National Institute for Public Health
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Bisphenol A

Part 2.
Recommendations for risk management

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In 2014 en 2015 zijn de Europese normen voor een veilige blootstelling aan Bisfenol A (BPA) van werknemers en consumenten aangescherpt. Het RIVM concludeert dat nieuwe inzichten voldoende aanleiding vormen om verdere aanscherping van de normen te overwegen en stelt voor op korte termijn aanvullende maatregelen te treffen die de blootstelling aan BPA verder verminderen.

Bisfenol A (BPA) is een stof die in veel producten zit, zoals kassabonnen, bouwmaterialen (verf en coatings), verpakkingsmateriaal van voedsel, speelgoed en medische hulpmiddelen. BPA is bij een te hoge blootstelling schadelijk voor de vruchtbaarheid en kan effect op het hormoonsysteem hebben.

Nieuwe studies laten zien dat BPA het immuunsysteem van de ongeboren vrucht of jonge kinderen kan schaden bij een lager blootstellingsniveau dan het niveau waarop de huidige normen zijn gebaseerd. Dit lagere blootstellingsniveau is van ongeveer dezelfde grootte als de dagelijkse blootstelling van consumenten en werknemers aan BPA. Als gevolg van deze blootstelling hebben mensen mogelijk meer kans om voedselintoleranties te ontwikkelen en kunnen ze gevoeliger voor infectieziekten worden.

Op basis van deze nieuwe inzichten wordt de rijksoverheid geadviseerd waar mogelijk op korte termijn de blootstelling aan BPA te verminderen. De bescherming van kleine kinderen, zwangeren en vrouwen die borstvoeding geven verdient hierbij bijzondere aandacht. Kleine en ongeboren kinderen zijn namelijk gevoeliger dan volwassenen voor de effecten van BPA doordat hun lichaam sterk in ontwikkeling is.

De blootstelling kan bijvoorbeeld worden verminderd door veilige alternatieven te ontwikkelen, of ervoor te zorgen dat er minder BPA vrijkomt uit producten waar deze stof in wordt gebruikt. Daarnaast kunnen werknemers tegen blootstelling aan BPA worden beschermd.

Een lagere blootstelling is ook van belang voor dieren in waterbodems, die nadelige effecten ondervinden bij de huidige BPA-concentratieniveaus.

Kernwoorden: Bisfenol A, normen, consumenten, werknemers, milieu, immuunsysteem, voedselintolerantie, infectieziekten

Synopsis

More stringent European standards for safe exposure of workers and consumers to bisphenol A (BPA) were proposed in 2014 and 2015. The Dutch National Institute for Public Health and the Environment (RIVM) has concluded that new insights sufficiently warrant consideration of even more stringent standards and has recommended taking supplementary measures in the near future for a further reduction of BPA exposure.

Bisphenol A (BPA) is a substance that occurs in numerous products, such as cash register receipts, building materials (paint and coatings), food packaging materials, toys and medical devices. Excessive BPA exposure is harmful to fertility and can affect the hormone system.

New studies show that BPA can impair the immune system of unborn and young children at a lower exposure level than the one on which the current standards are based. This lower level is roughly comparable to the current every day BPA exposure level of workers and consumers. As a result of this exposure, people could have a greater probability of developing food intolerances and could become more susceptible to infectious diseases.

Based on these new insights RIVM advises the national government to reduce BPA exposure in the short term wherever possible. Special attention needs to be devoted to protecting small children, pregnant women and women who breastfeed. This is because developing unborn and young children are more sensitive than adults to the effects of BPA.

Ways to reduce exposure include developing safe alternatives or ensuring that less BPA is released from products. Additionally, workers can be protected against BPA exposure.

Lower exposure is also important for sediment-dwelling animals that experience adverse effects due to current BPA concentration levels.

Key words: Bisphenol A, exposure levels, workers, consumers, environment, immune system, food intolerance, infection diseases

Contents

Summary

Bisphenol A (BPA) is widely used as a feedstock in the manufacture of polycarbonate (PC) plastics and epoxy resins, which are used in nearly every industry. It is also used as a colour developer in thermal paper. PC plastics can be found, for example, in construction materials, electrical/electronic devices, bottles/packaging and medical and healthcare devices. Epoxy resins are applied, for example, to electrical/electronic devices and are used in various coatings (including marine coatings, powder coatings, and can and coil coatings for food packaging materials).

BPA is a liver and kidney toxicant (after prolonged exposure) and is classified in the EU as a reproduction toxicant. Scientific studies have also associated BPA with adverse immune system effects, obesity, ADHD, diabetes and prostate cancer; these effects may be related to an interaction with the estrogen receptor.

On the basis of current human health hazard standards and information on exposure among consumers, patients (via medical devices and dental material) and workers, the RIVM summarizes that:

- there is no health concern for consumers for BPA at the levels of dietary exposure estimated by EFSA (2015);
- there is a low health concern related to the central (geometric mean) estimates of aggregated exposure to BPA from dietary sources and non-dietary sources (dust, toys, cosmetics and thermal paper) for the most exposed groups, which include infants, children and adolescents, adopting a high exposure scenario (EFSA, 2015);
- there may be a risk of adverse effects of BPA exposure among neonates in intensive care units, young children undergoing prolonged medical procedures and dialysis patients (SCENIHR, 2015);
- there is a risk for workers involved in the manufacture of BPA for product sampling and bag filling and possibly also in the manufacture of epoxy resins through inhalation (EC, 2008; UK, 2008);
- there is a risk of skin sensitization for workers in all industrial processes involving dermal contact with BPA (EC, 2008; UK, 2008);
- there is a risk for the fetuses of pregnant workers through dermal exposure to BPA in nearly all industrial processes involving dermal contact and for handling thermal paper (EC, 2008; UK, 2008; RAC, 2015).

Furthermore, recently published data on the effects of BPA on the development of the immune system published by Menard et al. (2014a,b) suggests that BPA exposure can lead to the development of food allergies and have adverse effects on resistance to infection at lower doses than anticipated by the current European standards (i.e. the OEL, t-TDI and dermal DNEL). Neonates, infants and young children are particularly susceptible to such immunological effects of BPA exposure. They are exposed through their mothers during pregnancy and through breast-feeding, but also via medical devices, packaged food and the handling of products that are not intended as toys. Following the approach as used by EFSA (2015) to derive the t-TDI, the RIVM concludes that these effects are observed in test animals at a human equivalent dose (HED) that may be more than a factor of 10 lower than the HED on which EFSA (2015) based its t-TDI. The RIVM concludes that this new data by Menard et al. (2014a,b) warrants a reconsideration of the current standards and of the health concerns for consumers, patients and workers, who may be exposed to risks not yet identified on the basis of the current standards.

The RIVM further concludes that the risk characterization ratios (RCRs)[1] for consumers, patients and workers may require revision in the light of the new insights into the immune system effects of BPA.

With regard to the environment, BPA is found in all surface water and sediment. The RIVM concludes that there is a risk for benthic organisms[2] in line with earlier conclusions presented by the EU RAR (EC, 2008). Emissions of BPA to the environment may result from its manufacture, its use in a broad range of products or the recycling and disposal of these products. More clarity on the contribution of various sources of BPA to its concentration in sediment is expected in the course of 2016 following the substance evaluation of BPA under the EU's Registration, Evaluation, Authorisation & Restriction of Chemicals (REACH) regulation, which is being performed by Germany.

The RIVM's recommendations are summarized below.

[1] Risk characterization is 'the estimation of the probability of occurrence and severity of known or potential adverse health effects in a given population based on hazard identification, hazard characterization and exposure assessment' (FAO/WHO, 2008). For consumers, the RCR is the quotient of the actual exposure divided by the tolerable daily intake. For workers inhaling BPA, for example, the RCR is the quotient of the actual exposure divided by the occupational exposure limit.

[2] Organisms living in sediment.

General recommendations:

It is recommended that all organizations importing, producing, transporting, storing, formulating into a preparation or otherwise processing, using and disposing of or recovering BPA or BPA-containing materials take into account the results of the present risk evaluation.

Because recent data suggests that BPA could have adverse effects on the development of food allergies and on resistance to infection at lower doses than anticipated in the current European standards, *it is recommended that the Dutch Government file a request to EFSA to revisit the TDI, to the European Commission to ask SCOEL to revisit the OEL, and to the ECHA to re-open the evaluation of the health hazards of BPA and the consequent exposure limit values, taking into account the most recent data on the effects of BPA on the immune system.*

Any reconsideration of the exposure limit values at EU level may take several years to complete. *It is therefore recommended that the responsible parties evaluate possible measures to reduce exposure to BPA among consumers, patients and workers and emissions to the environment in those exposure scenarios where risks are identified or may reasonably be expected on the basis of the initial assessments of recently published data on the immune system effects of BPA.*

Risk reduction may be achieved through the substitution of alternatives for BPA. The RIVM lists a number of possible alternatives but signals that, for most of these, toxicological characterization is lacking. More information on this is needed before a replacement of BPA can be successful. The RIVM concludes that further socio-economic analysis or cost–benefit assessment is needed for each alternative substance. *It is recommended not to substitute bisphenolic structural analogues for BPA, unless it has been demonstrated that the alternative is toxicologically preferable to BPA. It is further recommended to explore non-chemical substitutes and to evaluate design optimization techniques that may result in exposure reduction.*

In addition, it is recommended that the advice for managing the risks set out in this report be considered by the European Commission, the Member States and all market players.

Reduction of environmental risks:

With regard to environmental risks and possible exposure, further insight into the dominant sources of BPA in the environment is expected early 2016. *It is recommended taking into account the upcoming information on sources of BPA emissions and considering appropriate risk management measures to reduce the BPA concentration in sediment. These should include an evaluation of the need for emissions permits under the Industrial Emissions Directive and enforcing record keeping under the Waste Framework Directive.*

Based on the inventory of emission sources, further risk management options will be evaluated in the substance evaluation that is being performed by Germany under the REACH Regulation. *It is recommended that the Dutch Government evaluate the measures for reducing emissions of BPA in order to determine which is/are the most effective.*

Reduction of human health risks:

The RIVM identifies an occupational health risk resulting from the inhalation of BPA for workers involved in the manufacture of BPA for product sampling and bag filling and possibly for workers involved in the manufacture of epoxy resins; and a risk from dermal contact with BPA for workers involved in all industrial processes where dermal contact to free BPA may occur, and for workers handling thermal paper (e.g. the handling of cash receipts). *It is therefore recommended that the responsible parties evaluate potential substitutes in order to reduce exposure among workers at national level.*

Because the risk assessment for workers by the EU RAR (EC, 2008; UK, 2008) is based on data from before 2008, the RIVM concludes that it is well possible that changes in work practices and exposure models since that date have led to different exposure scenarios and hence different risk profiles. *It is therefore recommended that the responsible parties assess actual exposures resulting from industrial and professional use for the purpose of devising the most appropriate risk management measures.*

With respect to consumers and patients, the RIVM summarizes that, on the basis of the central (geometric mean) estimates of aggregated exposure (via food and non-food sources), there is a low health concern for the most exposed groups of infants, children and adolescents and, based on the current t-TDI, there is a risk for neonates in intensive care units, infants undergoing prolonged medical procedures and dialysis patients.

The RIVM further concludes that the new data regarding the effects of BPA exposure on the immune system add to the health concern for consumers and the possible risks identified for patients and workers. Relevant European legislation that could substantially contribute to reducing the exposure of these groups to BPA includes the Directives on Industrial Emissions, Waste, Toy Safety, Drinking Water, Medical Devices, Chemical Agents, Carcinogens and Mutagens, Young People at Work and Pregnant and Breastfeeding at Work, and the regulations on Cosmetics and on Plastic Materials in Contact with Food, the EU Ecolabel and the different aspects of REACH. *Early consideration of the options to reduce BPA exposure through each of these regulations is recommended. This includes the possible lowering of the specific migration limits (SMLs) in the Plastic Materials in Contact with Food Regulation and the Toy Safety Directive.* Specifically for The Netherlands, a revision of the SML at EU level would automatically be implemented in the Dutch National legislation on non-plastic food contact materials (Decree on Packaging and Utensils, Warenwet besluit).

The European Commission is already developing initiatives in this direction for food contact materials (FCM)[3], and proposals to amend the SML for BPA in FCM and toys based on the t-TDI (EFSA, 2015) are under discussion at EU level in the responsible working groups.

At national level, the maximum permitted concentration of BPA specified by the Dutch Drinking Water Directive should be revisited.

With regard to medical devices, this Directive is currently under revision and the regulatory consequences of this revision regarding the use of BPA in medical devices are yet unknown. When assessing risk management measures for patients, it is of importance to also take account of the health benefit of using medical devices containing BPA.

None of these initiatives will lead to an exposure reduction in the short term. *It is therefore recommended additionally that national governments evaluate measures at national level to promote substitution, reduce exposure among at least the most sensitive groups (neonates, young children, pregnant and breastfeeding women) and provide information to consumers and patients.*

[3] BPA Roadmap (European Commission, 11/2015) Proposal for a new measure on bisphenol A (BPA) in food contact materials: http://ec.europa.eu/smart-regulation/roadmaps/docs/2015_sante_534_bpa_measure_en.pdf

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Abbreviations

BPA	Bisphenol A
BMD	benchmark dose
BMDL	benchmark dose level
CMD	Carcinogens and Mutagens Directive
CAD	Chemical Agents Directive
CLP	(European regulation on) Classification, Labelling and Packaging
CMR	carcinogenic, mutagenic or reprotoxic
DNEL	derived no effect level
ECHA	European Chemicals Agency
EFSA	European Food Safety Authority
EU RAR	EU Risk Assessment Report
FCM	food contact materials
HED	human equivalent dose
HEDF	human equivalent dose factor
ICU	intensive care unit
LOAEL	lowest adverse effect level
MOS	margin of safety
MSCA	Member State competent authority
MTC	maximum tolerable concentration
NOAEL	no observed adverse effect level
OEL	occupational exposure limit
OELV	occupational exposure limit value
OSH	Occupational Safety and Health
PEC	predicted environmental concentration
PNEC	predicted no effect concentration
PPE	personal protective equipment
RAC	Risk Assessment Committee (of the ECHA
REACH	Registration, Evaluation, Authorisation & Restriction of Chemicals
RCR	risk characterization ratio
RWC	reasonable worst case
SCENIHR	Scientific Committee on Emerging and Newly Identified Health Risks
SCOEL	Scientific Committee on Occupational Exposure Limits
SEAC	Socio-Economic Assessment Committee
SEv	substance evaluation
SML	specific migration limit
TDI	tolerable daily intake
t-TDI	temporary tolerable daily intake
TWA	time-weighted average
WWTP	waste water treatment plant

1 Introduction

In 2014, the RIVM published the report *Bisphenol A, Part 1* (RIVM, 2014), summarizing the state of knowledge at 20 March 2014 regarding the adverse effects of BPA exposure on human health and the environment, remaining uncertainties, scientific initiatives for further clarification of the identified uncertainties, and the regulatory perspectives to the risk management of BPA. This report, *Bisphenol A, Part 2*, appraises the conclusions from the available risk assessments summarized in Part 1 and builds on the latter's findings with the aim of providing support for the Dutch Government's policy considerations.

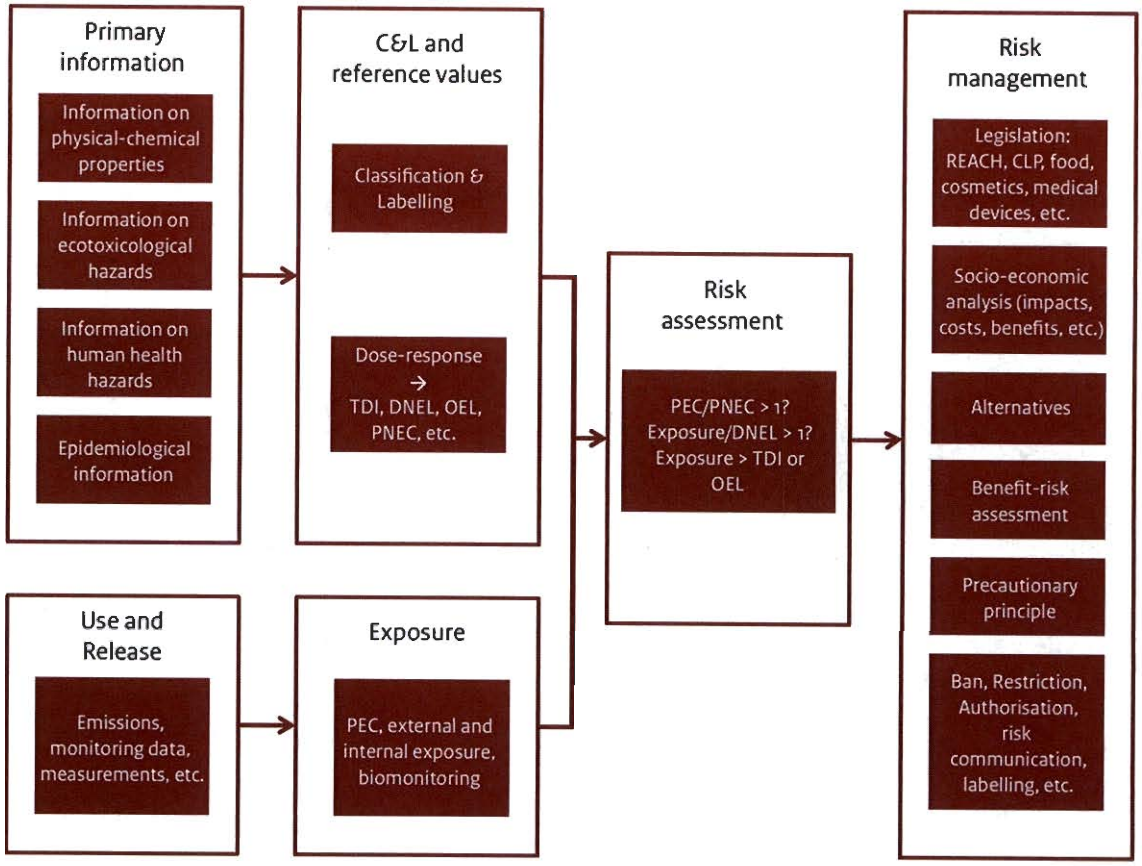
For *Part 2*, the state of knowledge described in *Part 1* has been updated, taking into account developments in ongoing regulatory initiatives and the findings and conclusions of:

(i) the scientific opinion of the European Food Safety Authority (EFSA) on consumer exposure to BPA (EFSA, 2015);
(ii) the opinion of the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) on the risks of BPA use in medical devices and patient exposure (SCENIHR, 2015);
(iii) the registration dossiers on BPA under REACH (ECHA website);
(iv) the opinions of the EHCA's Risk Assessment Committee (RAC) and the Socio-Economic Assessment Committee (SEAC) (2015) on the Annex XV dossier under REACH proposing the restriction of BPA use in thermal paper;
(v) the recommendation on occupational exposure limits by the Scientific Committee on Occupational Exposure Limits (SCOEL, 2014);
(vi) two publications describing pre- and perinatal effects of BPA on the immune system (Menard et al., 2014a, 2014b).

The scientific studies underlying the reports listed above have not been re-evaluated in this report, because they were extensively reviewed by the international risk assessment bodies indicated above.

However, the two publications by Menard et al. (2014a, 2014b) describing pre- and peri-natal effects of BPA on the immune system were published after the EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids endorsed its hazard assessment in December 2013, with the result that Menard et al.'s findings were not included in the health hazard assessment by EFSA (2015). These findings were judged by the RIVM to be of high importance for the risk assessment of BPA, and The Netherlands has submitted them as part of the public consultation process on the Annex XV restriction proposal to limit the concentration of BPA in thermal paper, and they have been evaluated by the RAC (2015). In addition, a meeting was held with experts to evaluate the Menard et al. studies. The results of that meeting are also included in this report.

Figure 1 From primary substance characteristics to risk assessment and risk management – a schematic view of key elements in the process of identifying the most appropriate risk management options.



1.1 This report

The assessment of BPA in this report is performed along the lines illustrated in Figure 1: assessing environmental and human health hazards and exposures to arrive at a risk assessment, in relation to which risk management options are discussed. The main part of the report consists of a management summary (Chapter 2) and a discussion of possible risk management options and consequent recommendations (Chapter 3). The management summary brings together the main findings, conclusions and recommendations for risk management. The underlying assessments of the environmental and human health risks of BPA are detailed in Appendixes I and II, respectively. Appendix III gives an overview of the current knowledge on possible alternatives to BPA for use in PC plastics, epoxy resins and thermal paper. Appendix IV provides details of the possible downstream consequences of BPA when it will be added to Annex VI of the CLP Regulation with a harmonized classification as Repro Cat.1B.

2 Management summary

2.1 Background on human health and environmental risk assessment

2.1.1 Production and use

Bisphenol A (BPA) is widely used as a feedstock in the manufacture of polycarbonate (PC) plastics and epoxy resins, which are used in nearly every industry. The EU Risk Assessment Report (EU RAR) (EC, 2008) indicates that BPA is predominantly used as a monomer in PC plastics (~75% of its production volume; ~1.1 Mt/year) and epoxy resins (~17% of its production volume; ~0.2 Mt/year). In addition to these main uses, BPA is used in the synthesis of flame retardants, as a colour-developing agent and as a component of polysulfone and polyacrylate resins.

PC plastics can be found in construction materials, electrical/electronic devices, automotive parts, bottles/packaging and medical and healthcare devices. Epoxy resins are used in electrical/electronic devices and in various coatings (e.g. marine coatings, protective coatings, powder coatings, can and coil coatings).

2.1.2 Human health hazard and exposure

BPA is a liver and kidney toxicant (after prolonged exposure) and is classified in the EU as a reproduction toxicant. Scientific studies have furthermore associated BPA with adverse immune system effects, obesity, ADHD, diabetes and prostate cancer; these effects may be related to its possible interaction with the oestrogen receptor.

In 2014, EFSA published a draft hazard assessment of BPA, in which a lowering of the tolerable daily intake (TDI) for consumers was proposed. Following a public consultation on this draft opinion, EFSA published its final opinion on the hazard and risk assessment for consumers in the spring of 2015. EFSA (2015) derived a temporary-TDI (t-TDI) of 4 µg/kg bw/day[4] and concluded, on the basis of this t-TDI, that there was no health concern for BPA at the estimated levels of dietary exposure to BPA. In addition, EFSA concluded that the central (geometric mean) estimates of aggregated exposure to BPA from dietary sources and non-dietary sources (dust, toys, cosmetics and thermal paper) among the most exposed groups, which include infants, children and adolescents adopting "high exposure" scenarios

[4] Microgram BPA per kilogram of body weight per day

were below the t-TDI of 4 µg/kg bw/day. For these highest exposed groups, the upper bound high exposure estimates exceeded the t-TDI and the lower bound estimates were considerably lower than the t-TDI. Considering the uncertainties underlying the exposure assessment, EFSA (2015) therefore indicated that the health concern for these groups was low. A more detailed overview of exposures and margins of safety (MOS) can be found in Appendix II, Table 9.

On the basis of this t-TDI, SCENIHR (2015) concluded that a risk of adverse effects from BPA exposure may exist for neonates in intensive care units, young children undergoing prolonged medical treatment and dialysis patients when the BPA is directly available for systemic exposure after non-oral exposure routes (see Appendix II, Table 9 for a detailed overview of exposure via medical devices and MOS values). Although the benefits to be derived from the use of these medical devices must also be considered, SCENIHR recommended that, where practicable, medical devices that do not leach BPA should be used. For the other groups of patients assessed, SCENIHR identified no risk of exposure via medical devices.

In addition, in 2014, the RAC published its opinion on the classification and labelling of BPA under the CLP Regulation, concluding that, on the basis of the available information, BPA met the criteria for classification as toxic for reproduction category 1B (Repro Cat.1B). In 2016, it is expected that this classification will be included in Annex VI of the CLP Regulation.

In 2015, the RAC published its opinion on the human health hazards presented by BPA in the context of a restriction proposal for the use of BPA in thermal paper under REACH, concluding a dermal DNEL for consumers and workers of 0.1 µg/kg bw/day and 0.2 µg/kg bw/day, respectively. The proposed restriction involved the setting of a maximum concentration of 0.02 w/w% BPA in thermal paper, focusing in the risk assessment on consumers and cashiers handling thermal paper receipts. For the risk assessment, the RAC took into account developmental effects on the mammary gland, and effects on the reproductive, immune, metabolic and neurobehavioural systems, in line with the hazard assessment by EFSA (2015). For consumers, the RAC concluded that the risks from BPA exposure via thermal paper receipts, where these are the only source of exposure, are adequately controlled. For cashiers, the RAC concluded that the risks of exposure via thermal paper receipts are not adequately controlled. These risks include potentially severe effects on the unborn children of pregnant female workers.

In the summer of 2014, SCOEL published its recommendation to lower the occupational exposure limit (OEL) for inhalation from 10 mg/m³ to 2 mg/m³. For workers, the EU RAR (EU, 2008) and the Annex XV Transition Report (UK, 2008) had already identified a risk from certain industrial processes involving the handling of free BPA as a substance (the manufacture of BPA for the processes product sampling and bag-filling, and the manufacture of BPA-based epoxy resins). Using this new OEL of 2 mg/m³ and the EU RAR and Annex XV Transition Report data, risks from BPA inhalation are identified only for workers in the manufacture of BPA (i.e. product sampling and bag filling). In addition to this and based on the dermal exposure data from EU (2008) and UK (2008) and the dermal DNEL derived by the RAC (2015), a risk is identified for workers in all industrial processes that involve the handling of free BPA and for workers involved in the handling of thermal paper cash receipts (see Appendix II, Table 8 and Table 10 for more details). As noted in RIVM (2014), the exposure scenarios described in EC (2008) and UK (2008) may no longer be representative of the current work situation and, in addition, occupational exposure models have been updated. Consequently, the risk characterization ratios (RCRs), as presented in Table 10, may need revisiting.

There may also be health concerns for workers other than cashiers that handle thermal paper. To the best of our knowledge, these have not been assessed quantitatively. The extent of exposure to BPA from thermal paper depends on various factors, including the frequency and type of contact, the concentration of BPA in the thermal paper and the paper quality and design.

2.1.3 Environmental health hazard and exposure

BPA is found in all surface water and sediment. Concentrations of BPA vary considerably depending on the location and sampling period, among other factors.

On the basis of the environmental concentrations of BPA published up to 2014 and the predicted no effect concentrations (PNECs) derived in EC (2008) and UK (2008), risk was identified for benthic organisms in fresh and marine waters sediment, but not for

pelagic organisms (RIVM, 2014). Appendix I and Table 4 and Table 5 give an overview of the relevant environmental concentrations and RCRs.

In addition, EC (2008) and UK (2008) concluded that BPA shows endocrine disrupting effects in environmental organisms, leading to adverse effects on reproduction and the development of offspring. These effects were judged not invalidate the current PNECs of BPA for the different environmental compartments.

