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

Bisphenol A

Part 1. Facts and figures on human and environmental health issues and regulatory perspectives

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Facts and figures on human and environmental health issues and regulatory perspectives

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Publiekssamenvatting

Bisfenol A (BPA) is een industrieel gefabriceerde stof die in veel producten zit, zoals verschillende soorten kunststof die worden toegepast in onder meer bouwmaterialen, verpakkingsmateriaal van voedsel, speelgoed en medische hulpmiddelen, kassabonnetjes en verven en coatings. BPA heeft effect op het hormoonsysteem, waardoor er momenteel discussie is over mogelijke schadelijke effecten. Het RIVM heeft een overzicht gemaakt van de belangrijkste afgeronde en nog lopende nationale en internationale beoordelingen van mogelijke risico's van BPA voor mens en milieu, en de onzekerheden daarin.

Op basis van wetenschappelijke studies die tot nu toe zijn gepubliceerd is niet duidelijk of BPA bij de huidige blootstellingsniveaus schadelijk is voor mensen. De blootstelling aan BPA via consumentenproducten, voeding en medische hulpmiddelen is lager dan de huidige waarde die acceptabel wordt geacht. Er zijn wel indicaties dat blootstellingen van werknemers die met BPA werken, een risico kunnen vormen. Vervolgonderzoek is nodig om hier meer duidelijkheid over te krijgen. Ook kunnen de nog lopende beoordelingen van BPA leiden tot een bijstelling van de nu gehanteerde waarde waaronder blootstelling acceptabel wordt geacht.

Daarnaast kunnen hormoonverstorende effecten bij organismen in het milieu optreden. Het is alleen niet duidelijk in welke mate en bij welke concentratie dat gebeurt. In het laboratorium zijn effecten waargenomen nadat waterorganismen direct aan hoge concentraties zijn blootgesteld. De voortplanting en de ontwikkeling van onder meer vissen en waterslakken raakt dan verstoord. In de praktijk zijn de concentraties in water lager en worden zulke effecten niet gezien. Wetenschappers verschillen van inzicht over de mogelijkheid dat deze effecten ook bij zeer lage blootstellingen optreden. Wel is zeker dat BPA zich ophoopt in sediment, waardoor lokaal hoge concentraties kunnen ontstaan die mogelijk schadelijk zijn voor in sediment levende organismen, zoals wormen.

In sommige wetenschappelijke studies wordt bezorgdheid geuit over mogelijke risico's van huidige blootstellingniveaus voor het ongeboren kind, baby's en jonge kinderen. Naar verwachting zijn zij gevoeliger voor hormoonverstorende effecten dan volwassenen doordat hun lichaam nog niet volgroeid en sterk in ontwikkeling is. Daarbij kunnen zij aan relatief hogere concentraties blootstaan, bijvoorbeeld door te sabbelen op speelgoed, en vanwege hun geringe lichaamsgewicht. Het is echter onzeker of deze blootstelling een gezondheidsrisico veroorzaakt.

De kennis over de mogelijke hormoonverstorende effecten van BPA op de gezondheid is sterk in ontwikkeling. In de EU en in verschillende Europese landen waaronder Nederland zijn preventief maatregelen genomen om de risico's op nadelige gezondheidseffecten te verminderen. Eind 2014, begin 2015 zullen verschillende belangrijke nu lopende Europese beoordelingen van BPA worden afgerond. In de loop van 2015 zal het RIVM de uitkomsten van deze nog lopende beoordelingen meenemen in een vervolgstudie waarin de risico's van BPA nader zullen worden geduid. Hierop wordt een beleidsadvies gebaseerd waarin zal worden aangegeven of eventuele aanvullende maatregelen in Nederland nodig zijn om de mogelijke risico's van BPA voor mens en milieu te beperken.

Kernwoorden: Bisfenol A, BPA, hormoonverstoring, gezondheidsrisico's, consument, milieu, werknemer

Abstract

Various organisations have raised concerns about the possible adverse effects of BPA on human health. Scientific studies have associated BPA with adverse immune effects, obesity, ADHD, diabetes and prostate cancer, which may be related to its possible interaction with the estrogen receptor. To date, scientific studies have not found conclusive evidence of possible adverse effects caused by BPA and a causal relationship between BPA exposure and endocrine-mediated effects is still uncertain. Debates are ongoing about possible adverse effects of BPA at low doses that may lead to endocrine disruption, and about the presence (or absence) of a possible non-monotonic dose response (NMDR) relationship. Although this issue raises a lot of concern, there is still no conclusive evidence available that proves a low-dose effect. BPA has been shown to have endocrine disrupting effects on environmental organisms like fish and snails, leading to problems with reproduction and development of offspring.

Over the years, BPA has been the topic of many different regulatory and scientific initiatives. It is still the topic of study in a vast number of ongoing initiatives. Consequently, the state of knowledge on BPA is a fast-developing field, especially regarding its possible endocrine-mediated effects. This report summarises the hazard and risk assessments on BPA and regulatory aspects available through 20 March 2014. The present data indicate a possible risk for a number of environmental compartments and for some occupational settings (EC, 2008). Knowledge about adverse effects, low-dose effects, NMDR and possible endocrine-mediated effects on human health is developing quickly. As of 20 March 2014, the available data do not indicate a risk for most groups of consumers and patients (EFSA draft, 2014; SCENIHR draft, 2014). However, some studies have expressed concern about the possible exposure of infants and young children in light of the present uncertainties and the higher sensitivity of people in these age groups (SCENIHR draft, 2014; GR, 2011).

In March 2014, ECHA's Risk Assessment Committee (RAC) adopted the opinion to strengthen the current classification of BPA to a harmonised classification as a category 1B reproductive toxicant (Repro Cat. 1B). This opinion has to be officially established via a REACH Comitology decision before it can be included in Annex VI of the CLP Regulation (1272/2008/EC). This decision making process will take place within the next one to two years.

It should be noted that this Part 1 report only gives an overview of the state of knowledge about BPA. It does not include an appraisal of the available information by the RIVM. That will follow in Part 2, which is expected to be published in 2015. Part 2 will evaluate the available scientific knowledge, discuss the possible health risks of BPA, include further support for policy considerations and, if relevant, propose further risk management measures.

Key words: Bisphenol A, BPA, endocrine disruption, environment, health risks, consumer, worker

Contents

This report

Background and scope

Bisphenol A (BPA) is a substance that currently receives a lot of attention in the news, in scientific research and in different regulatory frameworks. Both humans and the environment are constantly exposed to low concentrations of this weak estrogenic substance. Various societal organisations have raised concerns about the possible adverse effects of BPA on human health. Scientific studies have associated BPA with adverse immune effects, obesity, ADHD, diabetes and prostate cancer, which may be related to its possible interaction with the estrogen receptor. To date, scientific studies have not found conclusive evidence of possible adverse effects caused by BPA at relevant concentration levels and a causal relationship between BPA exposure and endocrine-mediated effects is still uncertain. Debates are ongoing about possible adverse effects of BPA at low doses that may lead to endocrine disruption, and about the presence (or absence) of a possible non-monotonic dose response (NMDR) relationship. This debate is especially important as it considers the possible toxicity of BPA for humans below exposure levels that up to now have been considered safe. BPA has been shown to have endocrine disrupting effects on organisms like fish and snails, leading to problems with reproduction and development of offspring.

In the Netherlands, RIVM is involved in a risk assessment being carried out by the Dutch Health Council (GR) to evaluate possible adverse effects related to prenatal exposure to chemicals, and to assess possible low-dose effects. At the European level, RIVM takes part in scientific committees (i.e. the European Food Safety Authority (EFSA) and the European Chemicals Agency (ECHA)). At a supranational level, RIVM takes part in the Organisation for Economic Co-operation and Development (OECD), which works internationally to assess the risks of individual substances and develop, discuss and accept new test protocols. In 2011, the OECD accepted a new test protocol for effects on fertility with additional endpoints to detect effects on the endocrine system. In addition to this work, RIVM takes part in a number of international projects, some of which focus on studying mechanisms that may link substances to endocrine disruption and on developing new strategies for identifying adverse effects on fertility, reproduction and development.

In 2013, the Ministries of Infrastructure and Environment (Min. I&M), Social Affairs and Employment (Min. SZW) and Health, Welfare and Sport (Min. VWS) commissioned RIVM to prepare an overview of the state of knowledge about BPA: its human and environmental health hazards, possible exposures and results of available risk assessments. Furthermore, RIVM was asked to summarise ongoing and prospective regulatory initiatives to manage the risks of BPA. The report was originally scheduled to be published by the end of 2013. Due to delays in some key European scientific committees, the full report cannot be published before the end of 2015. Therefore, the report will be presented in two stages. The overview presented here constitutes Bisphenol A, Part 1, Facts and figures on human and environmental health issues and regulatory perspectives. It includes the information available up to 20 March 2014. Part 1 does not interpret the summarised information.

In 2015, Part 1 will be complemented by Part 2, which will summarise, interpret and focus on the consequences of the outcome of:

- an EFSA re-evaluation of the hazards and risks of BPA exposure for consumers (drafts published for public consultation in August 2013 and January 2014, final opinion expected at the end of 2014)
- a Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) risk assessment of patients exposed to BPA (draft published for public consultation in January 2014, final opinion expected at the end of 2014)
- two advisory reports in preparation by GR: one on the risks of prenatal exposure to BPA and a second on BPA analogues (both published 19 March 2014).

Part 2 will include further support for policy considerations and, if necessary, propose risk management measures, which might include considerations of alternatives and will include socioeconomic aspects. It will also update the ongoing regulatory initiatives and their possible impacts.

Disclaimer

This report provides an overview of the current state of knowledge about adverse effects of BPA and possible risks for humans and the environment. It summarises legislation about BPA, both current and under development. The information included in this report is primarily based on the findings and conclusions of:

(i) the European Risk Assessment Report on BPA (2003) and its Addendum (2008) (hereafter referred to as EC, 2008)[1],
(ii) the Annex XV transition report on BPA (EC, 2009)[2],
(iii) the draft opinion on BPA consumer exposure by EFSA (2013)[3], and the draft opinion on risks of BPA for consumers by EFSA (2014)[4],
(iv) the draft opinion on risks of patients' exposure to BPA through medical devices by SCENIHR (2014)[5],
(v) the BPA registration dossiers under REACH (ECHA website), and
(vi) the recommendation of occupational exposure limits by the Scientific Committee on Occupational Exposure Limits (SCOEL, 2013)[6].

The scientific studies underlying the reports listed above have not been evaluated in this report. This was not done because there are hundreds of underlying studies that would require an in-depth case-by-case evaluation to judge both their quality and usability. Since this assessment is currently

[1] European Commission (2008). European Union Risk Assessment Report 4,4'-isoprpylidenediphenol (Bisphenol-A), Part 1 Environment, Environment Addendum of April 2008. European Commission, Joint Research Centre, Institute for Health and Consumer Protection.

[2] Annex XV Transitional Report, Submitted by United Kingdom, 30 November 2008, http://echa.europa.eu/documents/10162/13630/trd_uk_bisphenol_a_en.pdf

[3] Endorsed for public consultation draft scientific opinion; Draft scientific opinion on the risks to public health related to the presence of Bisphenol A in foodstuffs, Part: Exposure assessment, EFSA Panel on Food Contact Materials, Enzymes, Flavourings, and Processing Aids, 2013

[4] Endorsed for public consultation draft scientific opinion; Draft scientific opinion on the risks to public health related to the presence of Bisphenol A in foodstuffs, EFSA Panel on Food Contact Materials, Enzymes, Flavourings, and Processing Aids, 2014

[5] Preliminary Opinion on the Safety of the Use of Bisphenol A in Medical Devices, SCENIHR Adopted this opinion by written procedure on 27 February 2014

[6] SCOEL Recommendation for Bisphenol-A. March 2013 as adapted through Directive 2009/161/EU

Summary

The main observations presented in this report are summarised below. It should be stressed that this report contains an overview of facts and describes ongoing legal evaluation processes related to BPA. The observations are based partly on preliminary findings that are expected to be updated by the end of 2014 and which will be included in Part 2, expected to be published in 2015. The observations presented here should therefore be interpreted with the appropriate reservations.

Production and use

BPA is a high production volume (HPV) chemical that is widely used in manufacturing polycarbonate plastics and epoxy resins that are used in nearly every industry. In 2008, the EU production volume of BPA was just over 1.4 Mt/year. Globally, BPA production volumes may currently exceed 4 Mt/year and are forecast to increase to over 8 Mt/year in 2018. Based on the data in the EU Risk Assessment Report (EU RAR; EC, 2008), BPA is mainly used as a monomer in polycarbonate plastic (~75% of its production volume of ~1.1 Mt/year) and epoxy resins (~17% of its production volume; ~0.2 Mt/year). BPA is also used as a component of polysulphone and polyacrylate resins, and is used in thermal paper and the synthesis of flame retardants. Identified uses for polycarbonate plastic include construction materials, electrical/electronic devices, automotive parts, bottles/packaging and medical and healthcare devices. Epoxy resins are used in electrical/electronic devices and various coatings (e.g. marine coatings, protective coatings, powder coatings, can and coil coatings).

Human health

Hazards of BPA

Various organisations have raised concerns about the possible adverse effects of BPA on human health. BPA is being associated with adverse immune effects, obesity, ADHD, diabetes and prostate cancer, which may be related to its possible interaction with the estrogen receptor. To date, scientific studies have not found conclusive evidence of possible adverse effects of BPA at relevant concentration/exposure levels.

Debates are ongoing about possible adverse effects of BPA at low doses that may lead to endocrine disruption, and about the presence (or absence) of a possible non-monotonic dose response (NMDR) relationship. This debate is especially important as it considers the possible toxicity of BPA for humans below the exposure levels that have been considered safe.

In 2006, EFSA derived a tolerable daily intake (TDI) of 50 µg/kg bw/day for BPA based on adverse systemic effects in rats and mice. In 2012, an assessment by the Swedish Chemicals Agency (KEMI) suggested a TDI that may be 100 to 1000 times lower, based on a weight-of-evidence approach for different effects including both guideline and non-guideline studies and studies of more questionable quality (KEMI, 2012). The most sensitive effect identified by KEMI was developmental neurotoxicity.

In its 2014 draft opinion on BPA, EFSA proposed to lower the present TDI of 50 µg/kg bw/day to a temporary (t-)TDI of 5 µg/kg bw/day; this is based on adverse effects found in the kidneys of mice and new data on the metabolism of BPA, resulting in a more sophisticated calculation of human dose levels. The main uncertainties result from non-Good Laboratory Practice (non-GLP) studies and relate to the following human health effects:

- Possible low-dose effect
- Possible NMDR effects
- Possible developmental effects on the immune system
- Possible developmental neurotoxic and behavioural effects (e.g. ADHD, anxiety)
- Possible metabolic effects (e.g. diabetes, obesity, cardiovascular effects)
- Possible developmental effects on the mammary gland

EFSA is studying whether the t-TDI is sufficiently conservative to cover these uncertainties and has recently released a call for tender to address the relevance of NMDR curves in toxicology. The National Toxicology Program (NTP) in the US is currently addressing many of the uncertainties highlighted by EFSA in its 2014 draft in an extensive research project; results are expected in the near future.

Exposure

Consumers

EFSA (2013, 2014) assessed consumers' possible external exposure to BPA based on the available information for food (via oral exposure) and non-food sources (via dermal and oral exposure). The concentration data included mainly canned and non-canned foods and some foods sold in glass jars with metal lids. The highest concentrations were found in canned foods. The 2013 EFSA draft addres-

sed non-food sources such as air, dust, cosmetics, toys and thermal paper, but it is unclear whether there are more non-food sources. The concentration data for these non-food sources are very uncertain and are based on very few measurements. Aggregated high (oral plus dermal) exposures were estimated for all age groups by deriving the toxic equivalents for dermal exposure via the oral route. Exposures ranged from 1061 in adult men to 1543 ng/kg bw/day in teenagers. High oral exposure estimates for infants (all age groups) and toddlers were up to 873 ng/kg bw/day.

Human exposure via medical devices
Human exposure to BPA via medical devices has been assessed by the Scientific Committee for Emerging and Newly Identified Health Risks (SCENIHR draft, 2014). This sort of exposure typically occurs for a limited time. High exposures through medical devices may be of similar magnitude as the exposure of an average consumer via food consumption: estimated exposures range between 0 and 200 ng/kg bw/day. Prematurely born infants in intensive care units may be exposed to much higher levels of BPA: their estimated exposure was about 3000 ng/kg bw/day.

Occupational exposure
Possible occupational exposure to BPA comes through inhalation related to its manufacture (e.g. bagging and other filling activities) and the manufacture of BPA-containing epoxy resins. These have been identified as the occupational settings with reasonable worst-case (RWC) exposures up to 3 mg/m^3 (time-weighted average (TWA): 8 hrs), with peak exposures up to 11 mg/m^3 (EC, 2008). For other exposure scenarios (e.g. the production of liquid epoxy paints, powder coatings and thermal paper), inhalation exposure was estimated to be much lower (ranging from 0.000015 to 0.1 mg/m^3, TWA: 8 hrs) with peak exposures up to 1 mg/m^3.

The highest dermal BPA exposure was estimated to be 12 mg/kg bw/day for maintenance work (without the use of gloves). Dermal exposures were estimated using the worker dermal exposure estimation model EASE (Estimation and Assessment of Substance Exposure). Since this exposure assessment model is no longer regarded as state-of-the-art, higher tier models should be used to estimate dermal exposure. New insights show that dermal exposure may be more significant than previously thought, for example in cases where cashiers work with thermal paper. However, due to the current lack of data on human behaviour (e.g. handling thermal paper, oral behaviour) and dermal uptake kinetics, present estimates involve a high level of uncertainty.

At this moment it is very difficult to reliably calculate internal BPA exposure as a result of external inhalation and dermal exposure, because of the lack of route-specific kinetic data. As a result, it is also very difficult to reliably assess the health risks associated with external dermal exposure, since route-specific systemic toxicity data are not available. The new insights into the possible significance of dermal exposure for the risks of workers highlight the need for further study of internal exposure and the resulting toxicity of BPA as a consequence of dermal and inhalation exposure.

Human health risks

Risks for consumers
Since 2003, various organisations have assessed the possible risks of BPA for consumers. In 2003, the EU RAR (EC, 2003) concluded that there is a need for further testing of human health in relation to developmental toxicity. Since then, many studies on toxicity have emerged. In 2006, EFSA derived a TDI and concluded that, based on estimated exposures, the health effects of BPA for consumers is low; this was in line with non-European findings by the National Institute of Advanced Industrial Science and Technology (AIST, 2005) in Japan, the Food and Drug Administration (FDA, 2006) in the US and Health Canada (2006). This conclusion was again supported a few years later by an updated assessment by the EU RAR (EC, 2008).

EFSA's most recent consumer risk assessment (2014) concluded that the exposure of even the highest exposed groups in the population is well below the t-TDI proposed by EFSA in 2014, indicating that health concerns about BPA are low at the current level of exposure. This conclusion is in line with the current positions of AIST (latest update in 2011), the FDA and Health Canada (both last updated in 2013). However, EFSA also stated that much of the science underpinning this conclusion is still under development and will be revisited by the EFSA/CEF Panel after it completes its assessment of remaining uncertainties (due to be published later in 2014).

Risks for patients via exposure through medical devices
SCENIHR's 2014 draft report evaluated the possible risks to patients who are exposed to BPA through the use of medical devices and adopted a t-TDI of 5 µg/kg bw/day (EFSA draft, 2014). Most estimated exposures are below this t-TDI. Nevertheless, it was

concluded that although evidence for possible adverse effects at low doses are inconsistent and final conclusions cannot be drawn, the possibility of low-dose effects (especially after prenatal or perinatal exposure) raise some concerns about exposure to BPA via medical devices in prematurely born infants. The 2014 SCENIHR draft furthermore emphasised that these infants may have serious health problems that could justify the use of BPA-containing medical devices in view of the benefit-risk evaluation, despite the possible adverse effects of BPA.

Risks for workers
Possible occupational exposures related to the manufacture of BPA (e.g. bagging and other filling activities) and the manufacture of epoxy resins that contain BPA have been identified as occupational settings with a risk characterisation ratio (RCR) >1 (EC, 2008). The EU RAR (EC, 2003 and EC, 2008) concluded that inhalation of BPA during these activities needs to be limited. Other exposure scenarios (e.g. the production of liquid epoxy paints, powder coatings and thermal paper) had RCRs < 1. In all occupational exposure scenarios with a potential for skin contact, the EU RAR (EC, 2003 and EC, 2008) concluded that there was a need to limit the risks of BPA in relation to skin sensitisation.

The EU RAR (EC, 2008) assessment was based on the EASE model, which has since been updated. Recent insights suggest that routes besides inhalation (e.g. oral and dermal) may be important to workers' exposure. To assess the aggregated exposure of workers via inhalation, dermal uptake and, where relevant, oral uptake, a combined exposure estimate has to be derived either by route-to-route extrapolation or by calculating the total internal exposure to BPA as a consequence of the external exposure via the different routes. The EU RAR (EC, 2008) has not done this. In the near future, data may become available from an ongoing study by the National Institute of Environmental Health Sciences and the National Toxicology Program (NIEHS/NTP); this may facilitate the evaluation of workers' dermal exposure via other routes.

The environment

Hazards of BPA
BPA is classified under the Classification and Labelling of Packaging (CLP) Regulation (1272/2008/EC) as harmful to aquatic organisms. The EU RAR on BPA (EC, 2008) furthermore concluded that BPA shows endocrine disrupting effects in environmental organisms, resulting in adverse effects on reproduction and development of offspring. Predicted no-effect concentrations (PNECs) have been derived for water and sediment compartments.

Environmental exposure
BPA is ubiquitous in surface waters and sediment. Concentrations of BPA vary considerably depending on factors such as location and sampling period. Water concentrations analysed in Europe are in the ng/l to low µg/l range (EC, 2008; NORMAN-EMPODAT 2013). Sediment concentrations in Europe were found to range from the low µg/kg dw to the low mg/kg dw range maximum (EC, 2008; NORMAN-EMPODAT 2013). Emissions of BPA to the environment result from manufacturing, its use in a broad range of products and the recycling and waste stages of these products. It is unclear which specific BPA lifecycle steps are responsible for the observed environmental concentrations. This uncertainty is being addressed following Germany's substance evaluation under REACH, which demanded that industry provide more data on environmental emissions of BPA during the lifecycle of polymers and articles containing BPA, from production to waste.

Environmental risks
The EU RAR (EC, 2008) and Annex XV transition report (EC, 2009) suggested that BPA poses a risk for the sediment compartment. More recent BPA concentrations in the environment (found between 2003 and 2010) support this statement. The 95th percentile of the measured concentration of BPA in fresh water sediment and marine sediment exceeded the derived PNECs for these environmental compartments. For marine sediment, the mean measured BPA concentration is also higher than the derived PNEC. The Annex XV transition report (EC, 2009) furthermore concluded that, considering the uncertainties surrounding BPA's effect on snails as sediment-dwelling organisms, the PNEC for sediment should be re-evaluated if more information becomes available about snails or other sediment organisms.

The EU RAR (2008) and Annex XV transition report (EC, 2009) identified no present risk for the water compartment. The 95th percentile of measured concentrations of BPA in fresh water and marine water remain below the respective PNECs. Fresh water BPA concentrations found between 2003 and 2010 support this statement. The available monitoring data for BPA in fresh water in the Netherlands from that same period are comparable to the European concentration profile.

Since the latest European risk assessment (EC, 2008) and the Annex XV transition report (EC, 2009) were published, new data have emerged about BPA's possible adverse effects on environmental organisms (including possible endocrine effects) and its concentrations in water and sediment throughout Europe. There are indications that the No Observed Effect Concentration (NOEC) of BPA for fresh water organisms may be lower. Toxicity data that have emerged since 2009 were not taken into account when the PNEC for water was derived.

Legislation and initiatives

BPA and exposure to BPA are primarily managed by regulations at the EU level. In addition, the Netherlands has made specific provisions for BPA under the Dutch Food and Commodities Act (i.e. the Decree on Packaging and Utensils), which defines the maximum amount of BPA allowed to migrate from packaging material (specific migration limit). Various ongoing regulatory initiatives may give rise to a new classification of BPA under CLP, a specific restriction for use of BPA in thermal paper under REACH and more insight into environmental emission sources via the substance evaluation process under REACH.

The latest development is that, as of 14 March 2014, the Risk Assessment Committee (RAC) of ECHA (European Chemicals Agency) adopted a French proposal to classify BPA as category 1B reprotoxic substance. This classification will have a strong impact on further measures to regulate BPA. A more stringent classification as a Repro Cat.1B will also have major implications for BPA under several pieces of "downstream" legislation, such as the Industrial Emissions Directive (2010/75/EC), the Ecolabel Regulation (66/2010/EC), the Toy Safety Directive (2009/48/EC), the Young People at Work Directive (1994/33/EC), the Pregnant and Breastfeeding at Work Directive (1992/85/EEC), the Waste Framework Directive (2008/98/EC), the Medical Devices Regulation (in preparation) and the Plastic Materials in Contact with Food Regulation (10/2011/EC).

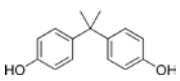
The European Commission is also working on a criteria document to identify and define endocrine disruption and endocrine disruptors, which may affect the discussion around BPA as a possible endocrine disruptor. The outcomes of these initiatives may be expected in 2014 and later, and may have major implications for other regulatory frameworks.

1 Introduction

1.1 What is Bisphenol A (BPA)

Bisphenol A (BPA) is a high production volume chemical that is widely used in all sorts of materials (e.g. plastics such as polycarbonate plastic (PC), epoxy resins, resins, thermal paper, the synthesis of flame retardants). BPA is non-volatile and when it is used in a material, it typically reacts by forming chemical bonds (like in plastic or resins). However, when BPA does not chemically react, it may leach from the material, resulting in exposure to humans or the environment.

The identification and physicochemical properties of BPA are included in Table 1 (EC, 2008).

Structural formula: 

1.2 Societal interests in BPA

Various organisations have raised concerns about the possible adverse effects of BPA on human health and the environment. In the Netherlands, this concern was explicitly expressed in early 2012 via a public letter[7] to the Ministry of Health, Welfare and Sport (VWS). More recently, in December 2013, this concern was raised via a letter from the Women in Europe for a Common Future (WECF) and PAN Europe to the Ministry of Economic Affairs (EZ)[8] and via questions asked by members of the Dutch house of representatives (Tweede Kamer) to VWS in the context of endocrine disrupting substances.[9] Figure 1 also shows that BPA has been a topic of interest for science, regulatory bodies, international organisations (including Civil Society Organisations (CSOs)) and industry over the last three years, as indicated by the number of publications that made the news every year.

