Guidance for Effective Use of Human Exposure Data in Risk Assessment of Chemicals

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EUROPEAN CENTRE FOR ECOTOXICOLOGY AND TOXICOLOGY OF CHEMICALS

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SUMMARY

This report details much of the current state-of-the-art of consumer exposure assessment data and models that can be used in chemical risk assessment, with a particular focus upon aggregate exposure assessment. Aggregate exposure considers all sources of exposure to a single chemical (e.g. hair care products, cosmetics, detergents, foods, environmental media, etc.) via all routes (oral, dermal, and inhalation). The report focuses on consumer products (not including the assessment of occupational exposure), considering the following product domains: cosmetics and personal care products, household products, food and other consumer products (such as surface coatings, adhesives, sealants, disinfectants, automotive care products, toys etc.).

Exposure assessment is, by necessity, an iterative process. If, in any tier, negligible or acceptable risk cannot be demonstrated, the assessment moves to a higher tier. The risk assessment is finished if (in any tier of the approach) it has been demonstrated that the risk for the population under consideration is negligible or acceptable, or if in the highest tier the risk is not acceptable and further refinements are not possible. This approach was proposed in the WHO/IPCS framework for risk assessment of combined exposure to multiple chemicals (Meek et al, 2011).

The report is divided into four sections.

Section One gives background on the tiered approach to exposure assessment, including aggregate exposure assessment in the consumer product domains.

Section Two provides an overview of the current exposure landscape, detailing the main data sources, models and tools that are available for chemical risk assessment in the food, cosmetics, household, and consumer products domains. Conclusions and recommendations on current opportunities for the development and provision of new tools and data are also presented based on the outcome of this landscaping exercise. This section is accompanied by a detailed spreadsheet referencing all identified data sources and tools identified for chemical exposure assessment.

Section Three presents examples of case studies of aggregate exposure to the chemicals triclosan and phenoxyethanol (PhE), outlining how current models and data can be best used for higher-tier exposure assessments. In addition, there is a literature review of the broader domain of aggregate exposure assessment, detailing other examples and approaches that exist for aggregate exposure assessment.

Section Four contains discussion and conclusions on areas of opportunity for exposure science over the next two to five years.

The key conclusions of this report are summarised as follows:

- Exposure assessments should involve an iterative process, and should be conducted using a tiered strategy, where the lowest tier (0) involves a semi-quantitative assessment of the all sources, pathways and routes contributing to aggregate exposure to a substance, the mid-tier (1) tends to be a deterministic estimate with conservative assumptions, the higher tier (2) is a more realistic estimation of population exposure with increased use of measured data using probabilistic methods,

and at the highest tier (3) exposure is modelled with a person-orientated approach using raw data sets.

- Many tools and databases exist to support consumer exposure assessment, as demonstrated in the landscaping effort. Users can select the data and tools that best fit their specific situation and level of assessment.

- Most consumer exposures tools are designed to evaluate single substance, single use assessments.

- Higher tier exposure assessments require more realistic and representative data to the situation being assessed and additional understanding of data correlations.

- Subject oriented aggregate tools (PACEM, Creme Care & Cosmetics) are available that allow aggregate exposure assessment within some consumer product domains. For example, in cosmetics and personal care products, the availability of robust tools and data sets (habits and practices data with product co-use, and the use of presence probabilities) allow refined estimates of aggregate exposure.

- A major challenge in estimating aggregate exposure in many product categories is obtaining representative information on exposure factors (Habits and Practices Data, Co-use Data, Chemical Concentration Data and Chemical Occurrence Data), as well as potential correlations between these factors. For some domains, such as household care products, the available data are limited.

- Guidance should be developed to indicate when higher tier aggregate assessments might be a priority. Considerations include relative contributions of different sources, level of conservatism in a screening single source assessment (for example, the case study indicates a higher tier aggregate assessment may produce a lower exposure estimate than the maximum screening exposure predicted for a single uses), and total exposure levels from representative biomonitoring studies.

- Model verification with real-life data (e.g. biomonitoring) on a representative range of chemicals would assist to promote use/acceptance of exposure model predictions.

Wider engagement of industry, the public and regulators into the generation, harmonisation and management of input data related to consumer exposure will foster the advances in aggregate exposure modelling, especially in domains where currently little data are available.

1. INTRODUCTION

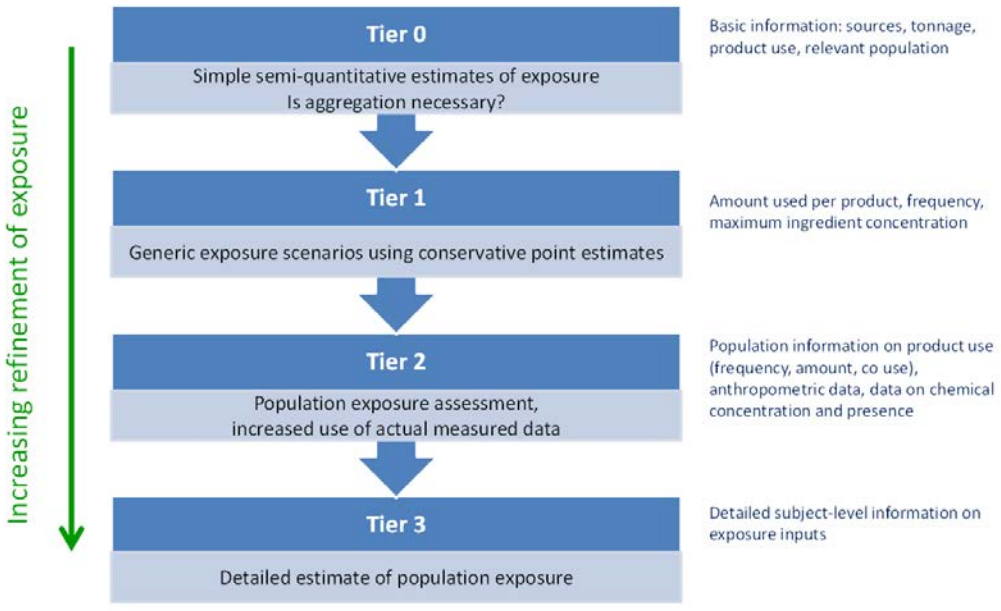
1.1 Background

A Tiered Approach

Exposure assessment is, by necessity, an iterative process. It has been recommended that assessing aggregate exposure should be a tiered approach (Delmaar JE and van Engelen JGM, 2006; Meek et al, 2011), where the lowest tier (0) consists of a rough sum (qualitative or semi-quantitative estimate) of exposure from each product, the mid-tier (1) tends to be a more quantitative estimate, such as a deterministic estimate with conservative assumptions, and the highest tiers (2 & 3) provide more realistic estimations of population exposure, modelled using probabilistic methods and person-orientated approaches, using more detailed exposure input data, such as population distributions or even raw data sets (usually at Tier 3). The rough or low tier estimates can be calculated quickly, often using default assumptions on inputs, yielding conservative exposure values, and if this approach is lower than the "safe" exposure threshold, then it may not be necessary to move to a higher tier. While exposure assessments at the highest tiers (2 & 3) will be data-intensive and often time consuming, they produce more refined and accurate estimates of population exposure, enabling the risk assessor to feel confident that the risk assessment is applicable to the population of interest.

The World Health Organization/International Programme on Chemical Safety (WHO/IPCS) held a workshop on Aggregate/Cumulative Risk Assessment in 2007, that led to development of an iterative framework that adopts the tiered approach for both exposure and hazard assessment (Meek et al, 2011). The exposure portion of this framework is shown in Figure 1**.** This framework is designed to aid risk assessors in identifying priorities for risk management.

Figure 1: Summary of the exposure component of the framework for tiered exposure and hazard assessment as proposed by Meek et al, 2011.



Humans are exposed to chemicals that originate from many sources, including indirect exposures via contact with environmental media (e.g. air, water) and direct exposures via food that is consumed, and consumer products used (e.g. household products, electronics, construction materials, cosmetics, textiles). Assessments of human exposure to chemicals may be conducted for different reasons and with different objectives, e.g. to get an estimate of the maximal level of a chemical to which the general population can be safely exposed or to obtain a detailed insight into the distribution of exposure within sub populations. One of the challenges in (regulatory) risk assessment is the estimation of aggregate human exposure originating from a variety of exposure sources often associated with the use of different products and possibly also different exposure routes. Examples of situations where aggregate exposure might be important to consider include the exposure to a chemical that was both a fragrance in cosmetic and household cleaning products and a flavour ingredient consumed in food. Another possible example is the exposure to a phthalate plasticiser via food, building materials and toys.

1.1.1 Aggregate Exposure

Aggregate exposure considers all sources of exposure to a single chemical (e.g. hair care products, cosmetics, detergents, foods, environmental media, etc.) via all routes (oral, dermal, and inhalation). The report focuses on consumer products, and not occupational exposure situations, including the following product domains: cosmetics and personal care products, household products (such as household cleaning products, laundry and dishwashing products, etc.), food and other consumer products (such as surface coatings, adhesives, sealants, disinfectants, automotive care products, toys etc.).

This report identifies sources of exposure data to consumer products, and tools for use in generating exposure estimates. It then focuses on more complex cases where an aggregate exposure assessment is useful, and investigates how this can be done using the new tools that are available. Aggregate exposure assessment may be important to consider when substances are present in a variety of products to which consumers might be regularly exposed.

Consumer exposure assessment covers the general use of household items. Assessments may be done for a general population or a subpopulation, for example a specific age, sex, or state of health. The chemical may be a directly added ingredient in a consumer product, or it may be present as residue in another ingredient. At the high tier, aggregate exposure assessments can be quite complex, due to the wide variety of consumer product types and formulations, and a variation in the behaviour patterns of consumers in populations. For many categories of consumer products representative exposure data including habits and practices data (frequency and amount) as well as chemical formulation data, are generally not available. In these circumstances, exposure assessors rely upon using worse case exposure assumptions or are faced with the need for generating new data.

Currently aggregate exposure is often assessed by simply adding up worst case exposure estimates per each exposure scenario, likely leading to unrealistically high and conservative estimates of exposures. Several consumer exposure models capable of aggregate exposure estimates have been developed in the past for specific areas of consumer exposures and are currently available to assist in exposure modelling, particularly

for cosmetics and personal care products (C&PCPs), e.g. ConsExpov.5.0[1] (Delmaar et al, 2005), Creme Care & Cosmetics™ (Creme Global, 2011[2]), Lifeline (The Lifeline Group[3]), Cumulative and Aggregate Risk Evaluation System – Next Generation (CARES NG, 2016[4]) and Stochastic Human Exposure and Dose Simulation or SHEDS (US EPA, 2015[5]). However, guidance is required as to how to perform aggregate exposure estimates, particularly at the higher tier when refinement is required.

Several publications have suggested methods for assessing aggregate exposure leading to more realistic worst case estimates. One example is a publication by Cowan-Ellsberry and Robison (2009), describing an approach for refining aggregate exposure estimates using data on 1) co-use and non-use patterns of product use, 2) extent of products in which the ingredient is used and 3) dermal penetration and metabolism data. Also, CEFIC-LRI completed a project on the estimation of realistic consumer exposure to substances from multiple sources and approaches to validation of exposure models. This involved developing a tiered approach to aggregate exposure assessment including the compilation of a computational platform, able to perform quantitative aggregate exposure assessments for environmental and consumer products, including case studies on decamethylcyclopentasiloxane (D5) and triclosan. The project is documented in an internal CEFIC report, and the case study on D5 is published in Dudzina et al, (2015).

Given these recent methodological developments in assessing aggregate exposure and increasing variety of tools and databases available for different purposes in exposure assessment, the ECETOC Scientific Committee established a task force to identify best practices and provide guidance with respect to the data and methods that might best be applied for different consumer exposure scenarios.

1.2 Scope of this project

This project provides exposure assessors with a review of available exposure data sources and guidance on how to incorporate data inputs for high tier aggregate exposure assessment for situations where aggregate exposure is considered relevant.

The report addresses:

- An overview of the current human consumer exposure landscape, which includes currently available databases and tools
- Opportunities to develop and gather exposure data related to specific product categories.
- Aggregate exposure assessment (how to combine multiple sources and routes of exposure) including case study examples for phenoxyethanol and triclosan

[1] Available at http://consexpo.nl/

[2] Creme Care & Cosmetics: Aggregate Exposure from Real Consumer Data. Available from http://www.cremeglobal.com/products/cosmetics/

[3] LifeLine Software Suite and Compendia available from http://www.thelifelinegroup.org/

[4] Available from http://caresng.org/

[5] Available at http://www2.epa.gov/chemical-research/stochastic-human-exposure-and-dose-simulation-sheds-estimate-human-exposure

- A proposed approach for understanding if overall exposure may be dominated by few or many sources to focus any further efforts on those of more importance.

Note: In the following, aggregate exposure is defined as combined exposure to a single chemical from multiple sources and pathways. This is distinct from cumulative exposure, which is taken to be defined as exposure to multiple chemicals from multiple sources and pathways.

2. LANDSCAPING EXERCISE AND GAP ANALYSIS

2.1 The Exposure Landscape: Databases and Tools

In order to conduct an exposure assessment for a chemical in any domain, two essential inputs are needed. The first is an algorithm (exposure scenario) with which to calculate an estimate of exposure, the form of which usually depends upon the source and route of exposure being considered. These range from low tier assessments involving simple deterministic calculations involving a single chemical, source, and route, to sophisticated high tier models involving multiple routes, sources and even multiple chemicals if mixtures are being considered. Once the appropriate model is decided upon the second essential is having suitable input data typically taking the form of exposure factors (exposure scenario parameters, consumer habits and practices, transfer coefficients etc.) and chemical concentration data (the frequency and level of chemical occurrence in the source of exposure).

While certain tools and databases have become standard practice in certain domains, a challenge still facing the risk assessor is knowing what model and data source to select for a given exposure assessment. Given the number of models and databases that are currently available, it is desirable to have a central location detailing and documenting these. The landscaping exercise presented in this section is not intended to be exhaustive or a systematic review of the available exposure tools and databases, rather it is an overview of what are considered to be the most commonly used and most useful sources for key consumer products as determined by the task force. The exercise is divided into two categories, data sources and tools.

