



NRK



Health Council of the Netherlands

Attn: Dr. S.R. Vink

PO Box 16052

2500 BB The Hague

The Netherlands

Email: draftOSH@gr.nl

Subject: Comments on DRAFT report Bisphenol A, Health-based recommendation on occupational exposure limits, dated July 17, 2017 (OCR GSW/2048 199-23)

Dear Dr. Vink,

The European PC/BPA group of PlasticsEurope, representing the Bisphenol A (BPA) and polycarbonate producers in Europe including two main BPA producers based in The Netherlands, with the support of the Epoxy Resin Committee of PlasticsEurope and Dutch industry associations VVVF, VLK, NRK and PlasticsEurope Nederland, appreciate the opportunity to comment on the DECOS draft version of its recommended occupational exposure limit (OEL) for Bisphenol A.

We have however serious concerns about the non-health-based methodology applied by DECOS to derive the proposed OEL for BPA of 2.5 $\mu\text{g}/\text{m}^3$ and the precedent it could set for future substance assessments and recommendations. In its evaluation of the BPA literature, DECOS concluded that recent studies reporting developmental and neurological effects at low oral doses of BPA (5 $\mu\text{g}/\text{kg}/\text{day}$) do not provide a reliable basis for deriving a health-based OEL, as they do not follow generally accepted guidelines and it is unclear if the reported effects are adverse or relevant to inhalation exposure. Despite this conclusion, DECOS still considered the possibility of low-dose effects of BPA in its approach to deriving an OEL. Rather than deriving a health-based OEL, DECOS applied what it called a "pragmatic" approach. This approach was to limit occupational BPA exposure to the level of BPA exposure in the general population, so that on average, the total exposure to BPA for a worker should not increase more than two-fold as a result of occupational exposure.

DECOS used the BPA exposure estimate for adults of reproductive age in the general population from the EFSA (2015a) exposure assessment (0.2 $\mu\text{g}/\text{kg}/\text{day}$) as a starting point for the BPA OEL. It calculated

the equivalent inhalation concentration ($1.4 \mu\text{g}/\text{m}^3$), and adjusted this value for the number of working days per year, with no additional corrections, resulting in a recommended OEL of $2.5 \mu\text{g}/\text{m}^3$.

DECOS also recommended the application of a skin notation, and stated that this was based on the European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC) strategy in which a skin notation is warranted when absorption through skin is estimated to exceed 10% of the systemic dose realized by inhalation at the OEL (ECETOC, 1993). DECOS estimated that, based on its physicochemical properties, the amount of BPA absorbed through the skin would easily exceed 10% of the value of its recommended OEL.

We agree with the conclusion of DECOS that the recent low-dose studies of BPA toxicity are not a reliable basis for deriving a health-based OEL; however, the "pragmatic" approach used by DECOS to derive the OEL is not supported by the current BPA database or by general risk assessment principles. "Pragmatic" or other non-health-based approaches that deviate from standard methodology for OEL derivation should only be used in cases where sufficient data are not available to derive a health-based OEL or when techniques are not available to measure a substance at very low levels dictated by a health-based OEL derivation. This is not the case for BPA since BPA is a very data-rich substance. The extensive database is sufficiently robust to support the derivation of a health-based OEL for BPA. Moreover, deviating from the standard approach requires sufficient justification which is not being provided by DECOS.

In light of this and our detailed comments provided below, we have serious concerns about the proposed OEL for BPA of $2.5 \mu\text{g}/\text{m}^3$ and the methodology that has been applied to derive this limit value. Therefore, we consider that DECOS should recommend the health-based SCOEL (2014) OEL of $2 \text{mg}/\text{m}^3$ BPA, with no application of a skin notation. Recommending this value will be consistent with the weight of evidence indicating a lack of clear adverse effects at low BPA exposures and with European Commission Directive 2017/164/EU. In addition, while we realize that only scientific comments will be taken into account by DECOS, we are concerned about the proportionality as well as the broader negative socio-economic impacts of the proposed limit value.

1. THE METHODOLOGY USED BY DECOS FOR DERIVING THE PROPOSED OEL FOR BPA DIFFERS CONSIDERABLY FROM OTHER AGENCIES AND ITS OWN GUIDANCE

We note that the "pragmatic" approach used by DECOS to derive its recommended BPA OEL is not consistent with approaches for derivation of OELs or other health-based exposure limits used by other agencies. It is also not consistent with guidance on OEL derivation from the European Commission Scientific Committee on Occupational Exposure Limits (SCOEL, 2013), ECETOC (2006), the American Conference of Governmental Industrial Hygienists (ACGIH, 2015), and the Health Council of the Netherlands (1996, 2000), nor with general risk assessment principles (US EPA, 2002). General guidance from these organizations indicates that using a point of departure for a critical, adverse health effect from a high quality human or animal study should be the basis of an OEL calculation. Uncertainty,

variability, and weakness in a substance-specific literature database is typically accounted for using a combination of uncertainty and adjustment factors.

Previously, DECOS and other European agencies have derived OELs for BPA using standard approaches, yielding inhalation limits three orders of magnitude higher (DECOS, 1996, as cited by DECOS, 2017; SCOEL, 2014; DFG, 2011) than the BPA OEL recommended by DECOS. All of these agencies considered the BPA database to be sufficiently robust for deriving an OEL. For example, SCOEL (2014) conducted a thorough assessment of the BPA literature and used standard methodology to derive a BPA OEL of 2 mg/m³, based on a no observed adverse effect concentration (NOAEC) for respiratory tract irritation from a 13-week rat inhalation study (Nitschke et al., 1988). SCOEL (2014) divided the 10 mg/m³ NOAEC from this study by an assessment factor of 3 to account for uncertainties related to interspecies extrapolation, then used the preferred value approach to round the 3 mg/m³ OEL to the recommended level of 2 mg/m³. SCOEL (2014) concluded that this OEL provides a sufficient margin of safety to be protective of systemic effects reported in chronic oral studies in rodents. SCOEL (2014) did not recommend a skin notation because recent studies conducted according to Organisation for Economic Co-operation and Development (OECD) guidelines (Morck et al., 2010; Demierre et al., 2012) reported that skin absorption may have only a minor contribution to systemic BPA levels at the recommended OEL of 2 mg/m³.

