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REACH registration and endocrine disrupting chemicals



REACH registration

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Executive summary

This report is concerned with five endocrine disrupting substances which are used in the EU, having been registered under REACH in several Member States. It focuses on the information requirements of the registration process. The report's findings reveal gaps between data available for review on the online ECHA chemical database of information on registered substances compared with published research findings on these substances. These differences suggest that: industry is not taking into account the body of knowledge on these substances; and that the potential of the principle of "no data, no market" is not being used to ensure a high level of protection of human health and the environment.

Background and methodology

Since 1999, when the EU Commission first published the Community Strategy for Endocrine Disruptors, there has been a significant increase in both scientific knowledge and public concern about the adverse effects of substances with endocrine disrupting properties. REACH provides mechanisms to establish chemical safety and to encourage innovative substitution. The effective operation of REACH depends on a registrant providing data about a substance at the registration stage of REACH which is fit for the ambitious and precautionary (regulatory) purposes intended by REACH.

The objective of this project was to compare information publicly available in ECHA's online database,¹ regarding substances registered under REACH which are known to have endocrine disrupting properties,² with the information requirements of the REACH registration process. The aim of this report was to see how far these requirements are reflected in the case of five substances which are found in widely-used consumer products: namely, diethyl phthalate (DEP), bisphenol A (BPA), tetrabromobisphenol A (TBBPA), triclosan and octyl-methoxycinnamate (OMC).

Scientific literature on the endocrine disrupting properties of each substance was researched and information publicly accessible in the REACH dossiers was considered. These scientific research findings were then analysed within an analytical framework consisting of four key questions derived from the REACH regulatory structure.³

¹ The ECHA database is available at: <http://echa.europa.eu/information-on-chemicals/registered-substances>

² The World Health Organisation has defined an endocrine disrupting chemical as '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', International Programme on Chemical Safety. 2002. Global assessment of the State of the Science of endocrine disruptors. Geneva: World Health Organisation.

³ Particularly Articles 10 and 12, Annexes VI-X.

1. Is there **available** and **relevant** information on the endocrine disrupting properties of the substance that has not been included in the dossier?
2. Is the information in the dossier **relevant** for assessing the endocrine disrupting properties of the substance?
3. Is the information in the dossier **reliable** for assessing the endocrine disrupting properties of the substance?
4. Is the information in the dossier **adequate** for assessing the endocrine disrupting properties of the substance?

Key findings and conclusions

The detailed research findings differed for each substance, but a number of common issues were identified from the analyses of the dossiers as a whole.

On **availability and relevance**:

- Available and relevant data identified through the scientific literature research carried out for the purpose of this report were found to be missing from the dossiers;
- Where material in a dossier was presented in the form of unattributed “robust study summaries”, it was not possible to undertake a critical review of those summaries against the source material;
- Where original studies could be accessed and compared with the summaries, it was found that relevant and available material contained in the original study had been omitted from the summary. Hence, it is also missing from the dossier;
- By using a research approach based on consideration of the weight of the evidence, it was possible to form a broader and more informed perspective on the available material which the registrant might be expected to have taken into account.

On **reliability and adequacy**:

- When assessing the reliability and adequacy of the information provided by the registrant, it was found that a weight of evidence approach provided a more comprehensive set of tools by which to reach substantive conclusions than was possible by reliance only, for example, on compliance with Good Laboratory Practice (GLP);
- There was no consistency in approach to the methodologies used to present the reliability or adequacy of the information for the purpose of establishing that human

health and the environment would not be adversely affected by the presence of the substance on the market;

- Within the dossiers, extensive reference was made to Klimisch categories 4 (not assignable) and 3 (not reliable) to record conclusions on the reliability of studies included.

From these findings, this report concludes that:

- The obligation in REACH for the registrant to identify and present all available and relevant information on substances with endocrine disrupting properties (as well as any adverse effects) is not being complied with;
- The principle of “no data, no market” has been replaced by the practice of “no registration number, no market”;
- Poor quality dossiers are not compliant with REACH requirements, result in unsafe products being placed on the market and constrain efforts to replace them with safer alternatives;
- Application of a scientifically based "weight of evidence" approach offers the best opportunity to ensure that REACH can provide effective regulatory treatment of endocrine disrupting chemicals and would enable a more informed, holistic and precautionary assessment to be made of information included in the dossiers;⁴
- The focus by registrants on recording compliance with GLP reporting standards deflects attention and effort from substantive ways to address the adverse impacts of endocrine disrupting chemicals;
- Widespread use of Klimisch categories 3 and 4 suggest that a number of relevant studies are not taken into account by registrants because it is easier to assign these categories than review for substantive content;
- The limited percentage of compliance checks conducted by ECHA does not seem to have had the effect of improving dossier quality overall;
- There is, currently, a lack of effective regulatory action to ensure the necessary quality of information included in dossiers; urging registrants to improve the quality of dossiers and reminding them of updating obligations is not sufficient and reliance on the compliance check procedure has too limited an impact.

⁴ Evans, R. Faust, M., Kortenkamp, A., Martin, O., McKinlay, R., Rosivats, E., 2011 State of the Art Assessment of Endocrine Disruptors, Final Report. Project Contract Number 070307/2009/550687/SER/D3.

Recommendations

- A mechanism is required which would hold a registrant to account for the quality of information in a dossier, both at the time of registration and on an ongoing basis; e.g. establishing both initial and ongoing enforceable legal responsibility on the part of senior management of a registrant for the preparation, submission and updating of a dossier;
- ECHA can improve guidance and provide clearer indications of how different approaches may be required for the collection and presentation of information relating to endocrine disrupting chemicals;
- A specific work programme should be launched by ECHA to develop a widely accepted and precautionary methodology to use for a weight of evidence approach to preparation of dossiers;
- Member States Competent Authorities (MSCA) could be more pro-active in the operation of their enforcement policies to investigate and apply sanctions in case of non-compliance with REACH information requirements;
- ECHA and MSCA should be fully transparent about action taken in relation to poor quality dossiers, follow-up processes and outcomes, particularly where improvements result.

Structure of report

This report is presented in two parts: the main report and a supporting annex. The main report is divided into three sections. Section 1 introduces and outlines the research undertaken and the analytical methodology used. Section 2 presents key findings and conclusions from the research. Section 3 suggests next steps to be taken to address the issues arising from the findings and conclusions.

The annex outlines the process by which five substances were selected for study, summarises the approach taken in conducting the scientific literature research, sets out the objectives of analysis of each substance and explains in more detail the analytical framework and methodology used to consider each of the selected substances.

Glossary

CoRAP	Community rolling action plan
CLP	Classification, labelling and packaging
CMR	Carcinogenic, mutagenic or toxic to reproduction
CSR	Chemical safety report
ECHA	The European Chemicals Agency
EEB	European Environmental Bureau
EU	European Union
DNEL	Derived no effect level (the level of exposure to the substance below which no adverse effects are expected to occur. It is usually calculated on the basis of an NOAEL or a BMD)
GLP	Good laboratory practice
HPV	High production volume
IUCLID	International Uniform Chemical Information Database
JRC	Joint Research Centre
MSCA	Member State Competent Authority
NIEHS	National Institute of Environmental Health Services
NOAEL	No observed adverse effect level. The highest tested dose or exposure level at which there are no statistically significant increases in the frequency or severity of adverse effects between the exposed population and an appropriate control group; some effects may be produced at this level, but they are not considered adverse or precursors of adverse effects.
OECD	Organisation for Economic Co-operation and Development
PBT	Persistent, bioaccumulative and toxic
PNEC	Predicted no effect concentration. Concentration of the substance below which adverse effects in the environmental sphere of concern are not expected to occur.
QSAR	Quantitative structure activity relationship
Read-across	Technique of filling data gaps from a tested chemical for a particular property or effect to a similar untested chemical
REACH	Regulation (EC) No 1907/2006 of 18 December 2006, concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals.
SIN List	Substitute it now! A list of hazardous chemicals recommended for inclusion in Annex XIV by ChemSec.
SVHC	Substance of very high concern
UNEP	United Nations Environment Programme
US FDA	United States Food and Drug Administration
WHO	World Health Organisation

Main report

1 Background and methodology

1.1 Background

Since the publication in 1996 of *Our Stolen Future*,⁵ there has been a significant increase in both scientific knowledge and public concern about the adverse effects of substances with endocrine disrupting properties. REACH provides mechanisms to protect human health and the environment from all harmful substances and encourages innovative substitution.

In 1999, the EU Commission issued its first policy document setting out a strategy for endocrine disruptors.⁶ The urgent need to address their adverse impacts on human health and the environment was recognised and short, medium and long-term measures were envisaged, including regulatory action.

The last two years have seen increasing activity on the part of both regulators and civil society, notably with: the publication of the report on "The State of the Art Assessment of Endocrine Disruptors",⁷ the findings of which were corroborated by the publication of the authoritative UNEP/WHO report on the State of the Science of Endocrine Disrupting Chemicals;⁸ the launch of SIN List 2.0⁹ and related advocacy by NGOs¹⁰; a two day conference organised by the Commission;¹¹ a joint JRC-NIEHS workshop on low dose effects;¹² the preparation and adoption of a report by the European Parliament;¹³ the release of the European Environment Agency's Weybridge+15 Report;¹⁴ the publication of Volume 2 of the European Environment Agency's 'Late lessons from early warnings' report;¹⁵ and, most recently, the publication of EFSA's Scientific Opinion on the hazard assessment of endocrine disruptors¹⁶ and the Report of the Endocrine Disruptors Expert Advisory Group¹⁷.

2013 is a critical year for the regulation of endocrine disruptors. Two regulatory developments are expected which will provide an opportunity for the EU authorities to take a more progressive, protective and precautionary approach to the regulatory treatment of endocrine disrupting

⁵ Colborn, T., Dumanoski, D. and Meyers, J.P. *Our Stolen Future* 1996, Dutton, Penguin Books (NY).

⁶ 1999 strategy http://ec.europa.eu/environment/endocrine/documents/comm1999_en.html

⁷ http://ec.europa.eu/environment/endocrine/documents/4_SOTA%20EDC%20Final%20Report%20V3%206%20Feb%2012.pdf

⁸ Joint UNEP/WHO report: The State of the Science of Endocrine-Disrupting Chemicals (EDCs). WHO press release:

http://www.who.int/mediacentre/news/releases/2013/hormone_disrupting_20130219/en/index.html UNEP press release:

<http://www.unep.org/hazardoussubstances/News/PressRelease/tabid/425/language/en-US/Default.aspx?DocumentID=2704&ArticleID=9403&Lang=en> 2002

report: http://www.who.int/ipcs/publications/new_issues/endocrine_disruptors/en/

⁹ The SIN list and the basis of compilation is available to view on ChemSec's website: <http://www.chemsec.org/what-we-do/sin-list/sin-list-20>

¹⁰ See, for example, the work of the Health and Environment Alliance <http://www.env-health.org/policies/chemicals>

¹¹ <http://ec.europa.eu/environment/endocrine/documents/120614press.pdf>

¹² http://ihcp.jrc.ec.europa.eu/our_activities/food-cons-prod/endocrine_disruptors/endocrine-active-chemicals-jrc-and-niehs-workshop

¹³ http://www.europarl.europa.eu/meetdocs/2009_2014/documents/envi/pr/912/912390/912390en.pdf

<http://www.europarl.europa.eu/sides/getDoc.do?pubRef=-//EP//TEXT+TA+P7-TA-2013-0091+0+DOC+XML+V0//EN&language=EN>

¹⁴ <http://www.eea.europa.eu/publications/the-impacts-of-endocrine-disruptors>

¹⁵ <http://www.eea.europa.eu/publications/late-lessons-2>

¹⁶ EFSA Scientific Committee: Scientific opinion on the hazard assessment of endocrine disruptors: scientific criteria for identification of endocrine disruptors and appropriateness of existing test methods for assessing effects mediated by these substances on human health and the environment. EFSA Journal 2013; 11(3):3132. www.efsa.europa.eu/efsajournal

¹⁷ European Commission, EUR 25929 Joint Research Centre Institute for Health and Consumer Protection; Munn, S. and Goumenou, M.: Key scientific issues relevant to the identification and characterisation of endocrine disrupting substances. Report of the Endocrine Disruptors Expert Advisory Group. March 2013.

chemicals:¹⁸ the establishment of legal criteria for the identification of endocrine disruptors under the biocides and plant protection products legislation; and the review of the criteria to authorise endocrine disruptors in the authorisation process.

Within the EU, the use of chemical substances (including endocrine disrupting chemicals) may be regulated under sector-specific product use measures.¹⁹ However, REACH²⁰ is the principal default regulatory regime²¹ under which chemicals produced over one tonne per annum are regulated in the EU. The way it applies to endocrine disrupting chemicals is, therefore, of critical importance to regulatory changes which will emerge in 2013. Most attention is being given to the question of how endocrine disrupting chemicals are dealt with under Article 57 REACH for the purposes of being listed in Annex XIV as requiring authorisation. Nevertheless, it is also important to examine the procedural underpinnings of the regulatory framework. In this way, it is possible to look at the wider impact of the regulatory treatment of **all** endocrine disrupting chemicals, in particular, the registrant's obligation to provide information on the adverse effects of substances.²²

The overall aim of REACH is to ensure a high level of protection of human health and the environment (while allowing the free movement of chemicals within the single market and enhancing competitiveness and innovation).²³ Responsibility is placed on manufacturers and importers to ensure that they manufacture, place on the market or use substances that do not adversely affect human health and the environment.²⁴ Inherent in the reversal in the burden of proof is the requirement that industry gathers and generates information which will prove that the substances concerned are used in ways that do not adversely affect human health and the environment.²⁵

Information is also critical to the processes in REACH which seek to promote innovation and the substitution (with safer alternatives) of harmful substances, particularly those identified as Substances of Very High Concern (SVHCs).

