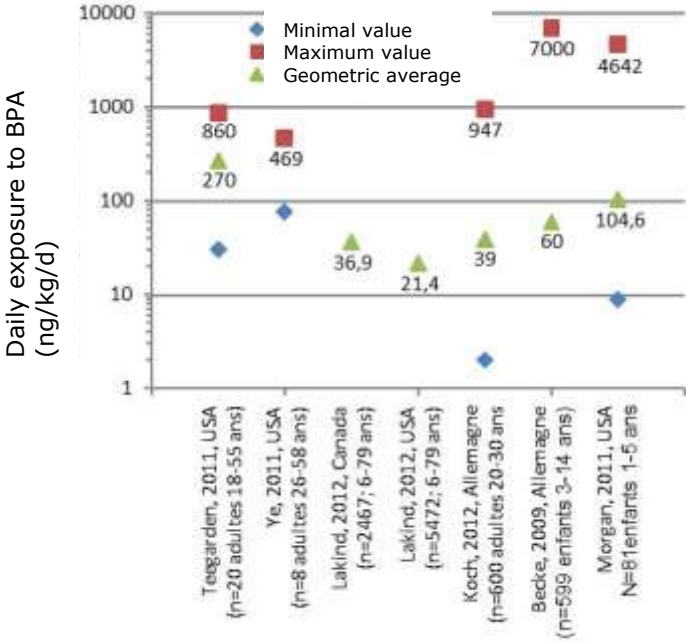

Figure 2: Daily exposure to BPA calculated from urinary excretion over 24h (ng total BPA /kg/day).

Although studies conducted on different animal models appear to indicate that unconjugated BPA represents a minor proportion of the total BPA (generally lower than 3%) (Doerge et al. 2010; Farbos et al. 2012), not all the studies conducted on human urine confirm this hypothesis, specifically the studies by Kim et al. (2003) and by Liao and Kannan (2012), which indicate a proportion of unconjugated PBA which may represent up to 20 to 30 % of the total BPA.

A study submitted during public consultation by Hormann et al. (2014) carried out several experiments. The results from one experiment indicated that the transfer of BPA from thermal paper to hands wetted with hand sanitizer is much higher than to dry hands.

Another experiment by Hormann et al. (2014) simulated the behaviour of consumers in a fast-food establishment. The subjects used hand sanitizers before handling the thermal receipt and then eating French fries. Thus, the subjects (n=6) were exposed dermally through hand contact with the cash receipts and orally from eating BPA contaminated French fries. The urinary concentration of total BPA was much higher following this exposure scenario (19.11±4.32 µg/l) compared with the baseline (0.46±0.24 µg/l). The respective contributions of the oral and dermal routes to the high reported exposure levels are not known. RAC considers that the experimental conditions used in the latter experiment represent worst case behavior. It is acknowledged that higher exposures can occasionally occur, as also reflected in Figure 1, but if the scenario were common, it would also be reflected in the existing biomonitoring data.

In another study submitted during public consultation by Porras et al. (2014), participants used a hand cream prior to holding the thermal paper receipt with 3-5 fingers. In contrast to the findings of Horman et al. (2014), only a slight increase in exposure was observed which remained close to or below the reference limit for non-occupationally exposed population. In Porras et al. (2014), oral exposure from thermal paper did not contribute to exposure levels which might explain the difference with the results from Horman et al. (2014). In addition, Hormann et al. (2014) used a large contact area (96 cm^2) corresponding to almost the surface of half a palm (~111 cm^2). Furthermore, in contrast toHorman et al. (2014), the hand cream in Porras et al. (2014) was allowed to absorb, thus hands were not wet. Moreover, the mixture applied was different (santizer versus hand cream). Lastly, the BPA content of the thermal paper used in the experiments might be a factor influencing the exposure (0.9% w/w in Porras et al. versus 2% in Hormann et al.).

Conclusion on biomonitoring for the general population

The total daily exposure to BPA expressed as geometric average is in the range of **10** to **100 ng/ kg bw/day**. EFSA (2015) reported 95th percentiles of **85 – 291 ng/kg bw/day**.

RAC notes that there are some indications that the use of hand sanitisers and similar penetration enhancing mixtures might increase dermal exposure from BPA in thermal paper. RAC considers this effect should already be reflected in the existing biomonitoring results.

1.2.2.2. Workers (cashiers)

Porras et al. (2014) studied BPA exposure via thermal paper receipts in simulation experiments performed by three volunteers, and examined urinary excretion of BPA. Background BPA excretion among the Finnish working-age population was also evaluated. The geometric mean BPA excretion among non-occupationally exposed working-age Finns (n = 121) was 2.6 µg/l, the range being 0.8–18.9 µg/l. The 95th percentile of the non-occupationally exposed people was **8 µg/l**, and this was set as the reference limit for the non-occupationally exposed population.

The first simulation experiment was conducted under conditions representing the most likely exposure associated with the work of a cashier in a supermarket. BPA excretion remained below the reference limit in all three participants. The calculated total excreted amounts of BPA per day (from the beginning of the experiment to 24 hours after the experiment) were 0.065, 0.051 and 0.152 µg/kg bw for volunteers 1, 2 and 3, respectively. RAC calculated the geometric average concentration of 0.08 µg/kg bw for all three volunteers. It should be noted that these values represent total BPA intake from diet and from exposure to BPA-containing receipts. The corresponding total excreted amounts in the experiment with BPA-free paper were 0.043, 0.017 and 0.103 µg/kg bw/day.

In the second experiment hands were thoroughly rubbed with a hand cream and the cream was allowed to absorb into the skin. Urinary excretion also remained at or below background levels in this experiment (the highest value being 10.3 µg/l). The calculated excreted amounts were 0.12 and 0.093 µg/kg bw/day for volunteers 1 and 2 (as volunteer 3 provided only a spot sample - no calculation could be done). When compared with the first experiment, these data might give some indication that hand cream can increase the dermal absorption, although other parameters in the study were different, hampering a direct comparison with the results from the first experiment (e.g., in the second experiment the paper was sometimes turned around so that also the thumb touched the BPA-containing side of the paper).

The calculated maximum BPA excretion per day after handling thermal paper was less than **0.2 µg/kg bw**. RAC notes that because of the limited number of volunteers involved, caution should be taken when interpreting the results.

The pilot study by Ehrlich et al. (2014), submitted during public consultation, is a simulation experiment in which participants handled BPA receipts continuously for 2 hours (conditions of the experiment not specified). The geometric mean urinary BPA concentration of the volunteers before exposure was 1.8 µg/l (95% confidence interval 1.3–2.4 µg/l; n=23) and 4 h after handling thermal papers without gloves 5.8 µg/l (95% confidence interval 4.0–8.4 µg/l; n=23). When nitrile gloves were used, no increase was seen. Because total urinary volume was not collected it is difficult to estimate total daily excretion based on these figures. RAC noted that the detailed conditions of the experiment are not specified and that the study did not explicitly simulate the work of cashiers.

Preliminary, unpublished results from an NTP study (Thayer et al. 2014b) were submitted during public consultation. The authors studied urinary levels of BPA, BPS and D-8[9] in cashiers pre-shift and within 2 hours post-shift. The authors found significantly higher post-shift levels (median of 4.37 µg/l) of total BPA in urine compared to pre-shift (median of 2.09 µg/l). Both the pre- and post-shift urinary

[9] D-8 is BPSIP or 4-hydroxyphenyl 4-isoprooxyphenylsulfone (CAS No 95235-30-6)

values were significantly higher in the cashier population (n=34) compared with the non-cashier population (median of 0.84 µg/l, n=25). Since only one spot sample was collected, it is difficult to estimate the total daily excretion (and intake) based on these figures. However, some rough estimates are presented in the Table 16. RAC underlines that a very high individual variability is shown and the concentration range of pre-shift samples partly coincides with the concentration range of post-shift samples.

Preliminary, unpublished results from Ndaw et al. (2014) were submitted during public consultation. Pre-shift, post-sift and first morning void samples were collected from each participant during 1 or 2 days. The median urinary total BPA concentration was 3.5 µg/l (2.9 µg/g creatinine adjusted) for non-occupationally exposed workers (n=44) and 8.9 µg/l (6.8 µg/g creatinine adjusted) for cashiers (n=90). It was not clear from the document whether these reported median values were post shift, first morning void or median values from all samples. For free BPA, the median urinary concentration was 0.22 µg/l (0.21 µg/g creatinine adjusted) for non-occupationally exposed workers and 0.28 µg/l (0.22 µg/g creatinine adjusted) for cashiers.

The authors also reported a median urinary total BPA concentration of 80.7 µg/l from 4 workers of a printing company.

Discussion on biomonitoring for workers

The calculated total excreted amounts of BPA per day in the Porras et al. (2014) study for three volunteers handling BPA containing thermal paper were 65, 51 and 152 ng/kg bw/day. These values are still largely within the range of geometric average values obtained in biomonitoring investigations for the general population (10 to 100 ng/kg bw/day). Other sources of exposure can play a great role as it was shown in Volunteer 1 before the start of simulation experiment. The authors of the study of Porras et al. (2014) observed that the urinary BPA concentration in all cases always increased after meals (except breakfast) followed from 30 hours before and 50 hours after the experiment started.

With 23 volunteers Ehrlich et al. (2014) was a larger study than Porras et al. (2014). The geometric mean urinary BPA concentration before exposure was 1.8 µg/l and 4 hours after handling thermal papers 5.8 µg/l, thus suggesting a contribution of 4 µg/l due to exposure from thermal paper. The values were still below 8 µg/l however (the 95th percentile of the non-occupationally exposed people in Porras et al. 2014).

The median BPA values in Thayer et al. (2014b) for pre-shift and post-shift samples (2.09 and 4.37 µg/l, respectively) suggest a contribution from exposure to thermal of 2.28 µg/l. The values lie below the background level in Porras et al. 2014 (8 µg/l, the 95th percentile of the non-occupationally exposed people).

Amongst the cashier studies, Ndaw et al. (2014) observed the highest difference (5.4 µg/l) in urinary total BPA concentration between cashiers and non-occupationally exposed workers from the same locations (means of 8.9 µg/l and 3.5 µg/l, respectively).

It should be noted that the results are difficult to compare and that studies might have taken urinary samples before or after the peak urinary level. It should also be stressed that the post shift exposure does not reflect the exposure over 24hours.

Many biomonitoring investigations including those reviewed above indicate the importance of sources other than exposure from thermal paper in the overall exposure to BPA (e.g., dietary exposure).

1.2.3. Overall summary of biomonitoring data and comparison with modelling results

1.2.3.1. Workers

Using the correlation between oral daily intake and urinary excretion given by Krishnan et al. (2010) it is possible to roughly estimate the oral daily intake (or total daily excretion[10]) as µg/kg bw/day from urinary BPA values and vice versa. This approach, however, assumes that measured urinary BPA levels represent an average or "steady state" level, which is not true in the case of occupational spot samples. Therefore, the results should be interpreted with caution and considered as indicative only. The proposed Biological equivalent corresponding to 25 ng/kg bw/day is 1 µg/l as steady state (or daily average) urinary concentration. The same relationship between dermally absorbed total BPA and urinary excretion is valid. Thus, a dermally absorbed total BPA dose of 200 ng/kg bw/day from thermal paper (corresponding to the dermal DNEL for workers) should result in an average daily urinary excretion of 8 µg/l.

Table 16 summarises the biomonitoring results for workers. The table also includes recalculated values using the Biological equivalent relationship of Krishnan et. al (2010). These recalculated values are, however, indicative only and should be interpreted with caution since most of them are based on single spot urinary measurements, which do not represent the average daily excretion. The table furthermore gives a comparison with modelled exposure.

[10] Krishnan et al. (2010) assumed that 100% of the applied oral dose is excreted into urine.