According to the European Commission Directive 2017/164/EU of 31 January 2017 (EC, 2017), the BPA OEL recommended by SCOEL (2014) represents an indicative occupational exposure limit value (IOELV), which is a health-based limit conventionally established only for substances for which it is possible to establish a threshold or a NOAEL considered to be protective of human health. Directive 2017/164/EU states that for any chemical agent for which an IOELV has been set at the European Union (EU) level, Member States should establish a national OEL value, taking into account the EU IOELV (EC, 2017). Although DECOS stated that it considered the Nitschke et al. (1988) study used as the basis for the IOELV to be suitable for risk assessment, it did not use this study as a basis for its recommended OEL and did not use standard methodology for deriving an OEL despite the availability of high quality studies in the BPA database. The resulting OEL recommended by DECOS is not health-based and is three orders of magnitude lower than the IOELV; clearly, the basis for this value does not take into account the IOELV as set in Directive 2017/164/EU.

Rather, the recommended BPA OEL was derived using an approach referred to as "pragmatic" by DECOS. "Pragmatic" or other non-health-based approaches that deviate from standard methodology for OEL derivation are typically used when sufficient data are not available to derive a health-based OEL, a threshold for the adverse effects of a substance cannot be identified (such as for genotoxic carcinogens or respiratory sensitizers), or when techniques are not available to measure a substance at very low levels dictated by a health-based OEL derivation (SCOEL, 1999; Health Council of the Netherlands, 2000; Schenk et al., 2008; ECHA, 2012). This is not the case for BPA, however, as there is a robust database of BPA toxicology studies, including several large, OECD guideline-compliant studies (discussed below). In addition, DECOS agreed with the European Food Safety Authority (EFSA) evaluation by Beausoleil et al. (2016) that the weight of the evidence indicates that a non-monotonic dose-response relationship

(NMDR) for BPA is not likely; thus, there is a threshold for the reported effects of BPA. For these reasons, a health-based BPA OEL can be established using standard methodology, such as that recommended by the Health Council of the Netherlands (1996, 2000), rather than a "pragmatic" approach.

Given the robust toxicity database and agreement by DECOS that there is no evidence for a NMDR for BPA, there are sufficient and reliable data from which to derive a health-based BPA OEL. Thus, a non-health-based, "pragmatic" approach that differs from standard guidance for OEL derivation is not scientifically justified and goes against European Commission Directive 2017/164/EU. We consider that DECOS should recommend the health-based OEL for BPA derived by SCOEL (2014), as this value was based on a study that European official bodies, including DECOS, considered to be suitable for risk assessment and it was derived using standard methodology.

2. DESPITE THEIR LOW RELIABILITY, RECENT BPA STUDIES, REPORTING LOW-DOSE EFFECTS, WERE TAKEN AS JUSTIFICATION FOR THE PROPOSED OEL

DECOS reviewed some of the most recent BPA studies that evaluated doses less than 9 mg/kg/day. It noted that some studies reported developmental effects on the immune system and neurobehavior at oral doses several orders of magnitude lower than equivalent concentrations used in BPA inhalation studies. DECOS also noted that these low-dose effects have questionable adversity and relevance to inhalation exposure and do not provide a reliable basis to derive a health-based OEL. Despite these limitations, DECOS concluded that the BPA OEL should provide protection against the reported low-dose, developmental effects, which led to its "pragmatic" approach in deriving the recommended OEL.

DECOS did not conduct a systematic and thorough review of the low-dose BPA literature that forms the basis for its "pragmatic" approach to derivation of the BPA OEL. Rather, DECOS briefly summarized the results and limitations of a selection of studies published from 2014 to January 2017 in a table in Annex D of the draft OEL document. There were no details provided as to how these studies were selected, such as literature search terms or study inclusion or exclusion criteria. There was also no consideration of study quality or how methodological issues impacted the interpretation of results. In addition, several other recent studies with robust study designs that used low doses of BPA were not included in the Annex D table, such as those by Delclos et al. (2014), Ferguson et al. (2014, 2015), Johnson et al. (2016), Rebuli et al. (2015), and Arambula et al. (2017). To address the uncertainty regarding potential effects in some low-dose studies, DECOS should have built on EFSA's extensive review of the BPA literature (EFSA, 2015b) by conducting a thorough review of the recent literature, including all available studies, regardless of their results, and incorporating study quality, adversity of effects, and relevance of effects to humans and to inhalation exposures. This would have demonstrated that an approach for deriving the BPA OEL based on uncertainty regarding potential effects from low-dose studies was not justified.

With regard to the studies DECOS did review, the committee focused on five recent studies that reported developmental effects on the immune system (Menard et al., 2014a,b; Luo et al., 2016) or neurobehavior (Jones et al., 2016; Komada et al., 2014), stating that these studies reported dose-

response relationships. For immune effects, DECOS noted the conclusion of what it referred to as a "weight-of-evidence" analysis conducted during an expert workshop organized by the Dutch National Institute for Public Health and the Environment (RIVM) in September 2015 to evaluate recent, key studies on the developmental immunotoxicity of BPA. The conclusion from this workshop was that these new studies provide credible evidence for adverse immune effects after developmental exposure to BPA at a dose of 5 µg/kg/day (Hessel et al., 2016). The workshop evaluation was not a thorough and systematic weight-of-evidence analysis, however, as it focused on only three studies (Menard et al., 2014a,b; Bauer et al., 2012) with brief mention of the results of a few "supportive" studies. This evaluation did not identify the significant limitations of the studies by Menard et al. (2014a,b), as discussed below, and did not evaluate and integrate the full database of BPA immunotoxicity studies.

In response to a request from the RIVM to evaluate the recent literature on BPA immunotoxicity, an EFSA panel critically reviewed the studies by Menard et al. (2014a,b) and incorporated them into the weight-of-evidence analysis for potential BPA immune effects previously conducted in support of the EFSA (2015b) opinion on BPA (EFSA, 2016). This analysis had already included the study by Bauer et al. (2012) that was a focus of the workshop noted above (Hessel et al., 2016). The EFSA panel concluded that the two studies by Menard et al. (2014a,b) add to the database for immunotoxicity of BPA, but their incorporation into the overall weight of the evidence is not sufficient to call for a revision of the EFSA (2015b) opinion, for which a temporary tolerable daily intake (t-TDI) of 4 µg/kg/day was derived for BPA.