2.2 Further assessment of human and environmental health risks

2.2.1 Human health hazards

In 2014, two studies were published on possible adverse effects of BPA on the immune system: with respect to the development of food allergies and resistance to infection (Menard et al., 2014a, 2014b). The RIVM judged these studies to be critical in terms of human health hazard assessment. The Netherlands therefore submitted them to the ECHA during the public consultation of the proposal for restriction of the use of BPA in thermal paper under REACH. The RAC took note of these studies but concluded that, in isolation, they did not enable quantification of a dose–response relationship. The RAC also concluded, however, that the studies did add to the overall likelihood of BPA exposure having adverse effects on the development of the immune system, thereby reinforcing the conclusions of EFSA (2015). In their opinion, the RAC was restricted to the information submitted to the evaluation process (either via the Annex XV restriction proposal or through public consultation). The two Menard studies were the only two studies on immune system effects to be submitted and the endpoint immunotoxicity was not included in the Annex XV proposal. Consequently, the RAC was not in a position to fully evaluate these studies against the background of other studies on immune system effects caused by BPA exposure.

In September 2015, at the request of the Dutch Government, the RIVM organized a meeting with experts from the US Environmental Protection Agency, the US National Institute of Health, the University of Rochester Medical Center, the French National Institute for Agricultural Research (INRA) Toulouse and the Norwegian Institute of Public Health, two former EFSA CEF[5] panel members and representatives of the RIVM to evaluate the robustness of the Menard et al. (2014a, 2014b) studies and their possible impact on human health hazard assessment in the context of a select number of other studies of immune system effects assessed by EFSA (2015). The method and study design were judged by these experts to be robust and the results to be appropriate for use in hazard assessment. Furthermore, it was concluded that there was strong evidence of the development of food allergies and changes in resistance to infection in rats at the lowest adverse effect level (LOAEL) of 5 µg/kg bw/day (see Appendix II, Section 5.1 for more details on the evaluation of studies). There was no consensus amongst the experts on the relevance of the finding in terms of adverse effects at a dose of 0.5 µg/kg bw/day.

2.2.1.1 Impact on human health risk assessment

As a result of discussion with external experts at the above-mentioned meeting on the immune system effects of BPA exposure, the RIVM considers that the studies by Menard et al. (2014a, 2014b) in combination with a number of other studies, e.g. Bauer et al. (2012), warrant reconsideration of the present evaluation of the human health hazard presented by BPA. Evaluating the impact of the observed effects on the hazard assessments as recently updated by EFSA (for consumers), by SCOEL (for workers) and by the RAC (for consumers and workers) would requires an in-depth analysis of the new data by Menard et al. (2014a, 2014b), which was beyond the scope of the discussion undertaken at the meeting. Appendix II, Sections 5.1.1 and 5.2.3, provides more information on the possible impact of the new immunotoxicity data by Menard et al. (2014a, 2014b) on the magnitude of the TDI, the dermal DNEL and the OEL, and what is needed to establish this impact quantitatively. In short, to assess the impact of the animal data, the LOAEL should be converted to an HED. Depending on the standard in question, this may involve extensive (exposure) modelling, route-to-route extrapolation of doses and effects and many assumptions regarding toxicokinetics and sensitive windows of exposure. Based on an initial assessment of this new data by Menard et al., the RIVM concludes that this data may lead to a lowering of the TDI and dermal DNEL standards by at least one order of magnitude (more than a factor of 10); for the OEL, the revision may be less.

[5] The Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF)

The above considerations notwithstanding, the RIVM summarizes the following based on the current t-TDI, OEL and dermal DNEL (see conclusions by EFSA, 2015, SCENIHR, 2015, and RAC, 2015, and Appendix II, Table 9):

- There is no health concern for consumers at the estimated levels of dietary exposure to BPA (EFSA, 2015).
- There is a low health concern related to the central estimates for aggregated exposure to BPA via dietary sources and non-dietary sources (dust, toys, cosmetics and thermal paper) for the highest exposed groups, which include infants, children and adolescents (EFSA, 2015).
- A risk of adverse effects from BPA exposure may exist for neonates in intensive care units, young children undergoing prolonged medical procedures and dialysis patients (SCENIHR, 2015).
- There is a risk via inhalation for workers involved in the manufacture of BPA (i.e. product sampling and bag filling) and possibly also for those involved in the manufacture of epoxy resins (EC, 2008; UK, 2008).
- There is a risk of skin sensitization for workers in all industrial processes involving dermal contact with BPA (EC, 2008; UK, 2008).
- There is a risk for the fetuses of pregnant workers in nearly all industrial processes involving dermal contact to free BPA and for handling thermal paper cash receipts (EC, 2008; UK, 2008; RAC, 2015).

Adverse effects on the development of food allergies and resistance to infection have been observed in animals tested with a BPA concentration close to the current t-TDI. The RIVM signals that this finding raises a concern that the current t-TDI, dermal DNEL and OEL may not be sufficiently protective. This concern warrants reconsideration of these standards and adds to the health concern for consumers, patients and workers, who may be exposed to risks not yet identified on basis of the current standards. Consequently, the RIVM signals that the present RCRs for consumers, patients and workers may need revisiting.

2.2.2 Environmental exposure

Since the publication of RIVM (2014), no new data has emerged regarding possible adverse effects of BPA exposure on environmental organisms.

In relation to environmental emissions, further in-depth analysis of the environmental monitoring data included in RIVM (2014) indicates that for 25% of the sampling sites in Europe (n=347), measured BPA concentrations in freshwater sediment exceed the PNEC for sediment. This strengthens the finding presented in RIVM (2014) that there may be a risk for benthic organisms in a significant number of locations in Europe.[6]

Regarding possible sources of BPA emissions into the environment, new data on emissions to surface water and waste water treatment plants (WWTPs) was published in 2014. This new data suggests that industrial processes using BPA are an important source of BPA emissions to water and WWTPs. For WWTPs, another important source was predicted to be the (indoor) use of PC plastic products. For surface water, BPA stems principally from leaching from polyvinyl chloride PVC products, followed by the outdoor use of PC plastics and of epoxy resins. A more detailed overview of modelled emissions is provided in Appendix I, Table 3. This pattern of possible sources closely matches the environmental monitoring data for BPA from North America and Europe, which finds higher concentrations in water and sediment in highly urbanized and industrial areas. More clarity on the actual sources of the observed emissions into the environment is expected in the first half of 2016, following the substance evaluation under REACH.

2.3 Conclusions regarding environmental and human health risks

2.3.1 Human health risks

The recently published data on developmental immune system effects suggests that BPA exposure could have adverse effects on the development of food allergies and on resistance to infection at lower doses than anticipated by the current European standards. The RIVM concludes that this new data adds to the health concerns for consumers and the risks identified for patients (EFSA (2015), SCENIHR (2015)) and workers (EC (2008), UK (2008) and RAC (2015)) and warrants reconsideration of the t-TDI, the dermal DNEL and the OEL. Neonates, young children and pregnant or breastfeeding women are particularly sensitive to the immunological effects of BPA exposure.

[6] The PNECs for BPA are being discussed in the context of the Water Framework Directive and the ongoing revision of the list of priority substances.

The RIVM concludes that the present RCRs for consumers, patients and workers may require revision in the light of the new information on the immunological effects of BPA exposure.

2.3.2 Environmental health risks

BPA is present in all surface water and sediment. Concentrations of BPA vary considerably depending on the location and sampling period, among other factors. Emissions of BPA to the environment result from its manufacture, its use in a broad range of products and the recycling and disposal of these products. More clarity on the actual sources of the observed emissions into the environment is expected in the first half of 2016, following the substance evaluation under REACH.

The currently available information suggests higher environmental BPA concentrations are often found in highly urbanized or industrialized areas, but it does not provide a better insight into the sources responsible other than hinting at the importance of leaching and waste streams to the emissions modelled.

The RIVM concludes that the current environmental monitoring data does not show a risk for fresh and marine water organisms but does show a risk for organisms living in fresh or marine water sediment in Europe at approximately 25% of the sampling sites in Europe.[7]

2.4 Recommendations for risk management measures

On the basis of the information on the health hazards of exposure to BPA presented in Sections 2.1 to 2.3 (and Appendix I and II), *it is recommended that the Dutch Government file a request to EFSA to revisit the TDI, to the European Commission to ask SCOEL to revisit the OEL, and to the ECHA to re-open the evaluation of the health hazards of BPA exposure and the consequent exposure limit values, taking into account the most recent data on the effects of BPA exposure on the immune system.*

The RIVM signals that any reconsideration of the t-TDI, OEL and DNELs at EU level may take several years to complete. The RIVM also signals that exposure scenarios for which no risk is presently identified may be found to involve a risk when the new insights into the adverse effects on food tolerance and resistance to infection are taken into account in the human health risk assessment. *It is therefore recommended that the responsible parties evaluate measures for reducing exposure to BPA among consumers, patients and workers and emissions to the environment in those exposure scenarios where risks are identified or may reasonably be expected on the basis of the initial assessment of the recently published immune system effects of BPA exposure.*

As illustrated in Figure 1, risk reduction may be achieved by either reducing or removing the hazard (for example, by removing the source through substitution) or by reducing or preventing exposure to BPA.

2.4.1 Substitution of BPA

Appendix III outlines the current knowledge on possible alternatives to BPA for use in PC plastics and epoxy resins, as a colour developer in thermal paper, and in materials used in medical devices. For each of these uses, alternatives are described (drop-in, material or non-chemical substitutes), but for most, toxicological characterization is lacking. More information on this is needed before a replacement of BPA can be successful. Moreover, the BPA analogues seem unsuitable on account of possibly having comparable hazard profiles to BPA.

The RIVM concludes that a further socio-economic study or cost–benefit analysis is needed when considering substitution for each alternative. In line with the advice of the Health Council of The Netherlands (2014), *it is recommended that no bisphenolic structural analogue be used as a substitute unless it has been demonstrated that the alternative is toxicologically preferable to BPA. It is further recommended to explore possibilities for bio-based alternatives and non-chemical substitution. For those applications where alternatives (chemical or non-chemical) are not identifiable, it is suggested to evaluate possibilities for design optimization that may result in exposure reduction.*

2.4.2 Reduction of exposure to BPA

Regarding measures to reduce exposure, various initiatives are already ongoing at EU level that may lead to exposure reduction in the coming years.

[7] Depending on the outcome of the discussion regarding the PNEC for BPA that is ongoing in the context of the Water Framework Directive and the revision of the list of priority substances, the RCR for BPA in water and sediment may have to be revisited.

These should be taken into account, and where possible should be built upon, when considering further risk management measures. Figure 2 provides an overview of ongoing initiatives that may lead to further regulation of the use of and exposure to BPA.

Furthermore, in an evaluation of the most appropriate risk management options it should be noted that measures taken to reduce the risk or exposure of one target group, e.g. consumers, may affect the risk or exposure of other target groups, and vice versa.

2.4.2.1 Risk management measures for the environment

The RIVM summarizes that there are risks for benthic organisms, but no risks for pelagic organisms.

Figure 3, in Section 3.2.1, illustrates ongoing initiatives within regulatory frameworks that have a direct impact on environmental exposure. Table 2 presents a detailed summary of the possible effect of the different Directives and Regulations on environmental exposure. The need to identify BPA as a priority substance has been discussed in the context of the EU Water Framework Directive (2000/60/EC) and is being discussed again in the context of the current review of the list of priority substances (Directive 2013/39/EC). When BPA is identified as a priority substance, priority will be given at EU level to meet the environmental quality standard established under this Directive.

Classification of BPA as Repro Cat.1B will trigger a number of downstream measures that will result in a reduction of emissions to the environment. For some of the regulations, additional steps will have to be taken before a reduction of exposure can be achieved:

- Industrial Emissions Directive (2010/75/EC): permission of a maximum exposure limit at company level has to be set (or granted);
- Waste Framework Directive (2008/98/EC): record keeping, protective measures and labelling are needed for waste containing BPA.

The Industrial Emissions Directive is the main regulation to manage industrial emissions of hazardous chemicals to the environment. Industrial emissions are usually regulated at municipality level. Whether this will indeed significantly reduce environmental exposure is currently uncertain, as the contribution of industrial emissions to the total concentration of BPA in the environment is unknown. The modelling data shown in Table 3 (Appendix I, Section 4.2.1) suggests that industrial emissions are of a similar order of magnitude to emissions from article use.

At national level, the Dutch Government has implemented specific requirements to minimize emissions for substances of very high concern according to the Dutch ZZS (Zeer Zorgwekkende Stoffen) policy[8]. When BPA is taken up in Annex VI of CLP as Repro Cat.1B, the substance fulfils the criteria for being a ZZS and will be added to the ZZS-list of substances. Industry is then obliged to minimize emissions to the environment, possibly through substitution.

All measures that result in a reduced exposure of workers and consumers will have an impact on emissions to the environment. The results of the ongoing substance evaluation under REACH, which are expected by mid-2016, may provide further insights into the dominant sources of BPA emissions to the environment.

It is recommended taking into account upcoming information on sources of BPA emissions while considering risk management measures to reduce the BPA concentration in sediment. This includes the evaluation of the need for setting (more stringent) emission permits under the Industrial Emissions Directive and to enforce record keeping under the Waste Framework Directive.

Depending on the results of the substance evaluation under REACH and whether BPA is classified as Repro Cat.1B, EU Member States may consider further risk management measures under REACH. A Risk Management Option Analysis is currently being drafted by Germany, focusing on a concern for the environment that may result in a proposal for Candidate listing and Authorization based on article 57f for endocrine disruption. Alternatively, as a Repro Cat.1B substance, BPA may meet the criteria for Authorization according to article 57c of REACH and a Member State may consider developing a proposal for Authorization with a concern for human health.

It is recommended that the Dutch Government evaluate measures for reducing emissions of BPA and identify the most effective measure(s).

[8] http://www.rivm.nl/rvs/Stoffenlijsten/Zeer_Zorgwekkende_Stoffen

2.4.2.2 Risk management measures for workers

The RIVM summarizes:
- a risk via inhalation for workers involved in the manufacture of BPA (i.e. product sampling and bag filling) and possibly also those involved in the manufacture of epoxy resins;
- a skin sensitization risk for workers in all industrial processes involving dermal contact with BPA;
- a risk for the fetuses of pregnant workers in nearly all industrial processes involving dermal contact with free BPA and for cashiers handling thermal paper cash receipts.[9]

The RIVM concludes that:
- RCRs for workers be recalculated before risk management measures are implemented;
- all exposure scenarios be updated (since current handling and risk reduction measures may differ from those in use when the EU RAR (EC, 2008) was drafted).

It should also be noted that a revision of the OEL and dermal DNEL to include immune system effects will have an impact on the severity of identified occupational health risks and may have an impact on the current conclusions with regard to "no risks of workers" in other exposure scenarios.

Figure 4, in Section 3.2.2, illustrates ongoing regulatory initiatives that have a direct impact on occupational exposure. Table 2 presents a detailed summary of the effect of the different Directives and Regulations on occupational exposure.

Regulations that directly affect occupational exposure and risk are the Chemical Agents Directive, REACH (the restriction proposal for the use of BPA in thermal paper, the withdrawal of the intended use of BPA in thermal paper from the registrations and the German Risk Management Option Analysis), the Carcinogens and Mutagens Directive, the Young People at Work Directive, and the Directive on Pregnant Workers and Workers who Have Recently Given Birth or are Breastfeeding (henceforth Directive on Pregnant Workers).

The Young People at Work Directive and the Directive on Pregnant Workers aim to protect the most vulnerable susceptible groups, i.e. young, pregnant or breastfeeding workers. The ongoing initiatives to restrict the use of BPA in thermal paper (via the registration dossier and via the restriction process) will have an impact on the exposure of workers, but will target only a limited fraction of the workers at risk.

If the harmonized classification as Repro Cat.1B is added to Annex VI of the CLP Regulation, this may have some impact on the exposure of young people at work and on pregnant and breastfeeding women at EU level. At Dutch national level, however, as a consequence of its present harmonized H-phrase H361f, the handling of BPA or exposure to BPA by young people at work, pregnant workers and workers who have recently given birth or are breastfeeding is already forbidden.

It should be noted that the current risk assessment for workers is based on data from before 2008, it is well possible that work practices have changed since that date, leading to different exposure scenarios and hence different risk profiles. *It is therefore recommended that the responsible parties assess actual exposures in industrial and professional use in order to determine the most appropriate risk management measures.*

2.4.2.3 Risk management measures for consumers and patients

The possible risks for consumers (EFSA, 2015) and patients (SCENIHR, 2015) are summarized below:
- There is no health concern for consumers at the estimated levels of dietary exposure to BPA.
- There is a low health concern related to the central estimates (geometric mean) for aggregated exposure to BPA from dietary sources and non-dietary sources (dust, toys, cosmetics and thermal paper) for the highest exposed groups, which includes infants, children and adolescents (EFSA, 2015);
- There may be a risk of adverse effects from BPA exposure for neonates in intensive care units, young children undergoing prolonged medical procedures and dialysis patients.
- There are no risks in all other patient exposure scenarios.

The RIVM concludes that revision of the t-TDI to include immune system effects will have an impact on the severity of identified health risks and may have an impact on the current conclusions with regard to no risks of consumers and patients in other exposure scenarios.

[9] There may also be occupational health risks due to dermal contact with BPA in other professions where workers handle thermal paper on a daily basis. To the best of our knowledge, a quantitative risk assessment is performed only for cashiers and not for workers handling thermal paper in other professions.

Figure 5, in Section 3.2.3, illustrates ongoing regulatory initiatives that have a direct impact on consumer and patient exposure. Table 2 presents a detailed summary of the effect of the different Directives and Regulations on consumer and patient exposure. Regulations that directly affect consumer and patient exposure and risk are the Plastic Materials in Contact with Food Regulation, the Cosmetics Regulation, the Medical Devices Regulation (in preparation), the Ecolabel Regulation, the Drinking Water Directive and the Toy Safety Directive.

For consumers and patients, the specific regulations will be affected only to a limited extent by the classification of BPA as Repro Cat.1B because BPA is currently on the 'positive list' of substances allowed in food contact materials (FCM). For some regulations, additional steps will have to be taken before a reduction of exposure can be achieved:

- Plastic Materials in Contact with Food Regulation (10/2011/EC) and Toy Safety Directive (2009/48/EC): derivation of a safe migration limit.
- Drinking Water Directive (98/83/EC): derivation of a maximum tolerable concentration (MTC) of BPA in drinking water.

These regulations are closely affected by the t-TDI and by the SML as defined in for FCM. The adjustment of the SML for BPA in FCM based on the current t-TDI may therefore be a first step towards a reduction in BPA exposure to food and non-food sources. A proposal to lower the SML for BPA in FCM based on the t-TDI (EFSA, 2015) is currently under discussion at EU level in the Working Group on Food Contact Materials of the Toxicological Safety Section of the Standing Committee on Plants, Animals, Food and Feed (SC-PAFF) and updating the SML for BPA used in toys is under discussion in the Expert Group on Toy Safety. In parallel to this, the indicative Roadmap, published in November 2015 by the European Commission[10], proposes further development of regulatory measures on BPA in FCM and includes a draft plan to implement the findings by EFSA (2015).

The Medical Devices Directive is currently under revision and the possible regulatory consequences of this revision for BPA are still unknown. However, when assessing the possibility for further risk management measures for patients, for example through exposure reduction, special attention should also be given to the benefit of using medical devices containing BPA.

With respect to cosmetics, BPA has been found in various products, as described by EFSA (2015). However, since the use of BPA in the formulation of cosmetics is not allowed, there are limited options to reduce the exposure from this source via the Cosmetics Regulation (1223/2009/EC).

It is recommended that the Dutch authorities invest in initiatives to reduce exposure to BPA in each of the regulations listed in Table 2. At EU level, initiatives to reduce the SMLs should be taken within the Plastic Materials in Contact with Food Regulation[11] and the Toy Safety Directive[12]. Specifically for The Netherlands, a revision of the SMLs for FCM at EU level will automatically be implemented in the Dutch National legislation on non-plastic FCM (Decree on Packaging and Utensils, Warenwet besluit).

At national level, it is recommended that the MTC of BPA specified by the Dutch Drinking Water Directive be revisited.

None of these initiatives will lead to a reduction in exposure in the short term. *It is therefore recommended that national governments additionally evaluate possible measures at national level to promote substitution and reduce the exposure of at least the most susceptible groups (neonates, young children, pregnant and breastfeeding women) and to provide information to consumers and patients.*

2.4.3 General recommendations

It is recommended that all organisations importing, producing, transporting, storing, formulating into a preparation or otherwise processing, using and disposing of or recovering BPA or BPA-containing materials take into account the results of the current risk evaluation.

In addition, it is recommended that the advice for managing the risks set out in this report be considered by the European Commission, the Member States and all market players.

[10] BPA Roadmap (European Commission, 11/2015) Proposal for a new measure on bisphenol A (BPA) in food contact materials: http://ec.europa.eu/smart-regulation/roadmaps/docs/2015_sante_534_bpa_measure_en.pdf

[11] Initiative ongoing in the SC-PAFF

[12] Initiative ongoing in the Expert Group on Toy Safety

3 Recommendations for BPA risk management

This section describes in detail the options for a risk reduction strategy for BPA, based on the results of the risk evaluations for the environment (Appendix I) and for workers, consumers and patients (Appendix II).

Since RIVM (2014), major new insights into the risks of BPA exposure have been obtained from the advice of the RAC that BPA be classified as toxic for reproduction category 1B and the finding that BPA causes immune toxicological effects in animals at the level of t-TDI set by EFSA in early 2015. Section 3.1 highlights the actions that are recommended as a consequence of the new information on the immune system effects of BPA exposure.

With respect to the information summarized in RIVM (2014), there have been no new insights into BPA emissions to the environment or exposure by workers, consumers or patients.

The combination of new hazard information and existing exposure information has revealed new risks to the environment, workers, consumers and patients (see Table 1 for an overview of key conclusions regarding the environmental and human health issues related to BPA exposure). For each of these, an analysis of various risk management options is presented in Section 3.2: for the environment in Section 3.2.1, for workers in Section 3.2.2 and for consumers and patients in Section 3.2.3. Section 3.2.4 addresses possible risk management measures at national level. Substitution is an option for risk management in relation to the environment, workers, consumers and patients, and Section 3.3 assesses the available alternatives.

Table 1 Overview key conclusions.

Human health	Consumers/patients	Workers	Environment
RIVM *(This report)*: immune system effects of BPA at LOAEL = 5µg/kg bw/day. Review needed: - t-TDI - OEL - dermal DNEL	EFSA *(2015)*: low health concern upon aggregated exposure (food and non-food) for infants, children and adolescents based on the t-TDI. SCENIHR *(2015)*: Possible risks for prematurely born infants, for infants undergoing prolonged medical procedures and for dialysis patients. RIVM *(This report)*: Based on LOAEL immune system effects, risks identified for consumers and patients need revisiting. RAC *(2015; Restriction proposal)*: No risks from handling thermal paper.	EC *(RAR, 2008)* and RIVM *(This report)*: Risks from inhalation during manufacturing of BPA and possibly also of epoxy resins. Risks from dermal contact in all industrial processes (manufacture and use). RIVM *(2014)*: Update of exposure estimates needed. RAC *(2015; Restriction proposal)*: Risks from handling thermal paper by cashiers.	EC *(RAR, 2008)* and RIVM (This report): Risk for benthic organisms. No risk for pelagic organisms. ECHA *(Substance evaluation)*: Sources of BPA need investigation.

3.1 Primary actions following the new hazard information on BPA

As a consequence of the analysis by the RIVM of recent data on the immune system toxicity of BPA (Appendix II, Sections 5.1 and 5.2), it is recommended that the following actions be initiated as soon as possible:
- Revisiting of the t-TDI;
- Revisiting of the dermal DNEL;
- Revisiting of the OEL.

EFSA's current t-TDI (EFSA, 2015) may not sufficiently protect consumers against the adverse effects on the immune system of BPA exposure. Consequently, it is recommended that EFSA reviews its derivation of the t-TDI, thereby including the data on immune system toxicity by Menard et al. (2014a, 2014b).

Furthermore, it is recommended that the dermal DNEL derived by the RAC (2015) and the OEL derived by SCOEL (2014) be revisited.

Regarding the dermal DNEL, the RAC adopted a similar point of departure as EFSA (2015), concluding that the studies by Menard et al. (2014a, 2014b) support the likelihood of immune system effects. However, the RAC was not in a position to fully evaluate these studies against the background of other studies on the immunotoxicity effects of BPA exposure; hence the dermal DNEL should be reconsidered in the light of the discussion in Appendix II, Sections 5.1 and 5.2.

Regarding the OEL, SCOEL (2014) concluded that the OEL of 2mg/m³, based on respiratory tract irritation, is sufficient to cover the kidney and liver effects that were judged to be critical by EFSA (draft, 2014; MOS of 17–25). The EFSA assessment has since been updated to include uncertain effects that were considered likely (EFSA, 2015). Like the current t-TDI for consumers, the OEL may therefore not be sufficiently protective of workers and hence should be revisited (see Appendix II, Sections 5.1 and 5.2).

Meanwhile, Bureau REACH (RIVM) will inform the other Member State competent authorities (MSCAs) under REACH and the ECHA of the effects of BPA exposure on the immune system. With this information, the ECHA could take action to initiate a Compliance Check requesting the DNELs for workers and consumers to be updated. This information will also be disseminated by Bureau REACH in the Risk Management Expert Meeting, via commenting on ongoing risk management analyses. These requests and information exchange processes have been set in motion. However, whether this leads to the actual revision of the existing limit values is uncertain, and reconsideration of the limit values may take several years.

A reassessment of the t-TDI in the light of the new insights into immune system effects is a prerequisite for determining the safe use of BPA-containing consumer products and will trigger, among other things, a reassessment of SMLs for BPA in food packaging materials and a risk assessment of BPA in medical devices. Similarly, revision of the OEL and dermal DNEL would permit the determination of the

safe use of BPA and BPA-containing products by workers.