Table 16 Comparison of BPA biomonitoring and modelling results for workers

	Expression of results	General population (2001-2012)*	Porras et al.(2014) (simulation, n=3)		Ehrlich et al.(2014) (simulation, n=23)		Thayer et al.(2014)			Ndaw et al.(2014)		Probabilistic modelling results for workers** (Scenario III; II; I)	Deterministic modelling results for workers**
			Individual background level	During and after contact up to 24 hours	Before	4 hours after contact	non-cashiers, n=21	pre-shift cashiers, n=34	post-shift cashiers, n=34	non exposed workers, n=44	cashiers, n=90		
Urinary level (µg/l)	Geometric mean	1-5	1.8, 1, 4.2	**3.2**	1.8	5.8						**0.44, 2.92, 6.88*** **	
	Individual measurements / calculations		1.8, 0.7, 4.2 (with BPA free paper)	**2.6, 2, 6.1**			0.13 - 8.04	<LOD - 96.70	0.36 – 372.17				**6.16 - 57.08**
	Median		1.7, 0.9, 4				0.84	2.09	4.37	3.5	8.9	**0.44, 3.36, 8*** **	
Total daily excretion (ng/kg bw/day)	Geometric mean	10-100 **(25-125)**	**45, 25, 105**	80	**45**	**145**						11, 73, 172*	
	Individual measurements / calculations		**43, 17, 105** (with BPA free paper)	65, 51, 152			**3.3 - 201**	**<LOD - 2418**	**9 - 9304**				154 - 1427
	Median		**43, 23, 100**				**21**	**52.3**	**109.3**	**88**	**223**	11, 84, 200***	
	95th percentile											16, 181, 430***	

Note: Recalculated values from urinary values or vice versa according to the Biological equivalent relationship by Krishnan et al. (2010) are in **bold**
* Contribution from all sources
** Contribution from thermal paper only;
*** Scenario I (Dossier Submitter);
LOD: level of detection

On the basis of the biomonitoring data presented in Table 16, modelling scenario III was discarded, as it significantly underestimates the exposure from contact with thermal paper.

Only the exposure estimate from scenario I seems rather consistent with the biomonitoring results from Ehrlich et al. (2014), bearing in mind that urine was collected after 4 hours of contact with thermal paper and that peak excretion of BPA can occur after 8-12 hours following contact (Ehrlich et al. 2014; Porras et al. 2014). On the other hand, the biomonitoring values reflect all sources of exposure, whereas the modelling only reflects the dermal exposure to thermal paper which further hampers direct comparison. Exposure estimates from scenario I and biomonitoring from Ehrlich et al. (2014) indicate somewhat higher exposure than the typical exposure range of non-occupationally exposed population.

Modelling scenario II is more or less comparable with the study result by Porras et al. (2014). Both estimates are within the range of exposure estimates for the non-occupationally exposed population indicating some underestimation of real exposure from thermal paper. RAC considers that the conditions in Porras et al. (2014) do not fully represent the real work of cashiers (thermal paper was constantly held by three fingers, the BPA-containing side of the paper being in contact with the pads of the forefinger and the middle finger only). Moreover, only three persons were involved instead of 23 participants in the Ehrlich et al. study.

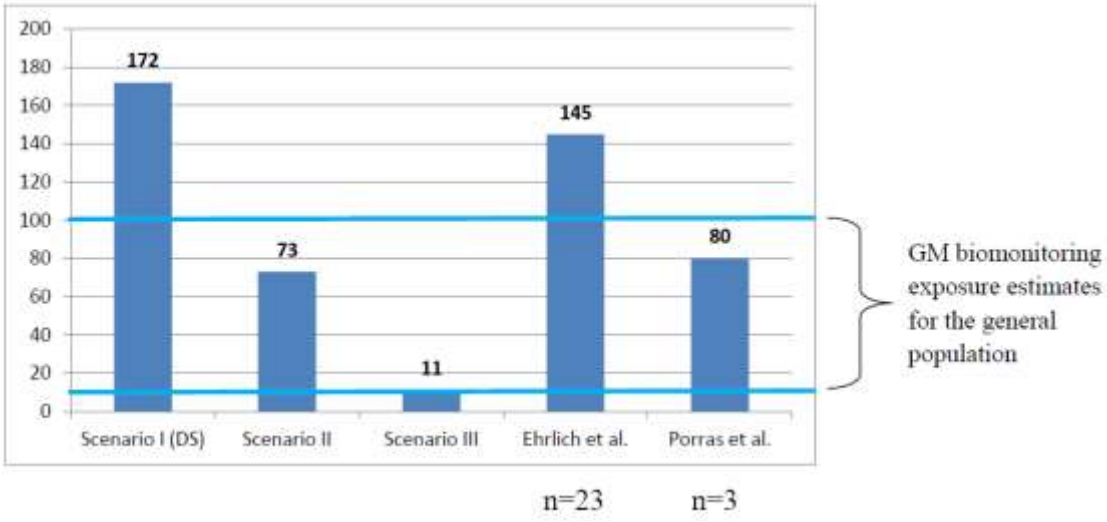

Figure 3: Comparison of BPA biomonitoring results and probabilistic modelling of exposure results for workers expressed as geometric means (ng/kg bw/day). Note 1: the calculated daily exposure levels from biomonitoring have limitations (spot samples) and thus are indicative only. Note 2: it is stressed that the biomonitoring values reflect all sources of exposure, whereas the modelling only reflects the dermal exposure to thermal paper.

Figure 4 provides a comparison of probabilistic exposure modelling scenario I for workers with preliminary biomonitoring results obtained by Thayer et al. (2014) and Ndaw et al. (2014) (all given as median concentration), as well as deterministic modelling results. It can be seen that scenario I compares quite reasonably to the aforementioned preliminary biomonitoring results. Since the exposure estimates from biomonitoring are expressed as the difference between cashier and non-cashier exposure, they reflect the impact of thermal paper only - similarly to the modelling exercise. The difference between modelling results and biomonitoring could be lower when taking into account that peak excretion of BPA can occur after 8-12 hours following contact with thermal paper.

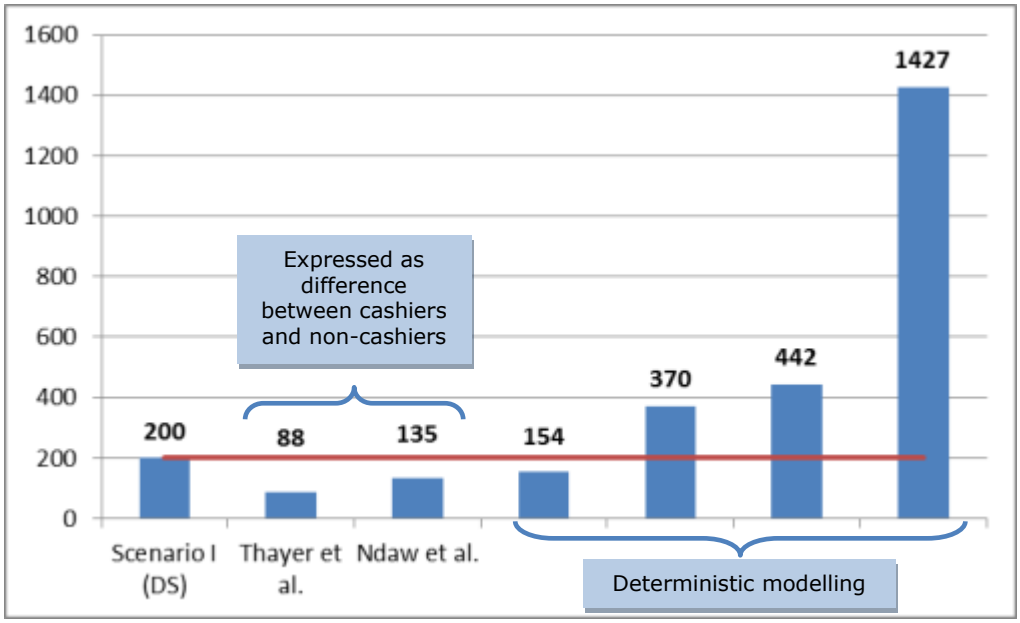

Figure 4: Comparison of exposure results from BPA biomonitoring and probabilistic modelling expressed as median exposure and deterministic modelling results representing respectively realistic case exposure (154 ng/kg bw/day) and reasonable worst case exposure for workers (370, 442 and 1427 ng/kg bw/day). The horizontal red line represents the dermal DNEL for workers of 200 ng/kg bw/day. Note 1: the calculated daily exposure levels from biomonitoring have limitations (spot samples) and thus are indicative only.

The realistic case worker exposure scenario from deterministic modelling is more or less comparable with the median exposure estimated from the probabilistic modelling scenario I as well as the median exposure estimates from preliminary biomonitoring results from Thayer et al. (2014) and Ndaw et al. (2014).

As no 95th percentile exposure values are available from Thayer et al. (2014), comparison with the reasonable worst case modelling scenarios is difficult. Nevertheless, the reasonable worst case exposure estimates from deterministic modelling fit rather well into the range of individual measurements obtained by Thayer et al. (2014) as shown in Table 16. In general, the reasonable worst case deterministic modelling scenarios are considered appropriate.

Conclusion

The reasonable worst case exposure estimates for workers from probabilistic and deterministic modelling are fairly consistent with exposure estimates from biomonitoring studies. RAC considered that 400 ng/kg bw/day represents an appropriate reasonable worst case exposure estimate for workers and used this selected value in risk characterisation.

1.2.3.2. Consumers

Comparison of exposure modelling and biomonitoring results for consumers is given in Table 17. All modelled results are within the range of geometric mean biomonitoring values for the general population (Figure 5). Furthermore, the modelled results are generally lower than the biomonitoring results or in the same range (results obtained by deterministic modelling scenarios) confirming the assumption that biomonitoring reflects the influence from all possible BPA exposure sources.

Table 17 Comparison of BPA biomonitoring and modelling results for consumers

Determinant	Expression of results	Biomonitoring of the general population (2001-2012)[1]	Probabilistic modelling results for consumers (absorption flow model)[2]	Deterministic modelling results for consumers by absorption flow model[2]	Deterministic modelling results for consumers by absorption rate model[2]
Urinary level (µg/l)	GM	1-5	**0.03-0.4**		
	Individual calculations			**1.24 - 3.52**	**2**
Total daily excretion (ng/kg bw/day)	GM	10-100 (**25-125**)	0.8 - 10		
	Individual calculations			31, 88	50
	95th percentile	85-291	2.9-50		

Note: Recalculated values from urinary values or vice versa according to the Biological equivalent relationship by Krishnan et al. (2010) are in **bold**.
[1] Contribution from all sources
[2] Contribution from thermal paper only

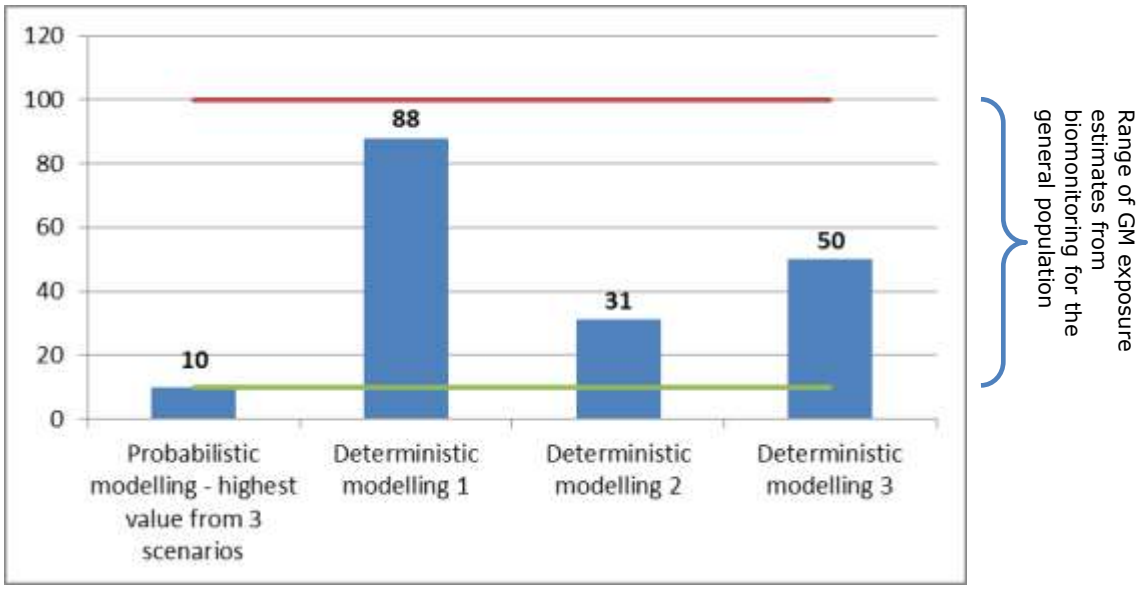

Figure 5: Comparison of BPA biomonitoring and probabilistic modelling results for consumers expressed as geometric mean concentration and reasonable worst case deterministic modelling results (ng/kg bw/day). The horizontal green line represents the lower bound of geometric mean exposure estimates from biomonitoring for the general population (10 ng/kg bw/day). The horizontal red line represents the dermal DNEL for consumers of 100 ng/kg bw/day and the upper bound of geometric mean exposure estimates from biomonitoring for the general population.