The EFSA panel noted that several limitations of the Menard et al. (2014a,b) studies confound their interpretation and prevent their use in human risk assessment (EFSA, 2016). These include high intra-individual variability in the results within treatment groups, resulting in high confidence intervals and limited dose-response, as well as the need for additional controls, the lack of standard toxicological parameters (such as immune organ histology), the use of only one dose for most of the evaluations, and the limited biological significance of the results on immunological host response to parasitic infection. A recent commentary by Kimber (2017) also noted some of these limitations, as well as the multiple inconsistencies in the results between the two Menard et al. (2014a,b) studies with regard to the impact of perinatal exposure to BPA on the effectiveness of tolerance induction, immune responses, antibody and cytokine production, and immune cell populations in the spleen. Kimber (2017) further noted that other studies of the effects of perinatal BPA exposure on oral tolerance reported little to no effects (Ohshima et al., 2007; Nygaard et al., 2015), and that studies of other immune-related effects, such as allergic inflammation in the airways, provide no evidence to suggest that BPA exposure influences their development.

Although DECOS noted some of the limitations of the Menard et al. (2014a,b) studies, such as the lack of relevance of effects on oral tolerance to inhalation exposures, it did not fully take the limitations of these studies into account when using them as a basis to consider the possibility of low-dose effects and deciding its approach to OEL derivation. DECOS also did not consider that the histopathologic evaluations of immune organs in well conducted, Good Laboratory Practice (GLP)-compliant studies have not demonstrated immunotoxic effects of BPA. For example, Delclos et al. (2014) observed no statistically significant histological effects on the spleen or thymus in rats exposed perinatally to BPA by

oral gavage at doses ranging from 2.5 µg/kg/day to 300 mg/kg/day. Similarly, Nitschke et al. (1988) reported no histological effects on the spleen, thymus, or various lymph nodes in rats exposed to BPA via inhalation at a concentration of 150 mg/m³.

Adverse histological effects on immune organs have also not been observed across a broad range of BPA doses (1 µg/kg/day to 600 mg/kg/day) in large, multigenerational, OECD and US EPA Office of Prevention, Pesticides and Toxic Substances (OPPTS) guideline-compliant studies (Tyl et al., 2002, 2008). The lack of adverse immune effects at low doses in high quality studies reduces the uncertainty raised by other, less reliable studies reporting developmental immune effects in rodents exposed to low doses of BPA. In addition, if the low-dose effects were either adverse themselves or precursors to adverse effects, they should have occurred and caused downstream functional effects at higher doses in well-conducted studies, given that there is no indication of a NMDR for BPA effects (as acknowledged by DECOS).

Regarding neurodevelopmental effects of BPA at low doses, DECOS stated that the studies by Komada et al. (2014) and Jones et al. (2016) suggest that BPA can cause neurological effects and behavioral changes in rodents prenatally exposed to BPA at doses of 5 µg/kg/day and higher. This is not an accurate summary of the results of these studies, however. Komada et al. (2014) reported some histological effects in neurons of mice exposed prenatally to 20 or 200 µg/kg/day BPA, with no dose-response relationships, but reported behavioral effects (hyperactivity) only in mice exposed to 200 µg/kg-day BPA. Jones et al. (2016) reported no effects of BPA on motor neuron survival or soma size when rats were perinatally exposed to doses of 5-5,000 µg/kg/day, although the authors did observe decreased soma size when adult rats were exposed to 5-5,000 µg/kg/day BPA for 28 days. There were no dose-response relationships for the BPA-induced decreases in soma size in two of the three brain regions examined.

DECOS noted that the adversity of the neurological effects reported by Komada et al. (2014) and Jones et al. (2016) is unclear and the functional effects should be clarified before the data can be used for risk assessment. The two studies were not conducted according to rigorous guidelines. By contrast, a developmental neurotoxicity study conducted according to OECD and US EPA OPPTS guidelines and in compliance with GLP principles reported that BPA does not cause neurodevelopmental effects in rats at doses of 10 µg/kg/day to 150 mg/kg/day (Stump et al., 2010). In addition, a recent inhalation toxicity study conducted by the Korean Occupational Safety and Health Agency reported no effects on spatial learning and memory in rats exposed to 90 mg/m³ BPA for 8 weeks (Chung et al., 2017). Similar to immunological effects, the lack of adverse neurological effects at low doses in a well-conducted oral study, as well as in an inhalation study that is directly relevant to OEL derivation, reduces the uncertainty raised by other, less reliable studies reporting low-dose neurodevelopmental effects.

We further note with concern that DECOS does not mention the two-year National Toxicology Program (NTP)/National Institute of Environmental Health Sciences (NIEHS)/US Food and Drug Administration (US FDA) study of BPA (i.e., the "CLARITY" study). The results are anticipated to be available later this year or in early 2018. This study uses robust, guideline-compliant methodology to evaluate the effects of BPA in

rats, including immunotoxicity and neurobehavioral effects, over a broad range of doses (including < 5 µg/kg/day) (Heindel et al., 2015), and may identify a conclusive point of departure for systemic effects that is appropriate for health-based risk assessment. It is notable that EFSA will conduct a thorough and systematic re-evaluation of BPA toxicity when the results of the CLARITY study are available (EFSA, 2017).

Even though DECOS concluded that there is uncertainty in the low-dose database for BPA based on a small group of studies, uncertainty is usually accounted for in the OEL derivation process by the application of uncertainty and adjustment factors. For example, the European Chemicals Agency Committee for Risk Assessment (ECHA-RAC, 2015) derivation of a BPA derived no-effect level (DNEL) for workers and the EFSA (2015b) derivation of a t-TDI for BPA accounted for uncertainty in the BPA database regarding effects on neurobehavioral, immune, reproductive, and metabolic systems by applying a factor of 6 in addition to the uncertainty factors for inter- and intraspecies differences. We therefore consider that DECOS did not provide sufficient justification for deviating from the standard approach for addressing uncertainty in the derivation of OELs and other health-based exposure limits.