¹⁸ In 2013, the Community Strategy on Endocrine Disruptors will come under review. Further, under Article 138(7) REACH, the Commission 'shall carry out a review to assess whether or not, taking into account latest developments in scientific knowledge, to extend the scope of Article 60(3) to substances identified under Article 57(f) as having endocrine disrupting properties.' Under section 3.6.5, Annex II of the Plant Protection Products Regulation (Regulation (EC) No 1107/2009 of the European Parliament and of the Council of 21 October 2009 concerning the placing of plant protection products on the market and repealing Council Directives 79/117/EEC and 91/414/EEC) the Commission shall present to the Standing Committee on the food chain and animal health 'a draft of the measures concerning specific scientific criteria for the determination of endocrine disrupting properties'. Under Article 5(3) of the Biocides Product Regulation (Regulation (EU) No 528/2012 of the European Parliament and of the Council of 22 May 2012 concerning the making available on the market and use of biocidal products), 'The Commission shall adopt delegated acts in accordance with Article 83 specifying scientific criteria for the determination of endocrine disrupting properties.' From the 1 September 2013, the Biocides Product Regulation will be operational. Further dates to note are the second REACH registration deadline on 31 May 2013, for substances with tonnage of 100 tonnes or more, and the February 2013 first submission date for applications for Authorisation of substances placed on the Authorisation List.

¹⁹ e.g. Food Packaging (Framework Regulation (EC) No 1935/2004 (and implementing measures e.g. Commission Implementing Regulation (EU) No 321/2011 on use of bisphenol A in plastic infant feeding bottles); Cosmetic Products (Regulation (EC) No 1223/2009); Plant Protection Products (Regulation (EC) No 1107/2009); Biocides (Regulation (EU) No 528/2012).

²⁰ Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) No 793/93 and Commission Regulation (EC) No 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2000/21/EC.

²¹ In the sense that there are other use specific measures and REACH aims at substances which are wide spread in the market.

²² Annexes VI-XI REACH.

²³ Article 1 REACH.

²⁴ Article 1(3) REACH.

²⁵ Annex VI REACH.

1.2 Methodology

The effective operation of REACH depends on a registrant providing substance-related data which enables the full regulatory potential of REACH to be exploited. This report examines the data provided for five substances which are found in widely-used consumer products, namely diethyl phthalate (DEP), bisphenol A (BPA), tetrabromobisphenol A (TBBPA), triclosan and octyl-methoxycinnamate (OMC).

The project focussed on how an essential component of the REACH regulatory framework, namely, the registration process,²⁶ applies to endocrine disrupting chemicals. It considered, in particular, the scope of data and information to be included in a registration dossier as required by Article 10(a) REACH. The preparation and submission of registration dossiers provide the foundation on which a manufacturer or importer can demonstrate that they are not placing on the market substances which adversely affect human health and/or the environment.²⁷ As indicated above, registration also provides a mechanism to generate information which is essential for the iterative processes which underpin the progressive and evolutionary nature of REACH; not only in relation to innovation and substitution, but also for the effective application of the evaluation and authorisation mechanisms available.²⁸

The project developed an analytical framework for identifying four essential characteristics of data required in the registration process. The objective of this approach was to determine the extent to which this critical entry point to the regulatory framework can ensure the identification of endocrine disrupting chemicals to which risk management measures (including cessation of use) should subsequently be applied.

The framework was used to identify and evaluate information relating to five substances selected for examination: **diethyl phthalate (DEP)**;²⁹ **bisphenol A (BPA)**;³⁰ **tetrabromobisphenol A (TBBPA)**;³¹ **triclosan**³² and **octyl-methoxycinnamate (OMC)**³³. The overall objective of the selection process was to include substances which are likely to be found in consumer products of common use. The substances selected have certain basic common characteristics,³⁴ namely: inclusion in SIN List 2.0,³⁵ either in combination with other effects (CMR or PBT) or solely due to their endocrine disrupting properties; for which a REACH registration dossier had been submitted; and they are each found in one of five selected groups of products present in consumer goods³⁶ – UV filters; preservatives; adjuvants; plasticisers and flame retardants. To further refine the selection, a number of other factors were considered, namely: identification as high production volume (HPV) substances; inclusion in Community rolling action plan (CoRAP) List; the application of regulatory controls apart from REACH; and likely exposure due to dispersal during use.

²⁶ Title II, Chapter 1, Articles 5-14 REACH; Chapter 4, Articles 20-22 REACH; Annex I, VI, VII-X on standard information requirements, Annex XI REACH.

²⁷ Article 1(3) REACH

²⁸ Registrants are also expected to use all available information for the purpose of preparing a chemical safety assessment for the substance.

²⁹ CAS No: 84-66-2; EC No: 201-550-6.

³⁰ CAS No: 80-05-7; EC No: 201-245-8.

³¹ CAS No: 79-94-7; EC No: 201-236-9.

³² CAS No: 3380-34-5; EC No: 222-182-2.

³³ CAS No: 5466-77-3; EC No: 226-775-7.

³⁴ See paragraph two of the Annex.

³⁵ The scientific methodology used to compile the SIN list required that all chemicals listed have at least one scientific robust study conducted in vivo or in vitro and published in a peer-review scientific journal. The substances on the list are oriented towards chemical used in consumer products.

³⁶ See footnotes 9-13 of Annex for examples of uses of the five substances.

A focussed scientific literature review was conducted for each of the selected substances. The research findings were based on:

- A literature review of studies addressing effects relevant for human health and the environment;
- Examination of evidence *in vivo* and *in vitro* as well as epidemiological research;
- A detailed consideration of the toxicological information contained in the registration dossier³⁷ at the time of the review;³⁸
- Identification of information that was available in the literature but not included in the dossier; and
- Recommendations for improvement.

In order to use these research findings for the purpose of identifying opportunities to improve the regulatory framework for endocrine disrupting chemicals, an analytical structure was developed which links the research findings and the toxicological information included in the registration dossier to REACH registration requirements.³⁹

In REACH, four key characteristics are fundamental to the information to be included in a registration dossier – availability, relevance, reliability and adequacy.⁴⁰ These characteristics are found in the legal obligations of the registrant set out in specific articles of REACH and related annexes.⁴¹ They are also addressed in some detail in the extensive guidance material offered by ECHA.⁴² To date, ECHA guidance has not been developed with specific reference to endocrine disrupting chemicals; and so this report was designed to show the relevance of the four characteristics (referred to above) to endocrine disrupting chemicals within the REACH registration process. Availability, relevance, reliability and adequacy provided the cornerstones for the analytical framework for the report.

³⁷ Throughout the Main Report and Annex, ‘registration dossier’ refers to the information available from the IUCLID record which is available from the online ECHA chemical database of information on registered substances under REACH. The ECHA database is available at: <http://echa.europa.eu/web/guest/information-on-chemicals/registered-substances>. As of 2 April 2013, the dossier for BPA could be found at: http://apps.echa.europa.eu/registered/data/dossiers/DISS-9d91680f-cd13-2fd2-e044-00144f67d249_DISS-9d91680f-cd13-2fd2-e044-00144f67d249.html. The dossier for DEP could be found at: http://apps.echa.europa.eu/registered/data/dossiers/DISS-9d82880f-aab1-5fcc-e044-00144f67d249_DISS-9d82880f-aab1-5fcc-e044-00144f67d249.html. The dossier for OMC could be found at: http://apps.echa.europa.eu/registered/data/dossiers/DISS-9ea053bf-39e2-163b-e044-00144f67d031_DISS-9ea053bf-39e2-163b-e044-00144f67d031.html. The dossier for TBBPA could be found at: http://apps.echa.europa.eu/registered/data/dossiers/DISS-9d928727-4180-409d-e044-00144f67d249_DISS-9d928727-4180-409d-e044-00144f67d249.html and the dossier for triclosan could be found at: http://apps.echa.europa.eu/registered/data/dossiers/DISS-9ea3b5cc-80fb-15ea-e044-00144f67d031_DISS-9ea3b5cc-80fb-15ea-e044-00144f67d031.html

³⁸ The reviews were carried out between March and September 2012. The dossiers were viewed again in January 2013. A number of minor changes were noted in the OMC dossier which did not affect any of the substantive conclusions drawn from the dossier.

³⁹ The elaboration of the framework is set out in the Annex, paragraphs 5-24.

⁴⁰ See paragraphs 5-24 of the Annex for definitions and explanations of these four concepts.

⁴¹ Article 12 REACH, ‘The technical dossier referred to in Article 10(a) shall include under points (vi) and (vii) of that provision **all** physiological, toxicological and ecotoxicological information that is **relevant and available to the registrant** ...’; Annex VI, Step 1, ‘The registrant should gather all existing available test data on the substance to be registered[and] should also collect **all other available and relevant information** on the substance **regardless whether testing for a given endpoint is required** or not at the specific tonnage level. **This should include information** from alternative sources (...) **which may assist in identifying the presence or absence of hazardous properties of the substance...**’; Annexes VII-X, ‘Any other **relevant** physicochemical, toxicological and ecotoxicological information **that is available shall be provided.**’

⁴² <http://echa.europa.eu/web/guest/support/guidance-on-reach-and-clp-implementation>

Four questions were formulated to assess the results of the research findings:

1. Is there available and relevant information in the literature on the endocrine disrupting properties of the substance that has not been included in the dossier?;
2. Is the information in the dossier relevant for assessing the endocrine disrupting properties of the substance?;
3. Is the information in the dossier reliable for assessing the endocrine disrupting properties of the substance?;
4. Is the information in the dossier adequate for assessing the endocrine disrupting properties of the substance?

These questions were applied to the dossier information reviewed for each of the five substances which was publicly available through the ECHA dissemination website.

2 Key findings

2.1 Overview

The studies from the literature reviewed confirmed the SIN list findings of endocrine disrupting properties and effects for each of the five substances. The research findings further indicated that the reviewed toxicological information in the registration dossiers did not satisfactorily reflect available, relevant, reliable or adequate information.

These results are described by reference to: available and relevant data; dossier presentation of information from studies; dossier omissions and justifications; use of weight of evidence approach; reliability; and adequacy.

2.2 Available and relevant data

In a notable number of instances, available and relevant information on endocrine disrupting properties of the five substances which had been identified in the scientific literature could not be found in the dossiers; in particular, this related to available and relevant information on endocrine disrupting effects, endocrine modalities and sensitive endpoints.

In the case of DEP, ten studies relevant to the substance's endocrine disrupting properties were located in the literature and identified in the research findings, nine of which recorded endocrine

disrupting effects of DEP.⁴³ By contrast, the relevance of the information for determining the endocrine disrupting properties contained in the studies potentially covering these effects which were included in the dossier was poor.⁴⁴ The endpoints measured were, for the most part, relatively insensitive and all but three of the studies used endpoints which could potentially be affected by both endocrine and non-endocrine modalities. In two of the three remaining cases,⁴⁵ the information about the methodology and the results included in the summary were so incomplete that it was impossible to tell whether or not other modalities may have been involved.

Ten studies were identified from the literature as relevant to assessing the endocrine disrupting properties of triclosan, and these covered a range of endocrine disrupting effects⁴⁶ and endocrine modalities.⁴⁷ However, in the dossier, only two studies examining ecotoxicity with endocrine disrupting relevant endpoints were included,⁴⁸ despite at least two further studies examining effects on the development of fish and amphibians existing in the literature;⁴⁹ only one study in the dossier covered development *in utero*, despite the availability of relevant studies on the effects of triclosan *in utero* on maternal and fetal thyroid homeostasis.⁵⁰ Furthermore, the triclosan dossier referred to a review article,⁵¹ which summarised reviewed toxicological data and included industry surveillance data, both of which were of such little relevance to triclosan's endocrine disrupting properties as to be of no use whatsoever.

The literature review for TBBPA⁵² revealed the availability of many studies on its toxicological and endocrine disrupting modes of action⁵³ considered relevant by the authors, yet few of these

⁴³ Missing available and relevant information included studies using assays determining the ability of a compound to bind to the compound oestrogen and androgen receptors; studies covering sensitive endpoints relevant to endocrine disruption and studies demonstrating that the thyroid and adrenal glands could be affected by low doses (Pereira, C. Mapuskar, K., Rao, C.V. 2007. A two-generation chronic mixture toxicity study of Clophen A60 and diethyl phthalate on histology of adrenal cortex and thyroid of rats. *Acta Histochemica* 109(1):29–36; Pereira, C., Mapuskar, K., Rao, V. C. 2008. A three-generation toxicity study of diethyl phthalate on histology of adrenal and thyroid glands of rats. *Toxicology International* 15(1):63-67). Notably, despite availability of studies, no information was included on effects of DEP on neurodevelopment. See Hokanson R., Chowdhary, R., Busbee, D. 2009, Diethylphthalate, Possible Interactions in Fetal Brain Development, *The Open Toxicology Journal* 3, 16-23. Another study located in the literature (Yu, X., Hong, S., Moreira, E.G., Faustman, E.M. 2009. Improving in vitro Sertoli cell/gonocyte co-culture model for assessing male reproductive toxicity: Lessons learned from comparisons of cytotoxicity versus genomic responses to phthalates. *Toxicology and Applied Pharmacology* 239(3):325-36) found significant changes in gene expression, which is a more sensitive endpoint than gross cell or tissue morphology.

⁴⁴ Information on DEP available from the ECHA database exists under joint submissions for an intermediate registration and a full registration.

⁴⁵ ECHA registered substances registration dossier for Diethyl Phthalate, Exp WoE Toxicity to reproduction: other studies.002 and 003.