Note 1: the biomonitoring values reflect all sources of exposure, whereas the modelling only reflects the dermal exposure to thermal paper. Note 2: The biomonitoring data cannot directly be compared with the dermal DNEL since a fraction of excreted BPA is attributable to oral exposure and the remaining fraction to dermal exposure.

1.3. Risk Characterisation

The Risk characterisation ratios (RCRs) for workers and consumers based on probabilistic exposure modelling are summarised in Table **18**. Table 20 and Table 21 present the RCRs from deterministic modelling for consumers.

Table 18 Worker and consumer risk characterisation using probabilistic modelling (absorption flow)

	Exposure scenario (from Table 12)	**GM** (µg/kg bw/day)	**95th p** (µg/kg bw/day)	**DNEL** (µg/kg bw/day)	**RCR from GM**	**RCR from 95th p**
Workers	I	0.172	0.43	0.2	0.86	**2.15**
Consumers	I	0.010	0.050	0.1	0.10	**0.50**
	II	0.005	0.028	0.1	0.05	**0.28**
	III	0.001	0.003	0.1	0.01	**0.03**

Table 19 Worker exposure assessment with different exposure determinants using the absorption flow model and deterministic modelling (DNEL= 0.2 µg/kg bw/d)

	Absorption flow (µg/cm^2/hour)	**Duration of exposure** (hours)	**Surface area** (cm^2)	**BW** (kg)	**Total BPA dose dermally absorbed** (µg/kg bw/day)	**RCR**
Median (realistic) case	0.09	10	12	70	0.154	**0.77**
Reasonable worst case	0.258	10	12	70	0.442	**2.21**
	0.09	24	12	70	0.370	**1.85**
	0.09	10	111	70	1.427	**7.14***

* The scenario using a surface area of 111 cm^2 might also be considered to be a worst case exposure scenario.

Table 20 Consumer risk characterisation with different exposure determinants using the absorption flow model and deterministic modelling, considered to represent a reasonable worst case of exposure (DNEL=0.1 µg/kg bw/d)

Absorption flow (µg/cm^2/hour)	**Duration of exposure** (hours)	**Surface area** (cm^2)	**Body weight** (kg)	**Total BPA dose dermally absorbed** (µg/kg bw/day)	**RCR**
0.258	2	12	70	0.088	**0.88**
0.09	2	12	70	0.031	**0.31**

Table 21 Consumer risk characterisation using the absorption rate model and deterministic modelling, considered to represent a reasonable worst case of exposure (DNEL=0.1 µg/kg bw/d)

Absorption rate (%)	**Quantity of the substance deposited by contact** (µg/finger)	**Number of fingers in contact with the till receipt**	**Body weight** (kg)	**Total BPA dose dermally absorbed** (µg/kg bw/day)	**RCR**
10	3.56	10	70	0.05	**0.50**

Conclusion

RAC concludes on the integrated exposure assessment that:

- **All modelling scenarios for consumers show that the risk from BPA exposure in thermal paper is adequately controlled (RCR<1), these modelling results are consistent with biomonitoring data for the general population;**
- **With respect to workers, the modelling for BPA exposure from dermal contact with thermal paper indicates that the risks are not adequately controlled (RCR=2), these modelling results are also consistent with biomonitoring data for workers.**

1.3.1. Uncertainties in the risk characterisation

The main source of uncertainty to the risk estimates comes from the uncertainties in the derivation of the DNELs. In particular, the available hazard data did not allow for a quantification of the dose-response relationship for effects on the mammary gland, or for the reproductive, immunotoxic, metabolic and neurobehavioural effects. Taking into account the uncertainty analysis carried out by EFSA (2015) and their consequent use of an assessment factor of 6, RAC accounted for these effects by also applying an additional assessment factor of 6 in the DNEL derivation.

The exposure estimates for consumers carry relatively few uncertainties, in part, because biomonitoring data confirms exposure does not exceed the DNEL. Thus the confidence about a correct conclusion is relatively high.

Regarding workers, the available biomonitoring data is scarce and of limited nature, thus providing a lower confidence level to the modelling results when compared to consumer exposure. However the integrated assessment of worker exposure performed by RAC is based on both modeling data and available biomonitoring data, giving reasonable consistency.

2. JUSTIFICATION THAT ACTION IS REQUIRED ON AN EU WIDE BASIS

Justification for the opinion of RAC

Based on the outcome of the risk characterisation, RAC considered that the risk for workers is not adequately controlled.

The nature and reversibility of effects of BPA to the fœtus of pregnant workers is considered to be uncertain, but the effects are potentially severe. Taking all uncertainties into consideration an RCR of 2 was calculated.

Placing on the market of BPA containing thermal paper occurs across the EU. The population at risk is large (cashiers/workers handling till receipts). There is no evidence the risk would be different in different EU countries. As the concern for workers is not limited geographically or nationally, and as the same thermal paper will in many cases be available on the market in several Member States, Union-wide action is justified.

RAC considers Union-wide action to be appropriate.

Justification for the opinion of SEAC

Summary of proposal:

To justify that action is required on an EU-wide basis, the dossier notes that the adverse health effects arising from exposure to BPA can occur to the descendants of exposed female cashiers and consumers in the EU, and hence the risks are extended across all the EU countries. It is also highlighted that an EU-wide restriction would remove any potential distorting effects that national restrictions might have on the free circulation of goods on the market, thereby ensuring a level playing field for all the actors in the internal market.

Key elements underpinning the SEAC's conclusion

Based on the key principles of ensuring a harmonised level of protection across the EU and of maintaining the free movement of goods within the EU, SEAC supports the view that any necessary action to address risks associated with BPA in thermal paper should be implemented in all Member States.

Consumers

RAC in its opinion has concluded that the risks from BPA in thermal paper to human health are adequately controlled for consumers across the EU. Based on this SEAC concludes that action in relation to risks for human health aimed at consumers is not justified on an EU wide basis.

Workers

RAC in its opinion has concluded that the risks from BPA in thermal paper to human health are not adequately controlled for workers across the EU, and that measures to minimise exposure should be implemented on a EU-wide basis. Based on this, SEAC concludes that action to address risks to human health aimed at workers is justified on an EU wide basis.

SEAC's conclusion

SEAC agree that action is justified on an EU wide basis.

3. JUSTIFICATION THAT THE SUGGESTED RESTRICTION IS THE MOST APPROPRIATE EU WIDE MEASURE

Justification for the opinion of RAC

Taking into account that for consumers the risk from BPA exposure in thermal paper is adequately controlled (RCR<1), RAC has focused its assessment on the risk to workers arising from the exposure to BPA containing thermal paper (RCR>1).

It should also be taken into account that substitution is the first risk management measure in the worker protection hierarchy and only where exposure cannot be prevented by other means, should individual protection measures including personal protective equipment be implemented (Chemical Agent's Directive 98/24/EC, Article 6(2)). The proposed restriction is consistent with this hierarchy.

The Dossier Submitter proposed two different Risk Management Options (RMOs):

- RMO 1: A limitation of the concentration of BPA contained in thermal paper
- RMO 2: A limitation of the migration of BPA from thermal paper.

These have been analysed by the Dossier Submitter and the issues relevant to RAC are compared in Table 22.

Table 22 Comparison of restriction RMOs by RAC

Assessment criteria		**RMO 1**	**RMO2**
Effectiveness	Risk reduction capacity	++	+(+)
Practicality	Implementability	++	+
	Enforceability	++	+
	Manageability	++	+
Monitorability		++	++

The restriction options assessed in the Background Document differ from each other as regards if BPA content or, the migration of BPA is restricted. Considering that no relationship between migration rates and exposure to BPA from thermal paper has been established, defining a BPA migration rate from the thermal paper that would result in adequate control is not possible.

Compared to RMO 1, the risk reduction capacity of RMO 2 would be similar or slightly lower since the migration limit would need to be as low as possible (as no safe migration level can be set). No major difference is expected to be observed between RMO 2 and RMO 1 regarding their monitorability (it is possible both to measure BPA migration and BPA content). However, migration testing is more complex, thus affecting practicality of RMO 2 (implementability/enforceability/manageability).

For the above reasons, RAC prefers RMO 1 (the restriction proposed by the Dossier Submitter) over RMO 2.

In addition to the two assessed RMOs, the Dossier Submitter assessed several other possible EU-wide risk management measures, which are further specified in the Background Document. RAC agrees with the Dossier Submitter's reasons for discarding these RMOs, but notes that the RMO "*Regulatory requirement for pregnant workers to wear protective gloves*" would have merited a further assessment by the Dossier Submitter.

Justification for the opinion of SEAC

Summary of proposal

Several measures are discussed in the dossier, and two restriction options have been chosen for further evaluation:

- RMO 1 (the proposed restriction): A concentration limit on BPA in thermal paper.

- RMO 2: A limit on the migration of BPA from thermal paper.

The dossier concludes that there is insufficient evidence to conclude that migration barriers, such as top coatings, would mitigate all migration and associated risks arising from thermal papers containing BPA. It is also stated that using protective barriers would probably imply a significant cost for industry. RMO 2 was thus deemed a less efficient and a less proportionate measure, compared to RMO 1.

An additional third RMO, namely a concentration limit on all bisphenols in thermal paper, was mentioned, but due to the current lack of toxicological data on some of the bisphenols, this option was not evaluated further.

The Dossier Submitter also acknowledges the possibility to use other EU wide risk management options, but they are all disregarded for different reasons:

- Authorisation
    - Does not cover risks from imported thermal paper
- Voluntary industry agreement
    - Does not give enough incentives for sufficient substitution
- Worker protection:
    - Regulatory requirement for pregnant workers to wear protective gloves
        - discriminatory measure among workers
        - would not protect workers who ignore their pregnancy
        - would not protect workers who have not declared their pregnancy yet or who wouldn't like to

        - would not protect consumers
    - Regulatory requirement for workstation re-layout, minimising cashiers contact with BPA containing receipts
        - would not be economically suitable
        - would not protect consumers

The Dossier Submitter points out that the low concentration limit in the proposed restriction is equivalent to a total ban. As a result, it is expected that BPA will be fully phased out, thereby removing all human exposure from thermal paper. However, the least expensive alternative to BPA is BPS, which is suspected to have many of the same adverse health effects as BPA. A restriction on BPA in thermal paper may thus only ensure that there is a reduction in risk if alternatives other than BPS are chosen by industry as a replacement.

The proposed restriction was considered to be the most appropriate EU wide measure due to its effectiveness, proportionality and practicality, compared to the other RMOs.

Key elements underpinning the SEAC's conclusion

Consumers

Since there is no identified risk to human health for consumers identified by RAC, SEAC concludes that no action is required on an EU wide basis to protect consumers' health.

Workers

RAC found that the RCR is above 1 for workers (cashiers), thus SEAC considers that risk management might be appropriate. However, some of the risk management options evaluated by the Dossier Submitter were discarded mainly due to their inability to protect consumers. This argument is no longer valid since RAC has concluded that the risks for consumers are adequately controlled.

The Dossier Submitter did not provide any cost estimates for the worker protection risk management measures, but claimed that workstation re-layout (i.e., consumers rather than workers take the receipt directly from the printer) would be economically infeasible. Without any more evidence to justify this claim, SEAC cannot exclude the possibility that rearranging the workstation might be equally or less expensive than the proposed restriction.

Another option that could have been worth investigating is a narrower scope, e.g., excluding non-Point of Sale (non-POS) tickets[11], top-coated paper (RMO 2) or ATM receipts. The Dossier Submitter did not provide information, or recommend that the committees evaluated a restriction option with a narrower scope. In case such a narrowing of scope was both technically practicable and possible without consequence for workers risks, then this option could reduce costs and make the restriction more likely to be proportionate. However, SEAC does not have any specific information on the possible risks and costs from a narrower scope. For example information related to whether workers only handle POS receipts or whether they also handle non-POS tickets, and if it is technically and/or financially viable for thermal paper producers to have separate production lines for different types of thermal paper, would be necessary to determine if a narrower scope would

[11] Self-adhesive labels, lottery tickets, fax paper and others, see Table 25

be a more appropriate measure than the proposed restriction. SEAC is not able to recommend any derogation from the original scope. SEAC notes that having a narrow scope could complicate enforceability of the restriction. Forum stated that from an enforcement perspective, it would be difficult to distinguish between thermal papers produced for one application or another.