BPA is widely used in nearly every industry. Both humans and the environment are constantly being exposed to low concentrations of BPA. With respect to human health, different scientific studies have

[7] Public letter (Burgerbrief) from Emeritus Professor J. Koppe to Minister Schippers of the Dutch Ministry of Health, Welfare and Sport, 17 February 2012

[8] Letter to S. Dijkstra about endocrine disruptors sent in response to a Dutch television production about hazardous substances by Zembla, broadcasted on 19 December 2013

[9] Questions to VWS from the Dutch house of representatives, nr. 2013Z25440, 23 December 2013

Tabel 1 The identification and physicochemical properties of BPA (EC, 2008).

IDENTIFICATION	
CAS number	80-05-7
EINECS number	201-245-8
IUPAC name	2,2-bis(4-hydroxyphenyl)propane
Common name	Bisphenol A (abbreviation BPA)
Molecular weight	228.29
Molecular formula	C15H16O2
Purity	99-99.8% depending upon the manufacturer
Impurities	Typically include phenol (<0.06%), ortho and para isomers of bisphenol A (<0.2%) and water (<0.2%)
PHYSICOCHEMICAL PROPERTIES	
Physical state at normal temperature and pressure	White solid flakes or powder with a mild phenolic odour
Melting point	155-157°C at atmospheric pressure
Boiling point	~360°C with decomposition at atmospheric pressure
Relative density	1.1-1.2 kg/m^3 at 25°C
Vapour pressure	5.3.10-9 kPa at 25°C
Solubility in water	300 mg/l used at ntp
Partition coefficient (Log Kow)	3.4
Flash point	circa 207°C
Autoflammability	circa 532°C
Oxidising properties	Not an oxidising agent

associated BPA with adverse immune effects, obesity, ADHD, anxiety, diabetes and prostate cancer. For environmental organisms like fish and snails, BPA has been shown to have endocrine disrupting effects that lead to adverse effects on reproduction and development of offspring (EC, 2008). There is ongoing debate about the possible adverse effects of low doses of BPA that may lead to endocrine disruption, and about the presence (or absence) of a possible NMDR relationship. This debate is especially important as it discusses the possible toxicity of BPA for humans and the environment below the exposure levels that have been considered safe up to now (the no observed effect level or concentration). To date, scientific studies have not found conclusive results about the possible adverse effects of BPA on these issues.

1.3 BPA, a fast-developing field

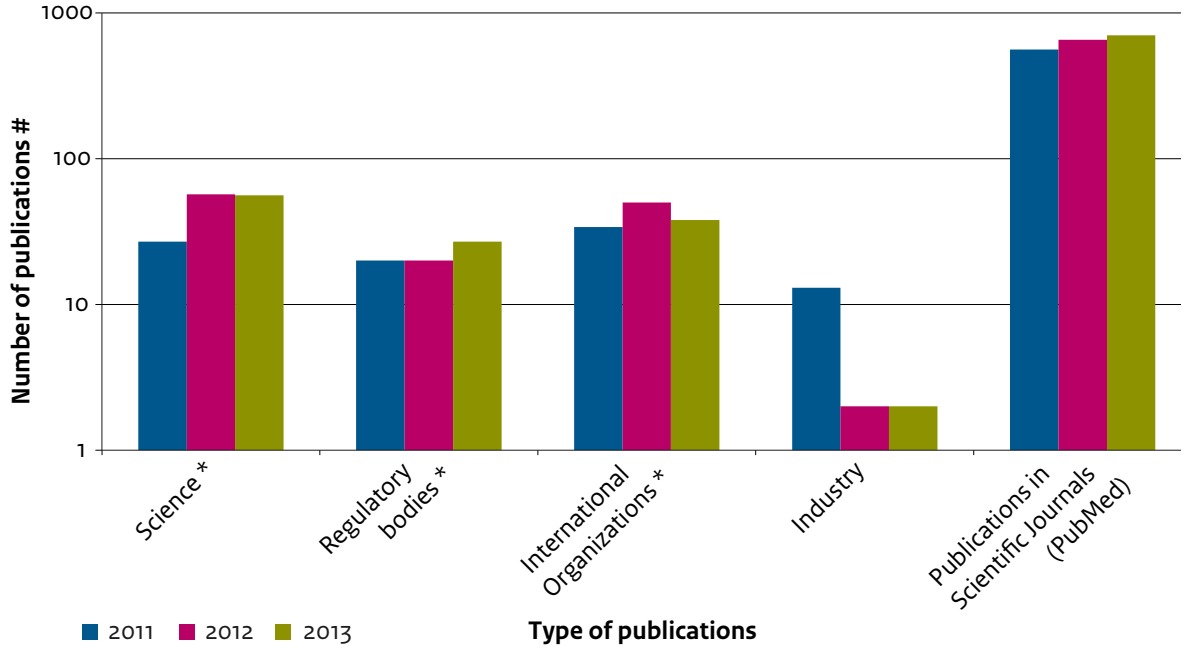
BPA has been a subject of interest for many years. Figure 1 gives an impression of the number of publications by science, regulatory bodies, international organisations (including CSOs) and industry between 2010 and March 2014. Figure 2 presents an overview of major risk assessment studies conducted within the EU, the US, Canada and Japan, and key risk assessment studies that are currently in preparation and for which results are expected in the near future. Each study aimed to assess all the available, reliable and relevant information about BPA's effects on human health or its environmental risks. The later the publication date, the more information was available to build upon.

Europe

The European Risk Assessment Reports, the 2003 EU RAR and its 2008 update[10] (hereafter referred to as EC, 2008), conducted under the Existing Substances Regulation (793/93/EEC) programme and published by the former European Chemicals Bureau, assessed the risks of BPA to humans (general population, consumers and workers) and the environment. In parallel to this work, the European Food Safety Authority (EFSA) assessed the risks BPA poses to consumers as a result of food consumption. Their first assessment was made in 2002; since then, EFSA has regularly updated its assessment to take into

[10] European Commission (2008). European Union Risk Assessment Report 4,4'-ISOPROPYLIDENEDIPHENOL (Bisphenol-A), Part 1 Environment, Environment Addendum of April 2008. European Commission, Joint Research Centre, Institute for Health and Consumer Protection.

Figure 1 Overview of publications about BPA. Data from science, regulatory bodies, international organisations (including CSOs) and industry reached the news in 2011, 2012 and 2013 (sources indicated by *). An indication of the number of scientific publications was obtained from PubMed by searching for all the 2011, 2012 and 2013 publications with the key word "Bisphenol A".



account new scientific insights on toxicity or exposure.

Their 2006 update[11] was particularly focussed on the carcinogenic and reprotoxic effects of BPA exposure on infants and on possible adverse effects at low doses of exposure. In 2011, the Dutch Health Council (GR) published an advisory report on the identification and protection of high-risk populations.[12] It noted that, in principle, the whole human society may be at risk of BPA exposure but that special at-risk groups include young children in the pre- and postnatal phases, people who consume a lot of canned food and people who metabolise BPA slowly. In 2012, the Swedish Chemicals Agency (KEMI)[13] assessed the available scientific literature about possible adverse effects of BPA on human health. With respect to the environment, the European Risk Assessment has not been updated since 2008 but more information on environmental concentrations of BPA have become available through the NORMAN-EMPODAT (2013) database.[14]

Outside Europe

In 2005, the Japanese National Institute of Advanced Industrial Science and Technology (AIST, 2005) conducted an assessment of the risks BPA poses to the environment and the general population.[15] In the US, the National Institute of Environmental Health Sciences (NIEHS) and the EPA (Environmental Protection Agency) organised a meeting in November 2006 to address the potential relationship between BPA exposure and negative trends in human health that have occurred in recent decades. The report from this meeting, also known as the

[11] European Food Safety Authority. Opinion of the Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food on a request from the Commission related to 2.2-bis (4-hydroxyphenyl) propane (bisphenol A). 2006. Available online at: www.efsa.europa.eu.

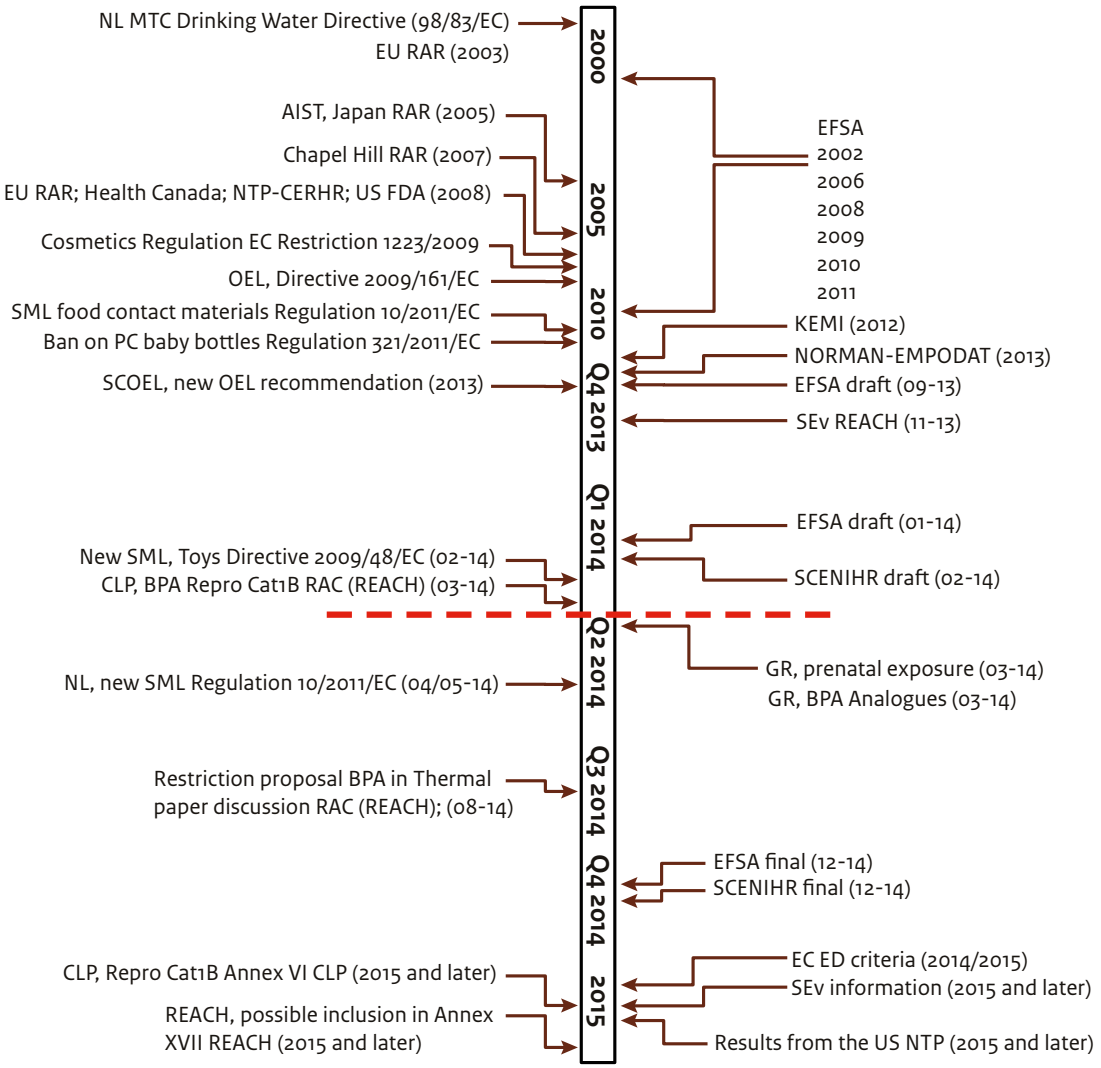
[12] Gezondheidsraad 2011, Leidraad voor identificatie en bescherming van hoogrisicogroepen, VGP/P&L/2581995, d.d. 14 December 2011

[13] KEMI 2012, Low dose effects of Bisphenol A, Institute of Environmental Medicine, Karolinska Institutet https://www.kemi.se/Documents/Publikationer/Trycksaker/PM/PM_8_12_BPA_low%20dose%20effects.pdf

[14] NORMAN (2013). NORMAN - EMPODAT Database. EMPODAT is a database of geo-referenced monitoring and bio-monitoring data on emerging substances in the following matrix: water, sediments, biota, SPM, soil, sewage sludge and air. NORMAN, Network of reference laboratories, research centres and related organisations for monitoring of emerging environmental substances.

[15] Japanese National Institute of Advanced Industrial Science and Technology Risk Assessment Document Series No 4: Bisphenol A. 2005. Available online at: www.aist.go.jp.

Figure 2 Chronological overview of regulatory measures and key risk assessments on BPA, implemented and under development. The red dashed line indicates the state of play as presented in this report (Part 1, 20 March 2014). Part 2 is expected to be published in the first half of 2015.



Chapel Hill consensus statement, concluded that human exposure to BPA is widespread and that the adverse health effects observed in animal studies raise significant concerns about the potential for similar effects in humans. In 2008, an expert panel at the National Toxicology Program Center for the Evaluation of Risks to Human Reproduction (NTP-CERHR) in the US conducted an assessment of BPA.[16] It assessed the risks of exposure via food and the environment and focussed specifically on evaluating the reproductive toxicity of BPA at low doses. That same year, the FDA conducted a risk assessment for the general population about the risks of BPA resulting from food consumption[17]; it has been updated regularly since (last updated in March 2013).[18] In Canada, the Canadian Health Authority issued an updated assessment in September 2012 that assessed the risks of BPA to the environment and to the general public.[19]

[16] National Toxicology Program Center for the Evaluation of Risks to Human Reproduction. Monograph on the potential human reproductive and developmental effects of bisphenol A. 2008. Available online at: http://cerhr.niehs.nih.gov/.

[17] US Food and Drug Administration. Draft assessment of bisphenol A for use in food contact applications. 2008. Available online at: www.fda.gov.

[18] http://www.fda.gov/newsevents/publichealthfocus/ucm064437.htm

[19] http://www.hc-sc.gc.ca/fn-an/securit/packag-emball/bpa/bpa_hra-ers-2012-09-eng.php

Where relevant, the findings of the above-mentioned studies on human health hazards, possible risks and adverse effects on the environment are summarised in sections 3.2 and 3.3 and chapter 4, respectively.

The most recent development in the context of assessing adverse effects on human health and possible risks to consumers is ongoing at EFSA, which has published two draft opinions in recent months. The first (published for public consultation in August 2013) assessed consumer exposure, taking into account not only possible exposure via food consumption, but also via non-food sources like dust, toys and thermal paper. In doing so, EFSA expanded their exposure assessment compared to their prior assessments. The second draft opinion (published for public consultation in January 2014) assessed all scientific information available about the possible adverse effects of BPA on human health in order to reassess the tolerable daily intake (TDI) for BPA and come to a risk assessment for consumers. A final risk assessment is expected from EFSA by the end of 2014. Because these draft opinions include both the older studies (included in previous risk assessments) and the most recent insights, this report largely builds on these draft findings.

Another recent development is a draft opinion from SCENIHR, published for public consultation at the end of January 2014, about possible risks BPA poses to patients from exposure via medical devices. A final opinion is expected by the end of 2014 and the draft findings are included in this report.

The most recent development is that, as of 14 March 2014, ECHA's RAC adopted a French proposal to classify BPA as a category 1B reprotoxic substance (also see sections 3.2 and 5.3). This classification will have a strong impact on further regulatory measures for BPA.

This report (Bisphenol A, Part 1) summarises the state of knowledge about the possible adverse effects of BPA to human health and the environment, as concluded in the risk assessment reports indicated in Figure 2. It includes the information available up to 20 March 2014 (see the red dashed line in Figure 2). This report will be completed with the addition of Part 2, in which RIVM will appraise the available knowledge on BPA and, if relevant, give advice on further risk management measures, including considerations of possible alternatives for substitution and socioeconomic issues.

However, as can be seen in Figure 2, results from a number of initiatives are still incomplete; these may impact the findings presented in this report. Due to the present pace of developments, the facts presented here may change in the near future. In the context of the REACH Regulation, a substance evaluation (SEv) is currently ongoing that will provide more insight into how BPA is emitted to the environment and the dermal uptake characteristics relevant for human exposure assessment (also see section 5.3). Furthermore, the GR recently published two advisory reports for the Dutch government: 1) a current assessment of the adverse effects of prenatal exposure to substances (including BPA) and 2) a report on the risks posed by BPA analogues (published 19 March 2014). Later in 2014, the European Commission is also expected to propose criteria for identifying endocrine disruption and endocrine disruptors, which may impact the way BPA is assessed. In 2015 or 2016, results from a large US research programme that is addressing a number of uncertain adverse effects of BPA on human health are expected to become available (the US-NTP, also see section 3.2).

Figure 2 also presents an overview of regulatory measures implemented over the last 10 to 15 years to manage the possible risks of BPA and summarises EU regulatory initiatives that are currently under development. These include provisions for specific migration limits (SML) in food contact materials and toys, a ban on BPA in baby bottles and a restriction proposal in the context of REACH for BPA in thermal paper. A more extensive overview of existing legislation and ongoing initiatives is presented in chapter 5.

1.4 What to find in this report

This report (Bisphenol A, Part 1) summarises the present state of knowledge (as of 20 March 2014) regarding the adverse effects of BPA on human health and the environment, remaining uncertainties, and scientific and legislative initiatives that are working to further clarify those uncertainties. It thereby strives to present an overview of the conclusions of exposure and hazard assessment studies available by 20 March 2014 in terms of clear facts. This report does not interpret the available toxicity and exposure data on BPA to arrive at a risk assessment for human health and the environment. There are two reasons: 1) the amount of available data is enormous and requires a case-by-case quality and relevance assessment, and 2) a number

of initiatives are already in the process of assessing possible adverse effects, exposures and their resulting risks (also see Figure 2), which makes it unnecessary to duplicate their work.

In 2015, this report will be complemented by a Part 2 that will appraise the conclusions from the available risk assessments summarised in Part 1. Part 2 will build on the findings of Part 1 with the aim of providing further support for the Dutch government's policy considerations. Part 2 will also consider socioeconomic aspects of BPA, including possible alternatives for substitution and elements to include in a cost-benefit analysis, and will elaborate on possible needs for further risk management measures.

The data reflected in this Part 1 report are primarily based on the findings and conclusions of:

(i) the European Risk Assessment Report on BPA (2003) and its Addendum (2008) (hereafter referred to as EC, 2008),
(ii) the Annex XV transition report on BPA (EC, 2009),
(iii) the draft opinion on BPA consumer exposure by EFSA (2014),
(iv) the draft opinion on risks of patients' exposure to BPA through medical devices by SCENIHR (2014),
(v) the BPA registration dossiers under REACH (ECHA website), and
(vi) the recommendation on occupational exposure limits by the Scientific Committee on Occupational Exposure Limits (SCOEL, 2013).

This report does not evaluate the scientific studies that underlie the reports listed above because there are hundreds of those studies and an assessment would require an in-depth case-by-case evaluation to judge the studies' quality and usability. Since such an assessment requires a lot of effort and this same assessment is currently ongoing at EFSA, it was decided not to duplicate the effort.

Figure 3 From primary substance characteristics to risk assessment and risk management, a schematic view of key elements that are involved in the process of identifying the most appropriate risk management options.

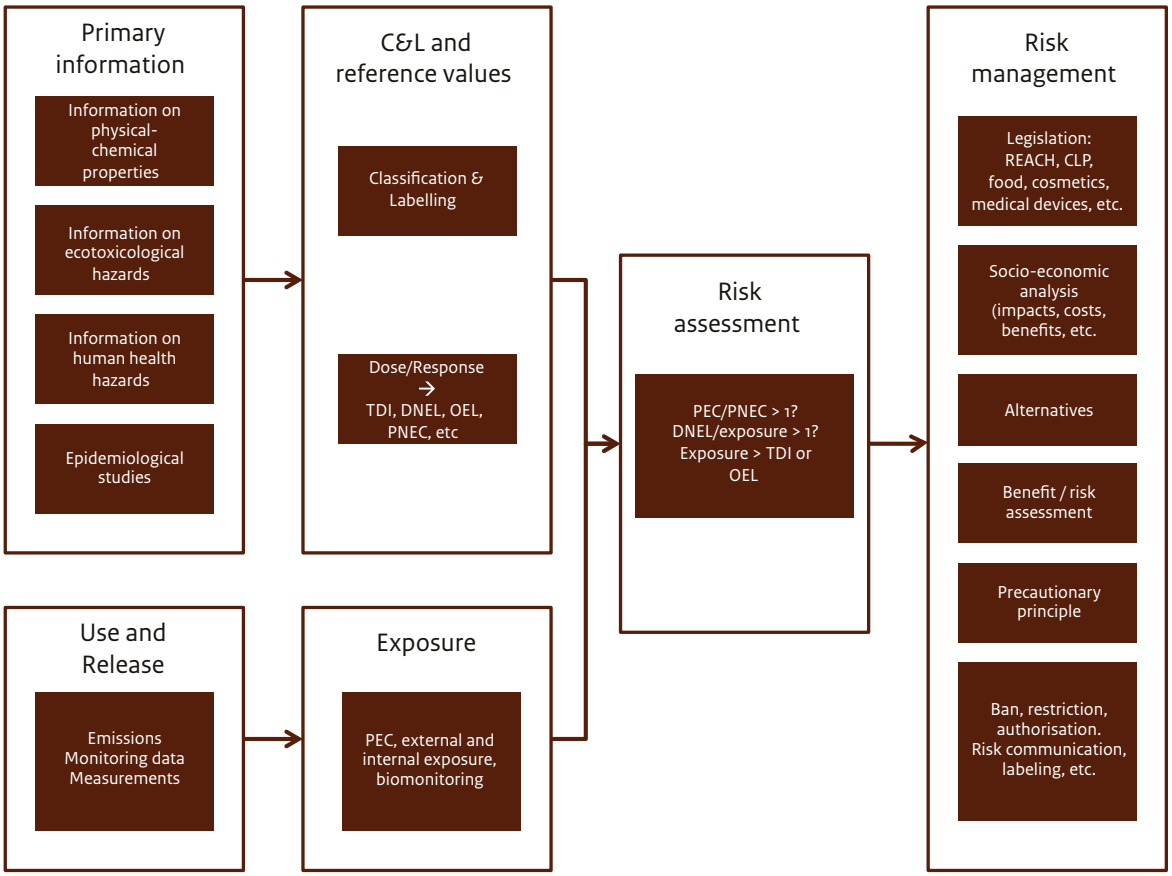


Figure 3 presents a schematic overview of the elements that feed into the process of identifying possible risk management measures. This report describes the current facts available to fill in the primary information on substance characteristics (including possible adverse effects), use and possible release of BPA, exposure characteristics of BPA for humans and the environment, the present state of play regarding classification and labelling and reference values available to assess a possible risk. It also gives on overview of regulatory measures in place and under development for managing BPA's possible risks.

As this report only includes information available through 20 March 2014, it should be emphasised that some of the key studies that form the basis of this work have only been published as draft opinions for public consultation (e.g. 2013 and 2014 EFSA drafts and 2014 SCENIHR draft). Part 2 will include the final findings and conclusions of the draft reports described in Part 1 and the findings of the GR's report on risks of chemicals during prenatal exposure and its findings on possible risks of BPA analogues, both published in March 2014. It is therefore possible that some information in Part 1 may need to be revised in Part 2 as a consequence of any further developments or scientific insights.
This report is organised as follows. **Chapter 2** gives an overview of the production and main uses of BPA, possible concentrations of BPA in consumer products and applications of BPA in medical devices. **Chapter 3** summarises the most recent exposure assessments for consumers published by EFSA (2013, 2014) and for patients via medical devices published by SCENIHR (2014). It also provides an overview of the present state of knowledge on human health hazards, known and still uncertain. **Chapter 4** summarises the current state of knowledge about BPA's presence in the environment and possible environmental health hazards. **Chapter 5** gives an overview of legislation in the Netherlands, Europe and worldwide that manages the possible risks of BPA, and legislative initiatives currently under development that may have a regulatory impact on BPA in the near future. **Chapter 6** summarises the main observations about the current state of knowledge on possible risks of BPA.

2 Production and use of Bisphenol A (BPA)

Based on the RAR (EC, 2008) BPA is a high production volume (HPV) chemical widely used in manufacturing polycarbonate plastics and epoxy resins that are used in nearly every industry. Four companies manufacture BPA in the EU; there are six manufacturing sites in Germany, the Netherlands, Spain and Belgium. In 2008, the EU production volume of BPA was just over 1.4 Mt/year. Globally, BPA production volumes may currently exceed 4 Mt/year and a marketing report from Global Industry Analysts Inc. forecasts it to grow to over 8 Mt/year in 2018 (EC, 2008).

Based on the data in the RAR (2003+ Addendum 2008), BPA is mainly used as:
- a monomer in polycarbonate plastic (~75% of its production volume; ~1.1 Mt/year)
- a monomer in epoxy resins (~17% of its production volume; ~0.2 Mt/year)[20].

BPA is also used as a component of polysulphone and polyacrylate resins and is used in thermal paper and the synthesis of flame retardants.
The main identified uses for polycarbonate (PC) are in construction materials (27%; ~0.3 Mt/year), optical media (23%; ~0.2 Mt/year), electrical/electronic uses (21%; ~0.2 Mt/year) and the automotive industry (12%; ~0.2 Mt/year). Only relatively small percentages of the total production volume of BPA account for the use in bottles/packaging (2.5%; ~0.03 Mt/year), medical and healthcare devices (2.5%; ~0.03 Mt/year) or domestic, safety, leisure and other uses (remaining 11.5%; ~0.2 Mt/year).

Epoxy resins are used for purposes such as marine coatings and protective coatings (20%; ~50 kt/year), powder coatings (18%; ~42 kt/year), electrical/electronic uses (16%; ~38 kt/year), civil engineering (15%;
~36 kt/year) and can and coil coatings (11%; ~26 kt/year). Smaller amounts account for composites (5%; ~12 kt/year), adhesives (4%; ~10 kt/year) and photo cure uses (2%; ~5 kt/year).

A minor use of BPA is for the production of several different polymers such as phenoplast cast resin and unsaturated polyesters, epoxy resin hardeners and other chemicals. About 0.16% (~2.4 kt/year) of BPA is used in thermal paper. BPA has been used as a stabiliser or antioxidant for PVC, but is no longer used in PVC in Europe according to the PVC industry. The majority of these uses contain BPA as a chemi-

[20] RAR (2003 with Addendum of 2008), European Union Risk Assessment Report, Bisphenol-A

cally bound part of the plastic polymer structure (e.g. in polycarbonate plastic and epoxy products) or as a reactive constituent in epoxy resins. The way BPA is contained (i.e. fixed in a polymer matrix or free in powder form) strongly influences the possibility of exposure to free BPA. Exposure to free BPA is typically low for PC plastics and slightly higher for cured epoxy coatings, as only the residual fraction of non-reacted (and therefore free) BPA has the potential to migrate from the material. Exposure to free BPA is typically high for thermal paper where BPA is present as reactive dye in powder form, applied to the surface of the paper sheet.