⁴⁶ A study by Rodriguez and Sanchez (2010) found that at all doses relevant to endocrine disruption, changes were seen in the decrease in the male:female sex ratios and delayed vaginal opening in the pups of all the dosed groups. A uterotrophic assay conducted as part of the same study which exposed immature female rats to the same concentration of triclosan as their mothers for three days found no increase in uterine weight. This suggests the physiological regulation of thyroid hormones during pregnancy is vulnerable to the effects of triclosan. Further endocrine disrupting effects included the suppression of steroidogenesis in the testis of adult males at doses down to the lowest dose, 5mg/kg bw/day (Kumar 2009). Another study showed effects as a potent anti-androgen and weak oestrogen receptor agonist (Chang Ahn et al 2008).

⁴⁷ Modalities covered included (Anti)-Androgen, thyroid and thyroid function, steroidogenesis, (Anti)-Oestrogen, effects on HPT/HPG axes and uterine/vaginal development.

⁴⁸ These endpoints were crude measures of fertility and fecundity.

⁴⁹ Veldhoen, N., Boggs, A., Walzak, K., Helbing, C.C. 2006. Exposure to tetrabromobisphenol-A alters TH-associated gene expression and tadpole metamorphosis in the Pacific tree frog *Pseudacris regilla*. *Aquatic Toxicology* 78(3):292-302; Ishibashi, H., Matsumura, N., Hirano, M., Matsuoka, M., Shiratsuchi, H., Ishibashi, Y., Takao, Y., Arizono, K. 2004 Effects of triclosan on the early life stages and reproduction of medaka *Oryzias latipes* and induction of hepatic vitellogenin. *Aquatic Toxicology* 14; 67(2):167-79.

⁵⁰ Paul, K.B., Hedge, J.M., Bansal, R., Zoeller, R.T., Peter, R., DeVito, M.J., Crofton, K.M. 2012. Developmental triclosan exposure decreases maternal, fetal, and early neonatal thyroxine: a dynamic and kinetic evaluation of a putative mode-of-action. *Toxicology* 300(1-2):31-45; Peters, R.J.B. 2005. Manmade chemicals in maternal and cord blood. TNO Environment and Geosciences report no. R2005/129.

⁵¹ The US Food and Drug Administration nomination profile for Triclosan.

⁵² Research has in part been generated as a result of the European Commission's Flame Retardants Integrated Risk Assessment for endocrine effects (FIRE) project; see <http://www.rivm.nl/fire>

⁵³ See, for example, Veldhoen, N., Boggs, A., Walzak, K., Helbing, C.C. 2006. Exposure to tetrabromobisphenol-A alters TH-associated gene expression and tadpole metamorphosis in the Pacific tree frog *Pseudacris regilla*. *Aquatic Toxicology* 78(3):292-302; Kitamura, S., Suzuki, T., Sanoh, S., Kohta, R., Jinno, N., Sugihara, K., Yoshihara, S., Fujimoto, N., Watanabe, H., Ohta, S. 2005. Comparative study of the endocrine-disrupting activity of bisphenol A and 19 related compounds. *Toxicological Sciences* 84(2):249-59; Mariussen, E., Fonnum, F. 2003. The effect of brominated flame retardants on neurotransmitter uptake into rat brain synaptosomes and vesicles. *Neurochemistry International* 43(4-5):533-42; Han, E.H., Park, J.H., Kang, K.W., Jeong, T.C., Kim, H.S., Jeong, H.G. 2009. Risk assessment of tetrabromobisphenol A on cyclooxygenase-2 expression via MAP kinase/NF-kappaB/AP-1 signaling pathways in murine macrophages. *Journal of Toxicology and Environmental Health, Part A* 72(21-22):1431-8; Samuelsen, M., Olsen, C., Holme, J.A., Meussen-Elholm, E., Bergmann, A., Hongso, J.K. 2001. Estrogen-like properties of brominated analogs of bisphenol A in the MCF-7 human breast cancer cell line. *Cell Biology and Toxicology* 17(3):139-51.

were included in the dossier.⁵⁴ Twelve studies were selected from the literature for their relevance to the endocrine disrupting properties of TBBPA.^{55 56 57 58} By contrast, the dossier only included seven studies, none of which covered relevant immunological, neurological, and ecotoxicological endpoints.⁵⁹ In fact, ecotoxicity in relation to endocrine disrupting effects was not covered at all, despite the availability of a study demonstrating reproductive impairment in fish that could lead to population level effects.⁶⁰ Only the repeat dose toxicity and toxicity for reproduction information section of the dossier contained studies relevant to TBBPA's endocrine disrupting effects. All but two of the included studies used very high doses of TBBPA,⁶¹ whilst, of the two using more environmentally realistic doses, one was disregarded and the other did not include sensitive developmental stages or endpoints. The former was disregarded on the basis of a letter to a journal which was subsequently successfully refuted by the authors of the study.⁶²

The dossier for BPA contained the greatest number of studies of the five dossiers reviewed, reflecting the vast number of studies which have been carried out on the endocrine disrupting properties of BPA and its use by some investigators as a model endocrine disrupting substance.⁶³ However, whilst many relevant studies had been included in the dossier, they did not appear to reflect in a consistent manner the available information on the endocrine disrupting properties of BPA. Effects of BPA on the reproductive and immune systems and on neurodevelopment and hormone-related cancer were only covered in part; and no information on emerging areas of research, such as effects on metabolic or cardiovascular development, was found in the dossier. This is despite the CT/EFSA/CEF final report citing studies of changes in sexual development, prostate and mammary development and tumorigenesis in response to pre- and neonatal exposure;⁶⁴ and a study linking perinatal exposure of rat pups with later impairment of glucose homeostasis.⁶⁵ Studies in the dossier used crude measures of endocrine effects, such as fecundity, growth or changes in gross anatomy, whilst studies using more sensitive endpoints, such as receptor⁶⁶ and gene expression⁶⁷ were available in the literature.

⁵⁴ Three studies which had formed part of the FIRE project were included in the dossier: Schauer, U.M., Völkel, W., Dekant, W. 2006. Toxicokinetics of tetrabromobisphenol A in humans and rats after oral administration. *Toxicological Sciences* 91(1):49-58; Lilienthal, H., Verwer, C.M., van der Ven, L.T., Piersma, A.H., Vos, J.G. 2008 Exposure to tetrabromobisphenol A (TBBPA) in Wistar rats: neurobehavioral effects in offspring from a one-generation reproduction study. *Toxicology* 246(1):45-54; van der Ven, L.T., Van de Kuil, T., Verhoef, A., Verwer, C.M., Lilienthal, H., Leonards, P.E., Schauer, U.M., Cantón, R.F., Litens, S., De Jong, F.H., Visser, T.J., Dekant, W., Stern, N., Håkansson, H., Slob, W., Van den Berg, M., Vos, J.G., Piersma, A.H., 2008. Endocrine effects of tetrabromobisphenol-A (TBBPA) in Wistar rats as tested in a one-generation reproduction study and a subacute toxicity study. *Toxicology* 245(1-2):76-89.

⁵⁵ See, for example: Rodríguez PE, Sanchez MS. 2010. Maternal exposure to triclosan impairs thyroid homeostasis and female pubertal development in Wistar rat offspring. *Journal of Toxicology and Environmental Health, Part A* 73(24):1678-88.

⁵⁶ Kumar, V., Chakraborty, A., Kural, M.R., Roy, P. 2009. Alteration of testicular steroidogenesis and histopathology of reproductive system in male rats treated with triclosan. *Reproductive Toxicology* 27(2):177-85.

⁵⁷ Paul, K.B., Hedge, J.M., DeVito, M.J., Crofton, K.M. 2010. Short-term exposure to triclosan decreases thyroxine in vivo via upregulation of hepatic catabolism in Young Long-Evans rats. *Toxicological Sciences* 113(2):367-379.

⁵⁸ Ahn, K.C., Zhao, B., Chen, J., Cherednichenko, G., Sanmarti, E., Denison, M.S., Lasley, B., Pessah, I.N., Kültz, D., Chang, D.P., Gee, S.J., Hammock, B.D. 2009. In vitro biologic activities of the antimicrobials triclocarban, its analogs, and triclosan in bioassay screens: receptor-based bioassay screens. *Environmental Health Perspectives* 116(9):1203-10.

⁵⁹ In particular, programming of the neuro-endocrine system *in utero* and testicular steroidogenesis were not covered in the dossier.

⁶⁰ Kuiper, R. V., van den Brandhof, E. J., Leonards, P. E. G., van der Ven, L. T. M., Wester, P. W., Vos, J. G., 2007. Toxicity of tetrabromobisphenol A (TBBPA) in zebrafish (*Danio rerio*) in a partial life-cycle test. *Archives of Toxicology* 81(1):1-9.

⁶¹ 10mg/kg bw/day-10 000mg/kg bw/day.

⁶² See section 2.4 below.

⁶³ A result of the vast number of studies available in the literature on the endocrine disrupting properties of BPA meant that for the focus of the scientific report was on reviewing studies which covered endpoints relevant to endocrine disruption. In total, two hundred and two studies included in the dossier were examined.

⁶⁴ EFSA Final Report, August 2010 – July 2011 CT/EFSA/CEF/2010/01.

⁶⁵ *ibid.*

⁶⁶ Zoeller, R.T., Bansal, R., Parris, C. 2005. Bisphenol-A, an Environmental Contaminant that Acts as a Thyroid Hormone Receptor Antagonist in Vitro, Increases Serum Thyroxine, and Alters RC3/Neurogranin Expression in the Developing Rat Brain. *Endocrinology* 146 (2): 607. Effects on RC3/Neurogranin expression at 1, 10, and 50 mg/kg, dosed orally; Iwamuro, S., Yamada, M., Kato, M., Kikuyama, S. 2006. Effects of bisphenol A on thyroid hormone-dependent up-regulation of thyroid hormone receptor alpha and beta and down-regulation of retinoid X receptor gamma in *Xenopus* tail culture. *Life Sciences* 2; 79(23):2165-71; Dose-dependent antagonistic effects detected when BPA administered at (10^{-7} - 10^{-5} M) in combination with 10^{-7} M T3; Heimeier, R.A., Das, B., Buchholz, D.R., Shi, Y.B. 2009. The Xenoestrogen Bisphenol A Inhibits Postembryonic Vertebrate Development by Antagonizing Gene Regulation by Thyroid Hormone. *Endocrinology* 150(6): 2964–2973. Effects seen in combination with 2nM/L T3 at 0.1 and 10µM/L BPA, via tank water (oral and dermal exposure).

Nine studies relevant to the endocrine disrupting properties of OMC were identified in the literature. By contrast, of the ten studies included in the dossier, few were relevant to endocrine disrupting properties of OMC. Only two studies covered sensitive endpoints of development *in utero*; other studies used adult animals and insensitive endpoints. The dossier did not include any *in vitro* studies despite *in vitro* studies being available and relevant and only two studies relevant to ecotoxicity appeared to have been included.

2.3 Presentation of information from studies

The regulatory definition in REACH of a robust study summary is clear:⁶⁸ it is to be detailed and include sufficient information to enable an evaluation of the relevance of the study without need to find and read through the full study. In our view, study summaries included in the dossiers across all five substances failed to meet this definition in several significant ways. Moreover, robust study summaries are required,⁶⁹ *inter alia*, for all key data used in hazard assessment.

Robust study summaries in DEP's dossier were not complete as regards information on one or more of the following matters: test guidelines; methodologies used; GLP compliance and funding sources as well as; crucially, the results obtained from the study. A common omission in the study summaries was the absence of information on the authors or titles of the study and no indication or explanation as to why this was the case. This made it difficult and, in most cases, impossible to locate the original study and compare the results and findings against what has been recorded in the dossier.

Some of the dossiers were more badly affected than others. The most problematic was OMC for which none of the studies could be identified, For TBBPA, only 2 of the 7 study summaries examined in the dossier could be identified; and, for triclosan, only 3 could be found. The dossier for DEP was better in this respect, with 6 of the 9 studies being identifiable. The dossier for BPA was the best of those examined where 184 out of 192 relevant studies (92%) could be identified. Where this information was absent, the results and conclusions of the original studies could not be compared with those contained in the study summary. In consequence, it could not be determined whether any data relevant to endocrine disruption were omitted.

Information on study methodology was so incomplete for two study summaries in DEP's dossier that it was impossible to determine whether or not sensitive developmental stages had been covered. Similarly, incomplete information in triclosan's dossier meant that it was not possible to determine whether or not reductions observed in fecundity and fertility were likely to be the result of endocrine disruption. For OMC, the ecotoxicity and toxicity sections of the dossier contained less information than would be expected based on the research undertaken for this report. This was not only observed when examining sections of the dossier supposed to contain information

⁶⁷ Marmugi, A., Ducheix, S., Lasserre, F., Polizzi, A., Paris, A., Priymenko, N., Bertrand-Michel, J., Pineau, T., Guillou, H., Martin, P.G., Mselli-Lakhal, L. 2012. Low doses of bisphenol A induce gene expression related to lipid synthesis and trigger triglyceride accumulation in adult mouse liver. *Hepatology*. 55(2):395-407. Lawson C, Gieske M, Murdoch B, Ye P, Li Y, Hassold T, Hunt PA. 2011. Gene expression in the fetal mouse ovary is altered by exposure to low doses of bisphenol A. *Biology of Reproduction* 84(1):79-86. Gene expression altered at 20ng/g bw, oral exposure. Sheng ZG, Tang Y, Liu YX, Yuan Y, Zhao BQ, Chao XJ, Zhu BZ. 2012. Low concentrations of bisphenol a suppress thyroid hormone receptor transcription through a nongenomic mechanism. *Toxicology and Applied Pharmacology* 15; 259(1):133-42. TR-mediated transcription suppressed by 10⁻⁹ to 10⁻⁷ M BPA.