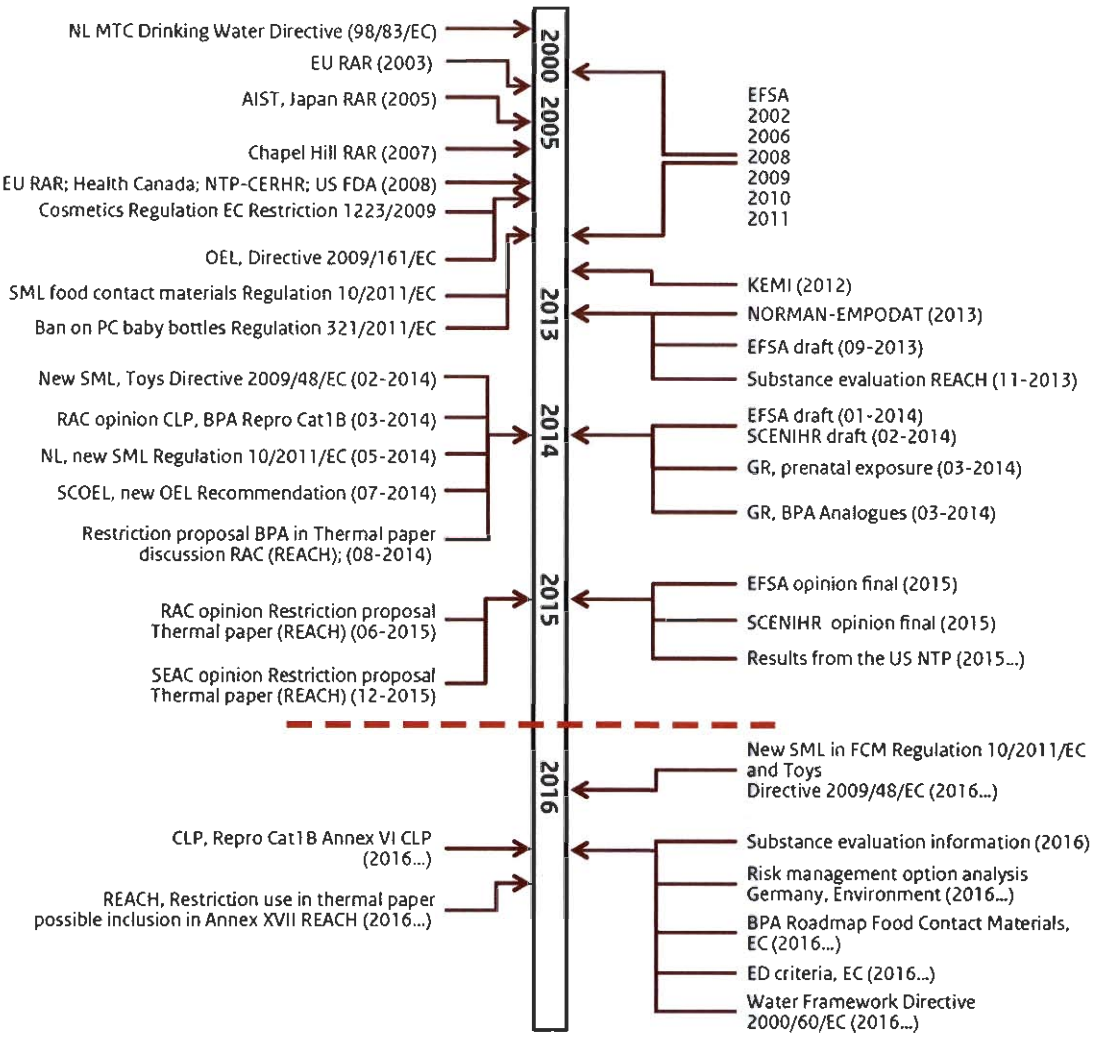
It is recommended that the Dutch Government file a request to EFSA to revisit the TDI, to the European Commission to ask SCOEL to revisit the OEL, and to the ECHA to re-open the evaluation of health hazards related to BPA exposure and the consequent exposure limit values, taking into account the most recent data on the effects of BPA exposure on the immune system. The bodies within The Netherlands responsible for initiating these requests are the Ministry of Welfare, Health and Sports or The Netherlands Food and Consumer Product Safety Authority (NVWA) for revision of the t-TDI, the Ministry of Social Affairs and Employment for revision of the OEL, and the Ministry of Infrastructure and the Environment and Bureau REACH for revision of the dermal DNEL.

The RIVM suggests that an evaluation of Menard et al. (2014a, 2014b) and various other studies on immune toxicological effects published after 2012 should be undertaken during the preparation of the requests to EFSA, SCOEL and the ECHA (see also Appendix II, Section 5.1).

3.2 Risk management options for BPA

Various risk management initiatives are already ongoing at EU level that may lead to exposure reduction or create an incentive for substitution in the coming years. An overview of these initiatives is given in Figure 2. These should be taken into account, and where possible built upon, when considering further risk management measures.

Figure 2 Chronological overview of regulatory measures and key risk assessments on BPA, implemented and under development, updated from RIVM (2014). The red dashed line indicates the state of play as presented in this report.



The RIVM identifies the following key developments that may directly or indirectly affect exposure to BPA and adverse effects in the environment and among workers, consumers and patients:

- the ongoing classification as reproductive toxicant category 1B;
- the finding that BPA causes immune toxicological effects in animals at the level of t-TDI set by EFSA in early 2015;
- the French proposal under REACH to restrict the use of BPA in thermal paper to below 0.2% w/w;
- the removal of the intended use of BPA in thermal paper by the REACH registrants;
- the indicative Roadmap of the EC Commission on further measures regarding BPA in FCM, including the implementation of the t-TDI derived by EFSA (2015) in the SML;
- the amendment of Directive (2009/48/EC) on toy safety and Regulation (10/2011/EC) on FCM to adjust the SML for BPA on the basis of the t-TDI derived by EFSA (2015).

Furthermore, regarding occupational exposure and emissions to the environment, actual exposure/emissions in 2015 may be different from actual exposure/emissions when the EU RAR (EC, 2008; UK, 2008) was drafted because of ongoing developments with respect to the handling of BPA and risk reduction measures. In addition, exposure estimation models may have evolved. Therefore, it is recommended that all exposure scenarios for the environment and for workers be updated (by the responsible parties) and that RCRs be recalculated before implementing risk management measures.

For consumers and patients, exposure scenarios have recently been re-evaluated (EFSA, 2015; SCENIHR, 2015). The exposure scenarios by EFSA and SCENIHR should be considered representative and sufficiently conservative to cover all of Europe. There are no reasons to suggest that the exposure of consumers and patients in The Netherlands will deviate from the European average modelled by EFSA and SCENIHR, respectively.

Section 7, in Appendix IV, provides a more in-depth explanation of the various relevant pieces of legislation as well as the legal consequences of the more stringent classification of BPA with regard to reproduction toxicity. Table 2 provides a detailed overview of the relevant pieces of legislation that explains the direct or indirect effects of BPA on the environment, workers, consumers and patients. Direct effects imply that the specific regulatory framework has a direct impact on the protection goal. For example, if emission permits for BPA under the Industrial Emissions Directive allow less BPA to be emitted, this would immediately affect emissions to the environment. Indirect effects imply that effects to a specific protection goal will be a result of regulating the emissions or exposure to another protection goal. An example of legislation with an indirect effect would be a regulation that decreased the BPA content migrating from FCM, which would eventually reduce emissions to the environment in the waste phase.

It is recommended that the Dutch authorities invest in reducing exposure to BPA via each of the regulations listed in Table 2.

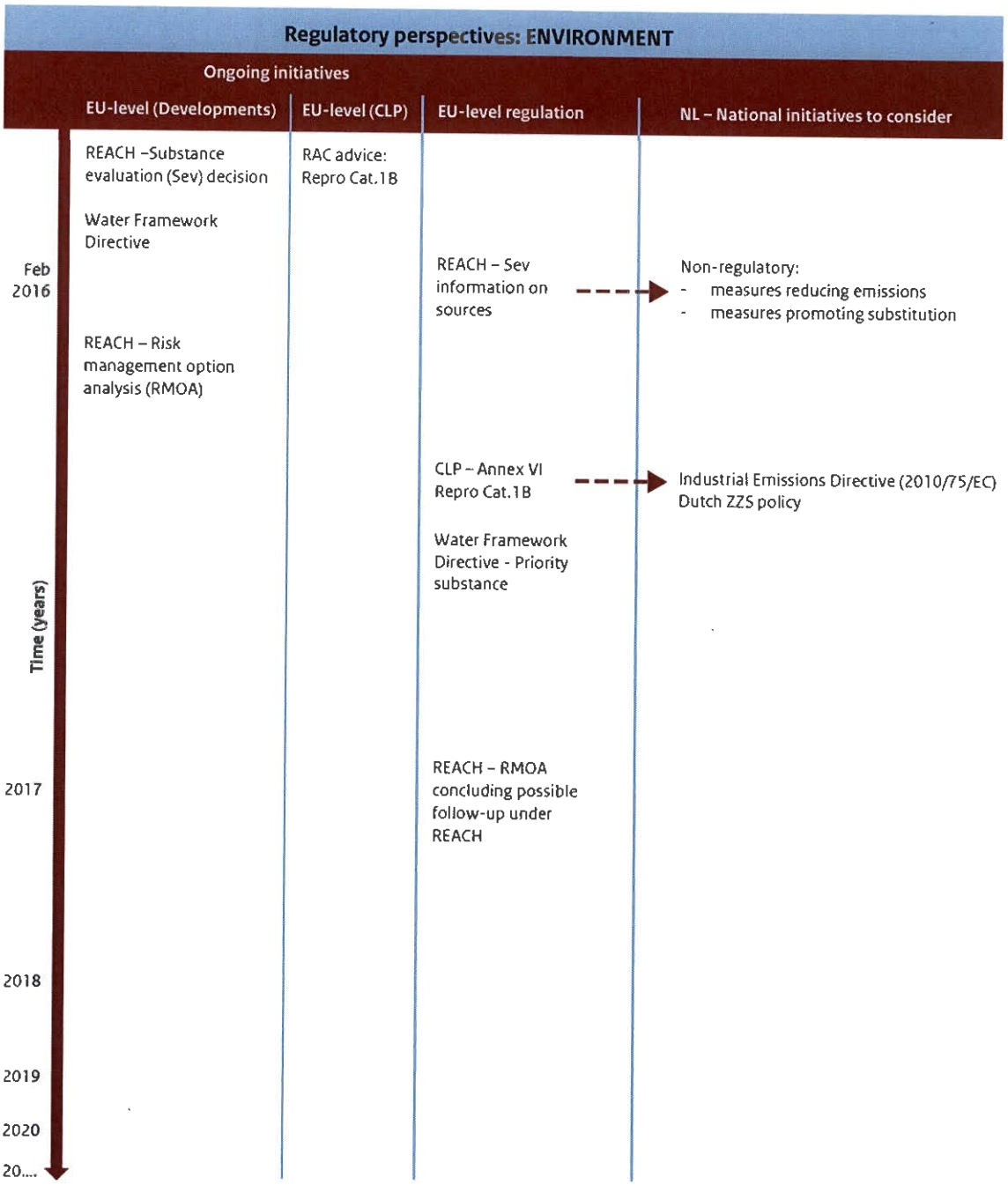
3.2.1 Risk management options for the environment

The RIVM summarizes risks for benthic organisms, but no risks for pelagic organisms.

The sources of BPA emissions to the environment are as yet not fully clear. However, as BPA is produced or formulated at various industrial sites and is commonly used in consumer products, it can be assumed that the sources are either industrial discharges or municipal activities. This is supported by monitoring data and by the modelled emission data summarized in Table 3. Table 3 also highlights the significance of BPA emissions from the use of PVC article use as an important source to the environment – especially those in which BPA is used as a plasticizer or antioxidant, e.g. cables and roofing sheets. It should be noted that according to the PVC industry, BPA is no longer used in the manufacture of PVC in Europe, which suggests that this source should reduce with time.

Given the information at hand, the best risk management options are thus likely to be those that reduce emissions to the aquatic environment. This can be achieved by reducing the amount of BPA produced or formulated at industrial sites, i.e. preventing BPA from being emitted at those sites as well as preventing it from ending up in consumer articles that later in their lifecycle might cause emissions to the aquatic environment. In addition, WWTPs and sewage treatment plants could be adapted to more efficiently trap or degrade BPA to reduce emissions to surface water and subsequently to sediment.

Figure 3 Regulatory perspectives: ENVIRONMENT
Schematic overview of the regulatory perspectives for reducing emissions of BPA to the environment, concentrating on direct measures: regulatory initiatives at EU level, expected results in terms of EU regulation and national initiatives that could contribute to further regulation of BPA at EU or national level as part of an environmental risk management strategy. More detailed information on each regulatory initiative can be found in Table 2.



A detailed overview of regulations that directly or indirectly affect environmental exposure is provided in Table 2. The main regulations that directly affect emissions to the environment are the Industrial Emissions Directive and the Water Framework Directive, and for The Netherlands specifically the Dutch ZZS policy. Regulations that indirectly or to a limited extent affect emissions to the environment are the Plastic Materials in Contact with Food Regulation, REACH (the restriction proposals for the use of BPA in thermal paper, the withdrawal of the intended use of BPA in thermal paper from the registrations and the German Risk Management Option Analysis), the Ecolabel Regulation, the Toy Safety Directive, the Waste Framework Directive, the Cosmetics Regulation, the Drinking Water Directive, the Medical Devices Regulation (in preparation), the Carcinogens and Mutagens Directive, the Young People at Work Directive, and the Directive on Pregnant Workers. Figure 3 illustrates the ongoing initiatives aimed at the reduction of emissions to the environment.

The classification of BPA as Repro Cat.1B will trigger a number of downstream measures that will result in a reduction of emissions to the environment. Additional steps will have to be taken before a reduction of exposure can be achieved under the:
- Industrial Emissions Directive (2010/75/EC): permission of a maximum emission limit at company level has to be set (or granted).
- Waste Framework Directive (2008/98/EC): record keeping, protective measures and labelling are needed for waste containing BPA.

The Industrial Emissions Directive is the main regulation that has a direct impact on emissions to the environment, but whether setting more stringent limits for industry on BPA emission to the environment it will significantly reduce environmental exposure is currently uncertain, as the contribution of industrial emissions to the total concentration of BPA in the aquatic environment is unknown. The modelling data shown in Table 3 (Appendix I, Section 4.2.1) suggests that industrial emissions are of a similar order of magnitude to emissions from the use of articles containing BPA.

The EU Water Framework Directive (2000/60/EC) lays down an integrated approach to river basin management in Europe. Directive (2013/39/EC) includes the list of substances that are identified as a priority for emission reducing measures (Annex I) to meet their established environmental quality standards (EQS, Annex II). BPA was reviewed as a candidate priority substance, but evidence was considered insufficient to include the compound in the final list. The need to identify BPA as a priority substance is being discussed again in the context of the current review of the list of priority substances. It is as of yet uncertain if BPA will be added to this list in the upcoming update.

At national level, the Dutch Government has implemented specific requirements to minimize emissions for substances of very high concern according to the Dutch ZZS (Zeer Zorgwekkende Stoffen) policy[13]. When BPA is taken up in Annex VI of CLP as Repro Cat.1B, the substance fulfils the criteria for being a ZZS and will be added to the ZZS-list of substances. In The Netherlands, industry is then obliged to minimize emissions to the environment, possibly through substitution.

3.2.2 Risk management options for workers

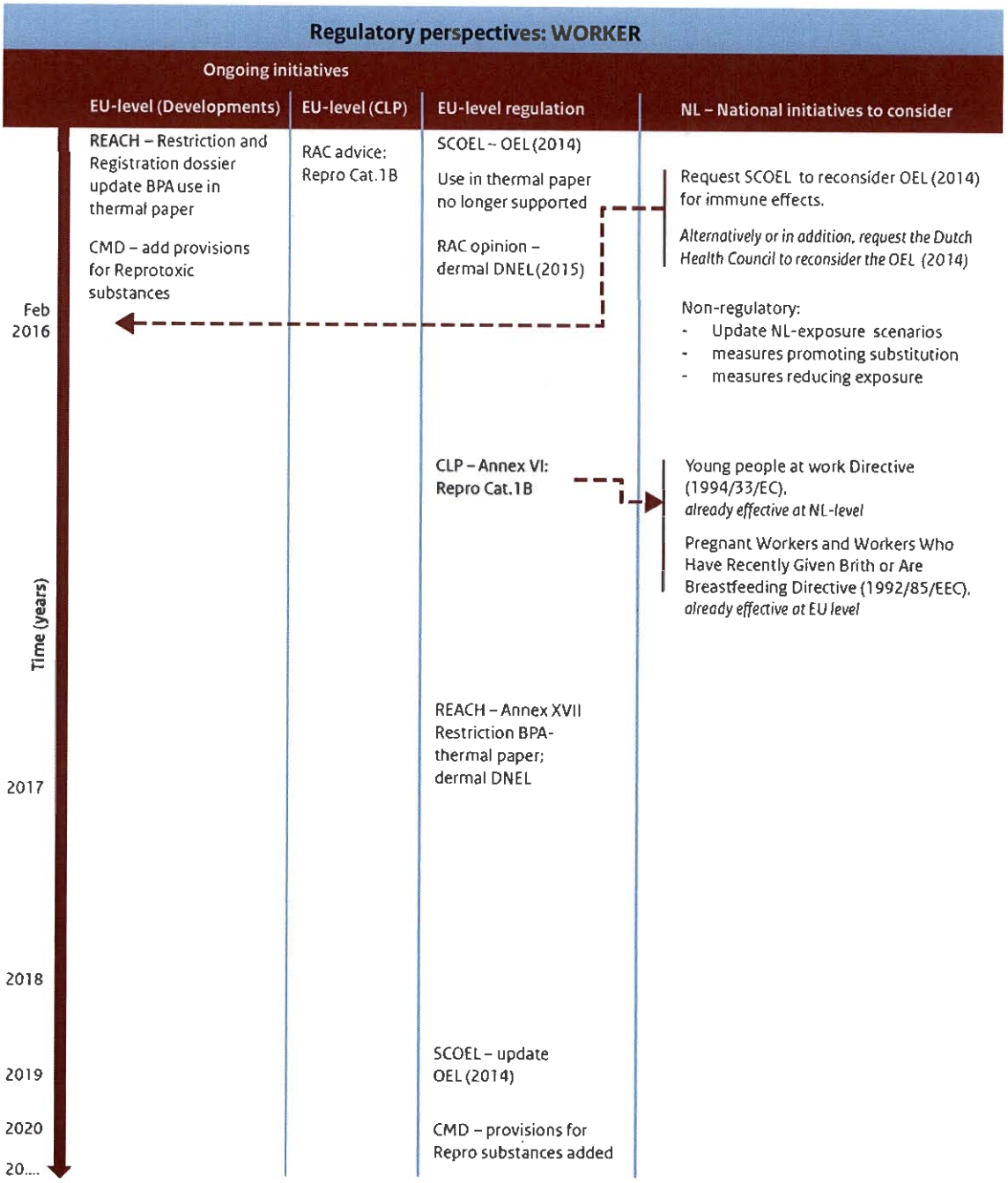
The RIVM summarizes:
- a risk for workers involved in the manufacture of BPA (i.e. product sampling and bag filling) and possibly also for workers involved in the manufacture of epoxy resins through inhalation (based on the modelled exposures as presented in EC, 2008 and UK, 2008);
- a skin sensitization risk for workers in all industrial processes involving dermal contact with free BPA (EC, 2008; UK, 2008);
- a risk for the foetuses of pregnant workers in nearly all industrial processes involving dermal contact with free BPA (based on the modelled exposures presented in EC (2008) and UK (2008) and the dermal DNEL as derived by the RAC (2015)) and for cashiers handling thermal paper cash receipts (RAC, 2015).

It is recommended that:
- *RCRs for workers be recalculated before risk management measures are implemented;*
- *all exposure scenarios be updated (since current handling and risk reduction measures may differ from those in use when the EU RAR (EC, 2008) was drafted).*

It should also be noted that a revision of the OEL and dermal DNEL to include immune system effects will have an impact on the severity of identified occupational health risks and may have an impact on the current conclusions with regard to 'no risks' of workers in other exposure scenarios.

[13] http://www.rivm.nl/rvs/Stoffenlijsten/Zeer_Zorgwekkende_Stoffen

Figure 4 Regulatory perspectives: WORKER
Schematic overview of the regulatory perspectives for reducing worker exposure to BPA, concentrating on direct measures: regulatory initiatives at EU level, expected results in terms of EU regulation and national initiatives that could contribute to further regulation of BPA at EU or national level as part of a worker risk management strategy. More detailed information on each regulatory initiative can be found in Table 2.



A detailed overview of regulations that directly or indirectly affect occupational exposure is provided in Table 2. Regulations that directly affect occupational exposure and risk are the Chemical Agents Directive, REACH (the restriction proposals for the use of BPA in thermal paper, the withdrawal of the intended use of BPA in thermal paper from the registrations and the German Risk Management Option Analysis), the Carcinogens and Mutagens Directive, the Young People at Work Directive, and the Directive on Pregnant Workers. Regulations that indirectly or to a limited extent affect occupational exposure and risk are the Industrial Emissions Directive, the Water Framework Directive, the Dutch ZZS policy, the Ecolabel Regulation, the Toy Safety Directive, the Waste Framework Directive, the Drinking Water Directive, the Medical Devices Regulation (in preparation), and the Plastic Materials in Contact with Food Regulation. Figure 4 illustrates ongoing initiatives aimed at risk reduction for workers.

Since 2015, the intended use of BPA in thermal paper is withdrawn from the REACH Registration, BPA is no longer allowed in the production of thermal paper within Europe. This has a direct effect for the workers involved in the production of thermal paper and processes directly or indirectly linked to it. It should be noted, however, that although the use of BPA in thermal paper production is now prohibited in Europe, the import of BPA-containing thermal paper is not.

Restricting the use of BPA in thermal paper does affect the import of BPA-containing thermal paper into Europe, which, if the restriction is adopted, will limit the maximum concentration of BPA allowed in imported thermal paper. When the proposed Restriction is adopted by the European Commission, this will lead to further a reduction in the exposure of workers through handling of thermal paper (but also of consumers and the environment). The RAC (2015) concluded that the risks for the unborn children of female workers, e.g. cashiers handling thermal paper (the RAC did not identify a risk to consumers in handing receipts), are not adequately controlled. SEAC considered that the socio-economic benefits of the proposed restriction were unlikely to be higher than the socio-economic costs of the proposed restriction (SEAC, 2015). However, SEAC also noted that other considerations could be in favour of the restriction: namely that that a relatively small population with low incomes – cashiers – is at risk, whereas the costs of the restriction would be spread across all EU consumers. The costs of the proposed restriction translate into increased prices of about €0.20–€0.60 per person per year, which was considered affordable by SEAC[14]. It is as yet uncertain how the European Commission will decide on this restriction proposal.

As can be deduced from Table 2, the classification of BPA as Repro Cat.1B will trigger a number of downstream measures that will result in a reduction of occupational exposure. For workers, there is a specific regulation in place that should allow the protection of the vulnerable groups, i.e. young or pregnant workers and workers who have recently given birth or are breastfeeding. Furthermore, the existing regulation will not result in a reduction of exposure for workers in general, which may be needed on account of the non-reprotoxicological effects of BPA. For pregnant workers and workers who have recently given birth or are breastfeeding, the measures should already be in place at EU level on the basis of the current classification of BPA as a Repro Cat.2, H361f substance. For young people at work, the measures will come into force at EU level directly after the Repro Cat.1B classification is added to Annex VI of the CLP Regulation. In The Netherlands, young people at work are additionally protected by article 4.105 of the National Health Decision, which prohibits young people from working with or being exposed to Repro Cat.1A, 1B and 2 substances.

3.2.3 Risk management options for consumers and patients

The possible risks for consumers (EFSA, 2015) and patients (SCENIHR, 2015) are summarized below:

- There is no health concern for consumers at the estimated levels of dietary exposure to BPA.
- There is a low health concern related to the central estimates for aggregated exposure to BPA from dietary sources and non-dietary sources (dust, toys, cosmetics and thermal paper) for the highest exposed groups, which include infants, children and adolescents.
- There may be a risk of adverse effects from BPA exposure for neonates in intensive care units, young children undergoing prolonged medical procedures and dialysis patients.
- There are no risks in all other patient exposure scenarios.

The RIVM concludes that revision of the t-TDI to include immune system effects will have an impact on the severity of identified health risks and may have an

[14] ECHA/PR/15/16, http://echa.europa.eu/view-article/-/journal_content/56/10162/22052209.

impact on the current conclusions of *no risks* of consumers and patients in other exposure scenarios.

A detailed overview of regulations that directly or indirectly affect consumer and patient exposure is provided in Table 2. Regulations that directly affect consumer and patient exposure and risk are the Plastic Materials in Contact with Food Regulation, the Cosmetics Regulation, the Medical Devices Directive (in preparation), the Ecolabel Regulation, the Drinking Water Directive and the Toy Safety Directive. Regulations that indirectly or to a limited extent affect consumer and patient exposure and risk are the Chemical Agents Directive, the Industrial Emissions Directive, REACH (the restriction proposal for the use of BPA in thermal paper and the withdrawal of the intended use of BPA in thermal paper from the registrations and the German Risk Management Option Analysis), the Waste Framework Directive, the Water Framework Directive, the Dutch ZZS policy, the Carcinogens and Mutagens Directive, the Young People at Work Directive, and the Directive on Pregnant Workers. Figure 5 illustrates the ongoing regulatory initiatives aimed at consumers and patients.

For some of the regulations directly affecting the exposure of consumers and patients, additional steps will have to be taken before a reduction of exposure can be achieved:

- Plastic Materials in Contact with Food Regulation (10/2011/EC), Toy Safety Directive (2009/48/EC): derivation of an SML;
- Drinking Water Directive (98/83/EC): derivation of a MTC of BPA in drinking water.

The Medical Devices Directive is currently under revision and the possible regulatory consequences of this revision for BPA are still unknown. However, when assessing the possibility for further risk management measures for patients, for example through exposure reduction, special attention should also be given to the benefit of using medical devices containing BPA.

With respect to cosmetics, BPA has been found in various products, as described by EFSA (2015). However, since the use of BPA in the formulation of cosmetics is not allowed, there are limited options to reduce the exposure from this source via the Cosmetics Regulation (1223/2009/EC).

For consumers and patients, the specific regulations are affected only to a limited extent by the classification of BPA as Repro Cat.1B because BPA is currently on the list of substances allowed in FCM. These regulations are closely affected by the t-TDI and by the SML as defined in for FCM. The adjustment of the SML for BPA in FCM based on the current t-TDI may therefore be a first step towards a reduction in BPA exposure to food and non-food sources. A proposal to lower the SML for BPA in FCM based on the t-TDI (EFSA, 2015) is currently under discussion at EU level in the Working Group on Food Contact Materials of the Toxicological Safety Section of the Standing Committee on Plants, Animals, Food and Feed (SC-PAFF) and updating the SML for BPA used in toys is under discussion in the Expert Group on Toy Safety. In November 2015, the European Commission further published a proposal for the development of regulatory measures on the use BPA in FCM.[15] This indicative Roadmap includes a draft plan to implement the findings of EFSA (2015). It also describes various scenarios to broaden the scope of the current SMLs at EU level. At present, the EU SML for FCM applies only to plastics. In its indicative Roadmap, the European Commission also sketches proposals for further evaluation to extend the current regulation to include SMLs for other FCM, such as coatings, metals, paper and board. At national level, SMLs for these other materials may already be in place, as is the case in The Netherlands. For FCM, a revision of the SML for plastic FCM at EU level will automatically be implemented in the Dutch national legislation on non-plastic FCM (Decree on Packaging and Utensils, Warenwetbesluit).