3. THE EXPOSURE-BASED APPROACH FOR DERIVATION OF THE PROPOSED OEL FOR BPA IS NOT SUPPORTED BY THE EXTENSIVE BPA DATABASE

The "pragmatic" approach of DECOS to limit occupational exposure to the level of BPA exposure in the general population, such that the total exposure would not increase more than two-fold as a result of occupational exposure, does not consider that the vast majority of regulatory agencies that have evaluated BPA toxicity have concluded that current exposures to BPA do not pose a human health risk (e.g., Health Canada, 2008, 2009, 2010, 2012; JECFA, 2010; AIST RISS, 2011; FSANZ, 2012; Aungst and Anderson, 2014). This approach of DECOS results in an OEL value far lower than any previously-derived, health-based exposure limit for BPA.

The standard practice for deriving OELs has been to set them at higher levels than typically used for the general population, which argues against the "pragmatic" approach applied by DECOS. ECHA (2012) provides specific guidance to derive DNELs, which includes different assessment factors for workers vs. the general population. ECHA (2012) guidance recommends a default assessment factor for intraspecies differences of 10 for the general population, to include the larger part of the population including children and elderly, whereas for workers, the standard procedure is to use a default assessment factor of 5. Similarly, ECETOC (2003) recommends default intraspecies assessment factors of 5 for the general population and 3 for workers. These approaches result in a higher exposure limit for workers compared to the general population. An example of this is the oral DNEL for BPA of 4 µg/kg/day for the general population and the corresponding oral DNEL for workers of 8 µg/kg/day (ECHA-RAC, 2015).

DECOS has not used its "pragmatic" approach for deriving OELs for other chemicals besides BPA, and acceptance of this approach would set a precedent for basing OELs on uncertain, low-dose effects reported in a small group of studies. As discussed above, the approach is not supported by the fact that there are no low-dose effects of BPA that are clearly adverse or on the pathway to adversity reported in

guideline-compliant studies, particularly multigenerational studies with exposures ranging up to several orders of magnitude higher.

4. THE APPLICATION OF A SKIN NOTATION FOR A NON-HEALTH-BASED OEL IS INAPPROPRIATE

The recommendation of DECOS to apply a skin notation to the BPA OEL is based on the ECETOC strategy for assigning a skin notation, but this requires the OEL to be based on a systemic toxicity endpoint (ECETOC, 1993). Because the recommended OEL is based on uncertainty in the context of exploratory low-dose effects rather than an actual endpoint, the DECOS recommendation does not fully follow the ECETOC strategy. DECOS also assumed that BPA is rapidly absorbed through the skin, but did not cite any studies on the dermal absorption of BPA.

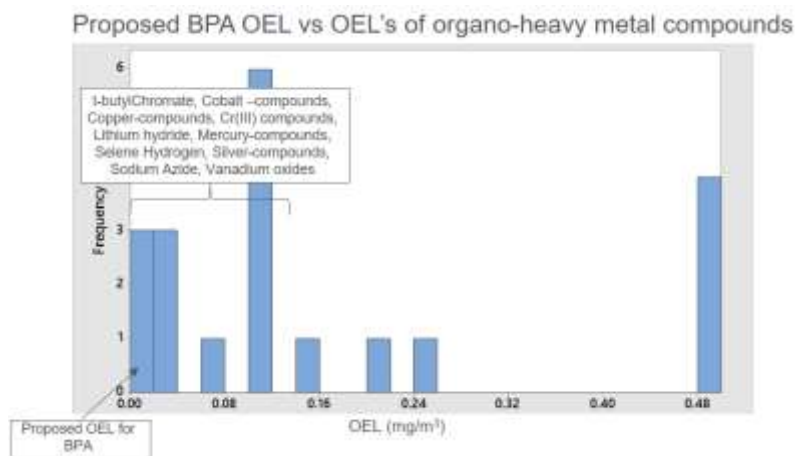
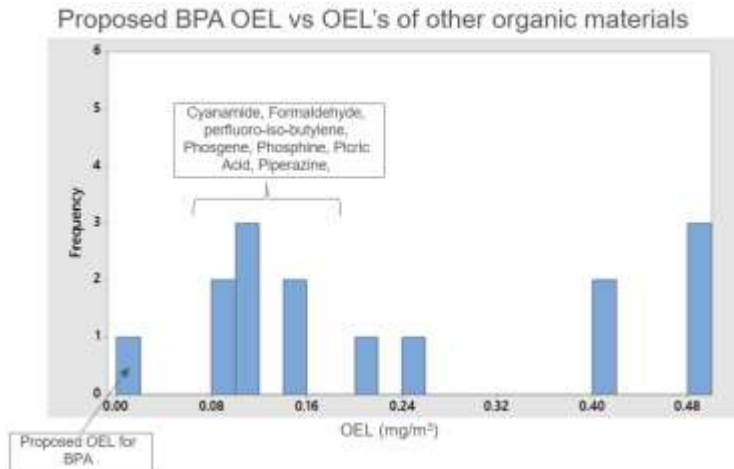
As discussed by SCOEL (2014), dermal absorption of BPA has been studied in both in vivo and ex vivo skin models. Three in vitro skin absorption studies conducted according to OECD Test Guideline 428 reported <10% absorption of BPA through the entire human skin into the receptor compartment (Morck et al., 2010; Demierre et al., 2012; Toner et al., unpublished), although the bioavailable dose may be higher (approximately 30% of the applied dose) (ECHA, 2017). SCOEL (2014) did not recommend a skin notation for BPA, noting that skin absorption may have only a minor contribution to systemic BPA concentrations at its recommended health-based OEL, which was derived using standard methodology. We therefore consider that an OEL should be recommended that is based on a systemic endpoint, such as the BPA OEL recommended by SCOEL (2014), and that the results of dermal absorption studies of BPA should be considered before considering a recommendation to apply the a skin notation.