To help the risk assessor decide what is useful or relevant amongst the available options the data are categorised into: Exposure Algorithms, Habits and Practices Data, Co-use Data, Chemical Occurrence Data, and Chemical Occurrence Data. The source or original reference is provided, as well as some details on the nature of the data. Within the section on tools, a number of additional headings are provided: Product Category, Type of Assessment that can be Performed, Built-in Data/Data Requirements, Regions Covered, Modelling Capabilities, Routes of Exposure Covered, Availability, Occupational or Consumer, and additional Comments. The information in the overview is, in most cases, based upon the experience of users in the task force or on publicly available information from websites or reports describing the listed tools and databases. This task force did not perform an in-depth review or test all the different sources listed and also was not always able to verify the data or information provided. That said, the Landscaping Database is an excellent starting point for selecting relevant tools and databases that are currently available.

It is hoped this effort will constitute the beginnings of a centralised database that will be added to and updated in the future, providing a resource risk assessors can draw from when undertaking an exposure assessment. In the following section, some discussion is provided on the different domains, while the full details of the landscaping exercise are provided in the appendix.

2.1.1 Cosmetics

In Europe, robust habits and practices data exist in the adult population for the common cosmetic products (including personal care products) covering the majority of daily exposure (Hall et al, 2007, Hall et al, 2011), which are published, together with other estimated values, in the SCCS's Notes for Guidance for the Testing of Cosmetic Ingredients and their Safety Evaluation (SCCS, 2012). This document also details the exposure scenarios and equations for calculating the daily exposure to chemicals. Other key published data sources include Loretz et al, (2005, 2006, 2008) providing frequency and amount data in the US adult population, and Biesterbos et al, (2013) providing the same in a Dutch population.

For aggregate exposure estimates, while in general there is agreement that tiered approach should be used (Delmaar JE and van Engelen JGM, 2006; Meek et al, 2011), which begins with a rough deterministic estimation of exposure and evolves to a more complex person-orientated probabilistic approach, to date there is no agreed methodology on the way to approach this. For cosmetic ingredients, aggregate exposure is estimated using a simplistic approach of adding deterministic exposures from all the individual product types in which the chemical might be present (SCCS, 2012). This is referred to as a low tier (tier 1), and provides a rough and very conservative estimation, since it assumes that everybody in the population uses all the products containing the chemical (at the maximum allowed concentration) every day. This has been regularly used in the past for cosmetic ingredient risk assessments for preservatives (SCCS, 2012). When these aggregate exposure estimates are used to calculate acceptable "safe levels" and/or conduct quantitative human risk assessments they result in overly conservative risk assessments. Thus, there is a need to use methods that are capable of producing refined, realistic aggregate exposure estimations (high tier estimates).

The landscaping exercise revealed two high tier aggregate models for estimating external exposure via different routes. The Research Institute of Fragrance Materials (RIFM) have partnered with Creme Global to build a model called the "Creme RIFM Model" (also available as Creme Care & Cosmetics) that allows estimation of aggregate exposure to fragrance ingredients in cosmetic products in European and US consumers (Comiskey et al, 2015; Safford et al, 2015), and the National Institute for Public Health and the Environment in the Netherlands (RIVM) have developed a higher tier Probabilistic Aggregate Consumer Exposure Model (PACEM) for ingredients, which contains exposure information for a population in the Netherlands (Dudzina et al, 2015; Manová et al, 2015; Nijkamp et al, 2015).

Aggregate exposure assessment for cosmetic products requires information on the chemical concentration used across product categories. The availability of such data in the public domain is limited as information on specific inclusion values is typically proprietary. Where chemical concentrations are quoted for example, the EPA Chemical/Product Categories Database (CPCat), then ranges are often quoted or maximum inclusion values and data are often only available for a limited number of chemicals in a limited number of products. Alternatively, if the chemical is restricted under regulation, the maximum regulated amount could be assumed as a conservative worse case assumption.

A major challenge in estimating aggregate exposure is obtaining information on how a chemical is used. Understanding how commonly a chemical is used in a cosmetic product, which is known as the chemical occurrence (presence probability) can lead to a significant refinement in the estimated aggregate exposure. Some data can be obtained from market survey databases such as Mintel and Codecheck, which relies on the

mandated ingredient labelling in Europe, although, some systems are not well maintained leading to the availability of out of date information.

A key enabler in the development of realistic aggregate exposure estimates is the incorporation of co-use data. Such data are not available for household products and therefore conservative assumptions are employed such as, all product types containing the chemical are used by the consumer simultaneously.

2.1.2 Foods

Regarding consumer habits and practices, the principle sources of data on food consumption are food consumption surveys, which are designed to be nationally representative datasets on food intake at the individual subject level. These typically use a food coding system specific to the country in question to describe the foods consumed by the population, and can have a number of days surveyed per subject typically varying from one to seven. Because they are designed to capture the variability in diets of consumers, they can readily be used to address the issue of aggregate exposure. While a large number of dietary surveys exist in different countries around the world, a central issue is the availability of the raw data, which for a few notable exceptions (US, UK, Netherlands) cannot be easily obtained. The European Food Safety Authority have taken most dietary surveys in Europe and recoded them into the FoodEx system and made summary statistics of food consumption available online, called the EFSA Comprehensive Database. While a useful source of exposure data, these do not provide the raw data which is required to do refined exposure analysis, both aggregate and cumulative (an increasingly important area for pesticides).

In terms of chemical concentration data, this typically depends on the domain. Regarding the nutrient composition of foods (which may be relevant for risk assessment), these typically accompany the dietary survey. For substances that are part of routine monitoring at a national level by control laboratories (e.g. pesticides and environmental contaminants) or examined by Total Diet Studies, there may be publicly available databases on chemical occurrence that provide representative levels of occurrence (such as the Pesticide Data Program in the US). However, for other food chemicals such as flavourings, additives, food contact materials, and several environmental contaminants, this information is lacking and is frequently required for regulatory purposes. One of the issues with providing refined data here is that is often proprietary, but concentration specific to level of an individual company is not always required – merely an indication of the range of use levels across the market.

Aggregate exposure is a well-established methodology within the food domain, as when considering dietary exposure to any chemical present in food the questions immediately presented are what different foods is the chemical present in and in what amounts. Performing an exposure assessment therefore requires knowledge of how foods are consumed in the diet and in what combinations and amounts across different demographics and geographies, as well as the level of chemical occurrence for those categories.

2.1.3 Household Products

Historically steps have been taken to collate and generate habits and practices data for household products. Information, including amount of product used and frequency of use, for consumer products in Western

Europe were originally identified and developed under the HERA project in 2002 and further complemented with company data and AISE consumer habits surveys in 2009. AISE developed SCEDs (Specific Consumer Exposure Determinants) in line with the DUCC/CONCAWE guidance to facilitate consumer exposure assessment for a range of consumer cleaning and air care products. The purpose of the SCEDs is to provide more realistic and representative data on product use. Exposure information available for 36 cleaning product categories is available from RIVM in the form of a cleaning products fact sheet (Prud'homme de Lodder et al, 2006). In the US, national usage survey data on household products are available from Westat (1987).

Aggregate exposure is not well established for household care products. Where consideration of aggregate exposure is required then a summing approach is usually adopted. The tools and approaches available in the public domain have not been specifically developed for the purposes of estimating aggregate exposure, and therefore the output is conservative.

Aggregate exposure assessment for household products requires information on the chemical concentration used across product categories. The availability of such data in the public domain is limited as information on specific inclusion values is typically proprietary. Where chemical concentrations are quoted for example, Household Products Database, Chemical/Product Categories Database (CPCat) then ranges are often quoted or maximum inclusion values and data are often only available for a limited number of chemicals in a limited number of products.

A major challenge in estimating aggregate exposure is obtaining information on how a chemical is used. Understanding the occurrence of a chemical in household products can lead to a significant refinement in the estimated aggregate exposure. Very limited data can be obtained from market survey databases such as Mintel and Codecheck; however, the available information may not be representative of the market due to a lack of legal obligation to label products. In addition, some systems are not well maintained leading to the availability of out of date information.

A key enabler in the development of realistic aggregate exposure estimates is the incorporation of co-use data. Such data are not publicly available for household products and therefore conservative assumptions are employed such as, all product types containing the chemical are used by the consumer simultaneously.

2.1.4 Chemicals in Other Consumer Products

This section considers chemical exposure from the use of consumer products other than personal care and cosmetic products, household products and foods. These products containing chemicals are used in a large variety of applications. The statutory definition of a consumer product is much broader than just traditional personal care and household cleaning products. It includes all products used in homes, such as surface coatings, adhesives, sealants, disinfectants, automotive care products, toys etc. The landscaping exercise indicated that tools and data are available to support individual product evaluations, particularly at a screening level. For higher tier individual product assessments modelling tools are available, but the level of data for refining the assessment, particularly for parameters that may be considered business confidential such as weight fraction, may be limited.

To our knowledge, limited work has been done on the development of aggregate exposure assessment methodologies and data sources for chemical substances used in consumer products and articles other than cosmetics, food and household care. Most effort in recent years has been dedicated towards development of exposure assessment tools and data that could be used as input for a large amount of chemical risk assessments performed for REACH. These tools (e.g. ECETOC TRA, ConsExpo) and data sources (e.g. RIVM factsheets) generally have two important features: they need to be able to cover a large amount of different chemicals and uses and need to be conservative (reasonable worst case) to ensure the assessments can be performed at a relatively generic level and still provide safe use conditions for the product or contributing activity of use under consideration. The tools generally allow summation of exposure or risk over different exposure routes (oral, dermal and inhalation) within a defined use. None of the main models and tools developed included the ability to assess exposure aggregation over different uses or product categories. The purpose of screening level tools such as TRA is to intentionally develop high end estimates of exposure (low tier assessments), so that if this high end exposure is safe all lower exposures would also be safe. High end exposures are not appropriate for addition because adding up exposures from individual high end scenarios effectively compounds conservatism, quickly resulting in unrealistically high exposure estimates. These values can be too far departed from reality to provide useful information. Tools designed to assess individual scenarios do not contain information on product co-use patterns or data on the market share for specific ingredients, as even within a single product type, the ingredient concentration and presence will vary).

Aggregate exposure assessment for chemicals in consumer products is complex for a number of reasons, including: 1) the consumer product category includes a wide range of substances/products and uses that are in many cases not clearly associated (e.g. fuel and Do-It-Yourself (DIY) products), and co-use patterns have not been identified; 2) a number of product categories like DIY products (coatings, glues) will generally have a very low use frequency, and 3) minimal information is available on formulation of commercial products, making it challenging to estimate how often a consumer may use products that contain a chemical of interest.

Table 1 provides an example of a mapping performed for a REACH chemical safety assessment of all the products and uses for a single chemical substance. The overview illustrates the variety and range of uses many of which occur simultaneously very infrequently. This said, for other product categories this may not necessarily be the case and more information on the likelihood of co-use and thus need for aggregate exposure assessment may be appropriate.

Table 1: Example of a mapping of generic consumer exposure scenarios (GES) and associated uses for a generically used solvent as part of the chemical safety assessment (Source: CEFIC/ESIG GES, v.2012)

Generic exposure scenario	Description of generic exposure scenario	Description of individual consumer uses included in GES
Uses in coating	Covers the use in coatings (paints, inks, adhesives, etc.) including exposures during use (including product transfer and preparation, application by brush, spray by hand or similar methods) and equipment cleaning	Use as: Adhesives, sealants Anti-freeze and de-icing products Biocidal products (e.g. disinfectants, pest control) Coatings and paints, thinners, paint removes Fillers, putties, plasters, modelling clay Finger paints Non-metal-surface treatment products Ink and toners Leather tanning, dye, finishing, impregnation and care products Lubricants, greases, release products Polishes and wax blends Textile dyes, finishing and impregnating products; including bleaches and other processing aid
Use in cleaning agents	Covers general exposures to consumers arising from the use of household products sold as washing and cleaning products, aerosols, coatings, de-icers, lubricants and air care products	Air care products Anti-freeze and de-icing products Biocidal products (e.g. disinfectants, pest control) Coatings and paints, thinners, paint removes Fillers, putties, plasters, modelling clay Finger paints Lubricants, greases, release products Washing and cleaning products (including solvent based products) Welding and soldering products (with flux coatings or flux cores.), flux products
Lubricants	Covers the consumer use of formulated lubricants in closed and open systems including transfer operations, application, operation of engines and similar articles, equipment maintenance and disposal of waste oil	Adhesives, sealants Lubricants, greases, release products Polishes and wax blends
Use in agrochemicals	Covers the consumer use in agrochemicals in liquid and solid forms.	Fertilisers Plant protection products
Use as a fuel	Covers Consumer Uses in Liquid Fuels	Fuels
Functional fluid	Use of sealed items containing functional fluids e.g. transfer oils, hydraulic fluids, refrigerants	Heat transfer fluids Hydraulic fluids
De-icing and anti-icing applications	De-icing of vehicles and similar equipment by spraying	Anti-freeze and de-icing products
Other consumers uses	Covers the use of the substance for the treatment of water in open and closed systems	Perfumes, fragrances Cosmetics, personal care products
Water treatment chemicals		Water softeners Water treatment chemicals

It is clear from the landscaping overview included in this report that for some product categories, like household products, steps have been taken to build relevant databases to better inform exposure assessment. Also in the personal care and cosmetics categories there have been large advances in available data sets (COLIPA exposure studies) and models (CONSEXPO, PACEM and Creme Care & Cosmetics) over the last decade. For other product categories, this is less clear but recent initiatives like SCED's (Specific Consumer Exposure Determinants), will lead to more representative data on use characteristics, and therefore, a more refined exposure assessment. This may in the end also enable assessors to look at aggregation of exposures over different uses.

Some of these key developments are discussed below, with consideration to what extent the available data and tools from other areas can provide information that could be used for chemical products. In addition, insight is provided on key data that needs to be generated to better estimate aggregate exposure. This will be further illustrated by several examples from both chemical products and cosmetics and food.