⁶⁸ 'Robust study summary: means a detailed summary of the objectives, methods, results and conclusions of a full study report providing sufficient information to make an independent assessment of the study minimising the need to consult the full study report.' (Article 3(28) of REACH).

⁶⁹ Section 1.1.4, Annex I, REACH.

relevant to the substance's endocrine disrupting properties; the section for information on carcinogenicity also did not contain any findings because this information had been waived, with no reason being given for its omission.

The relevance of studies included in the dossier for BPA and TBBPA which were identified in the research findings as potentially relevant to the assessment of the endocrine disrupting properties of the substances could not have their actual relevance evaluated because the studies had only been reported in part. The dossier for TBBPA did not report all relevant information from a study of TBBPA toxicokinetics.⁷⁰ In our view, this information would have been relevant to the toxicity to reproduction study summary toxicity section of the dossier.⁷¹ 27 studies out of the 198 examined were identified in BPA's dossier as potentially relevant to the assessment of the endocrine disrupting effects of BPA but were assigned reliability category 4 (not assignable) because insufficient information from the studies was available to allow them to be classified in another category. Another 67 studies, especially in the "Toxicity to reproduction: other studies"; "Key specific investigations: other studies", "Epidemiological data and exposure related observations in humans: other data sections" had no reliability categories assigned and no information was provided to indicate why no reliability categories had been assigned. All the relevant information was included in 64 of the 80 which could be accessed in the literature in their entirety. However, in the case of 118 of the 198 studies in the dossier, the studies could either not be identified or could be identified but not accessed, which undermines the dossier's transparency and made it impossible to draw a conclusion as to their relevance. There were also three instances where information about effects on the endocrine system were noted in the results sections of the study summaries, but were omitted or dismissed in the conclusions, including two out of the three studies included in the toxicity to reproduction section.

2.4 Omissions and justifications

Where original studies could be accessed and compared against the robust study summaries and study summaries, it was found that, in a significant number of instances, results which had been noted in the original studies were not included in the summaries.

In triclosan's dossier, robust study summaries omitted results from the original studies without any express justification and despite endocrine disrupting effects of the substance being detected in the original studies.⁷² Furthermore, the summary of one study failed to include the exact doses administered to the test animals; the US Food and Drug Administration nomination profile for triclosan was included as a supporting study but devoid of any information,⁷³ whilst the summary for the only study included on development *in utero* (from 1988) did not include key

⁷⁰ Schauer, U.M., Völkel, W., Dekant, W 2006. Toxicokinetics of tetrabromobisphenol A in humans and rats after oral administration. *Toxicological Sciences* 91(1):49-58.

⁷¹ The original study recorded decreases in T4 levels in all dosed male rats relative to the control group. The NOAEL reported in the dossier was not derived from this information but appears to have been derived from other measures of toxicity.

⁷² The original studies showed an increased overall expression of CYP450 enzymes in the liver and dose-dependent increases in steroid synthesis and metabolism in rats, which could impair the ability of the animals to maintain correct steroid hormone levels. Despite the relevance of this information to assessing hazardous properties of the substance, the conclusions of the robust study summary failed to refer to the findings.

⁷³ This was a literature review of studies on triclosan, available at: http://ntp.niehs.nih.gov/ntp/htdocs/Chem_Background/ExSumPdf/triclosan_508.pdf

endocrine sensitive reproductive endpoints despite the original study showing indications of triclosan's effects on the male reproductive tract.⁷⁴

Available information from the literature relevant to the assessment of the endocrine disrupting effects of DEP and identified in the research findings could not be located in the dossier. The dose at which an effect was seen in one original study was not the effect level used to derive the NOAELs given in the dossier.⁷⁵ In addition, an original study reported in the dossier had indicated endocrine disrupting effects of DEP seen *in vivo*,⁷⁶ although these effects were not included in the conclusion of the study report.⁷⁷

TBBPA's dossier did not include two studies that examined its effects for a range of doses (including low, potentially environmentally relevant, doses) on neurodevelopment found in the literature.^{78,79} These studies found evidence of a critical effect dose for perturbed neurodevelopment as low as 8mg/kg bw/day⁸⁰ when measuring the effects of TBBPA exposure *in utero* on the auditory response of rat pups and a critical effect dose of 2.2mg/kg bw/day for increases in male pup pituitary size. As such, they are studies that demonstrate a high, if not the highest, level of concern and, therefore, could be expected to have been included. As provided in REACH: 'If the study or studies giving rise to the highest concern are not used, then this shall be fully justified and included as part of the technical dossier, not only for the study being used but also for all the studies demonstrating a higher concern than the study being used.'⁸¹ The justification for non-inclusion was based on criticisms of the studies contained in published letters to the editor of the journal *Toxicology*.^{82, 83} However, these criticisms had been publicly rebutted by the authors of the original studies.^{84, 85} Therefore, in the absence of any requests from the journal editors for the authors to amend the studies, contrary to the justification for omitting these studies, the fact that they had been subjected to public peer review and survived is evidence, in our view, of both their relevance and adequacy.

Hazard categories were often omitted from the classification and labelling section of the dossiers.⁸⁶ Despite the subsequent public availability of hazard classifications for DEP,⁸⁷ the

⁷⁴ These included changes in testicular size, texture and colour in subsets of males in all the treatment groups but not the controls. The NOAELs derived from this study did not take this information into account and no justification was provided for this omission.

⁷⁵ Fujii, S., Yabe, K., Furukawa, M., Hirata, M., Kiguchi, M., Ikka, T. 2005. A two-generation reproductive toxicity study of diethyl phthalate (DEP) in rats. *The Journal of Toxicological Sciences* 30: 97-116.

⁷⁶ Jones, H.B., Garside, D.A., Liu, R., Roberts, J.C. 1993. The influence of phthalate esters on Leydig cell structure and function in vitro and in vivo. *Experimental Molecular Pathology* 58(3):179-93.

⁷⁷ DEP ECHA registration dossier, Exp WoE Toxicity to reproduction: other studies.001.

⁷⁸ Lilienthal, H., Verwer, C.M., van der Ven, L.T., Piersma, A.H., Vos, J.G. 2008. Exposure to tetrabromobisphenol A (TBBPA) in Wistar rats: neurobehavioral effects in offspring from a one-generation reproduction study. *Toxicology* 246(1):45-54.

⁷⁹ Van der Ven, L.T., Van de Kuil, T., Verhoef, A., Verwer, C.M., Lilienthal, H., Leonards, P.E., Schauer, U.M., Cantón, R.F., Litens, S., De Jong, F.H., Visser, T.J., Dekant, W., Stern, N., Håkansson, H., Slob, W., Van den Berg, M., Vos, J.G., Piersma, A.H., 2008. Endocrine effects of tetrabromobisphenol-A (TBBPA) in Wistar rats as tested in a one-generation reproduction study and a subacute toxicity study. *Toxicology* 245(1-2):76-89.

⁸⁰ Lilienthal, H., Verwer, C.M., van der Ven, L.T., Piersma, A.H., Vos, J.G. 2008. Exposure to tetrabromobisphenol A (TBBPA) in Wistar rats: neurobehavioral effects in offspring from a one-generation reproduction study. *Toxicology* 246(1):45-54.

⁸¹ Section 1.1.4, Annex I, REACH.

⁸² Banasik M, Hardy M, Harbison RD, Hsu CH, Stedeford T.2009. Tetrabromobisphenol A and model-derived risks for reproductive toxicity. *Toxicology* 260(1-3):150-2.

⁸³ Strain GM, Banasik M, Hardy M, Stedeford T.2009. Tetrabromobisphenol A (TBBPA) and model-derived risks for neurobehavioral effects in offspring from a one-generation reproduction study. *Toxicology* 260(1-3):155-7.

⁸⁴ Lilienthal, H., Slob, W., van der Ven, L.T.M., Piersma, A.H., 2009. Measurement and evaluation of neurobehavioral effects induced by tetrabromobisphenol A (TBBPA)-Response to Strain et al. (2009) *Toxicology* 260 (1):158-161.

⁸⁵ Van der Ven, L.T.M., Slob, W., Piersma, A.H., Opperhuizen, A., 2009. The benchmark approach is the preferred method to describe the toxicology of tetrabromobisphenol A (TBBPA)-Response to Banasik et al. (2009). *Toxicology* 260, (1) 153-154.

⁸⁶ This section should contain classifications of the hazards of the substance from the EU Classification and Labelling Regulation (REGULATION (EC) No 1272/2008 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL OF 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006, OJ L353/1 of 31 December 2008) which adopts the UN Globally Harmonised System of classification and labelling of chemicals.

hazard classifications in the dossier did not appear to have been updated to take this into account; instead, the hazard was reported as ‘conclusive but not sufficient for classification’. This was also the case for studies reported in the dossier for OMC. In the ECHA classification and labelling database,⁸⁸ OMC is listed in the aquatic chronic toxicity class as a skin irritant, acutely toxic and as an eye irritant.⁸⁹ However, the dossier did not appear to contain this information. Environmental and health classifications were not included, instead; ‘conclusive but not sufficient for classification’ or ‘data lacking’ had been inserted.⁹⁰ By contrast, the classification and labelling data contained in the dossier for TBBPA reflected the categories assigned in the ECHA classification and labelling database.

Where tests had been waived and the justification provided was ‘other’,⁹¹ it was impossible to determine the basis on which the data had been waived, raising the possibility that relevant information had been omitted. Test studies in the ecotoxicity section of OMC’s dossier had been waived on the basis of ‘other justification’.⁹² The justification to waive this data appears to have been based on the misunderstanding that there was no need to provide the data in order to determine the hazardous properties of the substance. However, we would submit that existing regulatory classification and labelling of OMC as an aquatic chronic toxicity hazard, an acute toxicant and a skin and eye irritant would indicate the relevance of studies on OMC’s long term toxicity to fish and long term toxicity to aquatic invertebrates.

Of the studies reported in BPA’s dossier, 12 of the 199 reviewed did not contain information which would assist in identifying the hazardous properties of the substance. In addition, no information was provided which could be used to identify the studies as they were incomplete, with justifications for omissions recorded as ‘other’.

2.5 Weight of evidence

Both the text of REACH⁹³ and the guidance on information gathering⁹⁴ require that the data included in the dossiers should be comprehensive enough to allow the identification of properties, such as endocrine disruption, which would trigger the inclusion of a substance in Annex XIV as required by Article 57. The information gathering strategy encourages a weight of evidence approach to avoid the need for additional testing⁹⁵ and practical guidance on how to use and report a weight of evidence approach is provided.⁹⁶ Despite this, the material seen in the dossiers examined raises questions about how effectively registrants are using this

⁸⁷ Classifications are publicly available from the ECHA classification and labelling website: <http://clp-inventory.echa.europa.eu/SummaryOfClassAndLabelling.aspx?SubstanceID=13888&HarmOnly=no?DisclaimerAgr=Agree&Index=84-66-2&ExecuteSearch=true&fc=true&lang=en>

⁸⁸ <http://echa.europa.eu/information-on-chemicals/cl-inventory>

⁸⁹ <http://clp-inventory.echa.europa.eu/SummaryOfClassAndLabelling.aspx?SubstanceID=41537&HarmOnly=no?DisclaimerAgr=Agree&Index=5466-77-3&ExecuteSearch=true&fc=true&lang=en>

⁹⁰ OMC was listed on the ECHA classification and labelling database (online). It is possible to conduct a search of the *harmonised* classification and labelling for a substance using this database. A search for the harmonised classification and labelling of OMC revealed no results.

⁹¹ Annex XI contains the general rules for adaptation of the standard testing regime.

⁹² OMC ECHA registration dossier NS NS Long-term toxicity to fish.001, NS NS Long-term toxicity to aquatic invertebrates.001, NS NS Sediment toxicity.001, NS NS Toxicity to soil macroorganisms except arthropods.001, NS NS Toxicity to soil macroorganisms except arthropods.002, NS NS Toxicity to terrestrial arthropods.001, NS NS Toxicity to terrestrial arthropods.002, NS NS Toxicity to terrestrial plants.001, NS NS Toxicity to terrestrial plants.002, NS NS Toxicity to soil microorganisms.001, and NS NS Toxicity to birds.001.

⁹³ REACH, Article 10, Annex VI, Annexes VII-XI.

⁹⁴ ECHA Guidance on Information Requirements, Chapter R.3 on Information Gathering.

⁹⁵ *ibid.*

⁹⁶ ECHA Practical Guide 2: How to report Weight of Evidence.

approach since the research findings demonstrated that, by applying an approach based on the weight of evidence available, it would be possible to form a broader and more informed view of the available material which the registrant might be expected to take into account in the dossier.

A weight of evidence approach allows the registrant to make best use of all available and relevant information on a substance. All types and sources of information can be used to draw conclusions on a substance's hazardous properties under a weight of evidence approach.⁹⁷ ECHA has already observed that registrants are not making proper, full or effective use of a weight of evidence approach in the submission of information in the dossiers. ECHA has remarked that, from its experience of the use of a weight of evidence approach, 'registrants are not relying on this approach properly to make the best use of several sources...'⁹⁸

In the 2011 Evaluation Under REACH Progress Report,⁹⁹ the use of different data sources when assessing evidence using a weight of evidence approach was not identified as a specific issue in need of improvement. However, the final decisions on compliance checks requested improvements in robust study summaries,¹⁰⁰ alongside numerous requests for study reports covering different toxicological aspects. It can also be noted from the ECHA report that the shortcomings addressed through quality observation letters also include requests for the inclusion of further information,¹⁰¹ such as more detail in robust study summaries. These information requests indicate that there are still shortfalls in the data submitted. In its more recent 2012 Evaluation Report,¹⁰² ECHA notes the recurrent shortcomings in registration dossiers; in particular, ECHA highlights the need for registrants to improve the quality of the information in dossiers.