2.1 BPA in consumer products

In 2013, EFSA published a draft scientific opinion on consumer exposure to BPA for public consultation. This draft provided the most up-to-date assessment of the concentrations of BPA in food, consumer products, air and dust, which eventually may result in consumer exposure. Early in 2014, EFSA published a draft risk assessment for consumer exposure to BPA for public consultation. The findings are described below. EFSA, 2013, 2014.

The 2013 EFSA draft summarised the information available about actual concentrations of free BPA in various food and beverage sources and in a number of non-food sources that may be relevant to consumer exposure (i.e. cosmetics, thermal paper, indoor air, dust and mouthed toys/rattles). Concentration data reported for foods and beverages described the data that was available for European countries and reported in the literature. The concentration data mainly included canned and non-canned foods, and some foods in glass jars with metal lids. The highest concentrations were found in canned foods. The concentrations of BPA in foods in glass jars with metal lids were comparable to the concentrations analysed in non-canned foods. Concentrations of BPA in foods packaged in other types of BPA-containing materials (e.g. recycled or new paper and board) were not reported in the draft opinion and it is unclear whether EFSA included them. The draft noted that the concentration data reported in non-food sources involved high uncertainties because of a general lack of concentration data. Also, some uncertainty remains about possible other important non-food sources that were not addressed.

2.1.1 BPA in food products

The summary on actual concentrations of free BPA in food sources presented in the 2013 EFSA draft covers the period between 2006 and 2012 and was based on a thorough literature review about BPA concentrations in food and an EFSA call for data.[21] Both data sources showed comparable results with respect to the concentrations of BPA in specific food products. BPA concentrations were also reported to be similar in food from outside and inside the EU. The highest BPA concentrations were found in canned foods: typical concentrations[22] ranged from 30–50 µg/kg food (also see Table 2). Lower BPA concentrations were found in non-canned food (ranging from 0–10 µg/kg), canned drinks and dairy products (ranging from 0.5–5 µg/kg) and non-canned drinks and dairy products (ranging from 0–1 µg/kg). Average BPA concentrations in initial and mature breast milk were reported to equal 3 and 1.5 µg/l, respectively.

The literature review and the EFSA call for data yielded BPA concentrations of over 2000 food samples from different European countries. There was little data on BPA levels in breast milk, but it was found to be representative (EFSA draft, 2014). Despite the voluminous data on BPA concentrations in foods and beverages, EFSA (2013, 2014) specified the following uncertainties:

- Some uncertainty remains about the representativeness of the data since the majority of the BPA concentrations obtained from the call for data originated from France (75.5%).
- Some uncertainty remains about what BPA level to assign to the samples that had a measured BPA concentration below the limit of detection or quantification.
- Only a limited number of food samples were available for some food categories, resulting in uncertainty about the BPA concentration in these categories.
- For some data, uncertainty remains about the analytical methods used.

From the 2013 EFSA draft it is furthermore unclear whether BPA concentrations in foods packaged in

[21] In total, EFSA received 2076 samples of food and beverages analysed for BPA. Most of the data were obtained from France (75.5%).

[22] Concentrations refer to medium bound concentrations: samples with a BPA concentration below the limit of detection (LOD) or quantification (LOQ) were assigned a BPA concentration equal to half of the LOD or LOQ.

Tabel 2 Overview of typical concentrations of BPA in food and beverages and non-food sources as reported by the 2013 EFSA draft.

Type of food product	Typical BPA concentration
Canned food	30–50 µg/kg
Non-canned food	0–10 µg/kg
Canned drinks and dairy products	0.5–5 µg/kg
Non-canned drinks and dairy products	0–1 µg/kg
Initial breast milk	3 µg/l
Mature breast milk	1.5 µg/l
Cosmetics	31 (<LOQ-88) µg/kg product
Thermal paper	0.8–3.2 µg/100 g
Indoor air	0.5–5.3 ng/m^3
Dust	117–20,000 µg /kg
Toys/rattles (mouthed)	0.14 (<LOQ-0.63) µg/kg product
Pacifiers (mouthed)	0.28-0.36 µg/product

materials other than cans (e.g. paper or cartons) from which BPA may leach into the foods are covered as a possible source of BPA for consumers. It is also unclear whether the 2013 EFSA draft took into account BPA concentrations in food that may occur as a result of heating the food in a BPA-containing material prior to consumption (e.g. heating packaged food in a microwave).

2.1.2 BPA in non-food

The 2013 EFSA draft opinion on exposure summarised the occurrence, migration and transfer data on BPA concentrations in cosmetics, thermal paper, indoor air, dust and mouthed toys/rattler. The data were obtained from scientific journals and risk assessment reports[23] [24], but only a limited amount of information was available from these sources. Table 2 presents an overview of the typical BPA concentrations as assessed by EFSA. EFSA concluded that the contribution of other sources (i.e. dental materials and swimming in surface water) is negligible with respect to consumers' chronic BPA exposure and therefore excluded these two sources from their exposure assessment.

2.1.2.1 BPA in dust and air

The 2013 EFSA draft's data on indoor air concentrations of BPA were taken from a limited French study. The average concentration was estimated at 1 ng/m^3, with a range between 0.5–5.3 ng/m^3. Based on a Greek study describing BPA concentrations of 6.8 ng/m^3 in outdoor air, EFSA recognised that the airborne exposure to BPA of people who live in Southern Europe and spend more time outdoors than the average European consumer may be underestimated.

The 2013 EFSA draft estimated the BPA concentration in dust at 1460 µg /kg, with a range between 117–20,000 µg /kg, based on the average mean concentration in a recent dust study available for Europe (Geens et al., 2009).[25] Other studies reported in the 2013 EFSA draft found slightly different median dust concentrations: a factor 4 higher (French) or 2.5 lower (German). A worst-case estimate would therefore be higher than the concentration estimated in the 2013 EFSA draft.

2.1.2.2 BPA in non-food consumer products

Concentration data are available for thermal paper, toys and cosmetics. The highest average concentra-

[23] FAO/WHO (Food and Agriculture Organization/World Health Organization), 2011. Toxicological and health aspects of bisphenol A. Proceedings of the Joint FAO/WHO Expert Meeting on Bisphenol A (BPA), Ottawa, Canada, 59 pp

[24] ANSES (Agence Nationale de Sécurité Sanitaire de l'Alimentation, de l'Environnement et du Travail), 2013. Opinion of the French Agency for Food, Environmental and Occupational Health and Safety on the assessment of the risks associated with bisphenol A for human health, and on toxicological data and data on the use of bisphenols S, F, M, B, AP, AF and BADGE, 13 pp

[25] Geens T, Roosens L, Neels H and Covaci A, 2009a. Assessment of human exposure to bisphenol-A, triclosan and tetrabromobisphenol-A through indoor dust intake in Belgium. Chemosphere, 76, 755-760.

tion of BPA in thermal paper was found in car park tickets (3.2 µg/100 g paper). The concentration of BPA in thermal paper ranged from 0.8–3.2 µg/100 g. For toys, BPA was found in 14 out of 80 toy products (KEMI, 2012; cited in the 2013 EFSA draft). The average migration of BPA into saliva was estimated to be 0.14 µg/kg product. EFSA concluded that the true average migration value is likely to be closer to 0 µg/kg product based on the low number of toys on the market made of polycarbonate. In 2005, the Dutch NVWA (Nederlandse Voedsel- en Warenautoriteit; in English: Netherlands Food and Consumer Product Safety Authority) performed a market survey of plastic toys in the Netherlands (screening plastic toys for chemical composition and hazards)[26] and found that only 5 of the 186 articles studied contained BPA.

BPA migration from pacifiers was estimated at 0.32 µg/product (ranging from 0.26–0.36 µg/product; Lassen et al. 2011 in the 2013 EFSA draft). However, Lassen et al. (2011) clearly stated that six out of the eight BPA migrations were below the detection limit.

For cosmetics, the 2013 EFSA draft provides a value of 31 µg/kg in face lotion. Lotion is used over a large surface area of the body and is largely absorbed by the skin. Since the study only analysed six products, EFSA concluded that BPA concentrations in cosmetics are unknown. The suggested concentration of 31 µg/kg is therefore highly uncertain but EFSA considers it to be the worst-case estimate.

It is unclear whether the 2013 EFSA draft summarised all the available, relevant BPA concentration data and addressed all known sources. The REACH[27] information on consumer uses does not provide more information on additional sources. However, the ECHA website on registered substances reports consumer use of thermal paper (AC8), use of articles made of PVC (AC13) and machinery, mechanical appliances, and electrical/electronic articles (AC2) that may be relevant as possible sources of non-food exposure.

2.2 BPA in medical devices

Medical devices are a specific product category in which BPA may be present. Recently, SCENIHR published its Preliminary Opinion for public consultation (SCENIHR 2014) about the safety of using bisphenol A in medical devices. This document includes an extensive list of examples of medical device types with materials derived from BPA.

BPA is a key building block of polycarbonate (PC) plastic and is a precursor for the manufacturing of epoxy resin monomers. PC is used in a wide variety of medical devices because of its balance of toughness, dimensional stability, optical clarity, high heat resistance and electrical resistance. Examples are connectors for infusion sets, dialyzer membrane housings, pacemakers and balloon catheters. In addition to PC medical devices, various dental materials (e.g. composites and sealants) are fabricated from monomers such as bisphenol A glycidyl methacrylate (Bis-GMA) and bisphenol A dimethacrylate (Bis-DMA), which are derived from BPA. In addition to BPA itself, polymers produced using BPA-like polysulfone (PSU) are used in medical devices (e.g. as a membrane in hemodialyzers). Medical devices based on PVC may or may not contain BPA, depending on their production method. European manufacturers have indicated that they discontinued the use of BPA in PVC devices over a decade ago.

The 2014 SCENIHR draft concluded that BPA can be present in medical devices as residue from the polymerization process or result from the hydrolysis of the polymer. In general, SCENIHR concluded that there was very limited information available for assessing the reliability of data on BPA in medical devices.

During use, BPA can leach from medical devices consisting of PC and/or PSU, the latter mostly being used in the form of membranes. To obtain insight into the possible migration of BPA from PC in medical devices, BPA extraction can be performed in vitro with water, methanol or organic solvents that result in dissolution of the product. It has been observed that extraction in methanol results in a higher release of BPA than water extraction does. For PC casings, SCENIHR found that the BPA release in water was 11–14 ng/casing; in methanol, the release was 296–345 ng/casing. Total concentrations of free BPA in a PC product were derived by dissolving the product. Results of free BPA for PC pellets used for the production of medical devices were 4–7

[26] http://www.nvwa.nl/actueel/bestanden/bestand/11243.

[27] http://apps.echa.europa.eu/registered/data/dossiers/DISS-9dbe071c-c12d-0fe1-e044-00144f67d249/AGGR-1a0f4010-386f-475a-9a55-3389b753893c_DISS-9dbe071c-c12d-0fe1-e044-00144f67d249.html#section_3_6

mg/kg after dissolution of the pellets. In response to SCENIHR's Call for Information, PC drinking cups values of 4-6 mg/kg were submitted. SCENIHR therefore concluded that PC used for the production of medical devices seemed to have BPA levels similar to those of PC commonly used as food contact materials (which is typically less than 10µg/g).

In hemodialyzers, water and bovine serum circulation resulted in a BPA recovery of 4–142 ng/module for water and 141–2090 ng/module for bovine serum, again indicating that water is not the best medium for BPA extraction. This was confirmed by other data showing BPA release of 6–71 ng/dialyzer in water and 55–4300 ng/dialyzer in 17.2% ethanol. Low water extraction was observed for three different dialyzers (141, 48 and 6 ng/dialyzer, respectively). In hollow fibres isolated from individual dialyzers and dissolved in hexane, BPA content was 8.3–12.2 µg/g (mg/kg) material. The highest values of BPA released corresponded to the two hemodialyzers tested, which consisted of PC casings and PSU fibres where releases were 1 and 2 µg/module. After sterilization procedures, some BPA may have already been released from the dialyzers. The highest amount of BPA measured for dental materials was 67 nmol/mm2, which amounts to 15 µg/mm2 for a resin bonding material that is not commonly exposed to saliva. For PC orthodontic brackets, the BPA release varied between 22 µg/g (crushed brackets) and 697 µg/g (retrieved after 40 months of use by patients). SCENIHR used these BPA migration values to model patients' exposure to BPA via medical devices.

3 BPA and human health

BPA is ubiquitous in humans and in the environment. Human exposure to BPA may primarily occur as a consequence of "free" BPA leaching or migrating from toys, (food) packaging materials and handling thermal paper. Possible at-risk groups addressed are consumers, workers and hospital patients. In 2011, the Dutch Health Council noted in its advisory report on the identification and protection of high-risk populations[28] that, in principle, the whole human society may be at risk of effects from BPA since all humans are expected to be exposed. However, the GR also noted that especially young children in the pre- and postnatal phase may be at risk. People in this age group typically consume more food per kilogram of body weight than the average person, may use more BPA-containing products than the average person, have immature metabolic systems (with fewer detoxicating enzymes) and are developing quickly, making them more sensitive to developmental influences. The GR identified other at-risk groups, including people who consume a lot of canned food and people who metabolise BPA relatively slowly due to a lower enzyme expression or slower enzymes.

The sections below describe the most recent findings on possible human exposure to BPA. Section 3.1 provides an overview of the levels of exposure, derived primarily from EFSA (2013, 2014), the EU RAR (EC, 2008) and SCENIHR (2014). Section 3.2 summarises the current state of knowledge on possible human health hazards posed by BPA as discussed in the EU RAR (EC, 2008) or by EFSA (2014). Section 3.2.5 presents the various reference values derived by EFSA (2014), SCOEL (2013) and BPA manufacturers in their registration dossier under REACH for safe consumption and use of BPA. Section 3.3 summarises BPA's risks for human health as assessed by the various risk assessment initiatives.

In 2015, this report will be complemented by a Part 2 discussing the possible human health risks of BPA. It will also include the completed draft opinions of EFSA (2013, 2014) and SCENIHR (2014), and the two reports from the Dutch Council for Public Health addressing pre- and perinatal exposure to chemicals and risks of BPA analogues (published in March 2014).

[28] Gezondheidsraad 2011, Leidraad voor identificatie en bescherming van hoogrisicogroepen, VGP/P&L/2581995, d.d. 14 December 2011

Tabel 3 Overview of external dietary and non-dietary exposure sources as derived by EFSA (2014). For a complete overview, see Table 23 A/B (EFSA 2014).[1]

Source	Average external exposure (ng/kg bw per day) Infant (6-12 months, 5 kg)	Toddler (1-3 years, 12 kg)	Child (3-10 years, 30 kg)	Teenagers (10-18 years, 44 kg)	Adult 18-≥65 years, 70 kg)
Dust#	8.8	7.3	2.9	2.0	0.6
Toys#	0.3	0.02	-	-	-
Dietary intake#	375	375	290	159	116-132
Air##	0.7	0.7	0.4	0.4	0.2
Thermal paper###	-	-	69	94	59
Cosmetics###	4.8	2.8	2.2	2.5	3.0

Source	High external exposure (ng/kg bw per day) Infant (6-12 months, 5 kg)	Toddler (1-3 years, 12 kg)	Child (3-10 years, 30 kg)	Teenagers (10-18 years, 44 kg)	Adult 18-≥65 years, 70 kg)
Dust#	14.6	12.2	4.9	3.3	1
Toys#	1.2	0.5	-	-	-
Dietary intake#	857	857	813	381	335-375
Air##	1.4	1.1	0.6	0.6	0.3
Thermal paper###	-	-	550	863	542
Cosmetics###	9.4	5.5	4.2	4.8	4.0

[1] EFSA Draft Scientific Opinion on the risks to public health related to the presence of bisphenol A (BPA) in foodstuffs. EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF) 2014. The figures for dermal exposure are corrected by the dermal absorption fraction of 0.3 and are scaled up to provide a 100% estimate of external dermal exposure. The dermal figures do not include the toxic equivalent oral dose derived by PBPK modelling. For this reason, the external exposures presented here cannot be summed to arrive at the overall total daily intake (presented in Appendix I).

\# External exposure via ingestion

\## External exposure via inhalation

\### External exposure via dermal contact

3.1 Human exposure to BPA

3.1.1 Consumer exposure to BPA

EFSA used different sources to evaluate consumer exposure to BPA: these included food, dust, toys, air, thermal paper and cosmetics (2013, 2014). In the average exposure scenario, the combined non-food exposures were significantly lower than the exposure via food. On the other hand, people older than 10 years of age in the high exposure scenario had more combined non-food external exposures than exposure via food (EFSA draft, 2014). For the toxicologically more relevant internal exposure, EFSA used extensive PBPK (Physiologically based pharmacokinetic) modelling that showed that the relevance of the various routes may shift when internal exposure is considered (see sections 3.2.2 and 3.3.1). See Table 3 for an overview of external exposures from the various sources. Note that because of the different exposure routes (oral and dermal) involved, these exposures cannot be simply summed. Total exposures are summarised in Appendix 1 and include the dermal-to-oral extrapolation that allows external oral and external dermal exposures to be summed for the different consumer age groups assessed by EFSA (2014).

3.1.1.1 Exposure via food

The exposure via food was calculated for all age groups listed in Table 3 by combining information on foods and beverages consumed per individual in different European dietary surveys[29] with average BPA concentrations[30] in canned and non-canned

[29] EFSA Comprehensive database; number of countries ranged from 4 in infants to 15 in child and teenagers

[30] Assuming that samples with a BPA concentration below the limit of detection (LOD) or quantification (LOQ) contained this chemical at BPA concentrations equal to half of the LOD or LOQ

foods (section 2.1). This resulted in a range of exposure estimates per dietary survey. The 2013 EFSA draft followed a conservative approach that used the following assumptions:

- Since not all dietary survey-specific food consumption data contained information on packaging, it was assumed that if a certain food (e.g. peas) had been codified as canned in at least one dietary survey, it was considered to be always consumed from cans in all dietary surveys.
- High external exposure to BPA was calculated by taking the maximum high exposure level calculated per dietary survey. For the average external exposure, the median exposure level of all average exposure levels per dietary survey was taken.
- Exposure was calculated by averaging the exposure per individual over the number of days present in the dietary survey (typically 2–7 days). This exposure was taken as a proxy for long-term exposure. It is known that this estimate overestimates the real long-term exposure.

It is unclear to what extent the 2013 EFSA draft included possible exposures to BPA from foods in contact with other types of materials like recycled or new paper and cartons (section 2.1).

Biomonitoring data on BPA reported in the 2013 EFSA draft were used as additional arguments to corroborate the idea that the estimated exposures in Table 3 are likely overestimates: modelled exposures were approximately four times higher (for the average exposure scenario) or three times higher (for the high exposure scenario) than the total exposure (all sources) approximated by the biomonitoring approach.

In infants (aged 0–6 months), exposure was calculated via breast milk (average: 119–225 ng/kg bw per day, high: 343–495 ng/kg bw per day) and infant formula (average: 30 ng/kg bw per day; high: 80 ng/kg bw per day). The information available for these assessments was very limited. The 2013 EFSA draft noted that exposure in infants who consume formula can be higher when infants are fed with old PC baby bottles (685 ng/ kg bw per day) and for those who live in buildings with old water pipes repaired with epoxy resins (high: 165 ng/kg bw per day). The modelled exposures are similar to earlier average daily intake estimates made by the FDA in October 2009: 200–400 ng/kg bw/day for infants and 100–200 ng/kg bw/day for children and adults.[31]

[31] http://www.fda.gov/newsevents/publichealthfocus/ucm064437.htm

The exposure modelled in the 2013 EFSA draft represents the European consumer average. However, cultural and behavioural differences may give rise to different exposures in specific populations.

3.1.1.2 Exposure via non-food

Table 3 shows that thermal paper is the highest contributing source of exposure to BPA from all non-food sources taken into account by the 2013 and 2014 EFSA drafts. The equations and parameters EFSA used to calculate exposure from thermal paper are commonly accepted. Dermal exposure from touching thermal paper was calculated by assuming that BPA is present on fingers after touching thermal paper (suggested concentration of BPA per fingertip).[32] The amount present was subsequently multiplied by the number of times a consumer is expected to handle cash receipts. EFSA reported that data for two parameters was lacking completely and therefore the assessment is highly uncertain. Information is needed with respect to:

- The BPA leave-on concentration on fingertips after thermal paper contact (where it should be noted that leave-on of BPA is correlated with the skin's greasiness and humidity), and
- The influence of multiple paper contacts on the BPA leave-on concentration.

[32] * Lassen et al. (2011) presented a figure explaining the different layers of thermal paper. BPA is located in the thermal reactive layer of the paper (i.e. the top layer). Therefore, the mean BPA concentration in paper presented in Table x underestimates the concentration in the top layer (i.e. the layer touched when handling thermal paper). Lassen et al. assumed that dermal contact results in 1.4 ug free BPA (mean of receipts) on a fingertip, which is similar to the 1.13 ug/fingertip reported by Biederman (2010). The 2013 EFSA draft used 14 ug/fingertip.

EFSA is not clear in which direction the true value may lie: it is either over- or underestimated.[33] The 2014 EFSA draft concluded that more data is needed to arrive at a conclusion on the external exposure to BPA via thermal paper.

In the average scenario for exposure to BPA via non-food sources, EFSA calculated that teenagers (aged 10-18 years) have the highest external dermal exposure (94 ng/kg bw per day). The average dermal exposure for adults was 59 ng/kg bw per day. In the high scenario, dermal exposures for teenagers and adults were 868 and 546 ng/kg bw per day, respectively. The latter BPA exposures were completely dominated by exposure via thermal paper. The contribution of dust, air and cosmetics to exposure were very low.

3.1.2 Human exposure via medical devices

Medical devices are a specific product category in which BPA may be present (see section 2.2). In this category, the exposure to BPA typically occurs for a limited time and is generally low. The exposure levels reported in the 2014 SCENIHR draft show that high exposures through medical devices may be of similar magnitude as the exposure of an average consumer to BPA via food consumption. The highest exposure levels were obtained for prolonged surgical procedures in infants and prolonged exposure to BPA-containing materials in intensive care units by prematurely born infants.

The 2014 SCENIHR draft concluded that the release of BPA from medical devices is influenced by a number of factors. The major factor influencing the residual amount of BPA in polymer materials is the use of incorrect operating conditions during processing. Moreover, the polycarbonate polymer can break down or hydrolysis can occur after manufacturing, giving rise to the free monomer from the polymer available for exposure.

In general there are few data available on patients' actual exposure to BPA via medical devices. Due to the limited availability of data, the 2014 SCENIHR draft estimated exposure levels. The estimates used in the 2014 SCENIHR draft ("worst-case scenarios") may not always reflect actual exposure. This implies that patients' exposure to BPA via medical devices may have been overestimated in the scenarios. However, given the current knowledge, this is a conservative approach.

Table 4 gives an overview of exposures reported in the 2014 SCENIHR draft. In the SCENIHR Opinion, six exposure scenarios were considered to arrive at an estimate of BPA exposure via medical devices. The highest exposures were found for prolonged surgical procedures in infants and prolonged exposure to BPA-containing materials in intensive care units by prematurely born infants. The exposure scenario for BPA exposure via PVC medical devices as indicated in the table was not included in the final safety evaluation in the 2014 SCENIHR draft since PVC manufacturers in Europe stated that they no longer use BPA in PVC production. In Vinyl 2010, Plastics Europe stated in their 2010 reporting activities[34] that BPA has been phased out of PVC resin production in

[33] Discussion of some parameters:
1. Concentration of BPA. From paragraph 2.1.1 (non-food), it is already clear that the first uncertainty is the concentration of BPA on the fingertip (dry fingers). The concentrations for lotion (grease) and humid fingers are factors of 2.5 and 9 times higher, respectively.
2. frequency handling cash receipts
3. finger surface area (number of fingertips).
Furthermore, EFSA did not adopt the scenario Lassen et al. (2011) used in their risk assessment. Lassen et al. used the higher humid finger concentration (factor 9) and more fingers (8 versus 6). EFSA adopted the number of handling events (mean 1 and high 4.6) per day. EFSA calculated adult exposures of 59 (mean) and 542 (high) ng/kg bw per day, while Lassen et al. calculated a high exposure of 6800 ng/kg bw per day. The exposure from thermal paper is driven by the choice of defaults. EFSA's and Lassen et al.'s thermal paper exposure value are uncertain. Lassen et al.'s defaults for dry, greasy and humid fingers are based on just four cash receipts and have wide result ranges. EFSA's approach may be sensible for the general population, but may not cover specific large subpopulations like housewives doing the grocery shopping (as Lassen et al. attempted). On the other hand, Biedermann et al. (2010) reported an equilibrium between the BPA in the paper and on the surface layer of the skin, and repeated contact with fresh recorder paper did not increase the BPA concentrations on the skin. Biedermann et al. showed that equilibrium was reached after holding the cash receipt (light pressure) once for 5 seconds. Using 4.6 handling events per day seems to overestimate the exposure. In view of all the uncertainties, it is impossible to say whether exposure is under- or overestimated.

[34] http://www.plasticseurope.org/documents/document/20110422155920-vinyl2010__progress_report_2011.pdf

Tabel 4 BPA exposure of patients from medical devices estimated for various use scenarios, taken from the 2014 SCENIHR draft, Table 6.

Exposure scenario	BPA exposure estimation in ng/kg b.w./day Prematurely born infant	infant	child	adult
External contact with a MD containing BPA (short-term)	1			0.08
Contact with dental material				
(short-term)	na	na		200
(long-term)	na	na	2	6
Contact with orthodontic equipment				
(short-term)			140	140
(medium-term)			13.5	7.5
(long-term)			12	6
Contact with an implant				
(medium-term)			11	6
(long-term)			0.8	0.4
Hemodialysis (long-term)				57
Prolonged surgical procedures (short-term)		685	114	57
Prolonged exposure to different sources of BPA in intensive care units (medium-term)	3000			
Breast pump and collection vessel made of PC (medium-term)		134		
Uses of PVC				
(short-term)	12000			5000
(long-term)	7000			1000

all European Council of Vinyl Manufacturers (ECVM) member companies since 2001. EVCM represents the five leading European PVC resin producing companies who produce 75% of the PVC resin manufactured in Europe.[35] SCENIHR therefore judged it unlikely that the high exposure to BPA estimated by the exposure scenario for BPA in PVC would be reached.

3.1.3 Occupational exposure

Occupational exposure to BPA occurs via inhalation and dermal and oral uptake. Oral exposure to chemicals is generally not an issue for workers when good hygiene practices are followed. To assess the risks for workers (also see section 3.3.4), the external inhalation exposure is normally compared to the occupational exposure limit (OEL; also see section 3.2.5). This only covers inhalation exposure. Dermal exposure is much more relevant than inhalation exposure for people in some professions (e.g. cashiers).