Current chemical exposure assessment approaches

In the EU, the exposure assessment of chemicals in consumer products is currently primarily driven by the obligations for REACH to provide chemical safety assessments for all substances and substance use in products in the European Union. A useful approach in the development of tools and data has been the assessment of generic exposure scenarios (e.g. covering many specific uses as shown in Table 1) for producing conservative estimates to assure safe use across these generic exposure scenarios. Since it was necessary to assess a large number of chemicals within a relatively short time frame, most assessments were performed using generic conservative tools. Inputs were generally conservative default parameters characterising the Generic Exposure Scenarios (GES). These parameters were defined based on knowledge from producers and downstream users on what would be reasonable worst case situations. An example of this is the extensive development of GES for solvents lead by the solvent trade organisation and several large companies. The solvent GES basically include a complete mapping of all relevant uses and products (both consumer and worker) and they were used to generate exposure assessments with tools like ECETOC TRA. Some of the modelling tools enable the user to conduct a more realistic consumer exposure assessment (e.g. EGRET, ConsExpo) based on the refined default input parameters.

For the assessment of consumer exposure as described above the assessor at least needs information on; 1) the substance properties, 2) the relevant consumer exposure scenarios, 3) conditions of use: general environmental and activity characteristics and risk control measures. This information can be used in one of the standard exposure assessment tools (e.g. ECETOC TRA or EGRET for solvents) to generate exposure estimates for each use and each exposure route.

It is the responsibility of individual companies to ensure the exposure scenarios defined in the chemical safety assessment are actually in line with actual work practices. This is in many cases communicated via the labels on the products and/or accompanying use instructions for consumers.

Current developments

Several activities were identified to improve the information available on consumer use of chemical substances. The scope of these activities is generally to improve the quality of the available data making them

more representative and underpin assumed default values. As mentioned some of these activities may generate data that will also enable or facilitate to some extend aggregate exposure assessments. Below we describe some of the key activities, data sources and models that are being developed.

SCED's

The Specific Consumer Exposure Determinants or SCEDs aim to enable exposure assessors to generate more representative exposure estimates (DUCC/CONCAWE, 2014). SCEDs are being developed by several sector organisations to transparently document the way consumer products are commonly used. The SCEDs document typical conditions of use of consumer products. This information is presented in such a format that can be directly used in commonly applied exposure assessment tools. The data provided by the SCEDs is intended to represent realistic assumptions for consumer exposure scenarios and thus lead to (more) realistic and representative assessments of consumer exposure. SCEDs focus on determinants related to consumer habits and practices (e.g. quantity of product used, frequency of use, place of use, etc.). Although not initiated with aggregate exposure in mind and also not including specific parameters that may be needed for aggregate exposure assessment like co-use, the SCEDs should result in a decrease of the level of conservatism which currently is one of the major obstructions for moving to aggregate exposure assessment.

Each determinant described in the SCEDs needs a reference to information sources that was/were used to define it. The data sources should preferably be open access (published) and peer reviewed. The data should as much as possible be representative to European users. The SCEDs are designed so that the resulting exposure scenario as a whole represents conservative, yet realistic exposure situations. Each individual determinant within a SCED is not necessarily a worst case value. Where habits and practices significantly vary across European countries/regions, then the SCEDs will reflect those areas with the highest uses/exposure conditions.

The SCEDs address use conditions relevant for systemic repeated long term exposure – i.e. they must be reviewed to confirm their relevance for local or acute end points (for example, frequency of use would not be an appropriate factor to modify for an acute assessment):

- They cover the direct uses of consumer products or articles. SCEDs specific to children will only be developed in cases where consumer products are actively marketed for use by children.
- They do not cover accidental exposures.
- They describe the use of a product. It is not substance specific; nevertheless, some limitations may apply depending on the substance properties (for example, handling/containment practices may vary depending upon volatility, such as the case for LPG vs. diesel fuels).

Consumer exposure factsheets

The RIVM General Factsheet has been updated in 2014 (te Biesebeek et al, 2014). The current version retains the defaults for room size (20 m3) and indoor ventilation (0.6 h-1) having included and analysed new available data. The default values for body weight, inhalation rate and exposed skin surface areas have been updated. In addition, the factsheet presents information on the ventilation in houses and includes a new chapter on time activity patterns (i.e. how people spend their time).

In 2015 RIVM initiated the review and update process of their cleaning products fact sheet (Prud'homme de Lodder et al, 2006). After the data compilation phase the new information sourced from large-scale consumer products use studies like EPHECT (Dimitroulopoulou, 2015a,b) will be analysed and compiled into the updated factsheet.

Models

The modelling tools, aimed at understanding aggregate exposure from non-occupational sources, e.g. use of consumer products or due to environmental contamination, are currently being developed. The INTEGRA (Integrated External and Internal Exposure Modelling Platform) computational platform is based on the existing platform developed in the frame of the CEFIC-LRI B4 INTERA and B5 TAGS projects. Merlin (*Modelling* **E***xposure to chemicals for* **R***isk assessment: a comprehensive* **L***ibrary of multimedia and PBPK models for* **I***ntegration, Prediction, u***N***c***ertainty and Sensitivity analysis* Expo tool[6] that is based on a library of models simulating the fate of chemicals (organic substances and metals) in the main environmental systems and in the human body.

Use of a maximum aggregate ratio approach in aggregate exposure assessment

Exposure modelling tools developed for REACH are generally overly/unrealistically conservative and hence, inappropriate for aggregate exposure assessment. For example, a quick reality check with the consumer ECETOC TRA for only painting products (assuming daily use by EU population and TRA defaults) resulted in an excessive annual production volume of the substance of over 8 trillion tonnes (Zaleski, 2011). Thus, while being useful to determine safety, lower tier tools may not provide a realistic estimate of general population exposure that could be summed up with other exposures to obtain realistic assessments of aggregate exposure. Similar issues are encountered when using the SCCS notes of guidance to determine consumer exposure to preservatives in personal care products and cosmetics, and methods of refining these estimates are presented in the triclosan and phenoxyethanol case studies later in this document.

Before carrying out an aggregate exposure assessment, it should be addressed whether there is in fact benefit or value in doing so. Little insight may be gained if it is a single source or use driving the exposure and other contributions are marginal. In addressing the somewhat parallel issue in cumulative exposure, the question is often asked whether a single chemical is driving risk or whether the risk is truly as a result of multiple chemicals in a mixture. One technique used to address this question in cumulative risk assessment is the Maximum Cumulative Ratio (MCR) developed by Price and Han (2011). In short, the purpose of this approach is to help determine if one or few of the multiple substances being assessed contribute to overall risk. The MCR is the total risk potential divided by the maximum risk value associated with a single component. An MCR value closer to one suggests that one or few constituents contribute significantly to overall risk, whereas an MCR closer to N (with N representing the number of constituents included in the assessment) suggests that the contribution of multiple constituents may be useful to consider. This concept can be applied to screening level results to determine if the extra effort of assessing all constituents should be done as a first prioritisation, or if a more focused effort on those contributing greatest to the estimates risk may be more pragmatic. An adaptation of such a technique may also be of use in aggregate exposure assessment when determining whether a detailed aggregate exposure will provide benefit. It is suggested to use an MAR or maximum

[6] Available at http://merlin-expo.eu/

aggregate ratio representing the total exposure from all sources divided by the maximum exposure from a single source. MAR, might be useful for understanding if overall exposure may be dominated by few or many sources, and to focus any further efforts on those of more importance. It is noteworthy that the MCR concept is to be applied to toxicity estimates derived from dose additive models. The additivity principle will also apply to aggregate exposure provided that single product exposures are aggregated/summed on an appropriate time scale that respected the chemical elimination kinetics. When developing an aggregate exposure estimate, a first step could be to screen the individual exposure scenarios for use information and divide the products into different groups according to their use frequency, duration and amount of use.

To investigate the usefulness of such an approach to a screening aggregate consumer exposure assessment we calculated consumer exposure to a hypothetical highly volatile solvent (VP>10 Pa at ambient temperature) using the EGRET model. The model embeds realistic estimates for exposure determinants derived from consumer use surveys and databases. The exposure predictions are thus representative of reasonable worst-case scenarios. The REACH use descriptor product categories (PCs) that are relevant for the solvent use were then allocated to individual groups based on their use frequency. The most frequently used product group included PCs that are used more than once a week. The next group embraced those PCs that are used more than monthly. The products that are used less than monthly and less than yearly, respectively, constituted the last two groups. The single PCs exposures as well as the resulted aggregate (i.e. summed) exposure across different product groups are provided in Table 2.

Table 2: Reasonable worst-case consumer exposure to a highly volatile solvent assessed using the EGRET v.1.0 model. Product categories highlighted in grey were excluded from aggregate exposure assessment

Descriptor	Product subcategory	Product Group	Frequency, 1/day	Duration, h/day	Predicted Dermal Exposure, Daily (mg/kg/d)	Predicted Oral Exposure, Daily (mg/kg/d)	Predicted Inhalation Exposure, Daily (mg/kg/d)	Total Daily Exposure, mg/kg/day	Products Contributions and MAR	Total Chronic exposure, mg/kg/day MULTIPLIED by USE FREQUENCY	Product contributions and MAR
PC3:Air care products	Air care, instant action (aerosol sprays)	Group 1: Products used not less than weekly	4	1	0	0	0.05	0.05	0.0%	0.21	0.1%
PC1:Adhesives, sealants	Glues, hobby use		1	4	1.8	0	4.7	6.5	0.1%	6.5	3.5%
PC1:Adhesives, sealants	Sealants		1	1	1.8	0	19.3	21.1	0.3%	21.1	11.3%
PC3:Air care products	Air care, continuous action (solid and liquid)		1	8	0.0001	0	0.09	0.09	0.0%	0.09	0.0%
PC4_n:Anti-freeze and de-icing products	Washing car window		1	0.017	0	0	0.00	0.0001	0.0%	0.0001	0.0%
PC4_n:Anti-freeze and de-icing products	Pouring into radiator		1	0.17	7.1	0	1.01	8.14	0.1%	8.1	4.4%
PC4_n:Anti-freeze and de-icing products	Lock de-icer		1	0.25	17.9	0	0.28	18.1	0.3%	18.1	9.7%
PC8_n: Biocidal products (excipient use only for solvent products)	Laundry and dish washing products		1	0.5	0.07	0	0.37	0.44	0.0%	0.44	0.2%
PC13:Fuels	Liquid (subcategories added): Home space heater fuel		1	0.03	35.0	0	0.13	35.1	0.6%	35.1	18.8%
PC18_n: Ink and toners	Inks and toners.		1	2.2	1.2	0	5.6	6.8	0.1%	6.8	3.6%
PC34_n: Textile dyes, finishing and impregnating products			1	1	0.14	0	9.9	10.0	0.2%	10.0	5.4%
PC35:Washing and cleaning products (including solvent based products)	Laundry and dish washing products		1	0.5	0.07	0	0.37	0.44	0.0%	0.44	0.2%

Descriptor	Product subcategory	Product Group	Frequency, 1/day	Duration, h/day	Predicted Dermal Exposure, Daily (mg/kg/d)	Predicted Oral Exposure, Daily (mg/kg/d)	Predicted Inhalation Exposure, Daily (mg/kg/d)	Total Daily Exposure, mg/kg/day	Products Contributions and MAR	Total Chronic exposure, mg/kg/day MULTIPLIED by USE FREQUENCY	Product contributions and MAR
PC8_n: Biocidal products (excipient use only for solvent products)	Cleaners, liquids (all purpose cleaners, sanitary products, floor cleaners, glass cleaners, carpet cleaners, metal cleaners)		0.35	0.12	7.1	0	0.46	7.6	0.1%	2.7	1.4%
PC8_n: Biocidal products (excipient use only for solvent products)	Cleaners, trigger sprays (all purpose cleaners, sanitary products, glass cleaners)		0.35	0.06	10.7	0	0.97	11.7	0.2%	4.1	2.2%
PC35:Washing and cleaning products (including solvent based products)	Cleaners, liquids (all purpose cleaners, sanitary products, floor cleaners, glass cleaners, carpet cleaners, metal cleaners)		0.35	0.12	7.1	0	0.46	**7.6**	**0.1%**	**2.7**	**1.4%**
PC35:Washing and cleaning products (including solvent based products)	Cleaners, trigger sprays (all purpose cleaners, sanitary products, glass cleaners)		0.35	0.06	10.7	0	0.97	**11.7**	**0.2%**	**4.1**	**2.2%**
PC13:Fuels	Liquid - subcategories added: Automotive Refuelling	**Group 2: Products used not less than monthly**	0.14	0.007	35.0	0	0.84	**35.8**	**0.6%**	**5.1**	**2.7%**
PC13:Fuels	Liquid - subcategories added: Scooter Refuelling		0.14	0.005	35.0	0	0.56	**35.6**	**0.6%**	**5.1**	**2.7%**
PC13:Fuels	Liquid - subcategories added: Lamp oil		0.14	0.002	35.0	0	0.07	**35.1**	**0.6%**	**5.0**	**2.7%**
PC23_n: Leather tanning, dye, finishing, impregnation and care products	Polishes, wax / cream (floor, furniture, shoes)		0.08	0.1	35.8	0	27.8	**63.6**	**1.0%**	**5.1**	**2.7%**
PC31:Polishes and wax blends	Polishes, wax / cream (floor, furniture, shoes)		0.08	0.1	35.8	0	70.5	**106**	**1.7%**	**8.5**	**4.5%**
PC13:Fuels	Liquid - subcategories added: Garden Equipment - Use		0.07	0.14	0	0	4.0	**4.0**	**0.1%**	**0.28**	**0.1%**
PC13:Fuels	Liquid (subcategories added): Garden Equipment - Refuelling		0.07	0.002	70.0	0	0.44	**70.4**	**1.1%**	**4.9**	**2.6%**