5. THE PROPOSED OEL FOR BPA RAISES SIGNIFICANT CONCERNS ABOUT THE PROPORTIONALITY, FEASIBILITY AND BROADER SOCIO-ECONOMIC IMPACTS

We realize that only scientific comments will be taken into account by DECOS in the finalization of their recommendation. However, given the significant concerns about the proportionality as well as the broader socio-economic impacts of the proposed limit value, we would also use this opportunity to inform you about our concerns:

- **Proportionality of the proposed limit value**

When comparing the proposed OEL for BPA with OELs that have been set for other substances, we note that the proposed OEL for BPA is 30 times lower than organic compounds with well-known and serious health risks and BPA would be put into the same OEL range of some highly hazardous organometallic compounds.



*In the histograms, frequency represents the number of substances and each block represents substances considered. Only some compounds are indicated as example.

For example, due to acute lethal effects, low OEL levels were set for phosgene (0.08 mg/m³) and phosphine (0.14 mg/m³). Regarding personal protection equipment, independent respiratory devices and personal monitoring 24/7 using dosimeters are required. In terms of other measures, secured and closed installation, with separate enclosure and security access, are required. With the DECOS draft version of its recommended OEL for BPA, BPA would be far below these extremely dangerous and life threatening compounds.

For the proposed BPA OEL, the main hazard endpoints are suspected and unreliable systemic toxicity effects following life-time exposure to low doses. Compared to other substances such as lead and inorganic compounds (0.15 mg/m³), and formaldehyde (0.15 mg/m³), with well-known consequences from long term exposure, their OELs are 60 times higher than the proposed BPA OEL.

This significantly lower OEL that is proposed for BPA, and the corresponding substantial personal protection equipment and engineering controls that would be required, would be disproportionate to the suspected health risk.

- **Feasibility and negative socio-economic impacts**

In The Netherlands, BPA is used in the production of polycarbonate at SABIC in Bergen op Zoom, epoxy resins at Hexion in Rotterdam and in some coatings made by AkzoNobel in Sassenheim and PPG in Amsterdam.

Production of polycarbonate

BPA is a key monomer in the production of polycarbonate. Without this building block, polycarbonate simply cannot be produced. Polycarbonates are complex speciality performance materials. In the form of resins and blends, they provide users with a range of highly-valued performance characteristics, most notably impact resistance, biocompatibility, heat resistance, transparency, fire resistance, and ductility. It is important to note that alternatives to polycarbonate do not have all of the same performance characteristics.

Polycarbonate has played an important role in helping to underpin the competitiveness of important parts of the Dutch manufacturing sector, including speciality chemicals, optical data storage, electrical and electronic engineering, plastics processing, domestic appliances, automotive parts, and medical devices. Many of these sectors are, moreover, major exporters to EU markets and beyond.

Due to its function as an enabling technology, approximately 21,000 jobs in The Netherlands depend upon the production and use of polycarbonate. This includes direct employment within enterprises producing, using or supplying polycarbonates, and indirect employment impacts from “multiplier” effects. Within the value chain, it is estimated that around 4,200 jobs depend upon the activities of the direct industry; almost 1,200 jobs depend upon the production of components and materials for “unique applications” by plastics processors; and 15,800 jobs depend upon the manufacture, wholesaling, and retailing of end products based on “unique applications” of polycarbonate.

The production and use of polycarbonate in The Netherlands also generated substantial wealth. It is estimated that, circa Euro 1.4 billion of value added in The Netherlands depended upon polycarbonate technology. The largest proportion of this (over 60% of total value added) resulted from the “critical applications” of polycarbonate in end use products, including advanced medical devices, automotive parts, optical media software and hardware, safety glasses, and consumer electronics

Production of epoxy resins

BPA is also a basic building block for the production of epoxy resins. Epoxy resins are selected because of their corrosion protection, thermal stability and mechanical strength. It is important

to note that alternatives to BPA-based epoxy resins do not have all of the same performance characteristics.

Epoxies are for instance used as protective and insulating coatings and primers to build ships and other vessels, aircrafts, spacecrafts and satellite systems. Due to their strength, they are used in the renewable energy sector to coat steel, wind turbine poles as well as to produce their blades, and protect the structures of hydroelectric power stations. Other relevant applications include pipes used for drinking water, waste, oil and gas.

In the construction sector, epoxies are used in structural parts, engineering adhesives and paints to enhance durability, strength and resiliency, guaranteeing longer lifespans and lowering the need for repainting and refurbishment. In applications such as flooring, they help maintain higher hygienic standards, as they allow the use of stronger cleaners. When used with materials such as marble, they also improve their aesthetic properties. Last, they are also used as fire protection on commercial and industrial installations.

In both the polycarbonate and epoxy resins production processes, the proposed OEL would imply “clean room” conditions that are not possible on a large industrial scale. If at all possible, clean room conditions are associated with huge investments. Based on the BPA solids handling equipment an investment between 50 to 100 million Euros is needed. BPA is a commodity and current economics do not allow an investment of that kind which could result in shutting down the plant. Shutting down BPA will also result in shutting down the neighboring resins plant as the major feedstock is no longer available. In terms of economic impact, it is estimated that in such a scenario about 300 Hexion people and about 1500 to 1800 contractors (indirect and direct) could lose their job. For SABIC it would impact about 1250 workers that are employed directly at the Bergen op Zoom site. Indirect staffing (contractors, logistic service providers) concerns > 500 additional resources.

The measures that would be caused by the extremely low proposed OEL may be extremely costly and difficult to implement. In addition to the on-site measures, substances with such low OELs also require a specific ultra-safe way to transport which would lead to significant additional investments and in the worst cases could make it impossible to continue operations in The Netherlands in an economically viable way. This would not only affect existing businesses in The Netherlands but would also have an impact on the attractiveness of new business opportunities in The Netherlands and may have other companies rethink doing business in The Netherlands.

Besides the concerns about the proportionality and consequences in terms of practical implementation, it is unclear whether the extremely low limit can be technically achieved and how it can ultimately be measured with the best available analytical techniques.