The Dossier Submitter also mentions a restriction option with a larger scope (RMO 3), where BPS is also included. Based on RAC's advice of avoiding BPS as an alternative, SEAC finds that preparation of a restriction proposal on BPS should be considered if a restriction on BPA will be implemented.

SEAC's conclusion

As a result of gaps in the assessment of risk management measures, SEAC expresses reservations to the conclusion of the Dossier Submitter that the proposed restriction is the most appropriate EU wide measure. However, SEAC has concluded that the proposed restriction cannot be rejected as an appropriate EU wide measure to address human health risks to workers. SEAC cannot exclude the possibility that a narrower scope of the restriction or another risk management measure might be more cost-effective.

3.1. Effectiveness in reducing the identified risks

Justification for the opinion of RAC

RAC notes that the risk reduction capacity of the proposed restriction depends on the alternatives that will be used to substitute BPA. BPS, the most likely substitute according to the Dossier Submitter, may have a toxicological profile similar to BPA and thus RAC advises against substitution with BPS. 'Pergafast 201' is already commonly used and seems to be a safer alternative having none of the human health hazard classifications of BPA[12]; it could however be dangerous if released into the aquatic environment. Due to how receipts are handled, most of them will probably not reach the aquatic environment and this is therefore considered an acceptable risk (Subsport 2015).

RAC suggests that the substitution trend towards BPS would be monitored following the entry into force of a possible restriction on BPA in thermal paper. If substitution trend towards BPS is observed, the need to propose a restriction on BPS should be considered.

[12] Bisphenol A is classified as Repr. 2 – H361f; STOT SE 3 – H335; Eye Dam. 1 – H318; and Skin Sens. 1- H317 under the CLP Regulation (Regulation 1272/2008). Recently RAC adopted its opinion in support of a classification Repr. 1B; H360F. Pergafast 201 is only classified as Aquatic Chronic 2 – H411.

Justification for the opinion of SEAC

Proportionality to the risks

Summary of proposal

Benefits

The benefits are based on the identified risks for the unborn child for the following human health endpoints:

- Female reproductive system
- Metabolism and obesity
- Mammary gland
- Brain and behaviour

The Dossier Submitter has performed a partial quantitative evaluation of health benefits for the progeny of cashiers and consumers who are exposed to BPA, through "eco-paper" Point of Sale (POS) tickets and receipts. The evaluation of benefits is based only on exposures related to "ecopaper" POS tickets and receipts, which constitute a 65% use share of all thermal paper in the EU. The Dossier Submitter suggests that 70% is a reasonable estimate for the share of all POS thermal tickets and receipts that contain BPA as a dye developer.

The estimations of disease burden are based on:

- A modelled internal exposure dose distribution for the two population groups (female cashiers and consumers)
- Modelled dose-response functions, based on linear extrapolation from animal studies, which are used to derive the excess risk of the relevant health effects
- The use of the DNEL as a toxicological benchmark to define an effect threshold

The dossier underlines that the quantified benefits of the restriction constitute only a part of the benefits, as there were identified health effects that were unquantifiable. Adverse effects from BPA that could not be quantified as monetised benefits were:

- Increase in ovarian cysts
- Disruption of ovarian cycles
- Alteration of spacial memory
- Alteration of learning functions

In the BD the Dossier Submitter also considers the kidney effects for the risk assessment. Two main conclusions were drawn:

- The kidney effects were only observed at quite high doses in animal studies, so it may be expected that no cases of kidney effects will occur in the human population.
- If any cases would occur, it would be difficult to clearly identify the disease (i.e. the actual impact on the individual and furthermore society) attributable to an increase in kidney weight.

The excess risk estimates from

Table 23 were used to calculate the benefits.

Table 23 Excess Risk estimates from Table 108 in the BD

	Excess Risk estimates from the BD	
	Consumers	**Workers**
*Terminal end buds (TEB)**	*0.06%*	*0.61%*
*Terminal ducts (TD)**	*0.05%*	*0.55%*
*Hyperplastic duct (HD)**	*0.01%*	*0.055%*
Mammary gland* - worst case	0.12%	1.22%
Neurobehavior	N/A	N/A
Reprotox*	0.006%	0.07%
Metabolic – cholesterol	0.07%	0.73%
Metabolic – obesity	0.032%	0.33%

* only female offspring are at risk for these endpoints.

The resulting quantified part of the benefits was estimated to be

Consumers: €1 677 218 - €2 552 485
Workers: €1 863 178 - €2 654 870

The total quantified benefits were than estimated to be in the range > [€3 540 395; €5 207 355] per year. The absolute worst case scenario was excluded, since this scenario involved adding up the different excess risk estimates for the mammary gland (TEB, TD and HD), which was not considered to be realistic.

These numbers were supposed to constitute the lower bound for the benefits, since part of the identified health effects were not quantified.

It is also made clear in the dossier that the benefits are highly contingent on the alternative chosen by industry to replace BPA. A transition from BPA to BPS is expected to yield very small or even zero benefits, while the Dossier Submitter expects a significant risk reduction if other alternatives are chosen.

The Dossier Submitter underlines that information provided by large retailers indicate that although BPS is technically and economically feasible and is already used as an alternative, it still may be expected that industry would not necessarily switch to BPS if it is expected that BPS will be regulated in the near future (INERIS 2013).

Costs

The Dossier Submitter's approach to cost estimation is based on estimating the substitution costs and compliance control[13] costs for the thermal paper producers. This includes thermal paper production both for EU use (58%) and for export (42%). The size of the import market of BPA containing thermal paper is unknown,

[13] The Dossier Submitter is here referring to testing costs.

and the costs to importers are thus not included[14].

To calculate the substitution costs, the Dossier Submitter has considered the expected price increase for thermal paper, when switching from BPA to other dye developers. The alternatives included in the analysis are: BPS, D8, and Pergafast 201. Three scenarios were constructed (low, medium and high) varying all the input prices as well as the concentration of the dye developers (loading) used in the thermal paper.

The main assumptions used in the substitution cost calculations included:

- Only costs for "ecopaper" POS tickets and receipts are calculated
- Period of analysis 2019-2030
- Growth in thermal paper market 5-7%
- Price decrease in alternatives of 8% between 2013 and 2023, and then 5% decrease from 2023-2030.
- All alternatives are treated as "drop-in" used in the same concentration as BPA

Based on these assumptions, as well as additional industry consultations performed by the ECHA secretariat and the Dossier Submitter (see Annex 9 to the BD), the medium scenario substitution costs are estimated to be in the range €1 million to €22 million per year. Excluding BPS the range is €19 million to €22 million per year.

In addition to the substitution costs compliance control costs in the range €150 000 – €250 000 per year are expected.

Proportionality

In the BD, proportionality is evaluated under two extreme scenarios:

1) All companies will move from Bisphenol A to Bisphenol S

2) No company will move to BPS and instead will move to non-bisphenol alternatives, including D8 (4-hydroxyphenyl 4-isoprooxyphenylsulfone) and Pergafast 201.

A summary of the Dossier Submitters' assessment is presented for the two scenarios in **Table 24**.

[14] The need to include costs for export in the cost estimate depends on whether industry will produce BPA free thermal paper for export as a consequence of the restriction or whether a separate production line for BPA containing thermal paper remains in place for export after the restriction. In the latter case, no costs for export would occur, and the costs would be overestimated. On the other hand, the costs borne by importers are not included, which will underestimate the costs. As long it is unknown whether the EU is a net exporter or a net importer of BPA containing thermal paper, it is not possible to determine whether the costs are under- or overestimated in this respect.

Table 24 Costs and benefits ratio in two scenarios (taken from section E.2.1.1.2.1 in the BD)

	Human health benefits (B)	Costs (substitution+control) (C)
Scenario 1 (BPS)	(likely) ≈ 0	medium cost = €1.4 million
Scenario 2 (non-bisphenol alternatives – D8 and Pergafast)	> €3.5 million and €5.2 million (not all benefits quantified and valued)	medium cost = [€19.3 million; €25.3 million] (upper bound likely to be overestimated)

The Dossier Submitter concludes that scenario 1 is not considered proportionate, but that the benefits may outweigh the costs for scenario 2 (if unquantified benefits would be large enough) and the restriction may thus be deemed proportionate.

Key elements underpinning SEAC's conclusion

Benefits

Consumers

The Dossier Submitter's assessment of benefits was premised on a risk being identified. However, given RAC's conclusion that the risks from BPA exposures for consumers are adequately controlled, there are consequently no expected impacts, and thus no benefits to society from implementing risk management measures directed towards consumer protection.

Workers

The quantitative analysis of the benefits of the restriction is based on a health impact assessment that estimates the change in the burden of disease as a result of the restriction. The disease burden is estimated by linking the number of progeny of females exposed to BPA at levels above the DNEL to the excess risk for the effects of concern.

According to RAC, the available data for effects on the mammary gland, the immune system, the reproductive system, metabolism and neurobehaviour was not robust enough to be used as a point of departure for DNEL derivation. Instead however, RAC has chosen to follow EFSA's approach by using the kidney weight changes as a starting point for DNEL derivation and to account for the uncertainty regarding the other potential effects by using an additional assessment factor of 6 (six). Based on a DNEL for the dermally absorbed total BPA dose and a reasonable worst case exposure estimate, RAC concluded that risk from dermal contact with thermal paper is not adequately controlled for workers (RCR=2).

According to RAC, the various endpoints considered in the risk assessment have a number of effect types that are of relevance for human health impact assessment. The identified endpoints of relevance to SEAC for undertaking its proportionality assessments are[15]:

- Mammary gland

[15] Note that the exact wording used for these endpoints in opinion of RAC and in the BD is variable.

- Immunotoxicity
- Female reproductive system
- Brain and behaviour
- Metabolism and obesity

All of these categories might lead to several possible health effects. RAC has considered studies related to the various endpoints used in the risk assessment, and evaluated the evidence on the associated health effects. In each case the target population is children of pregnant cashiers.

Since RAC concluded that the available data on these effects do not allow a quantification of the dose-response relationship, SEAC cannot use the benefit estimates described in the BD for its proportionality assessment.

It should be noted that the population at risk which is used in the break-even analysis is based on the worker population considered by the Dossier Submitter in their restriction proposal analysis, namely cashiers handling POS tickets and receipts only. This was also the population considered by the Dossier Submitter to be consistent with the risk assessment and for whom a risk was demonstrated and EU wide action found to be appropriate by RAC[16]. In assessing the exact number of such workers to be included in the break-even analysis, SEAC were mindful of a number of issues and uncertainties regarding the relevant population:

- As previously noted, the extent to which the risks to workers relate to exposures from POS applications as distinct from non-POS applications has not been assessed by the Dossier Submitter and hence it has not been possible to consider the risks and costs of a narrower scope. As such, and given that the risk assessment was focussed on cashiers handling till receipts (i.e., POS applications), it is also unclear whether the risks also apply to other workers besides cashiers, and hence to what extent such other workers e.g., in distribution industries, who are only exposed to non-POS applications should also be included within the relevant population at risk.

- The population of cashiers estimated by the Dossier Submitter potentially includes other workers employed in retail sales than just cashiers and hence may include workers who might never be exposed since they are not strictly in contact with tickets and receipts. According to estimates provided by the Dossier Submitter in the BD (section F1.1.1), it is possible that the number of cashiers actually in contact with receipts and tickets, may be 40% - 80% lower than indicated.

- The population of cashiers is not a static group of workers since there will be periodic turnover of staff. However it is unclear whether this will significantly affect the total population that should be included in the analysis since a significant part of staff turnover is likely to be within the same occupation. Moreover, the pregnancy incidence rates (upon which the number of offspring is calculated) are annual rates that relate to the possibility of pregnancy during a given whole year period. Turnover of staff within any

[16] The risk assessment was based on a scenario of occupational exposure focused on exposure via the cutaneous route of cashiers handling receipts with a particular focus on pregnant women. Other professions exposed to thermal papers (lottery tickets, self-adhesive labels) were not taken into account.

year would thus not have any impact on the number of offspring estimated on the basis of the static population of female cashiers.