Inhalation exposures are based on measurement data published in the 2003 EU RAR and its 2008 addendum (EC, 2008).[36] The highest inhalation exposures occur in workers who are involved in manufacturing BPA and epoxy resins, in particular during manufacturing steps that involve powder contact such as product bagging and filter changing (EC, 2008). The highest reasonable worst-case (RWC) eight-hours' time-weighted average inhalation exposures were estimated using industry measurement data: 3 mg/m^3 for BPA manufacturing and 0.7 mg/m3 for manufacturing of epoxy resins (see Table 5). Inhalation exposure concentrations in other scenarios are generally much lower and presented in Appendix 2. Short-term peak exposures up to 11 mg/mg3 may occasionally occur, but are generally accepted to be below 6 mg/m^3 (EC, 2008).

Dermal exposures were calculated without taking into account the use of chemical protective gloves, which lower dermal exposure by a factor of 10. Gloves are generally used during maintenance work

[35] ttp://www.pvc.org/en/p/ecvm

[36] European Risk Assessment Report on Bisphenol A (2003) and its Addendum (2008)

Tabel 5 Inhalation and dermal exposure to BPA during some work activities, based on both measured data and estimated data.

Work activities	Inhalation RWC 8hr TWA (mg/m^3)*	Inhalation RWC short-term (mg/m^3)	Dermal (mg/kg bw/day) NO GLOVES assumed**	Reference
BPA Manufacturing	3	6		RAR, 2008
- Product sampling			0.60	
- Bag filling			6	
Manufacture of epoxy resins and moderated epoxy resins	0.7	11		RAR, 2008
- charging reactors			6.0	
- maintenance			12	
Professional end use of thermal printing papers			3x10-8 – 0.017	ARCADIS, 2013

* RWC eight-hours' time-weighted average inhalation exposures

** Exposure estimation based on EASE calculation. For inhalation, SCOEL (2013) proposed an OEL of 2 mg/m^3 inhalable dust of BPA (also see section 3.2.5), SCOEL did not derive a dermal DNEL. A dermal DNEL was derived by industry for systemic effects at 1.4 mg/kg bw/day (also see section 3.2.5).

and BPA manufacturing. The highest dermal exposure mainly takes place during the manufacturing of BPA and BPA epoxy resins and during specific activities like charging reactors or maintenance activities (see Table 5). The highest value for dermal exposure was estimated to be 12 mg/kg bw/day for maintenance work. Appendix 2 gives a more detailed overview of dermal exposure to BPA.

All dermal exposure values were estimated using EASE. This exposure assessment model is currently no longer regarded as state-of-the-art, but was at the time the 2003 RAR was completed. EASE was adjusted for use in the ECETOC TRA dermal exposure assessment route (ECETOC, 2004[37], 2009[38], 2012[39]). ECETOC TRA has been accepted as a conservative first tier model for calculating dermal exposures within the REACH framework. When a more refined exposure assessment is needed to improve the risk assessment, a more sophisticated second tier model may be used. The RISKOFDERM exposure assessment model can be applied for this purpose (TNO, 2006).[40]

Under the conditions of good hygienic practice, oral exposure is not considered relevant for workers by default, and only exposure via the skin or inhalation is assessed. However, the oral route of exposure may be relevant to workers who frequently handle thermal printing paper (e.g. cashiers) due to transfer of BPA from fingers/hands to the mouth (e.g. licking of fingers, contamination of food eaten during the workday, general hand-to-mouth contact). This route of exposure needs further attention as the contribution of the oral component in the total daily intake for people like cashiers may be as high as or even higher than the contribution from the dermal exposure route.

New insights show that dermal exposure may be more significant than previously assumed.[41] Calculations of workers' dermal exposure following contact with thermal paper (cashiers) found a dermal exposure between $3x10^{-5}$–17 µg/kg bw/day. The spread reflects the high uncertainty in these estimates and results from differences in the many assumptions that had to be made to come to these estimates.

To assess the aggregated exposure of workers via inhalation, dermal uptake and (where relevant) oral uptake, a combined exposure estimate has to be derived either via route-to-route extrapolation or by calculating the total *internal* exposure to BPA as a

[37] Ecetoc 2004, Targeted risk assessment, Technical report No. 93, Brussels, Belgium

[38] Ecetoc 2009, Addendum to ECETOC Targeted Risk Assessment Report No. 93, Technical Report No. 107, Brussels, Belgium

[39] cetoc 2012, Ecetoc TRA version 3: Background and rationale for the Improvements, Technical Report No. 114, Brussels, Belgium

[40] TNO, 2006, The RISKOFDERM Dermal Exposure Model, Version 2.0 – Guidance Document, The Netherlands

[41] Arcadis (2013) BPA dermal exposure assessment, report in preparation

consequence of the *external* exposure via the different routes. This was not done by the RAR (EC, 2008). Significant differences in internal exposure following the route of exposure result from the high rate at which BPA is metabolised following oral exposure (i.e. the first-pass effect) when passing the liver following gastro-intestinal uptake. Uptake following dermal exposure or via inhalation lacks this first-pass effect, resulting in relatively higher systemic concentrations.

It is very difficult to reliably calculate the *internal* BPA exposure caused by *external* dermal BPA exposure because of a lack of kinetic data. Too many assumptions have to be made to make a good estimate of the *internal* BPA exposure. As a result, it is also quite difficult to very reliably assess the health risks caused by *external* dermal exposure, since route-specific systemic toxicity data are not available. In addition, the limited amount of information available on BPA kinetics, especially via the inhalation and dermal routes, hinders a reliable health risk assessment based on oral toxicity data using application of route-to-route extrapolation. This will be further discussed in sections 3.2.2 and 3.3.1. However, these data may become available in the near future since an ongoing study of NIEHS/NTP cashiers will measure BPA and BPA conjugates in cashiers' blood and urine samples before and after their work shifts (see Birnbaum et al, 2012).[42] This study is expected to yield insights about the degree to which thermal receipt paper contributes to BPA exposure and may also facilitate the evaluation of workers' dermal exposure via other routes.

Furthermore, NIEHS/NTP and the National Institute for Occupational Safety and Health (NIOSH) are conducting an occupational exposure study in workers who directly handle BPA where it is produced or processed (Wang et al., 2012). They have developed a study protocol for assessing the routes and levels of exposure among such workers. The study aims to evaluate the levels of BPA exposure among occupationally exposed people and to identify factors contributing to occupational exposures. Urine samples from 120 workers, as well as samples of BPA in the air and on workers' hands during their work shifts, will be collected and analysed. In addition, as a result of the substance evaluation conducted under REACH, industry will be required to deliver further dermal-specific kinetic uptake information.

3.1.3.1 Conclusion

This paragraph focusses entirely on the information that is relevant to the assessment of workers' *external* exposure through inhalation of and dermal contact with BPA. Through inhalation, the BPA exposure of workers involved in manufacturing BPA or BPA epoxy resins may reach levels up to 3 mg/m3 during an eight-hour workday, which is close to the OEL of 2 mg/m3 derived by SCOEL. Dermal exposure without the use of gloves is generally considered to be <12 mg/kg bw/day. Dermal exposure can be controlled when adequate protective gloves are used. The estimated *external* dermal exposure level should be validated using more sophisticated first or second tier dermal exposure assessment models (ECETOC TRA and RISKOFDERM, respectively). For some professions, oral exposure in the workplace seems to be underestimated.

There is a strong need for insight into *internal* BPA exposure. The currently available data on kinetics do not allow for a reliable estimation of *internal* exposure via dermal or inhalation contact. In absence of this insight, it is not possible to perform a reliable risk assessment for workers, since route-specific toxicity data are not available for dermal exposure and adequate route-to-route extrapolation is not possible.

3.2 Human health hazards of BPA

Different scientific studies associate BPA with adverse human health effects like immune effects, obesity, ADHD, and diabetes, possibly induced by an endocrine mode of action. BPA is considered to be a weak estrogenic substance with a relatively low potency for activation of the estrogen receptor[43] and is being studied widely for health effects that may be related to this activity. The pre- and early postnatal periods are considered to be possible periods of relatively high sensitivity, given that organ systems are still developing during those phases.
The effects of BPA on all classical end points of toxicity have been studied extensively using OECD

[42] Birnbaum et al., (2012) Consortium-Based Science: The NIEHS's Multipronged, Collaborative Approach to Assessing the Health Effects of Bisphenol A. Environm. Hlth. Perspect., 120, 1640-1644

[43] The potency of BPA for activating the estrogen receptor is of around four orders of magnitude lower than that of the endogenous female reproductive hormone estradiol17β

test guidelines, both within Europe (i.e. European Committee, EFSA) and beyond (e.g. the US, Canada and Japan; also see the overview of risk assessments presented in section 1.3). At present, scientists are focussed on the relevance of emerging toxicity data on possible low-dose effects, and on possible NMDR effects. Moreover, additional toxic effects are being investigated in relation to BPA, including immune effects, obesity, diabetes, and behavioural effects. However, the available scientific data about guideline-based and non-guideline-based toxicity test systems are not conclusive about possible adverse effects of BPA on these end points.
An important initiative in the area of BPA hazard assessment is currently being carried out by EFSA and a draft hazard and risk assessment was published for public consultation in January 2014. Section 3.2.1 describes the current classification and labelling of BPA. Section 3.2.2 describes BPA's toxicokinetics. Sections 3.2.3 reflect on the RAR (EC, 2008) and EFSA (2014) findings on the likely health effects of BPA. Section 3.2.4 continues with the 2014 EFSA draft's conclusions with respect to remaining uncertainties about the adverse effects of BPA. Section 3.2.5 provides an overview of other reference values derived to date to evaluate the safe use of BPA-containing materials and products, including the main findings, conclusions and remaining uncertainties in the 2014 EFSA draft opinion that led to the t-TDI being proposed as the most recent estimate for assessing the human health risks of BPA following oral exposure.

In 2015, this report will be complemented by a Part 2 discussing the possible human health risks of BPA. This will also include EFSA's final findings and the two reports from the Dutch Council for Public Health addressing pre- and perinatal exposure to chemicals and risks of BPA analogues (published in March 2014).

3.2.1 Classification and labelling

BPA is classified as a skin sensitiser (category 1; H317), damaging for the eye (category 2; H318), specific target organ toxicity following single exposure (category 3; H335) and toxic for reproduction (category 2; H361f). As concerns the latter, BPA is 'suspected of damaging fertility or the unborn child' and 'suspected of damaging fertility'. The Committee for Risk Assessment recently adopted an opinion to strengthen the existing harmonised classification and labelling (CLH) of BPA from a category 2 reproductive toxicant to a category 1B reproductive toxicant (also see section 5.3.1).[44]

3.2.2 Toxicokinetics

Extensive kinetic data are available although they predominantly follow oral exposure. Topics that are addressed include interspecies differences and differences in metabolic maturation. The main findings described in the 2014 EFSA draft are summarised below.

The 2014 EFSA draft concluded that BPA is rapidly absorbed following oral administration (i.e. up to 85% in rats and monkeys). Human data also suggest near or complete absorption. Percutaneous penetration, relevant for dermal exposure, appears to be low (approximately 2.3–8.6% in 24 hours) as estimated from *in vitro* and *in vivo* experiments. Not enough data were available to reliably estimate the extent of skin metabolism. The 2014 EFSA draft proposed absorption percentages for oral and dermal exposure (90% and 10% in 24 hours, respectively).

Although no data are available on absorption following inhalation, SCOEL assumed that appreciable absorption will occur. Further, it is considered likely that some of the inhaled BPA will be ingested and absorbed from the gastro-intestinal tract (SCOEL, 2013). The 2013 SCOEL report noted that since the first-pass effect in the liver is missing following inhalation exposure, higher blood levels of free BPA may be present after inhalation than after oral dosing. There are neither data to quantify the absorption nor the amount to be ingested following inhalation exposure. In the absence of data, it is assumed that the fraction of the ingested inhaled dose will be limited.

After oral administration, BPA is rapidly metabolised (conjugated) to BPA-glucuronide in the gut wall and the liver before reaching the systemic circulation. Consequently, the level of unconjugated BPA is <0.5% of total serum BPA in humans and monkeys, following oral exposure. The percentage of unconjugated BPA following oral administration is only a few percent of total BPA in several animal species. Although polymorphisms have been described in humans for this conjugation pathway, inter-individual

[44] ECHA news, published 19 March 2014, ECHA/PR/14/07, http://echa.europa.eu/view-article/-/journal_content/title/rac-proposes-to-strengthen-the-classification-of-bisphenol-a

variations in unconjugated BPA blood levels appear to be small due to other conjugation pathways (e.g. the formation of BPA-sulphates). BPA-glucuronide is considered to have no affinity for estrogen receptors. Levels of unconjugated BPA found in the blood of people who consume canned food were below the limit of detection. The available data indicates that rodents' metabolic capacity matures with age whereas monkeys' metabolic capacity is similar between adults, juvenile and newborn animals. However, the first-pass effect also appears to be relevant in early postnatal rodent pups. Compared to neonatal rats, the level of maturation appears to be higher in newborn monkeys and thus in non-human primates the kinetic differences between neonatal and adult animals are smaller than in rodents (EFSA draft, 2014). In their 2011 opinion, the Dutch Health Council stated that modelling estimates of BPA concentrations in the blood of young children may be up to three times higher than in adults given a similar oral uptake due to a relatively lower capacity of detoxicating enzymes (GR, 2011).

BPA is rapidly distributed in all tissues and does not accumulate in the body. Unconjugated BPA can pass the placenta and be conjugated in the foetal compartment. Both unconjugated and conjugated BPA have been detected in the milk of rat dams, but pup exposure via lactation is concluded to be extremely low (EFSA draft, 2014).

Clear interspecies differences in excretion have been observed. Due to hepatic recirculation, faecal excretion is the predominant route of elimination in rodents. In humans and monkeys, the primary elimination route is urinary excretion of BPA conjugates. Because of hepatic recirculation, rats appear to have a longer elimination half-life for unconjugated BPA levels in blood than primates (EFSA draft, 2014).

In summary, extensive kinetic data are available, predominantly from oral exposure data. Differences in kinetics between species and with age have been found and should be accounted for where necessary. A considerable first-pass effect is present after oral administration, which should be taken into account in route-to-route extrapolation. The absorption estimates in the 2014 EFSA draft for the oral and dermal routes of exposure (90% and 10% over 24 hours) are reasonable estimates for risk assessment. No information about absorption after inhalation is available.

3.2.3 Likely effects of BPA on human health

The 2014 EFSA draft identified likely adverse effects in animals (i.e. on kidneys, liver and mammary glands) using a weight-of-evidence approach to hazard identification. These are summarised below.

3.2.3.1 Acute and chronic toxicity

The RAR (EC, 2010)[45] concluded that BPA is of low acute toxicity by all routes of exposure relevant to human health. The 2014 EFSA draft also concluded that BPA is of low acute toxicity. The RAR (EC, 2010) reported an oral two-generation study in mice that confirmed that BPA's repeated dose toxicity involves effects on body weight gain, liver and kidney. This study identified a NOAEL of 50 mg/kg/day. The 2014 EFSA draft reported that the lowest NOAEL for subchronic oral exposure, based on effects on the liver as a target organ, is approximately 5 mg/kg bw/day.

The data available about BPA's acute toxicity indicate that BPA is of low acute toxicity by all routes of exposure relevant to human health (EC, 2008, 2010a,b). Oral LD50 values above 2,000 mg/kg bw/day have been reported in rats and mice, and dermal LD50 values above 2,000 mg/kg bw/day have been reported in rabbits. For inhalation, a six-hour exposure to 170 mg/m^3 (the highest attainable concentration) produced no deaths in rats; only slight and transient nasal tract epithelial damage was observed. The effects of a single oral exposure to BPA in humans are not well documented. In a kinetic study using healthy volunteers, a 5 mg dose of BPA (range 54.3–87.7 µg/kg) was well tolerated (Völkel et al., 2002).

The chronic toxicity of BPA has been studied by Tyl et al. (2002, 2008), who conducted a dose range finding study and two large multigenerational studies using dietary administration of BPA to rats and mice with doses ranging from 1 or 3 µg/kg bw/day up to 500 or 600 mg/kg bw/day. These studies demonstrated effects on the liver, kidney and body weight at doses of 50 mg/kg bw/day and higher. Chronic inflammation of the liver was seen from 50 mg/kg bw/day in the three-generation study, but no convincing dose-response relationship was found. These liver effects in rats were thus considered to be back-

[45] European Union Risk Assessment Report, 4,4-Isopropylidenediphenol (Bisphenol A) Complete Risk Assessment in one document, 2010

ground variation and not treatment related. Renal tubule degeneration of the kidney was also seen in this three-generation study in females at 500 mg/kg bw/day but not at 50 mg/kg bw/day. Hence, the NOAEL for kidney effects is 50 mg/kg bw/day. In mice, the NOAEL based on effects on the liver was 5 mg/kg bw/day. Stump et al. (2010), used a wide dose range in rats, performing a study on neurotoxicity according to OECD 426 and based on reduced body weight or body weight gain, respectively. They identified a lowest NOAEL of 5.85 mg/kg bw/day.

3.2.3.2 Sensitisation

The RAR (2010) concluded that skin reactions can be a potential consequence of repeated skin exposure in humans. BPA is capable of inducing skin sensitisation responses in humans with low prevalence being a weak sensitiser (EFSA, 2010; FAO/WHO, 2011; EC, 2010a; ANSES, 2011). In addition, some individual cases have been reported that describe contact dermatitis against BPA (Aalto-Korte et al., 2003).

The RAR (2010) concluded that there are several reports of patients with dermatitis that responded to BPA in patch tests. However, it is unclear whether BPA or related epoxy resins were the underlying cause of the hypersensitive state. Anecdotal information indicates skin inflammation in workers handling BPA, although given the uncertain reliability of this information no conclusions can be drawn from it. No skin sensitisation test performed to current regulatory standards is available for animals.

The available studies are negative, but the test reports lack detail and no reliable justifications were given for the choice of concentrations used. The study using the highest challenge concentration (50% in a guinea pig closed-patch test) found a 12.5% sensitisation rate. It is possible that the concentrations used in all the available studies were not maximised and a greater response might have been obtained with higher induction and challenge concentrations.

Based on the findings from the most robust study, the RAR (EC, 2010) concluded that BPA may possess a skin sensitisation potential, albeit a limited one. In the presence of UV light, BPA can also elicit skin responses in humans, and reproducible positive results for photosensitisation have been obtained in mouse ear swelling tests. Mechanistic studies in mice have suggested this is an immune-mediated process. Therefore, examination of the available human and experimental animal studies leaves the picture somewhat unclear as to whether one or more of the following are properties of BPA: 1) orthodox skin sensitisation, 2) photosensitisation, or 3) BPA eliciting a response in people previously skin sensitised to another substance (e.g. epoxy resins).

Thus, taking all the available data into account, RAR (EC, 2010) considered BPA to be capable of producing skin sensitisation responses in humans. RAR (EC, 2010) also concluded there are no data from which to evaluate BPA's potential to be a respiratory sensitiser.

3.2.3.3 Genotoxicity

The 2014 EFSA draft concluded that BPA is unlikely to pose a genotoxic hazard to humans. The RAR (EC, 2010) concluded that BPA has no significant mutagenic potential in vivo.

Available data indicate that BPA does not induce *in vitro* gene mutation in bacteria (Masuda et al., 2005; Tiwari et al., 2012) and *in vivo* micronuclei in rodent bone marrow assays (Masuda et al., 2005; Pacchierotti et al., 2008; Naik et al., 2009; De Flora et al., 2011). BPA was aneugenic in an in vitro study in mammalian cells conducted by Johnson and Parry (2008), due to BPA's spindle disrupting effects. However, BPA does not act with DNA directly but acts on the mitotic spindle apparatus, an effect which is thought to have a threshold (COM Guidance on a Strategy for Testing of Chemicals for Mutagenicity, Department of Health, UK, 2000). The large margin between the dose levels found negative in vivo for induction of aneuploidy in rodent germ cells (Pacchierotti et al., 2008) and for induction of micronuclei in somatic bone marrow cells (Masuda et al., 2005; Pacchierotti et al., 2008; Naik et al., 2009; De Flora et al., 2011), which provides adequate reassurance on the lack of aneugenic effects caused by BPA *in vivo*.

3.2.3.4 Reproductive toxicity

The RAR (2010) concluded that a two-generation study in mice conducted by Tyl et al. (2007) provided a comprehensive, definitive investigation of BPA's effects on reproduction at exposure levels spanning the low (µg/kg bw/day) to high (mg/kg bw/day) ranges. Tyl et al. (2007) showed that BPA causes adverse effect on pregnancy and offspring at 600 mg/kg bw/day, an exposure level that also caused mild parental toxicity. The RAR (EC, 2010) concluded that fertility is not affected by BPA exposure, which resolves the previous uncertainty regarding the

NOAEL for fertility in mice. A study NOAEL for reproductive toxicity of 50 mg/kg bw/day has been identified. As there was no evidence of an adverse effect on the development of the male reproductive tract at µg/kg bw/day doses of BPA, the RAR (EC, 2010) concluded that the study resolves the uncertainties surrounding the potential to produce adverse effects on development at low doses. Thus it was concluded that a NOAEL of 50 mg/kg/day for reproductive toxicity should be used in the risk assessment. The RAR (EC, 2010) could draw no conclusions with respect to a possible association between recurrent miscarriage and BPA exposure. The 2014 EFSA draft concluded that BPA is essentially not a specific reproductive or developmental toxicant. It reported that female reproductive toxicity occurred with an overall NOAEL of 50 mg/kg bw/day and a LOAEL of 500 mg/kg bw/day, as derived from the multigenerational study by Tyl et al. (2002). In that study, ovarian weights as well as total pups and live pups/litter on postnatal day (PND) 0 were decreased at 500 mg/kg bw/day, which exceeded the adult maximum tolerated dose (MTD). However, significant body weight reduction and hepatic toxicity occurred at the LOAEL for female reproductive effects. As to developmental toxicity, BPA does not cause malformations or birth defects in rats or mice at levels up to the highest doses evaluated: 640 mg/kg bw/day (rats) and 1250 mg/kg bw/day (mice) (Morrissey et al., 1987). BPA does not alter male or female fertility after gestational exposure up to doses of 500 mg/kg bw/day in rats (Tyl et al., 2002) and 600 mg/kg bw/day in mice (Tyl et al., 2008), the highest dose levels evaluated. BPA does not permanently affect prostate weight at doses up to 475 mg/kg bw/day in adult rats or 600 mg/kg bw/day in mice. BPA does change the age of puberty in male or female rats at high doses (ca. 500 mg/kg bw/day). Neurodevelopmental toxicity was not observed at the highest dose tested (164/410 mg/kg bw/day, Stump et al., 2010). However, the 2014 EFSA draft noted that non-guideline-based animal studies give rise to uncertainties about effects of pre- and perinatal exposure related to obesity, diabetes and behavioural effects (also see section 3.2.4).

In 2013, the French competent authority prepared a dossier under the CLP Regulation (the European Classification and Labelling Regulation, also see section 5.3.1) arguing that BPA should be classified as a presumed human reproductive toxicant (Category 1B). The dossier included toxicity data from both guideline and non-guideline studies and epidemiologic data on BPA. The proposal concluded that BPA is a reproductive toxicant for the following reasons. An adverse effect on fertility following exposure to BPA was reported in multigenerational studies for rats and mice: toxic effects on male and female reproductive organs were observed and the adverse effects were considered to be a primary effect of BPA and not secondary effects of systemic toxicity. It was furthermore concluded that the adverse effects observed *in vivo* in test animals were relevant to humans, where the main mode of action causing effects on fertility in test animals is considered to be a disruption of the estrogenic signalling (based on current knowledge), the endocrine-active form of BPA influencing this estrogenic signalling is found in human serum, cord blood and the placenta, and the estrogenic signalling is highly conserved across species, which leads to the conclusion that the signalling in test animals is representative for humans.

Recently ECHA's Risk Assessment Committee discussed this proposal to come to a conclusion on the proposed harmonised classification. The outcomes of this discussion were published on the ECHA website on 19 March 2014[46]: RAC adopted the opinion to strengthen the existing harmonised classification and labelling (CLH) of BPA from a category 2 reproductive toxicant to a category 1B reproductive toxicant, due to the adverse effects on sexual function and fertility in line with the proposal from the French competent authority. This RAC opinion solely covers the adverse effects on sexual function and fertility, as France only proposed these types of main reproductive toxic effects for revision. The RAC adopted its opinion by consensus after comparing the available evidence to the CLP criteria. Studies performed according to standard test guidelines were given the most weight. The RAC concluded that oral exposure to BPA led to adverse effects on reproductive capacity (functional fertility) in a multigenerational guideline study of mice and rats. Impaired female reproductive capacity was also observed in several supplementary non-guideline studies. In addition, several studies observed toxic effects for reproductive organs.

[46] http://echa.europa.eu/view-article/-/journal_content/title/rac-proposes-to-strengthen-the-classification-of-bisphenol-a

3.2.4 Uncertainties in current hazard assessment

In addition to the likely effects of BPA on human health, several areas can be identified where emerging research on the adverse effects of BPA continues to give rise to uncertainties. Examples include those areas that are currently under debate in relation to BPA (e.g. immune effects, mammary gland development, obesity, diabetes, behavioural functions and metabolic activity). This debate has been ongoing for several years; it is reflected in reports such as the 2006 EFSA update of their initial hazard assessment of BPA focussing particularly on carcinogenic and reprotoxic effects of BPA exposure on infants and on possible adverse effects at low doses of exposure, and by a 2008 review by the National Toxicology Program Center for the Evaluation of Risks to Human Reproduction, part of the US National Institutes of Health,[47] in which they expressed 'some concern for effects on the brain, behaviour, and prostate gland in foetuses, infants, and children at current human exposures to BPA', '*minimal concern* for effects on the mammary gland and an earlier age for puberty for females in foetuses, infants, and children at current human exposures to BPA' and '*negligible concern*' for other outcomes.

The ongoing presence of these uncertainties was taken as a reason for the EFSA Scientific Panel on Food Contact Materials, Enzymes, Flavourings and processing Aids (EFSA/CEF Panel) to re-evaluate the available data and led them to lower the previous TDI of 50 µg/kg bw/day to a temporary t-TDI of 5 µg/kg bw/day (also see section 3.2.4). This temporary value reflects the current uncertainties surrounding the effects of BPA on the mammary gland and other potential health effects, which the EFSA/CEF Panel considered less than 'likely' in their weight-of-evidence approach.

The main uncertainties result from various non-GLP studies and concern the following adverse effects on human health:

- Possible low-dose effect
- Possible NMDR effects
- Possible developmental effects on the immune system
- Possible developmental neurotoxic and behavioural effects (e.g. ADHD, anxiety)
- Possible metabolic effects (e.g. diabetes, obesity, cardiovascular effects)
- Possible developmental effects on the mammary gland

Further research on BPA's potential adverse health effects is needed, using validated, robust methodology, in particular on reproductive, neurobehavioral, immunological and metabolic endpoints. To this end, the US NIEHS/NTP has designed a study to bridge the gap between regulatory GLP studies and experimental research studies on BPA. This study involves dedicated investigations by the US NIEHS/NTP that will be carried out as part of the ongoing two-year guideline study in rats, involving both pre- and postnatal exposure to BPA. The results of this study will depend very much on inclusion of parameters for investigating potential reproductive, neurobehavioral, immunological and metabolic effects. At present, it is unclear which exact parameters will be included.