6. CONCLUSION

In conclusion, we appreciate this opportunity to provide comments on the DECOS draft version of its recommended OEL for BPA. We have serious concerns about the methodology applied by DECOS to derive the proposed OEL for BPA of 2.5 µg/m³ and the precedent it could set. "Pragmatic" or other non-health-based approaches that deviate from standard methodology for OEL derivation should only be used in cases where sufficient data are not available to derive a health-based OEL or when techniques are not available to measure a substance at very low levels dictated by a health-based OEL derivation. This is not the case for BPA since the database is sufficiently robust to support the derivation of a health-based OEL for BPA. Moreover, deviating from the standard approach requires sufficient justification. We consider that DECOS should recommend the health-based SCOEL (2014) OEL of 2 mg/m³ BPA, with no application of a skin notation. Recommending this value will be consistent with the weight of evidence indicating a lack of clear adverse effects at low BPA exposures and with European Commission Directive 2017/164/EU.

We hope that these comments are useful and will be taken into consideration in the finalization of the recommendation. We remain at your disposal for any questions you may have and would be available to discuss any of these scientific comments further with DECOS.

P. Vangheluwe
PlasticsEurope
Director Consumer &
Environmental affairs

J. Zandbergen
NRK
Algemeen directeur

J. Feenstra
VVF - VLK - VVH
Directeur

T. Stijnen
PlasticsEurope Nederland
Directeur

References

- American Conference of Governmental Industrial Hygienists (ACGIH). 2015. "Operations Manual." Threshold Limit Values for Chemical Substances Committee. 78p., February 19. Accessed at http://www.acgih.org/docs/default-source/TLV-BEI-Guidelines/tlv-bei-committee-operations-manuals/approved_revised_tlv-cs_comm_ops_manual-final.pdf?sfvrsn=10.
- Arambula, SE; Fuchs, J; Cao, J; Patisaul, HB. 2017. "Effects of perinatal bisphenol A exposure on the volume of sexually-dimorphic nuclei of juvenile rats: A CLARITY-BPA consortium study." *Neurotoxicology* 63:33-42. doi: 10.1016/j.neuro.2017.09.002.
- Aungst, J; Anderson, S. 2014. Memorandum to S. Ostroff (US FDA, Chemical and Environmental Science Council (CESC)) re: Final report for the review of literature and data on BPA (Draft). US Food and Drug Administration (US FDA), Bisphenol A Joint Emerging Science Working Group. 2p., June 6.
- Bauer, SM; Roy, A; Emo, J; Chapman, TJ; Georas, SN; Lawrence, BP. 2012. "The effects of maternal exposure to bisphenol A on allergic lung inflammation into adulthood." *Toxicol. Sci.* 130(1):82-93. doi: 10.1093/toxsci/kfs227.
- Beausoleil, C; Beronius, A; Bodin, L; Bokkers, BGH; Boon, PE; Cao, Y; De Wit, L; Fischer, A; Hanberg, A; Leander, K; Litens-Karlsson, S; Rousselle, C; Slob, W; Varrett, C; Wolterink, G; Zilliacus, J. 2016. "External Scientific Report: Review of Non-Monotonic Dose-Responses of Substances for Human Risk Assessment." Report to European Food Safety Authority (EFSA) EFSA Supporting Publication 2016:EN-1027. 290p.
- BfR. 2008. "New studies on bisphenol A do not challenge earlier risk assessment." BfR Information No. 036/2008. 1p., September 19. Accessed at http://www.bfr.bund.de/cm/349/new_studies_on_bisphenol_a_do_not_challenge_earlier_risk_assessment.pdf.
- Bruhn, C. 2012. "Method for the determination of bisphenol A." doi: 10.1002/3527600418.am8005e0013. In The MAK-Collection Part III: Air Monitoring Methods (Volume 13). Deutsche Forschungsgemeinschaft (DFG), Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, Germany. p85-92.
- Delclos, KB; Camacho, L; Lewis, SM; Vanlandingham, MM; Latendresse, JR; Olson, GR; Davis, KJ; Patton, RE; da Costa, GG; Woodling, KA; Bryant, MS; Chidambaram, M; Trbojevich, R; Juliar, BE; Felton, RP; Thorn, BT. 2014. "Toxicity evaluation of bisphenol A administered by gavage to Sprague Dawley rats from gestation day 6 through postnatal day 90." *Toxicol. Sci.* 139(1):174-197. doi: 10.1093/toxsci/kfu022.
- Demierre, AL; Peter, R; Oberli, A; Bourqui-Pittet, M. 2012. "Dermal penetration of bisphenol A in human skin contributes marginally to total exposure." *Toxicol. Lett.* 213(3):305-308. doi: 10.1016/j.toxlet.2012.07.001.

Deutsche Forschungsgemeinschaft (DFG). 2011. "MAK value documentation for bisphenol A." doi: 10.1002/3527600418.mb8005e5014. In The MAK Collection for Occupational Health and Safety: Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, Germany. p1-31.

European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC). 1993. "Strategy for Assigning a "Skin Notation" (Revised)." ECETOC Document No. 31. 12p., August.

European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC). 2006. "Guidance for Setting Occupational Exposure Limits: Emphasis on Data-Poor Substances." Technical Report No. 101. 90p., October. Accessed at <http://members.ecetoc.org/Documents/Document/TR%20101.pdf>.

European Chemicals Agency (ECHA). 2012. "Guidance on information requirements and chemical safety assessment. Chapter R.8: Characterisation of dose [concentration]-response for human health (Version 2.1)." ECHA-2010-G-19-EN. 195p., November.

European Chemicals Agency, Committee for Risk Assessment (ECHA-RAC). 2013. "Meeting agenda for the 24th Meeting of the Committee for Risk Assessment, 5-8 March 2013, Helsinki, Finland [re: Reference DNELs derived for DEHP]." RAC/24/2013/08 rev. 2. 8p., April 12.

European Chemicals Agency, Committee for Risk Assessment (ECHA-RAC). 2015. "Opinion on an Annex XV dossier proposing restrictions on bisphenol A." ECHA/RAC/RES-O-0000001412-86-56/F. 69p., June 5.

European Commission (EC). 2017. "Commission Directive (EU) 2017/164 of 31 January 2017 establishing a fourth list of indicative occupational exposure limit values pursuant to Council Directive 98/24/EC, and amending Commission Directives 91/322/EEC, 2000/39/EC and 2009/161/EU (Text with EEA relevance)." *Off. J. Eur. Union* L 27:115-120. February 1.