The uncertainties surrounding the population at risk are pulling in different directions, so there are no indications of systematic over- or underestimation.

Costs

SEAC in principle agrees with the approach taken by the Dossier Submitter to estimate the costs of the proposed restriction. SEAC however made some modifications in order to correct for some errors identified, to include new cost information received, as well as to incorporate other changes considered necessary by SEAC. In particular, the following assumptions are different from the Dossier Submitter assumptions:

- New information was obtained from industry by the ECHA secretariat and the Dossier Submitter (Annex 9 to the BD) late in the opinion making process. This additional information from several stakeholders indicates that Pergafast-containing thermal paper is only 10-35% more expensive than BPA-containing thermal paper. SEAC has used this new information as a basis for producing new cost estimates.

- The Dossier Submitter had assumed that the thermal paper market would grow by 5-7% per year. Although SEAC found some justification for assuming a growing thermal paper market, evidence on specific growth rates was lacking. Furthermore, there are aspects like the growing paper-free alternatives market, which might lead to a decrease in market size, but, SEAC has no corroborating evidence to support this. In the public consultation for the SEAC draft opinion, an additional report was brought to SEAC's attention, stating that the European market is increasing between 0-10% per year (Danish EPA 2014). Nevertheless, since no conclusions would change, SEAC has for simplicity not changed its assumption that the tonnages will be constant during the period of analysis, though this means that the resulting costs are likely to be underestimated.

- The Dossier Submitter assumed an 8% (followed by 5%) yearly price decline for the alternatives. SEAC could not find any justification for this assumption. Furthermore, new information obtained from industry (Annex 9 to the BD) indicated that raw material inputs were the main driver of the cost of alternatives, and that no significant economies of scale were to be expected. As such, the price difference when using an alternative dye developer in the manufacture of thermal paper is expected to persist over time. Based on this information, SEAC has assumed a constant price difference over time between the alternatives and BPA.

- The scope of the restriction includes both thermal paper used for Point-of-Sale (POS) and non-Point-of-Sale (non-POS) applications:

Table 25 Applications of thermal paper in Europe (Table 6 from the BD)

Application	Share over total thermal paper (2008-2012)
Point-of-sale receipts	50% - 65%
Self-adhesive labels	20% - 30%
Lottery tickets	≈10%
Fax	≈5% - 10%
Other	< 0.5%

TOTAL	100%

However, the costs estimates derived by the Dossier Submitter only included the POS applications. SEAC could not find any justification for assuming that there would be no costs connected to non-POS applications, so the cost estimates produced by SEAC were extended to include the entire scope. SEAC assumed that the cost of using an alternative in non-POS thermal paper would be the same as using alternatives in POS thermal paper[17].

- The Dossier Submitter estimated that a switch to D8 or Pergafast 201 would lead to a 13.5% or 15% price increase in thermal paper respectively (medium cost scenario). SEAC has based its cost assessment on three different cost scenarios using 10%, 20% and 35% as the respective increases in the price of thermal paper, which will cover both these alternatives. This range corresponds to the range of price increases for Pergafast reported in the new information gathered by the ECHA Secretariat and the Dossier Submitter, which showed a price increase between 10-35% (Annex 9 to the Background Document).[18]

Based on these updates, as well as the price and tonnage information from the dossier, SEAC has estimated the cost of the restriction as presented in **Table 26**.

Table 26 Three cost scenarios for the average yearly costs in € over the period 2019 – 2030

Alternative	Cost scenarios		
Cost scenario	**low (10%)**	**medium (20%)**	**high (35%)**
Average yearly costs over the period 2019 - 2030	43 000 000	86 000 000	151 000 000

SEAC has taken into account the RAC advice: "*[BPS]… may have a toxicological profile similar to BPA and thus RAC advises against substitution with BPS. […] If substitution trend towards BPS is observed, the need to propose a restriction on BPS should be considered.*" Furthermore, evidence from consultation with industry suggests that even though BPS is the cheapest alternative, many actors would nevertheless switch to a more expensive alternative with less hazardous properties. Due to the assumed very limited risk reduction associated with BPS, as well as doubts as to whether industry would choose this option, a quantitative proportionality assessment was not undertaken for BPS. Instead, SEAC only evaluated those alternatives for which there was strong evidence of risk reduction, namely D8 and Pergafast 201[19]. Still, it is important to keep in mind that if industry chooses BPS as an alternative, the restriction might be less costly, but achieve little reduction in risk.

Proportionality

[17] As noted above, a narrower scope would be worth investigating. However, SEAC does not have the necessary information about potential costs or risks associated with a narrower scope, and is thus only evaluating the proposed restriction. Please also see the section on benefits for a discussion of the uncertainties surrounding the population at risk.

[18] SEAC does not distinguish between D8 and Pergafast in calculating the price increase scenarios, since both are within the same thermal paper price increase interval.

In accordance with the proportionality considerations of the Dossier Submitter, and alongside the RAC advice noted in the previous paragraph, SEAC agrees that the restriction is unlikely to be proportionate if industry primarily uses BPS as the alternative for BPA. The largest benefits are likely to be achieved if substitution from BPA was to a non-bisphenol alternative, whereupon the corresponding costs would be €43 - €151 million per year as indicated above. In case of substitution with non-bisphenol alternatives, it is assumed that any risks to workers from thermal paper would be adequately controlled.

As mentioned above, the available information does not allow the quantification of dose-response relationships necessary to perform a health impact assessment and corresponding cost-benefit assessment of the proposed restriction. One approach, used in previous restrictions where fully quantified cost-benefit comparisons have not been possible, is to instead perform a 'break-even' analysis in order to aid the proportionality assessment.

One complication in the present case is that it is not clear how the DNEL should be interpreted, since it encompasses uncertainties associated with multiple endpoints. Before undertaking the full, more complex analysis, a simpler example displaying the principals behind a break-even analysis can be helpful.

Consider a toxic chemical (chemical A) affecting only one endpoint, and the risks are related to one specific disease with an unknown dose-response function. Since the dose-response function is unknown, there is no way of determining if or how many cases of the disease is expected to occur in the population at risk. Instead, one can try to ask a different question: "What is the minimum number of cases of the disease that would have to occur for the substitution costs to be offset (break-even), that is, the number of cases that would need to be exceeded for the net benefits of a restriction would be positive?"

The following information would then be used to construct a break-even analysis:

1) Switching from chemical A to an alternative (chemical B) induces substitution costs of €1 million per year.
2) The identified population at risk is estimated to be 100 000 workers per year.
3) The disease is estimated to yield a loss to society of €5000 per case.

The necessary number of cases = substitution costs/cost per case
= €1 000 000 / €5 000
= 200

Thus, the occurrence of more than 200 cases of disease in the worker population caused by exposure to chemical A will ensure that the net benefits of a restriction on chemical A is positive. To get the necessary occurrence rate in the population at risk, the number of cases is divided by the population: 200/100000=0.002. The result from this break even analysis shows that a restriction on chemical A will yield net benefits to society if the occurrence rate in the population at risk is at least 0.2%.

Keeping in mind that the dose-response function is unknown, expert advice on the likelihood of observing an occurrence rate of said order of size is needed to interpret the result (i.e., to evaluate the balance of costs and benefits).

Whilst the above example demonstrates the case in which only a single endpoint contributes to adverse effects in the population, the actual situation is somewhat more complex, and the break-even analysis is not as straight forward as presented

above. In accordance with the risk characterisation performed by RAC, there may be possible adverse health effects related to more than one endpoint. As such, the break-even approach requires that the costs of the restriction are apportioned across all potentially contributing endpoints (and their associated adverse effects) included in the risk characterisation. The extent to which each of the endpoints included in the risk characterisation will actually generate adverse effects is not known. Neither is there any indication that any one endpoint is likely to contribute more or less to the benefits than another. Based on this and in order to keep the analysis transparent, SEAC has apportioned the costs in this break even analysis equally across the different endpoints included in the risk characterisation performed by RAC in this break-even analysis. Since there are 5 endpoints this

means that each endpoint is allocated 20% of the cost. Based on this cost allocation, the implied minimum absolute risk reductions that would be necessary to offset the costs can be computed.

For each endpoint, the required risk reduction is calculated as shown in the 'single endpoint' example shown above, using the population with RCR>1. The main difference as compared to the 'single endpoint' example is that the cost allocated to each endpoint is lower, as it is divided across the different effects.

The relevant population at risk are the unborn children of cashiers exposed to BPA from thermal paper. From Table 12 in the RAC opinion it is known that the 50th percentile (median) exposure is approximately at the DNEL, i.e. RCR=1. SEAC therefore assumed that out of the offspring 50% are exposed above the DNEL (RCR>1) and 50% below the DNEL (RCR<1). In the break-even analysis a population size of 39 500 daughters (at risk) was used for the mammary gland and the reproduction toxicity endpoints. For immunotoxicity, neurobehaviour and effects on the metabolism, the relevant population at risk includes both daughters and sons of exposed cashiers, bringing the population at risk to 81 149 per year.

In computing the break-even number of cases for each effect, SEAC has taken the valuation factors provided by the Dossier Submitter as the starting point, but where necessary these have been updated to correct for missing or insufficiently justified values. All corrections by SEAC increased the valuation factors compared to the ones provided by the DS. The valuation factors included are used to represent the entire spectrum of illness and disease associated with exposure to BPA for each endpoint. As such they are not be considered as only representing one single disease for each endpoint. Indeed for some of the endpoints the valuation factor is constructed using the average of the valuations found in the literature for a number of different diseases that are relevant. It is not known how representative the valuation factors are for the entire spectrum of health effects associated with the exposure to BPA. However, since the factors are constructed using diseases indicative of the class of health effects associated with the endpoint, they can be used as average indicators for the likely order of magnitude of the willingness to pay to avoid diseases within that class. Furthermore, it should be noted that the valuation factors chosen to be representative could equally be over- or underestimated, thus the end results are considered to be unbiased. The complete list of valuation factors, the derivation and the corresponding sources can be found in Annex 5.

The results of the break-even analysis can be found in the Table 27 below. Three scenarios are constructed by combining high valuation factors with low costs, medium valuation factors with medium costs and low valuation factors and high costs. As such they represent possible upper and lower bounds for a range of the necessary absolute risk reduction. Although these ranges incorporate some of the

uncertainties associated with the cost and valuation factors, a number of additional uncertainties are discussed in Annex 6. Details of the derivation of the valuation factors used across the 3 sensitivity scenarios and for each endpoint are further described in Annex 5.

Table 27 Absolute necessary risk reductions to offset the cost of the proposed restriction. Due to the underlying uncertainties (see Annex 6) the figures should be interpreted as indicators representing orders of sizes rather than accurate estimates

Absolute risk reduction necessary to offset the cost				
Endpoint	Cost division	low cost - high WTP	medium cost - medium WTP	high cost - low WTP
Mammary gland*	20 %	2 %	7 %	162 %
Immunotox	20 %	0.6 %	2 %	5 %
Neurobehavior	20 %	0.4 %	3 %	16 %
Reprotox*	20 %	7 %	20 %	70 %
Metabolic	20 %	4 %	12 %	41 %

* only female offspring are at risk for these endpoints.

Interpretation and conclusions from the Break-Even analysis

The percentages displayed in the above table represent the absolute risk reductions necessary to offset the costs. This is equivalent to the proportion of the known population at risk (i.e. RCR>=1) who would have to experience effects within the given endpoints. It should be noted that the break-even analysis does not imply that any effects actually will occur. It only describes the incidence rates that would be necessary in order for the benefits to offset the costs of the restriction.

To be able to correctly interpret the results, one need to look at each column as a whole, i.e. all of the absolute risk reductions within a given scenario (column) would have to happen in the same year, for the cost to be offset[20]. In general, the higher the proportion of the population at risk that needs to experience effects in order for the costs to be offset, the less likely is it that the restriction is proportionate.
The above results thus suggest that in order for the health benefits of the restriction to offset the total costs of transition to a non-bisphenol alternative (D8 or Pergafast 201), the hypothetical absolute risk reduction resulting from the reduction of exposure to BPA in thermal paper for the given adverse effects would have to be (medium cost-medium valuation WTP shown with upper and lower bound in parenthesis): 7% (2-162%[21]) having mammary gland changes, 2% (0.6-5%) having immunotoxicity-related allergies, 3% (0.4-16%) having neurobehavioral effects, 20% (7-70%) experiencing adverse reprotoxic effects and 12% (4-41%) having hypercholesterolemia or weight gain. These risk reductions would be incremental to the baseline rates of these adverse effects in the general

[20] Note that if a risk reduction on one endpoint is larger than required for break-even, this can in principle compensate for a smaller than required risk reduction on one of the other endpoints. This is equivalent to using a different cost division among the endpoints.