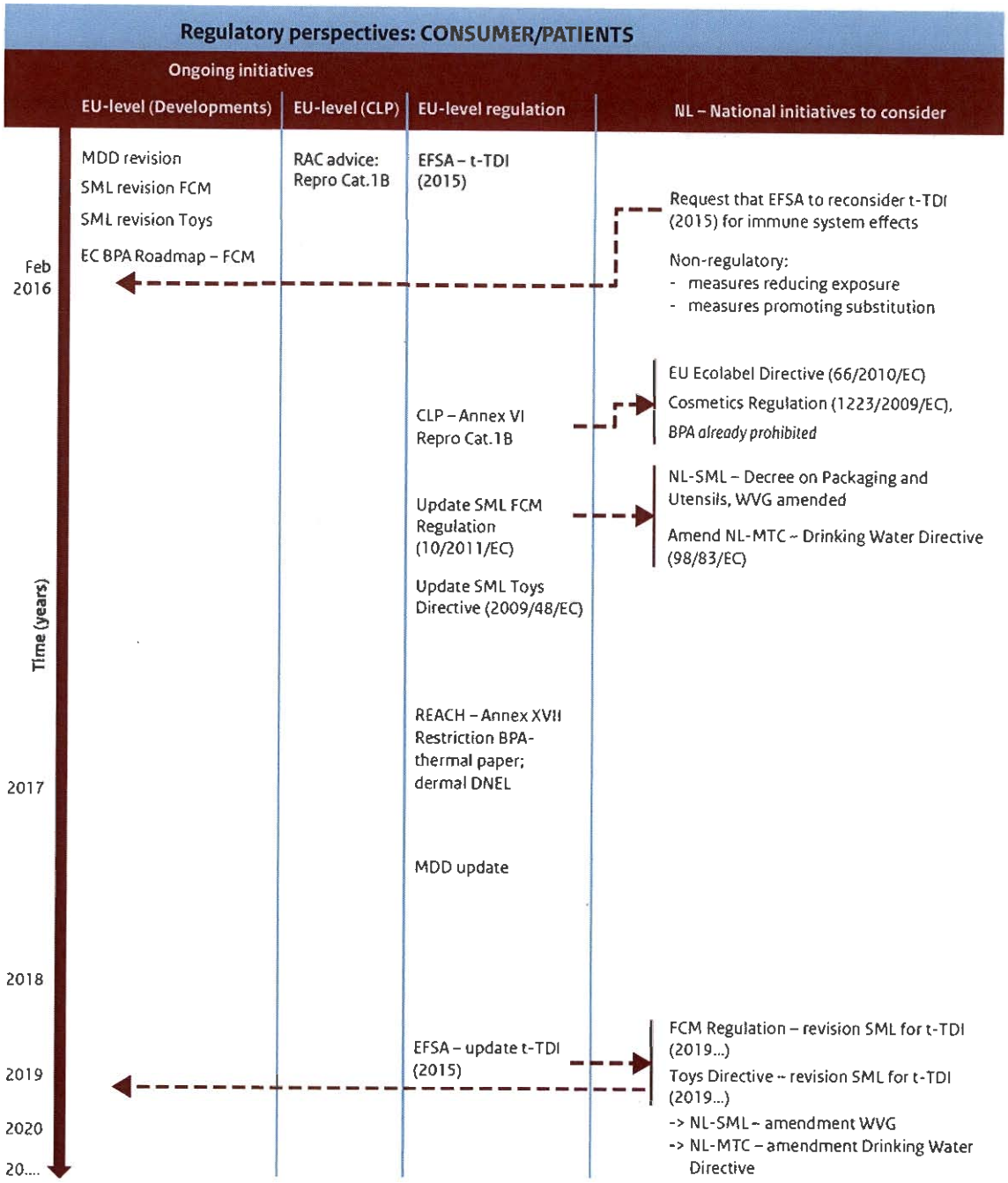
It is recommended that the Dutch authorities invest in reducing exposure to BPA via each of the regulations listed Table 2. At EU level, initiatives to reduce SMLs should be taken within the Plastic Materials in Contact with Food Regulation and the Toy Safety Directive.[16] *For FCM, a revision of the SML at EU level is already ongoing and will automatically be implemented in the Dutch national legislation on non-plastic FCM (Decree on Packaging and Utensils, Warenwetbesluit). At national level, it is recommended that the MTC of BPA specified by the Dutch Drinking Water Directive be revisited.*

None of these initiatives will lead to an exposure reduction in the short term because these follow the established legislative process steps. *It is therefore recommended additionally that national governments evaluate measures at national level to promote substitution, reduce exposure among at least the most susceptible groups (neonates, young children, pregnant and breastfeeding women) and provide information to consumers and patients.*

[15] BPA Roadmap (European Commission; 11/2015) Proposal for a new measure on bisphenol A (BPA) in food contact materials: http://ec.europa.eu/smart-regulation/roadmaps/docs/2015_sante_534_bpa_measure_en.pdf

[16] Both of which initiatives are currently ongoing.

Figure 5 Regulatory perspectives: CONSUMER/PATIENTS
Schematic overview of the regulatory perspectives for reducing exposure to BPA among consumers and patients, concentrating on direct measures: regulatory initiatives at EU level, expected results in terms of EU regulation and national initiatives that could contribute to further regulation of BPA at EU or national level as part of a consumer and patient risk management strategy. More detailed information on each regulatory initiative can be found in Table 2.



3.2.4 Advice on risk management measures at national level

In addition to its requests to revise the various exposure limits, i.e. the t-TDI, the OEL and the dermal DNEL, *it is recommended that the Dutch Government simultaneously take measures to reduce environmental exposure, worker exposure and the exposure of consumers, especially for those age groups that are susceptible to adverse effects on their immune system: unborn children, infants and young children.* Prior to this, an in-depth analysis is needed as to which sources most significantly contribute to environmental and human exposure to prepare for regulatory or non-regulatory interventions.

Promoting substitution for BPA or BPA-containing materials (Figures 3, 4 and 5) will eventually reduce emissions to the environment and exposure for workers, consumers and patients.

The main sources of consumer exposure to BPA identified by EFSA (2015) are epoxy resin coated FCM, PC plastic FCM and thermal paper. Quantitative information on sources of BPA exposure can be used to:
- inform consumers, allowing them to reduce their individual BPA exposure;
- consider restriction of BPA application in specific articles or product categories.

3.3 Alternatives to BPA

In the context of the new information on the environmental and human health hazards of BPA use, an analysis of potential alternatives to BPA, which takes into account availability, technical performance, economic feasibility and safety for humans and the environment, is provided in Appendix III. The analysis of alternatives is an essential part of the overall set of socio-economic considerations that – together with a risk assessment – provide a rational basis for providing our advice to policy makers on the proportionality of proposed risk management measures.

Though there are initiatives to collate the available information on alternatives[17], information on specific alternatives to BPA is scarce, most often scattered and in most cases lacking a feasibility assessment.

The first step in the assessment of alternatives is to define the function of the element that may be replaced. This can be done at different levels: the function of BPA in a material, the function of such a material in an article and the function of the article itself. Consequently, three levels of substitution may be distinguished:
- **Drop-in replacement** – The direct replacement of BPA by an alternative chemical substance, based on comparable functionality. Alternatives within this category may be BPA structural analogues or substances with less structural resemblance that are nevertheless capable of performing the required chemical function.
- **Material substitution** – The indirect substitution of BPA by replacing the material it is used in by another material with comparable functionality. In the case of BPA, this could be the use of an alternative polymer or glass instead of polycarbonate.
- **Non-chemical substitution** – Non-chemical solutions or solutions that otherwise replace the function of an article, including changes to its design. An example of such a solution is the replacement of BPA-containing thermal paper receipts by electronic receipts issued via the internet.

At each level of substitution, introducing alternatives will have an impact at company level that may involve changes in the supply chain, in the production process of the material or article in question, in the use of these materials or articles further down the supply chain and in their disposal or recycling. The need for substitution may, however, also result in or stimulate smart and sustainable innovation. In comparison with material substitution, drop-in replacement is generally characterized by a lower impact, which is focused at a fixed point in the supply chain where the use takes place, whereas material substitution is typically more complex and time-consuming to achieve and typically involves more actors. Non-chemical substitution can be of both higher or lower impact in comparison to drop-in or material substitution, depending on the complexity of this non-chemical substitution and the number of supply chains involved.

From the assessment published by EFSA (2015), PC plastics and epoxy resin coatings for FCM and thermal paper (containing BPA as a colour developer) were identified as the main sources of consumer exposure to BPA. In addition, SCENIHR (2015) identified BPA exposure from medical devices as a possible risk for infants and young children. The present summary of possible alternatives therefore focuses on these materials and uses.

[17] Two examples of initiatives aimed at searching for possible alternatives to BPA are the Service national d'assistance substitution-BPA, organized by INERIS for general uses of BPA (http://www.ineris.fr/substitution-bpa/en), and Healthcare without Harm, for medical devices in particular (https://noharm.org/).

It should be noted that a full analysis of substitution requires a complex, integrated risk assessment and socio-economic analysis approach with the required functionality of the material for each specific application (article) as its starting point. It is beyond the scope of the current advice to conduct such an analysis of the socio-economic impact of substances, materials and non-chemical solutions that could substitute for BPA-containing materials and articles for every possible use. To the best of our knowledge, such an analysis is not available for all of the uses of BPA. What is available in terms of assessments of alternatives to BPA is reflected in the sections below.

For PC plastics, alternatives that seem promising on the basis of the limited information available are:
- **Drop-in level:** diphenolic acid (CAS: 126-00-1, and derivatives);
- **Material substitutes for food contact materials:** PE, PP or PLA.

For epoxy resins, alternatives that seem promising on the basis of the limited information available are:
- **Drop-in level:** diphenolic acid (CAS: 126-00-1, and derivatives) and lauryl gallate CAS: 1166-52-5 (or other gallic acid derivatives);
- **Material substitutes for food contact materials:** isosorbide-based resins, polyacrylates or oleoresin (toxicological information on the monomer and additives is too limited to draw firm conclusions), aseptic cartons and glass.

Because BPA is used as a monomer, substitution usually translates into material substitution rather than replacement by a functional alternative at drop-in level. To the best of our knowledge, the technical and economic feasibility of these alternatives has not been assessed to date.

From the studies reviewed, the following alternatives to the use of BPA as a colour developer in thermal printing are promising:
- DD70 (CAS: 93589-69-6);
- D90 (CAS 191680-83-8);
- Pergafast 201 (CAS: 232938-43-1);
- Urea Urethane (UU) (CAS: 321860-75-7);
- Diphenolic acid (CAS: 126-00-1, and derivatives);
- Lauryl gallate (CAS: 1166-52-5, or other gallic acid derivatives).

Some of these are non-phenolic and may be produced from renewable resources.

In some applications, the use of thermal printing paper can also be replaced by electronic alternatives. An electronic alternative may have an advantage over the use of chemical alternatives with a possibly incomplete or unknown hazard profile. For those applications where an electronic alternative is not an option, chemical alternatives may be considered.

With regard to medical devices, Health Care Without Harm recently published an overview of possible alternatives to BPA (Amaral, 2014). Amaral (2014) states that a number of the alternatives for use in PC plastics or epoxy resins are also possible alternatives for use in medical devices. Amaral (2014) lists nine alternatives that are already used in medical devices. Five of these, however, were identified by Amaral (2014) as having a possible link to oestrogenic activity or leaching substances with oestrogenic activity. The four remaining alternatives were:
- Cyclic olefin polymers – COC/COP (CAS: 2600-43-2); already in use in medical syringes, catheters and medical diagnostic components;
- Poly-lactic acid – PLA (CAS: 26199-51-6); already in use in medical implants and bone fixation devices;
- Polyetherimide (CAS: 61128-46-9); already in use in resins for healthcare applications, sterilization trays, dentist devices and pipettes;
- Polyphenylsulfone – PPSU (CAS: 25608-64-4); already in use in medical tubing and orthopaedic, dental and surgical instruments.

These may look promising, though it should be noted that for all of these Amaral (2014) concluded a general lack of data and further research on the toxicity profile of these alternatives is needed to determine their appropriateness for substitution. This is in line with SCENIHR (2015) that concluded that the toxicological profile of possible alternatives to BPA is much less known, and that at present it is not possible to compare the potential risk associated with alternatives to the risk due to BPA exposure.

In evaluating the possibilities for substitution of BPA in medical devices, it is important to consider the health benefit as part of a broader socio-economic analysis or cost–benefit assessment. To the best of our knowledge, no such assessment exists for BPA in medical devices and its possible substitution.

The RIVM concludes that there are several alternatives to BPA, among them drop-in substances, material substitutes and non-chemical alternatives. For most chemical substitutes, hazard information is lacking, while the use of BPA analogues seems unsuitable on the basis that they have comparable hazard profiles to BPA. In any case, a broader socio-economic study or cost–benefit analysis is needed for each alternative.

3.4 General recommendations

It is recommended that all organisations importing, producing, transporting, storing, formulating into a preparation or otherwise processing, using and disposing of or recovering BPA or BPA-containing materials should take into account the results of the current risk evaluation.

In addition, *it is recommended that the advice for managing the risks set out in this report should be implemented by the European Commission, the Member States and all market players.*

Table 2 Overview of direct and indirect effects of the risk management of BPA by relevant regulatory frameworks on the environment, workers, consumers and patients. A summary of each regulatory framework is provided, as well as an indication of how it might affect risk management for the environment, for workers, for consumers and for patients. For some of these regulatory frameworks, BPA needs to have a harmonized classification as reproduction toxic substance in the category 1A or 1B in Annex VI of the CLP Regulation in order for the regulation to become effective. This is indicated in the table where applicable.

Regulatory framework	Regulatory context	Environment	Workers	Consumers and patients
Industrial Emissions Directive (2010/75/EC)	When BPA is classified as Repro Cat.1B, industrial installations likely to emit BPA require an emission permit. This permit sets a limit to the amount of BPA permitted to be emitted by the specific installation. The Directive does not require BPA to be replaced.	Direct measure to regulate and reduce industrial emissions to the environment. Setting emission limits would result in a reduction of environmental concentrations.	Setting emission limits for the environment is likely to indirectly reduce occupational exposure.	Setting emission limits for the environment may indirectly reduce exposure for consumers.
REACH - Restriction proposal BPA in thermal paper	Discussed by the ECHA's scientific committees, RAC and SEAC, and to be concluded by the REACH Committee. When this restriction is adopted in Annex XVII of REACH, the concentration of BPA used in thermal paper will significantly reduce.	Indirect measure that will lead to a reduction of the emission of BPA during the lifetime of thermal paper and waste, thus reducing emission to the aquatic environment eventually.	Direct measure that will lead to a reduction of exposure of workers manufacturing thermal paper and dealing with waste, and cashiers handling thermal paper. The restriction will affect all sectors of thermal paper use.	Indirect measure that will lead to a reduction of exposure of consumers handling thermal paper.
REACH - Registration	The REACH registrants removed the intended use of BPA in thermal paper from their registration dossier such that BPA may no longer be used in thermal paper produced inside the EU. Any update of the registration dossier comes into force immediately, starting from the date of the update.	Indirect measure that will lead to a reduction of emissions of BPA during the lifetime of thermal paper and waste, thus eventually reducing emissions to the aquatic environment.	Indirect measure that will lead to a reduction of exposure for workers manufacturing thermal paper and dealing with waste, and all workers handling thermal paper, including cashiers.	Indirect measure that will lead to a reduction of exposure for consumers handling thermal paper.
REACH - Risk management measures	Germany is currently addressing possible needs for further risk reduction measures in the context of the substance evaluation (SEv) results, which are expected beginning of 2016. Measures that may be considered include further restriction of uses or authorization under REACH on the basis of an equivalent level of concern for endocrine disrupting effects on the environment.	Development that may result in a reduction of emissions of BPA to the aquatic environment.	Development that may affect the production and use of BPA and consequently may lead to a reduction in occupational exposure.	Development that may affect the use of BPA and consequently may lead to a reduction in consumer and patient exposure.

Table 2

Regulatory framework	Regulatory context	Environment	Workers	Consumers and patients
Ecolabel Regulation (66/2010/EC)	Repro Cat.1B substances are not permitted in Ecolabel products. Consequently, when BPA is included in Annex VI of the CLP Regulation, goods containing BPA will no longer meet Ecolabel requirements.	Indirect measure. Assuming that classification as Repro Cat.1B will lead to the substitution of BPA in Ecolabel products, this classification will reduce emissions of BPA during the lifetime of the goods and waste, thus eventually reducing emissions to the aquatic environment.	Indirect measure. Classification as Repro Cat.1B will imply that Ecolabelled goods should be BPA-free, which will thus limit occupational exposure to BPA during production and waste handling.	Direct measure. Classification as Repro Cat.1B implies that Ecolabelled goods should be BPA-free, which will limit consumer exposure to Ecolabelled goods. Furthermore, this will allow consumers to make informed choices with regard to lowering their exposure to BPA.
Waste Framework Directive (2008/98/EC)	Repro Cat.1B substances are considered hazardous waste. Consequently, when BPA is added to Annex VI of the CLP Regulation as Repro Cat.1B, waste containing BPA will be considered hazardous waste, which may not be mixed and requires record keeping, protective measures and labelling.	Indirect measure. When BPA is classified as Repro Cat.1B, its waste will be considered hazardous; consequently any emissions from waste to the environment will eventually be reduced.	Indirect measure. Classification as Repro Cat.1B will limit occupational exposure to BPA during the handling of waste, including the use of waste in the production of new materials, products and articles.	Indirect measure. Classification as Repro Cat.1B will affect consumer exposure to BPA during waste handling.
Plastic Materials in Contact with Food Regulation (10/2011/EC)	BPA is on the positive list of substances permitted for use in plastic food contact materials (FCM) with a specific migration limit (SML). This means that BPA is authorized for use in FCM based on a risk assessment showing safe use. Classification as Repro Cat.1B will not necessarily affect its risk assessment. At present, at EU level, the SML is due for revision based on the t-TDI published by EFSA (2015) and is being discussed in the SC-PAFF. In parallel, the indicative Roadmap, published in November 2015 by the European Commission, proposes further development of regulatory measures on BPA in FCM and includes a draft plan to implement the findings by EFSA (2015). When the SML is revised, this may trigger revision of SMLs for other types of FCM at national level within each of the EU Member States. >>	Indirect measure. When the SML for FCM is revised, this will eventually lead to a reduction of BPA emissions to the aquatic environment.	Indirect measure. When the SML for FCM is revised, this will lead to a reduction of occupational exposure to BPA for workers involved in the production, use and waste handling of FCM.	Direct measure. When the SML for FCM is revised, this will lead to a reduction of exposure to BPA for consumers.

Table 2

Regulatory framework	Regulatory context	Environment	Workers	Consumers and patients
Plastic Materials in Contact with Food Regulation (10/2011/EC)	>> For The Netherlands, this may involve the revision of the SMLs for paper and board, metals and coatings. It may also trigger revision of other SMLs established under the regulations for Toys (2009/48/EC) (initiatives already ongoing) and the MTC for drinking water (98/83/EC).			
Toy Safety Directive (2009/48/EC)	BPA may be used in toys with a specific migration limit (SML). As of 31 May 2015, the maximum concentration of BPA should not exceed 0.3% in toys, in components of toys or in micro-structurally distinct parts of toys accessible to children. BPA may be used in higher concentrations in components of toys or in micro-structurally distinct parts of toys inaccessible to children when the toys are used as intended or in a foreseeable way. For substances not specifically addressed in this directive, the allowed concentration in accessible parts refers to the SML for FCM (10/2011/EC). A proposal to lower the SML for BPA in toys on the basis of the t-TDI by EFSA (2015) is under discussion in the Expert Group on Toy Safety.	Indirect measure. When the SML for FCM is revised, this may induce a proposal for revision of the toys SML. If this happens, it will eventually lead to a reduction of BPA emissions to the aquatic environment.	Indirect measure. When the SML for FCM is revised, this may induce a proposal for revision of the toys SML. If this happens, this will lead to a reduction of occupational exposure to BPA for workers involved in the production, use and waste handling of toys.	Direct measure. When the SML for FCM is revised, this may induce a proposal for revision of the toys SML. If this happens, this will lead to a reduction of exposure to BPA for consumers.
Cosmetics Regulation (1223/2009/EC)	When BPA is added to Annex VI of the CLP Regulation as a Repro Cat.1B substance, its use in cosmetic products will become prohibited unless safe use can be shown in accordance with article 15.2 of this regulation, which refers to its possible safe use in FCM. Annex II to this regulation, however, already includes BPA on the list of substances that cannot be actively added to cosmetic products. It is therefore expected that classification as a Repro Cat.1B substance will have a limited effect on the concentration of BPA in cosmetics.	Indirect measure. As BPA is already prohibited via Annex II, emissions of BPA from cosmetic products will probably be reduced no further during their lifetime or waste cycle by classification as Repro Cat.1B. Emissions to the aquatic environment are therefore not expected to reduce.	Indirect measure. As BPA is already prohibited via Annex II, emissions of BPA from cosmetic products will probably be reduced no further during their lifetime or waste cycle by classification as Repro Cat.1B. No further reduction of occupational exposure to BPA is therefore expected during production or waste handling.	Direct measure. As BPA is already prohibited via Annex II, emissions of BPA from cosmetic products will probably be reduced no further during their lifetime or waste cycle by this regulation or the classification of BPA as Repro Cat.1B. No further reduction of exposure by consumers is therefore expected.

Table 2

Regulatory framework	Regulatory context	Environment	Workers	Consumers and patients
Drinking Water Directive (98/83/EC)	For substances that come into contact with drinking water, article 10 reads: 'Member States shall take all measures necessary to ensure that no substances or materials for new installations used in the preparation or distribution of water intended for human consumption, or impurities associated with such substances or materials, remain in water intended for human consumption in concentrations higher than is necessary for the purpose of their use and, either directly or indirectly, reduce the protection of human health'. In The Netherlands, BPA is included in the list of substances allowed in drinking water (subject to an MTC) (Annex B of the 'Regeling materialen en chemicaliën drink- en warm tapwatervoorziening'), warm or cold. Reconsideration of the MTC may be proposed on the basis of the new t-TDI published by EFSA (2015).	Indirect measure. When the MTC is revised, this may lead to a reduction of BPA emissions to the aquatic environment.	Indirect measure. When the MTC is revised, this may lead to a reduction of the concentration of BPA in materials used in the preparation or distribution of water for human consumption. This may in turn lead to a reduction of occupational exposure for all workers involved in the production of these materials, their installation, application and use, their dismantling and the handling of waste.	Direct measure. When the MTC is revised, this may lead to a reduction of consumer exposure to BPA.
Medical Devices Directive (93/42/EEC, 2007/47/EC) (a new medical devices regulation is currently under discussion)	Based on the Medical Devices Directive (93/42/EEC) and its amendments, risk reduction should be aimed for to obtain acceptable risks when weighed against the benefits to the patient and are compatible with a high level of protection of health and safety. The current regulatory framework requires that risk assessment and risk management be carried out on a case-by-case basis with special attention given to substances that are carcinogenic, mutagenic or reprotoxic (CMR), in accordance with the CLP Regulation. EC proposals to revise the regulatory framework are currently being negotiated in the Council Working Group and the European Parliament. A preliminary text is available. The proposals do not contain specific provisions for BPA.	Indirect measure. If stringent conditions are included on the use of reprotoxic chemicals in medical devices, it is likely that it will impact on the emission of BPA from these devices to the aquatic environment.	Indirect measure. If stringent conditions are included on the use of reprotoxic chemicals in medical devices, it is likely that it will impact on the exposure of workers involved in the production, use and handling of waste of BPA containing medical devices and when working with patients undergoing medical treatment using BPA containing medical devices.	Direct measure. If stringent conditions are included on the use of reprotoxic chemicals in medical devices, it is likely that it will limit patients' exposure to BPA during medical treatment.

Table 2

Regulatory framework	Regulatory context	Environment	Workers	Consumers and patients
Chemical Agents Directive (98/24/EC; CAD)	Lays down minimum requirements for the protection of workers from risks of substances, including (i) conduction of a risk assessment, (ii) minimization of risks, preferably by substitution, and (iii) the execution of a health surveillance if appropriate to the nature of the risk. Health surveillance is compulsory for substances for which a binding OEL (BOEL) is set – which is not the case with BPA. A BOEL can be established for reprotoxic substances.	Indirect measure. Risk reduction measures taken to protect workers will impact on emissions of BPA to the environment.	Direct measure regulating the safe use of substances in the workplace.	Indirect measure. Risk reduction measures taken to protect workers may impact on the exposure of consumers and patients to BPA.
Carcinogens and Mutagens Directive (2004/37/EC; CMD)	At present, this Directive does not cover substances which are reprotoxic – except if they are also carcinogenic and/or mutagenic. The introduction of reproduction toxicants to this Directive is under debate, but the debate is currently reported as being frozen and its outcome is uncertain. There is agreement, though, that awareness-raising and specific guidance for working with reproduction toxicants are urgently needed. If reproduction toxicants are introduced in this Directive, substitution of these substances will be stimulated in a similar way as currently is the case for the carcinogens and mutagens.	Indirect measure. When reproduction toxicants are added to this Directive, this will form an incentive for substitution and impact the way workers handle BPA and BPA-containing products at all lifecycle stages. This will eventually lead to reduced emissions to the environment.	Direct measure. When reproduction toxicants are added to this Directive, this will form an incentive for substitution and impact the way workers handle BPA and BPA-containing products at all life cycle stages, aiming at reducing occupational exposure.	Indirect measure. When reproduction toxicants are added to this Directive, this will form an incentive for substitution and impact the way workers handle BPA and BPA-containing products at all lifecycle stages. Especially substitution of BPA will impact the exposure of consumers and patients to BPA.
Young People at Work Directive (1994/33/EC)	Member States shall ensure that young people are protected from any specific risks to their safety, health and development, notably those presented by work 'involving harmful exposure to agents which are toxic or carcinogenic, or cause heritable genetic damage or harm to the unborn child or which in any other way chronically affect human health'. This applies to Repro Cat.1A and 1B substances, among others, but not to Repro Cat.2 substances. Member States may also have additional provisions in place at a national level to protect young people at work against hazards of substances. In The Netherlands, young people at work are additionally protected through article 4.105 of the National Health Decision, which prohibits young people from working with or being exposed to Repro Cat.1A, 1B and 2 substances (See also Section 7.8 of Appendix IV of this report)..	Indirect measure. Reduction of the exposure of young workers will eventually lead to reduced emissions to the environment.	Direct measure. At EU level, the inclusion of BPA as Repro Cat.1B in Annex VI of the CLP Regulation will have an impact on the exposure of young people at work. The impact on exposure reduction will depend on the additional legislation in place at national level. In The Netherlands, classification as Repro Cat.1B will not add to the protective measures in place for young workers based on the existing H phrase H361f.	Indirect measure. Reduction of the exposure of young workers may have an impact on the exposure of consumers and patients to BPA.