The subsections below provide an overview of the current uncertainties in the BPA hazard assessment as identified in the draft opinion published for public consultation by EFSA in January 2014.

3.2.4.1 Low-dose effects and non-monotonic dose-responses

In their draft opinion on BPA, EFSA addressed the controversial issues of low-dose effects and NMDR curves. The 2014 EFSA draft report states that:

> *'Reviewing the toxicological profile of BPA and other endocrine-active substances, a particularly controversial area has been the reported occurrence of effects at low doses (doses below the current TDI of 50 µg BPA/kg bw per day) and non-monotonic dose-response curves (NMDRC). The term "low-dose effects" is not synonymous with or equivalent to NMDRC. The NMDRC can be characterized by a change in slope direction along the dose interval studied, contrary to conventional monotonic dose response, which shows a consistent increase in (adverse) effects along the dose range. (...)*
> *(...) In evaluating study results reporting adverse BPA effects at low doses and with NMDRC, a well described dose-response curve in the low-dose area is often lacking. Usually the magnitude of the effects is low and statistically significant effects are observed for only one or two doses, which makes it difficult to rule out that the results are not due to chance. (...)*
> *(...) The results from the NMDRC findings have not been taken into account in the risk characterization of BPA until such time as the findings can be reliably replicated*

[47] NTP-CERHR Monograph on the Potential Human Reproductive and Developmental Effects of Bisphenol A, NIH Publication No. 08-5994, September 2008

and toxicological relevance can be established. As concluded in the scientific opinion on the hazard assessment of endocrine active substances (EFSA Scientific Committee, 2013), more work needs to be conducted on NMDRCs to agree on the definitions of the respective terms, and in practical terms to consider whether or how it could impact upon risk assessment and testing strategies.'

The 2014 EFSA draft and 2014 SCENIHR draft agree with these conclusions about low-dose effects and NMDR curves.

Scientific studies have been inconclusive. For many of the emerging studies, the experimental study design and data quality are topics of extensive debate. This particularly involves the sensitivity of measurement techniques, the reproducibility of data, the absence of a proper dose-response assessment and low statistical power. Furthermore, the fact that BPA is a constituent of many components that may or may not be part of the experimental 'hardware' may unintentionally influence the scientific data results and may give rise to misinterpretations. Given the vast numbers of studies on endocrine disruption in general and on BPA in particular (of both good and questionable quality) that emerge daily in the scientific literature, it is extremely difficult to keep an up-to-date comprehensive overview of the state-of-the-art.

3.2.4.2 Uncertainties about carcinogenicity and mammary gland development

The RAR (EC, 2010) concluded that, based on the information available at that time, BPA did not possess any significant carcinogenic potential. The 2014 EFSA draft concluded that recent studies raise concerns about BPA's possible carcinogenic effects.

In standard carcinogenic testing protocols according to OECD (US-NTP, 1982; FAO/WHO, 2011), BPA was found to have no carcinogenic activity. Furthermore, additional multigenerational studies found no indication of carcinogenicity (Tyl et al., 2002, 2008); in particular, pre-neoplastic lesions of the mammary gland were absent in all offspring.

In contrast to these findings, the 2014 EFSA draft summarised several studies in rats using subcutaneous exposure via osmotic pumps that demonstrated an effect of prenatal BPA exposure on mammary gland development (see the 2014 EFSA draft and references therein). Similar effects were indicated in studies in mice and rhesus monkeys, supporting the observations in rats. The 2014 EFSA draft noted that the reliability of the rat studies is under discussion because of a low estrogen dose present in the feed that might have influenced the test results. However, the observed differences between the non-treated and prenatal/postnatal BPA exposed animals is clear and an effect of BPA on mammary gland development can therefore not be excluded. The biological significance of the effects on mammary gland development is not clear as long-term outcome was not yet investigated. It is not clear whether it is an early onset of a further normal mammary gland development or an early onset of mammary gland cancer. The 2014 EFSA draft states that these studies should be considered an indicator for a possible concern, although the relevance for humans is unclear.
Furthermore, the 2014 EFSA draft summarised studies that indicating that BPA may act as a promoter, increasing the effects of well-known carcinogens even at very low BPA levels. These studies had limitations that render them unsuitable for assessing whether BPA can have a similar effect following prenatal or perinatal exposure. One main limitation is that the studies that found positive outcomes included additional treatment with a strongly initiating or additional promoting agent(s). An additional limitation is that statistical testing was performed in most of the studies without proper adjustment for multiple testing to avoid false positives.

The 2014 EFSA draft concluded that existing studies performed according to OECD guidelines did not find that BPA has a carcinogenic effect. However, studies indicating adverse effects on mammary gland development do raise some concern for a possible carcinogenic effect of BPA after prenatal exposure.

3.2.4.3 Uncertainties regarding neurotoxicity and behavioural toxicity

The 2014 EFSA draft summarised indications that BPA may exhibit neurotoxic and behavioural toxic effects that remain uncertain, based on the available studies. The uncertainties arise from inconsistency of results across studies, possible confounding factors in epidemiological studies and methodological (mainly statistical) shortcomings in animal studies.

Observations in epidemiological prospective studies were related to child behaviour associated with BPA exposure during pregnancy, in a sex-dependent manner. Some animal studies published since 2010

reported increased anxiety-like behaviour after BPA exposure, while others reported significant impairment of either learning and/or memory capacities. A few studies also reported effects on social behaviour and sensorimotor function. The 2010 EFSA opinion recognised the potentially significance of BPA-related biochemical changes (e.g. altered receptor or protein expression) in different brain regions. A number of new studies discussed in the 2014 EFSA draft reported similar changes that may indicate BPA's effects on brain development (e.g. effect on neurogenesis and on gene expression, neuroendocrine effects, effects on the morphology of certain brain regions). It remains to be clarified whether such changes are mechanistically related to the reported neurobehavioral effects following BPA exposure.
The 2014 EFSA draft concluded that the variety of parameters and the effects observed warrant further investigation of the possible neurological and behavioural effects of BPA.

3.2.4.4 Uncertainties regarding effects on the immune system

BPA is capable of inducing skin sensitisation responses with low prevalence in humans, thus BPA being a weak sensitiser (EFSA, 2010; FAO/WHO, 2011; EC, 2010a; ANSES, 2011). In addition, some individual reported cases described contact dermatitis against BPA (Aalto-Korte et al., 2003).

The 2014 EFSA draft stated that since the 2010 EFSA opinion, various human and animal studies have been published that found a possible relationship between immunotoxic effects in humans and prenatal and/or postnatal BPA exposure. Based on these studies, the 2014 EFSA draft concluded that there are indications that BPA may be linked to adverse immunological effects in humans, including defence against viral infection and allergic asthma. However, the 2014 EFSA draft also concluded that in view of the studies' limitations, only limited conclusions can be reached and the possibility that the results are confounded by diet or concurrent exposure factors cannot be ruled out. The associations between exposure and adverse effects do not provide sufficient evidence for inferring a causal link between BPA exposure during pregnancy or in childhood and immune effects in humans. Animal studies also lend support to the notion that BPA may elicit immunological effects. However, these studies also suffered from shortcomings in experimental design and reporting. Therefore, the 2014 EFSA draft concluded that dose-response relationships between BPA and immunotoxic effects cannot be confidently established.

For these reasons, the 2014 EFSA draft concluded that it is currently unclear whether immunotoxicity is an endpoint of concern for BPA. Immunotoxicity is insufficiently addressed by current testing guidelines and potential immunotoxicity therefore presents an area of uncertainty in BPA risk assessment.

3.2.4.5 Uncertainties regarding metabolic activity

The 2014 EFSA draft concluded that there is insufficient evidence to judge whether BPA is obesogenic in humans.

The 2014 EFSA draft summarised a number of epidemiological studies that reported associations between BPA exposure and obesity, and animal studies that reported body weight changes and effects on related metabolic functions after BPA exposure. Most epidemiological studies that found an association between BPA exposure and obesity were cross-sectional and were therefore not suitable for demonstrating a causal relationship between BPA exposure and metabolic effects. The few prospective studies available did not support such a positive association.

A number of studies in pre- and postnatally exposed rats and mice evaluated in the 2014 EFSA draft indicate that BPA exposure has an effect on metabolic function, as evidenced by effects on glucose, insulin regulation or lipogenesis, and body weight gain in short-term studies. However, there is inconsistency across studies regarding the sex-specificity of the effects observed, effective dosages and the directionality of effects (both increases and decrease of body weight have been observed). Based on the results from several studies, the 2014 EFSA draft stated that there is no convincing evidence that BPA is obesogenic after intrauterine exposure or in longer-term studies.

In the absence of robust consensus animal models that can be extrapolated to humans, the 2014 EFSA draft stated that it is not possible to identify the causal link between metabolic effects and BPA exposure. In view of the multifactorial nature of metabolic effects and related confounding, even well-designed additional epidemiological studies are unlikely to provide conclusive evidence about hypothesised causality between BPA exposure and effects.

Tabel 6 Hazards of BPA to man, taken from the publicly available registration for BPA (ECHA website).

	Short- or long-term	DNEL	Most sensitive endpoint	Point of departure	Assessment factor
Worker					
Inhalation	Long-term, systemic	10 mg/m³	Repeated dose	NOAEC	
	Acute / short-term, systemic	10 mg/m³	Repeated dose	NOAEC	
	Long-term, local	10 mg/m³	Irritation (respiratory tract)	NOAEC	
	Acute / short-term, local	10 mg/m³	Irritation (respiratory tract)	NOAEC	
Dermal	Long-term, systemic	1.4 mg/kg bw/day	Repeated dose toxicity	NOAEL	35
	Acute / short-term, systemic	1.4 mg/kg bw/day	Repeated dose toxicity	NOAEL	35
General population					
Inhalation	Long-term, systemic	0.25 mg/m³	Repeated dose toxicity	NOAEC	
	Acute / short-term, systemic	5 mg/m³	Repeated dose toxicity	NOAEC	
	Long-term, local	5 mg/m³	Irritation (respiratory tract)	NOAEC	
	Acute / short-term, local	5 mg/m³	Irritation (respiratory tract)	NOAEC	
Dermal	Long-term, systemic	0.7 mg/kg bw/day	Repeated dose toxicity	NOAEL	70
	Acute / short-term, systemic	0.7 mg/kg bw/day	Repeated dose toxicity	NOAEL	70
Oral	Long-term, systemic	0.05 mg/kg bw/day	Repeated dose toxicity	NOAEL	
	Acute / short-term, systemic	0.05 mg/kg bw/day	Repeated dose toxicity	NOAEL	

3.2.5 Reference values for BPA

Table 6 provides an overview of derived no-effect levels (DNELs) as reported in the public part of the REACH Registration of BPA.

3.2.5.1 Occupational exposure limits

To evaluate worker exposure to BPA via the inhalation route, SCOEL derived and recommended an OEL of 2 mg/m³ (inhalation of BPA) in 2013. As can be seen in Table 6, this recommended OEL is lower than the DNEL indicated in the registration dossier under REACH for occupational exposure via inhalation. SCOEL recommended that the new OEL replace the indicative OEL of 10 mg/m³, which SCOEL derived in 2004. The new OEL (SCOEL, 2013) was calculated from a NOAEL of 10 mg/m³, observed in a 90-day inhalation study in rats, where only local effects (respiratory tract irritation / inflammation) were observed at the higher levels of exposure (50 and 150 mg/m³). SCOEL argued that this OEL was also sufficient to cover systemic effects other than the liver and bodyweight changes observed in rodents after oral exposure to BPA, since based on route-to-route extrapolation, the inhalation NOAEL was less than the inhalation equivalent of the oral NOAEL (5 mg/kg bw/day). However, SCOEL also mentioned that because of the high first-pass effect observed after oral exposure, inhalation exposure may result in higher internal exposure to unconjugated BPA (the biologically endocrine-active form). The absence of a first-pass effect following inhalation may therefore raise questions about the assumption that the OEL is also protective for other systemic effects.
SCOEL does not derive limit values for dermal exposure. To evaluate worker exposure to BPA via the dermal route, a DNEL for long-term dermal contact was derived for the registration of BPA under REACH. Endpoint-specific DNELs were separately

derived for reproductive toxicity (2.5 mg/kg bw/day) and the repeated dose effects in the liver (6 mg/kg bw/day) and on bodyweight/kidney (1.4 mg/kg bw/day) to identify which of these DNELs is the critical DNEL for assessing workers' long-term dermal exposure. The lowest DNEL (1.4 mg/kg bw/day) for systemic effects was derived for the repeated dose effects on bodyweight and kidneys (with a NOAEL in a two-generation study in mice of 50 mg/kg bw/day) and was chosen as the critical DNEL for evaluating workers' long-term dermal exposure.
BPA is furthermore considered to be a moderate skin sensitiser. The DNEL for systemic effects following a dermal exposure route does not address BPA's skin sensitising potential and may not be adequate to protect against skin sensitisation in situations where there is a potential for direct skin contact with BPA. A DNEL for skin sensitisation could not be derived.

3.2.5.2 Tolerable daily intake

The TDI for BPA is currently under debate. The TDI proposed by EFSA in 2006 has been criticised by KEMI (2012), who also considered all available information on BPA's low-dose effects and proposed an alternative TDI that should be 100 to 1000 times lower. At this moment, EFSA is re-evaluating the TDI and proposes a t-TDI that is a factor of 10 lower than the TDI from 2006.

In 2006, EFSA assessed the human health hazards of BPA and derived a TDI of 50 µg/kg bw/day based on a NOAEL of 5 mg/kg bw/day (EFSA, 2006).[48] This NOAEL was based on systemic toxicity including reduced body weight and organ weight gain.[49] Reproductive and postnatal NOAELs derived in this same study were 10 times higher: 50 mg/kg bw/day.

In 2012, the Swedish Chemical Agency KEMI (KEMI, 2012)[50] assessed the available information on possible low-dose effects of BPA, with the aim to identify a NOAEL or LOAEL for developmental neurotoxicity, mammary gland development, effects on the female reproductive system and lipogenesis and to derive an alternative reference dose for BPA (TDI). KEMI (2012) concluded that a large number of research studies reported effects of BPA in animals at doses well below 5 mg/kg bw/day. However, regulatory bodies had not considered these studies to be relevant or reliable enough to use as a basis for deriving the TDI or other health-based guidance values for BPA. KEMI's literature review primarily considered studies that used BPA administration via the oral route to pregnant and/or lactating females or directly to neonatal offspring, since these scenarios reflect relevant exposure scenarios in the general population. Many of the studies reviewed by KEMI (2012) were judged to have methodological limitations or to be poorly reported; no single study was considered reliable enough to serve as a key study for the identification of a NOAEL or LOAEL. Instead, KEMI (2012) considered the data as a whole and used it to identify several NOAELs or LOAELs for each type of effect from different studies that were considered to be the most reliable and relevant. In general, the selected NOAELs range from 2–50 µg/kg bw/day depending on the type of effect, which is two to three orders of magnitude lower than the NOAEL on which EFSA (2006) based its TDI. Alternative reference doses calculated from these NOAELs/LOAELs range from 0.01–0.8 µg/kg bw/day and are considerably lower than the TDI derived by EFSA (2006) of 50 µg/kg bw/day. The lowest reference doses were calculated for developmental neurotoxicity.

Overall, KEMI (2012) concluded that although no single study they reviewed was considered reliable enough to serve as a key study for the derivation of an alternative reference dose, if the data were considered as a whole, effects were consistently observed at doses well below those which served as the basis for the TDI derived by EFSA (2006). KEMI (2012) concluded that even if confidence in a specific alternative reference dose based on this data material is low, the results of this review indicate that it may be prudent to consider a reference dose lower than EFSA's (2006) TDI when conducting risk assessments of BPA.

EFSA is currently re-assessing its 2006 TDI and has recently proposed a new t-TDI that was published for public consultation in January 2014 (EFSA draft, 2014). It identified 'likely' adverse effects in animals (i.e. on kidney, liver and mammary glands) using a weight-of-evidence approach to hazard identification. With respect to the former TDI, a revised method was used to derive the current t-TDI for the calculation of internal systemic doses based on new

[48] EFSA Risk Assessment BPA for consumer exposure (2006). The TDI is currently under review and will be published in 2014.

[49] Tyl et al. (2002) from a three-generation study performed in Sprague Dawley rats using dietary doses of 0.001–500 mg/kg/day.

[50] KEMI 2012, Low dose effects of Bisphenol A, Institute of Environmental Medicine, Karolinska Institutet https://www.kemi.se/Documents/Publikationer/Trycksaker/PM/PM_8_12_BPA_low%20dose%20effects.pdf

data on the metabolism of BPA. Benchmark dose response modelling was applied to identify the BMDL10 for changes in male mouse kidney weight in a two-generation toxicity study that was identified as the critical endpoint. The EFSA/CEF Panel converted this BMDL10 to an oral human equivalent dose (HED) of 113 µg/kg bw /day in a conservative way using data on interspecies differences in toxicokinetics, and applied an uncertainty factor of 25 to account for remaining interspecies and intraspecies differences to derive a t-TDI of 5 µg/kg bw /day. This temporary value reflects the current uncertainties in the scientific data surrounding effects of BPA that EFSA considered less than 'likely'. Section 3.2.4 summarises these uncertainties. EFSA emphasised that much of the science underpinning the conclusions in their 2014 draft is still developing. The EFSA/CEF Panel will complete the assessment of the remaining uncertainties in the final version of the opinion, due to be published later in 2014.

3.2.6 Overall conclusion

Various organisations have raised concerns about the possible adverse effects of BPA on human health. Different scientific studies have associated BPA with adverse immune effects, obesity, ADHD and diabetes, related to its possible interaction with the estrogen receptor. Debate is ongoing about possible adverse effects of BPA at low doses that may be subsequent to endocrine disruption, and about the presence (or absence) of a possible NMDR relationship. This debate is especially important as it discusses the possible toxicity of BPA for humans below the exposure levels that up to now have been considered safe. To date, scientific studies have not found conclusive evidence of possible adverse effects of BPA on these issues.

In 2006, EFSA derived a TDI of 50 µg/kg bw/day for BPA. In 2012, an assessment by the Swedish Chemicals Agency KEMI suggested a TDI that may be 100 to 1000 times lower based on a weight-of-evidence approach for different effects including both guideline and non-guideline studies. The weight-of-evidence approach implies that no single study reviewed was considered reliable enough to serve as a key study for the derivation of an alternative reference dose. The most sensitive effect was found to be developmental neurotoxicity. Recently, in its 2014 draft opinion on BPA, EFSA proposed lowering the present TDI (50 µg/kg bw/day) to a t-TDI (5 µg/kg bw/day). This proposed t-TDI was derived based on adverse effects in the kidneys of mice and new data on BPA metabolism used for calculation of possible internal systemic doses in humans. The main uncertainties result from non-GLP studies and concern the following adverse effects on human health:

- Possible low-dose effect
- Possible NMDR effects
- Possible developmental effects on the immune system
- Possible developmental neurotoxic and behavioural effects (e.g. ADHD, anxiety)
- Possible metabolic effects (e.g. diabetes, obesity, cardiovascular effects)
- Possible developmental effects on the mammary gland

EFSA is currently studying whether the t-TDI is sufficiently conservative to cover these uncertainties. EFSA recently released a call for tender to address the relevance of NMDR curves in toxicology.

For worker exposure, SCOEL (2013) recently recommended a new OEL to assess risks from inhalation exposure that is five times lower (e.g. 2 mg/m^3) than the OEL they recommended in 2004 (SCOEL, 2004). SCOEL did not derive a DNEL for dermal exposure to BPA. A DNEL to evaluate worker exposure to BPA via the dermal route has been derived for the registration of BPA under REACH. This DNEL for long-term dermal exposure in workers is 1.4 mg/kg bw/day, based on systemic effects for the repeated dose effects on bodyweight and kidneys.
BPA is also considered to be a moderate skin sensitiser (EFSA, 2010l; FAO/WHO, 2011; EC, 2010a; ANSES, 2011). The DNEL for systemic effects following a dermal exposure route does not address the skin sensitising potential of BPA and may not be adequate to protect against skin sensitisation in situations where there is a potential for direct skin contact with BPA. A DNEL for skin sensitisation could not be derived.

3.3 Risks for human health

3.3.1 Considerations regarding route-to-route extrapolation

The most important routes of BPA exposure for the general population are the oral and dermal routes. The 2014 EFSA draft concluded that the inhalation route contributed to only a very small fraction of total BPA exposure from all sources for the general population, so it did not take this route of exposure into account. Hence, in its 2014 draft, EFSA decided

to estimate the contribution of dermal and inhalation exposure routes to the total internal exposure, and compared these estimates to a reference level derived from an oral toxicity study. The most important routes for workers, however, are inhalation and dermal contact.

Most BPA toxicity data are obtained for oral administration, though SCOEL (2013) used the inhalation toxicity data as a basis for recommending an OEL for workers. Since no dermal toxicity data are available, exposure via the dermal route has to be evaluated using either inhalation or oral toxicity data. That raises the question of which data route is most suitable to address human health effects from dermal exposure. Route-to-route extrapolation is generally a highly uncertain exercise for which several criteria need to be met to assure a sufficient reliability (Pepelko, 1985[51]; Rennen et al., 2004[52]). The basic consideration to which these criteria point is that route-to-route extrapolation can be performed if the internal exposure pattern is similar for both routes considered, or if differences between routes are known and can be quantified (e.g. differences in absorbed fraction). Important considerations regarding internal exposure include the absorbed dose, the rate of entry to systemic circulation in combination with the first-pass effect, biotransformation and knowledge on the toxicity of BPA or its metabolites.

To assess the risk of dermal exposure to BPA, route-to-route extrapolation based on inhalation toxicity data may be considered for the following reasons:

- Internal exposure to a chemical (and thus its toxicity) is determined by both the absorbed dose **and** by the rate of which it enters systemic circulation. In inhalation exposure, the administered dose is absorbed over a period of several hours (often six hours in an animal experiment), which is considered to be more comparable to the relatively slow entry of a similar dose via dermal administration than the entry following oral exposure via diet (which is the method of administration in the critical oral toxicity study).
- The distribution pattern and shape of BPA's plasma-time curve following dermal exposure is considered to be more comparable to that after inhalation exposure than after oral administration. This is more so since the extensive first-pass metabolism following oral exposure is a contra-indication for oral-to-dermal exposure. Since this first-pass effect is missed in both dermal and inhalation exposure, we may expect higher levels of free BPA after inhalation or dermal exposure than after oral dosing from a similar dose, assuming the same total absorption.

3.3.2 Risks for consumers

The RAR (EC, 2003) concluded that the information then available indicated a need for further information or testing for human health in relation to developmental toxicity. They judged that further research was needed to resolve the uncertainties surrounding BPA's potential to produce adverse effects on development at low doses. Since that time, many toxicity studies have emerged; a few years later, the RAR (EC, 2008) concluded that based on the information available at that time, there was no need for further information and/or testing and no need for risk reduction measures to protect consumers beyond those which are already being applied. These conclusions applied to all consumer exposure scenarios in relation to eye and respiratory tract irritation, skin sensitisation, repeated dose local effects on the respiratory tract, systemic effects following repeated exposure and reproductive toxicity. They also applied to both regional and local exposure scenarios in relation to repeated dose systemic effects and reproductive toxicity.

Also in 2008, the US Food and Drug Administration conducted a risk assessment for the general population that considered risks of BPA resulting from food consumption.[53] It has been updated regularly (most recently in March 2013).[54] As of March 2013, the FDA's assessment was that BPA is safe at the very low levels that occur in some foods. This assessment is based on FDA scientists' reviews of hundreds of studies, including the latest findings from new studies initiated by the agency. Because of concerns expressed in the last few years about the safety of

[51] Pepelko, W.E. and J.R. Withey, Methods for route-to-route extrapolation of dose. Toxicol Ind Health, 1985. 1(4): p. 153-70.

[52] Rennen, M.A., et al., Oral-to-inhalation route extrapolation in occupational health risk assessment: a critical assessment. Regul Toxicol Pharmacol, 2004. 39(1): p. 5-11

[53] US Food and Drug Administration. Draft assessment of bisphenol A for use in food contact applications. 2008. Available on-line at: www.fda.gov.

[54] http://www.fda.gov/newsevents/publichealthfocus/ucm064437.htm

BPA, the FDA initiated additional studies to help determine whether or not BPA is safe as it is currently used in food packaging and containers. Some of these studies have been completed and others are ongoing.

Health Canada last updated its assessment of risks associated with BPA used in food packaging applications in August 2008.[55] At that time, they determined Probable Daily Intakes (PDI) for BPA of 0.18 µg/kg bw/day for the general population and 1.35 µg/kg bw/day for infants. Since that time, Health Canada has conducted a number of additional surveys to measure the concentrations of BPA in canned drink products and bottled water products (in 2009), in canned food products and soft drink and beer products (in 2010) and in total diet samples (in 2011). Based on the results of these surveys, in 2012 Health Canada conducted a probabilistic assessment in an effort to generate a more refined and detailed insight of Canadians' dietary exposure to BPA.[56] The results demonstrate that infants are exposed to the greatest amount of BPA, as they generally consume more food per unit of body weight relative to older people. The BPA PDIs varied from 0.083 µg/kg bw/day for 0–1 month old infants to 0.164 µg/kg bw/day for 4–7 month old infants. For the general population, on average, the BPA intake estimates were found to be approximately threefold lower than those previously derived as part of the 2008 assessment. Health Canada's conclusion was therefore similar to that of the FDA: current dietary exposure to BPA through food packaging uses is not expected to pose a health risk to the general population, including newborns and young children.

In 2011, the Dutch Health Council (GR) published a guideline for the identification and protection of high-risk groups,[57] in which BPA was one of the substances looked at in more detail. In this guideline, GR noted that, in principle, the entire human population might be at risk depending on the level of BPA exposure, since all humans could be expected to be exposed. The GR also noted that young children in the pre- and postnatal phases may be especially at risk since, on average, this group consumes more food per kilogram of body weight, may use more products that contain BPA, have an immature metabolic system and are developing quickly (making them more sensitive to developmental influences than the average person). Other at-risk groups identified by the GR were people who consume greater than average amounts of canned food and people who metabolise BPA relatively slowly due to a lower enzyme expression or slower enzymes.