European Commission, Health & Consumer Protection Directorate-General, Scientific Committee on Occupational Exposure Limits (SCOEL). 1999. "Methodology for the Derivation of Occupational Exposure Limits: Key Documentation." 35p., January.

European Commission, Health & Consumer Protection Directorate-General, Scientific Committee on Occupational Exposure Limits (SCOEL). 2013. "Methodology for the Derivation of Occupational Exposure Limits: Key Documentation (Version 7)." 38p., June.

European Commission, Health & Consumer Protection Directorate-General, Scientific Committee on Occupational Exposure Limits (SCOEL). 2014. "Recommendation from the Scientific Committee for Occupational Exposure Limits for Bisphenol A." SCOEL/SUM/113. 29p., June.

European Food Safety Authority (EFSA). 2015a. "Scientific opinion on the risks to public health related to the presence of bisphenol A (BPA) in foodstuffs: Part I - Exposure assessment." Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF). *EFSA J.* 13(1):3978. Accessed at <http://www.efsa.europa.eu/en/efsajournal/pub/3978.htm>.

European Food Safety Authority (EFSA). 2015b. "Scientific opinion on the risks to public health related to the presence of bisphenol A (BPA) in foodstuffs: Part II - Toxicological assessment and risk characterisation." Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF). *EFSA J.* 13(1):3978. Accessed at <http://www.efsa.europa.eu/en/efsajournal/pub/3978.htm>.

European Food Safety Authority (EFSA). 2016. "A statement on the developmental immunotoxicity of bisphenol A (BPA): answer to the question from the Dutch Ministry of Health, Welfare and Sport." Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF). *EFSA J.* 14(10):4580. doi: 10.2903/j.efsa.2016.4580.

Ferguson, SA; Law, CD; Kissling, GE. 2014. "Developmental treatment with ethinyl estradiol, but not bisphenol A, causes alterations in sexually dimorphic behaviors in male and female Sprague Dawley rats." *Toxicol. Sci.* 140(2):374-392. doi: 10.1093/toxsci/kfu077.

Ferguson, SA; Paule, MG; He, Z. 2015. "Pre- and postnatal bisphenol A treatment does not alter the number of tyrosine hydroxylase-positive cells in the anteroventral periventricular nucleus (AVPV) of weanling male and female rats." *Brain Res.* 1624:1-8. doi: 10.1016/j.brainres.2015.07.013.

Food Standards Australia New Zealand (FSANZ). 2012. "FSANZ Activities in Relation to Bisphenol A." 27p. Accessed at <http://www.foodstandards.gov.au/science/monitoring/surveillance/documents/BPA%20paper%20October%202010%20FINAL.pdf>.

Health Canada. 2008. "Minister's remarks on bisphenol A." 3p., April 18. Accessed at http://www.hc-sc.gc.ca/ahc-asc/minist/speeches-discours/2008_04_18_e.html.

Health Canada. 2009. "Survey of Bisphenol A in Bottled Water Products." Bureau of Chemical Safety, Food Directorate, Health Products and Food Branch. 10p., July.

Health Canada. 2010. "Bisphenol A." 3p., December 8 Accessed at <http://www.hc-sc.gc.ca/fn-an/securit/packag-emball/bpa/index-eng.php>.

Health Canada. 2012. "Health Canada's Updated Assessment of Bisphenol A (BPA) Exposure from Food Sources." 6p., September. Accessed at http://www.hc-sc.gc.ca/fn-an/securit/packag-emball/bpa/bpa_hra-ers-2012-09-eng.php.

Health Council of the Netherlands, Dutch Expert Committee on Occupational Safety (DECOS). 2017. "Bisphenol A: Health-based recommendation on occupational exposure limits (Draft)." 37p., July 17.

Health Council of the Netherlands. 1996. "Toxicology-based recommended exposure limits." Committee on Health-based Recommended Exposure Limits. Publication No. 1996/12E. 58p., August.

Health Council of the Netherlands. 2000. "Health-based Reassessment of Administrative Occupational Exposure Limits." Committee on Updating of Occupational Exposure Limits. Publication No. 2000/15OSH. 18p., December 14.