Descriptor	Product subcategory	Product Group	Frequency, 1/day	Duration, h/day	Predicted Dermal Exposure, Daily (mg/kg/d)	Predicted Oral Exposure, Daily (mg/kg/d)	Predicted Inhalation Exposure, Daily (mg/kg/d)	Total Daily Exposure, mg/kg/day	Products Contributions and MAR	Total Chronic exposure, mg/kg/day MULTIPLIED by USE FREQUENCY	Product contributions and MAR
PC9b:Fillers, putties, plasters, modelling clay	Fillers and putty	**Group 3: Products used several times per year**	0.033	0.13	0.12	0	2.9	**3.1**	**0.0%**	**0.10**	**0.1%**
PC9b:Fillers, putties, plasters, modelling clay	Plasters and floor equalisers		0.033	0.07	2.9	0	367	**370**	**5.9%**	**12.2**	**6.5%**
PC23_n: Leather tanning, dye, finishing, impregnation and care products	Polishes, spray (furniture, shoes)		0.022	0.0079	35.8	0	9.6	**45.4**	**0.7%**	**1.00**	**0.5%**
PC31:Polishes and wax blends	Polishes, spray (furniture, shoes)		0.022	0.007	35.8	0	6.0	**41.8**	**0.7%**	**0.92**	**0.5%**
PC1:Adhesives, sealants	Glue from spray		0.016	0.07	1.8	0	44.1	**45.9**	**0.7%**	**0.76**	**0.4%**
PC24: Lubricants, greases, and release products	Sprays		0.016	0.003	35.7	0	6.7	**42.5**	**0.7%**	**0.70**	**0.4%**
PC9a:Coatings, paints, thinners, paint removers	Solvent rich, high solid, water borne paint		0.016	0.04	19.7	0	285	**305**	**4.9%**	**4.9**	**2.6%**
PC15_n: Non-metal surface treatment products	Solvent rich, high solid, water borne paint		0.016	0.04	19.7	0	285	**305**	**4.9%**	**4.9**	**2.6%**
PC9a:Coatings, paints, thinners, paint removers	Waterborne latex wall paint		0.011	0.02	1.1	0	57.7	**58.8**	**0.9%**	**0.65**	**0.3%**
PC15_n: Non-metal surface treatment products	Waterborne latex wall paint		0.011	0.02	1.1	0	57.7	**58.8**	**0.9%**	**0.65**	**0.3%**
PC16_n: Heat transfer fluids	Liquids		0.011	0.002	78.0	0	2.2	**80.2**	**1.3%**	**0.88**	**0.5%**
PC17_n: Hydraulic fluids	Liquids		0.011	0.002	78.0	0	2.2	**80.2**	**1.3%**	**0.88**	**0.5%**

Descriptor	Product subcategory	Product Group	Frequency, 1/day	Duration, h/day	Predicted Dermal Exposure, Daily (mg/kg/d)	Predicted Oral Exposure, Daily (mg/kg/d)	Predicted Inhalation Exposure, Daily (mg/kg/d)	Total Daily Exposure, mg/kg/day	Products Contributions and MAR	Total Chronic exposure, mg/kg/day MULTIPLIED by USE FREQUENCY	Product contributions and MAR
PC24: Lubricants, greases, and release products	Liquids		0.011	0.002	78.0	0	2.2	**80.2**	**1.3%**	**0.88**	**0.5%**
PC9a:Coatings, paints, thinners, paint removers	Removers (paint-, glue-, wall paper-, sealant-remover)		0.008	0.02	71.5	0	326	**398**	**6.4%**	**3.3**	**1.7%**
PC15_n: Non-metal surface treatment products	Removers (paint-, glue-, wall paper-, sealant-remover)		0.008	0.02	71.5	0	326	**398**	**6.4%**	**3.3**	**1.7%**
PC9a:Coatings, paints, thinners, paint removers	Aerosol spray can	**Group 4: Products used less than yearly**	0.005	0.002	0	0	18.8	**18.8**	**0.3%**	**0.09**	**0.1%**
PC15_n: Non-metal surface treatment products	Aerosol spray can		0.005	0.002	0	0	18.8	**18.8**	**0.3%**	**0.09**	**0.1%**
PC1:Adhesives, sealants	Glues DIY-use (carpet glue, tile glue, wood parquet glue)		0.003	0.02	5.5	0	3548	**3553**	**57.1%**	**9.59**	**5.1%**
Aggregate exposure for Group 1 (N of PCs = 16):								126	3.6	114	3.2
Aggregate exposure for Groups 2-4 (N of PCs = 25):								6,101	1.7	73	6.0
Aggregate exposure ALL (N of PCs = 41):								**6,227**	**1.8**	**187**	**5.3**

The example in Table 2 demonstrates that introducing the annual use frequency into aggregate exposure calculations by means of product grouping can result in a significant reduction of the estimated exposure. For example, aggregate acute exposure, on a day of use, for frequently used products only (i.e. Group 1) was 50 times lower than the aggregate exposure from all the PCs identified for that solvent use. In the case of long term exposure, the reduction was less prominent, i.e. 60%, however it may still impact the outcomes of the follow-up health risk assessment. An exposure assessor may also consider carrying out a feasibility check and calculate the total duration of aggregate exposure. In this example the total time needed to perform only frequent tasks (i.e. application of PCs in Group 1) would amount to 19 h suggesting that all exposure events are unlikely to occur on the same day. Given the conservative nature of the tool, it is important to understand that addition of the individual estimates would only be used to indicate safety; additive exposures greater than a benchmark value indicate that further refinement of the exposure assessment is needed.

Contributions of individual PCs into aggregate exposure varied depending on exposure route and the type of exposure (i.e. acute versus chronic). On the day of use only few products (e.g. DIY glues, paints and coating removers) contributed significantly to the total aggregate exposure from all PCs. MARs were closer to 1 rather than to N (where N = number of PCs in the assessment), showing that the aggregate exposure was dominated by few PCs. In the case of chronic exposure when the annual use frequency parameter came into play the situation changed – more frequently used products in Group 1 outweighed the contributions from occasionally used PCs (Groups 2-4). Increase in MARs for infrequent and all PCs indicates that higher exposure infrequent events are less frequent leading to a more even profile of contributions across the scenarios.

It is worth mentioning that the total exposure over routes was calculated assuming identical health endpoints that are independent of the route of entry into the human body. If this assumption cannot be proven, the total exposure, PCs contributions and MARs should be calculated on the basis of Risk Characterisation Ratio (RCR) that are the ratios of estimated exposure to derived no observed effect levels for the substance of interest. The MAR approach is seen as a complementary tool for screening aggregate exposure assessment that can help to identify whether higher tier assessment is indeed needed. It can also highlight application scenarios requiring further refinement.

The described approach enables identification of product groups with different potential relevance for aggregate exposure assessment. The information generally available is not real co-use data but rather reasonable worst case information on use frequency and use duration. The exposure assessor should always use expert judgement to determine if the data available makes sense or really is only generated to create a worst case but not very realistic exposure scenario. If the data is reasonable it could be used for a first decision on the potential need for an aggregate exposure assessment and in addition used to screen for uses and products to include in a first tier aggregate exposure assessment. An initial focus may be on products that are likely to be used daily, and constituents that are assumed to have large market share in those products. These considerations may help to direct additional efforts to refine defaults and better represent population variability, the types of data needed to conduct a meaningful aggregate assessment. However, other considerations may also apply, such as chemical half-lives, relative toxicity, route-specific effects. A total aggregate assessment would then sum exposure estimates over all types of sources including, but not necessarily limited to, household products, food and cosmetics.

2.2 Summary

When performing an exposure assessment to a chemical, it is important to understand what tier the assessment is being performed at. This in turn informs which models and data are the most appropriate. The output of this landscaping exercise indicates some of the available data sources and tools, and what uses they are appropriate for. In general, tools and data exist to support development of exposure estimates for individual consumer products, particularly at a screening level.

For chemicals where consumer exposures are generally low, occur infrequently, and/or presence in co-used products is uncommon, aggregate exposure assessment may not be required. In situations where it is appropriate to assess aggregate exposure, and the initial exposure assessment shows a likelihood of being unrealistically high, a more refined assessment should be performed. If moving to a higher tier assessment, then it will be necessary to identify data and a methodology that can be used to generate realistic aggregate exposure. Screening level tools are not very useful since their conservative single use estimates will lead to very biased over conservative estimates of aggregate exposure when simply added up. As can be seen from cosmetics or food, most tools that exist for aggregate exposure assessments are probabilistic tools that allow the user to define a distribution for parameters that reflect (true) variability and uncertainty for both the input and the estimates exposure (output), and are built upon databases of consumer habits and practices that detail real co-use and non-use of products. In addition, such tools also allow the user to study the impact of different parameters on the outcome and study the uncertainty drivers in the predicted exposure. This information can be used to determine what additional data should be collected. As mentioned for the broader chemical domain such tools do not exist. Depending on the focus of the exposure assessment the assessor may feel that sufficient information is available for part of the product groups included (e.g. household products) to perform a (partially) probabilistic assessment and can generate a simple probabilistic algorithm using an off-the-shelve statistical program. The drawback is that this will generally be labour intensive and some basic understanding of the statistical programs is needed. In addition, such a model will not be validated and may overlook certain important factors especially if availability of data is limited.

In the foods domain, aggregate exposure is performed somewhat as a matter of course and therefore there is a greater abundance of data available than in other domains. One of the reasons for this is that food consumption surveys are often routinely carried out for the purposes of nutritional status assessment, and the data can be subsequently used for chemical exposure assessment as it typical details co-consumption of foods at the individual level. Due to the challenges of characterising and capturing the complete diet of consumers, it is known there are some significant shortcomings of these datasets, particularly under-reporting and the lack of data on infrequently consumed foods. Equally, lack of access to necessary raw data on food consumption is an issue in Europe and so thus represents a barrier to be able to perform higher-tier exposure assessments. Finally, as per other domains, there is a lack of information on chemical concentrations for formulations that are proprietary, which again is a required input for refined exposure assessment.

To be able to perform a high tier aggregate exposure assessment that will be realistic, data on product co-use, chemical concentration and chemical occurrence in formulation are vital to prevent a level of conservativeness that will generally result in very biased and unrealistic results. Market survey databases such as those provided by Mintel, Kantar Worldpanel and Euromonitor International are becoming increasingly used to provide such data in exposure assessments. This is because they can be used to refine exposure parameters by providing

data such as the occurrence of a chemical in food using labelling data in a given food category. Other examples include "crowdsourced" data such as the Swiss database Codecheck, where consumers can submit labelling information to a publicly available database. There are undoubtedly opportunities to exploit such data sources and other "Big Data" in exposure assessment, such as data from diet tracker smartphone applications which have the potential to provide unprecedented sample sizes and detail. However, many of scientific issues and associated uncertainties still need to be addressed in a comprehensive manner.

3. APPROACHES FOR HIGH TIER AGGREGATE ASSESSMENT OF CHEMICALS

This chapter gives an overview of current approaches to aggregate exposure assessment and examples of aggregate exposure assessment published in the literature. An outline of a tiered approach to aggregate exposure assessment from WHO/IPCS (Meek et al, 2011) is shown in Figure 1 of Section 1.1. In this section the tiered approach to exposure assessment is illustrated using two case studies: 1) triclosan in cosmetic products, and, 2) phenoxyethanol in cosmetic and household products.

3.1 Literature review of existing approaches to aggregate exposure assessments

Historically, chemical exposure assessments carried out for regulatory compliance were aimed at the derivation and demonstration of safe use of a substance contained in an individual product (Existing Substances Regulation or ESR). In the early 1990s, the concept of aggregate exposure assessment began to receive more attention and dedicated methods and tools started evolving. The development of regulatory frameworks requiring aggregation of exposure supported these initiatives. One of the policy documents that instigated guidance on aggregate exposure assessment was the US Food Quality Protection Act (1996). This act introduced the concept of pesticide safety as "reasonable certainty that no harm will result from aggregate exposure to the pesticide chemical residue, including all anticipated dietary exposures and all other exposures for which there is reliable information". The publication of this act raised a number of science policy issues, which resulted in the development of the General Principles for Aggregate Exposure and Risk Assessment (US-EPA, 2001). The legislation was also one of the triggers for the Health and Environmental Science Institute to organise a workshop on aggregate exposure (ILSI HESI, 2000), having an objective to evaluate the methodologies currently available for aggregate exposure assessment, with an emphasis on the practical scientific issues and data requirements for pesticides. In Europe aggregate dietary exposure assessment for pesticides is also required under the Regulation on maximum residue levels of pesticides in food (European Commission (EC No 396/2005), 2005).

Currently aggregate exposure assessments are executed in a tiered manner (Delmaar JE and van Engelen JGM, 2006; Meek et al, 2011). Recent examples of consumer aggregate exposure assessments include multiple case studies illustrating approaches developed for cosmetics and personal care products, some demonstrating applicability to cleaning and household care products, with a limited number of instances developed for a wider range of consumer goods covering coatings, medical devices and food contact materials.

In 2012, the Norwegian Scientific Committee for Food Safety (VKM) published a risk assessment on vitamin A in cosmetics (VKM, 2013). This included a low tier deterministic exposure estimate derived from summing worse case population estimates of dietary and cosmetic exposure.

More refined approaches providing more realistic estimates of exposure include examples such as Dudzina et al (2015), who developed and validated a person-oriented Probabilistic Aggregate Consumer Exposure Model (PACEM) using decamethylcyclosiloxane (D5) as a showcase compound. The aggregation of exposure in the

model was performed at the individual level, making use of the detailed consumer exposure factor databases on product use and co-use and biometric details for 516 Dutch adults. The model allows estimation of product contributions to total internal dose as well as stratification of aggregate exposure by route, gender and age. By comparing the doses derived in different modelling tiers with relevant human biomonitoring data (Biesterbos et al, 2015) the authors could verify the applicability of the developed probabilistic model for risk assessment. The higher tier estimates were more realistic, but still reasonably conservative than those obtained following the deterministic worst-case approach. A pilot version of PACEM has been also tested by Gosens et al (2013) who estimated aggregate exposure to four parabens from baby care products for Dutch children between 0 and 3 years old. Additional validation of the PACEM tool was performed by Delmaar et al (2014) in a diethyl phthalate case study. It is worth noting that only the baseline end-exhaled air monitoring data for D5 acquired by Biesterbos et al (2015) provided a 'true' snapshot of aggregate exposure, since the measurements reflected the total systemic doses received collectively via all sources and pathways. Contrariwise, the modelling case studies focused on specific categories of consumer products overlooking other potentially relevant exposure pathways (e.g. via drinking water, ingestion of dust) that may contribute to aggregate exposure.

Manová et al (2015) also evaluated aggregate consumer exposure to ethylhexyl methoxycinnamate (EHMC) via the use of personal care products (PCP). The authors adopted a probabilistic approach to modelling aggregate exposure at an individual level. The products use data for 1196 adults and children in German-speaking part of Switzerland was fed into the model together with the analytical concentration data on EHMC in PCPs. The internal aggregate exposure estimates for the studied population were below the Derived No Effect Level (DNEL) for EHMC. However, it was shown that the predicted aggregate exposure may exceed the DNEL for thyroid-disrupting effects for children aged ≤4years, when an intense short-term exposure via sunscreen during a sunbathing day is accounted for. Considering the paucity of quantitative data on transdermal penetration of EHMC and the long-term effects of endocrine disruptors, comprehensive risk assessment could not be performed. The finding of the study highlighted the need for an alignment between advances in exposure modelling and the development of reference dose values for accurate risk evaluation.