Table 2

Regulatory framework	Regulatory context	Environment	Workers	Consumers and patients
Directive on Pregnant Workers and Workers Who Have Recently Given Birth or Are Breast-feeding (1992/85/EEC)	At EU level, employers are obliged to assess the nature, degree and duration of worker exposure to substances carrying specific risk for female workers who are pregnant, have recently given birth or are breastfeeding and shall inform these workers of the results of the assessment. This Directive applies to substances classified under the CLP Regulation as Repro Cat.1A, 1B and 2, among others.	Indirect measure. As BPA is already classified as a Repro Cat.2 substance, no further reduction of emissions to the environment is expected when BPA is classified as Repro Cat.1B.	Direct measure. As BPA is already classified as a Repro Cat.2 substance, no further reduction of occupational exposure is to be expected when BPA is classified as Repro Cat.1B.	Indirect measure. As BPA is already classified as a Repro Cat2 substance, no further reduction of consumer exposure is expected when BPA is classified as Repro Cat.1B.
Dutch policy on substances of very high concern (ZZS)	On a national level, the Dutch Government has implemented specific requirements to minimize emissions for substances of very high concern in the context of the Dutch ZZS (Zeer Zorgwekkende Stoffen) policy. When BPA is taken up in Annex VI of the CLP Regulation as Repro Cat.1B, the substance fulfills the criteria for being a ZZS. When a substance is a ZZS, industry is obliged to minimize emissions to the environment. Further, the substance will be added to the ZZS-list.	Direct measure. When BPA will be added to the ZZS-list, industry is obliged to minimize emissions to the environment.	Indirect measure. Reduction of exposure is foreseen for workers involved in all processes that produce or use BPA or BPA containing articles, and from which emission to the environment can be expected.	Indirect measure. Reduction of exposure is foreseen for consumers via 'exposure via the environment', and for consumers and patients via reduction of the migration of BPA from materials and articles.
Water Framework Directive (2000/60/EC; WFD) and Directive (2013/39/EC)	The EU Water Framework Directive (2000/60/EC) lays down an integrated approach to river basin management in Europe. Directive (2013/39/EC) includes the list of substances that are identified as a priority for emission reducing measures (Annex I) to meet the established environmental quality standards (EQS, Annex II). BPA was reviewed as a candidate priority substance, but evidence was considered insufficient to include the compound in the final list. The need to identify BPA as a priority substance is being discussed again in the context of the current review of the list of priority substances.	Direct measure. When BPA will be added to the priority-list of substances under the WFD, priority will be given to meet the environmental quality standards. Possibly by further reduction of environmental emissions.	Indirect measure. Reduction of exposure is foreseen for workers involved in all processes that produce or use BPA or BPA containing articles, and from which emissions to the environment can be expected.	Indirect measure. Reduction of exposures is foreseen for consumers via 'exposure via the environment', and for consumers and patients via reduction of the migration of BPA from materials and articles.

4 Appendix I: Environmental risk assessment

The information presented in this Appendix is largely a summary of the findings presented in RIVM (2014). In addition, new insights into possible sources of BPA emissions are discussed.

4.1 Environmental health hazards

Regarding the possible adverse effects of BPA on environmental health, the RIVM concluded that BPA shows endocrine disrupting effects in environmental organisms, leading to adverse effects on reproduction and the development of offspring (RIVM, 2014). The RIVM further observed that, since the European risk assessment (EC, 2008) and the Annex XV Transition report (UK, 2008), new data had emerged regarding the possible adverse effects of BPA on environmental organisms, including possible endocrine effects, and its concentrations in water and sediment throughout Europe. It was pointed out that this new data had not been taken into account in the derivation of the PNECwater, and that there are indications that the NOEC of BPA for fresh water organisms may be lower than the NOEC used for the derivation of the present PNEC. However, upon further analysis, these indications were judged not robust enough to warrant lowering the PNEC.

To the best of our knowledge, from February 2014 to February 2015, no new scientific information was published that validated a lower NOEC of BPA in environmental organisms than the NOEC used to derive the PNECs (EC, 2008; UK 2008). The policy advice in the present Part 2 is therefore based on the PNECs as described in Bisphenol A, Part 1 (RIVM, 2014)[18]. It should be noted though, that the PNECs for BPA (for the sediment and water compartment) are currently under discussion in the context of the

[18] The Netherlands has identified are so-called indicative environmental quality standards for BPA (64 ug/L for surface water and 22.9 mg/kg dry weight for sediment; see http://www.rivm.nl/rvs/). However, these BPA values are not officially approved and furthermore the scientific background is lacking. For these reasons these values are not used in the current environmental risk assessment and the EU RAR PNECs are adopted.

upcoming revision of the list of priority substances of Directive 2013/39/EC in the context of the EU Water Framework Directive (2000/60/EC) where BPA is evaluated as possible priority substance candidate. If this will lead to a revision of the PNEC is as of yet unknown.

4.2 Emissions and environmental exposure

This section provides an update on releases of BPA to and exposure of the environment. This update is based on a report published by the German Federal Environment Agency (Umweltbundesamt) (Fisher et al., 2014). This report provides updated information on emission pathways and environmental exposure to BPA. The aim of this report was to fill knowledge gaps with regard to uses of BPA and the mass flow of BPA to the environment. A summary of the relevant updated information is presented below. Some parts of the report by Fisher et al. (2014) contain confidential data, which is not shown in the present summary.

4.2.1 Releases to the environment

Information on emissions of BPA into the environment has been published previously, in the 2003 European Risk Assessment Report (EC, 2003) and the Environment Addendum to the Risk Assessment Report of 2008 (EC, 2008). This

Table 3 Summary of emissions data from EC (2003, 2008) and Fisher et al. (2014); emissions data is extracted from Fisher et al. (2014) unless otherwise indicated. Figures in brackets are extracted from EC (2008); figures followed by an asterisk are extracted from EC (2003). N.r. indicates 'not reported'.

Process	Air (kg/year)		Emission to WWTP (kg/year)		Emission to waters (kg/year)	
	Regional	Continental	Regional	Continental	Regional	Continental
Bisphenol-A production	575 (575)	481 (409)			113 (113)	148 (115.6)
Polycarbonate						
Polycarbonate processing		0.22			0	0.0
Total losses from PC articles in use:			0.63 - 101.1 (0.23)	5.63 - 909.9 (2.05)	7.6 - 283 (0.05)	68.7 - 2,547 (0.52)
PC articles indoor	0	0	0.63 - 101.1	5.63 - 909.9	0.13 - 20.2	1.13 - 181.9
PC articles outdoor	0	0	-	-	7.5 - 262.8	67.6 - 2,365
Polycarbonate bottle washing			(0.23)	(2.05)	(0.05)	(0.52)
Epoxy resin						
Epoxy resin production					246 (242)	213 (209)
Use of epoxy resins					29.3 - 124	262.2 - 1,116
Lining of water pipes						82
Other polymers						
Phenoplast cast resin processing			(4.8)	(43)	(1.2) 6*	(11) 54*
Unsaturated polyester resins	(0)	(0)				
Can coating production	(0)	(0)				
Thermal paper production					63 (49)	120 (95)
Thermal paper recycling					0.7 (0.68)	6.3 (6.25)
PVC						
PVC – Inhibitor during production			(n.r.) 5,810*	(n.r.) 52,290*	(n.r.) 2,490*	(n.r.) 22,410*
Total PVC - compounding:			274	1,549	43.46	371.79
Anti-oxidant during processing			274 (77)	1,549 (693)	43.5 (19)	371.8 (174)
Preparation of additive packages			(37)	(44)	(2.76)	(0.79)
Use of additive package			(77)	(693)	(19)	(174)
Anti-oxidant in plasticiser production			n.r. (73)	n.r. (28)		
Plasticiser use			(10)	(91)	(2.7)	(23)
Losses from PVC articles in use	1,560 (1,560)	14,040 (14,040)			2,250 (2,250)	20,450 (20,450)
Total	(2,135)	(14,449)	(279)	(1,594)	(2,699)	(21,260)

information was included in the environmental exposure assessment by the RIVM (2014), which stated that emissions of BPA to the environment result from its manufacture, its use in a broad range of products and the recycling and disposal of these products. At the same time, RIVM (2014) noted that it was unclear which specific lifecycle steps are responsible for the observed emissions into the environment – for which reason Germany is currently conducting a substance evaluation under REACH.

Since the publication of RIVM (2014), Fisher et al. (2014) has provided an update on environmental emissions based on recent production statistics and an analysis of data on emissions from sources not included in the EU reports. The updated information relates mainly to emissions to waste water and surface water. Fisher et al. (2014) provided new estimates on emissions of BPA from polycarbonate (PC) articles. These estimates are characterized by a high uncertainty but may constitute as much as 10% of the total emissions of BPA to the environment. Other than PC articles, Fisher et al. (2014) quantified two sources of BPA emissions that were previously not considered: epoxy resins and BPA-containing water pipe linings. These two new sources may constitute as much as 5% of the total emissions of BPA to waste water. An overview of the updated emissions estimates by Fisher et al. (2014) and the previous emissions estimates from EC (2008) is presented in Table 3.

The data presented in Table 3 suggests that industrial processes using BPA make up an important part of total emissions of BPA to water and to waste water treatment plants (WWTPs). Indoor use of PC articles may be another important source of emissions of BPA to WWTPs. Emissions of BPA to water stem mainly from BPA leaching from PVC articles that are currently in use, secondarily by the outdoor use of PC articles and thirdly by the use of epoxy resins. The use of BPA in thermal paper and the recycling of thermal paper contributes relatively little to either total emissions or emissions to water. The emissions ranges indicated in Table 3 point to the leaching of BPA from articles and waste (water) mass flows as important sources of emissions of BPA to the environment. This emphasis is supported by Klecka et al. (2009), who provided an overview of monitoring data on BPA in water and sediment in North America and Europe from the period 1999–2007 and concluded that higher concentrations in water and sediment relate to highly urbanized and industrial areas.

A recent study by Kassotis et al. (2015) assessed the possible contribution to both human and environmental exposure of emissions of BPA to the air. Atmospheric BPA is considered to have a short half-life and has been modelled to contribute little to overall environmental exposure to BPA (EC 2003, 2008). Kassotis et al. (2015) suggest that atmospheric BPA might contribute to surface water concentrations and that research is needed to quantify this contribution and its significance in relation to other sources. The substance evaluation ongoing under REACH might provide relevant insights.

4.2.2 Environmental concentrations

The Bisphenol A, Part 1 report (RIVM, 2014) included an overview of environmental concentrations of BPA. Since then, Fisher et al. (2014) have undertaken a review of recent environmental monitoring data, taking into consideration additional environmental compartments, including soil, groundwater and landfill leachates. The focus of the present report is on the sediment compartment, because it was concluded from the overview presented by RIVM (2014) that there is a possible environmental risk due to the exceedance of the PNEC for fresh and marine surface water sediment.

Fisher et al. (2014) concluded that BPA mean (median) concentration values found in marine water sediment were generally in the same concentration range as in freshwater sediment and were in accordance with BPA levels reported previously for the EU (Klecka et al., 2009):

- freshwater sediment: mean concentrations of 10.4–14.1 µg/kg dry weight;
- marine sediments: mean concentrations of 5.7–19.7 µg/kg dry weight.

Tables 4 and 5 give an overview of typical concentrations of BPA in the environment.

Table 4 Fresh water environment concentrations of BPA and risk characterisation ratios (RCR).

Concentrations:	Fresh water (µg/l)	Freshwater sediment (µg/kg dw)	Fresh water RCR[1)]	Freshwater sediment RCR[2)]
Median*	0.01	16	0.007	0.25
Mean*	0.13	60	0.087	0.95
SD*	1.5	134	1.0	2.13
5th percentile*	0.0005	0.5	0.0003	0.01
95th percentile*	0.35	256	0.233	4.06
Max	0.14 – 43**	1.1 – 118***	0.009 – 29**	0.017 – 2***
Median**	0.021	-	0.014	-
95th percentile**	0.25	346	0.17	5.49
NL, Heel 2012**	<0.5	-	<0.33	-

* EU RAR, (EC, 2008)
** NORMAN-EMPODAT database (NORMAN, 2013)
*** Flint et al., 2012; Wright-Walters et al., 2011
1) PNEC Fresh water = 1.5 µg/l
2) PNEC Freshwater sediment = 63 µg/kg sediment dw

Table 5 Marine environment concentrations of BPA and risk characterisation ratios (RCR).

Concentrations:	Marine water (µg/l)	Marine sediment (µg/kg dw)	Marine water RCR[1)]	Marine sediment RCR[2)]
Median*	0.0016	8.5	0.01	1
Mean*	0.017	75	0.11	12
SD*	0.052	209	0.35	33
5th percentile*	0.00005	1.1	0.0003	0.17
95th percentile*	0.088	566	0.59	90
Max	0.00005 –0.10**	1.1 – 118***	<0.67**	<0.03***
Median**	-	-	-	-
95th percentile**	-	-	-	-
NL, Heel 2012**	-	-	-	-

* EU RAR, (EC, 2008)
** NORMAN-EMPODAT database (NORMAN, 2013)
*** Flint et al., 2012; Wright-Walters et al., 2011
1) PNEC Marine water = 0.15 µg/l
2) PNEC Marine sediment = 6.3 µg/kg sediment dw

4.3 Environmental risk assessment

Based on the information available up to 2013, the RIVM (2014) indicated that there was no risk for the water compartment (fresh water and marine water) (EC, 2008; UK, 2008; NORMAN-EMPODAT, 2013). This information included measurement data on BPA concentrations in Europe from the period 2003–2010 and monitoring data for BPA in fresh water in The Netherlands.

A risk was identified for benthic organisms (Annex XV Transitional Report (EC, 2009) and NORMAN-EMPODAT (2013)). Tables 4 and 5 give an overview of typical concentrations of BPA in the environment and resulting risk characterization ratios (RCRs). For freshwater sediment and marine sediment, the 95th percentile of the measured concentrations in Europe exceeded the respective PNECs (EC, 2008). For marine sediment, the mean BPA concentration was also higher than the $PNEC_{marine\ sediment}$ (i.e. higher than 6.3 µg/kg dw). The mean BPA concentration measured in freshwater sediment was close to the $PNEC_{freshwater\ sediment}$ of 63 µg/kg dw.

From the data reported by Klecka et al. (2009), whose article was not explicitly referred to in the Bisphenol A, Part 1 report, it can further be concluded that for 25% of the sampling locations in Europe, measured BPA concentrations in freshwater sediment (n=347) exceed the $PNEC_{freshwater\ sediment}$. This further strengthens the finding presented in RIVM (2014) that there may be a risk for benthic organisms in a significant number of locations in Europe.

4.4 Conclusions with regard to environmental risk

BPA is present in all surface water and sediment. Concentrations of BPA vary considerably depending on the location and sampling period, etc. Emissions of BPA to the environment result from BPA manufacture, its use in a broad range of products and the recycling and disposal of these products. More clarity on the sources of the observed emissions into the environment is expected in the course of 2015/2016, following Germany's substance evaluation under REACH.

The currently available information suggests that higher concentrations of environmental BPA are related to highly urbanized or industrialized areas, but does not provide a clearer insight into the sources of BPA emissions other than that BPA is leaching from BPA-containing articles that and waste streams contribute to the emissions modelled.

The RIVM concludes that the current environmental monitoring data does show a risk for benthic organisms living in freshwater sediment and in marine water sediment at approximately 25% of the sampling sites in Europe. This conclusion should be reviewed when ongoing discussion in the context of the Water Framework Directive result in a change of the PNECs adopted here.

5 Appendix II: Human risk assessment

RIVM (2014) gave an overview of human health issues as assessed in studies published by RAR, EFSA, SCENIHR, RAC and SCOEL up to March 2014. The sections below provide an update of this work, taking into account the evaluation of human health hazards, exposure and resulting risks for consumers by EFSA (EFSA, 2015) and for patients (including both medical and dental patients) by SCENIHR (SCENIHR, 2015). With regard to the occupational health implications of BPA exposure, the most recent evaluation by the Risk Assessment Committee of ECHA (RAC), which evaluated a proposal for restricting the use of BPA in thermal paper under the REACH Regulation (RAC, 2015), is taken into account.

In addition to these studies, the RIVM identified a number of recent scientific publications on the developmental effects of BPA exposure on the immune system. These publications were submitted for evaluation as part of the process of assessing the proposal for restricting the use of BPA in thermal paper under REACH. Section 5.1.1 outlines these findings in more detail as part of the overall human health hazard assessment in Section 5.1. Section 5.2 addresses the different exposure limit values derived for consumers, patients and workers and Section 5.3 summarizes their exposures. The consequent risk characterization of consumers, patients and workers is discussed in Section 5.4. Section 5.5 summarizes the conclusions regarding human health risks.

5.1 Human health hazards

With respect to human health, BPA has a harmonized classification under the CLP Regulation as a skin sensitizer cat. 1, STOT SE 3 (may cause respiratory irritation) and reproduction toxicant cat. 2 (suspected of damaging fertility). In 2014, the RAC evaluated a proposal to classify BPA as a reprotoxic substance under the CLP Regulation and published the opinion that BPA classifies as a Repro Cat.1B substance (RAC, 2014). RIVM (2014) furthermore summarized that various scientific studies had

associated BPA with adverse immune system effects, obesity, ADHD, diabetes and prostate cancer, which may be related to an interaction with the oestrogen receptor.

In early 2015, EFSA updated its opinion on the human health hazards of BPA exposure based on extensive assessment of the available literature up to 2012 (EFSA, 2015). EFSA concluded that alteration in kidney weight was the most critical effect (i.e. appeared at the lowest dose and other effects were only seen to occur at higher doses) and concluded additionally that there are remaining uncertainties about possible toxic effects below the dose at which effects on the kidney are observed. These possible toxic effects are on the mammary gland as well as the reproductive, metabolic, neuro-behavioural and immune systems. EFSA (2015) included these effects in an overall uncertainty evaluation to derive a temporary tolerable daily intake (t-TDI). Section 5.2.1 summarizes this derivation of the t-TDI by EFSA (2015) in more detail.

5.1.1 Developmental immunotoxicity of BPA

With regard to the developmental effects of BPA exposure on the immune system, EFSA states that, on the basis of the scientific data available up to 2012, 'there are indications that BPA may be linked to immunological outcomes in humans, although in view of the limitations of the studies only limited conclusions can be reached'. The CEF Panel further noted that this type of effect was insufficiently covered by current testing guidelines, and potential immunotoxicity therefore presented an uncertainty area in BPA risk assessment, deserving further consideration (EFSA, 2015).

More recently, scientific studies on the immune system effects of BPA exposure have appeared. These new publications have included both epidemiological studies in human populations and experimental animal studies. Two of these studies, by Menard et al. (2014a, 2014b), on possible adverse effects of BPA exposure on the immune system – namely on the development of food allergies and on resistance to infection – were judged by the RIVM as critical in the human health hazard assessment. Because of their possible impact on the hazard assessment, the studies were submitted by The Netherlands as part of the public consultation on the restriction proposal for BPA in thermal paper under REACH. The RAC took note of these studies and concluded that the studies in isolation do not allow a quantification of a dose–response relationship. The RAC also concluded, however, that the studies did add to the overall likelihood of immune system effects, thereby reinforcing the conclusion by EFSA (2015). In their opinion, the RAC was restricted to the information submitted to the evaluation process (either via the Annex XV restriction proposal or through public consultation). The two Menard studies were the only two studies on immune system effects submitted and the endpoint immunotoxicity was not included in the Annex XV proposal. Consequently, the RAC was not in a position to evaluate these studies against the background of other studies on the possible immunotoxicity effects of BPA exposure.

Subsequently, the Dutch Government commissioned the RIVM to organize a meeting in which a group of international experts in the field of immunotoxicity and BPA were consulted to assess these and other recent studies.[19] The focus of the meeting, which was held in The Netherlands on 29 September 2015, was to assess the impact of the Menard et al. (2014a, 2014b) studies on the evaluation of animal and human data on immunotoxicity published up to December 2012. It should be stated that neither the RIVM nor the experts present at the meeting performed a comprehensive new literature search on this subject.

The discussions focused on the studies that showed effects at the lowest dosages of BPA (Menard et al., 2014a, 2014b; Bauer et al., 2012). These studies were presented by the authors and the experimental design and results were discussed extensively during the meeting, as detailed below. Table 6 summarizes the dosages of BPA at which immunomodulation was demonstrated in the different studies.

Menard studies

Several animal studies indicate immunological effects of BPA exposure at doses as low as 0.5 µg/kg bw/day (Menard et al., 2014a; Bauer et al., 2012). Menard et al. (2014a, 2014b) studied perinatal exposure to BPA (at 0.5, 5 and 50 µg/kg bw/day) on the immune-specific response to the allergen ovalbumin (OVA) from gestation day 15 to weaning. In Menard et al. (2014a), increases of anti-OVA IgG titers were identified at all BPA dosages in OVA-

[19] Invited experts participating at the meeting consisted of representatives of the US Environmental Protection Agency (US EPA), the US National Institute of Health (NIH), the French National Institute for Agricultural Research (INRA), the Rochester.URMC and the Norwegian Institute for Public Health (FHI), a member of the EFSA CEF panel and a former member of the Working Group BPA of the EFSA CEF Panel, as well as representatives of the National Institute of Public Health and the Environment in The Netherlands.

tolerized rats, and at 5 µg/kg bw/day in OVA-immunized rats compared with vehicle-treated control rats. In BPA-treated and OVA-tolerized rats, increased anti-OVA IgG titers were associated with higher IFNγ secretion by the spleen. This result is in accordance with the increase of activated CD4+CD44highCD62Llow T lymphocytes observed in the spleen of BPA-exposed rats compared with controls. Finally, when 5 µg/kg bw/day BPA-treated OVA-tolerized rats were orally challenged with OVA, colonic inflammation occurred, with neutrophil infiltration, increased IFNγ, and decreased TGFα. In another study by the same group (Menard et al. 2014b), it was shown that perinatal exposure to a low dose of BPA (5 µg/kg bw/day) led to impairment of systemic cellular immune responses to ovalbumin as well as the nematode Nippostrongylus brasiliensis; the latter in fact evidenced by decreased resistance to this parasite.

It was noted that the effects observed at 5 µg/kg bw/day were considered adverse, that 5 µg/kg bw/day represents the LOAEL (lowest observed adverse effect level), and that the effects are therefore relevant for the risk assessment for BPA. The observations that at this exposure level, BPA impaired host resistance as well, as shown by an increased susceptibility to intestinal parasitic infections (Menard et al., 2014a), strengthens this conclusion.

In Menard et al. (2014b), a significant increase of OVA-IgG titers was observed at 0.5 µg/kg bw/day as well. There was however no consensus amongst the experts on the relevance of this finding in terms of adversity, because this effect, although relevant in view of adverse effects on the immune system, was the only parameter studied by Menard at this dose level.

Bauer study

Bauer et al. (2012) administered BPA (at 0, 0.5, 5, 50 and 500 µg/kg bw/day) by gavage to pregnant C57Bl/6 dams from gestational day 6 until post-natal day 21. To induce allergic inflammation, adult offspring were mucosally sensitized with inhaled OVA containing low-dose lipopolysaccharide or intraperitoneally sensitized using ovalbumin with alum, followed by an OVA aerosol challenge. In the mucosal sensitization model, female offspring maternally exposed to 50 µg/kg bw/day or higher displayed enhanced lymphocytic and lung inflammation, assessed by histopathology, compared with controls. This effect was evident in female but not in male offspring.

Bauer et al. (2012) furthermore showed that BPA interferes with the immune system at concentrations of 0.5 µg/kg bw/day. In their systemic sensitization model, this exposure led to a decreased immune response. In the mucosal sensitization model, though, the respiratory allergy response was significantly enhanced at 50 µg/kg bw/day whereas at 0.5 and 5 µg/kg bw/day (the same BPA doses as were tested in the systemic sensitization model) no effects were observed. Bauer et al. (2012) thereby demonstrated that the immune system effects of BPA exposure are clearly dependent on the experimental model used.

Table 6 Overview of immune system effects observed at low doses of perinatal BPA exposure.

Experimental model	Parameters affected by BPA	BPA (µg/kg bw/day)	Reference
Oral tolerance induction at d45	Increase in OVA-specific IgG titers	0.5	Menard 2014b
Oral tolerance induction at d45	Increase in OVA-specific IgG titers Increase in systemic cellular responses in spleen Increase in mucosal immune response in colon	5	Menard 2014b
Oral tolerance induction at d45	No effect on OVA-specific IgG titers Suppression of cellular immune responses	5	Menard 2014a
Host resistance	Increased susceptibility to the intestinal nematode infection	5	Menard 2014a
Respiratory allergy Systemic sensitization	Reduced inflammation in the airways in females but not in males Reduced number of regulatory T lymphocytes in airways Reduced levels of OVA-specific IgE titers in serum No effect on airway hyper responsiveness	0.5	Bauer 2012
Respiratory allergy Mucosal sensitization	Increase of airway inflammation in females, but not males	50	Bauer 2012

Conclusion
At the joint meeting, it was concluded that there was strong evidence that pre- or perinatal exposure to BPA at a dose of 5 µg/kg bw/day had effects on the immune system. The majority of the experts regarded these effects as adverse, although there was no full consensus amongst the experts on the relevance of the findings to the adversity of the effect; nor was there consensus on the relevance of effects seen at a dose of 0.5 µg/kg bw/day.

The RIVM concludes that adverse effects on the immune system can be expected from pre- or perinatal exposure to BPA at a dose of 5 µg/kg bw/day. The RIVM furthermore concludes that effects on the immune system are possible at 0.5 µg/kg bw/day, but notes that a more detailed analysis of the underlying data is needed to determine whether effects at this lower dose level should be considered adverse.

Consequently, the RIVM considers 5 µg/kg bw/day as the LOAEL, which may result in increased risk of food intolerance, inflammation and infections. the RIVM concludes that reconsideration of the t-TDI, the OEL and the dermal DNEL is warranted based on these findings.

5.1.2 Metabolic effects

Van Esterik et al. (2014) studied metabolic effects in offspring up to 20 weeks of age after BPA exposure during gestation and lactation in mice on a 15kcal% fat diet. Dose–response analysis through benchmark dose analysis showed statistical significance in some metabolic parameters. The $BMDL_{10}$ was derived for interscapular fat pad weight decrease at a dose of 233 µg/kg bw/day (Van Esterik et al., 2014).

In her PhD thesis, Van Esterik (2015) discusses that this benchmark dose level (BMDL) may give rise to a TDI which is 38 times lower than the current t-TDI (EFSA, 2015). However, the RIVM is of the opinion that this conclusion on the t-TDI by Van Esterik (2015) is premature. In the opinion of the RIVM, the variation in the control groups in the metabolic parameters is high in relation to the effect size for these parameters in the highest dose tested. Furthermore, as effects were observed only in the highest dose (3 mg/kg bw/day) group, the highest dose was, in retrospect, considered too low to produce definitive conclusions.

Therefore, the RIVM concludes that, although the results reported by Van Esterik et al. (2014) do show effects on the metabolic system at a low dose, the biological significance of these findings in terms of adversity is unclear. Consequently, the RIVM concludes that the present study in itself does not warrant reassessment of the current TDI of BPA. A repeat study with higher doses and/or different fat regimes (to make the study more suited to model possible metabolic changes in humans) might clarify the situation.