[21] The reason for the large difference in the min and max absolute risk increases for the mammary gland changes is due the assumption of a clear link between BPA and cancer in the medium and maximum, whilst no such link is assumed in the low valuation scenario.

population. Accordingly, this means that if, for example, the general population risk level for reprotoxic effects would be 0.2%[22], one would need to observe this disease in 0.2%+6%=6.2% of the population at risk from BPA from thermal paper. Note that care needs to be taken in any interpretation of background incidence rates in the general population since the population at risk is very small compared to the general population and thus high incidences in the population at risk would not necessarily be at odds with observing low rates in the general population.

For the restriction to be proportionate, it would thus need to reduce the risks of all the different health effects (across the population at risk from BPA exposure from thermal paper) by at least the order of magnitudes ('break-even' risk change levels) indicated above. As such, in order for SEAC to conclude on the proportionality of benefits and costs it is necessary to assess the plausibility of these hypothetical break-even risk change estimates for each effect individually, as well as concurrently across the population at risk. In the absence of any directly applicable information or data, SEAC consulted RAC on the plausibility of observing such risk estimates in reality. Specifically, SEAC asked RAC for their expert judgement on the likelihood of observing the hypothesised 'break-even' risk change levels (incidence percentage point change) in the population at risk. In response RAC concluded (by simple majority) that *"In general, concurrent incidences of such high magnitude for these types of effect* [are] *exceptionally unlikely for any substance"*. Moreover RAC emphasised that *"it is exceptionally unlikely that all of the incidence rates* [shown in the table] *would occur concurrently in the population at risk due to exposure of workers to BPA from thermal paper"*.

It should be noted that the risk estimates presented to RAC were different from those given here, since those estimates were based on a preliminary analysis undertaken by SEAC. SEAC notes that the estimates shown to RAC were lower than the 'high cost – low WTP' scenario, and SEAC concludes that the respective occurrence rates must be considered exceptionally unlikely. For the 'medium cost – medium WTP' scenario, some of the estimates are lower, and some are higher than the estimates shown to RAC, and as such, SEAC concludes that also this scenario is considered to be exceptionally unlikely. For the 'low cost – high WTP' – scenario, the estimates are either equal or lower than the ones shown to RAC, but still within the same order of magnitude. RAC was informed that the presented estimates were uncertain and could change. Bearing in mind the context of disease incidence rates directly attributable to individual chemicals, SEAC considers this scenario to be unlikely.

The full question posed to RAC and the response of RAC to SEAC can be found in Annex 10 to the BD.
Table 28 below shows the estimates from the preliminary analysis that was shown to RAC, alongside the final estimates.

Table 28 Comparison of the different necessary risk reduction estimates

Endpoint	Medium estimates from the preliminary analysis (shown to RAC)	Medium estimates used in the break-even analysis (Table 27)

[22] For the purposes of this example the general population risk level for reprotoxic effects is based on the rates for endometrial hyperplasia as an exemplar of disease/illness in humans associated with reprotoxic effects. The risk level is from Lancey et al. (2012).

Mammary gland*	17%	7%
Immunotox	13%	2%
Neurobehavior	N/A	3%
Reprotox*	7%	20%
Metabolic	4%	12%

* only female offspring are at risk for these endpoints.

SEAC's break-even analysis discussed above has assumed, despite the uncertainties and lack of conclusive evidence, that there would indeed be observed impacts in terms of the above disease and illness effects in human populations, and that these are causally linked to exposure of BPA in thermal paper. Moreover, SEAC notes that although there are other uncertainties with the break-even analysis[23], there is no indication that these will change the conclusion regarding proportionality.

Hence, SEAC concludes that the proposed restriction is unlikely to be a proportionate measure in terms of standard benefit cost considerations. It is also worth noting that since no risk was found for consumers, the same conclusion would have been reached using the dossier submitter's cost and benefit estimates (see **Table 24**), since these suggest that costs outweigh benefits by around an order of magnitude[24].

Distributional equity and 'affordability' considerations

In order to gain additional insights regarding the consequences of the restriction and thereby aid the policy-making process further, SEAC considered additional impact assessment criteria beyond those considered in the Dossier Submitter's analysis. In particular, SEAC considered that distributional equity and affordability aspects of the restriction could be relevant elements to consider.

SEAC considered the impacts of the restriction in terms of 'affordability' for the cost bearing actors. Affordability in this case can be defined[25] as the actor's ability to pay, e.g., in terms of income or profits, relative to the size of the enforced costs. As long as the actor is able to pay, that is, the enforced cost is not larger than the income or profit, the measure can be seen as 'affordable'. However, it should be underlined that an affordable measure is not necessarily economically feasible, and affordability does not imply a measure is (net) beneficial for society. Still, SEAC considered this to be an additionally relevant and potentially helpful factor to be included in the opinion.

Accordingly, SEAC notes that the cost of the restriction in terms of the price increase per roll of thermal paper amounts to around 5 to 18 cents (10%-35%), whilst the additional cost expressed in terms of the increase per cashier in the affected business sectors is around €4 – €15 per year per cashier. This amounts to a very small proportion of total personnel costs (<0.1%) or gross operating surplus (<0.05%) in the affected sectors in the EU[26]. Furthermore, no comments were

[23] See Annex 6 for an overview of the identified uncertainties.

[24] Although it is acknowledged that not all benefits were quantified and valued in the Dossier Submitter's assessment, SEAC has not been provided with any indication that these non-monetised benefits would eclipse the order of magnitude difference in monetised costs and benefits.

[25] There is no general definition of affordability, as it is not an analytically defined concept.

[26] Based on total personnel costs and gross operating surplus (2009 – latest year available) in the retail sector in the EU of around €300 Billion and €160 Billion respectively (Eurostat: sbs_na_dt_r2).

received in the public consultation on possible affordability issues for industry. If the costs are transferred into increased prices of consumer goods, the amount per working EU-citizen will amount to ca. €0.2 – €0.6 per person per year. As such, SEAC considers that the restriction is unlikely to have serious affordability concerns at the micro level.

With regards to distributional equity, the BD contained no specific information on the likely impacts of the restriction on affected subpopulations. Nevertheless, SEAC was able to surmise that exposure to BPA in thermal paper may have disparate and unequal impacts in terms of adverse health consequences befalling a relatively small and vulnerable sub-population, namely, the progeny of cashiers/workers, as compared to the general EU population. To the extent that the restriction might reduce the degree that this sub-population are 'disproportionately' affected by these health impacts, whilst at the same time sharing the economic impact in terms of small (on a per household basis) cost increases (in the form of higher prices that are passed on) evenly across the wider EU population, it can be said to have favourable distributional equity effects. In this respect SEAC finds that the restriction might lead to a more 'equitable' distribution[27].

Given that it has not been possible to assess the extent that there are actual health impacts in the relevant population, the risk assessment undertaken by RAC can be used as a proxy of the health impacts, with which to assess the distributional change. As indicated elsewhere in the opinion, the results of the risk assessment indicate that risks are distributed specifically amongst workers rather than the general population (consumers), and that as a result of the restriction the risks to workers would be controlled. However, it should be noted that (as a general rule) the output from risk assessment are an imperfect proxy of health impacts, since such outputs (e.g., risk characterisation ratio) do not easily translate into measures of actual human health impacts that are the ultimate objective of the distributional analysis. Even though the restriction will reduce the risk to workers there still exists the possibility that health impacts might not actually occur in reality in the first place. In this case the restriction will not have positive distributional effect, and could result in distorting risk management priorities away from actual health impacts[28].

SEAC's conclusion

Based on the results from the break-even analysis, the proposed restriction is unlikely to be proportionate from an efficiency perspective (i.e., benefit-cost comparison). Moreover, even though there is a risk to workers, due to the lack of dose-response relationships, it cannot be determined to what extent illness or disease will actually occur in the population at risk. On the other hand, assuming adverse human health impacts are occurring as a result of BPA exposure in the worker population, some support for the restriction may be derived from considerations of distributional equity (i.e., who gains and who loses) and affordability, which can also be considered alongside economic efficiency arguments. Whether the proposed restriction is socially acceptable will then depend on the extent to which any distributional equity and affordability considerations override economic efficiency arguments and concerns. SEAC does not have any information on societal preferences for different distributional compositions.

[27] 'Equitable' distribution as seen from an environmental justice perspective – see for example, USEPA (2014).

[28] To the extent that exposures would not in reality result in actual health impacts, then the restriction would indeed have unfavourable distributional effects.

In conclusion, from an economic efficiency perspective, comparing the socio-economic benefits to the socio-economic costs, the proposed restriction is considered unlikely to be proportionate. However, there may be favourable distributional and affordability considerations.

3.2. Implementability, including enforceability

Justification for the opinion of RAC

As it is difficult to define a 'safe' level of BPA content in thermal paper, the choice has been made to propose the lowest limit as possible, in line with the detection limits of BPA. The limit has thus been set at the average of the detection limits of the different existing methods. Although various test methods exist, there is currently no standard analytical method to detect BPA specifically in thermal paper.

The proposed restriction (RMO 1) is considered by RAC to be implementable, enforceable and manageable on the following grounds:

- Industry actors should be able to comply with the restriction as test methods to measure concentration in thermal paper exist (even though no standard test applies). It would be useful if the European Commission considers the development of such a standard test methods.
- The restriction proposal is enforceable as relevant test methods exist.
- The means for implementation are clear and understandable and substitution is already ongoing. In fact, many leading supermarket chains have opted for using BPA-free paper. The most commonly used alternatives are BPS and Pergafast.

Based on the availability of test methods, the clarity of the proposed restriction and the on-going substitution with safer alternatives, RAC agrees with the Dossier Submitter that the restriction is implementable, enforceable and manageable. This also reflects the Forum advice.

Justification for the opinion of SEAC

Summary of proposal

The Dossier Submitter considers the restriction implementable, since the industry actors affected by the proposed restriction should be capable of complying with the requirements in practice, since concentration tests and alternatives are available and are technically and economically feasible.

There is no standard analytical method to measure the content of BPA in thermal paper today in the EU, but several methods exist to measure BPA in other materials and could be used for that purpose. Therefore, given that test methods exist, the absence of an EU standard analytical method is not considered as a hindrance to the enforceability of the proposed restriction.

The means of implementation of the proposed restriction (concentration tests, substitution of BPA, etc.) are clear and understandable to the actors involved, in particular because substitution of BPA in thermal paper is already underway. Some market actors might have to get some information and make additional training efforts in order to be able to carry out the compliance tests needed, but overall, the

restriction is considered manageable.

The transitional period of 3 years (36 months) is deemed reasonable in terms of timing and manageability in order to give enough time for the supply chain to comply and for the control authorities to organise and anticipate the controls.

Key elements underpinning the SEAC's conclusion

For ecopaper, some of the alternatives seem to be widely available and already in use. This means that at least to some extent there exist technically and economically feasible alternatives. For the remaining 35% of the thermal paper market, which is not categorized as ecopaper, there is little information in the dossier. It is thus uncertain whether the conclusion that technically and economically feasible alternatives exist and are available applies to the entire thermal paper market.

However, based on the draft Forum's Advice, which states that the proposed restriction is practicable and enforceable, SEAC concludes that the proposed restriction can be considered implementable, enforceable and manageable.

The dossier does not present any information on the time it will take to sell out of existing stock nor did the public consultation reveal any new information about the transition period. According to the information gathered by the ECHA Secretariat and the Dossier Submitter (see Annex 9 to the BD) some industry actors indicated that 3 years would be sufficient time to adjust the production of phenol free thermal paper to an increase in demand. Albeit based on limited evidence, SEAC thus considers it likely that 3 years would be sufficient time for industry to complete the substitution process.

SEAC's conclusion

SEAC agrees that the proposal is implementable, enforceable and manageable.

3.3. Monitorability

Justification for the opinion of RAC

The Dossier Submitter considers the restriction proposal (RMO 1) as monitorable as there are test methods to monitor BPA content of thermal paper. The Dossier Submitter has put forward that no single TARIC code exists that covers thermal paper. However the TARIC codes under which 'thermal paper' falls are known and hence the restriction can be monitored.