Tozer et al, (2015) developed a probabilistic aggregate exposure model, using Creme Global software, to estimate consumer exposure from several rinse off personal cleansing products containing the anti-dandruff preservative zinc pyrithione. The model incorporates large habits and practices surveys from Europe and North America, containing data on frequency of use, amount applied, co-use along with market share, and combines these data at the level of the individual based on subject demographics to better estimate exposure.

The developed models for aggregate consumer exposure assessment are also being used in skin sensitisation risk assessment, as demonstrated by Nijkamp et al (2015) who investigated the fragrance ingredient, geraniol, in cosmetics and household cleaners using the PACEM model. The survey data, underpinning the model, allowed predicting body part specific aggregate dermal external exposure at an individual level and deriving the percentage of general population at risk. The authors, however, acknowledge that ideally the risk to sensitising agents should be assessed based on the internal exposure (e.g. the amount of substance that enters the epidermis and becomes available for recognition by Langerhans cells) rather than the external dermal load. Also, the timeframe of aggregation of exposures relevant for skin sensitisation is not known and may be longer than 24 hours assumed in this study, since the available test data are highly uncertain and suggest the induction phase may occur during both the acute/peak and chronic time periods.

Along the lines of this study, Safford et al (2015) also used a probabilistic aggregate exposure model to estimate consumer exposure to fragrance materials in personal care and cosmetic products using the Creme Global software Creme Care & Cosmetics. The model is described in detail in this report in the case studies for triclosan and phenoxyethanol and so will not be described in further detail here. However, it is worth noting that the model is now used as the standard approach in the safety assessment of fragrances, which is performed routinely by the Research Institute of Fragrance Materials (RIFM) when combined with surveys of use levels gathered in collaboration with the institute's member companies.

More recently, Dimitroulopoulou et al (2015a) have estimated aggregate exposure for a range of VOCs (formaldehyde, benzene, acrolein, d-limonene, a-pinene) being emitted from cleaning and surface treatment products including all-purpose cleaners, kitchen cleaners, floor cleaners, glass and window cleaners, furniture and floor polish products, combustible products, sprays, electric and passive air fresheners, coating products for leather and textiles, hair styling products, spray deodorants and perfumes. The modelling was carried out using CONC-CPM microenvironmental (ME) model. The simulations of indoor air concentrations and calculations of inhalation exposure were predicted from a single product use as well as from simultaneous use of multiple products that were documented in the form of 'most representative worst-case scenarios'. The predictions of aggregate exposure took into account product co-use profiles developed for over 4,000 adults split into two specific consumer groups: housekeepers and retired people in different European regions (Dimitroulopoulou et al, 2015b). The questions considered for the development of these scenarios were related to the use of consumer products in the domestic environment resulted in acquisition of the information on frequency, the amount, the time and location of product use for every single individual.

With regards to chemicals occurring in products other than cosmetics and cleaning products, Koontz et al (2006) conducted a study on modelling occupational aggregate exposure for ethylene glycol butyl ether (EGBE) and dipropylene glycol methyl ether (DPGME) from sequential application of floor stripper, floor cleaning agent and floor protective finish using PROMISE and MCCEM exposure modelling tools. Although the models were run for professional use, the input parameters used were also valid for consumer applications (e.g. AER=1/hour, the applied amount relative to treated surface area). Aggregation of internal exposure was done over all routes and across products (where applicable) by simple summation. The paper also includes basic uncertainty analysis (for DPGME exposure only) and some validation. The toxicological endpoints of both compounds were not discussed; thus, it is not clear whether aggregation of exposure across compounds (potentially acting through a common MOA) would have been beneficial. Despite its limitations, the study exemplifies nicely considerations and the level of detail required for input data to model appropriately use scenarios for aggregate exposure. One of the conclusions that can be made is that the exposure may be aggregated across consumer products that are intended for use within a specific activity (e.g. wall painting, carpet installation, house cleaning).

Overall, most aggregate assessments published to date focus on specific substances and specific types of use (food, cosmetics, etc.). These are consistent with the current state of modelling tools, availability of exposure factors data, and understanding of data correlations needed to support higher tier predictions of aggregate exposure.

Recommended approaches for High Tier Aggregate Assessment of Chemicals

Background

Aggregate exposure should be estimated using a tiered approach (Delmaar JE and van Engelen JGM, 2006; Meek et al, 2011), which begins with a rough deterministic estimation of exposure and evolves, as needed, to a more complex person-orientated probabilistic approach. This is recently described, and applied to the exposure assessment of D5 and triclosan in CEFIC-LRI project ETHZ-B7 (Bakker 2014). This report introduces the concept that data can be refined where necessary at the highest tier, by incorporating data on chemical occurrence and product market share, to give a population-based aggregate exposure estimate to an ingredient that incorporates the best available data.

Aggregate exposure assessment is becoming a consideration in safety assessments in some sectors, whereas in other consumer product categories it is deemed to be less relevant. In the food sector, it is normal practice to look at a person's daily exposure to a nutrient or food ingredient by considering their total exposure from the diet, which is in effect the daily aggregate exposure from all food sources, though it is not referred to as aggregate exposure. In other consumer products categories, such as household products, aggregate exposure is not considered, which may be because exposure to products is low, as many products are not directly applied to the skin, or because the products are not frequent, daily use products, for example household cleaning products that are used only on a weekly basis or less.

Aggregate exposure assessment is becoming an area of interest in the sector of cosmetics and personal care products in Europe. For example, in the SCCS Notes of Guidance for the Testing of Cosmetic Ingredients and their Safety Evaluation, the aggregate exposure assessment of preservatives is estimated using a simplistic approach of adding deterministic exposures from all the individual product types in which the chemical might be present (SCCS, 2012). In addition, the SCCS has requested the consideration for aggregate exposure for a number of chemicals including citral, farnesol, and phenylacetaldehyde, silver (SCCS, 2008), ethyl lauroyl arginate (SCCS, 2014), cetyl pyridinium chloride (SCCS, 2015) and decamethylcyclopentasiloxane (D5). Furthermore, in the European Cosmetics Regulation (EC 2009), substances classed as carcinogenic, mutagenic or toxic to reproduction (aka CMR) class 1A/1B should be assessed for total (aggregate) exposure, considering their simultaneous presence in cosmetics, foods, medicines, and in products legislated under REACH (i.e., Registration, Evaluation, Authorisation and Restriction of Chemicals). Therefore, there is a requirement to assess aggregate exposure across consumer product categories, although no published guidance is available.

There are no standard methods recognised for aggregate exposure assessments, although it is recommended to estimate it using a tiered approach (Delmaar JE and van Engelen JGM, 2006; Meek et al, 2011), which begins with a rough deterministic estimation of exposure and evolves to a more complex person-orientated probabilistic approach. Deterministic additive methods, such as the SCCS preservative method (SCCS, 2012), assume that everybody in the population uses all the products each day, and that all of the products contain the chemical of interest, which is not a realistic scenario. This technique may be sufficient for a low tier screening level assessment, or for chemicals with a wide margin of safety, but as it does grossly exaggerate the aggregate exposure, a more refined approach will be needed for some risk assessments. An approach has been described for refining a deterministic aggregate exposure assessment to the paraben preservatives (i.e., methy-, ethyl- and isopropyl paraben) in personal care products by incorporating data on co-use and non-use

patterns of product usage, and the occurrence of the ingredient (Cowan-Ellsberry and Robison, 2009). This has led to considerable refinement in exposure (51-92%). Co-use is the term describing the combination of products used by the same subject and by applying the co-use statistics, a more refined aggregate exposure model can be developed that better reflects population exposure. Since product use data are readily available for many cosmetic products (Hall et al, 2007, 2011; Loretz et al, 2005, 2006, 2008) the co-use approach offers a practical method to refine aggregate exposure assessments.

Recently co-use data from European and US subjects has been incorporated into high tier exposure estimates for chemicals in consumer products using subject-oriented probabilistic models with Creme Global software (Tozer et al, 2015, Comiskey et al, 2015, Safford et al, 2015).

Another refinement to more accurately reflect aggregate exposure estimations in populations is the incorporation of chemical occurrence data or market share data, which describe the likelihood the chemical is present in a product, since only the consumers using products containing the ingredient will be exposed. This factor (usually expressed as a value between zero and one or a percentage) can be used in probabilistic modelling to estimate the likelihood of co-exposure to a given substance that is potentially present in a given category. Incorporation of chemical occurrence data into exposure assessments is being done already in the area of food safety (Mistura et al, 2013). To give a cosmetics example, consumers using only "fragrance/perfume free" cosmetics would not be exposed to perfume raw materials through the use of these products. When chemical occurrence data is combined with reliable market share data for the products it can be used to determine the probability of exposure, which can be incorporated to refine the exposure assessment. Incorporation of chemical occurrence data including non-use data into exposure modelling brings refinement by discounting exposures where the chemical is not present in the product of interest. In Tozer et al, (2015) the exposure of zinc pyrithione was modelled by incorporating chemical occurrence data on the proportion of the population who are users of antidandruff shampoos, as zinc pyrithione is only present in anti-dandruff shampoos. For infrequently used substances, what is often the most conservative assumption in an assessment is that a substance is always present in every product category it can be used in. For aggregate exposure assessments, this assumption has an additive effect giving rise to a very conservative estimate of exposure.

As there is little guidance on how to refine high tier exposure assessments using chemical occurrence data and more realistic data on the concentrations of chemicals in product, two case studies are presented to demonstrate the technique, using triclosan and phenoxyethanol, where the exposure assessments are conducted at tier 0, 1 and 2. As tier 3 requires very detailed exposure input data, such as raw data sets on specific product use including ingredient concentration and presence in product, which can be difficult to attain, these examples will only be taken to Tier 2:

Tier 0 Qualitative Exposure Assessment

The purpose of the tier 0 exposure assessment is to provide a preliminary overview of all possible exposure sources, pathways and routes for the chemical of interest, in order to determine whether an aggregate exposure assessment is appropriate.

Tier 1 Worst-Case Scenario Assessment

The aim of the tier 1 assessment is to determine a realistic upper bound of the aggregate consumer exposure to the chemical in a population.

Tier 2 probabilistic assessment

The aim of the tier 2 assessment is to determine more realistic estimates of aggregate consumer exposure to the chemical, by increased use of measured data, using probabilistic methods.

To note that these case studies are not intended to provide definitive exposure assessments for these chemicals, but rather have been selected for illustrative purposes to demonstrate the refinement techniques.

3.2 Case Study 1: Triclosan in Personal Care Products and Cosmetics

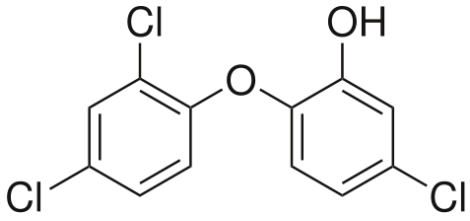
Consumer exposure to triclosan was studied in considerable detail in a previous CEFIC-LRI B7 report (Bakker et al, 2014). The goal in this case study is not to duplicate this work or to present alternative estimates of consumer exposure to triclosan; rather it is a study of how to systemically refine exposure estimates to arrive at a high tier estimate of exposure, starting from a conservative estimate and then introducing more data and analysis techniques in order to improve the estimate of exposure.

The starting point is an opinion on the safety of triclosan by the Scientific Committee on Consumer Safety (SCCS), which uses a tier 1 type assessment of consumer exposure by deterministically summing exposure from individual products (SCCS, 2012). In order to refine the estimate in this opinion, a number of different data sources and models are introduced in a systematic manner. This is with a view to both providing guidance on how to perform a higher-tier exposure assessment when required, and also how to best use available data in order to estimate exposure for a given purpose.

3.2.1 Substance profile

The properties and characteristics of triclosan were presented in detail in the previous CEFIC-LRI B7 report, and so rather than duplicate the same material here the principal points will instead be summarised.

Physiochemical Properties



CAS: 3380-34-5
Molecular Weight: 289.54

Triclosan is a chlorinated aromatic compound that has functional groups of both phenols and ethers. It has a vapour pressure of 5.33 x 10^{-4} mm Hg at 20°C and a Log Kow of 4.67. Other key physiochemical properties of the compound are described in Table 2, Appendix 4 of the CEFRIC-LRI B7 report.

Kinetics

The kinetics of triclosan have been described in detail previously (Bakker et al, 2014). The key points are that the buccal absorption of triclosan is around 7.3% from 0.03% mouthwash (Lin, 2000), and the principal route of excretion are the in urine and faeces where, it is found primarily in the form of conjugates (Moss et al 2000). Mean percutaneous absorption in humans calculated from urinary excretion was 5.9% of the dose after a 12-hour application (Queckenberg et al, 2010), and triclosan has a half-life of about 11 hours (Sandborgh-Englund, 2006).

Toxicity

Triclosan is a skin and eye irritant when used in the neat form, but it is virtually nontoxic after single ingestion or single skin contact. The substance does not cause skin sensitisation, is not mutagenic or a reproductive toxicant. Several live-time studies were conducted in mice, rats and hamsters that can serve as points of departure for a risk assessment. In mice, a species-specific, receptor-mediated mechanism of action leads to peroxisome proliferation with concomitant liver hypertrophy which eventually results in the formation of liver tumours. In rats, liver toxicity is also the most prominent effect, however, peroxisome proliferation was not observed in this species and liver tumours did not occur. The hamster is the species most similar to humans in terms of distribution, metabolism and excretion of triclosan. Whereas mice and rats exhibit enterohepatic re-circulation of triclosan and excrete it via the faeces, hamsters and humans do not exhibit re-circulation and excrete via the urine. This may explain why in hamsters, triclosan toxicity is not observed in the liver but in kidneys. Based on benchmark dose modelling, nephrotoxicity in hamsters occurs at a slightly lower dose level than liver toxicity in rats and can therefore also be regarded as the most sensitive endpoint for human risk assessment.