The failure to include all relevant studies when meeting information requirements for the substances is evident when comparing studies which were included in the dossier with studies that were available in the literature and taken into account in the research findings. In the TBBPA dossier, studies available in the literature and covering the immunological¹⁰³ and neurological¹⁰⁴ effects of this substance did not appear to have been considered. Whilst these were not definitive studies, they could still have been included in the dossier using a weight of evidence approach. Similarly, epidemiological studies focusing on reproductive endpoints and the effects on the thyroid hormones exist for brominated flame retardants, and these could also have been included.^{105 106 107}

⁹⁷ See paragraph 11 and footnote 36 of the Annex for discussion and explanation of weight of evidence.

⁹⁸ ECHA Practical Guide 2: How to Report Weight of Evidence, section 5.

⁹⁹ <http://echa.europa.eu/en/regulations/reach/evaluation>

¹⁰⁰ See Table 8 of the ECHA Evaluation Report 2011.

¹⁰¹ See Table 9 of the ECHA Evaluation Report 2011.

¹⁰² ECHA Progress Report: Evaluation under REACH, section 2.

¹⁰³ Watanabe, W., Shimizu, T., Sawamura, R., Hino, A., Konno, K., Hirose, A., Kurokawa, M. 2010. Effects of tetrabromobisphenol A, a brominated flame retardant, on the immune response to respiratory syncytial virus infection in mice. *International Immunopharmacology* 10(4):393-7. Effects on immunity of mice dosed orally with an average of 13mg/g bw/ day TBBPA. Hurd, T., Whalen, M.M. 2011 Tetrabromobisphenol A decreases cell-surface proteins involved in human natural killer (NK) cell-dependent target cell lysis. *Journal of Immunotoxicology* 8(3):219-27. Expression of cell surface proteins on human natural killer lymphocytes necessary for the cells to bind to their targets reduced by exposure to 5 µM TBBPA *in vitro* for 24 hours.

¹⁰⁴ Saegusa, Y., Fujimoto, H., Woo, G.H., Ohishi, T., Wang, L., Mitsumori, K., Nishikawa, A., Shibutani, M. 2012. Transient aberration of neuronal development in the hippocampal dentate gyrus after developmental exposure to brominated flame retardants in rats. *Archives of Toxicology* 86(9):1431-42. Dams exposed pre- and postnatally to 1000ppm TBBPA in diet produced pups with transient aberrations in hippocampal development. Reistad, T., Mariussen, E., Ring, A., Fonnum, F. 2007 In vitro toxicity of tetrabromobisphenol A on cerebellar granule cells: cell death, free radical formation, calcium influx and extracellular glutamate. *Toxicological Science* 96(2):268-78. Decrease in cerebellar cell viability in vitro after exposure to 10 or 20 µM TBBPA. Incubation with 5µM for 24 hours caused changes in nuclear morphology indicative of apoptosis in 63% of cells. DNA fragmentation was also found. Concentration-dependent reactive oxygen species formation detected when cells incubated with 3, 6, 10 and 12 µM TBBPA.

¹⁰⁵ Jamieson, D.J., Terrell, M.L., Aguocha, N.N., Small, C.M., Cameron, L.L., Marcus, M. 2011. Dietary exposure to brominated flame retardants and abnormal Pap test results. *Journal of Women's Health* 20(9):1269-78.

¹⁰⁶ Small, C.M., Murray, D., Terrell, M.L., Marcus, M. 2011. Reproductive outcomes among women exposed to a brominated flame retardant in utero. *Archives of Occupational and Environmental Health* 66(4):201-208.

Under a weight of evidence approach, screening and adjunct tests could have covered sensitive endpoints relevant to endocrine disruption and epidemiological studies on the effects of exposure to DEP on the adult male reproductive tract could have been included in the DEP dossier.^{108 109 110} In addition, several studies involving large cohorts of mothers and children that associate prenatal phthalate exposure with perturbed neurodevelopment manifesting in a sexually dimorphic manner could have been referred to under a weight of evidence approach.^{111 112 113}

For triclosan, a weight of evidence approach would have been useful to make use of findings of studies, available and relevant in the literature, to reach conclusions on the effects of triclosan *in utero*, on maternal and fetal thyroid homeostasis, and the mis-programming of hypothalamic-pituitary-thyroid and hypothalamic-pituitary-gonadal axes. Under a weight of evidence approach, studies which have shown that, whilst there is insensitivity to triclosan in adults, fetal development is affected by exposure to triclosan,^{114 115} could have been included in the dossier.

Where studies were listed as having used a weight of evidence approach, it did not appear to have been used to its full potential. In the dossier for triclosan, information had been described as ‘health surveillance data’ and labelled as ‘weight of evidence’. However these ‘data’ were, in reality, a statement that workers in the production of triclosan receive regular health check-ups. As a statement rather than a study, it is unclear to us what purpose – if any – this information could usefully serve in support of the findings of the key studies. Therefore, in our view, it was inappropriate to include it as ‘weight of evidence’.¹¹⁶

In the past, ECHA has also noted instances where weight of evidence is used inappropriately by registrants; namely, single studies labelled as ‘weight of evidence’, including insufficient documentation provided for justifying use of such an approach; and ‘weight of evidence’ used to label information which had, in fact, been waived and for which a justification for waiving should have been provided.¹¹⁷

¹⁰⁷ Hagmar, L., Rylander, L., Dyremark, E., Klasson Wehler, E., Erfurth, E.M. 2001, Plasma concentrations of persistent organochlorines in relation to thyrotropin and thyroid hormone levels in women. *International Archives of Occupational and Environmental Health* 74 (3) 184-188.

¹⁰⁸ Hauser, R., Meeker, J.D., Duty, S., Silva, M.J., Calafat, A.M. 2006. Altered semen quality in relation to urinary concentrations of phthalate monoester and oxidative metabolites. *Epidemiology* 17(6):682-691.

¹⁰⁹ Jönsson BA, Richthoff J, Rylander L, Giwercman A, Hagmar L. 2005. Urinary phthalate metabolites and biomarkers of reproductive function in young men. *Epidemiology*. 16(4):487-93.

¹¹⁰ Hauser R., Meeker J.D., Singh N.P., Silva M.J., Ryan L., Duty S., Calafat A.M. 2007. DNA damage in human sperm is related to urinary levels of phthalate monoester and oxidative metabolites. *Human Reproduction* 22(3):688-695.

¹¹¹ Engel, S.M., Zhu, C., Berkowitz, G.S., Calafat, A.M., Silva, M.J., Miodovnik, A., Wolff, M.S. 2009. Prenatal phthalate exposure and performance on the Neonatal Behavioral Assessment Scale in a multiethnic birth cohort. *Neurotoxicology* 30(4):522-528.

¹¹² Engel SM, Miodovnik A, Canfield RL, Zhu C, Silva MJ, Calafat AM, Wolff MS. 2010. Prenatal phthalate exposure is associated with childhood behaviour and executive functioning. *Environmental Health Perspectives* 118(4):565-571.

¹¹³ Miodovnik, A., Engel, S.M., Zhu, C., Ye, X., Soorya, L.V., Silva, M.J., Calafat, A.M., Wolff, M.S. 2011. Endocrine disruptors and childhood social impairment. *Neurotoxicology* 32(2):261-267.

¹¹⁴ Allmyr, M., Harden, F., Toms, L.M., Mueller, J.F., McLachlan, M.S., Adolfsson-Erici, M., Sandborgh-Englund, G. 2008. The influence of age and gender on triclosan concentrations in Australian human blood serum. *Science of the Total Environment* 393(1):162-7.

¹¹⁵ Calafat, A.M., Ye, X., Wong, L.Y., Reidy, J.A., Needham, L.L. 2008. Urinary concentrations of triclosan in the U.S. population: 2003-2004. *116(3):303-307*.

¹¹⁶ See ECHA Practical Guide 2: How to Report Weight of Evidence, section 4.2.1, page 11.

¹¹⁷ Substance Information Exchange Forum Webinar: Weight of Evidence Approach, http://echa.europa.eu/documents/10162/13566/weight_of_evidence_approach_en.pdf

2.6 Reliability

This same weight of evidence approach would have provided a more comprehensive set of tools to assess the reliability and adequacy of the information provided for the purposes of substance registration. Reliability is defined here in accordance with ECHA's guidance as whether or not the test report or publication and its methodology give clear and plausible findings, as opposed to relevance, which is similarly defined as the extent to which data and tests are appropriate for a particular hazard identification or risk characterisation.¹¹⁸

Consideration of the dossiers suggested a wide variation in the way registrants assigned reliability categories (ranked "one" to "four") to studies, including those where this was done on the basis of whether or not the study complied with GLP. In our view, this approach undermined the value of such rankings because they do not adequately reflect the actual reliability of the study assessed on the basis of factors other than GLP/non-GLP; for example, issues with the study's methodology.¹¹⁹ Despite the recognition that tests using non-GLP methods may be used for the purpose of compiling a dossier,¹²⁰ a GLP-compliant approach to the assessment of reliability appears to us to be encouraged by ECHA's reference in guidance notes to the use of the Klimisch scoring system (which ranks studies for reliability between "one" and "four" and assigns reliability category "one" to GLP studies).¹²¹ It is possible that, as a result of this, the approach taken by registrants was very conservative, rather than adopting the expansive, precautionary and progressive approach outlined in section 1.1 of Annex 1 REACH. In the dossier for OMC, all the studies included which had complied with GLP were assigned a reliability category "one" (most reliable) apparently disregarding other factors that can affect a study's reliability.¹²² Where a study was assigned a reliability category "two", the justification provided was that it was non-GLP; again, seemingly regardless of other factors that might affect the particular study's reliability. Similarly, the dossier for TBBPA ranked all its GLP studies and none of its non-GLP studies as category "one", although in this case, its GLP studies were conducted according to OECD guidelines, whereas the others were not, and a study conducted to equivalent guidelines was disregarded.

The rationale used by registrants to assign reliability categories was not clear, with inconsistent approaches found within the dossiers in the way reliability categories were assigned to reported studies. In the DEP dossier, a developmental toxicity study was assigned a reliability category of "two", yet no information on the methodology of the study, the test guidelines used, or validations for the used guidelines could be found. Three other studies reported in the dossier with incomplete information were identified as falling within reliability category of "four" (unassignable). Similar inconsistencies in the way that reliability categories appeared to have been assigned to studies were also noted in the dossier for triclosan. Reliability category "two" was assigned to one study that was GLP compliant,¹²³ but was not conducted according to the validated test guideline. Yet another study which was also GLP compliant, but had not been conducted according to a validated test guideline, was assigned a reliability category of "three" without additional justification.

¹¹⁸ See ECHA guidance on information requirements and chemical safety assessment. Chapter R.4: Evaluation of available information, section R.4.1, page 1

¹¹⁹ For example, the methodology is out of date having been superseded by a more recent study; there are problems with the test species or actual exposure levels; weights or histology of endocrine organs have not been recorded.

¹²⁰ Section 1.1 Annex 1, REACH.

¹²¹ See paragraph 16 and footnote 49 of the Annex.

¹²² See paragraphs 17-20 of the Annex.

¹²³ The term "GLP Compliant" is used to refer to the situation where a study has been documented according to GLP rules. On the other hand, validated test guidelines provide a methodology to follow when conducting the tests. The two concepts are often used interchangeably, but, as they serve different purposes, such lack of clarity and consistency gives rise to confusion.

For triclosan, a study was reported as GLP compliant but had applied a methodology with an assumption that undermined the results;¹²⁴ this study was still assigned a reliability category “one”. Two reproductive developmental studies included in triclosan’s dossier could be considered to have severe shortcomings in their methodologies in the presence of skeletal malformations in the pups of both the dosed and the un-dosed animals. The study’s reliability could be seen as undermined if the malformations indicated a problem with the rats themselves or the way the studies were conducted. Despite this uncertainty, one of these two studies was assigned a reliability category “one”.

Of the 7 studies examined in TBBPA’s dossier, one could not be assigned a category because its reliability was compromised by its status as a pilot investigation only. Another study was disregarded for lack of reliability, with the justification that there had been inappropriate use of lower confidence limit bench-mark dose modelling to derive risks and there were factors in the methodology which invalidated the findings despite both these points being refuted by the study’s authors in the literature.¹²⁵

For DEP, the reliability of a third of the studies examined in the dossier were listed as category “four” (“unassignable”), meaning that the information available has been deemed inadequate by the registrant for the evaluation of study reliability. For triclosan, 2 of the 7 studies reviewed did not have a category assigned at all. In the dossier for BPA, the assignment of reliability categories did not appear to be wholly dependent on the study’s GLP status. However, there were still failures to assign reliability categories in some sections, most notably in Toxicity to reproduction: other studies; Key specific investigations: other studies; Epidemiological data; and Exposure related observations in humans: other data, in which no reliability category data were provided for any of the studies examined.

The wholesale allocation of category “four” and omission of reliability category give rise to questions because it may mean that important and relevant studies are not being considered, because it is easier to assign category “four”, or no category, than to consider more carefully the reliability of the studies in question.

Alongside a study’s methodology, funding source, guidelines followed and peer-review status, a study’s publication date can also be an indicator of study reliability.¹²⁶ Publication dates are particularly salient to study reliability where the OECD protocols are updated over time and the area of scientific research is fast-paced, as is the case for research on the effects of chemicals on the endocrine system of humans and animals. This presents the possibility of a risk that findings of older studies have been superseded by more recent ones. In DEP’s dossier, the literature review revealed that a more recent 2009 study superseded a study from 1993 which had been reported in the dossier.¹²⁷ Similarly for DEP, more recent studies available, but not

¹²⁴ This study was reported to have followed a similar protocol to OECD Test Guideline 416. However, the methodology did not have an assessment of the weights or histology of the endocrine organs or any measure of semen quality beyond reproductive performance. It was assumed that if the rats could breed, then reproductive performance was not affected. This assumption weakens the reliability of the study as reproductive performance is an insensitive endpoint compared to gamete morphology or the histology of the reproductive tract (Linder, R.E., Strader, L.F., Slott, V.L., Suarez, J.D. 1992. Endpoints of spermatotoxicity in the rat after short duration exposures to fourteen reproductive toxicants. *Reproductive Toxicology* 6(6):491-505.)