In 2012, EFSA asked its Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids to provide a scientific opinion of the risks for public health related to BPA exposure from foodstuffs and other sources. A two-step approach for public consultation on the draft opinion about BPA has been taken and a draft exposure assessment was released for public consultation in 2013 (EFSA draft, 2013). The 2014 EFSA draft addressed the hazard assessment and health risk characterisation. A t-TDI of 5 µg/kg bw/day was derived based on the BMDL10 for changes in male mouse kidney weight (the critical endpoint) in a two-generation toxicity study. Aggregated high (oral plus dermal) exposures were estimated for all age groups by deriving the toxic equivalents for dermal exposure via the oral route. Exposures ranged from 1061 ng/kg bw/day in adult men to 1543 ng/kg bw/day in teenagers. High oral exposure estimates for infants (all age groups) and toddlers were up to 873 ng/kg bw/day. For these groups, no dermal exposure was identified or anticipated. The panel concluded that exposure in the population, even for the highest exposed groups, is well below the t-TDI of 5 µg/kg bw/day, indicating that health concerns about BPA are low at the current level of exposure (EFSA draft, 2014). KEMI (2012), however, derived reference doses in a range 5–500 times lower than the t-TDI proposed by EFSA (EFSA draft, 2014), based on a weight-of-evidence approach that used the available information on low-dose effects (also see section 3.2.5.2). EFSA concluded that much of the science underpinning the conclusions in their 2014 draft assessment is still developing. The panel will complete an assessment of the remaining uncertainties around adverse effects on human health in the final version of the opinion, due to be published later in 2014. Hence, EFSA's risk assessment as summarised above will be revisited once the assessment of human health hazards is finalised.

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[55] Health Risk Assessment of Bisphenol A from food and packaging materials, Health Canada 2008, ISBN: 978-0-662-48686-2

[56] http://www.hc-sc.gc.ca/fn-an/securit/packag-emball/bpa/bpa_hra-ers-2012-09-eng.php

[57] The Dutch Health Council (GR, 2011), Leidraad identificatie en bescherming van hoogrisicogroepen VGP/P&L 2581995

3.3.3 Risks for patients via exposure through medical devices

SCENIHR (SCENIHR draft, 2014) evaluated the possible risks BPA posed to patients resulting from exposure through the use of medical devices. For this evaluation, SCENIHR used the t-TDI (5 µg/kg bw/day) determined by EFSA (EFSA draft, 2014).

SCENIHR concluded that although evidence for possible effects at low doses is inconsistent and final conclusions cannot be drawn, the possibility of low-dose effects, especially after prenatal or perinatal exposure, does raise some concern about BPA exposure of prematurely born infants via medical devices. SCENIHR furthermore emphasised that these infants may have serious health concerns that could justify the use of BPA-containing medical devices in view of the benefit-risk evaluation, despite the possible adverse effects of BPA.

The 2014 SCENIHR draft explicitly concluded the following:

> 'The parenteral[58] exposure via medical devices, taking treatment of neonates in intensive care units as the worst case scenario, is before adjustment for route specific systemic availability, below the oral t-TDI of 5 µg/kg bw/day derived from the BMDL10[59] of 3.76 mg/kg bw/day in animal studies. However, the kinetic differences between routes of exposure indicate that the bioavailability after oral route of exposure is significantly lower when compared to the parenteral one. Based on the analysis of oral versus intravenous toxicokinetic data, the oral systemic bioavailability of unconjugated BPA is 2.8%, 0.2%, 0.9% and less than 1% in rats, mice, monkeys, and dogs, respectively. The systemic availability of unconjugated BPA in humans has not been evaluated experimentally, however, modelled data as well as controlled biomonitoring studies indicated that internal exposure in humans to unconjugated BPA is very low (1-10%). Therefore, the SCENIHR considered it appropriate to make the comparison using the internal dose rather than the external one. Considering the internal BPA exposure for the worst case scenario (the estimated exposure in neonatal intensive care units of 3 µg/kg bw/day), and using a 100% bioavailability of BPA for the exposure via medical devices, the internal exposure is higher than the internal exposure based on the t-TDI (being 0.05 µg/kg bw/day as 1% bioavailability – taken as worst case - of 5 µg/kg bw/day). However, when comparing this systemic exposure due to medical devices (3 µg/kg bw/day) to the internal exposure of a dose at the BMDL10 in rats of 3.76 mg/kg bw/day (37.6 µg/kg bw/day), the highest internal exposure of BPA via medical devices is about 12-fold lower than the internal dose of the BMDL10 observed in rats. The factor of 12 is lower than the usual safety factor of 100 for assessing a margin of safety (MOS) when extrapolating low to no risk exposure doses for humans based on results obtained in animal studies. For prolonged medical procedures in infants with an estimated exposure of 685 ng/kg bw/day, the margin of safety is 55, while for the other long and short-term exposure scenarios estimated for medical devices, the MOS is well above 100.'

Based on these data. SCENIHR concluded that BPA may pose some risk of adverse effects when it is directly available for systemic exposure after non-oral exposure routes, especially when neonates in intensive care units are concerned. However, it also concluded that better data on exposure would be beneficial for refining this risk assessment. It further concluded that some BPA alternatives are available (e.g. Bisphenol S and Bisphenol F), but that, in general, much less is known about the toxicological profiles of these alternatives.

3.3.4 Risks for workers

In 2003, the EU RAR (EC, 2003) concluded that there was a need to limit the risks of BPA exposure during the manufacture of BPA and epoxy resins. This conclusion was related to eye and respiratory tract irritation, effects on liver and toxicity for reproduction (effects on fertility and development). In addition, the EU RAR (EC, 2003) expressed concerns about skin sensitisation in all occupational exposure scenarios where there is the potential for skin contact. Five years later, the EU RAR (EC, 2008) concluded there is a need to limit risks during the manufacture of BPA and epoxy resins and that risk reduction measures that are already being applied should be taken into account. This conclusion was based on the risk characterisation for workers related to repeated dose systemic effects and reproductive toxicity. Again, this same conclusion was also reached in relation to skin sensitisation in

[58] Exposure via all routes, excluding the gastrointestinal tract

[59] BMDL10, Bench Mark Dose Low 10, this is the lower value of the 90% confidence interval calculated for the dose, inducing a 10% deviation from the control values

all occupational exposure scenarios where there is the potential for skin contact. However, the RAR (EC, 2008) also concluded that there was no need for further information, testing or risk reduction measures for all remaining scenarios in relation to other endpoints.

The exposure assessment performed by the RAR (EC, 2008) applied the EASE model that since then has been updated (see section 3.1.3). Recent insights furthermore suggest that routes besides inhalation (e.g. oral and dermal) may be important to workers' exposure. To assess the aggregated exposure of workers via inhalation, dermal uptake and, where relevant, oral uptake, a combined exposure estimate has to be derived, either via route-to-route extrapolation or by calculating the total *internal* exposure to BPA as a consequence of *external* exposure via the different routes. The RAR has not done this.

At this moment, it is very difficult to reliably calculate the *internal* BPA exposure caused by *external* dermal BPA exposure because of the lack of kinetic data. Too many assumptions have to be made to make a good estimate of *internal* BPA exposure. As a result, it is also very difficult to very reliably assess the health risks caused by *external* dermal exposure, since route-specific systemic toxicity data are also not available. In addition, the limited amount of information available on BPA kinetics, especially via the inhalation and dermal routes, hinders a reliable health risk assessment based on oral toxicity data under application of route-to-route extrapolation (see sections 3.2.1 and 3.3.1). However, in the near future, these data may become available since an ongoing NIEHS/NTP study of cashiers is measuring BPA and BPA conjugates in cashiers' blood and urine samples before and after their work shifts (see Birnbaum et al., 2012).[60] This study is expected to yield insights about the degree to which thermal receipt paper contributes to BPA exposure and may also facilitate the evaluation of workers' dermal exposure via other routes.

3.3.5 Risks from combined exposure

The RAR (EC, 2003) concluded that there is a need to limit the risks of BPA exposure for workers, consumers and people in general via the environment and to limit combined exposure in relation to developmental toxicity. It was concluded that the risk reduction measures already being applied should be taken into account.

The RAR (EC, 2008) stated that the worst-case combined exposure would be for someone exposed via the environment near a BPA production plant to be also exposed via food contact materials (oral exposure from canned food and canned beverages and from polycarbonate tableware and storage containers).

The RAR (EC, 2008) also concluded that given the very large safety margins, there are no concerns about repeated dose toxicity and reproductive toxicity. Hence there is need for further information and/or testing and no need for risk reduction measures beyond those which are already being applied.

The 2014 EFSA draft also concluded that consumer exposure via the environment was negligible with respect to exposure via food and non-food sources.

Neither assessment took into account the possible combined exposure of workers and consumers.

[60] Birnbaum et al., (2012) Consortium-Based Science: The NIEHS's Multipronged, Collaborative Approach to Assessing the Health Effects of Bisphenol A. Environm. Hlth. Perspect., 120, 1640-1644

4 BPA and the Environment

4.1 Environmental exposure to BPA

4.1.1 Sources of BPA emissions

Emissions of BPA to the environment result from manufacture, its use in the production of polycarbonate plastics and epoxy resins, the wide dispersive uses of articles based on polycarbonate and epoxy resins and epoxy resin coated products, and the recycling and waste stages of these materials and articles (e.g. thermal paper and PVC articles).

BPA is thought to be mainly emitted to surface waters, and the effluent from municipal and industrial wastewater treatment plants is considered to be an important source of BPA. However, measured concentrations of BPA in the environment can hardly be traced back to individual sources. It is therefore unclear to which extent certain specific processes or uses are responsible for the observed emissions into the environment. This uncertainty is being addressed in the substance evaluation under REACH, which demands that industry provide more data on environmental emissions of BPA during the lifecycle of polymers and articles containing BPA, from production to waste (also see section 5.3.2).

4.1.2 Environmental concentrations of BPA

BPA is ubiquitous in surface waters but the concentrations of BPA vary considerably depending on, among others, the location and sampling period. Concentrations in the European Union are in the ng/l to low µg/l range (about 0.0005–0.35 µg/l) with maximum concentrations of 0.014–43 µg/l for fresh water and lower observed concentrations (about 0.00005–0.10 µg/l) in marine waters (EC, 2008; Flint et al., 2012[61]; Wright-Walters et al., 2011[62]).

More recent concentration data in the NORMAN–EMPODAT database (NORMAN, 2013) contains 11,000 individual results of monitoring data for the fresh surface water compartment from the period between 2002 and 2010 in 12 European countries, including the Netherlands. The median BPA concen-

[61] Flint S., Markle T., Thompson S., Wallace E. (2012) Bisphenol A exposure, effects, and policy: A wildlife perspective. Journal of Environmental Management 104 p. 19-34

[62] Wright-Walters M., Volz C., Talbott E., Davis D. (2011) An updated weight of evidence approach to the aquatic hazard assessment of Bisphenol A and the derivation a new predicted no effect concentration (Pnec) using a non-parametric methodology. Science of the Total Environment, 409, p. 676–685. doi:10.1016/j.scitotenv.2010.07.092

Tabel 7 Summary of measured levels for water and sediment from the EU RAR (EC, 2008) and NORMAN-EMPODAT (2013). Also see Table 8 for an overview of PNECs in the various media.

	Fresh water	Freshwater sediment	Marine water	Marine sediment
Concentrations:	*(µg/l)*	*(µg/kg dw)*	*(µg/l)*	(µg/kg dw)
Median[#]	0.01	16	0.0016	8.5
Mean[#]	0.13	60	0.017	75
SD[#]	1.5	134	0.052	209
5th percentile[#]	0.0005	0.5	0.00005	1.1
95th percentile[#]	0.35	256	0.088	566
Max	0.014 – 43[##]	1.1 – 118[###]	0.00005-0.10[##]	1.1 – 118[###]
Median	0.021[##]	-	-	-
95 percentile	0.25[##]	346[##]	-	-
NL, Heel 2012	<0.5[##]			

[#] EU RAR, 2008
[##] NORMAN–EMPODAT database (NORMAN, 2013)
[###] Flint et al., 2012; Wright-Walters et al., 2011

tration of this dataset is 0.021 µg/l and the 95th percentile is 0.25 µg/l.

For the Netherlands, the available monitoring data for BPA in fresh water stem from 2003–2010 and show a similar profile to the European concentrations measured (WaterSTAT and NORMAN database, 2013; reported as of January 2014). For the period from 2003 to 2010, the majority of the monitoring data were below the detection limit (ranging between 0.1–0.5 µg/l). Since 2003, the number of BPA monitoring locations in the Netherlands has gradually decreased, from 10 in 2003 to only 1 in 2014 (i.e. Heel at the river Meus). In 2012, all the measured concentrations at Heel were below the 0.5 µg/l limit of detection.

BPA was detected in freshwater sediment, marine sediment and suspended matter samples with concentrations in the range of < 1.1–118 µg/kg dw (Flint et al., 2012; Wright-Walters et al., 2011). Additionally, sediment concentrations measured in German rivers in the late 1990s and 2000 ranged from <2.1 to 379.6 µg/kg dw (ECHA, 2009).[63] These levels are comparable to the ranges reported in the EU risk assessment report (EC, 2008; see Table 7).

The EMPODAT database also contains monitoring data for the sediment compartment: the 95th percentile of the 113 individual results is 346 µg/kg dw. This data refers to the years 2003-2005 and the majority of the sampling sites are located in Eastern Europe.

BPA concentrations in freshwater sediment and marine sediment are very similar, deviating no more than a factor of 2 or 3. BPA concentrations in the fresh water and marine water compartments deviate more, by an approximate factor of 10.

Median concentrations of BPA in effluents from municipal wastewater treatment plants and industrial wastewater treatment plants are typically higher than freshwater BPA concentrations, ranging from 0.028–1.410 µg/l (Flint et al., 2012). An average BPA concentration of 0.65 µg/l was derived for the effluents from six Dutch municipal wastewater treatment plants sampled in 2005 (Pieters et al., 2011).[64]

4.1.3 Concluding remarks

BPA is ubiquitous in surface waters and sediment. For the water environment, concentrations in the European Union are in the ng/l to low µg/l range. For sediment, BPA concentrations are higher and typically in the 1–300 µg/kg dw range. Since the last European environmental risk assessment in 2008, a

[63] European Chemicals Agency (2009). 4-[2-(hydroxyphenyl) propan-2-yl)]phenol (Bisphenol A), ANNEX XV TRANSITIONAL REPORT, Documentation of the work done under the Existing Substance Regulation (EEC) No 793/93 and submitted to the European Chemicals Agency according to Article 136(3) of Regulation (EC) No 1907/2006. Prepared by the United Kingdom, November 2008.

[64] Pieters B.J., Hehenkamp M., Janmaat, L.M. (2011). Improvement estimation of effluents RWZI's, Grontmij Holland B.V. Amsterdam, 28 October 2011

large amount of monitoring data has emerged on the presence of BPA in the environment. The data represent a broad area of the European Union with most data being available for Germany and France. This monitoring database has not been thoroughly analysed for the purpose of risk assessment.

4.2 Environmental hazards

The RAR (EC, 2008) provided an overview of the adverse effects of BPA on the environment and environmental organisms. The sections below describe possible environmental health hazards and current uncertainties.

4.2.1 Classification and labelling

BPA is classified under the CLP Regulation as harmful to aquatic organisms (H411, previously R52).

4.2.2 Environmental hazards

In addition to the toxicity to aquatic organisms, the EU RAR (EC, 2008) furthermore concluded that BPA can act as an endocrine disruptor in various water organisms (e.g. fish and molluscs) with a clear relationship between toxicological mode of action and adverse effects (i.e. reproduction, embryonic development).

In particular for fish, a link can be made between the proposed mode of action as an estrogen receptor agonist and the observed adverse effects on reproduction. The EU RAR (EC, 2008) concluded that adverse effects may occur in fish at a lowest concentration of about 1 µg/l. Effects observed include changes in vitellogenin synthesis, secondary sexual characteristics and spermatogenesis. The relevant observed NOEC for fish range between 1.7–17 µg/l depending on the organism.[65]

In molluscs and crustaceans or insects, BPA seems to act as a steroid receptor agonist, affecting estrogen- and ecdysteroid-mediated processes. In these species, there is evidence for a causal relationship between exposure to BPA and adverse effects on embryonic development, reproduction and, in the case of arthropods, on moulting.

However, there are indications that the NOEC of BPA may be lower than 1.7–17 µg/l. Some studies evaluated by the EU RAR (EC, 2008) suggest that snails may show adverse effects (i.e. increased egg production) occurring at concentrations below 1 µg/l. New calculations on these respective data may indicate effect concentrations lower than 1 µg/l (namely <0.1 µg/l) for snails (Ratte, 2009).[66] These new calculations were based on a reproducible adverse effect of BPA on egg production, which was only observable during a seasonal period with natural low egg production and which appeared to be masked during the seasonal reproduction period when egg production is naturally high. However, these calculations have been the topic of debate and the validity of the results is uncertain (EC, 2009). Results from another study (Benstead et al., 2008)[67] on these possible lower dose effects were not robust enough to warrant a lower NOEC (EC, 2009).

Another effect discussed in the EU RAR (EC, 2008) but not considered further in their environmental risk assessment because of data quality is a finding from fish multigenerational studies hinting that the NOEC for BPA may decrease for successive generations by a factor of 5 to 10, with tentative results also observed for sediment-dwelling organisms. The Scientific Committee on Toxicity, Ecotoxicity and the Environment (CSTEE, 2002) commented that these possible effects on fish and their offspring should be addressed more seriously. CSTEE considers this issue (F1 more sensitive than Fo; F2 more sensitive than F1) to be critical, particularly when comparing the laboratory NOEC values with the measured concentrations. This multigenerational effect has been further studied (Staples et al., 2011),[68] showing that F1 and F2 may indeed become more sensitive to

[65] RAR (2003 with Addendum of 2008), European Union Risk Assessment Report, Bisphenol-A

[66] Ratte HT (2009) Statistical Analysis of a Laboratory Study About the Effects of Bisphenol A on the Reproduction of the Ramshorn snail Marisa cornuarietis (Mesogastropoda: Ampullariidae) - Draft. Anonymous. Sponsor: German Federal Environmental Agency. FKZ: 363 01 245:1-38.

[67] Benstead, R., Routledge, E. and Jobling, S. (2008). Effects of Bisphenol-A on the fecundity of adult European gastropod snails during simulated Spring and Autumn conditions. Final report to Defra and the Environment Agency, October 2008. Environment Agency and Institute for the Environment, Brunel University, UK. Referred to by ECHA (2009).

[68] Staples C.A., Tilghman A., Hall A.T., Friederich U., Caspers N., Klecka G.M. (2011). Early life-stage and multigeneration toxicity study with bisphenol A and fathead minnows (Pimephales promelas) Ecotoxicology and Environmental Safety, 74,p.1548–1557

Tabel 8 Hazards of BPA to the environment, taken from the publicly available registration for BPA (ECHA website, 2014) and the RAR (EC, 2008).

Type of organism	Medium	PNEC (ECHA)	PNEC (EC)
		µg/l	µg/l
Aquatic	Fresh water	18	1.5
	Marine water	16	0.15
	Intermittent releases	10	
	STP	320 mg/l	
Sediment	Freshwater	2.2 mg/kg sediment dw	63 µg/kg sediment dw
	Marine	0.44 mg/kg sediment dw	6.3 µg/kg sediment dw
Terrestrial	Soil	3.7 mg/kg soil dw	3.7 mg/kg soil dw
Predators	Secondary poisoning	13.8 mg/kg food (PNEC oral)	

adverse effects from BPA with a NOEC of 16 µg/l for the hatching success of the second generation of fish (fathead minnow).

4.2.3 Biodegradability and bioaccumulation

BPA is considered to be rapidly biodegradable in the aquatic environment and does not accumulate in organisms. With respect to its biodegradability, the CSTEE (2002) commented on some contradictory data about the biodegradation potential of BPA as presented in the EU RAR (EC, 2003) draft.[69] The CSTEE noted that, in some environmental compartments and particularly in sediments, existing evidence suggests that BPA may not readily biodegrade. The CSTEE emphasised that in some areas where no specific emissions are reported, concentrations in surface water and sediments are relatively high and can only be related to either a widely dispersed distribution of the local emission points, covering large areas of the EU, or a lower biodegradation than expected. The CSTEE argued that these points should be further investigated.

4.3 Predicted no-effect concentrations

Table 8 provides an overview of the PNECs that have been reported in the publicly available registration document for BPA under REACH.

4.3.1 PNEC in fresh water

From the data available as of 2008, the EU RAR (EC, 2008) concluded that the most sensitive effect of BPA with clear ecological relevance is egg hatchability in the fathead minnow, with a NOEC of 16 µg/l. This is also the NOEC for vitellogenin production in males of the same species (seen as an indicator of endocrine effects) and oviduct formation in male carp. The study is of high quality and was considered reliable by the EU RAR (EC, 2008). The EU RAR (EC, 2008) used a statistical approach to arrive at a $PNEC_{water}$ of 1.5 µg/l. This is about 10 times lower than the PNEC reported by industry in the ECHA registration dossier.

This $PNEC_{water}$ left out some of the observed effects on snails. The EU RAR (EC, 2008) indicated that these effects were not included when determining the $PNEC_{water}$ because of the reliability and reproducibility of these data. The EU RAR (EC, 2008) report nevertheless concluded that there remains a possibility that the PNEC for fresh water does not take full account of the potential effects of BPA on snails. Refinement of the PNEC for aquatic organisms is therefore still under discussion.

The annex XV transition report for BPA (EC, 2009) discussed the results of Benstead et al. (2008), but the EC concluded that those results were not robust enough to warrant a revision of the $PNEC_{water}$. However, the results did hint at an effect, suggesting a need for further work. Meanwhile, additional testing has been done on the susceptibility of snails (Bannister et al., 2013)[70] and other aquatic species (Mihaich et al., 2009),[71] including a multigenerational

[69] C2/AST/csteeop/Bisph A ENV27062002/D(02)

[70] Bannister R., Beresforda N., Granger D.W, Pounds N.A., et al. (2013). No substantial changes in estrogen receptor and estrogen-related receptor orthologue gene transcription in Marisa cornuarietis exposed to estrogenic chemicals. Aquatic Toxicology 140– 141 p. 19– 26.

[71] Mihaich E.M., Friederich U., Caspers N., Hall A.T., Klecka G.M.,

toxicity study on fish (Staples et al., 2011). The $PNEC_{water}$ has not been re-assessed in light of these new data.

4.3.2 Predicted no-effect concentration in marine water

The EU RAR (EC, 2008) evaluated the information available on a number of tests with marine organisms to conclude that none of the studies were suitable to directly derive a $PNEC_{marine\ water}$. However, the results for fish appear to show effects at levels similar to those in freshwater fish and no indication of increased sensitivity in the marine species. The most sensitive organisms appear to be molluscs, with effects at similar levels to those with *Marisa* in freshwater (with the same reservations about the studies' limitations). For the assessment factor approach, an additional factor of 10 would be used on a PNEC from freshwater data only, to take account of the wider range of species in the marine environment. The same approach will be adopted here, giving a $PNEC_{marine\ water}$ of 0.15 µg/l. Industry also derived an approximately 10 times high $PNEC_{marine\ water}$ in their registration dossier for BPA (see Table 7).

4.3.3 Predicted no-effect concentration in sediment

The EU RAR (EC, 2008) concluded that limited data is available to derive a PNEC for organisms living in sediment. A $PNEC_{sediment}$ of 36 µg/kg dry weight was calculated based on the results from a test performed in saltwater sediment medium using an assessment factor of 1,000. For comparison, the $PNEC_{sediment}$ was derived using an alternative method (the equilibrium partitioning method) and arrived at $PNEC_{sediment}$ (63 µg/kg dry weight) that is quite similar to that for $PNEC_{water}$ (1.5 µg/l). According to the EU RAR's (EC, 2008) evaluation of existing data, there are indications in one study that snails may also be more sensitive when exposed to BPA in sediment. This also supports the importance of developing a result or results for molluscs that can be used with confidence. For the marine compartment, there are no specific data in additional to that used above, so the equilibrium partition method was used on the marine aquatic PNEC of 0.15 µg/l, giving a $PNEC_{marine\ sediment}$ of 2.4 µg/kg wet weight (6.3 µg/kg dry weight).

In the Annex XV transition report (EC, 2009), the EC concluded that, considering the uncertainties surrounding the effect on snails as sediment-dwelling organisms, the $PNEC_{sediment}$ should be re-evaluated if more information becomes available about snails or other sediment organisms.

4.3.4 Predicted no-effect concentration for terrestrial organisms

As snails are sensitive to BPA in freshwater environments, the EU RAR (EC, 2008) indicated that terrestrial molluscs could be an important group to protect. Unfortunately, no relevant toxicity tests are available for that species. The EU RAR (EC, 2008) used a soil assessment scheme consistent with the approach taken for other endocrine-active chemicals (e.g. nonylphenol; EC, 2002). The results of long-term tests with earthworms, springtails and plants are available, with NOEC values of >100, 500 and 20 mg/kg dry weight, respectively. Correcting for the respective concentrations of natural organic matter and applying an assessment factor of 10 yields a $PNEC_{soil}$ of 3.7 mg/kg dry weight.

4.3.5 Concluding remarks

BPA is classified under CLP as harmful to aquatic organisms (H411, R52). The EU RAR (EC, 2008) concluded that BPA can act as an endocrine disruptor in various water organisms like fish and molluscs with a clear relationship between toxicological mode of action and adverse effects. The NOEC for fish in water ranges between 1.7–17 µg/l. All available PNECs have been derived from the $PNEC_{fresh\ water}$.

Since 2009, new data has emerged about BPA's toxicity for environmental organisms. These data have not been used to re-assess the PNECs for the various environmental compartments. There is a significant difference between most PNECs derived in the ECHA registration dossier on BPA and those in the EU RAR (EC, 2008). This difference can be as large as a factor of 10.

Dimond S.S., Staples C.A., Ortego L.S., Hentges S.G. (2009). Acute and chronic toxicity testing of bisphenol A with aquatic invertebrates and plants. Ecotoxicology and Environmental Safety, 72 p. 1392–1399

4.4 Environmental risks

The EU Risk Assessment Report on BPA (EC, 2008) concluded that BPA shows endocrine disrupting effects in environmental organisms, leading to adverse effects on reproduction and development of offspring.

The EU RAR (EC, 2008) furthermore concluded that there was no emerging risk for the environment for either environmental compartment based on the toxicity data and environmental concentrations available at that time. For the freshwater and marine PNEC for any scenario, the EU RAR (EC, 2008) concluded that there were still some uncertainties about the potential effects of BPA on snails, despite the thorough testing undertaken. It also concluded that once new information becomes available, it should be used to re-assess these PNECs. For the terrestrial and atmospheric compartments and for secondary poisoning through the aquatic, terrestrial and marine food chains, the EU RAR (EC, 2008) concluded that there was no need for further information and/or testing and no need for risk reduction measures beyond those applied. This last conclusion also applies to the risks to wastewater treatment plant micro-organisms.