3.2.2 Exposure Assessment

Tier 0

Exposure Sources

Triclosan is commonly used as an antibacterial and antifungal agent in a variety of applications in personal and medical care products. It generally comes in the form of a white powdered solid with a slight aromatic odour and is only slightly soluble in water. Common uses of triclosan in and personal products include antibacterial soap, mouthwashes, toothpastes, deodorants, shampoos, and it is also used as a preservative in cosmetics. Other uses include cleaning supplies, toys, bedding, socks, bin liners, textiles, carpets, and plastics.

Triclosan has been added to the surface of cutting boards, food storage containers and other kitchen utensils to stop microorganisms growing on them. However, since March 2010, triclosan cannot be used in the EU in food contact materials or as an additive in plastics that come into contact with food. Triclosan is not used as a disinfectant in food and feed production and it is not approved as a food preservative in Europe. It is also used in biocidal products for veterinary hygiene but it is banned as a preservative in animal food.

Owing to its uses, the primary routes of exposure to triclosan in consumers are via the oral (e.g. toothpaste and mouth wash) and dermal routes (e.g. personal care products and cosmetics), which will be the focus of the subsequent analysis.

Tier 1

The starting point for the exposure assessment is based upon an SCCS opinion on triclosan, which uses the exposure scenarios in the SCCS notes of guidance for consumer exposure assessment to personal care products and cosmetics (SCCS, 2012), and assumes two concentration levels:

- A maximum EU regulatory use level of 0.3% in all categories
- A combination of the maximum use level at 0.3% and typical use levels of 0.15% and 0.2% in different categories

In accordance with the SCCS notes of guidance, the assessment uses standard exposure scenarios, and aggregation across products is performed via deterministic summing of individual product exposures. These amounts are upper estimates of product use, based upon the 90th percentile of product use in each individual category using values derived from previous studies performed by the cosmetic trade association, which at the time was called Colipa, but is now called Cosmetics Europe (Hall et al, 2007, 2011). The product categories considered are listed in Table 3, along with the relevant exposure parameters relating to retention factor and dermal absorption:

Table 3: SCCS Exposure Values and Dermal Absorption Estimates for Triclosan

SCCS Product	Retention Factor	Dermal Absorption (%)
Toothpaste	0.17	100
Mouthwash	0.1	100
Deodorant Stick	1	7.7
Body Lotion	1	13.3
Hand Soap	1	7.2
Shower Gel/Body Soap	1	7.2
Face Powder	1	11.3
Blemish Concealer	1	11.3

In the original study, the dermal penetration value is calculated using a value of flux for a given concentration, measured in µg/cm^2. This was used to estimate the percentage dermal penetration, reported in the above table. Aggregate exposure was calculated by deterministically summing the individual product exposures for assumed exposure amounts, giving rise to the following estimates of systemic exposure (Table 4):

Table 4: Total aggregate exposure estimates to triclosan in European consumers calculated assuming a maximum EU regulatory use level of 0.3% in all categories

SCCS Product	Estimated Absorbed Dose (mg/kg bw/day)
Toothpaste	0.0234
Mouthwash	0.15
Deodorant Stick	0.0015
Body Lotion	0.1646
Hand Soap	0.0066
Shower Gel/Body Soap	0.0268
Face Powder	0.0060
Blemish Concealer	0.0006
Total Aggregate Exposure	**0.3795**

A similar assessment was performed, where marginal-use products (mouthwash, body lotion, face powder, and stick concealer) were assigned concentrations ranging from 0.15-0.2%, giving rise to the values shown in Table 5.

Table 5: Total aggregate exposure estimates to triclosan in European consumers calculated assuming a combination of the maximum use level at 0.3% and typical use levels of 0.15% and 0.2% in different categories

SCCS Product	Estimated Absorbed Dose (mg/kg bw/day)
Toothpaste	0.0234
Mouthwash	0.1000
Deodorant Stick	0.0015
Body Lotion	0.0823
Hand Soap	0.0066
Shower Gel/Body Soap	0.0268
Face Powder	0.0040
Blemish Concealer	0.0003
Total Aggregate Exposure	**0.2449**

The assumptions in this method of exposure assessment, whether implicit or explicit, are:

- Triclosan is present in every product category all the time
- Triclosan is present at a maximum or combination of maximum and usual use levels (therefore no variability in concentrations are considered)
- Every consumer uses every product category at a high use level
- Exposure (and therefore risk) is the same for every subpopulation of consumers

The exposure assessment is conservative by design, and offers many advantages such as allowing a quick and simple assessment of risk to be determined. However, in the event that exposure is considered to be

unacceptably high, a refined assessment exposure (rather than a risk management measure) is the next logical step in order to provide a more accurate determination of aggregate consumer exposure.

Tier 2

A number of refinements are possible when performing a higher-tier exposure assessment, by examining the various factors driving the conservative nature of a screening level type exposure assessment. Given that a number of refinements are possible and that time and resources are often scarce for the risk assessor, a logical question to ask is what are the relative impacts of the different refinements that can be achieved? Having an idea of this can in turn help with deciding where to focus resources when performing a refined exposure assessment.

Creme Care & Cosmetics

Aggregate exposure assessments were calculated with the Creme Care & Cosmetics model. This is a probabilistic exposure model and software for determining high-tier estimates of aggregate exposure to substances in personal care products and cosmetics. It is built upon a habits and practices database of over 36,000 consumers from a product use survey developed by Kantar Worldpanel for Europe and the United States, detailing frequency of product use, co-use and site of application for 25 product categories over a seven-day period. Amount per application data is based upon clinical studies for the same products, which are in the form of statistical distributions. Additional required parameters for exposure estimates such as bodyweight, height and skin surface areas are also included in the form of statistical distributions from published sources (e.g. NHANES) and standard calculations (e.g. the Dubois formula). The model calculates aggregate exposure to a chemical via the dermal, inhalation and oral routes, with systemic exposure expressed on an absolute or per unit bodyweight basis and dermal exposure as per unit of skin surface area by site of application.

The model works by combining data on the concentration of a substance within each product category with the data in the habits and practices database. Concentration values can be point estimates or statistical distributions, described empirically or parametrically, and with or without presence probabilities (i.e. the likely occurrence in each product category). Daily exposures are simulated for each individual consumer based on selected inputs, which are used to calculate distributions of chronic or acute exposure in the population being assessed, which can be stratified by age, gender, or geography. The calculated exposure distribution (described using the appropriate measure to compare with the reference dose in question) is in turn described using appropriate statistics, and can be broken down to assess the relative contribution of each product category to exposure, or alternatively to assess the relative magnitude of the exposure at each application site.

The model is accessed via a secure cloud computing software application, which allows for computation on the large accompanying data sets and multiple iterations of Monte Carlo simulations as required.

Three scenarios were considered:

1. Triclosan always present, concentration = 0.3% (max authorised)
2. Using triclosan presence probabilities, concentration = 0.3% (max authorised)
3. Using triclosan presence probabilities, concentration at current use (0.15% - 0.3 %)

In order to have a like-with-like comparison with the SCCS notes of guidance and to examine the impact of various refinements, retention and penetration factors were kept consistent with the original assessment. The product categories in the SCCS assessment were in turn matched with the product categories in the Creme Care & Cosmetics model, which are based upon those that were in the original Kantar Worldpanel survey.

3.2.3 Presence Probabilities

For this study, presence probabilities were derived from an online available database called Codecheck.info (Table 6), which lists the labelling information for a large number of products in a number of cosmetic categories, gathered from crowd-sourced data. While the representativeness and uncertainty associated with using such a database is open to debate, the goal in this assessment is to understand the impact of using chemical occurrence data in a probabilistic exposure assessment to account for instances when a substance is not present in a given product category a certain portion of the time.

To derive the likely presence of triclosan in the products used in this assessment, the total number of products in each category was counted, and the proportion of these that contain triclosan based on whether it was listed on the label or not was used to estimate the chemical occurrence. Note that this approach therefore assumes equal market shares; if a product that does or does not contain triclosan has a large market share then the chemical occurrence in reality will be reduced or increased accordingly. However, for simplicity an equal market share approach is used initially as market shares or sales volumes are not readily available. To reduce uncertainty and err on the side of conservatism, presence probabilities were rounded to the nearest upper 10%.

Table 6: Chemical occurrence values for triclosan derived from Codecheck.info database

Product Type	Total Number of Products	Number of Products with Triclosan	Original Chemical Occurrence (between 0 and 1)	Chemical Occurrence (between 0 and 1)
Toothpaste	552	35	0.063405797	0.1
Mouthwash	328	3	0.009146341	0.1
Deodorant Stick	284	19	0.066901408	0.1
Body Lotion	1710	8	0.004678363	0.1
Face Powder	835	2	0.00239521	0.1
Blemish Concealer	435	3	0.006896552	0.1
Hand Soap	171	5	0.029239766	0.1
Shower Gel/Body Soap	4000	7	0.00175	0.1

Finally, only European consumers, both male and female, were selected for the assessments. This gave rise to a population sample size of n = 26,209.

As a distribution of exposure is the resulting output of the assessment, characterising this distribution can be done in a number of ways. In the following, two exposure statistics are presented. The first is the arithmetic mean of exposure to represent the average exposure, and the other is the 95th percentile of exposure is used to represent the upper exposure in the population. Additionally, when using real habits and practices data, exposure statistics can be calculated over two populations. The first is the Total Population, i.e. all subjects in the survey, and the other is the Exposed Population, i.e. all those consumers who are exposed to the substance.

Given that there are two potential populations that can be used to characterise exposure, an immediate question posed is to determine which one is most appropriate. One guiding principle is that for aggregate exposure resulting from multiple sources that are used by the majority of the population (e.g. all categories of cosmetics and personal care products or most foods in the diet), then exposure is well represented by the Total Population. However, if exposure is due to a small number of products or is due to an infrequently occurring substance, then the Exposed Population is likely the more appropriate set to use. This is so that there is not inappropriate dilution of exposure statistics by the inclusion of large number of zeroes in their calculation. The initial problem formulation step of the assessment should consider this aspect by defining if a general population exposure or the exposures to the population of product users is the assessment goal.

3.2.4 Summary of Results

Scenario 1 – Triclosan Always Present at Max Use Levels

The only refinement introduced at this point is the use of a probabilistic model with which to assess consumer exposure that is based on real consumer habits and practices, as opposed to deterministically summing the contribution from each product category. All other assumptions regarding substance presence, concentration, product retention and penetration remain consistent as in the first case Tier 1 assessment (results in Table 4).

Moving to a probabilistic and subject oriented model can provide refinement of the estimates of exposure (although not always), but also offers a framework with which to introduce further inputs that can be used to improve estimates of exposure. In general, a probabilistic modelling methodology allows:

- The use of statistical distributions to characterise substance concentrations
- The use of presence probabilities to account for occurrence of chemicals
- The ability to stratify exposure by subpopulation
- The ability to examine the relative contribution of different sources to the overall exposure

Some of these refinements are examined in scenarios two (Table 7) and three (Table 8).

Table 7: Estimated exposure levels (absorbed dose) – Total Population

Product	Mean (µg/kg)	P95 (µg/kg)
Toothpaste	9.272	24.498
Mouthwash	20.555	104.629
Shower Gel	10.984	44.547
Face Powder	2.878	7.535
Blemish Concealer	0.288	0.754
Body Lotion	0.865	3.211
Deo/AP non-spray	0.662	3.227
Soaps	27.040	71.258
All Assessed Products	72.556	184.224

Table 8: Estimated exposure levels (absorbed dose) – Exposed Population

Product	Mean (µg/kg)	P95 (µg/kg)
Toothpaste	10.621	25.353
Mouthwash	53.339	155.883
Shower Gel	19.944	56.214
Face Powder	5.681	8.163
Blemish Concealer	0.568	0.816
Body Lotion	11.330	38.661
Deo/AP non-spray	1.469	4.370
Soaps	28.397	72.271
All Assessed Products	72.590	184.344

In this instance aggregate exposure results are very similar for the total and exposed population. In addition, aggregate estimates at the P95 level are similar to the maximum individual scenario Tier 1 value in Table 2 (164 ug/kg); the mean aggregate estimate is about a factor of 2 lower than this value.

Scenario 2 – Triclosan Present at Max Use Levels and Including Presence Probabilities

Here, it is no longer assumed that triclosan is always present in each product category, but rather it is assumed to be present with a probability of 10%. When the model runs and a subject in the database records using a given product category that can contain triclosan, then the presence of the substance is simulated with a probability of 10%. This means that on average, the subject will be exposed 10% of the time. Thus, the mean exposure is reduced by a factor of 10, which is not necessarily the case for higher percentiles as these will be driven by consumers exposed to triclosan with a higher frequency.

Note that for certain product categories in the Total Population, a P95 of zero is observed while the mean is non-zero. This is due to a combination of both a low proportion of product users and a low chemical occurrence giving rise to less than five percent of the population being exposure to the substance. This is not the case for the Exposed Population, where statistics are only calculated over the non-zero results. Such behaviour is not unusual in population based studies of exposure; however, care is required when communicating such results.

Table 9: Estimated exposure levels (absorbed dose) – Total Population

Product	Mean (µg/kg)	P95 (µg/kg)
Toothpaste	0.959	7.964
Mouthwash	1.962	0.000
Shower Gel	1.115	3.655
Face Powder	0.279	0.000
Blemish Concealer	0.030	0.340
Body Lotion	0.101	0.000
Deo/AP non-spray	0.067	0.000
Soaps	2.845	19.722
All Assessed Products	7.366	38.443

Table 10: Estimated exposure levels (absorbed dose) – Exposed Population

Product	Mean (µg/kg)	P95 (µg/kg)
Toothpaste	10.560	25.623
Mouthwash	49.476	138.437
Shower Gel	20.080	53.193
Face Powder	5.605	7.925
Blemish Concealer	0.570	0.815
Body Lotion	13.065	51.932
Deo/AP non-spray	1.451	4.521
Soaps	19.956	56.948
All Assessed Products	18.626	65.591

Table 9 & 10 show the results for the total population and the exposed population respectively. In this case the exposed population estimate is about twice that of the general population. The exposed population value at the P95 level is less than half of the maximal single use exposure predicted in Tier 1.

Scenario 3 – Triclosan Present at Max and Usual Use Levels and Including Presence Probabilities

In scenario 3 usual use levels of triclosan are modelled, so the only difference between scenarios two and three are a refinement of concentration levels. Results are shown in Table 11 and Table 12 for the total population and the exposed population respectively.