¹²⁵ Van der Ven, L.T.M., Slob, W., Piersma, A.H., Opperhuizen, A., 2009. The benchmark approach is the preferred method to describe the toxicology of tetrabromobisphenol A (TBBPA)-Response to Banasik et al. (2009). *Toxicology* 260, (1) 153-154; Lilienthal, H., Slob, W., van der Ven, L.T.M., Piersma, A.H., 2009. Measurement and evaluation of neurobehavioral effects induced by tetrabromobisphenol A (TBBPA)-Response to Strain et al. (2009) *Toxicology* 260 (1):158-161

¹²⁶ See paragraph 20 of the Annex.

¹²⁷ Jones, H.B., Garside, D.A., Liu, R., Roberts, J.C. 1993. The influence of phthalate esters on Leydig cell structure and function *in vitro* and *in vivo*. *Experimental Molecular Pathology* 58(3):179-93 was the older study which was superseded by Yu, X., Hong, S., Moreira, E.G., Faustman, E.M. 2009. Improving *in vitro* Sertoli

included in the dossier,¹²⁸ demonstrated that thyroid and adrenal glands could be affected at much lower doses than those used in examining the effects of DEP on the reproductive tract.¹²⁹

The literature review revealed the availability of recent studies on the endocrine disrupting properties for all five substances. The studies selected for consideration for TBBPA were all more recent than 2000; by contrast, half the studies included in the dossier were pre-1980 and did not demonstrate the endocrine disrupting effects of TBBPA.¹³⁰ The studies selected from the literature on the endocrine disrupting properties of OMC had publication dates from 2003 to 2011. By contrast, half the studies included in the dossier had publication dates in the early 1980s.¹³¹ Of the 9 studies reported in DEP's dossier, 4 had a publication date in the 1980s and one a date of 1979.

2.7 Adequacy

For the purposes of this report, adequacy of information was judged with respect to how well the information provided enabled the identification of endocrine disrupting properties of the substance.¹³² Adopting this approach suggested to us that registrants had failed to consider information for the purposes of identifying the hazardous properties of the substance. In the dossier for triclosan, information which would have assisted in the identification of endocrine disrupting properties was omitted and NOAELs derived from the studies included in the dossier were not always accurate.¹³³

It was often the case that they were derived from non-ED effects seen at higher doses than ED effects and/or from studies which had used high doses. For example, for all but two of the studies examined in TBBPA's dossier, the doses used were very high and not, therefore, a representation of a realistic exposure scenario. In addition, one study reported in TBBPA's dossier showed that T4 levels had decreased in all dosed male rats relative to the control group, but the NOAEL was not derived using the data from the original study;¹³⁴ instead, the NOAEL appeared to have been derived from other measures of toxicity, although no other toxic effects were reported at any dose. Of the two studies included which had used more environmentally sensitive doses, one had been disregarded and the other measured only relatively insensitive endpoints.¹³⁵ Similarly, for OMC, a study contained a LOAEL based on toxicity at a dosage of 1000mg/kg bw/day, yet NOAELs derived from studies in the literature were much lower.¹³⁶

cell/gonocyte co-culture model for assessing male reproductive toxicity: Lessons learned from comparisons of cytotoxicity versus genomic responses to phthalates. *Toxicology and Applied Pharmacology* 239(3):325-36.

¹²⁸ Two studies by Pereria et al (2007;2008) found the lowest dose to cause degenerative changes in the adrenal cortex and thyroid gland and depletion of thyroid hormone precursors in the offspring of F0 animals dosed was 2.85mg/kg bw/day and in the offspring of F1 rats dosed was 1.425mg/kg bw/day.

¹²⁹ Fugit et al (2005). The lowest dose found to cause reproductive abnormalities in offspring was 197/mg be/day.

¹³⁰ The endocrine modalities covered were gross histopathological changes, rather than hormone receptors, neural signalling and oestrogen action (all covered in the relevant studies available in the literature).

¹³¹ Two studies were from 1984, two from 1983 and one from 1981.

¹³² See paragraphs 21-24 of the Annex.

¹³³ In some study summaries for triclosan they were not provided at all whilst in others they could not be derived due to the type of study reported.

¹³⁴ Schauer, U.M., Völkel, W., Dekant, W 2006. Toxicokinetics of tetrabromobisphenol A in humans and rats after oral administration. *Toxicological Sciences* 91(1):49-58.

¹³⁵ The study, which had been described by Lilenthal et al (2008) and Van der Ven et al (2008), was disregarded based on criticisms made by Banasik et al (2009).

¹³⁶ In a two generation reproduction toxicity study using Wistar rats and a dietary administration of OMC, a NOAEL was derived for a dose of 450mg/kg bw/day (Schneider, S., Deckardt, K., Hellwig, J., Küttler, K., Mellert, W., Schulte, S., van Ravenzwaay, B. 2005. Octyl methoxycinnamate: two generation reproduction toxicity in Wistar rats by dietary administration. *Food and Chemical Toxicology* 43(7):1083-92). Effects on blood serum thyroid hormone levels were found in adult ovariectomised rats treated for five days with 10, 33, 100, 333 or 1000 mg/kg bw/day Klammer, H., Schlecht, C., Wuttke, W., Schmutzler, C., Gotthardt, I., Köhrle, J., Jarry, H. 2007. Effects of a 5-day treatment with the UV-filter octyl-methoxycinnamate (OMC) on the function of the hypothalamo-pituitary-thyroid function in

On examination of the dossiers, it was not always clear why the registrant had drawn the conclusions that they had, based on the information that was publicly available. For example, effect levels in the dossier submitted for DEP had been determined using NOELs from a study that was not representative of the available literature.¹³⁷ Studies available in the literature recorded endocrine disrupting effects of DEP at lower doses, yet these had not been used to derive NOELs for the purposes of compiling the dossier. For another study reported, it was not clear why the positive results from an experiment conducted *in vivo* had not been included, whilst the negative results of the *in vitro* study had been included.¹³⁸ Justifications for this did not appear to have been provided in either case.

The dossier for BPA stood out in terms of the quantity of studies provided and a large number of studies covering its endocrine disrupting properties were included. There was, however, a lack of consistent approach to the presentation of information across the different sections of the dossier, which tended to undermine its adequacy by creating an imbalance in the information available within the dossier. Within the toxicological section, containing specific investigations, 918 studies were included. However, other information sections in the dossier, such as the acute toxicity inhalation section, carcinogenicity section and neurotoxicity section, were found to refer only to a single study.

rats. *Toxicology* 238(2-3):192-199. Effects on maternal and pup blood serum thyroid hormone levels, male pup testosterone levels and sexual development and neurodevelopment of both sexes in Wistar rats prenatally exposed to 0, 500, 750 or 1000 mg/kg bw/day OMC. Axelstad, M., Boberg, J., Hougaard, K.S., Christiansen, S., Jacobsen, P.R., Mandrup, K.R., Nellemann, C., Lund, S.P., Hass, U. 2011. Effects of pre- and postnatal exposure to the UV-filter octyl methoxycinnamate (OMC) on the reproductive, auditory and neurological development of rat offspring. *Toxicology and Applied Pharmacology* 250(3):278-290.

¹³⁷ Fujii, S., Yabe, K., Furukawa, M., Hirata, M., Kiguchi, M., Ikka, T. 2005. A two-generation reproductive toxicity study of diethyl phthalate (DEP) in rats. *The Journal of Toxicological Sciences* 30: 97-116.

¹³⁸ Jones, H.B., Garside, D.A., Liu, R., Roberts, J.C. 1993. The influence of phthalate esters on Leydig cell structure and function in vitro and in vivo. *Experimental Molecular Pathology* 58(3):179-93.

3 Conclusions

3.1 Overview

From the findings on availability, relevance, reliability and adequacy of information, it can be concluded that, for the substances studied, the registrants are failing in their primary responsibilities under REACH which are 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.¹³⁹ Indeed, registrants are avoiding that part of the system which would report adverse effects of EDCs and selecting the studies which are of less concern. In many cases, the most recent studies were disregarded in favour of studies that are decades old which, from a scientific and policy perspective, does not make any sense. As a result, the potential of REACH is not being fully utilised to achieve a high level of protection of human health and the environment and questions are raised as to the safety of the substance. In particular, for substances with endocrine disrupting properties, for which standard tests and routine procedures that adequately capture endocrine disruption effects are not well established, it is essential that an approach, based on weight of evidence, is actively encouraged and supported.

3.2 Availability and relevance

The REACH regulatory framework provides clear mechanisms whereby registration dossiers can identify and address the endocrine disrupting properties of substances placed on the market. However, our research revealed a wider range of studies and information than appeared in the dossiers in relation to sensitive endpoints relevant to endocrine disruption.

This has led us to conclude that the registrants did not address and evaluate the availability and relevance of material to include in the dossier in the way that REACH foresees, in particular, the requirements of Article 12(1). It is not immediately obvious why this should be the case. The registrant may have prioritised expediency (i.e. securing market access for a substance) over accuracy and thoroughness. Alternatively, a registrant may have focussed on the types of study listed in the relevant Annexes of REACH rather than the more extensive mandate given in the universally applicable steps set out in Annex VI.¹⁴⁰ Whatever the explanation, it appears that registrants have not taken the opportunity provided by REACH to present a holistic and up-to-date picture of scientific findings, either at initial registration or on an ongoing basis.

A registrant may be reluctant to include in the dossier an explicit recognition of uncertainties, gaps or observations on the lack of appropriate testing mechanisms. However, it is essential for these issues to be identified. They are all of critical importance for: the preparation of a chemical safety report; action which may subsequently be taken by ECHA to evaluate a dossier for compliance;¹⁴¹ or to assist Member States in evaluating substances included in the CoRAP. This information is also required in order to be able to answer questions which may be raised by downstream users.

¹³⁹ Article 1(3) REACH.

¹⁴⁰ See paragraph 5 of the Annex.

¹⁴¹ If the dossier is selected for Evaluation, ECHA will evaluate whether *all relevant data that is available* through public information sources and previous regulatory decisions has been taken into account.' [emphasis added]. ECHA Practical Guide 4, How to report data waiving, page 6.

As an additional consideration, articulation of "known unknowns" is critical to the ability of regulators to use REACH mechanisms to stimulate advances in protection of human health and the environment from endocrine disrupting chemicals. Failure to identify such matters puts significant limitations on the ability of all stakeholders to look, or press, for safer alternatives.

3.3 Relevance and weight of evidence

An appropriate use of a weight of evidence approach was an essential tool for reviewing the scientific literature when assessing the relevance of data relating to endocrine disrupting chemicals. This approach provided a more extensive range of information for consideration than appeared in the dossiers.¹⁴² In consequence, identification and assessment of endocrine disrupting chemicals were significantly improved.

Under a weight of evidence approach, a wider range and greater number of studies, available in the literature, are treated as relevant for review. Under REACH, the dossier can and should accommodate a range of studies, including: studies which are not conclusive in themselves on a substance's properties but, nonetheless, provide enough information to support conclusions reached in other studies; studies which have not been endorsed by some organisations but, nonetheless, have significant results; studies which, whilst not definitive, do cover endpoints relevant to endocrine disruption; and studies conducted by scientists with an understanding of endocrinology and scientific areas relevant to endocrine disruption, such as low dose effects of hormones and hormone mimicking substances and the influence which different endocrine mediated cell signalling pathways can have on each other.

Little may be found in ECHA's current guidance documents on factors which focus specifically on endocrine disrupting chemicals. This does not, of course, relieve the registrant from the regulatory requirement to provide available and relevant information, or to explain reasons for omissions, or to assess information where it is not possible to derive DNELS, or to identify information gaps, or to suggest that new data should be generated or a testing strategy proposed.

3.4 Reliability and adequacy

ECHA's guidance on reliability gives prominence to the Klimisch scoring system.¹⁴³ The disadvantage of specifically identifying this system arises because it seems to encourage a tendency for registrants to use studies which fulfil GLP reporting requirements as a reference point for allocating reliability scores. Our research and analysis demonstrated the availability of relevant and reliable studies which had not followed GLP documentation requirements. By not including such studies which had been conducted under equally rigorous conditions as those of GLP, the dossiers presented a distorted and incomplete picture of the adverse effects of the substance.

As a result of such a limited interpretation of what constitutes reliability, it may well be that studies with a reliability rating of "one" have been included in a dossier solely because the

¹⁴² See paragraph 11 and footnote 36 of the Annex.

¹⁴³ See paragraphs 16-20 of the Annex.

reporting requirements of GLP have been met. However, a range of other factors may undermine the reliability of studies with a rating of “one” based on GLP compliance.¹⁴⁴ Further confusion and distortion arise where studies with ratings less than “one” or “two” have been included in a dossier with no explanation or comment; which might suggest that registrants have chosen to lower the profile of certain results which they could not avoid including in the dossier.

The inconsistent and patchy use of the scoring system also adversely affects the use of information which could be assessed under a weight of evidence approach. It may do so by providing a false picture of the information presented in the studies, the reliability of which would be more fairly assessed under a weight of evidence approach.

Even where endocrine disrupting chemical relevant studies appear to have been considered in the dossier, the level of analysis of the information was of variable quality, ranging from doubtful conclusions drawn from studies through to inconsistencies with the publicly available classification and labelling regulatory information.