5.2 Exposure limit values

5.2.1 Temporary tolerable daily intake (t-TDI)

Based on data from multi-generation reproductive toxicity studies on rats (Tyl et al., 2002) and mice (Tyl et al., 2008), EFSA recently calculated a $BMDL_{10}$ of 8.96 mg/kg bw/day by applying the benchmark dose (BMD) approach (EFSA, 2015). The $BMDL_{10}$ represents the lower level of the confidence interval of the effect resulting in a 10% deviation from vehicle-treated control animals. The critical endpoint (i.e. the endpint appearing at the lowest dose) for this $BMDL_{10}$ was the alteration in kidney weight in mice (Tyl et al., 2008; EFSA, 2015). In its recent evaluation, EFSA (EFSA, 2015) included both oral and dermal (via thermal paper) exposure to BPA.

The $BMDL_{10}$ was translated into a human dose inducing similar effects, the human equivalent dose (HED). The HED was determined by considering the correlation between internal exposure in mice and the internal exposure in humans based on toxicokinetic studies (EFSA, 2015). So, the $BMDL_{10}$ of 8,960 µg/kg bw/day in mice translates to an HED of 609 µg/kg bw/day. There are remaining uncertainties about possible toxic effects below this $BMDL_{10}$ and its corresponding HED.

The overall uncertainty evaluation by EFSA (2015) included the effects on the mammary gland as well as on the 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 the 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 100–1,000 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, the most critical effect is identified by EFSA (2015) as 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.

To cover these more uncertain effects, EFSA applied an extra safety factor of 6 in addition to the factor 25 (factor of 2.5 for interspecies differences, and factor of 10 for intraspecies differences), resulting in a total uncertainty factor of 150 to be applied on the HED, to establish a t-TDI of 4 µg/kg bw/day (EFSA, 2015). In addition, EFSA (2015) suggested that more research is needed on the possible effects of BPA exposure on parameters that currently give rise to uncertainty.

The most recent insights into the effects of BPA exposure on the immune system (Menard et al., 2014a, 2014b), as described in Section 6.1.1, have not been taken into account in the derivation of the t-TDI presented here. The experts present at the meeting convened by the RIVM agreed, however, that the publications by Menard et al. (2014a, 2014b) provide strong evidence for effects on the immune system at 5 µg/kg bw/day that clearly warrant reconsideration of the EFSA (2015) t TDI in the context of all other available information.

A direct comparison between a given lowest observed adverse effect level with a calculated $BMDL_{10}$ is not possible, as these are different entities and, in this particular case, obtained in different test animals. Nevertheless, when the RIVM compared the 5 µg/kg bw/day adverse immune system effect dose in the Menard (2014b) study with the overall lowest calculated $BMDL_{10}$ of 8,960 µg/kg bw/day (EFSA, 2015), given the fact that the adverse effect level of 5 µg/kg bw/day was at least 20 times lower than the HED adopted by EFSA as its point of departure to derive the t-TDI, the RIVM and the experts present at the meeting concluded that these new publications by Menard et al. (2014a, 2014b) do provide strong evidence of immune system effects at a dose level of 5 µg/kg bw/day, which clearly warrants reconsideration of the EFSA (2015) t-TDI in the context of all other available information.

5.2.2 Occupational exposure limit (OEL) and derived no effect levels (DNELs)

In 2014, SCOEL amended its original recommendation for an occupational exposure limit (OEL) for BPA from 10 mg/m³ to 2 mg/m³ (SCOEL, 2014). The basis for this revised OEL remained the same, i.e. the NOAEC of 10 mg/m³ as observed in a 90-day inhalation study in rats, where only local effects (mild respiratory tract irritation/inflammation) but no systemic effects were reported at the higher levels of exposure (50 and 150 mg/m³).

Furthermore, SCOEL applied an extra assessment factor to this NOAEC, to cover for uncertainties related to the interspecies extrapolation in relation to these local effects. In their discussion on the derivation of the OEL, SCOEL noted a concern over long-term systemic effects (kidney and liver effects), which may not have been fully addressed in the subchronic inhalation study. However, SCOEL considered the margin of safety of the NOAEC of these effects and the $BMDL_{10}$ for inhalation effects 'sufficient to cover the extrapolation to long-term exposure, and also to cover possible remaining inter- and intra-species differences in toxicokinetics and toxicodynamics'.

For the dermal route, the RAC (2015) recently established a DNEL for workers of 0.2 µg/kg bw/day for the total BPA dose dermally absorbed. For the oral route, the RAC established a DNEL for workers of 8 µg/kg bw/day. The basis of these DNELs was the $BMDL_{10}$ of 8,960 µg/kg bw/day for kidney effects in a two-generation study in mice. While establishing these DNELs, RAC accounted for the fact that developmental effects on the mammary gland and on the reproductive, neurobehavioral, immune and metabolic systems could be more critical than the kidney effects (RAC, 2015).

The most recent insights into the effects of BPA exposure on the immune system (Menard et al., 2014a, 2014b), as described in Section 5.1.1, have not been taken into account in the derivation of the OEL and DNELs presented here. As with the reconsideration of the t-TDI, the RIVM concludes that the immunotoxicity data warrants reconsideration of the dermal DNEL and the OEL.

5.2.3 Possible impact of the new immunotoxicity data

When establishing the impact of the new immunotoxicity data by Menard et al. (2014a, 2014b) on the magnitude of the TDI, an accepted approach is to convert the effect dose level observed in the test animals (rats) to a human equivalent dose (HED) by using a human equivalent dose factor (HEDF). EFSA (2015) adopted this method, deriving BPA-specific HEDFs for the conversion of effect doses in different types of test animals (rats, mice, monkeys) over different critical windows of exposure (adult and neonate) (see EFSA, 2015, for a detailed description and discussion on the derivation). The HEDF is defined by a common relationship between the external dose given to an animal and the resultant internal exposure (area under the curve, AUC) and the external dose given to a human and the corresponding AUC. EFSA (2015) indicates that 'overall, the main sources of uncertainty in the determination of the HEDF are (i) the variability in the experimental animals and in the dosing and sampling procedures, and (ii) the uncertainty about the serum concentration-time course of unconjugated BPA in humans as predicted by PBPK modelling', which leads to a typical uncertainty judged by EFSA to range between 0.5 and 2 times the HEDF estimate for rats and monkeys. For mice, the uncertainty was judged higher because of the very low AUC values, the limited number of positive detects and the relatively many 'non-detects' (experimental data showed low serum levels of free BPA that were difficult to quantify). The HEDF derived by EFSA (2015) for mice led to a conservative HED.

The HEDFs derived by EFSA (2015) for the oral route, which are relevant to this report in view of the comparison between the point of departure adopted by EFSA (2015) and the effects on the immune system observed by Menard et al. (2014a, 2014b), are: $HEDF_{oral,mice,adult}$ = 0.068, $HEDF_{oral,mice,neonate}$ = 8.7, $HEDF_{oral,rat,adult}$ = 0.72, and $HEDF_{oral,rat,neonate}$ = 19. From these factors it can be concluded that, to obtain the same plasma levels, human neonates need a higher oral dose than neonatal mice and rats (HEDF >1). It is also important to note here that the HEDF for neonates is higher than the HEDF for adult animals, which can be explained by differences in metabolism, which is especially low in neonate rodents in comparison with primates.

The HEDF that should be used to derive the HED depends on the window of exposure of the test animal and the effect observed. In case of developmental effects induced in the pup in-uterus via exposure of the mother, the difficulty arises that the actual exposure of the pup is difficult to measure and highly uncertain. As a first approach, when there is no good exposure data for the pups, the exposure of the mother and the HEDF of the mother are adopted to derive the HED of the effect. When there is good exposure data for the pups or when the pups are exposed only after birth, i.e. via gavage or lactation[20], it is more appropriate to apply the HEDF for the juvenile or the neonate animal. In the case of the Menard et al. (2014a, 2014b) studies, the pups were exposed both in-uterus and post-natally. The effect observed on the immune system by Menard et al. (2014a, 2014b) may therefore be a combination of effects of BPA exposure induced in-utero and/or post-natally. In this situation, more complex HED derivation is needed, including a detailed analysis of the experimental set-up and resulting data, and no simple conversion is possible using the HEDFs derived by EFSA (2015).

The main factors adding to the complexity of deriving an HED from the Menard studies at methodological level are (the uncertainty in) (i) the actual exposure of the pup (both in-uterus and via lactation); the BPA concentration to which the pup is exposed is very low and consequently difficult to determine and highly uncertain (see also EFSA, 2010), (ii) the sensitivity of the pups at their different life stages and (iii) the window of effective exposure leading to the observed changes in the immune system. In principle, when the data is strong enough, it is possible to derive an HED via modelling of the exposure. Detailed analysis of the underlying data of the Menard et al. (2014a, 2014b) studies is needed to evaluate the possibility to derive an HED via modelling. For BPA the HEDFrat,adult is much lower than the HEDFrat,neonate. In this situation, if it could be established that the critical window of exposure to effect in both rats and humans is post-natal, then the HEDFrat,adult could be adopted as a first (conservative) approach for derivation of the HED.

Based on the Menard et al. (2014a, 2014b) data and considering the results of other immunotoxicity studies, EFSA may judge the effect of BPA on the immune system as likely, but it may find the studies by Menard insufficient to derive a $BMDL_{10}$. If the Menard data is judged insufficient to derive a

[20] Actual exposure to BPA is also highly uncertain in the case of exposure via lactation, as it is difficult to establish how much BPA from the mother's diet ends up in the milk.

Table 7 Possible impact of the new immunotoxicity data by Menard et al. (2014a, 2014b) on the magnitude of the human equivalent doses (HEDs). This table should be interpreted as indicative only. Detailed assessment of the Menard et al. data and study design is needed before reconsideration of the t-TDI by EFSA (2015).

	Effect concentrations (µg/kg bw/day)	
	RIVM	EFSA
Type of effect	Developmental immune system effects	Kidney effects
Ref.	Menard et al. (2014a, 2014b)	Tyl et al. (2008)
Test animal	Rat	Mouse
Type of measure	LOAEL	$BMDL_{10}$
External dose	5	8,960
Accounting for likely effects (EFSA, 2015, correction factor 6)	5	1,493
HED (adult)	3.6 (HEDF = 0.72)	102 (HEDF = 0.068)
HED (neonate)	95 (HEDF = 19)	12,992 (HEDF = 8.7)

$BMDL_{10}$, EFSA may consider modifying the factor of 6 that was applied to take account of likely effects with poor dose-response data in the derivation of the t-TDI (EFSA, 2015). However, if EFSA concludes that the data on immune system effects of BPA is conclusive enough to use the LOAEL of 5 µg/kg bw/day as a point of departure for the derivation of the t-TDI, the factor of 6 will probably no longer be applicable.

Table 7 shows the possible impact of the immunotoxicity data by Menard et al. (2014a, 2014b) on the magnitude of the TDI, assuming that the LOAEL of 5 µg/kg bw/day is adopted as the point of departure and appreciating the uncertainties as indicated above. When following a similar approach to that adopted by EFSA in their derivation of the TDI, the new data from the Menard studies may lead to calculated HEDs for immune system effects of between a factor of 1.1 and a factor of 28 lower than the HED of 102 µg/kg bw/day derived by EFSA (2015) and used to establish the current t-TDI (see also Table 7). It should be noted that an additional safety factor may have to be adopted that takes account of using a LOAEL instead of a $BMDL_{10}$ when deriving a TDI.

As above, reconsideration of the dermal DNEL from the effect doses leading to the developmental immune system effects observed in rats requires the conversion of the animal effect dose to the HED, with similar uncertainties involved. Additionally, to derive a dermal DNEL, route-to-route extrapolation is required to account for differences between oral and dermal uptake and toxicokinetics. The RAC (2015) performed this exercise starting from the same toxicological point of departure as EFSA (2015) to arrive at dermal DNELs for consumers and workers. From the method adopted by the RAC (2015) to derive the dermal DNEL it can be deduced that the magnitude of the dermal DNEL scales with the HEDF – in this case for oral exposure by mice. As the RAC (2015) started from the same $BMDL_{10}$ and adopted the same safety factor of 6 to account for likely effects that are uncertain as adopted by EFSA (2015), a factor of 28 may, as with the TDI, be assumed as a first rough estimate of the impact of the Menard et al. (2014a, 2014b) data on the magnitude of the dermal DNEL.

This same assumptions hold for the estimation of the impact of the immunotoxicity data by Menard et al. (2014a, 2014b) on the OEL recently derived by SCOEL. At present, the OEL is derived on the basis of respiratory tract irritation after BPA inhalation. To estimate this impact, effects observed on the immune system after oral uptake must be converted to an equivalent dose upon inhalation via a route-to-route extrapolation, which requires detailed information on the toxicokinetics of BPA (RIVM, 2014). SCOEL identified respiratory tract irritation as the most critical effect of BPA upon inhalation, which is different from the point of departure adopted by EFSA. Assuming 100% absorption of BPA and continuous sub-chronic exposure, SCOEL derived a factor of ~10 to convert the $BMDL_{10}$ or NOAEL (mg/kw bw/day) adopted by EFSA (draft, 2014; same as adopted in the final opinion by EFSA, 2015) for kidney effects induced by oral dosing to an occupational exposure limit value (mg/m^3) for inhalation (8 hours/day, 5 days/week) in humans. From this conversion, SCOEL (2014) established a 17–25-fold margin of safety (MOS) between the OEL of 2 mg/m^3 based on respiratory tract irritation and exposure level at which the systemic effects are observed that were adopted as most critical by EFSA.

The MOS for systemic effects as calculated by SCOEL is of a similar order of magnitude as the possible impact of the immunotoxicity data by Menard et al. (2014a, 2014b) on the t TDI, implying that the MOS established for systemic effects by SCOEL may not apply to possible immune system effects. A detailed analysis is needed to assess the impact of the Menard et al. (2014a, 2014b) data on the derivation of the OEL.

Conclusion

The RIVM concludes that the new data by Menard et al. (2014a, 2014b) on developmental immune system effects – food intolerance and resistance to infection – may give rise to reductions of the TDI and the dermal DNEL of more than one order of magnitude (more than a factor of 10). For the reasons outlined above, giving a first rough estimate of the impact of the Menard data on the magnitude of the OEL is not possible. The RIVM stresses that the factor of 28 indicates the possible order of magnitude of the impact of the newly observed immune system effects on the magnitude of the t-TDI and possibly the dermal DNEL, but should by no means be interpreted as an absolute value or conversion factor to be used in updating these standards. The RIVM highlights that a detailed analysis of the Menard et al. (2014a, 2014b) data, together with other data on the immunotoxicity of BPA, is needed to quantify its impact on the TDI, the dermal DNEL and the OEL.

5.3 Human exposure

Systemic exposure to free BPA depends on the route of exposure (via inhalation, oral uptake or dermal update). Systemic exposure via oral intake is lower (namely 1–10%) than via dermal intake (namely 25–30%) or via parenteral exposure; although for the latter routes of exposure, biotransformation (mainly in the liver) quickly reduces free circulating BPA (half-life: 1–3.5 hours).

Three main human exposure groups can be distinguished: consumers, workers and patients. These groups are addressed below, followed by a summary table with estimated exposures and derived MOS values.

5.3.1 Consumers

EFSA (2015) assessed exposure for various groups in the population, including several vulnerable groups (e.g. pregnant women, infants and children) in three different ways: (i) external, (ii) systemic and (iii) aggregated exposure (EFSA, 2015). A summary of average daily exposures derived by EFSA (2015) is presented in Table 9. EFSA (2015) estimated that diet is the main route of external BPA exposure in all population groups. Dietary BPA exposure is highest in infants and toddlers older than six months, mainly because of their higher consumption of foods and beverages per kilogram body weight relative to other age groups. The estimated average dietary exposure within this group is 0.375 µg/kg bw/day and the highest dietary exposure is 0.857 µg/kg bw/day.

Of the non-dietary external exposure routes, thermal paper constituted the largest source in all population groups above 3 years of age. The modelled estimates for 3–10-year-old children, adolescents, adults (including women of childbearing age) and the elderly/very elderly ranged from 0.059 to 0.094 µg/kg bw/day for average exposure and from 0.542 to 0.863 µg/kg bw/day for high external exposure. The highest aggregated exposure of 1.449 µg/kg bw/day was estimated for adolescents. Biomonitoring data was in line with the estimated internal exposure to BPA from all sources (EFSA, 2015).

5.3.2 Workers

Table 8 gives an overview of worker exposure to BPA via inhalation or dermal contact as identified in the EU RAR (EC, 2008), Arcadis (2013) and RAC (2015).

5.3.2.1 Exposure through inhalation

The EU RAR (EC, 2008) identified the following occupational settings as of highest concern for inhalation of BPA:

- BPA manufacture (i.e. bagging and other filling activities);
- Manufacture of epoxy resins.

The EU RAR concluded that there is a need for limiting the risks in these settings ('risk reduction measures which are already being applied should be taken into account') for repeated dose systemic effects and for reproductive toxicity. In addition, the EU RAR (EC, 2008) concluded that there is a need to limit the risk of skin sensitization in all occupational exposure scenarios where there is the potential for dermal contact with BPA or BPA-containing articles.

For these occupational settings, reasonable worst case (RWC) exposures of up to 3 mg/m³ TWA_{8h}

(time-weighted average) were derived, with peak exposures of up to 11 mg/m³ (EC, 2008). For other exposure scenarios, such as the production of liquid epoxy paints, powder coatings and thermal paper, inhalation exposure was estimated to be much lower (ranging from 0.001 to 0.5 mg/m³ TWA_{8h}) with peak exposures of <4 mg/m³ (see also the overview presented in RIVM, 2014[21]). The RAR concluded that there was no need for further information and/or testing, nor for risk reduction measures beyond those that are being applied already in relation to repeated dose systemic effects and reproductive toxicity for workers in the following industry sectors: manufacture of PC plastics, manufacture of articles made from PC plastics, manufacture and use of powder coatings, manufacture of thermal paper and manufacture of tin plating additive. This conclusion also applied in relation to eye and respiratory tract irritation and repeated dose local effects in the respiratory tract in all scenarios.

Since the EU RAR (EC, 2008), these exposure estimates have not been updated. The RIVM signals that, since then, work activities, methods and procedures might have changed. Risk management measures and exposure measurements may be may also have been updated, making the exposure estimates presented here outdated.

5.3.2.2 Exposure through dermal contact

In terms of exposure per cm² of skin exposed and total area exposed, the EU RAR (EC, 2008) estimated the highest dermal exposure to BPA, i.e. 12 mg/kg bw/day, to be that of maintenance workers involved in the manufacture of epoxy resins, although it was recognized that this task is not a full-shift activity, and that the use of personal protective equipment (PPE), such as gloves, was not accounted for. When the appropriate PPE is used and worn correctly, the EU RAR indicates that modelled dermal exposures will typically be a factor of 10 lower. The EASE model used in the dermal exposure estimation for the various scenarios has since been updated, however; hence RIVM (2014) concluded that the dermal exposure of workers to BPA should be reassessed, preferably by using higher tier models. These should also take account of the new studies that suggest that dermal exposure may be more significant than previously thought, for example in the case of cashiers working with thermal paper.

In 2013, Arcadis (2013) evaluated the available literature published since the EU RAR (EC, 2008) on potential dermal exposure to BPA due to contact with thermal paper and reported that estimated exposures varied strongly depending on the assumptions made with regard to the w/w% BPA in thermal paper, contact area, contact time, frequency of contact and duration of handling per day, as well as the quantity of BPA transferred from the paper to the skin, the percentage of uptake (dermal flux or absorption %) and skin factors (whether the skin is dry, humid, wet, creamed or recently washed with a detergent or alcohol). From the available information on dermal exposure, Arcadis (2013) derived an average exposure estimate of 0.0007 mg/kg bw/day, assuming humid skin, four-finger contact, a constant BPA load on the skin as described by Biedermann et al. (2010) and using the transdermal permeation coefficient as described by Weschler and Nazaroff (2012). No uncertainty analysis was included.

In 2015, the RAC assessed the exposure of shop cashiers to BPA via contact with thermal paper, in the context of a proposal prepared by the French competent authority of REACH to restrict the use of BPA at a concentration ≥0.02%w/w in thermal paper (RAC, 2015). BPA is typically present in thermal paper at a concentration of 1–2%w/w, and exposure to BPA from this paper 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. The exposure of shop cashiers was modelled using a percutaneous absorption flow model, applying both probabilistic and deterministic modelling (for details, see RAC, 2015). Based on probabilistic modelling, the RWC estimates (95th percentile) for the total BPA dose dermally absorbed ranged from 0.016 to 0.43 µg/kg bw/day, whereas those based on deterministic modelling ranged from 0.37 to 1.427 µg/kg bw/day. More realistic, median, estimates were in the order of 0.011–0.2 µg/kg bw/day (probabilistic) or 0.154 µg/kg bw/day (deterministic).

5.3.2.3 Comparison with biomonitoring data

The RAC compared the modelled dermal exposure estimates to measured urinary BPA concentrations in workers and in the general population in order to evaluate the plausibility of the scenarios adopted and the assumptions made.

For the general population, a number of biomonitoring studies indicate a fairly consistent

[21] Small differences between the ranges indicated by RIVM (2014) and the RAR (EC, 2008) stem from two use scenarios that were included in the EU RAR (EC, 2008) but are no longer applicable: manufacture of PVC and manufacture of TBBPA.

Table 8 Worker exposure via inhalation and dermal uptake. Data based on the exposures reported in the EU RAR (EC, 2008) unless otherwise indicated.

Work activities	Inhalation RWC TWA8hr [1] (mg/m^3)	Inhalation RWC short-term [1] (mg/m^3)	Dermal [2] (mg/kg bw/day)
BPA manufacturing	3	6	
- product sampling			0.6
- bag filling			6
Manufacture of PC plastic	0.001		0.0006
Manufacture of articles from PC plastic	0.001		0.0006
Manufacture of epoxy resins and moderated epoxy resins	0.7	11	
- charging reactors			6
- maintenance			12
PVC manufacture *NB: use is being phased out*	0.1	1	0.6
Manufacture of liquid epoxy paints, lacquers and powder coatings	0.01		0.028
Use of epoxy resin-based powder coatings, paints and lacquers		0.3	0.033
- powder paints	0.01		
- spraying coating powders	0.5		
- dip-painting	0.005		
Manufacture of thermal papers	0.1	4	
- charging reactors			0.6
Manufacture of tin-plating additive	0.05		
- charging reactors			0.6
Manufacture of tetra brominated flame retardants (TBBA)	1.5E-05		
- bag filling			0.00002
Professional end use of thermal printing papers			0.0007 [3] 0.0004 [4]

1) Exposures based on monitoring data.
2) Exposures as obtained from the RAR (EC, 2008) are based on EASE modelling assuming no PPE. When the appropriate PPE are used and worn correctly, dermal exposures will be a factor of 10 lower.
3) Arcadis (2013)
4) RAC (2015)

picture of a total daily exposure to BPA in the order of 10 to 100 ng/kg bw/day (geometric average; EFSA, 2015, reported 95th percentiles of 85–291 ng/kg bw/day). For workers, the available biomonitoring data was scarce and of limited nature, which made it difficult to draw firm conclusions on work-related daily exposure. From the data available, an increase in mean exposure ranging roughly from 50 to 150 ng/kg bw/day of urinary BPA concentration after working with thermal paper is derived.

The RAC further noted that the biomonitoring data should be interpreted with caution, particularly because of the relatively fast excretion of BPA and the potentially large fluctuations in intake (exposure) over a day (24 hours). Furthermore, the RAC noted that the biomonitoring data represents the sum of all routes of exposure and may be strongly influenced by other sources of BPA (e.g. dietary sources), whereas the modelling data focuses exclusively on dermal uptake. Nevertheless, the RAC found that the RWC exposure estimates for workers from probabilistic and deterministic modelling were fairly consistent with exposure estimates from the available biomonitoring studies on cashiers, and that 0.4 µg/kg bw/day represents an appropriate RWC exposure estimate for the total BPA dose dermally absorbed by workers using thermal paper (see RAC, 2015, for a more detailed discussion).

5.3.3 Patients

Medical devices and dental materials might contain BPA. Six critical exposure scenarios were evaluated by SCENIHR (2015) to estimate potential exposure to BPA during hospital and dental care. The highest exposures estimated occurred in infants during prolonged medical procedures (0.685 µg/kg bw/day), the treatment of neonates in intensive care units (ICUs) (3 µg/kg bw/day) and the treatment of dialysis patients (0.057 µg/kg bw/day). For all other groups of

Table 9 Overview of exposure estimates for consumers and patients as derived by EFSA (2015) and SCENIHR (2015), respectively, and related MOS. For consumers, average daily exposures are shown for the average-exposure scenario and the high-exposure scenario. For patients, only the highest values of the estimated exposures of BPA from medical devices and dental materials are indicated.

Population	Average daily exposure (µg/kg bw/day) average/high	MOS (t-TDI; 4 µg/kg bw/day) safety factor 150
Infants (1 day-6 months) - first most important source: dietary	0.145 - 0.225/0.435 - 0.600	28 - 18/9.2 - 6.7
Infants (6-12 months) and toddlers (1-3 years) - first most important source: dietary	0.375/0.857	11/5
Children (3-10 years) - first most important source: dietary	0.290/0.813	14/4.9
Adolescents (10-18 years) - first most important source: dietary	0.159/381	15/10
Women (18-45 years) - first most important source: dietary	0.132/0.388	30/10
Men (age 18-45 years) - first most important source: dietary	0.126/0.335	32/12
Children (0-3 years, except for infants in the first few days of life) - second most important source: house dust	0.009/0.015	444/267
Children (3-10 years), adolescents (10-18 years), adults (18-65+ years) - second most important source: thermal paper	0.059-0.094/0.542-0.863	68-43/7.4-4.6
Average external exposure to BPA from non-dietary sources such as toys and cosmetics	<0.001/<0.005	>4,000/>800
Prematurely born infants in neonatal intensive care units (ICU)	3	1.3
infants undergoing prolonged medical procedures	0.685	5.8
Children exposed to dental materials (<24 h)	0.14	29
Adults exposed to dental materials (<24 h)	0.2	20
Long-term exposures to dental materials	0.002 - 0.012	2,000 - 333
Dialysis patients	0.057	70
Long-term exposures to medical devices	0.0004 - 0.012	10,000 - 333

patients, SCENIHR (2015) concludes that exposures are similar to the exposures modelled for consumers by EFSA (2015), with similar consequent risks.

These levels of exposure often occur only over a limited period, with the exception of hemodialysis practices (SCENIHR, 2015).

5.4 Human health risk characterization

5.4.1 Consumers

Comparison of the estimates of high dietary exposure for all age groups with the t-TDI of 4 µg/kg bw/day showed that dietary exposure in all age groups (including the most exposed groups, i.e. 6–12 months infants and toddlers, with a level of 0.857 µg/kg bw/day) was more than four times lower than the t-TDI, from which EFSA (2015) concludes that this is indicating no health concern for current dietary exposure alone. The additional contribution from other oral sources, like dust and the mouthing of toys (exposure up to 0.015 µg/kg bw/day) does not change this conclusion for total oral exposure (EFSA, 2015).