- Heindel, JJ; Newbold, RR; Bucher, JR; Camacho, L; Delclos, KB; Lewis, SM; Vanlandingham, M; Churchwell, MI; Twaddle, NC; McLellen, M; Chidambaram, M; Bryant, M; Woodling, K; Costa, GG; Ferguson, SA; Flaws, J; Howard, PC; Walker, NJ; Zoeller, RT; Fostel, J; Favaro, C; Schug, TT. 2015. "NIEHS/FDA CLARITY-BPA research program update." *Reprod. Toxicol.* 58:33-44. doi: 10.1016/j.reprotox.2015.07.075.
- Hessel, EV; Ezendam, J; van Broekhuizen, FA; Hakkert, B; DeWitt, J; Granum, B; Guzylack, L; Lawrence, BP; Penninks, A; Rooney, AA; Piersma, AH; van Loveren, H. 2016. "Assessment of recent developmental immunotoxicity studies with bisphenol A in the context of the 2015 EFSA t-TDI." *Reprod. Toxicol.* 65:448-456. doi: 10.1016/j.reprotox.2016.06.020.
- Johnson, SA; Javurek, AB; Painter, MS; Ellersieck, MR; Welsh, TH III; Camacho, L; Lewis, SM; Vanlandingham, MM; Ferguson, SA; Rosenfeld, CS. 2016. "Effects of developmental exposure to bisphenol A on spatial navigational learning and memory in rats: A CLARITY-BPA study." *Horm. Behav.* 80:139-148. doi: 10.1016/j.yhbeh.2015.09.005.
- Joint FAO/WHO Expert Committee on Food Additives (JECFA). 2010. "Toxicological and Health Aspects of Bisphenol A: Report of a Joint FAO/WHO Expert Meeting (2-5 November 2010) and Report of Stakeholder Meeting on Bisphenol A (1 November 2010)." World Health Organization (WHO) 59p. Accessed at http://whqlibdoc.who.int/publications/2011/97892141564274_eng.pdf.
- Jones, BA; Wagner, LS; Watson, NV. 2016. "The effects of bisphenol A exposure at different developmental time points in an androgen-sensitive neuromuscular system in male rats." *Endocrinology* 157(8):2972-2977. doi: 10.1210/en.2015-1574.
- Kimber, I. 2017. "Bisphenol A and immunotoxic potential: A commentary." *Regul. Toxicol. Pharmacol.* doi: 10.016/j.yrtph.2017.08.022.
- Komada, M; Itoh, S; Kawachi, K; Kagawa, N; Ikeda, Y; Nagao, T. 2014. "Newborn mice exposed prenatally to bisphenol A show hyperactivity and defective neocortical development." *Toxicology* 323:51-60. doi: 10.1016/j.tox.2014.06.009.
- Luo, S; Li, Y; Li, Y; Zhu, Q; Jiang, J; Wu, C; Shen, T. 2016. "Gestational and lactational exposure to low-dose bisphenol A increases Th17 cells in mice offspring." *Environ. Toxicol. Pharmacol.* 47:149-158. doi: 10.1016/j.etap.2016.09.017.
- Menard, S; Guzylack-Piriou, L; Lencina, C; Leveque, M; Naturel, M; Sekkal, S; Harkat, C; Gaultier, E; Olier, M; Garcia-Villar, R; Theodorou, V; Houdeau, E. 2014b. "Perinatal exposure to a low dose of bisphenol A impaired systemic cellular immune response and predisposes young rats to intestinal parasitic infection." *PLoS ONE* 9 (11) : e112752. doi: 10.1371/journal.pone.0112752.
- Menard, S; Guzylack-Piriou, L; Leveque, M; Braniste, V; Lencina, C; Naturel, M; Moussa, L; Sekkal, S; Harkat, C; Gaultier, E; Theodorou, V; Houdeau, E. 2014a. "Food intolerance at adulthood after perinatal exposure to the endocrine disruptor bisphenol A." *FASEB J.* 28(11):4893-4900. doi: 10.1096/fj.14-255380.

Morck, TJ; Sorda, G; Bechi, N; Rasmussen, BS; Nielsen, JB; Ietta, F; Rytting, E; Mathiesen, L; Paulesu, L; Knudsen, LE. 2010. "Placental transport and in vitro effects of bisphenol A." *Reprod. Toxicol.* 30(1):131-137. doi: 10.1016/j.reprotox.2010.02.007.

National Institute of Advanced Industrial Science and Technology (AIST), Research Institute of Science for Safety and Sustainability (RISS) July 2011. "Updated Hazard Assessment of Bisphenol A." 80p. Accessed at <http://www.aist-riss.jp/main/modules/product/rad.1.html>.

Nitschke, KD; Lomax, LG; Schuetz, DJ; Hopkins, PJ; Weiss, SW. 1988. "Bisphenol A: 13-Week Aerosol Toxicity Study with Fischer 344 Rats (Final Report)." 85p., March 18.

Occupational Safety and Health Administration (OSHA). 2013. "OSHA Method 1018: Bisphenol A, Diglycidyl Ether of Bisphenol A." 18p., December.

Ohshima, Y; Yamada, A; Tokuriki, S; Yasutomi, M; Omata, N; Mayumi, M. 2007. "Transmaternal exposure to bisphenol A modulates the development of oral tolerance." *Pediatr. Res.* 62(1):60-64. doi: 10.1203/PDR.0b013e3180674dae.

Rebuli, ME; Camacho, L; Adonay, ME; Reif, DM; Aylor, DL; Patisaul, HB. 2015. "Impact of low-dose oral exposure to bisphenol A (BPA) on juvenile and adult rat exploratory and anxiety behavior: A CLARITY-BPA Consortium study." *Toxicol. Sci.* 148(2):341-354. doi: 10.1093/toxsci/kfv163.

Schenk, L; Hansson, SO; Ruden, C; Gilek, M. 2009. "Are occupational exposure limits becoming more alike within the European Union?" *J. Appl. Toxicol.* 28(7):858-866.

Stump, DG; Beck, MJ; Radovsky, A; Garman, RH; Freshwater, LL; Sheets, LP; Marty, MS; Waechter, JM Jr.; Dimond, SS; Van Miller, JP; Shiotsuka, RN; Beyer, D; Chappelle, AH; Hentges, SG. 2010. "Developmental neurotoxicity study of dietary bisphenol A in Sprague-Dawley rats." *Toxicol. Sci.* 115(1):167-182. doi: 10.1093/toxsci/kfq025.

Toner, F; Allan, G; Dimond, SS; Waechter, JM Jr.; Beyer, D. 2017. "In vitro percutaneous absorption and metabolism of bisphenol A (BPA) through fresh human skin (Final Draft)." *Toxicol. In Vitro* (Submitted) 28p.

Tyl, RW; Myers, CB; Marr, MC; Sloan, CS; Castillo, NP; Veselica, MM; Seely, JC; Dimond, SS; Van Miller, JP; Shiotsuka, RS; Beyer, D; Hentges, SG; Waechter, JM Jr. 2008. "Two-generation reproductive toxicity study of dietary bisphenol A in CD-1 (Swiss) mice." *Toxicol. Sci.* 104(2):362-384. doi: 10.1093/toxsci/kfn084.

Tyl, RW; Myers, CB; Thomas, BF; Keimowitz, AR; Brine, DR; Veselica, MM; Fail, PA; Chang, TY; Seely, JC; Joiner, RL; Butala, JH; Dimond, SS; Cagen, SZ; Shiotsuka, RN; Stropp, GD; Waechter, JM. 2002. "Three-generation reproductive toxicity study of dietary bisphenol A in CD Sprague-Dawley rats." *Toxicol. Sci.* 68(1):121-146. doi: 10.1093/toxsci/68.1.121.

US EPA. 2002. "A Review of the Reference Dose and Reference Concentration Processes (Final)." Risk Assessment Forum, Reference Dose/Reference Concentration (RfD/RfC) Technical Panel. EPA/630-P-02/002F. 192p., December. Accessed at <http://www.epa.gov/raf/publications/pdfs/rfd-final.pdf>.