The recurring absence of publicly available information in the dossier about the authors or other publication details of studies cited in the dossier makes an informed critical assessment, by both the public and ECHA and other stakeholders, more difficult. As mentioned above, it may be that ECHA has decided not to disseminate the references of the studies used by registrants in the compilation of the dossier. However, lack of availability of this information undermines public confidence in ECHA, as anyone reviewing the information on the database cannot determine whether or not the submitted dossier actually contained this information. Equally, anyone without this information would have difficulty in completing a thorough evaluation of the dossier and, indeed, the substance.

The adequacy of material included in the dossiers is undermined by its mixed quality in terms of how results and data are used to reach conclusions. Again, this casts doubt on how far such information provides a sound basis for any subsequent dossier or substance evaluation. It also raises the question of how the registrant can be satisfied that it has fully met its duties under REACH.

¹⁴⁴ See paragraphs 17-20 of the Annex.

4 Next steps

4. 1 Overall conclusions

The authors have drawn a number of overall conclusions from the findings presented above:

- The regulatory requirement to include in registration dossiers relevant information on substances with endocrine disrupting properties (as well as any adverse effects) is not being complied with;
- The principle of “no data, no market” has been replaced by the practice of “no registration number, no market”;
- Poor quality dossiers are not compliant with REACH requirements, result in unsafe products being placed on the market and constrain efforts to replace them with safer alternatives;
- Application of a scientifically based "weight of evidence" approach offers the best opportunity to ensure REACH can provide effective regulatory treatment of endocrine disrupting chemicals and would enable a more informed, holistic and precautionary assessment to be made of information included in the dossiers;¹⁴⁵
- The focus by registrants on recording compliance with GLP reporting standards deflects attention and effort from substantive ways to address the adverse impacts of endocrine disrupting chemicals;
- Widespread use of Klimisch categories "three" and "four" suggest that a number of relevant studies are not taken into account by registrants because it is easier to assign these categories than review for substantive content;
- A limited percentage of compliance checks conducted by ECHA does not seem to have had the effect of improving dossier quality overall;
- There is, currently, a lack of an effective regulatory action to ensure the necessary quality of information included in dossiers; urging registrants to improve the quality of dossiers and reminding them of updating obligations is not sufficient and reliance on the compliance check procedure has too limited an impact.

¹⁴⁵ Evans, R. Faust, M., Kortenkamp, A., Martin, O., McKinlay, R., Rosivats, E., 2011 State of the Art Assessment of Endocrine Disruptors, Final Report. Project Contract Number 070307/2009/550687/SER/D3.

4. 2 Opportunities for action

The opportunities for action by different stakeholders to address these issues fall into two main areas:

- Using mechanisms to hold registrants accountable for the identification of the known or suspected endocrine disrupting properties of a substance they are registering; recognition and recording of “known unknowns”; their assessment for inclusion (or non-inclusion) in Annex XIV and the contents of dossiers prepared for such chemicals, and;
- Ensuring regulators take a proactive and pre-emptive approach to regulation of endocrine disrupting chemicals.¹⁴⁶

4. 3 Holding registrants to account

One of the key objectives of REACH was to move away from detailed, interminably slow regulatory micro-management of the use of chemical substances (paralysis by analysis) and put the responsibility and burden on industry to prove that only safe substances are placed on the market. With that change also comes a significant responsibility for industry to fully observe and support the critical “no data, no market” principle. The operation of the REACH regulatory system means that, for the most part, once a registration number is obtained for a substance, market access is secured. The significance of getting initial registration right is, therefore, of utmost importance.

Specific rules are, of course, applied to SVHCs as a category of substances meriting closer regulatory attention and control. The operation of CoRAP and the candidate list go some way to focussing attention on particular substances. However, these mechanisms do not remove the core responsibility of a registrant to prepare dossiers with available, relevant, reliable and adequate information, for all purposes, including the identification of SVHCs and any subsequent regulatory evaluation of substances and dossiers.

After registration, the requirement that ECHA carries out compliance checks on at least 5% of registration dossiers means that, given limited available resources, there is insufficient opportunity for detailed investigation of the contents and compilation of a dossier. In their report on ECHA,¹⁴⁷ EEB and ClientEarth identified concerns about inadequate dossiers and only very recently has ECHA decided to pursue the possibility of withdrawal of a registration number.

It is recognised that ECHA is not empowered to investigate generally whether registrants have included “all available information” in the registration dossiers or engage in detailed research (e.g. literature reviews), but can ask for further information when carrying out a compliance check.

¹⁴⁶ Which ECHA confirms is the aim of its annual evaluation reports under Article 54, REACH.

¹⁴⁷ EEB and ClientEarth “Identifying the bottlenecks in REACH Implementation: the role of ECHA in REACH’s failing implementation”. October 2012.
<http://www.eeb.org/EEB/?LinkServID=53B19853-5056-B741-DB6B33B4D1318340>

On the other hand, it is possible for Member States' competent authorities to check compliance with REACH provisions and to apply penalties for flawed registrations. Despite this, there is no evidence that a chemical has been withdrawn from the market or penalties applied by reason of non-compliance with the information requirements of REACH.

Where action is proposed and/or taken by regulators, then it is critically important that there is full transparency and discussion of the issues addressed and the outcome of regulatory action.

However, prevention is generally better than cure. The authors suggest that all aspects of registration documentation (not just parts of the CSR) could be underwritten by declarations by senior authorised corporate representatives. These declarations should reference the process undertaken to compile and complete a registration dossier and the procedures in place to ensure any subsequent changes or amendments necessary to reflect current scientific research. Mechanisms could be developed which would provide a greater incentive for registrants to submit substantively high quality dossiers at the time of registration so that registrants are not relying on the risk of being subject to subsequent regulatory enforcement action.

4.4 Proactive and pre-emptive approach to regulation of endocrine disrupting chemicals

It is becoming increasingly unacceptable for regulatory bodies to ignore the growing body of scientific evidence and concern within civil society regarding the adverse impacts of endocrine disrupting chemicals on human health and the environment. This applies to all regulatory bodies at both an EU and Member State level, regardless of their different competences.

All regulators should publicly acknowledge that endocrine disrupting chemicals do not fit the mould of chemicals regulation to date. There is no point in using inappropriate test methods, assessment strategies or regulatory procedures when there is appropriate capability within regulatory authorities to secure updates.¹⁴⁸

The EU Commission must move on from the research/information gathering mode of its 1999 Endocrine Disrupting Chemical strategy¹⁴⁹ and use the recommendations of the State of the Art Report which it commissioned (as endorsed by the latest UNEP/WHO report to 'answer policy relevant questions'¹⁵⁰). The need for a different approach is fundamental and goes beyond the SVHC debate. Acknowledgment of the validity of the methodology behind the SIN 2.0 list for endocrine disrupting chemicals would be a minimum first step.

ECHA should remind registrants of substances included in the SIN 2.0 list as endocrine disrupting chemicals of the full scope of registration requirements and continue to prompt them to review and update their dossiers, particularly where new information and research on endocrine disrupting properties is appearing with increasing regularity.

¹⁴⁸ The scientific expertise required for the updating of test methods, assessment strategies and regulatory procedures already exists in the form of the SETAC Global Advisory Group on Endocrine Disruptor Testing and Risk Assessment.

¹⁴⁹ The EU Commission has indicated that it will move past the information gathering mode in its Staff Working Paper on the 4th Report on the 'Community Strategy for Endocrine Disruptors'. At page 16 it notes that 'it will review the present EU strategy and if appropriate adopt a revision'.

¹⁵⁰ EU Commission Staff Working Paper on the 4th Report on the 'Community Strategy for Endocrine Disruptors', page 16.

ECHA should also make good use of its multi-stakeholder fora to review and update its different forms of “guidance” where particular characteristics of endocrine disrupting chemicals are not, but could be, fully addressed;¹⁵¹ in particular, an appropriate way to identify and address “known unknowns”. This is needed in addition to new guidance on the interpretation of criteria for identifying endocrine disrupting chemicals currently being developed by the Commission.

Such a group could also work on the formulation of options for establishing scientifically robust mechanisms for operating a regulatory “weight of evidence” approach to collection and assessment of data on endocrine disrupting chemicals. Moreover, it could provide advice on which test methods need to be updated to better address these substances, what new test methods are needed and which should be mandated in different legislative instruments.

Work with other regulators and science bodies, such as OECD EDTA, could be undertaken to establish acceptable testing strategies or protocols, to improve the way reliability is scored to reflect all aspects of a study, not weighted in favour of GLP compliance and to provide clarification of use of scoring mechanics and reporting.

It would be useful for ECHA and/or Member States competent authorities to, at least, alert registrants of SIN 2.0 endocrine disrupting chemicals to the data/information requirements which they should observe.

Disclosure of the analytical and review processes used by MSCA for CoRAP reports would assist in clarifying the approaches being used to evaluate endocrine disrupting chemicals.

4. 5 Enforcement authorities

Article 125 of REACH requires Member States to have a system of official controls and other activities as appropriate to the circumstances and according to Article 126, Member States must set penalties for the infringement of the provisions of REACH. The results of the inspections must be included in the report that Member States have to submit to the European Commission. However, these reports do not specify if, in cases of non-compliance, penalties have been applied.¹⁵²

The registration dossiers analysed in the project fail to comply with a number of enforceable provisions under Title II of REACH, in particular the requirement to include in the technical dossier all physicochemical, toxicological and ecotoxicological information that is relevant and available to the registrant (Article 12(1)). Further, the requirements to keep the CSR up to date (Article 14(7)) and the obligation to update the registration whenever needed (Article 22(1)) may not have been observed.

Member States' penalties specifically address the breach of Article 12(1) provisions only in certain countries (e.g. Italy, France), but other countries (e.g. UK, Belgium, Netherlands) do not

¹⁵¹ Including formal “Guidance documents” which can be considered under the existing Guidance Consultation Procedure as well as practical guides or other explanatory material prepared by ECHA.

¹⁵² Results of inspections between 2007 and 2010 can be found here: http://ec.europa.eu/environment/chemicals/reach/art_117_en.html

address the requirement to include relevant and available information in the registration dossier. However, all Member States provide for penalties for breaching Article 22(1) (e) of REACH which requires the registrant to update their registration dossier with new knowledge of the risks of the substance to human health and/or the environment which may lead to changes in the safety data sheet or the CSR.

Therefore, the EU strategy on endocrine disruptors should also push for enforcement authorities to check that the registration dossiers include the information available on the endocrine disrupting properties of substances in the EU market, particularly those in the EU priority list of endocrine disrupting substances.

4.6 Transparency of information

Transparency of information is essential in order to fully assess the operation of the registration process under REACH and the operation of the principle of “no data, no market”. In particular, information on the provenance of studies relied on in a registration dossier – e.g. authors, title, date of publication - should be accessible.

Also, as required by REACH, a clear explanation should be provided as justification for waiving or omitting information from a dossier.¹⁵³

¹⁵³ ECHA’s view is that this cannot be done because the justifications **may** contain confidential business information.

5 Concluding remarks

This report makes clear recommendations for holding registrants to account and for taking a proactive and pre-emptive approach to regulation of endocrine disrupting chemicals. The recommendations for action are based on conclusions from findings following the examination of toxicological information contained in dossiers for five endocrine disrupting chemicals. Information in the dossiers and the literature was examined through the prism of four key questions. Together with a weight of evidence approach, the questions addressed key concepts under REACH: availability, relevance, reliability and adequacy of information on the endocrine disrupting properties of the substance.

This report's recommendations are made with the objective of realising the potential of REACH to regulate endocrine disrupting chemicals without the need to revise the text of the legislation itself. As such, the authors believe they are recommendations which can be acted on immediately. Realising the potential REACH has to regulate endocrine disrupting chemicals is the shared responsibility of registrants, the European Commission, ECHA and MSCAs. They are intended to capitalise on the regulatory and scientific resources that are already available. What is needed is both the will of the regulator to use them and clear acceptance of responsibility by registrants of data required for market access.

Annex

Objectives and methodology

Introduction

1. The objective of this project was to compare information publicly available in ECHA's online database regarding substances registered under REACH which are known to have endocrine disrupting properties with the information requirements of the REACH registration process. For this purpose, two streams of research and evaluation were developed. The first was to carry out a scientific literature search on specific substances and to compare the results with the dossier information which was available online. The second was to develop a framework within which to analyse the information requirements of the REACH registration process. For each substance, the existing literature was reviewed and the publicly available information about the registration technical dossier examined in light of the registrant's legal obligations under REACH.

Substance selection

2. A number of substances were identified for possible consideration on the basis of whether they met the following conditions:
 - Are included in the SIN List 2.0 either as substances of equivalent concern or as a reproductive toxicant or more specifically, solely due to their endocrine disrupting properties;
 - For which a registration dossier has been submitted under REACH;
 - Can be found within one of five widely used applications in consumer products (ultraviolet (UV) filters; preservatives; adjuvants (emulsifiers, stabilisers, surfactants, dispersal and wetting agents etc.); plasticisers and plastic intermediates; and flame retardants) where potential exposure is faced by vulnerable receptors.
 - Further criteria were used to reduce the number of substances which could be studied. The additional factors considered were whether:
 - The substance is a high production volume (HPV) chemical;
 - It is included in the Community Rolling Action Plan (CoRAP) list for REACH evaluation;
 - And to what extent, the substance is subject to regulatory controls apart from REACH;
 - They are likely to present the risk of wide dispersal during use.

3. A final short list was established comprising the following five substances: diethyl phthalate (DEP), bisphenol A (BPA), triclosan, 2-ethylhexyl 4-methoxycinnamate (OMC) and tetrabromobisphenol A (TBBPA). These substances reflected the broad range of use categories considered to be most relevant to the scope of the inquiry, namely: a plasticiser (DEP); an adjuvant (BPA, DEP); a flame retardant (TBBPA); a UV filter (OMC); and a preservative (triclosan).