Overall, RAC agrees the proposal is monitorable. This also reflects the Forum advice.

Justification for the opinion of SEAC

Summary of proposal

Given that several existing analytical methods could be used to measure BPA content in thermal paper (although no standard exists), the restriction proposed is considered to be monitorable by control authorities and customs services. However,

as regards monitorability there might be some concern about the exact product to be monitored since no specific existing TARIC (or Prodcom) code is attributed to 'thermal paper'.

Key elements underpinning the SEAC's conclusion

SEAC agrees with both the Dossier Submitter and Forum in that the restriction is monitorable. Forum also mentions the possibility to use biomonitoring in addition to the methods described in the dossier. A concern could be the control of imported thermal paper into the EU, since no specific existing TARIC code is attributed to thermal paper.

SEAC's conclusion

SEAC agrees that the restriction is monitorable.

4. BASIS FOR THE OPINION

The Background Document, provided as a supportive document, gives the detailed grounds for the opinions.

Basis for the opinion of RAC

The basis for restriction is the restriction dossier proposed by France, with additional information, including the relevant opinion from EFSA (2015) and information submitted in the Public Consultation, considered by the Rapporteurs and included in the final Background Document.

Basis for the opinion of SEAC

The basis for SEAC's conclusion on the restriction as proposed in the Annex XV restriction Dossier Submitted by France, is related to the information presented in the Background Document, the justification to the opinion and information submitted by interested parties.

5. ADDITIONAL REFERENCES

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Annex 1. Studies investigating effects on mammary gland development after pre- and/or postnatal exposure to BPA administered orally to pregnant or lactating females

Reference	Species/ strain	Route	Dose Exposure period	Effects NOAEL/LOAEL
Delclos et al. (2014) / US FDA/NCTR (2013)	Sprague-Dawley rats	Oral (gavage)	2.5, 8, 25, 80, 260, 840, 2700, 100 000, 300 000 µg BPA/kg bw/day Negative controls: naïve and vehicle Positive control: EE2 0.5 and 5 µg/kg bw/day F0: females exposed from GD 6 up to labour onset Pups from PND 1 until tissue harvesting, up to PND 90 GLP study. (Mod. OECD TG 408)	PND 21: significant elevated incidences mammary gland duct hyperplasia of minimal severity was reported in the female groups at 2 700 and 100 000 µg/kg bw/day, but not at 300 000 µg/kg bw/day. PND 90: minimal severity of mammary gland duct hyperplasia was also reported in the high dose female BPA groups, increase was statistically significant at 300 000 µg/kg bw/day group (Poly-k test) and 2700, 100 000 and 300 000 µg/kg bw/day (JT/SW or RTE statistical tests). BPA did not cause duct hyperplasia in the mammary glands of male rats, while conversely the reference estrogen EE2 induced hyperplasia in the male but not the female mammary gland. In the 100 000 and 300 000 µg/kg bw per day female BPA groups, significantly higher plasma levels of oestradiol and prolactin were found whereas the EE2 values were only mildly elevated in comparison to controls. LOAEL for ductal hyperplasia 2700 µg/kg bw/day. NOAEL of 840 µg/kg bw/day

Betancourt et al. (2010)	Sprague-Dawley Rats	Oral	0 – 25 - 250 µg BPA/kg F0: Exposure in mothers to BPA from GD10 to GD21 followed by single dose of DMBA on PND50 or PND100 . F1: exposure not checked	**<u>Effects observed:</u>** - *In utero* exposure to 250 µg/kg of BPA **associated with a single exposure to DMBA (dimethylbenzathrancene)** at 100 days postnatally (but not on PND50), produced an increase in the incidence of enhanced cell proliferation assiociated with increased cancer susceptibility and shift of the window for susceptibility for DMBA-induced tumourigenesis and a shorter latent time compared to the control group. - **Without DMBA**, an increase in cell proliferation and overexpression of some proteins involved in cell proliferation was observed. **<u>Critical effect:</u>** - Amplification of breast tumour development (number/rat and time to occurrence) in a DMBA model - Expression of proteins involved in cell proliferation - Changes in proteins which influence cell proliferation on PND100 (250 µg/kg) - ERα, PR-A, Bcl-2, steroid receptor coactivators, (SRCs), EGFR, IGF-1R, and phospho-c-Raf. **Doses** are not known in the offspring and are possibly less than: **NOAEL 25 µg/kg bw/day** **LOAEL 250 µg/kg bw/day**
Betancourt et al. (2010)	Rats	Oral	0 – 25 - 250µg BPA/kg GD10 - GD21. Female descendants were humanely killed on PND21 and PND 50.	Changes in the expression of some proteins that are important for signalling pathways involved in mammary carcinogenesis, as cell proliferation. ↗ phospho-AKT, ↗ c-Raf, phospho-ERKs-1 and 2, ↘ TGF-β in breast tissues at 50 days postnatally

				Important signalling pathways are disrupted by BPA. **LOAEL 25 µg/kg bw/day**
Jenkins et al. (2009)	Female Sprague Dawley rat pups	Oral	0 - 25 and 250 µg/kg bw/d, 5 d/week Administered to lactating mothers from PND 2 to PND 202 (equivalent to 15 administrations/mother). The female pups were treated with a single dose of DMBA on PND50.	With DMBA: ↗ increased cell proliferation and reduced apoptosis incidence at high dose. Changes in expression of a number of proteins linked with apoptosis and changes in progesterone receptor (PR)A, steroid recetor activator (SRC) 1 to 3, and erbB3. Shorter tumour latency. Without DMBA: Increase in proliferation and decreased apoptosis and overexpression of a number of proteins. NOAEL 25 µg/kg bw/day LOAEL 250 µg/kg bw/day
Moral et al. (2008)	Sprague-Dawley rats	Gavage	25 et 250 µg/kg pc GD10 à GD21	Increase in the number of undifferentiated epithelial structures (TEB and TD). No effects on proliferation; BPA exposure changes the gene expression signature: - altered gene expression signature of the mammary gland maximal at 100 d with the high dose (genes up-modulated at the two doses, including a cluster related to immune response; underexpressed genes including differentiation-linked genes at high dose). - At low dose, the expression profile is changed most at 50 d. **NOAEL (structural changes) 25 µg/kg bw/day** **LOAEL (structural changes) 250 µg/kg bw/day** **LOAEL (Gene expression) 25 µg/kg bw/day**
Tharp et al. (2012)	Rhesus monkey (*M. mulatta*).	Oral	400 µg/kg bw/Day. GD 100 to term.	Increased density of mammary buds, overall accelerated development of mammary gland. **LOAEL 400 µg/kg bw/d**

Annex 2. Studies investigating effects on mammary gland development after pre- and/or postnatal exposure to BPA administered subcutaneously to pregnant or lactating females

Reference	Species/ strain	Route	Dose Exposure period	Effects NOAEL/LOAEL
Acevedo et al. (2013)	Sprague Dawley Rats	Subcutaneous pump	0.25, 2.5, 25, 120 µg/kg/d GD9- GD23	Atypical ductal hyperplasia, one out of five shows ductal carcinoma in situ at PND 50. One animal had adenocarcinoma observed at PND 90 at the 2.5 µg/kg/d group. No statistically significant increase of incidences of proliferative lesions and tumours compared to the control groups.
Dhimolea et al. (2014)	Wistar-Furth Rats	Subcutaneous pump	25, 250 µg/kg bw/day	The authors concluded that prenatal exposure to BPA alters the epigenome of the mammary gland of Wistar-Furth rats and increases the propensity to neoplastic development. Subcutaneous doses of 250 µg/kg bw/day triggers changes in the postnatal (PND50) and adult mammary gland epigenome and alters gene expression patterns.
Doherty et al. (2010)	CD1 Mice	Intra-peritoneal	0 - 10 µg/kg-5 m/kg GD9 to GD26	↗ histone H3 trimethylation ↗ of EZH2 (2X) expression in mammary tissues compared to the control
Durando et al. (2007)	Female Wistar rats	Sub-cutaneous pump	25 µg/kg GD8 to GD23	↗ proliferation/apoptosis ratio ↗ ductal hyperplasia ↗ sign of desmoplasia ↗ neoplastic lesion. **No NOAEL/LOAEL 25 µg/kg bw/day**
Jones et al. (2010)	BRCA1 deleted mice	Sub-cutaneous pump	250 ng BPA/kg bw/d	Difficult to interpret (transgenic mice) BRCA1 deletion followed by BPA exposure stimulates mammary glands leading to hyperplasia compared to the control
Munoz del Toro et al. (2005)	CD1 mice	Sub-cutaneous pump	25 - 250 ng/kg bw dissolved in DMSO GD9 to PND4	↗ response to oestrogens ↗ expression of progesterone receptors.

				LOAEL 0.025 µg/kg bw/day
Murray et al. (2007)	Wistar-Furth rats	Sub-cutaneous pump	2.5 – 25 – 250 – 1000 µg/kg bw GD9 to PND1	↗ number of intraductal hyperplasia in mammary gland at all doses (more pronounced at PND50 compared to PND95). CIS present in mammary glands of animals exposed to the highest doses at puberty and at 3 months. **LOAEL 2.5 µg/kg bw/day**
Vandenberg et al. (2007)	Female CD1 mice	Sub-cutaneous pump	250 ng BPA/kg bw/d GD8 to GD18	↗ ductal area ↘ cell size Delay in lumen formation Adverse changes in mammary gland phenotype **LOAEL 0.25 µg/kg bw/day**
Vandenberg et al. (2008)	Female CD1 mice	Sub-cutaneous pump	0 - 0.25 - 2.5 - 25 µg/kg bw/d GD8 to PND16	Deterioration in development of mammary glands ↗ proliferation indexes compared to control group, Intraductal hyperplasia **LOAEL 0.25 µg/kg bw/day**
Vandenberg et al. (2013)	Male CD1mice	Subcutaneous pump	0.25, 2.5, 25, 250 µg/kg/d GD 9 until PND 90	Proliferation (Ki67) and number of branching points and ductal area at doses of 0.25 and 2.5 µg/kg/d. No NOAEL was identified.
Wadia et al. (2007)	Outbred CD-1 mice Inbred C57B16 mice	Sub-cutaneous pump	0 - 250 ng/kg bw/d Mixed exposure BPA and E2 GD8 to PND2	Perinatal exposure to BPA does not adversely affect the uterine response to E2 administered from PND25 to PND35 but does adversely affect the uterine response of the mammary gland. **LOAEL 0.25 µg/kg bw/day**

Annex 3. Input parameters for consumer exposure assessment using the absorption rate model

	Probabilistic			Deterministic	EFSA (2015)
Input parameter	**Scenario IV*** (proposed by the Dossier Submitter)	**Scenario V***	**Scenario VI***		
R_{abs}: Level of absorption (absorption rate)	Triangular distribution with **10 %**, **27 %** and **60 %** Based on ANSES expert judgment in relation to RAR of the European Commission (EC, 2010) and the study of Biedermann et al. (2010). A minimum of 10 % is used by default in the RAR. A mode of 27 % from the study of Biedermann et al. (2010) - the amount of BPA transferred onto the skin of the finger after 5 seconds of contact with a ticket, which was no longer removable from the skin by water and soap 2 hours after this contact. Maximum of 60 % which corresponds to the amount	Discrete value **10 %** RAC assessment based on 10 % which is used by default in the RAR of the European Commission (EC, 2010) and Demierre et al. (2012)	Discrete value **27 %** RAC assessment based on a mode of 27 % from the study of Biedermann et al. (2010)	**10 %** Default value from the RAR of the European Commission (EC, 2010) and EFSA (2015) Demierre et al. (2012)	Discrete value **10 %** Demierre et al. (2012)

	deposited in the skin 2 hours after the immersion of the finger in a BPA / ethanol solution (Biedermann et al. 2010).				
Q_{subs}: Quantity of the substance deposited by contact	Uniform distribution within the range **0.035-3.75** µg/finger Based on the studies of Biedermann et al. (2010) and the Danish EPA (2011). The measurements were made using a similar protocol. The first study was performed on five types of thermal papers obtaining 14 measures BPA deposited on a finger ranging from 0.035 to 3 µg. The second measured deposition from four types of thermal receipts obtaining the range from 0.58 µg to 3.75 µg BPA.	Uniform distribution within the range **0.035-3.75** µg/finger Based on the studies of Biedermann et al. (2010) and the Danish EPA (2011). The measurements were made using a similar protocol. The first study was performed on five types of thermal papers obtaining 14 measures BPA deposited on a finger ranging from 0.035 to 3 µg. The second measured deposition from four receipts of thermal paper obtaining the range from 0.58 µg to 3.75	Uniform distribution within the range **0.035-3.75** µg/finger Based on the studies of Biedermann et al. (2010) and the Danish EPA (2011). The measurements were made using a similar protocol. The first study was performed on five types of thermal papers obtaining 14 measures BPA deposited on a finger ranging from 0.035 to 3 µg. The second measured deposition from four receipts of thermal paper obtaining the	**3.56 µg/finger** 95th percentile value from uniform distribution range given by the Dossier Submitter and based on Biedermann et al. (2010) and the Danish EPA (2011) studies	**1.375 µg/finger** Lassen et al. (2011); similar in Biedermann et al. (2010) In addition, EFSA assumed that **each new handling event adds 1.375 µg/finger** Average exposure: **1 event** (adolescents and adults) High exposure: **4.6 events** (adolescents and adults)