Table 11: Estimated exposure levels (absorbed dose) – Total Population

Product	Mean (µg/kg)	P95 (µg/kg)
Toothpaste	0.912	7.473
Mouthwash	1.323	0.000
Shower Gel	1.188	3.868
Face Powder	0.186	0.000
Blemish Concealer	0.014	0.162
Body Lotion	0.043	0.000
Deo/AP non-spray	0.066	0.000
Soaps	2.734	18.882
All Assessed Products	6.470	34.736

Table 12: Estimated exposure levels (absorbed dose) – Exposed Population

Product	Mean (µg/kg)	P95 (µg/kg)
Toothpaste	10.578	24.964
Mouthwash	35.471	105.851
Shower Gel	20.882	58.624
Face Powder	3.744	5.419
Blemish Concealer	0.280	0.401
Body Lotion	5.730	21.306
Deo/AP non-spray	1.449	4.306
Soaps	19.499	57.111
All Assessed Products	16.536	58.986

In this case, it is interesting to note that the exposed population P95 and mean values associated with a single product (mouthwash) exceed the aggregate exposures. This suggests that this single product, when used dominates total exposure. At the same time, it also suggests that its use is less frequent than many other products examined in the assessment. The Tier 1 value for this product (150 ug/kg) would have been conservative both for the exposed population at a higher tier, and also for the exposed population at an aggregate exposure level.

3.2.5 Conclusion

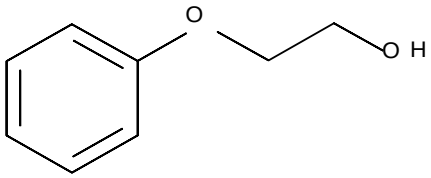
When performing any safety assessment, the first step is generally to perform a screening type exposure assessment to establish a margin of safety. Should the established margin of safety prove inadequate, the next step is to perform a more refined exposure assessment. A number of possible refinements are available, such as improving habits and practices data, refining concentration data, and the inclusion of presence probabilities. Bringing such refinements into an assessment has varying impacts and requires a probabilistic modelling framework in order to do so. In this specific example of triclosan in cosmetics and personal care products, it can be seen that the greatest refinements result from better habits and practices data with product co-use, and the use of presence probabilities. The refinement of concentration values has less impact on predicted exposure, which makes sense in light of the fact that refinement in concentration is directly

proportional to the resulting exposure, whereas refining product co-use and the frequency of occurrence can reduce the estimated exposure by several orders of magnitude. In addition, for this example the higher tier 2 aggregate exposure assessment was similar to or lower than the maximal exposure predicted for a single use in the Tier 1 assessment.

3.3 Case Study 2: Phenoxyethanol Exposure Assessment

3.3.1 Substance profile

Physicochemical properties



CAS: 122-99-6
Molecular Weight: 138.16

Phenoxyethanol is an oily colourless organic aromatic ether, that is freely soluble in alcohol, ether, and sodium hydroxide. It exists as a liquid at room temperature, and has a vapour pressure of 0.01 mm Hg (20 °C), and is lipophilic (log kOW 1.16).

Kinetics

Following dermal application phenoxyethanol penetrates the skin well and estimates of 80% dermal penetration are suggested for risk assessment (ANSM 2009, 2012).

Following oral administration the pharmacokinetics of phenoxyethanol has been well characterised. Studies in rats indicated that phenoxyethanol is rapidly and near completely absorbed after oral administration and > 90% of the administered dose is excreted in urine within 24 hr post-dosing (BASF, 2007). Phenoxyacetic acid (PhAA) is a major metabolite following oral and dermal routes of exposure to phenoxyethanol in rodents and humans, including preterm infants (BASF, 2007; Bührer, 2002; Howes, 1991). With a plasma half-life of 20–30 min, phenoxyethanol is rapidly and extensively metabolised in the organism by means of alcohol dehydrogenase and aldehyde dehydrogenase via acetaldehyde to PhAA (Johnson and Johnsson, 1990; Gross et al, 2009).

Toxicity

This report focuses on exposure, therefore, a detailed review of the toxicological data on phenoxyethanol and choice of critical study for the risk assessment is beyond the scope of this report. However, a brief review of

the key toxicity data is provided in order to provide an example of the risk assessment using the different exposure scenarios.

Phenoxyethanol has low acute toxicity. Numerous repeated dose toxicity studies in laboratory animals have been conducted on phenoxyethanol (briefly described in Troutman et al, (2015)). Based on these studies the target organs for toxicity are the hematopoietic system, liver and kidneys. From the entire data set of subchronic and chronic studies for phenoxyethanol, the lowest reported LOAEL is 400 mg/kg/day based on renal changes observed in a subchronic rat oral gavage study. The highest oral NOAEL below this oral LOAEL in the same species is the NOAEL of 369 mg/kg/day from a subchronic rat drinking water study, which is a suitable point of departure for the hazard assessment.

Phenoxyethanol was negative for genotoxicity in several *in vitro* (bacterial reverse mutation, mammalian cell cytogenetics, and gene mutation assays) and *in vivo* (chromosomal aberration (cytogenicity) and mouse micronucleus assay) studies. Two drinking water carcinogenicity studies in rats and mice demonstrated no increased incidence of tumours resulting from chronic exposures to PhE in rats and mice. A dermal developmental toxicity study in rabbits resulted in no teratogenic or developmental effects when administered at doses of up to 600 mg/kg bw/day. In addition, a two generation oral feeding study in mice revealed a parental NOAEL of 1875 mg/kg bw/day and an offspring NOAEL of 375 mg/kg/day.

3.3.2 Exposure Assessment

Tier 0 Assessment

Exposure Sources

Phenoxyethanol has several functions as an ingredient in consumer products, including as a preservative, antibacterial, solvent and fixative. Due to its multiple functions, it can be found in a number of consumer products, such as cosmetics and personal care products, pharmaceuticals and household care products.

In a project for the Consumer Product Safety Commission (CPSC), The American Chemistry Council Ethylene and Propylene Glycol Ethers Panel has tabulated uses of various ethylene glycol ethers in consumer products, suggesting common use in paints, coatings, dyes and cleaners (OECD SIDS, 2004), as shown in Table 13:

Table 13: Percentage of Phenoxyethanol Production used For Consumer Products. From OECD SIDS, 2004

Types of Consumer End Products	Consumer Products Vol (metric tons)	Consumer Products % Production	Consumer Products Approx. Weight	Percent Industrial/Consumer Use
Paint/coatings	< 4.500	37.5%	37-15%	
Cleaners	< 2.300	19.0%	5-15%	37/63
Dyes	< 450	6.5%	5-15%	

The highest human exposure to phenoxyethanol comes from nearfield exposure scenarios that have direct skin contact, and aggregate exposure will be greatest for products containing phenoxyethanol that are

frequently used, particularly if used in combination with other phenoxyethanol-containing products. According to the Danish EPA, phenoxyethanol is the most commonly used preservative in cosmetic and personal care products, and a recent survey reported that phenoxyethanol was present in 40.7% of 629 products. In addition, the US Department of Health and Human Services Household Products Database, which is available online at http://householdproducts.nlm.nih.gov/cgi-bin/household/brands?tbl=chem&id=745, shows that phenoxyethanol is present in several household products were direct skin contact is expected, such as hand dishwashing liquids, general purpose cleaners and laundry liquids.

Exposure Pathways

Consumer use of phenoxyethanol may result in dermal and inhalation exposures. However, due to its low vapour pressure, inhalation exposure is much lower than dermal exposure. Inhalation exposure is also limited by its relatively rapid degradation in the atmosphere. Occasional systemic exposure may occur via vaccines containing phenoxyethanol as a preservative. Therefore, as inhalation is considered not to be the major route it is not selected for further study here. In reality, phenoxyethanol, will evaporate to some extent during the application of a product, reducing the amount remaining on the skin. Accounting for the evaporation could conceivably lead to a further reduction of the dermal exposure estimate, but with some additional inhalation exposure.

Tier 1 Assessment

The products selected are the daily use of cosmetics and personal care products and household care products, which have direct skin contact on a frequent basis.

Cosmetic and Personal Care Products

The tier 1 assessment was based on exposure data from the SCCS Notes of Guidance 8th Revision SCCS/1501/12 (SCCS, 2012), shown in Table 14, using the conservative assumption that all of the products contain phenoxyethanol at a maximum concentration of 1% in product (worse case), which is the maximum level permitted under EU regulation. Dermal penetration of 80% was assumed for the dermally exposed products and 90% oral bioavailability was assumed for products that might be consumed orally. The output of the tier 1 assessment is shown in Table 15. In order to estimate the aggregate exposure, the phenoxyethanol exposures from the individual products were summed.

Table 14: Estimated daily exposure levels for different cosmetic product types according to Colipa data [SCCNFP/0321/02; Hall et al ***2007, 2011]***

Product	External Product Exposure g/day	External Product Exposure mg/kg/day	Retention Factor	Calculated daily exposure (g/day)	Calculated relative daily exposure (mg/kg/day)
Shower Gel	18.67	279.20	0.01	0.19	2.79
Shampoo	10.46	150.49	0.01	0.11	1.51
Hair Conditioner*	3.92	-	0.01	0.04	0.67
Hair Styling	4,00	57.40		0.40	5.74
Liquid Foundation	0.51	7.90	1.0	0.51	7.90
Makeup Remover*	5.00	-	0.1	0.50	8.33
Hand Wash soap*	20.00	-	0.01	0.20	3.33
Body Lotion	7.82	123.20	1.0	7.82	123.20
Face Cream	1.54	24.14	1.0	1.54	24.14
Hand Cream	2.16	32.70	1.0	2.16	32.70
Deo non-spray	1.5	22.08	1.0	1.50	22.08
Eye makeup*	0.02	-	1.0	0.02	0.33
Mascara*	0.025	-	1.0	0.03	0.42
lipstick	0.057	0.90	1.0	0.06	0.90
Eyeliner*	0.005	-	1.0	0.01	0.08
Toothpaste	2.75	43.29	0.05	0.14	2.16
Mouthwash	21.62	325.40	0.1	2.16	32.54

*Product types not covered by the Colipa studies: existing daily application amounts are divided by the mean human body weight of 60 kg.

The assessment assumes chronic (average, [mg/kg bw/day]) aggregate external exposure, and the results are shown in the table below.

Table 15: Tier 1 exposure data to cosmetic products. External exposures are calculated from SCCS 2012

Product	External Product Exposure g/day	External Product Exposure mg/kg/day	Fraction of Phenoxyethanol in Product	External Phenoxyethanol Exposure (mg/kg/day)	Estimated Absorbed Dose of Phenoxyethanol Assuming 80% Dermal Penetration, or 90% Oral Bioavailability* (mg/kg/day)
Shower gel	0.19	2.79	0.01	0.03	0.02
Shampoo	0.11	1.51	0.01	0.02	0.01
Hair conditioner	0.04	0.67	0.01	0.01	0.01
Hair styling	0.40	5.74	0.01	0.06	0.05
Liquid foundation	0.51	7.90	0.01	0.08	0.06
makeup remover	0.50	8.33	0.01	0.08	0.07
Hand wash soap	0.20	3.33	0.01	0.03	0.03
Body lotion	7.82	123.20	0.01	1.23	0.99
Face cream	1.54	24.14	0.01	0.24	0.19
Hand cream	2.16	32.70	0.01	0.33	0.26
Deo non-spray	1.50	22.08	0.01	0.22	0.18
Eye makeup	0.02	0.33	0.01	0.00	0.00
Mascara	0.03	0.42	0.01	0.00	0.00
lipstick	0.06	0.90	0.01	0.01	0.01*
Eyeliner	0.01	0.08	0.01	0.00	0.00
Toothpaste	0.14	2.16	0.01	0.02	0.02*
Mouthwash	2.16	32.54	0.01	0.33	0.29*
Total	**17.38**	**268.82**		**2.69**	**2.19**

The key contributors to aggregate chronic exposure to phenoxyethanol in this tier 1 estimate are the leave-on (non-rinse) products including body lotion, hand cream, face cream and non-spray deodorant (Deo) and also mouthwash, which has a high product exposure due to the fact that the habits and practices data suggest that a high amount of product, 21.62g/day, is applied with each use and it is assumed that 10% is swallowed (SCCS, 2012).

Household Products

The tier 1 assessment for household products was conducted using the REACH Exposure Assessment Consumer Tool (REACT) developed by The International Association for Soaps, Detergents and Maintenance Products (AISE) to specifically address washing and cleaning product exposure assessment. The tool was used to calculate Phenoxyethanol exposure via dermal and oral routes separately. Both direct dermal (i.e. during product use) and indirect dermal and oral (i.e. skin contact with residues in laundry and ingestion of residues from contact with crockery and cutlery) exposure was calculated.

The algorithms within AISE REACT for calculating the external exposure are as follows:

Direct dermal exposure in mg/kg/day

Expsys = F1 x C x Tder x F2 x F3 x F4 x Sder x n / BW

Where, F1: ingredient fraction by weight, C: concentration in wash solution (mg/cm^3), Tder: thickness of product in contact with skin (cm), F2: fraction transferred from solution to skin, F3: fraction remaining on skin, F4: fraction absorbed through skin, Sder: dermal surface area (cm^2), n: product use frequency (tasks/day) and BW: body weight (kg).

Indirect dermal exposure from clothes in mg/kg/day

Expsys = F1 x (M x (F'/W) x FD x FL) x Sder x F2 x F3 x F4 / BW

Where, F1: Ingredient fraction by weight, M: amount of undiluted product used (grams), F: fraction remaining in final liquor before spinning, W: total fabric weight (grams), FD: fabric density (mg/cm^2), Sder: dermal surface area (cm^2), F2: fraction transferred from solution to skin, F3: fraction remaining on skin, F4: fraction absorbed through skin and BW: body weight (kg).

Oral exposure from residues in mg/kg/day

Exp_{sys} = F1 x C x Ta x SA / BW

Where, F1: Ingredient fraction by weight, C: concentration in product (mg/ml), Ta: amount of water left on dishes after rinsing (ml/cm^2), SA: area of dishes in daily contact with food (cm^2) and BW: body weight (kg).