Comparison of the aggregated estimates of exposure to dietary and non-dietary sources of children 3–10 years old and adolescents with the t-TDI showed that, even when the high exposure estimates for dietary sources and non-dietary sources (dust, toys, cosmetics and thermal paper) are combined, the aggregated exposure for children 3–10 years old (1.258 µg/kg bw/day) and adolescents (1.449 µg/kg bw/day) are approximately three times lower than the t-TDI. However, appreciating the uncertainties underlying the exposure assessment, EFSA indicated that the health concern for these groups is low, reflecting the finding that the upper bound high exposure estimates exceed the t-TDI and the lower bound estimates are considerably lower than the t-TDI (EFSA, 2015).

The aggregated high dietary and non-dietary exposures (including oral and dermal sources) for women (1.063 µg/kg bw/day) and men (1.010 µg/kg bw/day) are almost identical and lower than those for adolescents and children 3–10 years old. EFSA considered that the exposure estimates for men, women (including pregnant women) and prenatally exposed children would be approximately four times lower than the t-TDI of 4 µg/kg bw/day (EFSA, 2015).

Having evaluated the overall uncertainty of this assessment, the upper boundary of the uncertainty interval for dietary BPA exposure alone did not exceed the t-TDI for any age group (EFSA, 2015). The wide uncertainty intervals are caused by uncertainty about the magnitude of external exposure to BPA from thermal paper and about the proportion of BPA absorption through the skin (EFSA, 2015; SCENIHR, 2015). In October 2014, Hormann et al. published an article that studied dermal absorption in relation to a variety of skin conditions. It had previously been shown that leave-on of BPA on the skin is correlated with the skin's greasiness and humidity. Hormann et al. (2014) produced data suggesting that wet skin may give rise to higher unbound BPA serum concentrations within 90 minutes of holding thermal paper for 4 minutes than dry skin (up to a maximum of 6.95 ng/ml serum concentration compared with 0–0.5 ng/ml serum concentration of dry skin).

5.4.1.1 Impact of immune effects on the risk characterization

The above considerations on the risk characterization of consumers should be revisited in the light of the new data on developmental immunotoxicity described in Section 5.1.1. The adverse effects observed (Menard, 2014a, 2014b) at 5 µg/kg bw/day in animal studies warrant reconsideration of reference values t-TDI and DNEL, which may in turn demand a reappraisal of the characterization of risks by EFSA (2015).

When taking into account the most recent insights showing adverse effects of BPA on the immune system at a LOAEL of 5 µg/kg bw/day, the RIVM concludes that the exposures modelled by EFSA (2015) as resulting from dietary and non-dietary sources do suggest a risk for consumers in several age groups from aggregated and non-aggregated exposure. The LOAEL is at a similar level to the t-TDI, and the RIVM is of the opinion that since consumer exposure is only a factor of 3–4 below the LOAEL, the possibility of effects at the level of the TDI should be seriously reconsidered. The RIVM therefore concludes that the exposures modelled by EFSA (2015) and were concluded by EFSA (2015) to be of no risk may in fact pose a risk for consumers, in particular for the groups that are most affected by developmental effects on the immune system, i.e. foetuses, infants, toddlers and young children. Analysis of the modelled exposures by EFSA (2015) further shows that applying the LOAEL for developmental effects on the immune system may result in a risk for all age groups; a reduction of the current exposure of consumers to BPA may therefore be warranted.

5.4.2 Workers

Table 10 gives an overview of risk characterization ratios (RCRs) for the inhalation and dermal exposures summarized in Table 8. With regard to a possible risk for workers following inhalation, assuming an OEL of 2 mg/m³, RWC exposures to BPA in BPA manufacturing (i.e. bagging and other filling activities) give rise to an RCR of about 1.5. Based on the same OEL, the RCR is below 1 for inhalation in all other scenarios. This is different from the conclusion by the EU RAR (EC, 2008), which identified also a risk from inhalation of BPA in the manufacture of epoxy resins due to repeated dose systemic effects and reproductive toxicity. The RIVM concludes that there is a risk from inhalation of BPA for workers involved in the manufacture of BPA (i.e. bagging and other filling activities), and possibly for those involved in the manufacture of epoxy resins.

With regard to dermal exposure, the RIVM concludes that re-evaluation of the exposure assessment is a first priority, as the models on which the current assessment is based are no longer considered state-of-the-art. Based on the information available, the dermal DNEL of 0.2 µg/kg bw/day and the dermal exposures estimated using the EASE model (EC, 2008, as summarized in RIVM, 2014, Annex 2) give rise to an RCR of >1 for all occupational exposure scenarios, implying a risk for the unborn children of pregnant workers. For cashiers, the RWC exposure estimate of 0.4 µg/kg bw/day derived by the RAC for the total BPA dose dermally absorbed by cashiers, an RCR of 2 is obtained. All these scenarios indicate a current risk from dermal contact.

5.4.2.1 Impact of immune system effects on the risk characterization

The risk characterization of workers should be revisited in the light of the new data on developmental immunotoxicity, as described in Section 5.1.1. The adverse effects observed by Menard et al. (2014a, 2014b) at 5 µg/kg bw per day in animal studies warrant reconsideration of reference values OEL and dermal DNEL. Taking these into consideration may reveal more pronounced risks for workers. Nevertheless, irrespective of the possible lower adverse effect level due to effects on the immune system, the current OEL and dermal DNEL point to an occupational exposure risk for the

Table 10 Worker risk characterization ratios (RCR) for inhalation and dermal exposure. Data based on the exposures reported in the EU RAR (EC, 2008) unless otherwise indicated.

Work activities	RCR Inhalation RWC TWA_{8hr} [1]	RCR Dermal [2]
BPA manufacturing	1.5	
- product sampling		3,000
- bag filling		30,000
Manufacture of PC	0.0005	3
Manufacture of articles from PC	0.0005	3
Manufacture of epoxy resins and moderated epoxy resins	0.35	
- charging reactors		30,000
- maintenance		60,000
PVC manufacture *NB: use is being phased out*	0.05	3000
Manufacture of liquid epoxy paints, lacquers and powder coatings	0.005	140
Use of epoxy resin-based powder coatings, paints and lacquers		
- powder paints	0.005	165
- spraying coating powders	0.25	
- dip-painting	0.0025	
Manufacture of thermal papers	0.05	
- charging reactors		3,000
Manufacture of tin-plating additive	0.025	
- charging reactors		3,000
Manufacture of tetra brominated flame retardants (TBBA)	7.5E-06	
- bag filling		0.1
Professional end use of thermal printing papers		3.5 [3]
		2 [4]

[1] RCR calculated by adopting an OEL = 2 mg/m³ (SCOEL, 2014)
[2] RCR calculated by adopting a dermal DNEL = 0.2 µg/kg bw/day (RAC, 2015). Exposures obtained from the EU RAR (EC, 2008) are based on EASE modelling, assuming no PPE. When the appropriate PPE is used and worn correctly, dermal RCRs will be a factor of 10 lower.
[3] Arcadis (2013)
[4] RAC (2015)

unborn children of pregnant workers during the manufacturing and handling of BPA, and for the unborn children of pregnant workers when working with BPA-containing thermal paper. In line with the RAC, and given that the modelling results are consistent with biomonitoring data for workers (shop cashiers), the RIVM concludes that with respect to shop cashiers, the modelling of BPA exposure from dermal contact with thermal paper indicates that the risk for the unborn children of female shop cashiers is not adequately controlled (RCR=2).

5.4.3 Patients

The highest exposure estimates related to infants undergoing prolonged medical procedures (0.685 µg/kg bw/ day), neonates in ICUs (3 µg/kg bw/day) and dialysis patients (0.057 µg/kg bw/day) (SCENIHR, 2015). Assuming 100% bioavailability of BPA for the parenteral exposure via medical devices, SCENIHR (2015) concludes that the systemic exposure is higher than the recently established t-TDI. For all other groups of patients, SCENIHR (2015) concludes that exposures are similar to the exposures modelled for consumers by EFSA (2015), with similar consequent risks.

5.4.3.1 Impact of immune system effects on the risk characterization

The above considerations should be revisited in the light of the new data on developmental immunotoxicity, as described in Section 5.1.1. The RIVM concludes that, based on the exposures modelled by SCENIHR (2015), the new insights into possible immune system effects of BPA exposure may reveal further risks for patients, in particular for those groups most affected by developmental effects on the immune system – infants, toddlers and young children – and that a reduction of current exposure of these groups to BPA is warranted where possible.

5.5 Conclusions with regard human health risk

EFSA (2015) established a t-TDI of 4 µg/kg bw/d based on effects observed on the kidney and possible effects on the mammary gland and reproductive, metabolic, neurobehavioural and immune systems. EFSA based this assessment on scientific data available up to 2012. Since then, several studies have been published showing BPA to have adverse effects on the immune system, on the basis of which the RIVM concludes a LOAEL of 5 µg/kg bw/d for developmental immune system effects. The RIVM concludes that the current t-TDI, OEL and dermal DNEL should be reconsidered taking this new insight into account.

5.5.1 Consumers

The overall conclusion of EFSA (2015) is that dietary exposure to BPA for the highest exposed groups, which include infants, children and adolescents, is below the t-TDI of 4 µg/kg bw/day, indicating that there is no health concern for BPA at the estimated levels of exposure. In addition, EFSA concludes that the central estimates (geometric mean) for aggregated exposure to BPA via dietary sources and non-dietary sources (dust, toys, cosmetics and thermal paper) for the highest exposed groups, which include infants, children and adolescents, are also below the t-TDI of 4 µg/kg bw/day. However, appreciating the uncertainties underlying the exposure assessment, EFSA indicates that the health concern for infants, children and adolescents is low at the estimated levels of exposure, reflecting the finding that the upper bound high exposure estimates exceed the t-TDI and the lower bound estimates are considerably lower than the t-TDI (EFSA, 2015; SCENIHR, 2015).

The RIVM concludes that the above considerations should be revisited in the light of the new data on developmental immunotoxicity described in Section 5.1.1. The RIVM notes that adverse effects on food tolerance and resistance to infections have been observed in test animals at a concentration close to the t TDI and that this may give rise to an HED that is more than a factor of 10 lower than is currently adopted in the derivation of the t-TDI. When taking into account the most recent insights into the adverse effects of BPA exposure on the immune system at a LOAEL of 5 µg/kg bw/day, RIVM concludes that the exposures modelled by EFSA (2015), resulting from dietary and non-dietary sources, suggest that there is a risk for consumers in different age groups from aggregated and non-aggregated exposure. The LOAEL is at a similar level to the t-TDI and the RIVM is of the opinion that, since consumer exposure is only a factor of 3–4 below the LOAEL, the possibility of effects at the level of the TDI should be seriously reconsidered. The RIVM therefore concludes that the exposures modelled by EFSA (2015) may lead to a risk for consumers, in particular for those groups most affected by developmental effects on the immune system, i.e. unborn children, infants, toddlers and young children. Analysis of the exposures modelled by EFSA (2015) further shows that applying the LOAEL for developmental effects on the immune system may reveal a risk for all age groups and that a reduction of the current exposure of consumers to BPA is warranted.

5.5.2 Workers

An overview of the information available on occupational exposure to BPA and threshold limit values for safe work has been provided by the RIVM (2014). In summary, the information on occupational exposure mainly referred back to the EU RAR (EC, 2008), revealing a need to limit risk during the manufacture of BPA and the manufacture of epoxy resins. More recent insights further suggest that routes other than inhalation (e.g. oral and dermal) may be of greater importance to the exposure of workers than previously thought. To assess the aggregated exposure of workers via inhalation, dermal uptake and, where relevant, oral uptake, a combined exposure estimate must be derived either via route-to-route extrapolation or by calculating the total *internal* exposure to BPA as a consequence of the external exposure via the different routes. This has not been done by the EU RAR (EC, 2008) for these three routes and such an estimate is currently very difficult to make because of a lack of kinetic data.

For workers, the current information on exposure and exposure limit values leads the RIVM to conclude that there is a risk for workers from inhalation of BPA during the manufacture of BPA, and possibly during the manufacture of epoxy resins. Regarding dermal exposure, on the basis of the current information on exposure and exposure limit values, the RIVM concludes that there is a risk for the unborn children of pregnant workers in all exposure scenarios described in the EU RAR (EC, 2008) in

relation to the manufacture and use of BPA, and for cashiers working with thermal paper.

In the light of the recent insight into the effects of BPA exposure on the immune system (see Section 5.1.1) and the possibility of adverse effects at a lower level than is currently assumed, the RIVM concludes that both the OEL for inhalation and the derived DNEL for dermal exposure should be revisited. This reassessment may have an important impact on the identification of risks for the relevant workers. Consequently, the risks from occupational exposure should be reevaluated once the OEL and dermal DNEL have been revised.

The RIVM further notes that the exposure scenarios for workers involved in the manufacture and use of BPA (other than cashiers) date from before 2008. The updating of these scenarios is therefore considered to be a priority, before the actual design of risk management measures to limit the exposure of workers.

5.5.3 Patients

Exposure via medical devices generally occurs for a limited period. The highest systemic exposures estimated are those that occur in infants during prolonged medical procedures, in neonates in ICUs and in dialysis patients. These may be above the systemic exposure levels inferred from the current t-TDI of 4 µg/kg bw/day. On the basis of this data it is concluded that there may be a risk of adverse effects of BPA exposure, when the BPA is directly available for systemic exposure after non-oral exposure routes especially when the exposure of neonates in intensive care units is assessed (SCENIHR, 2015).

The above considerations should be revisited in the light of the new data on developmental immunotoxicity, as described in Section 5.1.1). The RIVM concludes that adverse effects on food tolerance and resistance to infection have been observed in test animals at a concentration close to the t-TDI. The RIVM signals that this finding raises concern that the t-TDI may not be sufficiently protective, and hence urges its reconsideration. The RIVM also indicates that when the t-TDI is revised, the present RCRs for patients may need revising, noting that in the consideration of risk management measures any risk should be weighed against the benefit of the treatment.

5.5.4 Overall conclusion

The RIVM summarizes that, on the basis of the currently established t-TDI, OEL dermal DNEL and the modelled exposures, there is a low health concern from aggregated exposure to BPA among consumers in the most sensitive groups (unborn children, infants, toddlers and young children, and adolescents), that there is a risk for the unborn children of pregnant workers from dermal exposure to free BPA and a risk for workers from exposure via inhalation, and there is a risk for infants and young children and for dialysis patients from exposure to BPA via medical devices when under prolonged medical treatment (see conclusions by EFSA, 2015, SCENIHR, 2015, and RAC, 2015).

With regard to risks for workers, the RIVM concludes that the exposure scenarios for workers involved in the manufacture and use of BPA (other than cashiers) may require updating before actual risk management measures are designed to limit occupational exposure.

The RIVM concludes that several recent studies on developmental effects on the immune system indicate that adverse effects on the immune system may occur below the current $BMDL_{10}$ derived by EFSA (2015). Additionally, the RIVM concludes that new information on the absorption of BPA through the skin may impact the dermal uptake modelled to date. On the basis of these findings, the RIVM concludes that the t-TDI, the OEL and the dermal DNEL need to be reconsidered.

With regard to possible risks for consumers and patients, the RIVM concludes that since the LOAEL identified for developmental immune effects is at the same level as the current t-TDI and the MOS is less than 10 for multiple exposure scenarios, a reduction of exposure to BPA is recommendable for those groups that are most sensitive to developmental effects.

Once the t-TDI, the OEL and the dermal DNEL are revised, the RIVM concludes that the RCRs for consumers, patients and workers may need revising.

6 Appendix III: Alternatives to BPA

6.1 Introduction

In the context of the present uncertainty as to the human health hazards presented by exposure to BPA and the discussion on the potential risks resulting from its use, it is important to have an overview of potential alternatives to BPA, taking into account their availability, technical performance, economic feasibility and safety for humans and the environment.

The analysis of alternatives is an essential part of the socio-economic considerations that – together with a risk assessment – provide a rational basis for providing advice to policy makers on the proportionality of proposed risk management measures.

Section 6.2 of this Appendix sketches the various approaches to finding alternatives and the levels of substitution that may be considered. Section 6.3 summarizes the available information. Section 6.4 gives an overview of possible alternatives to BPA in PC plastics and epoxy resins (Section 6.4.1), in thermal paper (Section 6.4.2) and for use in medical devices (Section 6.4.3). Section 6.5 presents the main conclusions and recommendations.

6.2 Approaches to substitution

Information on specific alternatives to BPA is scarce, scattered and, in most cases, lacking an assessment on their feasibility. Furthermore, within the field of regulatory risk management of chemicals, the analysis of alternatives has only recently been initiated and is a process that requires clear scoping, in-depth knowledge on chemical functioning and collaborative assessment involving stakeholders and authorities. A prerequisite for proper substitution is knowledge on the availability of safe(r) alternatives.

Scoping of the assessment of alternatives is an extremely important step, consisting of defining the

regulatory perspective and assessing the proportionality of the measures proposed. Such an assessment can be performed from the perspective of a single company (actor in a supply chain), one or more interlinked supply chains or society at large. The perspective chosen will affect the evaluation of possible alternatives and their suitability for substitution.

The first step in the assessment of alternatives is to define the function of the chemical that needs substitution, which can be done at different levels: the function of the substance in a material, the function of such a material in an article and the function of the article itself. Consequently, three levels of substitution may be distinguished:

- **Drop-in replacement**
  This involves the direct replacement of BPA by an alternative chemical substance, based on comparable functionality (a so-called drop-in alternative). Alternatives within this category may be BPA structural analogues or substances with less structural resemblance that are nevertheless capable of performing the required chemical function. Drop-in replacement in general is characterized by a relatively low impact on companies at a fixed point in the supply chain.

- **Material substitution**
  This involves indirect substitution for BPA by replacing the material it is used in by another material with comparable functionality. This could be the use of an alternative polymer in place of PC. If the new material must be newly developed, this level of substitution is more complex and time-consuming than drop-in replacement. Moreover, replacement at the level of materials will affect more one company in a supply chain or even multiple, interlinked supply chains. Even if material alternatives are already available on the market, the socio-economic impacts of the substitution are likely to be substantial, since it might result in a shift between supply chains, affect the technological requirements for equipment further down the supply chain and/or could have a large impact on recycling and disposal.

- **Non-chemical substitution**
  Non-chemical substitution involves solutions that replace the function of an article. Changing the articles design is an example of such a solution. This alternative could make a specific chemical functionality of BPA redundant. An example of such redundancy is the replacement of the use of thermal paper receipts by electronic receipts issued via the internet. As in case of material substitution, non-chemical substitution can have significant socio-economic impacts but can also result in or stimulate smart and sustainable innovation.

The type of substitution that is possible or preferred depends on the scope of the substitution assessment, the materials and articles in which the substance is used, the complexity of the value chain and the actors within that chain, and the availability and technical and economical feasibility of safe(r) or less hazardous alternatives.

6.3 Available information on possible alternatives to BPA

In the assessment published by EFSA (2015), PC plastics, epoxy resins and thermal paper (containing BPA as a colour developer) were identified as the main sources of consumer exposure to BPA. In addition, SCENIHR (2015) identified BPA exposure via medical devices as a possible risk for infants and young children and dialysis patients. The current summary of possible alternatives therefore focuses on these uses of BPA.

It should be noted that a comprehensive analysis of the question of substitution requires a complex, integrated risk assessment and a socio-economic study based on the required functionality of the material for each specific application (article) is the starting point of the assessment. It is beyond the scope of the current advice to actually conduct an analysis of the socio-economic impact of possible substance or material or non-chemical-substitutes for BPA-containing materials for each of its uses. To the best of our knowledge, such an analysis is not available for all of the uses of BPA. What is available in terms of information on alternatives to BPA is reflected in the sections below.

6.3.1 Polycarbonate plastics, epoxy resins and colour developers

The current summary of alternatives for the function of BPA in PC plastics, epoxy resins and thermal paper is based on four recently published overviews:
- Arcadis (2013): A study commissioned by the RIVM on dermal exposure to BPA by workers and

possible alternatives to BPA for its most important applications: PC plastics, epoxy resins, thermal paper;
- Health Council of The Netherlands (2014): An advisory letter on the health risks posed by BPA analogues;
- Wageningen University (2014): A study commissioned by the RIVM providing an overview of potential alternatives to BPA with a focus on its application in thermal paper but also briefly addressing its two other main uses: the production of polycarbonates and epoxy resins. The study specifically addressed so-called 'biobased' alternatives, i.e. those that may be produced from renewable feedstock instead of fossil sources.
- United States Environmental Protection Agency (US EPA) (2014): A report providing information on BPA and possible alternatives for use in thermal paper.

In 2013, Arcadis published a report on BPA exposure at the workplace and possible alternatives, with the aim of providing an overview of potential substitutes for BPA on the basis of available literature and of evaluating their suitability. For the investigation of substitutes the report refers back to the inventories prepared by:
- the French governmental institute ANSES (2012, 2013);
- the Swedish Chemicals Inspectorate KEMI (2012);
- the US EPA (2014);
- the Maine Department of Environmental Protection (US) (2012).

ANSES (2012, 2013) analysed 73 alternatives (21 for polycarbonate uses, 19 for epoxy resins and 34 for thermal paper use). The Maine Department of Environmental Protection (US) reported on alternatives to BPA in infant formula cans and baby food jar lids. The report focused on material-level replacement and provided a scorecard evaluating and categorizing plastic products based on environmental benchmarks for feedstock production, chemical and plastics manufacturing, use and end of life. KEMI (2012) and the US EPA (2014) focused on alternatives for use in thermal paper only. KEMI listed 17 alternatives for thermal paper use, of which 12 were analysed with respect to their hazard profiles and 5 were stated to be available on the Swedish market. US EPA analysed the hazards of 19 alternatives that are commercially available for use in thermal paper.

In addition to these works, in 2014, the RIVM commissioned a study on potential alternatives to BPA (for use in PC plastics, epoxy resins and thermal paper) with a focus on their possible production from renewable resources. The review included an expert evaluation of the data on alternatives presented in the French Restriction dossier on the use of BPA in thermal paper submitted under REACH. Key criteria used in the assessment of alternatives were availability, technical feasibility and economic feasibility.

6.4 Possible alternatives to BPA

These studies suggest that for each critical application of PBA, i.e. in PC plastics, epoxy resins and thermal paper, there are alternatives that might be preferable to BPA in terms of their effects on humans or the environment. Alternatives are identified at drop-in and material substitution level. However, each of these studies also clearly points out that, before conclusions can be drawn on acceptability as an alternative, more information is needed for each alternative on:
- possible health hazards for humans and the environment;
- technical and economic feasibility;
- availability on the market.

With respect to drop-in replacement, several substances have been identified that are close structural analogues to BPA. In 2014, the Health Council of The Netherlands advised the Dutch Minister of Health, Welfare and Sports on the health risks of BPA analogues, i.e. compounds chemically related to BPA. The main conclusion of the Council was that BPA analogues are not necessarily suitable substitutes for BPA, since they may have similar toxicological properties. The Council based this conclusion on the finding that available data on receptor binding and hormonal disruption shows that the hormonal effects of BPA analogues vary significantly, their potency ranging between far below and above the level of BPA. The Council states that some of these BPA analogues have been authorized for use where otherwise BPA would have been used, without specifying which 'authorization schemes' it is referring to. The Health Council advised the Dutch government to take the position that replacement of BPA with analogues is currently inadvisable and to advocate using alternatives unrelated to BPA.

The Health Council advice is not fully clear on the specific BPA analogues addressed in its assessment. From the list of references in the advice it is assumed

that the assessment is limited to other bisphenolic compounds with similar chemical structures, such as Bisphenol S, Bisphenol F (both of which are specifically mentioned). However, many other (bis) phenolic alternatives to BPA have been identified, such as BPM, BPB, BPAP, BPAF and BAD. The RIVM acknowledges that data on receptor binding and hormonal disruption is probably not readily available for all analogues and that read-across considerations based on weight of evidence may have played an important role in the Health Council's advice against the replacement of BPA by BPA analogues. The RIVM is of the opinion that such a cautious approach is defendable from the perspective of authorities and by best means could act as an incentive to industry as to develop BPA alternatives that are safe for use.

6.4.1 Polycarbonate plastics and epoxy resins

For BPA in PC plastics and epoxy resins, promising material substitutes already exist. A range of polymers and materials exist that could potentially replace PC plastics and BPA-based epoxy resins. Some of these are already commercially available, others are under development. Some alternative polymers seem more promising than others in terms of hazard on the basis of an initial assessment of the properties of their monomers and additives.

Functional drop-in alternatives for BPA uses in PC plastics and epoxy resins also exist. Most of these are close structural analogues and hence may not be suitable alternatives (unless is proven that their hazard profile is preferred over that of BPA). From the studies assessed, however, two drop-in alternatives are promising from a hazard perspective because they are not close structural analogues to BPA and may be produced from renewable resources.

For PC plastics, alternatives that seem promising on the basis of the limited information available are:
- **Drop-in level:** diphenolic acid (CAS: 126-00-1, and derivatives);
- **Material substitutes for food contact materials:** PE, PP or PLA.

For epoxy resins, alternatives that seem promising on the basis of the limited information available are:
- **Drop-in level:** diphenolic acid (CAS: 126-00-1, and derivatives) and lauryl gallate CAS: 1166-52-5 (or other gallic acid derivatives);
- **Material substitutes for food contact materials:** isosorbide-based resins, polyacrylates and oleoresin (toxicological information on the monomer and additives is too limited to draw firm conclusions), aseptic cartons and glass.

Because BPA is used as a monomer, substitution usually translates into 'material substitution', rather than replacement by a functional alternative at drop-in level. As stated above, it is beyond the scope of the current advice to conduct an analysis on the socio-economic impact of potential substitutes. To the best of our knowledge, the technical and economic feasibility of these alternatives have not been assessed to date.

6.4.2 Thermal paper

From the studies reviewed, the following alternatives to BPA as a colour developer in thermal paper seem promising:
- DD70 (CAS: 93589-69-6);
- D90 (CAS 191680-83-8);
- Pergafast 201 (CAS: 232938-43-1);
- Urea Urethane (UU) (CAS: 321860-75-7);
- Diphenolic acid (CAS: 126-00-1, and derivatives);
- Lauryl gallate (CAS: 1166-52-5, or other gallic acid derivatives).

Some of these are non-phenolic and may be produced from renewable resources.

For some applications, the use of thermal printing paper can be replaced by electronic alternatives, which may have an advantage over chemical alternatives with a possibly incomplete or unknown hazard profile. For those applications where an electronic alternative is not an option, chemical alternatives may be considered. A full impact assessment should be conducted to address the desirability of possible substitution scenarios. As is indicated above, such an assessment is beyond the scope of the current advice.

The French restriction proposal included a socio-economic analysis, which the Socio-Economic Assessment Committee (SEAC) is in the process of reviewing. The SEAC's preliminary conclusion using a break-even analysis primarily of D8 and Pergafast 201 was: 'From an economic efficiency perspective, i.e. 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' (SEAC draft opinion). The final SEAC opinion is expected early 2016.