REACH registration requirements

4. Under REACH, a number of requirements are applied in relation to registration of a substance. When analysing the legal obligations of the registrant under REACH, ECHA guidance was consulted alongside the legal text of the regulation. The guidance has been created as a tool to assist registrants in meeting their legal obligations. It reflects ECHA's interpretation of the legal text and of ECHA's duties under REACH. In conducting the research and analysis, the assumption was made that registrants of the dossiers would take account of ECHA's interpretation of the legal text to assist them in meeting their legal obligations. Extracts from both the guidance and the legal text have been presented in order to indicate what, in our view, can be expected of the registrant in order to be REACH compliant.

Availability

5. The registrant must provide all available and relevant information on the substance. In meeting this obligation, the registrant would be expected to gather all existing available test data and collect all other available and relevant information, which should include information from sources other than test studies. To determine what information was available on the endocrine disrupting properties of each of the five substances, a literature search was conducted using the search engine databases: Google Scholar, PubMed, Web of Knowledge and ScienceDirect. The name of the substance (placed in quotation marks to limit the inclusion of articles not relevant to that substance or term, e.g. 'diethyl phthalate' rather than diethyl phthalate to exclude other phthalates or diethyl compounds) plus an additional search term were used to generate available studies.
6. The additional search terms were "endocrine disruptor", "estrogen", "androgen", "neuro*", "immune*", "metabolic syndrome", "corticosteroid" and "adrenal". Some of the searches conducted were endpoint specific (e.g. 'bisphenol A AND prostate') and some were substance specific, which was particularly the case when few studies were available for a substance (e.g. 'triclosan AND endocrine disrupt*'). In addition to conducting searches using the search engines, recent review papers were located. Their reference lists were searched for further relevant articles and used to pinpoint further papers in which studies were reported.

Presentation of information

7. Under REACH, the registrant is required to present the available and relevant information in the technical dossier. A technical dossier must include study summaries and robust study

summaries which are to include information derived from the application of Annexes VII to XI. In addition, these summaries must include all physiochemical, toxicological and ecotoxicological information which is relevant and available to the registrant.

8. A complete robust study summary will provide 'detailed information on the applied methodology, test materials, the study results and conclusions'. In the general instruction for the robust study summary, ECHA's guidance notes that: 'It should also be demonstrated whether specific validity, quality or repeatability criteria for the study have been met as specified in the description of the corresponding (EU or OECD) test method. In the 'Applicant's summary and conclusions' field of the study record endpoint it should be clear 1) whether or not the validity criteria have been fulfilled and 2) which conclusions were derived from the underlying data'.

Relevance

9. Where the registrant has found more than one study 'addressing the same effect, then the study or studies giving rise to the highest concern shall be used to draw a conclusion'. This approach is consistent with the REACH objective to protect human health and the environment and upholds REACH as an iterative process, where the identification of hazards and risks depends on the accurate presentation of the properties of a substance.
10. The REACH legal text does not provide a specific definition of "relevance". However, ECHA guidance interprets relevance as 'covering the extent to which data and tests are appropriate for a particular hazard identification or risk characterisation', and lists aspects of a study that could be considered when assessing its relevance:
 - 'Was the substance tested representative for the substance as being registered?
 - Has the appropriate species been studied?
 - Is the route of exposure relevant for the population?
 - Were appropriate doses/concentrations tested?
 - Were the critical parameters influencing the endpoint considered adequately?

Approach taken for research and analysis

11. When assessing the relevance of available information for the five substances, the information considered appropriate for hazard identification or risk characterisation of the endocrine disrupting properties of each substance was information which could be used to identify endocrine disrupting mediated changes. This led to a more focussed and detailed set of questions being asked for the purpose of assessing the relevance of available information. A weight of evidence approach was used in order to increase the range of sources to be used and the following questions related to “relevance” were included:

- Endocrine disrupting effects recorded, (neurodevelopment, reproductivity, development and function of the adrenal and thyroid glands);
- Whether the substance had toxic effects to one or more organs or systems in the body at doses which perturbed the endocrine system;
- Route of exposure;
- Concentrations tested;
- Controls used (positive or negative);
- Endocrine and non-endocrine disrupting endpoints examined;
- Endocrine modalities covered;
- Sensitive developmental stages covered;
- Test material used;
- Dose level;
- The lowest doses at which endocrine disrupting relevant changes took place;
- Species of animal used in testing;
- Whether the studies had been or could be used to derive NOAELs; and
- The effects levels the NOAELs were derived from.

12. In addition to providing all the available and relevant information on a substance, the registrant must ensure that this information is reliable and adequate. A purposive reading of the REACH text provides the legal justification for why the information that is submitted by the registrant needs to be reliable and adequate. Information collected by the registrant and submitted to ECHA needs to be of a quality which enables the regulatory process to function as intended. Under REACH, registration is the foundation of information required

for substance evaluation. Where this information is not reliable or adequate, the evaluation procedure is rendered futile and a whole process and part of REACH is thereby undermined. Moreover, a principal aim of REACH is not achieved. Without adequate and reliable information in the registration dossier, it is impossible to reach meaningful conclusions on the hazardous properties of a substance. Information that is unreliable or inadequate undermines a fundamental purpose of REACH - protection of human health and the environment - and means that the duty placed on manufacturers and importers to ensure that substances placed on the market 'do not adversely affect human health or the environment' may not be fully observed.

Reliability and adequacy

13. Definitions for reliability and adequacy are provided in ECHA Guidance and are re-stated below. The ECHA definitions were used as a guide when examining the quality of information contained in the dossiers and when presenting the findings. It should be noted, however, that although references to 'adequate and reliable' are made in REACH no definitions for 'adequate' and 'reliable' appear in the REACH text itself and so ECHA's interpretation of the concepts need not be considered definitive.
14. According to ECHA Guidance, 'the evaluation of data quality includes assessment of adequacy of the information for hazard/risk assessment and, furthermore, the two basic elements of relevance and reliability'. The definition for relevance has been provided above; ECHA Guidance defines "reliability" and "adequacy" as:

Reliability – "evaluating the inherent quality of a test report or publication relating to preferably standardised methodology and the way the experimental procedure and results are described to give evidence of the clarity and plausibility of the findings. Reliability of data is closely linked to the reliability of the test method used to generate the data".

Adequacy – "defining the usefulness of data for hazard/risk assessment purposes. Where there is more than one study for each end point, the greatest weight is attached to the studies that are most relevant and reliable. For each endpoint, robust summaries need to be prepared for the key studies."

15. On reliability, ECHA guidance indicates that 'the quality of the study, the method, the reporting of the results, and the conclusions that are drawn, must be evaluated carefully'. ECHA Guidance also notes that: 'Reasons why existing study data may vary in quality include the use of outdated test guidelines, the failure to characterise the test substance properly (in terms of purity, physical characteristics, etc.), the use of crude techniques/procedures that have since become refined, and the fact that certain endpoint information, now recognised as being important, may have not been recorded or measured. Moreover, other reasons could be poor reporting of information and poor quality assurance.'

16. In addition, the guidance introduces the Klimisch scoring system as a tool for the registrant to rank the studies for reliability. This system ranks reliability of a study on a scale of “one” to “four”. “one”, indicates that a study is “reliable with no restrictions”; “two”, that it is “reliable with restrictions”; “three”, that it is “not reliable”; and “four”, there are “insufficient data to assign it a category”.

Approach taken for research and analysis in this report

17. The ECHA guidance was not considered exclusively in assessing reliability and adequacy. Our emphasis was placed on the possible pertinence of the data for specific endocrine disruption endpoints, taking into account the following:

- Reliability of a study was not judged with preference to those studies that had complied with GLP or which had followed international or national test guidelines; studies that had followed GLP and/or international/national test guidelines were given equal weight to those that had been peer-reviewed and conducted according to other rigorous standards;
- Whether the study complied with GLP or an equally rigorous laboratory practice procedure;
- The funding entity; and
- How recently the study was reported.

18. When assessing the reliability of the available studies for each substance, the Klimisch scoring system was not used to give a ranking on reliability. Ranking study reliability using the Klimisch scoring assigns highest reliability scores to GLP studies or those which are equivalent to GLP. When assessing reliability of the available studies, preference was not afforded to GLP studies or studies which had followed international or national test guidelines. The approach taken for the analysis recognises that, if non-GLP studies are well-documented, peer-reviewed and conducted according to other rigorous standards, there is no reason for their findings to be assigned a lower reliability status than GLP studies. Moreover, non-GLP studies have a significant part to play in the evaluation of evidence on the adverse effects of substances with endocrine disrupting properties. Whilst GLP studies are well-documented and validated according to strict scientific guidelines, GLP is an accreditation tracking system and offers no guarantee that test protocols used are fit for purpose. For example, to detect endocrine disrupting properties, testing is required at low doses; effects on sensitive developmental stages and development endpoints vulnerable to the actions of endocrine disrupting chemicals need to be covered, including endpoints other than those involving estrogen, androgens and thyroid hormones. If these factors are not taken into account, then the reliability or adequacy of the studies cannot be assured, no matter how well they have been documented.

19. Other factors that were taken into account when assessing the reliability of studies for evidence of adverse effects of endocrine disrupting chemicals included the funding entity and how recently the study was reported. The funding source can be an indication of a study's quality or credibility. The funding entity may also play a key role in establishing the quality standards to be used in a study. For example, the proposal and methodology of a study funded by the US National Institute of Health undergo two rounds of peer review to ensure funding objectives are met and that the study is scientifically sound. In addition, public health service policies on research misconduct must be adhered to. This requires detailed documentation of the research undertaken and data retained.
20. The year in which the study is reported was also a factor considered when assessing reliability. The rationale is that the older the study, the greater the risk that it has used out-dated test methods or followed out-dated test guidelines and practices. Given: the amount of literature produced on the effects of endocrine disrupting chemicals since 2000; the fast-moving pace of research in environmental toxicology generally; the fact that recent studies better reflect current knowledge, and are more likely to contain endpoints or to use methodologies that enable endocrine disruption to be identified, the year of publication is a significant indicator of reliability for studies on endocrine disrupting chemicals.
21. On adequacy, ECHA guidance focuses on utility of data 'for hazard/risk assessment purposes'. In doing so, the focus of ECHA guidance is on the need for the information to enable the registrant to determine the substance's classification and labelling as well as the DNEL/PNEC values for the substance.
22. The approach taken to assess the adequacy of available information, as well as the adequacy of information contained in the registration dossiers for the five substances studied, focussed on whether the information in the dossier enabled the identification of potential endocrine disrupting effects of the substance. As part of this approach, the first three of the five categories (definitive, adjunct, and screening) for hazard assessment according to the OECD guidance document on the validation and international acceptance of new and updated test methods for hazard assessment were taken into account. The other two categories, replacement test methods and test batteries were not deemed relevant since, as referred to in the guidance document, in a strict sense, only the first three categories are actually categories of test method. The other two deal with testing strategies and any test method in the first three categories can be a replacement test method and/or part of a test battery.
23. When assessing the adequacy of available information on the substance, the ability to derive the DNEL/PNEC values was not considered to be of primary importance because these values are required for the management of risk, whereas the registration stage of REACH is concerned with the presence or absence of hazardous properties. The focus of this report is on the information contemplated by Article 10(a) of REACH which has a critical impact on all stages of the registration and evaluation process. In addition, Kortenkamp *et al.* observe that "experts increasingly question the current dichotomy in risk assessment, which deals with non-carcinogens by assuming thresholds... [and so]... it has been proposed to put this dichotomy aside and to deal with pollutants in a uniform manner where threshold-independent action can also be assumed for non-carcinogens'. In the context of

this approach and the increasing focus of scientific inquiry on the low dose effects and non-monotonic dose-response relationship seen for endocrine disrupting chemicals, we took the view that there is little to be gained from using derived thresholds as an indicator of adequacy of information included in a dossier.

24. The reliability and adequacy of information was assessed using a weight of evidence approach. A weight of evidence approach is required for the assessment of the effects of endocrine disrupting chemicals because the available evidence on their harmful effects exists in the conclusions and findings of studies which are not necessarily standard toxicological animal tests. Whilst ECHA practical guidance exists for a weight of evidence approach, the overall emphasis of ECHA guidance is placed on the use of the standard toxicological animal tests and the subsequent identification of key studies.

Analytical framework

25. In light of the key characteristics which apply to the information on a substance registered under REACH, the review and analysis of the detailed scientific evaluation of the dossiers for the selected substances was restructured around the following four questions:
 1. Is there available and relevant information on the endocrine disrupting properties of the substance that has not been included in the dossier?
 2. Is the information in the dossier relevant for assessing endocrine disrupting properties of the substance?
 3. Is the information in the dossier reliable for assessing endocrine disrupting properties of the substance?
 4. Is the information in the dossier adequate for assessing endocrine disrupting properties of the substance?

Elizabeth Hiester
Senior Lawyer
ClientEarth
t +44 20 7749 5970
e ehiester@clientearth.org
www.clientearth.org

Vito Buonsante
Lawyer/Juriste
ClientEarth
t +32 2 808 34 65
e vbuonsante@clientearth.org
www.clientearth.org

Rosemary Simpson
Researcher
ClientEarth
www.clientearth.org

Rebecca McKinlay
Research Associate
ClientEarth
www.clientearth.org

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Brussels

4ème Etage
36 Avenue de Tervueren
Bruxelles 1040
Belgium

London

274 Richmond Road
London
E8 3QW
UK

Warsaw

Aleje Ujazdowskie 39/4
00-540 Warszawa
Poland