		µg BPA.	range from 0.58 µg to 3.75 µg BPA.		
N: Number of fingers in contact with the till receipt	Uniform distribution within the range **1-10** fingers Based on ANSES expert judgment. The ticket can only be held with the thumb in contact with one face containing BPA and the maximum – 10 fingers.	Uniform distribution within the range **1-5** fingers RAC assessment	Uniform distribution within the range **1-5** fingers RAC assessment	**10 fingers**	Average exposure: **3 fingers** High exposure: **6 fingers** (3 fingers, 2 hands)
D: Absorption duration	Uniform distribution up to 2 h/day as a maximum	Uniform distribution up to 2 h/day as a maximum	Uniform distribution up to 2 h/day as a maximum	**-**	24 h
BW: Body weight	Discrete distribution of probabilities illustrating the body weight for the pregnant woman The EDEN study	Discrete distribution of probabilities illustrating the body weight for the pregnant woman The EDEN study	Discrete distribution of probabilities illustrating the body weight for the pregnant woman The EDEN study	**70 kg** EFSA (2011) default assumption for adults	44 kg (adolescents) 70 kg (adults)

*The formula used for these calculations included a factor for duration of exposure: IED = (R_{abs} x Q_{subs} x N x D)/BW x 2. RAC used a corrected formula without the absorption duration as a factor: IED = (R_{abs} x Q_{subs} x N)/BW. It was not possible to correct the results without running the (corrected) probabilistic model since a uniform distribution of up to 2 hours was used in probabilistic modelling.

Annex 4. Marquet et al. (2011): results from ex vivo study of skin penetration on fresh human skin explants (6 donors, duplicate or triplicate measurements)

	Percutaneous absorption flow of BPA (µg/cm²/h)		
	Value 1	**Value 2**	**Value 3**
Donor 1	0.331	0.212	0.136
Donor 2	0.101	0.131	0.026
Donor 3	0.13	0.116	0.029
Donor 4	0.026	0.043	-
Donor 5	0.136	0.226	-
Donor 6	0.081	0.049	-
95th percentile	0.258		
Geometric average value	0.09		

Annex 5. Valuation factors

All of the valuation factors must be seen as proxy representatives for the group of human health effects within each endpoint. There might be considerable variation in outcomes and their severity, so there will be uncertainty connected to the representativeness of the different factors. However, SEAC considers the derived valuation factors to be based on sufficiently robust evidence and hence appropriate to be used in the analysis. For the valuation factor for which no low and high estimates exist, a default ±50% is used for the lower and upper bound estimates.

Mammary gland effects

In accordance with the opinion of RAC, some mammary gland changes may be reversible and their adversity is not clear, while some mammary gland changes may develop into breast cancer if the individual is also co-exposed to carcinogenic agents. In general, however, it is unknown whether the observed effects on the architecture of the mammary gland, including effects on terminal end buds and terminal ducts do lead to increased susceptibility to cancer when co-exposed to carcinogens. SEAC errs on the side of caution and assumes in the analysis that there is a clear link between BPA and breast cancer when constructing the medium and high valuation factor. SEAC uses a 5.5% conditional probability of getting breast cancer if an individual has mammary gland changes. As explained in section F.1.1.4 of the BD, this is based on information from American Cancer Society (ACS 2015) about the increased risk of breast cancer from different types of mammary gland changes. It is furthermore assumed that all of the mammary gland changes are of such severity that a biopsy is necessary. Costs of a needle biopsy (from ABIM Foundation 2015) is thus added to all the mammary gland change valuation factors.

For the medium valuation factor, the willingness to pay to avoid a statistical cancer case (which incorporates the survival rate of cancer) is used from Alberini and Ščasný (2014), while the high valuation factor assumes a 50% higher WTP to avoid a statistical cancer case.

Since there are significant uncertainties about the nature of any actual relationship between BPA and cancer, the low valuation factor is based on the assumption that no breast cancer cases actually arise. However, cost of the biopsy procedure is still included, implying correspondingly severe and noticeable mammary gland changes. The average onset was assumed to be at age 50.

Immunotoxic effects

The valuation factor for immunotoxicity was constructed as a simple average of a valuation factor for food allergies (Gupta et al. 2013) and a derived valuation factor for respiratory allergy. The latter was derived from a metastudy on medical costs (Simoens 2012) and a single study on societal costs of respiratory allergy (Suijkerbuijk et al. 2013). An average of the low, medium and high valuation factor estimates from the respiratory allergy studies were respectively used (together with the food allergy estimates where the default ±50% were used for sensitivity) for the low, medium and high valuation factors for immunotoxicity. It is assumed that an average case duration is 10 years and the average onset was assumed to be at age 10 ((AAAAI 2015; FARE 2015).

Neurobehavioral effects

Neurobehavioral effects may be diverse, but for the purpose of this analysis SEAC has chosen to use the value of an IQ point as a proxy valuation factor for neurobehavioral changes. IQ loss is a commonly used health valuation endpoint used to assess neurobehavioral deficits associated with exposure to hazardous substances. The low, medium and high estimates were based on values found in previous REACH restriction dossiers and corresponding SEAC opinions on lead in jewellery (ECHA 2011) and lead in consumer products (ECHA 2014). Although SEAC is aware of potential deficiencies in the existing measures of IQ point value, a discussion of this issue is beyond the scope of the present assessment since it relates to the problem of IQ valuation more generally and not specifically in the context of the present case. The average onset was assumed to be at age <1.

Reprotoxic effects

As a valuation factor for the potential reprotoxic effects, SEAC has used the valuation factor for endometrial hyperplasia derived by the Dossier Submitter. See section F.1.1.2.2 of the BD for more information. The average onset was assumed to be at age 35 (OWH 2015; Reed et al. 2009; MNT 2015)

Metabolic effects

For the metabolic effects SEAC has combined the two valuation factors for cholesterol and obesity derived by the Dossier Submitter by a simple average. See sections F.1.1.3.2 and F.1.1.3.1 of the BD for more information on the valuation factor for cholesterol and obesity respectively. The average onset was assumed to be at age 30 (CDC 2015; AIHW 2015)

Table 29 Average discounted valuation factor estimates for 2019-2030 used in the break-even analysis, and the corresponding sources

Endpoint	Valuation factors EUR/incidence			Sources
	Low	Medium	High	
Mammary gland*	473	6 301	9 228	ABIM Foundation (2015); Alberini and Ščasný (2014)
Immunotox	7 240	12 810	18 380	Simoens (2012); Suijkerbuijk et al 2013; Gupta et al (2013)
Neurobehavior	2 140	7 134	22 292	ECHA (2011,2014)
Reprotox*	1 097	2 194	3 291	BD
Metabolic	902	1 814	2 749	BD

* only female offspring are at risk for these endpoints.

Annex 6. Assumptions and Potential Bias

Table 30 presents the assumptions and potential biases in the break-even analysis.

Legend to the table:

↑ (↓) means that the uncertainty evaluation indicates that the "benefits" tend to be overestimated (underestimated) as compared to the cost, i.e. it pulls in the direction of making the proposal less (more) proportional.

? means that it is unknown in which direction the uncertainty will pull, thus the uncertainty is considered 'a priori' unbiased.

Table 30 Assumptions and potential biases in the break-even analysis

Assumption	Effect on proportionality	Explanation
Percent of thermal paper containing BPA	↑	In the Background Document the Dossier Submitter states that the data from their own survey indicates that the "*estimated share of BPA-containing thermal paper compared to the total thermal paper placed on the EU market ranging from 75% (1 claim) to 100% (1 claim) with a central estimate between 90% and 99% (3 claims). ETPA indicates that around 70-80% of thermal paper produced in Europe contains BPA (ETPA 2013 consultation)*". SEAC has accepted the 70% market share proposed by the Dossier Submitter, but based on the above, this is likely to underestimate the costs of the restriction.
Constant baseline tonnages of thermal paper containing BPA	↑	The Dossier Submitter presented some evidence showing an increase in the use of thermal paper containing BPA in the coming years. Due to the increasing use of paper free receipt solutions, SEAC chose to keep the market constant instead of increasing. In the public consultation on the SEAC draft opinion, another report (Danish EPA 2014) was highlighted, and this report states that the European market is increasing between 0-10% per year. Keeping the tonnages constant is thereby likely to underestimate the costs.
Mammary gland valuation factor	↑	It is not clear from the literature that these mammary gland changes are adverse, and will lead to cancer. This will pull in a direction of too high valuation factor for mammary gland changes. This link is not assumed in the high cost/low valuation factor scenario.

Immunotox valuation factor	↓	There is uncertainty around the representativeness of the factor for all the immunotox effects (respiratory allergies and food allergies are used). Some of the studies used do only include medical costs and productivity loss and no additional welfare loss, which means that the factor is likely to be underestimated.
Metabolic valuation factor	?	There is uncertainty around the representativeness of the factor for all the metabolic effects (obesity is used instead of weight gain, and this is combined with a cholesterol valuation factor). Some of the studies used do only include medical costs and productivity loss and no additional welfare loss, which means that the factor is likely to be underestimated. On the other hand, BPA may cause weight gain, but weight gain does not equal to overweight, and using obesity instead of weight gain leads to an overestimation of the actual societal costs. As a consequence of this, it is unknown whether the factor is under- or overvalued, and thus the effect on the proportionality balance is unknown.
Neurobehavior valuation factor	?	There is uncertainty around the representativeness of the factor for all the neurobehavioral effects (reduction of 1 IQ point is used). As a consequence of this, it is unknown whether the factor is under- or overvalued, and thus the effect on the proportionality balance is unknown.
Reprotox valuation factor	?	The reprotox evaluation factor was based on the highest estimate for endometrial hyperplasia found in the dossier, but there is still uncertainty around the representativeness of the factor for all the reprotoxic effects (increase in occurrence and bursting of ovarian cysts). As a consequence of this, it is unknown whether the factor is under- or overvalued, and thus the effect on the proportionality balance is unknown.
Not accounting for export of thermal paper	↓	Including the exported part of the thermal paper market in the cost estimate may mean that the costs within the EU can be overestimated (depending on the ability to separate the production process for exported and domestic paper).
Not accounting for import of thermal paper	↑	Not taking into account the imported part of the thermal paper market may mean that the costs within the EU are likely to be underestimated.
Net export	?	The net effect from not taking into account export and import is not known, since the two effects pull in opposite directions and most likely differ in magnitude.
Population at risk	?	There are several uncertainties connected to the population at risks: - Only cashiers has been considered, while other workers may potentially also be at risk - The number of cashiers at risk may be overestimated, as many workers called "cashiers" is not actually handling receipts to a large extent. - The population at risk may change over time The effect on the proportionality balance from

		uncertainties around the population at risks is unknown.
Identified Hazards and risks and resulting health effects	?	The DNEL is based on assessment factors and expert judgement. Per endpoint there is uncertainty about the actual human health effects that will occur due to exposure to BPA. Some effects might not be relevant at all, in which case other effects would need to be more pronounced to break-even. It is unknown whether this causes under- or overestimation, and thus the effect on the proportionality balance is unknown.
Cost share	?	The division of the costs amongst the different endpoints is highly uncertain, in the sense that any cost division could be possible, as long as it sums up to 100% of the costs.