Whether or not a restriction on BPA in thermal paper is appropriate is a political question that should in the view of the RIVM incorporate risk and proportionality considerations as estimated by the RAC and SEAC and wider socio-economic information such as distributional effects, affordability and societal concern around BPA and endocrine disrupting chemicals. The RIVM is of the opinion that this broader context is especially important in the case of BPA, as the risks are uncertain and ambiguous. For dossier with uncertain and ambiguous risks holds that a precautious type of risk management is appropriate (GRG, 2008).

6.4.3 Medical devices

With regard to medical devices, Health Care Without Harm recently published an overview of possible alternatives to BPA (Amaral, 2014). To the best of our knowledge, this is the only inventory of possible alternatives to BPA in medical devices. Amaral (2014) indicates that a number of the possible alternatives indicated for use in PC plastics or epoxy resins for FCM are also possible alternatives for use in medical devices, and lists nine alternatives that are already used in medical devices. For five of these, Amaral indicates the potential disadvantage that they may have estrogenic activity or leach substances with estrogenic activity.

The four remaining alternatives are:
- Cyclic olefin polymers – COC/COP (CAS: 2600-43-2); already being used in medical syringes, catheters and medical diagnostic components;
- Poly-lactic acid – PLA (CAS: 26199-51-6); already being used in medical implants and bone fixation devices;
- Polyetherimide (CAS: 61128-46-9); already being used in resins for healthcare applications, sterilization trays, dentist devices and pipettes;
- Polyphenylsulfone – PPSU (CAS: 25608-64-4); already being used in medical tubing and orthopedic, dental and surgical instruments.

Although these alternatives look promising, it should be noted that for all of them a general lack of data was concluded and further research on the toxicity profile of these alternatives is needed for reliable conclusions to be made as to their appropriateness for substitution.

In evaluating the possible substitutes for BPA in medical devices, it is important to include the health benefit for the patient in the final risk–benefit evaluation of the possible substitute. The health benefit of the patient should also be considered in the wider socio-economic analysis or cost–benefit assessment. To the best of our knowledge, no such assessment exists either for BPA in medical devices or for its possible substitution. This is in line with the opinion of SCENIHR (2015), which found the toxicological information on BPA alternatives to be limited and considered that it was not possible to compare the potential risk associated with alternatives with the risk due to BPA.

6.5 Conclusions and policy considerations

Various institutions, including the Health Council of The Netherlands, advise against the use of BPA structural analogues, such as BPS and BPF, as alternatives to BPA, since a hormone mode of action similar to those of BPA are expected on the basis of the limited data currently available and read-across evaluation. The RIVM supports this position. To prevent an undesirable substitution of BPA, it is recommended that possible alternatives are better characterized for their hazard profile.

The RIVM emphasizes that the information on possible alternatives and their current use is scattered, and their possibilities for substitution is difficult to assess. Two examples of initiatives aiming to create a portal for a more comprehensive search for possible alternatives to BPA are the Service national d'assistance substitution-BPA, organized by INERIS, for general uses of BPA[22] and Healthcare Without Harm for medical devices in particular[23]. Such initiatives may support substitution by disclosing information on suitable alternatives to a broad public.

Conclusions regarding alternatives to BPA in PC plastics and epoxy resins

Several possible alternatives for BPA have been identified for use in PC plastic and epoxy resins. At present, there is insufficient insight into their possible health hazards, or the absence thereof, for reliable conclusions to be reached on the feasibility or possible desirability of most of these alternatives, including close structural analogues. In addition, PC plastics and epoxy resins are used in a wide variety of products and articles, including food packaging

[22] http://www.ineris.fr/substitution-bpa/en
[23] https://noharm.org/

and can linings, for each of which the technical and economic feasibility of substitution needs to be assessed.

Conclusions regarding alternatives to BPA in thermal paper

A REACH restriction proposal on the use of BPA in thermal paper is currently being processed. In addition to this proposed measure, the registration dossier for PBA has been updated by its registrant such that it no longer supports the use of BPA in the production of thermal paper. The production of BPA-containing thermal paper in the EU is therefore no longer permitted[24]. As a result, it can be expected that there will be a shift towards BPA alternatives in the thermal paper market in the near future.

A shift to BPS or other close structural analogues is one possibility but is considered undesirable, given the potentially hazardous properties of such alternatives, and would reduce the effectiveness of any measure restricting BPA use in thermal paper. Some thermal paper producers have indeed already indicated that they will not consider BPS as a suitable drop-in alternative.

Potential bio-based alternatives to BPA in thermal paper that may be less hazardous have been identified and are promising. Further study is, however, required on hazard properties and technical and economic feasibility before reliable conclusions can be drawn on the feasibility of these alternatives.

Alternatively, electronic alternatives to thermal paper may be considered for uses where these are feasible. Electronic alternative may prevent the introduction of substances with an uncertain hazard profile for humans and the environment and may also have other advantages, such as more sustainable properties (paperless).

Conclusions with regard to alternatives to BPA in medical devices

In the case of substitution for BPA in medical devices, the technical requirements of the material play an important role in finding viable alternatives. Some alternatives to BPA or BPA-containing materials are already available on the market for a number of applications of medical devices. However, for some devices, replacement of BPA by less hazardous substances at drop-in or material substitution level may be a lengthy process. Therefore, when possible, changing the design of a device in order to reduce exposure to BPA could be considered. In fact, it is uncertain to what extent such a design-oriented approach has already been put into practice.

Feasibility analysis of alternatives to BPA in PC plastics, epoxy resins, thermal paper and medical devices

For uses where exposures indicate the highest concern, an assessment of alternatives, including a detailed analysis of their technical and socio-economic aspects, is required before reliable decisions can be made on their feasibility. This analysis should include broader assessment of the expected impact of substitution on society as a whole. In addition, for most of the possible alternatives indicated, there is limited information on their toxicological profile. More information on this is needed before a replacement of BPA can be successful.

[24] Unless a downstream user decides to register this use.

7 Appendix IV: Downstream consequences of Repro Cat.1B classification

The following regulatory frameworks have been screened for specific requirements of substances with a harmonized classification as reproductive toxicant category 1A or 1B (Repro Cat1A or 1B)

- Industrial Emissions Directive (2010/75/EC);
- Ecolabel Regulation (66/2010/EC);
- Toy Safety Directive (2009/48/EC);
- Waste Framework Directive (2008/98/EC);
- Cosmetics Regulation (1223/2009/EC);
- Medical Devices Directive (93/42/EEC, 2007/47/EC) (a new medical devices regulation is currently under discussion);
- Plastic Materials in Contact with Food Regulation (10/2011/EC);
- EU OSH legislation:
  - Chemical Agents Directive (98/24/EC; CAD);
  - Carcinogens and Mutagens Directive (2004/37/EC; CMD);
  - Pregnant Workers and Workers Who Have Recently Given Birth or Are Breastfeeding Directive (1992/85/EEC);
  - Young People at Work Directive (1994/33/EC).

The implication of harmonized classification as Repro Cat.1B under the CLP Regulation for these frameworks is summarized below. For the complete legal text, the respective framework should be consulted.

7.1 Industrial Emissions Directive (2010/75/EC)

(Activiteitenbesluit and other legislation)

The information included below may change as a consequence of the ongoing revision of the Activiteitenbesluit.

7.1.1 Special provisions for installations and activities using organic solvents (Chapter V)

Article 58:
Substances or mixtures which, because of their content of volatile organic compounds classified as carcinogens, mutagens, or toxic to reproduction under Regulation (EC) No 1272/2008, are assigned or need to carry the hazard statements H340, H350,H350i, H360D or H360F, shall be replaced, as far as possible by less harmful substances or mixtures within the shortest possible time.

Article 59.5:
The emissions of either volatile organic compounds which are assigned or need to carry the hazard statements H340, H350, H350i, H360D or H360F or halogenated volatile organic compounds which are assigned or need to carry the hazard statements H341 or H351, shall be controlled under contained conditions as far as technically and economically feasible to safeguard public health and the environment and shall not exceed the relevant emission limit values set out in Part 4 of Annex VII.

As BPA is a solid with a low vapour pressure (0.00000000161 hPa at 20°C) and is not a volatile solvent (liquid), articles 58 and 59.5 do not apply to BPA.

7.1.2 Permit conditions

Article 14.1:
Member States shall ensure that the permit includes all measures necessary for compliance with the requirements of Articles 11 and 18.
Those measures shall include at least the following:
a. emission limit values for polluting substances listed in Annex II, and for other polluting substances, which are likely to be emitted from the installation concerned in significant quantities, having regard to their nature and their potential to transfer pollution from one medium to another.

Annex II – on permit conditions
Air:
12. Substances and mixtures, which have been proved to possess carcinogenic or mutagenic properties or properties which may affect reproduction via the air.

Water:
4. Substances and mixtures, which have been proved to possess carcinogenic or mutagenic properties or properties which may affect reproduction in or via the aquatic environment.

The above implies for the harmonized classification of BPA in Repro Cat.1B that for industrial installations likely to emit BPA a permit with an emission limit is required.

7.2 Ecolabel Regulation (66/2010/EC)

Consolidated version 04.09.2013.

7.2.1 Substances not allowed in EU Ecolabel goods

Paragraph 6:
The EU Ecolabel may not be awarded to goods containing substances or preparations/mixtures meeting the criteria for classification as toxic, hazardous to the environment, carcinogenic, mutagenic or toxic for reproduction (CMR), in accordance with Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on [the] classification, labelling and packaging of substances and mixtures, nor to goods containing substances referred to in Article 57 of Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency.

7.2.2 Derogations to substances not allowed in EU Ecolabel goods

Paragraph 7:
For specific categories of goods containing substances referred to in paragraph 6, and only in the event that it is not technically feasible to substitute them as such, or via the use of alternative materials or designs, or in the case of products which have a significantly higher overall environmental performance compared with other goods of the same category, the Commission may adopt measures to grant derogations from paragraph 6. No derogation shall be given concerning substances that meet the criteria of Article 57 of Regulation (EC) No 1907/2006 and that are identified according to the procedure described in Article 59(1) of that Regulation, present in mixtures, in an article or in any homogeneous part of a complex article in concentrations higher than 0.1 % (weight by weight). Those measures, designed to amend non-essential elements of this Regulation, shall be adopted in accordance with the regulatory procedure with scrutiny referred to in Article 16(2).

This means for the harmonized classification of BPA in Repro Cat.1B that goods containing BPA do not meet the Ecolabel requirements, and hence can no longer be brought onto the market carrying that label.

7.3 Toy Safety Directive (2009/48/EC)

Consolidated version 20.07.2014.
(Warenwet besluit speelgoed, 2011)

7.3.1 Particular safety requirements for toys (Annex II)

7.3.1.1 Chemical properties (Section III)

Point 3:
Without prejudice to the restrictions referred to in the second paragraph of point 1, substances that are classified as carcinogenic, mutagenic or toxic for reproduction (CMR) of category 1A, 1B or 2 under Regulation (EC) No 1272/2008 shall not be used in toys, in components of toys or in micro-structurally distinct parts of toys.

Point 4:
By way of derogation from point 3, substances or mixtures classified as CMR of the categories laid down in Section 3 of Appendix B may be used in toys, in components of toys or micro-structurally distinct parts of toys provided that one or more of the following conditions is met:

a. these substances and mixtures are contained in individual concentrations equal to or smaller than the relevant concentrations established in the Community legal acts referred to in Section 2 of Appendix B for the classification of mixtures containing these substances;
b. these substances and mixtures are inaccessible to children in any form, including inhalation, when the toy is used as specified in the first subparagraph of Article 10(2);
c. a decision in accordance with Article 46(3) has been taken to permit the substance or mixture and its use, and the substance or mixture and its permitted uses have been listed in Appendix A.

That decision may be taken if the following conditions are met:

i. the use of the substance or mixture has been evaluated by the relevant Scientific Committee and found to be safe, in particular in view of exposure;
ii. there are no suitable alternative substances or mixtures available, as documented in an analysis of alternatives; and
iii. the substance or mixture is not prohibited for use in consumer articles under Regulation (EC) No 1907/2006.

The Commission shall mandate the relevant Scientific Committee to re-evaluate those substances or mixtures as soon as safety concerns arise and at the latest every five years from the date that a decision in accordance with Article 46(3) was taken.

Point 7:
Points 3, 4 and 5 shall not apply to materials that comply with the specific limit values set out in Appendix C, or, until such provisions have been laid down, but not later than 20 July 2017, to materials covered by and complying with the provisions for food contact materials set out in Regulation (EC) No 1935/2004 and the related specific measures for particular materials.

BPA is not included in Appendixes A or C.

The above means for the harmonized classification of BPA in Repro Cat.1B that BPA shall not be used in toys, in components of toys or in micro-structurally distinct parts of toys unless the concentration is below 0.5% (until 31 May 2015) or 0.3% (after 31 May 2015) or BPA is inaccessible to children when the toys are used as intended or in a foreseeable way.

According to the guidance accompanying the Toy Safety Directive, the steps described in Clauses 8.3; 8.4; 8.5; 8.7; 8.8; 8.9; 8.10 of EN 71-1:2011 have to be performed in order to ensure inaccessibility. These criteria are, however, not exhaustive, since they do not cover inhalation exposure.

7.4 Waste Framework Directive (2008/98/EC)

7.4.1 Properties of waste which render it hazardous (Annex III)

H 10 'Toxic for reproduction': substances and preparations, which, if they are inhaled or ingested or if they penetrate the skin, may induce non-hereditary congenital malformations or increase their incidence (as defined in Annex VI of CLP: 67/548/EEC).

7.4.1.1 Control of hazardous waste (Article 17)

Member States shall take the necessary action to ensure that the production, collection and transportation of hazardous waste, as well as its storage and treatment, are carried out in conditions providing protection for the environment and human health in order to meet the provisions of Article 13, including action to ensure traceability from production to final destination and control of hazardous waste in order to meet the requirements of Articles 35 and 36.

7.4.1.2 Ban on the mixing of hazardous waste (Article 18)

Paragraph 1:
Member States shall take the necessary measures to ensure that hazardous waste is not mixed, either with other categories of hazardous waste or with other waste, substances or materials. Mixing shall include the dilution of hazardous substances.

Paragraph 2:
By way of derogation from paragraph 1, Member States may allow mixing provided that:
- the mixing operation is carried out by an establishment or undertaking which has obtained a permit in accordance with Article 23;
- the provisions of Article 13 are complied with and the adverse impact of the waste management on human health and the environment is not increased; and
- the mixing operation conforms to best available techniques.

Paragraph 3:
Subject to technical and economic feasibility criteria, where hazardous waste has been mixed in a manner contrary to paragraph 1, separation shall be carried out where possible and necessary in order to comply with Article 13.

7.4.1.3 Labelling of hazardous waste (Article 19)

1. Member States shall take the necessary measures to ensure that, in the course of collection, transport and temporary storage, hazardous waste is packaged and labelled in accordance with the international and Community standards in force.
2. Whenever hazardous waste is transferred within a Member State, it shall be accompanied by an identification document, which may be in electronic format, containing the appropriate data specified in Annex IB to Regulation (EC) No 1013/2006.

7.4.1.4 Record keeping (Article 35)

1. The establishments or undertakings referred to in Article 23(1), the producers of hazardous waste and the establishments and undertakings which collect

or transport hazardous waste on a professional basis, or act as dealers and brokers of hazardous waste, shall keep a chronological record of the quantity, nature and origin of the waste, and, where relevant, the destination, frequency of collection, mode of transport and treatment method foreseen in respect of the waste, and shall make that information available, on request, to the competent authorities.

2. For hazardous waste, the records shall be preserved for at least three years except in the case of establishments and undertakings transporting hazardous waste[,] which must keep such records for at least 12 months.

In addition, there are some requirements of the competent authorities regarding the periodic inspection of hazardous waste.

This means for the harmonized classification of BPA in Repro Cat.1B that waste containing BPA is considered hazardous waste and may not be mixed with other waste, that record should be kept of this waste by the owner, protective measures should be taken to prevent emission and exposure and that the waste should be labelled.

7.5 Cosmetics Regulation (1223/2009/EC)

Consolidated version 16.07.2015.

7.5.1 Substances classified as CMR substances (Article 15)

2. The use in cosmetic products of substances classified as CMR substances, of category 1A or 1B under Part 3 of Annex VI to Regulation (EC) No 1272/2008, shall be prohibited.

However, such substances may be used in cosmetic products by way of exception where, subsequent to their classification as CMR substances of category 1A or 1B under Part 3 of Annex VI to Regulation (EC) No 1272/2008, all of the following conditions are fulfilled:

(a) they comply with the food safety requirements as defined in Regulation (EC) No 178/2002 of the European Parliament and of the Council of 28 January 2002 laying down the general principles and requirements of food law, establishing the European Food Safety Authority and laying down procedures in matters of food safety;

(b) there are no suitable alternative substances available, as documented in an analysis of alternatives;

(c) the application is made for a particular use of the product category with a known exposure; and

(d) they have been evaluated and found safe by the SCCS for use in cosmetic products, in particular in view of exposure to these products and taking into consideration the overall exposure from other sources, taking particular account of vulnerable population groups.

Specific labelling in order to avoid misuse of the cosmetic product shall be provided in accordance with Article 3 of this Regulation, taking into account possible risks linked to the presence of hazardous substances and the routes of exposure.

In order to implement this paragraph, the Commission shall amend the Annexes to this Regulation in accordance with the regulatory procedure with scrutiny referred to in Article 32(3) of this Regulation within 15 months of the inclusion of the substances concerned in Part 3 of Annex VI to Regulation (EC) No 1272/2008.

On imperative grounds of urgency, the Commission may use the urgency procedure referred to in Article 32(4) of this Regulation.

The Commission shall mandate the SCCS to re-evaluate those substances as soon as safety concerns arise, and at the latest five years after their inclusion in Annexes III to VI to this Regulation, and at least every subsequent five years.

This means for the harmonized classification of BPA in Repro Cat.1B that it is prohibited for use in cosmetic products unless all the conditions set out in article 15.2 are fulfilled.

7.6 Medical Devices Directive (93/42/EEC)

7.6.1 Essential requirements (Annex I)

I. General requirements

1. The devices must be designed and manufactured in such a way that, when used under the conditions and for the purposes intended, they will not compromise the clinical condition or the safety of patients, or the safety and health of users or, where applicable, other persons, provided that any risks which may be associated with their intended use

constitute acceptable risks when weighed against the benefits to the patient and are compatible with a high level of protection of health and safety.

6. Any undesirable side-effect must constitute an acceptable risk when weighed against the performances intended.

II. Requirements regarding design and construction
7. Chemical, physical and biological properties
7.1. The devices must be designed and manufactured in such a way as to guarantee the characteristics and performances referred to in Section I on the 'General requirements'. Particular attention must be paid to:
- the choice of materials used, particularly as regards toxicity and, where appropriate, flammability,
- the compatibility between the materials used and biological tissues, cells and body fluids, taking account of the intended purpose of the device.

7.5. The devices must be designed and manufactured in such a way as to reduce to a minimum the risks posed by substances leaking from the device. Special attention shall be given to substances which are carcinogenic, mutagenic or toxic to reproduction, in accordance with Annex I to Council Directive 67/548/EEC of 27 June 1967 on the approximation of laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances (1).

If parts of a device (or a device itself) intended to administer and/or remove medicines, body liquids or other substances to or from the body, or devices intended for transport and storage of such body fluids or substances, contain phthalates which are classified as carcinogenic, mutagenic or toxic to reproduction, of category 1 or 2, in accordance with Annex I to Directive 67/548/EEC, these devices must be labelled on the device itself and/or on the packaging for each unit or, where appropriate, on the sales packaging as a device containing phthalates.

If the intended use of such devices includes treatment of children or treatment of pregnant or nursing women, the manufacturer must provide a specific justification for the use of these substances with regard to compliance with the essential requirements, in particular of this paragraph, within the technical documentation and, within the instructions for use, information on residual risks for these patient groups and, if applicable, on appropriate precautionary measures.

7.7 Plastic Materials in Contact with Food Regulation (10/2011/EC)

7.7.1 Precautionary measures

With regard to food contact materials (FCM) there is limited space for national precautionary measures, given the plastics regulation 10/2011/EC and its impact on the regulation of other FCM.

7.7.2 Plastics

The EU Regulation 10/2011/EC on plastic materials and articles intended to come into contact with food sets out which substances may be used in FCM. Substances which have been approved for use in plastics are placed on a 'positive list'. BPA is on the positive list and has a specific migration limit (SML) of 0.6 mg/kg food that is binding for all Member States. The limits for substances mentioned in 10/2011/EC have been assessed as safe by EFSA. Adjustment of these limits is possible only through the Standing Committee on Plants, Animals, Food and Feed (SC-PAFF), after voting by the Member States. Proposals for adjustments put forward for voting are written by the European Commission, based on input from the WGE FCM, and are consistent with the EFSA Opinion.

BPA is also used in coatings for cans. The Plastic Materials in Contact with Food Regulation does not cover coatings. National legislation may apply to substances used in coatings provided that it does not interfere with mutual recognition. Of all the Member States, only the Netherlands has a positive list for substances used in coatings. BADGE (bisphenol A DiGlycidyl Ether, made from BPA) is on this list with the annotation: 'according to chapter 1'. Chapter 1 refers to the plastics chapter, which ultimately refers to Regulation 10/2011. Given this cross-reference, the SML for BPA in plastics also applies to coatings.

7.7.3 Non-plastics

Regulation 10/2011/EC does not apply to materials other than plastics. In the absence of EU regulation on other materials, national legislation applies, with the condition that limits must not be lower than necessary from a risk perspective, in order to maintain a level playing field for international trade.

In the absence of national legislation, the SMLs adopted in other Member States apply, based on the principle of mutual recognition. Alternatively, the limits for substances in plastics stipulated in 10/2011/EC apply to the substance, if used in other FCM, as a way to fulfill the requirement of Art. 3 of the Framework Regulation that 'a substance intended for use in FCM should not pose a public health risk'.

EFSA considered the SML for BPA of 0.6 mg/kg food as safe. Only on the basis of scientific data showing a probable risk at this level may the substance limit be adjusted at national level.

7.7.4 Impact of Repro Cat.1B classification

Classification of a substance as reprotoxic does not directly influence whether it may be included on the positive list. If a dossier has been submitted to apply for authorization of use of a substance in FCM, a risk assessment will be performed. If this risk assessment indicates that the substance can be used in a safe way, the substance can be placed on the positive list. Thus, there is a risk-based, and not hazard-based, procedure in place. Substances in FCM that are not on the positive list but which are allowed to be used in FCM due to very limited migration (<10 ppb) should, however, not be classified as CMR.

7.8 EU OSH legislation

7.8.1 Chemical Agents Directive (98/24/EC; CAD)

The CAD includes no specific provisions for substances classified as Repro besides the general requirements for hazardous substances, including:

- Conducting of a risk assessment;
- Elimination of risk to a minimum, preferably by substitution;
- Execution of health surveillance if it is appropriate to the nature of the risk; note that health surveillance is compulsory for substances for which a BOEL (binding OEL) is set – which is not the case with BPA. However, the establishment of a BOEL for reprotoxic (R) substances is possible, as demonstrated by the example of lead and its compounds.

7.8.2 Carcinogens and Mutagens Directive (2004/37/EC; CMD)

The CMD does not apply to substances which are only classified as Repro but does apply ot substances that have a harmonized classification with C- or M- (Carcinogenic or Mutagenic classification) in the category 1 or 2. This may change in the near future, since the CMD is currently under revision and there is a proposal to expand its scope to include substances classified as Repro Cat1A and 1B. If this amendment is included in the Directive, there will be more pressure on the replacement of BPA (and Repro Cat1A and 1B substances in general), as the CMD stipulates that substitution is compulsory if technically feasible, or otherwise that such substances shall exclusively be used in closed systems and exposure reduced to a minimum. However, as the revision of CMD is pending, further speculation in this respect is not justified.

Additional obligations on Repro substances stem from the EU OSH legislation relating to the Young People at Work Directive (1994/33/EC) and the Directive on Pregnant Workers and Workers Who Have Recently Given Birth or Are Breastfeeding (1992/85/EEC). These additional obligations are summarized below.

7.8.3 Directive on Pregnant Workers and Workers Who Have Recently Given Birth or Are Breastfeeding (1992/85/EEC)

This Directive applies to substances classified under CLP as Repro Cat1A, 1B and 2. Most prominent in this Directive is the obligation imposed on the employer, in Article 4(1), to assess the nature, degree and duration of exposure to substances posing a specific risk to workers who are pregnant, have recently given birth or are breastfeeding and to inform these workers of the results of the assessment.

If it is determined that the workers are or may be exposed to risks due to exposure to Repro substances, the employer is to take the necessary measures to ensure that such exposure is avoided. If exposure reduction is not technically and/or objectively feasible, or cannot reasonably be required on duly substantiated grounds, the employer shall move the worker concerned to another job. If this is not technically and/or objectively feasible or cannot reasonably be required on duly substantiated grounds, the worker concerned shall be granted leave for the whole of

the period necessary to protect her safety or health (art. 5 (2)(3)).

7.8.4 Young People at Work Directive (1994/33/EC)

Young people, within the meaning of the Directive, are workers under 18 years of age. Article 7 of the Directive states that Member States shall ensure that young people are protected from any specific risks to their safety, health and development, notably from work 'involving harmful exposure to agents which are toxic [or] carcinogenic, cause heritable genetic damage, or harm to the unborn child or in any other way chronically affect human health'. The Annex to the Directive specifies various hazards, such as may cause heritable genetic damage, may impair fertility and may cause harm to the unborn child. These hazard specification applies to Repro Cat1A and 1B substances.

In addition to these provisions, Member States may have specific provisions in place at a national level. In The Netherlands, young people at work are protected through article 4.105 of the National Health Decision, which prohibits young people to work from being exposed to Repro Cat1A, 1B and 2 substances.

7.8.5 Additional protection at Member State level

Some Member States have additional national regulations in place to protect workers against the risks of Repro substances; see Table 11.

Table 11 Additional protective measures at Member State level directed at substances that are toxic for reproduction.

Member State	Additional protection
France	For all substances with a harmonized classification as C, M or R substances, the CMD applies.
Austria	For substances with a harmonized classification as Repro Cat.1A and 1B, the CMD applies.
Czech Republic	For substances with a harmonized classification as Repro Cat.1A and 1B, the CMD applies.
Germany	For substances with a harmonized classification as Repro and for which there is an OELV*: • Exposure below OELV – the CAD applies • Exposure above OELV – the CMD applies For substances with a harmonized classification as Repro without an OELV, the CMD applies.
Finland	Additional protection from substances with a harmonized classification as Repro Cat.1A and 1B and identified as biological and physical reprotoxicants.
Sweden	Additional protection from specific reprotoxicants, but not for all Repro Cat.1A and 1B substances.

*OELV: Occupational Exposure Limit Value[25]

[25] https://osha.europa.eu/en/seminars/workplace-risks-affecting-reproduction-from-knowledge-to-action/speech-venues/day-ii-16.01.2014-prevention-policies-and-practices/eu-legislation-and-practical-guidance-on-occupational-reproductive-risks

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