For fresh water, recent BPA measurement data (from 2003–2010) indicate that the 95th percentile in fresh water is still lower than the derived PNECs (NORMAN-EMPODAT, 2013). As described in section 4.1.2, the 95th percentile BPA concentration in fresh water is 0.25 µg/l, compared to a $PNEC_{fresh\ water}$ of 1.5 µg/l. For the marine environment, no additional data are available in the NORMAN-EMPODAT (2013) database.

For sediment, the Annex XV transitional report (EC, 2009) concluded that there is an identifiable risk for organisms living in a sediment environment. This is supported by the more recent measurement data from NORMAN-EMPODAT (2013). For both freshwater and marine sediment, the 95th percentile of the measured concentrations was found to exceed the derived PNECs (EC, 2009). For marine sediment, the mean concentration BPA measured was also higher than the derived $PNEC_{marine\ sediment}$ of 6.3 µg/kg dw. The mean concentration of BPA measured in freshwater sediment is close to the derived $PNEC_{fresh\ water\ sediment}$ of 63 µg/kg dw.

4.4.1 Concluding remarks

The EU RAR (EC, 2008) and Annex XV transition report (EC, 2009) suggest that BPA poses risks for the sediment compartment. More recent measurement data on BPA concentrations in the environment support this statement. In the Annex XV transition report (EC, 2009), it was furthermore concluded that, considering the uncertainties surrounding the effect on snails as sediment-dwelling organisms, the $PNEC_{sediment}$ should be re-evaluated if more information about snails or other sediment organisms becomes available.

For the water compartment, the EU RAR (2008) and Annex XV transition report (EC, 2009) identified no risk at present. Toxicity data that has emerged since 2009 was not taken into account in the derivation of the $PNEC_{water}$.

4.5 Conclusions

The EU Risk Assessment Report on BPA (EC, 2008) concluded that BPA shows endocrine disrupting effects in environmental organisms, leading to adverse effects on reproduction and development of offspring.

BPA is ubiquitous in surface waters and sediment. Concentrations of BPA vary considerably depending on factors such as the location and sampling period. Emissions of BPA to the environment result from manufacture, its use in a broad range of products and the recycling and waste stages of these products. It is unclear which specific lifecycle steps are responsible for the observed emissions into the environment. This uncertainty is currently being addressed following Germany's substance evaluation under REACH, which demands that industry provide more data on environmental emissions of BPA during the lifecycle of polymers and articles containing BPA, from production to waste.

The EU RAR (EC, 2008) and Annex XV transition report (EC, 2009) suggest that BPA poses risks for the sediment compartment. More recent measurement data on BPA concentrations in the environment (from 2003–2010) support this statement. The 95th percentile of the measured concentrations of BPA in freshwater and marine sediment exceed the derived PNECs for these environmental compartments. For marine sediment, the mean concentration BPA measured is also higher than the derived $PNEC_{marine\ sediment}$. In the Annex XV transition report (EC, 2009), it

was furthermore concluded that, considering the uncertainties surrounding the effect on snails as sediment-dwelling organisms, the $PNEC_{sediment}$ should be re-evaluated if more information about snails or other sediment organisms becomes available.

For the water compartment, the EU RAR (EC, 2008) and Annex XV transition report (EC, 2009) identified no present risk. The 95th percentile of measured concentrations of BPA in fresh water and marine water remain below the respective PNECs. Recent measurement data on BPA concentrations from 2003–2010 support this statement for BPA in fresh water. The available monitoring data for BPA in fresh water in the Netherlands from that same period are comparable to the European concentration profile.

Since the latest European risk assessment (EC, 2008) and the Annex XV transition report (EC, 2009) were published, new data has emerged about BPA's possible adverse effects on environmental organisms, including possible endocrine effects, and its concentrations in water and sediment throughout Europe. There are indications that the NOEC of BPA for fresh water organisms may be lower. Toxicity data that has emerged since 2009 have not been considered in the derivation of the $PNEC_{water}$.

5 Legislation

Various existing and possible additional regulatory measures can be used to control human or environmental exposure to BPA. Depending on the nature of the source of exposure, reduction of the emissions at the source, exposure control, waste treatment and risk communication have been or can be considered under different regulatory frameworks. Over the last 15 years, various regulatory measures have been implemented to manage the possible risks of BPA and a number of regulatory initiatives are ongoing that may lead to changes in measures in the near future. This section summarises the main regulatory measures that have been implemented or are under development to manage the possible risks of BPA in the Netherlands, the European Union and worldwide, also highlighting the role of the precautionary principle. Figure 4 gives a brief overview of the measures that specifically address BPA.

5.1 Regulatory measures in the Netherlands

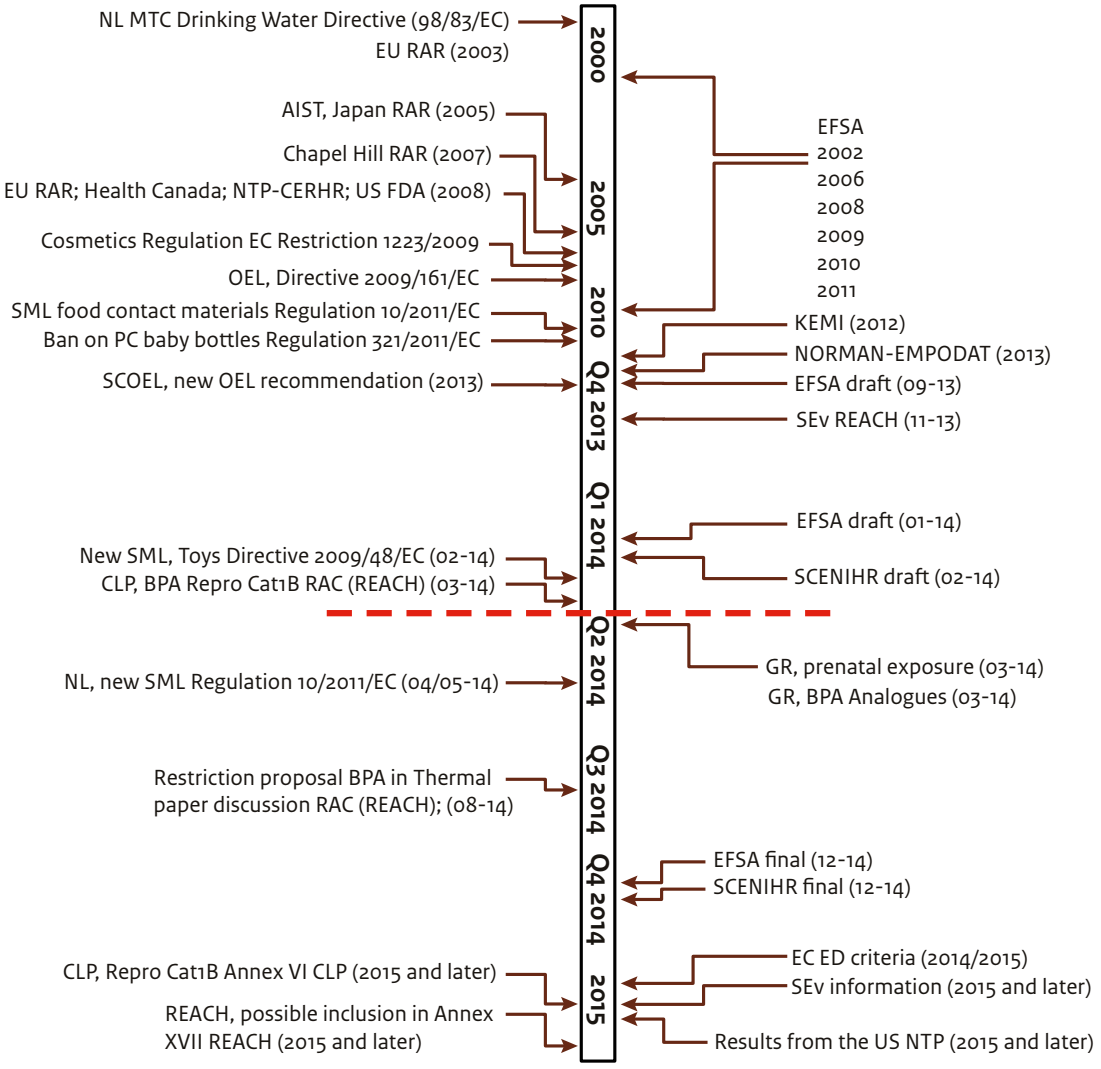
In the Netherlands, the majority of regulatory measures are embedded in European legislation. Food contact materials are regulated according to the Dutch Food and Commodities Act, in particular in the Decree on Packaging and Utensils (WVG; Warenwetbesluit Verpakkingen en Gebruiksartikelen). Since substances used in food contact materials fall outside the scope of EU Regulation 10/2011 (the "plastics regulation"), the decree sets the same specific migration limits for BPA as for plastics.

The WVG has been under revision since 2011. Before the start of this updating process, the SML for BPA mentioned in the Dutch Food and Commodities Act was 15 mg/kg food. In the Netherlands, an SML for BPA is also listed in the positive lists for Paper and Board and Metals and Coatings. In 2013, the updated WVG was formally notified to the European Commission. In this updated version, the SML was lowered from 15 mg/kg food to 0.6 mg/kg food, in line with EU Regulation 10/2011. This updated decree will be published in April/May 2014.

5.2 European regulatory measures

Most of the current European regulatory measures focus on human health.

Figure 4 Overview of regulatory measures and key risk assessment studies that specifically address BPA and those presently under development. The red dashed line indicates the state of play presented in this report (Part 1; 20 March 2014). Part 2 is expected to be published in the first half of 2015. This figure is an exact copy of Figure 2.



5.2.1 Classification and labelling

Under Annex VI of the CLP Regulation (1272/2008/EC), BPA has a harmonised classification under the index number 604-030-00-0, which includes the following classifications under the new nomenclature: Repr. Cat. 2 (H361f), STOT SE 3 (H335), Eye Dam. 1 (H318), and Skin Sens. 1 (H317). Under the former nomenclature (following 67/548/EEC), the classifications were: Repr. Cat. 3, R62, Xi, R37-41, R43 and R52.

The Committee for Risk Assessment (RAC) recently adopted an opinion to strengthen the existing harmonised classification and labelling (CLH) of BPA from a category 2 reproductive toxicant to a category 1B reproductive toxicant (also see section 5.3.1).[72]

5.2.2 Occupational exposure levels

Council Directive 98/24/EC aims to protect the health and safety of workers from the risks related to

[72] ECHA news, published 19 March 2014, ECHA/PR/14/07, http://echa.europa.eu/view-article/-/journal_content/title/rac-proposes-to-strengthen-the-classification-of-bisphenol-a

chemical agents at work. In the daughter directive 2009/161/EC, the OEL for BPA is set at 10 mg/m^3, measured or calculated in relation to a reference period of eight hours' time-weighted average (8h-TWA). France, the Netherlands and Belgium currently use this 10 mg/m^3 OEL, whereas Germany, Finland, Austria and Sweden use an OEL of 5 mg/m^3 and Denmark uses the strictest OEL, 3 mg/m^3.

Recently, the SCOEL[73] published a recommendation for an OEL of 2 mg/m^3 (8h-TWA) via inhalation for inhalable BPA dust based on the uncertainties in extrapolating adverse effects from in vivo studies to humans.

Furthermore, Directive 94/33/EC (Annex I.3 a-c) on the protection of young people at work, classified BPA as an irritant (STOT SE 3) and a sensitiser (Skin Sens. 1).

5.2.3 EU ecolabel regulation

Regulation 1980/2000/EU aims to promote products that have more of a potential to reduce negative environmental impacts than other products in the same product group, thus contributing to the efficient use of resources and a high level of environmental protection. Based on BPA's hazard classification under CLP, Regulation 1980/2000/EU implies that products containing BPA are not eligible for an ecolabel.

5.2.4 Cosmetics regulation

Regulation (EC) No 1223/2009 establishes rules that any cosmetic product made available on the market must comply with in order to ensure the functioning of the internal market and a high level of protection of human health. Annex II includes BPA on the list of substances that cannot be actively added to cosmetic products.

5.2.5 Toy Safety Directive

The Toy Safety Directive (2009/48/EC, European Norm EN 71-9) lays down rules about the safety of toys and their free movement in the EC. As of February 2014, it includes a migration limit value of 0.1 mg BPA/l saliva stimulant.

[73] SCOEL Recommendation for Bisphenol-A. March 2013 as adapted through Directive 2009/161/EU

5.2.6 Food contact materials

Food safety is covered by a range of regulations for which the general principles are laid down in Regulation (EC) No 178/2002. As part of the authorisation procedure, a substance has to be evaluated by EFSA before that substance can be authorised for use in foods in the EU. Food contact materials are covered by Framework Regulation (EC) No 1935/2004, which provides generally applicable rules with respect to safety, testing and management/control. The general principle in food contact materials legislation with regard to safety focusses on minimising exposure by minimising the migration of ingredients from food packaging or other food contact materials into food. Regulation EU (EC) 1935/2004 also provides for the optional introduction of separate regulations for specific materials. For example, EU Regulation No 10/2011 covers the authorisation of use of substances in the manufacture of plastics. For many other types of food contact materials, there is no harmonised European legislation. Hence, the Netherlands have addressed these in the abovementioned decree in the Food and Commodities Act (see section 5.1).

Although there are more food contact materials than plastics in which BPA may be used, EU Regulation No 10/2011 is the only regulation at the European level that specifically addresses BPA migration. As mentioned above, Regulation (EU) No 321/2011, which is in fact an amendment to Regulation No 10/2011, prohibits the use of BPA in baby bottles (also see section 5.2.6.1); these are the only two EU Regulations with direct relevance for BPA. For BPA in plastics, an SML of 0.6 mg/kg food was established in Regulation (EU) No 10/2011. This SML is based on the EFSA TDI of 10 µg/kg bw/day, which was established in 2003.

5.2.6.1 EU ban on BPA in baby bottles

Since June 2011, there has been a European ban on the production, import and marketing of BPA in polycarbonate baby bottles (Directive 2001/8/EC; Regulation 321/2011/EC). Interestingly, this ban was not motivated by solid scientific evidence that BPA causes adverse effects in humans. Instead, it was based on the scientific uncertainty related to adverse effects and the specific vulnerability of infants. Given the indications of a relatively limited economic impact on industry, the European Commission operationalised the precautionary principle, which is applicable in a situation of scientific uncertainty, even if the risk, notably to human health, has not yet

been fully demonstrated (Article 7 of Regulation (EC) No 178/2002 of the European Parliament and of the Council of 28 January 2002).

France banned the use of BPA in baby bottles in 2010, extended the ban in 2013 to food packaging materials for children up to three years of age, and will extend the ban to all other food contact materials by January 2015. In Denmark, a wider ban exists for BPA in food contact materials for children between 0–3 years of age since July 2011. The Austrian ban on BPA in pacifiers and teething rings has existed since October 2011. Belgium expanded the ban on the use of BPA in baby bottles to food packaging materials for children up to 3 years of age as of January 2013.

-The Drinking Water Directive (98/83/EC) set rules 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 do not, either directly or indirectly, reduce the protection of human health". In the Netherlands, BPA is included in the national positive list (Annex B of the "Regeling materialen en chemicaliën drink- en warm tapwatervoorziening"). The maximum concentration of BPA allowed (MTC) in drinking water in the Netherlands, warm or cold, is 30 µg/l.

5.2.8 Medical devices

Currently, three directives set out procedures for market access of medical devices:[74]

- Active Implantable Medical Devices Directive (90/385/EEC; EU, 1990)
- Medical Devices Directive (93/42/EEC; EU, 1993)
- In Vitro Diagnostic Medical Devices Directive (98/79/EC; EU, 1998c)

These directives are supplemented by a number of amending or implementing directives, commission regulations and several other legal reference documents. The legislation is supported by a series of MEDDEV (Medical Devices Directive) guidelines,[75] consensus statements[76] and interpretative documents.[77] There is also an important role for 'harmonised standards'.

The current regulatory framework contains no specific provisions for BPA. It does, however, require that careful risk assessment and risk management be carried out on a case-by-case basis before products are brought onto the market. This implies that any risk related to BPA should be thoroughly evaluated in the technical documentation required by the directives. The availability of alternatives and the clinical benefits of the products should also be taken into account in this process. One of the more specific requirements is that:

> '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).'[78]

EC proposals to revise the regulatory framework[79] are currently being negotiated in the Council Working Group and the European Parliament. The proposals include provisions for endocrine disruptors. They do not contain specific provisions for BPA.

5.3 Ongoing and anticipated European legal initiatives

5.3.1 CLP

In 2013, France proposed that BPA receive a more stringent harmonised classification as Repro. Cat 1B under CLP. Recently ECHA's Risk Assessment

[74] See http://ec.europa.eu/health/medical-devices/documents/index_en.htm

[75] See http://ec.europa.eu/health/medical-devices/documents/guidelines/index_en.htm.

[76] See http://ec.europa.eu/health/medical-devices/documents/consensus-statements/index_en.htm.

[77] See http://ec.europa.eu/health/medical-devices/documents/interpretative-documents/index_en.htm.

[78] Regulation on Medical Devices No. 934/2010/EC

[79] See http://ec.europa.eu/health/medical-devices/documents/revision/index_en.htm.

Committee discussed this proposal and came to a conclusion on the proposed harmonised classification. The outcome of this discussion was published on the ECHA website on 19 March 2014[80]: it stated that RAC has adopted an opinion to strengthen the existing harmonised classification and labelling (CLH) of BPA from a category 2 reproductive toxicant to a category 1B reproductive toxicant regarding the adverse effects on sexual function and fertility in line with a proposal from the French competent authority. The RAC opinion solely covers the adverse effects on sexual function and fertility, as only these types of main reproductive toxic effects were proposed for revision by France.
RAC adopted its opinion by consensus after comparing the available evidence with the CLP criteria. The studies performed according to standard test guidelines were given the most weight. RAC concluded that there were adverse effects on reproductive capacity (functional fertility) following oral exposure to BPA in a multigenerational guideline study in mice and in rats. Impaired female reproductive capacity was also observed in several supplementary non-guideline studies. In addition, several of the studies observed that BPA had effects that were toxic to reproductive organs.
The next step will be a REACH Comitology decision, which is needed to include the new classification in Annex VI of the CLP Regulation. This decision and the inclusion in Annex VI of CLP may take one to two years. The new classification will be effective from that time; it will also apply to downstream legislation. Further implications of the more stringent classification proposed by France will be explained in section 5.4.

5.3.2 REACH

Early in 2014, France submitted a proposal to restrict the use of BPA in thermal paper in the EU; it will be reviewed by ECHA's two scientific committees, RAC and SEAC (Socio-Economic Analysis Committee). RAC and SEAC need to provide their opinions in early 2015. If the ECHA committees support the proposal, the European Commission will need to initiate a legislative follow-up to include the restriction in Annex XVII of the REACH Regulation. This may take some time and the restriction will become effective even later.
In 2014, Germany finalised its substance evaluation under REACH. It demanded that the registrants of BPA provide an in vitro skin absorption test and data on environmental emissions of BPA during the lifecycle of certain products. This new information will be used to further refine the risk assessment. If appropriate, this may lead to the proposal of more stringent regulatory measures, or to no further action.

As BPA is likely to be classified as a reprotoxic substance 1B (Repro. Cat. 1B), one of the European Member States or ECHA, on behalf of the European Commission, may identify BPA as a Substance of Very High Concern under REACH, following article 57. If this identification were adopted by ECHA's Member State Committee (MSC), BPA would enter the Candidate List for authorisation. This process could take place within approximately one year. The inclusion of a substance in the Candidate List creates legal obligations for companies manufacturing, importing or using such substances, whether as a compound, in preparations or in articles. Furthermore, as the new Medicals Devices Regulation refers to the Candidate List, the use of BPA in medical devices could become limited. If BPA were to be identified as an endocrine disruptor under REACH but not covered under current CMR (Carcinogenic, Mutagenic or toxic to Reproduction) classifications, it could be placed on the Candidate List for authorisation as well, under the heading 'equivalent concern' (article 57f).

5.3.3 EC – identifying endocrine disruptors

The EC announced that it would propose criteria for defining endocrine disruption and endocrine disruptors (endocrine disrupting substances) no later than the end of 2013. However, instead of proposing criteria, the EC launched an impact assessment to investigate the socioeconomic impact of various "criteria scenarios", and delayed the announced criteria proposal to 2014. In the meantime, heavy debate has been ongoing about the principal existence of threshold values for endocrine disruptors (e.g. is it possible to derive threshold values for adverse effects for endocrine disruptors or does their mode of action imply no threshold, like for carcinogenic substances) and the information needed to define whether a substance should be called an endocrine disruptor.

Experts in the field of endocrine disruption generally agree that the working definition proposed by the WHO is acceptable, but it is very difficult to establish

[80] http://echa.europa.eu/view-article/-/journal_content/title/rac-proposes-to-strengthen-the-classification-of-bisphenol-a

Tabel 9 Summary of regulatory initiatives and scientific opinions on BPA, their progress and possible implications.

Legislation / Scientific Committee	Actors for Advice / Decision	Progress in 2014	Progress in 2015 and beyond
CLP	ECHA / EC	Reprotox 1B?	As agreed by ECHA, then likely inclusion in CLP Annex VI
REACH	ECHA	Demanding industry: a) provide better insight into sources of emission into the environment, b) provide dermal absorption data	Possible: a) further risk management measures to reduce emissions to the environment and b) human health-related risk reduction measures
	ECHA / EC	Restriction for use in thermal paper?	Inclusion of restriction in REACH Annex XVII
	ECHA		If reprotox 1B, then conditions for meeting criteria as SVHC are met and inclusion in Candidate List is possible. If ED, then conditions for meeting criteria as SVHC may be met and inclusion in Candidate List is possible.
Food packaging materials	EFSA / EC	Refined exposure assessment	Possible implications for food safety legislation
	EFSA / EC	New TDI	
Medical devices	EC	New regulation	Reference to CLP (reprotox 1B) and REACH (candidate list) with possible implica-tions for use in medical devices
Endocrine disruption	Dutch Health Council	Criteria endocrine disruptors	Possible implications for specific legislation (REACH, biocides, medical devices)
Scientific Committees	SCENIHR	Prenatal exposure	Possible implications for various legislation
		Medical devices	Possible implications for medical devices legislation

CLP = Regulation (EC) No 1272/2008 on classification, labelling and packaging of substances and mixtures; EC = European Commission; EFSA = European Food and Safety Authority; REACH = Regulation (EC) No 1907/2006 on registration, evaluation, authorisation and restriction of chemicals; SCENIHR = Scientific Committee on Emerging and Newly Identified Health Risks; SVHC = Substance of Very High Concern (cf article 57 of REACH); TDI = Tolerable Daily Intake; ED = Endocrine Disruptor.

threshold values for adversity.[81] The WHO/IPCS definition is as follows: 'An endocrine disrupter is an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub)populations' (IPCS; cited in European Commission, 1999).

5.4 Possible implications of ongoing European regulatory initiatives

Table 9 summarises the results of the various regulatory initiatives, in combination with the outcomes of several scientific opinions. These outcomes may directly or indirectly affect the marketing and use of BPA or the need for further regulatory measures.

5.4.1.1 CLP

The possible more stringent classification of BPA as a category 1B toxicant for reproduction in Annex VI of

[81] "Minutes of the expert meeting on endocrine disruptors", Brussels, 24 October 2013.

the CLP Regulation would have major implications for several pieces of downstream legislation. These include the Industrial Emissions Directive (2010/75/EC), the Ecolabel Regulation (66/2010/EC), the Toy Safety Directive (2009/48/EC), the Young People at Work Directive (1994/33/EC), the Pregnant and Breast Feeding at Work Directive (1992/85/EEC), the Waste Framework Directive (2008/98/EC), the Cosmetics Regulation (1223/2009/EC), the Medical Devices Regulation (in preparation) and the Plastic Materials in Contact with Food Regulation (10/2011/EC).

5.4.1.2 REACH

If the proposal to restrict the use of BPA in thermal paper is supported and placed in Annex XVII of REACH, it will take some years for the restriction to become effective. The direct implication will be a ban of the use of BPA in thermal paper. The likely indirect implication is that other uses of BPA may become restricted as well. However, the outcome of the opinions of ECHA's RAC and SEAC committees in early 2015 is important.

5.4.1.3 EFSA opinions

EFSA's opinion on exposure and on the new proposal for a TDI will have no direct impact. However, the opinions are greatly relevant as the review of the temporary ban on the use of BPA in infant bottles will rely on them, as well as possibly the implications for BPA in food packaging materials.

5.4.1.4 EC criteria for endocrine disrupting chemicals

The criteria for endocrine disrupting chemicals (EDCs) that the European Commission has promised to publish in 2014 will indicate which chemicals are EDCs and will probably include various classes of EDCs (e.g. similar to the various classifications for toxicity to reproduction). It is not yet known whether the available information on the toxicology of BPA will then be sufficient to classify BPA as an EDC. Furthermore, the criteria alone are not sufficient for managing EDCs; legislation-specific amendments are probably also needed. It will therefore take some years to find out whether BPA should be classified as an EDC and what the possible implications will be.

5.4.1.5 SCENIHR opinion

SCENIHR's opinion of the safety of using BPA in medical devices may impact the use of BPA in some or more specific medical devices. The use of alternative materials for the production of medical devices may be considered to mitigate potential high exposures to BPA.

5.4.1.6 Dutch Health Council opinion

The Dutch Health Council's opinion about the risks of prenatal or perinatal chemical exposure (addressing BPA among other chemicals) was published on 19 March 2014 and has not been included in this report. This opinion may impact the assessment of possible risks of prenatal or perinatal chemical exposure for the unborn child, infants and young children, which may also have consequences for the assessment of the risks of BPA. A second opinion of the GR on possible risks of BPA analogues, also published on 19 March 2014, may shed more light on the risks posed by substances that are structurally very similar to BPA and which may serve as possible substitutes. Both studies will be addressed in Part 2 of the RIVM report on BPA that is expected in 2015 and will focus on the consequences of the current state of knowledge (summarised in this Part 1) and appraise the possible human and environmental health risks posed by BPA, including further support for policy considerations, possible alternatives for substitution, socioeconomic aspects and, if relevant, possible needs for further risk management measures.

5.5 Global regulatory measures

In the US, at least 26 states are considering or have enacted legislation and policy changes that would restrict or label the use of BPA in thermal paper (e.g. receipts), children's products and food packaging (http://www.saferstates.com/2013/01/legislation.html). These restrictions of BPA in food packaging seem to be in contrast to the FDA's position, stated on its website, that BPA is safe at the levels that occur in some foods. The FDA is awaiting the results and interpretation of a two-year chronic toxicology study of BPA being conducted at its National Center for Toxicological Research before issuing further assessments.

In addition to some of the US states, a number of countries have banned the use of BPA in baby bottles. Canada has banned it since March 2010, and amended that ban in 2012. China banned BPA from baby bottles and baby food packaging in June 2011. The use of BPA in baby bottles has also be banned by Brazil (in September 2011) and Taiwan (in September 2013).

With respect to the environment, a notice published in Canada on 14 April 2012 under Part 4 of the *Canadian Environmental Protection Act, 1999* (CEPA 1999) required the preparation and implementation of pollution prevention plans for BPA in industrial effluents. Environment Canada and Health Canada concluded that BPA may be harmful to human health and the environment at current levels of exposure. It was further concluded that releases of BPA to water are the main source of concern for the environment. In order to manage the environmental risk posed by BPA, the Pollution Prevention Planning Notice requires industrial facilities subject to the notice to adopt pollution prevention practices. These practices must meet the Risk Management Objective, which is to achieve and maintain the lowest total feasible concentration of BPA (i.e. less than 1.75 µg/l in effluent).

5.6 Legislation and the precautionary principle

So far, the only severe legal restriction on BPA we know of is the restriction of BPA in plastic baby bottles (EC, 2011), based explicitly upon the precautionary principle. The Commission Directive 2001/8/EC explained the motivation for the temporarily ban of the use of BPA in the manufacture of plastic materials that come into contact with food intended for children aged 0-3; this is very interesting to analyse in the context of the present uncertainties about the possible adverse effects of BPA and regulatory perspectives (EC, 2011). This full text citation can be found in Appendix 3.

In short, the EC temporarily banned the use of BPA in baby bottles based on the precautionary principle after making a thorough evaluation of the toxicological properties, identifying the uncertainties (in particular the vulnerability of small children) and taking into account the availability of alternatives on the market.
The text on the Precautionary Principle in Regulation (EC) No 178/2002 allows the European Union to provisionally adopt measures on the basis of available pertinent information, pending an additional assessment of risk and a review of the measure within a reasonable period of time.
REACH mentioned the precautionary principle twice in the preamble:

- (9): '... the need to do more to protect public health and the environment in accordance with the precautionary principle'.
- (69) 'To ensure a sufficiently high level of protection for human health, including having regard to relevant human population groups and possibly to certain vulnerable sub-populations, and the environment, substances of very high concern should, in accordance with the precautionary principle, be subject to careful attention'.

Furthermore, REACH explicitly mentioned the precautionary principle in article 3:

> 'This Regulation is based on the principle that it is for manufacturers, importers and downstream users to ensure that they manufacture, place on the market or use such substances that do not adversely affect human health or the environment. Its provisions are underpinned by the precautionary principle.'

Therefore, REACH seems to allow regulatory measures to be taken in the case of vulnerable subpopulations, such as small children or unborn children who require a high level of protection.

5.7 Concluding remarks on legislation

The manufacture and marketing of BPA and exposure to BPA are primarily managed by regulations at the EU level. In addition, the Netherlands have specific provisions for BPA under the Dutch Food and Commodities Act (i.e. the Decree on Packaging and Utensils). Various ongoing regulatory initiatives will probably give rise to a new classification of BPA under CLP, and may give rise to a specific restriction of the use of BPA in thermal paper under REACH and more insight into environmental emission sources via the process of substance evaluation under REACH. For example, the likely more stringent classification of BPA as a category 1B toxicant for reproduction in Annex VI of the CLP Regulation would have major implications for several pieces of 'downstream' legislation, included the Industrial Emissions Directive (2010/75/EC), the Ecolabel Regulation (66/2010/EC), the Toy Safety Directive (2009/48/EC), the Young People at Work Directive (1994/33/EC), the Pregnant and Breast Feeding at Work Directive (1992/85/EEC), the Waste Framework Directive (2008/98/EC), the Medical Devices Regulation (in preparation) and the Plastic Materials in Contact with Food Regulation (10/2011/EC).
Furthermore, the European Commission is working on a criteria document for identifying and defining endocrine disruption and endocrine disruptors, which may affect the discussion around BPA as a possible endocrine disruptor. The outcomes of these

initiatives may be expected in 2014 and later and may have major implications for other regulatory frameworks.

6 Summary of main observations

The main observations described below are partly based on preliminary findings that are expected to be updated by the end of 2014. The observations presented here should therefore be interpreted with the appropriate reservations. It should furthermore be noted that this report only gives an overview of the state of knowledge on BPA. It does not include an appraisal of the available information by the RIVM. An appraisal of the available information will be presented in Part 2, expected to be published in 2015. Part 2 will focus on evaluating the available scientific knowledge, discussing the possible human and environmental health risks of BPA, providing support for further policy considerations and, if relevant, proposing further regulatory measures.

BPA is a HPV chemical that is widely used in manufacturing polycarbonate plastics and epoxy resins used in nearly every industry. Both humans and the environment are constantly being exposed to low concentrations of BPA.

6.1 Human health

6.1.1 Human exposure

6.1.1.1 Consumer exposure

BPA is used in the production of a broad range of products containing, among others, polycarbonate plastic (parts), epoxy polysulphone and polyacrylate resins and flame retardants. EFSA (EFSA draft, 2013, 2014) assessed consumers' possible external exposure to BPA based on the available information on food (via oral exposure) and non-food sources (via dermal and oral exposure).

Concentration data reported for foods and beverages in the 2013 EFSA draft opinion mainly included canned and non-canned foods and some foods in glass jars with metal lids. Human breast milk was also included. The highest concentrations were found in canned foods. Concentrations of BPA in foods packaged in other materials that may contain BPA (e.g. recycled or new paper and board) were not reported and it is unclear whether they were represented or included in EFSA's exposure assessment. It is also unclear whether the concentration of BPA included measurements after heating (e.g. cooking packed precooked meals in a microwave oven).

Regarding non-food sources, EFSA's drafts (2013, 2014) addressed air, dust, cosmetics, toys and thermal paper, but it is unclear whether there are more non-food sources. The concentration data for these sources are very uncertain and are based on a very low number of measurements. The exposures are therefore highly uncertain and dominated by the assumptions made for the external exposure to thermal paper. In view of the uncertainties, EFSA concluded that it is impossible to say whether the external exposure derived from non-food sources is under- or overestimated (EFSA draft, 2014).

The combined exposure estimates for both food and non-food sources, aggregated high (oral plus dermal), for all age groups ranged from 1061 ng/kg bw/day in adult men to 1543 ng/kg bw/day in teenagers. High oral exposure estimates for infants (all age groups) and toddlers were up to 873 ng/kg bw/day.

6.1.1.2 Human exposure via medical devices

SCENIHR assessed human exposure to BPA via medical devices in their 2014 draft report. This sort of exposure typically occurs for a limited time. High levels of exposure through medical devices may be of a similar magnitude as the exposure of an average consumer via food consumption, with estimated exposures ranging between 0–200 ng/kg bw/day. Prematurely born infants may be exposed to much higher levels of BPA: their estimated exposure was on the order of 3000 ng/kg bw/day.

6.1.1.3 Occupational exposure

Possible occupational BPA exposure through inhalation related to the manufacture of BPA (i.e. bagging and other filling activities) and the manufacture of BPA-containing epoxy resins have been identified as occupational settings with reasonable worst-case exposures up to 3 mg/m^3 (TWA: 8 hrs), with peak exposures up to 11 mg/m^3 (EC, 2008). For other exposure scenarios (e.g. production of liquid epoxy paints, powder coatings and thermal paper), inhalation exposure estimates were much lower (ranging from 0.000015–0.1 mg/m^3, TWA: 8 hrs) with peak exposures up to 1 mg/m^3.

The highest dermal BPA exposure was estimated to be 12 mg/kg bw/day for maintenance work (without the use of gloves). Dermal exposures were estimated using EASE. However, this exposure assessment model is no longer regarded as state-of-the-art, so higher tier models should be used to estimate dermal exposure.

New insights furthermore show that dermal exposure may be more significant than previously thought (e.g. for cashiers working with thermal paper). However, due to the current lack of data on human behaviour (i.e. handling of thermal paper, mouthing behaviour) and dermal uptake kinetics, present estimations involve a high level of uncertainty.

At this moment, the lack of route-specific kinetic data makes it very difficult to reliably calculate internal BPA exposure as a result of external inhalation and dermal exposure. As a result, it is also difficult to very reliably assess the health risks associated with external dermal exposure, since route-specific systemic toxicity data are not available. The new insights on the possible significance of dermal exposure for risks to workers call for further study of the internal exposure and resulting toxicity of BPA as a consequence of dermal and inhalation exposure.

6.1.2 Human health hazards of BPA

Various organisations have raised concerns about the possible adverse effects of BPA on human health. With respect to human health, different scientific studies have associated BPA with adverse immune effects, obesity, ADHD, diabetes and prostate cancer, which may be related to its possible interaction with the estrogen receptor. To date, scientific studies have not found conclusive evidence of possible adverse effects of BPA on these issues. Debates are ongoing about possible adverse effects of BPA at low doses that may lead to endocrine disruption, and about the presence (or absence) of a possible NMDR relationship. This debate is especially important as it considers the possible toxicity of BPA for humans below the exposure levels that up to now have been considered safe.

In 2006, EFSA derived a TDI of 50 µg/kg bw/day for BPA based on adverse effects in the kidneys of mice. In 2012, an assessment by the Swedish Chemicals Agency KEMI suggested a TDI that may be 100 to 1000 times lower based on a weight-of-evidence approach for different effects including both guideline and non-guideline studies, and studies of more questionable quality. The most sensitive effect identified by KEMI (2012) was developmental neurotoxicity. In its recent draft opinion on BPA (EFSA draft, 2014), EFSA proposed lowering the present TDI (50 µg/kg bw/day) to a t-TDI (5 µg/kg bw/day). That t-TDI was based on adverse effects observed in the kidneys of mice and new data about BPA metabolism that was used to calculate possible

internal systemic doses for humans. The main uncertainties result from non-GLP studies and concern the following adverse effects on human health:

- Possible low-dose effect
- Possible NMDR effects
- Possible developmental effects on the immune system
- Possible developmental neurotoxic and behavioural effects (e.g. ADHD, anxiety)
- Possible metabolic effects (e.g. diabetes, obesity, cardiovascular effects)
- Possible developmental effects on the mammary gland

EFSA is currently studying whether the t-TDI is sufficiently conservative to cover these uncertainties. It recently released a call for tender to address the relevance of NMDR curves in toxicology. The outcome of this work will impact the evaluation of BPA's hazards.

An extensive research project by the US National Toxicology Program is currently addressing many of the uncertainties highlighted by EFSA in their 2014 draft, with results expected in the near future.

6.1.3 Human health risks

6.1.3.1 Risks for consumers

Since 2003, various organisations have assessed the possible risks of BPA for consumers. In 2003, the EU RAR (EC, 2003) concluded that there was a need for further testing of the relationship between human health and developmental toxicity. Since then, many toxicity studies have emerged. In 2006, EFSA derived a TDI and concluded that, based on estimated exposures, consumers should have few health concerns about BPA. This was in line with findings outside Europe by the Japanese National Institute of Advanced Industrial Science and Technology (AIST, 2005), the US FDA (2006) and Health Canada (2006). This conclusion was again supported in an updated assessment by the EU RAR (EC, 2008). However, a 2012 review of BPA's adverse effects by KEMI suggested that in view of current uncertainties regarding low-dose effects, it might be prudent to consider a lower reference dose than the TDI proposed by EFSA (2006).
EFSA is currently evaluating the TDI of BPA for consumers and is updating the risk assessment. In its 2014 draft risk assessment for public consultation, EFSA proposed a t-TDI of 5 µg/kg bw /day (10 times lower than the 2006 TDI), which was derived to reflect the current uncertainties surrounding the adverse effects of BPA at low doses.

EFSA also concluded in 2014 that even the population groups with the highest BPA exposure have exposure levels well below the t-TDI (5 µg/kg bw/day), indicating that there should be few health concerns about BPA at the current level of exposure (EFSA draft, 2014). This conclusion is in line with the current positions of the US FDA and Health Canada. However, EFSA stated that much of the science underpinning this conclusion is still developing and will be revisited after the EFSA/CEF Panel finishes assessing the remaining uncertainties and publishes its findings, due later in 2014.

6.1.3.2 Risks to patients via exposure through medical devices

In its 2014 draft report, SCENIHR evaluated the possible risks BPA poses to patients exposed through the use of medical devices and adopted the t-TDI proposed in the 2014 EFSA draft (5 µg/kg bw/day). Most estimated exposures are lower than this t-TDI. Nevertheless, SCENIHR concluded that although evidence for possible effects at low doses is inconsistent and final conclusions cannot be drawn, the possibility of low-dose effects, especially after prenatal or perinatal exposure, raise some concern about prematurely born infants' exposure to BPA via medical devices. SCENIHR furthermore emphasised that these infants may have serious health concerns that could justify the use of BPA-containing medical devices in view of the benefit-risk evaluation, despite the possible adverse effects of BPA (SCENIHR draft, 2014).

6.1.3.3 Occupational health risks

Possible occupational exposures related to the manufacture of BPA (i.e. bagging and other filling activities) and the manufacture of BPA-containing epoxy resins have been identified as occupational settings with a risk characterisation ratio >1 (EC, 2008). The EU RAR (EC, 2003, 2008) concluded that there was a need to limit the risks of inhaling BPA during these activities. Other exposure scenarios (e.g. production of liquid epoxy paints, powder coatings and thermal paper) with RCRs less than 1 were identified. In all occupational exposure scenarios where there is the potential for skin contact, the EU RAR (EC, 2003, 2008) concluded that there was a need to limit the risks of BPA in relation to skin sensitisation.

The EU RAR (EC, 2008) assessment was based on the EASE model, which has since been updated. Recent insights furthermore suggest that routes besides inhalation (e.g. oral and dermal) may be important to workers' BPA exposure. To assess the aggregated exposure of workers via inhalation, dermal uptake and, where relevant, oral uptake, a combined exposure estimate has to 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. The EU RAR (EC, 2008) has not done this. In the near future, data from an ongoing NIEHS/NTP study may become available; it may facilitate the evaluation of workers' dermal exposure via other routes.

6.2 The environment

6.2.1 Hazards of BPA

BPA is classified under the CLP Regulation as harmful to aquatic organisms. The EU RAR on BPA (EC, 2008) furthermore concluded that BPA shows endocrine disrupting effects in environmental organisms, leading to adverse effects on reproduction and development of offspring. PNECs have been derived for water and sediment compartments.

6.2.2 Environmental exposure

BPA is ubiquitous in surface waters and sediment. Concentrations of BPA vary considerably depending on things such as the location and sampling period. Water concentrations found in Europe are in the ng/l to low µg/l range (EC, 2008; NORMAN-EMPODAT 2013). For sediment, concentrations in Europe were found from the low µg/kg dw to the low mg/kg dw range (EC, 2008; NORMAN-EMPODAT 2013). Emissions of BPA to the environment result from manufacture, its use in a broad range of products and the recycling and waste stages of these products. It is unclear which specific BPA lifecycle steps are responsible for the observed environmental concentrations. This uncertainty is being addressed by Germany's substance evaluation under REACH, which demands that industry provide more data on environmental emissions of BPA during the lifecycle of polymers and articles containing BPA, from production to waste.

6.2.3 Environmental risks

The EU RAR (EC, 2008) and Annex XV transition report (EC, 2009) suggest that BPA poses risks for the sediment compartment. Recent measurement data on BPA concentrations in the environment (from 2003–2010) support this statement. The 95th percentile of the measured concentrations of BPA in freshwater sediment and marine sediment exceed the derived PNECs for these environmental compartments. For marine sediment, the mean measured BPA concentration is also higher than the derived $PNEC_{marine\ sediment}$. In the Annex XV transition report (EC, 2009), it was furthermore concluded that, considering the uncertainties surrounding the effect on snails as sediment-dwelling organisms, the $PNEC_{sediment}$ should be re-evaluated if more information becomes available about snails or other sediment organisms.

For the water compartment, the EU RAR (2008) and Annex XV transition report (EC, 2009) identified no present risk. The 95th percentile of measured concentrations of BPA in fresh water and marine water remained below the respective PNECs. Recent measurement data on BPA concentrations (from 2003–2010) support this statement about BPA in fresh water. The available monitoring data about BPA in fresh water in the Netherlands from that same period are comparable to the European concentration profile.

Since the latest European risk assessment (EC, 2008) and the Annex XV transition report (EC, 2009) were published, new data has emerged regarding BPA's possible adverse effects on environmental organisms, including possible endocrine effects, and its concentrations in water and sediment throughout Europe. There are indications that the NOEC of BPA for fresh water organisms may be lower. Toxicity data that has emerged since 2009 was not taken into account in the derivation of the $PNEC_{water}$.

6.3 Legislation and initiatives

BPA and exposure to BPA are primarily managed by regulations at the EU level. In addition, the Netherlands have enacted specific provisions for BPA under the Dutch Food and Commodities Act (i.e. the Decree on Packaging and Utensils). Various ongoing regulatory initiatives may give rise to a new classification of BPA under CLP, a specific restriction for use of BPA in thermal paper under REACH and more insight into environmental emission sources via the process of substance evaluation under REACH. For example, a possible more stringent classification of BPA as a category 1B toxicant for reproduction in

Annex VI of the CLP Regulation would have major implications for several pieces of downstream legislation, including the Industrial Emissions Directive (2010/75/EC), the Ecolabel Regulation (66/2010/EC), the Toy Safety Directive (2009/48/EC), the Young People at Work Directive (1994/33/EC), the Pregnant and Breast Feeding at Work Directive (1992/85/EEC), the Waste Framework Directive (2008/98/EC), the Medical Devices Regulation (in preparation) and the Plastic Materials in Contact with Food Regulation (10/2011/EC).
The European Commission is also working on a criteria document for identifying and defining endocrine disruption and endocrine disruptors, which may affect the discussion around BPA as a possible endocrine disruptor. The outcomes of these initiatives are expected in 2014 and later, and may have major implications for other regulatory frameworks.

Annex 1.

Overall exposure of consumers

This table summarises the external exposure levels estimated by EFSA in its 2014 draft report and used in the preliminary risk assessment of the exposure of BPA for consumers. This table corresponds to Table 18 in that report (EFSA draft, 2014).

Tabel 10 Summary table on average and high ingestion (oral) and dermal (external and dermal equivalent oral dose) exposure to BPA in the general population (ng/kg bw per day) taken from Tables 23A and 23B in Appendix VI of the EFSA draft, and Tables 4 and 5 in section 3.1.7.3.

Age group	Ingestion		Dermal		Dermal (Equivalent oral dose by PBPK modelling)	
Average	Average	High	Average	High	Average	High
Infants 1–5 days (breastfed)	225	435	0	0	-	-
Infants 6 days–3 months (breastfed)	189	361	4.8	9.4	-	-
Infants 4–6 months (breastfed)	168	319	4.8	9.4	-	-
Infants 0–6 months (formula fed)	39	96	4.8	9.4	-	-
Infants 6–12 months	384	873	4.8	9.4	-	-
Toddlers 1–3 years	382	870	2.8	5.5	-	-
Other children 3–10 years	293	818	71	554	59	470
Teenagers 10–18 years	161	384	96	868	126[#]	1152[#]
Women 18–45 years	132	389	61	546	79[*]	725[*]
Men 18–45 years	127	336	61	546	79	725
Other adults 45–65 years	127	342	61	546	79[*]	725[*]
Elderly and very elderly 65 years and older	117	376	61	546	79[*]	725[*]

[*] It is anticipated that the dermal equivalent oral dose exposure for men aged 18–45 years is also representative for women aged 18–45 years, other adults aged 45¬–65 years, and elderly and very elderly adults aged 65 years and older. It is assumed that the toxicokinetics are not significantly different between these age groups.

[#] To estimate the dermal equivalent dose for teenagers, the PBPK model used the physiological parameters for adult males. For the exposure parameters, it used the oral and dermal doses for teenagers. The dermal equivalent oral doses were obtained from the combination of oral dietary exposure and dermal exposure through thermal paper.

Annex 2.

Overview of inhalation and dermal worker exposure to BPA

Tabel 11 Overview of inhalation and dermal exposure to BPA during various work activities, based on measured and estimated data.

Nr.	Work activities	Inhalation RWC 8 hr TWA (mg/m³)*	Inhalation RWC short-term (mg/m³)	Dermal (mg/kg bw/day) NO GLOVES assumed**	Reference
1	BPA manufacturing - product sampling - bag filling	3	6	 0.60 6	RAR, 2008
2	Manufacture of PC	0.001		0.0006	RAR, 2008
3	Manufacture of articles from PC	0.001		0.0006	RAR, 2008
4	Manufacture of epoxy resins and moderated epoxy resins - charging reactors - maintenance	0.7	11	 6.0 12	RAR, 2008
5	PVC manufacture NB: use is being phased out	0.1	1	0.6	RAR, 2008
6	Manufacture of liquid epoxy paints, lacquers and powder coatings	0.01		0.028	RAR, 2008
7	Use of epoxy resin-based powder coatings, paints and lacquers - powder paints - spraying coating powders - dip-painting	 0.01 0.5 0.005	0.3	 0.033	RAR, 2008
8	Manufacture of thermal papers - charging reactors	0.1	4	 0.6	RAR, 2008
9	Manufacture of tin-plating additive - charging reactors	0.05		 0.6	RAR, 2008
10	Manufacture of tetra brominated flame retardants (TBBA) - bag filling	0.000015		 0.00002	RAR, 2008
11	Professional end use of thermal printing papers			$3x10^{-8}$ - 0.017	ARCADIS, 2013

* Reasonable worst case eight-hours' time-weighted average inhalation exposures
** Exposure estimate based on EASE calculation

Annex 3.

Citation of the explanatory text for the ban on the use of BPA in baby bottles in the Commission Directive 2001/8/EC

'An EFSA Panel was consulted for an opinion on the toxicity of BPA and concluded that based on the comprehensive evaluation of recent human and animal toxicity data, no new study could be identified, which would call for a revision of the current tolerable daily intake (hereinafter 'TDI') of 0,05 mg/kg bodyweight per day. This TDI was based on the no adverse effect level of 5 mg/kg bodyweight per day from a multi-generation reproductive toxicity study in rats, and the application of an uncertainty factor of 100, which is considered as conservative based on all information on BPA toxicokinetics. However, in a minority opinion one Member of the Panel concluded that the effects observed in certain studies raised uncertainties which may not be covered by the current TDI which should therefore be considered temporary until more robust data becomes available in the areas of uncertainty.

The Panel noted that some animal studies conducted on developing animals have suggested other BPA-related effects of possible toxicological relevance, in particular biochemical changes in brain, immune-modulatory effects and enhanced susceptibility to breast tumours. These studies have many shortcomings. The relevance of these findings in relation to human health cannot be assessed at present. In case any new relevant data becomes available in the future, the Panel will reconsider its opinion.

Infant formula or breast milk is the only source of nutrition for infants up to the age of 4 months, and it remains the major source of nutrition for some additional months. In its opinion of 2006 EFSA concluded that infants aged 3 and 6 months fed using polycarbonate infant feeding bottles have the highest exposure to BPA, though below the TDI. For this group of infants the level of exposure to BPA decreases once feeding from polycarbonate bottles is phased out and other sources of nutrition become dominant.

The EFSA opinion pointed out that an infant's system to eliminate BPA is not as developed as that of an adult and it only gradually reaches the adult capacity during the first 6 months. Nevertheless, the infant has sufficient capacity to eliminate BPA sufficiently rapid to maintain very low levels of unconjugated BPA, even at exposure levels equivalent to the worst-case exposure estimates.

Even if the infant has sufficient capacity to eliminate BPA at worst-case exposure the EFSA opinion pointed out that an infant's system to eliminate BPA is not as developed as that of an adult and it only gradually reaches the adult capacity during the first 6 months.

The potential toxicological effects may have a higher impact in the developing organism. According to the opinions of the Scientific Committee on Food (SCF) of 1997 and 1998 certain effects, in particular endocrine and reproductive effects, effects on the

immune system and the neurodevelopment are of particular relevance to infants. Reproductive effects and neurodevelopmental effects of BPA have been studied extensively in standard multigenerational toxicological tests and in other studies, which took account of the developing organism and did not reveal effects in doses below the TDI. However, studies which could not be taken into account for setting the TDI due to many shortcomings showed BPA-related effects of possible toxicological relevance. These effects, in particular those on the biochemical changes in the brain, which may affect neurodevelopment, and on immune modulation are reflecting the area of particular concern for infants highlighted in the SCF opinions of 1997 and 1998. In addition, the EFSA opinion of 2010 mentions the enhancing effect of an early exposure to BPA on tumour formation later on in life when exposed to a carcinogen. Also in this case the sensitive stage is the developing organism. Thus, the infant can be identified as the particular vulnerable part of the population as regards those findings for which the relevance for human health could not yet be fully assessed.

According to the EFSA opinion of 2006 polycarbonate feeding bottles is the main source of exposure to BPA for infants. Alternative materials to polycarbonate that do not contain BPA exist on the EU market, in particular glass and other plastic infant feeding bottles. These alternative materials have to comply with the strict safety requirements set out for food contact materials. Therefore, it is not necessary to continue the use of BPA-containing polycarbonate for infant feeding bottles.

Given that there exists a possible particular vulnerability of infants to potential effects of BPA, although also the infant is deemed to be able to eliminate BPA and even where the risk, notably to human health, has not yet been fully demonstrated, it is appropriate to reduce their exposure to BPA as much as reasonably achievable, until further scientific data is available to clarify the toxicological relevance of some observed effects of BPA, in particular as regards biochemical changes in brain, immune-modulatory effects and enhanced susceptibility to breast tumours.

The precautionary principle referred to in Article 7 of 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 allows the Union to provisionally adopt measures on the basis of available pertinent information, pending an additional assessment of risk and a review of the measure within a reasonable period of time.

Taking into account that there are uncertainties in the present state of scientific research with regard to the harmfulness of BPA exposure to infants through polycarbonate infant feeding bottles that would need to be clarified, the Commission is entitled to take a preventive measure regarding the use of BPA in polycarbonate infant feeding bottles on the basis of the precautionary principle which is applicable in a situation in which there is scientific uncertainty, even if the risk, notably to human health, has not yet been fully demonstrated.

Thus, it is necessary and appropriate for the achievement of the basic objective of ensuring a high level of human health protection to obviate sources of danger to physical and mental health that may be caused to infants by BPA exposure through feeding bottles.

The Commission evaluated the infant feeding bottle market and received an indication by the relevant producers that voluntary action by the industry for replacements on the market are ongoing and the economic impact of the proposed measure is limited. Therefore, all BPA-containing infant feeding bottles on the EU market should be replaced by the middle of 2011.

Until further scientific data are available to clarify the toxicological relevance of some observed effects of BPA, in particular as regards biochemical changes in brain, immune-modulatory effects and enhanced susceptibility to breast tumours, the use of BPA in the manufacture and placing on the market of polycarbonate infant feeding bottles should be temporarily banned. Directive 2002/72/EC should therefore be amended accordingly. The Authority has a mandate to monitor new studies to clarify these endpoints.'

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