The REACT tool was run using the defaults in the tool and assuming a maximum use concentration of 15% phenoxyethanol (OECD SIDS, 2004), a dermal penetration value of 80% and an oral bioavailability value of 90%. The default values in the REACT tool are largely based on habits and practices data developed by AISE within the Human and Environmental Risk Assessment (HERA) project. The approach assumes that consumers use all products simultaneously and that the substance is present in each product category. The results are shown in Table 16. As with the personal care product assessment, the aggregate exposure to Phenoxyethanol was estimated by summing the exposures of the individual products.

Table 16: Tier 1 assessment of consumer exposure to phenoxyethanol from household products

Product	Exposure Scenario	Fraction of Phenoxyethanol in Product	Absorbed Dose (mg/kg/day)
Laundry liquid	Direct skin contact hand wash laundry	0.15	0.583
	Direct skin contact pre-treatment laundry	0.15	8.580
	Indirect skin contact wearing clothes	0.15	0.002
Hand dish wash	Direct skin contact dishwashing	0.15	0.125
	Indirect oral exposure to residues	0.15	0.001
General Purpose Cleaner	Direct skin contact cleaning surfaces	0.15	0.377
Total			**9.67**

In this Tier 1 assessment the key contributor to the aggregate exposure to phenoxyethanol from household products is laundry liquid. The estimate could be refined through the application of specific consumer exposure determinants (SCEDs). The SCEDs were not specifically developed for the purposes of aggregate exposure but could reduce the conservatism related to consumer habits and practices (for example, amount used, frequency of use and skin surface area).

Tier 2 Assessment

For this example, no tool or data were readily identified that could be used to assess aggregate exposure at tier 2 for the household products. Therefore, the cosmetics, personal care products were assessed using Creme Care and Cosmetics and PACEM, but the household care assessment was not further refined, and remain a tier 1 assessment. Note however, work is underway for both models to be expanded to include household products at a higher tier, by integrating data at the individual subject level.

Cosmetic and Personal Care Products

In tier 2, exposure assessment is refined in two respects. Firstly, realistic data on use and co-use of cosmetics in the population is considered. The use of this information accounts for the fact that not all products are used by all consumers to the same extend. Secondly, more realistic information on the concentration of phenoxyethanol in the products was considered.

The assessment of exposure from a particular use of a single product itself was not further refined. As in the first tier assessment, product dermal retention factors are taken as suggested in the SCCS Notes of Guidance for the Testing of Cosmetic Ingredients and their Safety Evaluation (SCCS, 2012). In addition, the same dermal and oral absorption fractions as used in the tier 1 assessment are assumed (i.e. 80% dermal absorption and 90% oral absorption).

The same personal care and cosmetic product types were included as used in the Tier 1 assessment, to allow consistency in approaches, and to enable the refinement of exposure by incorporating chemical occurrence values to be measured.

The higher tier models considered in this refinement are population based models, which means that they assess the distribution of exposure in a population. For comparison with the first tier approach, the 95th percentile was chosen as representative of population exposure in both the Creme and PACEM analyses.

Phenoxyethanol Concentration

Two exposure inputs were varied. Firstly, considering the concentration of phenoxyethanol in the products, in the more conservative estimates a maximum concentration of 1% was assumed in all personal care and cosmetics products (worse case), and in the more realistic scenario Danish EPA data, where the phenoxyethanol concentration was measured in a number of marketed formulations, was assumed (Danish EPA, 2015), as shown in Table 17.

Table 17: Danish EPA data on the analytical results of phenoxyethanol measurement in cosmetic and personal care products.

Product	Concentration of Phenoxyethanol in Cosmetic Formulations (%)
Shower gel	1.00*
Shampoo	1.00*
Hair conditioner	1.00*
Hair styling	1.00*
Liquid foundation	0.69
makeup remover	0.80
Hand wash soap	0.50
Body lotion	0.85
Face cream	0.84
Hand cream	0.40
Deodorant non-spray	0.51
Eye makeup	0.89
Mascara	1.00*
lipstick	1.00*
Eyeliner	1.00*
Toothpaste	1.00*
Mouthwash	0.30

*For product types that weren't included a concentration of 1% phenoxyethanol was assumed.

Secondly, the chemical occurrence of phenoxyethanol was considered, and in the more conservative case all products were assumed to contain phenoxyethanol, where as in the more realistic scenario chemical occurrence data obtained from the Mintel GNPD database was assumed.

Chemical Occurrence

Chemical occurrence data was used to infer the proportion of formulations on the market that contained phenoxyethanol. Mintel GNPD (http://portal.mintel.com/) is an online database that tracks consumer product launches across the globe. The Global New Products Database monitors product innovation and retail success in consumer packaged goods markets worldwide. More than 20,000 new products are added every month from 50 countries worldwide, ensuring GNPD users have access to comprehensive coverage, reliable data and robust reporting on products on the market.

The database is divided into categories such as Face/Neck Care, Body Care, Eye Care, and Lip Care. Using the site's search function returns the total number of products in that category. Adding the ingredient name (phenoxyethanol) gives the subset of those products containing this ingredient. By determining the number of SKUs within a product category that contain phenoxyethanol relative to the total number of SKUs, the chemical occurrence can be derived, which in this model is assumed to be the likelihood that a product phenoxyethanol.

This simple method was used to derive the presence probabilities for phenoxyethanol in the cosmetic categories. The presence probabilities for phenoxyethanol in Europe (EU) and North America (NA) were calculated using the method described, and the highest value was assumed for each product and then these values were rounded up to the nearest 10 to remain conservative as there is no understanding for relative market share of those products identified which could have an impact on likelihood for consumer use. The rounded up presence probabilities that were used in the tier 2 assessment are shown in Table 18.

Table 18: A summary of chemical occurrence data obtained from Mintel GNPD for Europe and the US. Calculated percentages are rounded up to the nearest 10%.

Product	Mintel Chemical Occurrence (%)
Shower gel	20
Shampoo	20
Hair conditioner	40
Hair styling	30
Liquid foundation	50
makeup remover	40
Hand wash soap	20
Body lotion	50
Face cream	50
Hand cream	50
Deodorant non-spray	10
Eye makeup	40
Mascara	40
Lipstick	10
Eyeliner	20
Toothpaste	10
Mouthwash	20

Creme Care & Cosmetics Model

The Creme Care and Cosmetics model is described on page 32, in the triclosan case study section.

The Probabilistic Aggregate Consumer Exposure Model (PACEM)

PACEM is a probabilistic exposure model based on product usage data collected in a survey on cosmetics use in the Dutch population. The survey included 512 adults (210 male and 302 female). PACEM contains information on use frequency and amounts used for 32 PCPs. Information on gender, age and body weight is available and linked with the product usage information for each individual in the model's database.

To run the model input is required on:

- the subpopulation to be considered (e.g. gender, age cohort to be considered);
- the products that are to be included in the assessment;
- the concentration of the substance in the product. These can be single values for each product or distributions of values to account for variability or uncertainty in the concentration data;
- the exposure per product use. This is to be expressed as an exposure fraction: the fraction of substance that is applied per use that the person is actually exposed to (e.g. is absorbed, inhaled, or is retained on the skin). Exposure fractions are specified for each product separately and can either be single values or distributions.

To assess aggregate exposure, PACEM simulates daily product use for a population based on the realistic product usage data. Next, this daily product use is combined with the product concentration data to assess daily total exposures for each individual in the model population. Chronic exposures are assessed by simulating exposures over multiple days and determining the daily average over this period.

PACEM can be used to simulate acute (single day) and chronic (daily average) exposure. Metrics included external exposure, absorbed dose and dermal load (for the risk assessment of sensitising materials).

Aggregate exposure assessment in the second Tier:

In the second tier refinements in the assessment are made in two respects. First, realistic use and co-use data of cosmetic products is taken into account. Second, more realistic information on product concentrations of phenoxyethanol, including presence probabilities are considered. The Creme Global and PACEM models, that are used in this second Tier include realistic product use information. Product concentration refinements are included in four different scenarios:

1. Phenoxyethanol always present in products at a concentration of 1%;
2. Phenoxyethanol always present in all products, concentrations assumed from the Danish EPA report (see concentrations in Table 7);
3. Assumed Mintel chemical occurrence rounded up to the nearest 10% (see chemical occurrence in Table 17) concentration is 1%;
4. Assumed Mintel chemical occurrence rounded up to the nearest 10%, concentrations assumed from the Danish EPA report (see concentrations in Table 17.

Assessment using PACEM

In the PACEM assessments the following inputs were used:

- The subpopulation of female, adult consumers was selected. the same list of products as used in the first tier was selected;
- Exposure amounts were calculated based on the retention factors given in (SCCS, 2012) and the assumptions on the absorption fractions of 80% for the dermal route and 90% of the oral route;
- Concentrations of the substance in the product varied among the four scenarios considered. For each scenario, a set of products was simulated based on the scenario assumptions. This was done as follows: in scenarios in which a chemical occurrence of less than 100% was considered, the product set was constructed by adding products with zero concentration in the proportion specified in the Mintel database. For the other (non-zero concentration) products, the concentration was set to the level assumed in the scenario. This assures that when products are sampled at random from this set the correct proportion of products considered in the daily product use contain phenoxyethanol.

Using these inputs, chronic absorbed doses from cosmetics use were modelled by simulating daily exposures for a period of 28 days and averaging over this period.

Assessment using Creme Care & Cosmetics:

- the subpopulation of female, adult consumers from the EU and the US were selected. The same list of products as used in the first tier was selected;
- exposure amounts were calculated based on the retention factors given in (SCCS, 2012) and the assumptions on the absorption fractions of 80% for the dermal route and 90% of the oral route;
- concentrations of the substance in the product varied among the four scenarios considered. For each scenario, the model iterates through each subject in the habits and practices survey and simulates a daily exposure resulting from the products selected for inclusion. By iterating through each day of product use for each subject, total daily exposure is calculated for each individual, to give their seven-day average or chronic exposure and their one-day maximum or acute exposure. For concentrations that are in the form of statistical distributions and/or with presence probabilities, these are simulated at each exposure event using random sampling to reflect the concentration and presence parameters inputted.

Using these inputs, chronic absorbed doses from cosmetics use were modelled by simulating daily exposures for a period of 7 days and averaging over this period.

Summary of Selected Results

Assessment in PACEM

The daily average absorbed dose of phenoxyethanol was assessed in each of the four refinement scenarios defined above. The 95th percentiles of the population for each scenario are shown in Table 19.

Table 19: Internal exposure estimates to phenoxyethanol generated in PACEM

Scenario	Statistic	Estimated Average Daily Absorbed Dose in Total Population of Adult Females (mg/kg/day)
Phenoxyethanol always present at 1%	P95	2.7
Phenoxyethanol always present at Danish EPA use concentrations	P95	2.3
Refined with phenoxyethanol chemical occurrence, when present 1% assumed	P95	1.5
Refined with phenoxyethanol chemical occurrence and Danish EPA use concentrations	P95	1.3

The results show that by progressively incorporating more realistic information on the product composition and chemical occurrence of phenoxyethanol, the aggregate exposure estimate is reduced. In scenario 1, which assumes that phenoxyethanol is present in every product used by the subjects, the mean internal aggregate exposure is 2.7 mg/kg/day, and by incorporating both the specific concentration data and the chemical occurrence data, exposure is refined. Indeed, in scenario 4 where both factors are considered in the model, the P95 internal exposure (absorbed dose) is reduced by a factor of two to 1.3 mg/kg/day.

Assessment in Creme Care & Cosmetics

The output of the Creme aggregate exposure model is the internal exposure to phenoxethanol shown in Table 20.

Table 20: Internal exposure estimates to phenoxyethanol generated in Creme Care and Cosmetics

Scenario	Statistic	Estimated Average Daily Absorbed Dose in Total Population of Adult Females (mg/kg/day)
Phenoxyethanol always present at 1%	P95	1.14
Phenoxyethanol always present at Danish EPA use concentrations	P95	0.78
Refined with phenoxyethanol chemical occurrence, when present 1% assumed	P95	0.50
RCR Refined with phenoxyethanol chemical occurrence and Danish EPA use concentrations	P95	0.38

The results show a comparison of the P95 summary statistics for Creme scenarios 1 through 4.

From scenario 1, which assumes that phenoxyethanol is present in every product used by the subjects, the mean internal aggregate exposure is 1.14 mg/kg/day. When the exposure estimate is refined with the more specific product use concentrations for phenoxyethanol, the mean internal exposure is refined by about 30% to 0.78 mg/kg/day. Similarly, when chemical occurrence is incorporated, to take into account that not all cosmetic and personal care products on the market contain phenoxyethanol, the P95 internal exposure is refined by as 56% to 0.5 mg/kg/day compared to scenario 1. The greatest refinement is achieved by incorporating both the specific concentration data and the chemical occurrence data in scenario 4, where the P95 internal exposure is 0.38 mg/kg/day, which is a reduction of 67% as compared to scenario 1, and a reduction of 82% as compared to the deterministic tier 1 assessment.

Key summary statistics for the Creme scenarios are presented in Table 21 showing the distribution of exposure. In this case when the chemical occurrence data is included (in scenario 3 & 4) the P5 exposures become zero owing, to a portion of the population not using certain products in the aggregate scenario.

Table 21 Summary percentile statistics of aggregate exposure showing estimated average daily absorbed dose in total population (ug/kg/day)

	Product	P5	P25	P50	Mean	P75	P95
1	Phenoxyethanol always present at 1%	43.75 ± 2.04	120.54 ± 1.47	247.95 ± 2.11	377.93 ± 5.10	459.36 ± 5.52	1140.78 ± 26.06
2	Phenoxyethanol always present at Danish EPA use concentrations	20.10 ± 0.58	63.05 ± 0.86	152.04 ± 2.31	243.72 ± 2.40	300.99 ± 3.69	777.72 ± 10.62
3	Refined with phenoxyethanol chemical occurrence, when present 1% assumed	0.00 ± 0.00	2.18 ± 0.21	22.51 ± 1.04	116.06 ± 1.85	124.32 ± 3.16	499.25 ± 13.70
4	Refined with phenoxyethanol chemical occurrence and Danish EPA use concentrations	0.00 ± 0.00	1.36 ± 0.12	17.21 ± 0.75	91.23 ± 1.75	90.76 ± 4.75	378.05 ± 9.93

Discussion

In this exposure estimate for phenoxyethanol in cosmetic and personal care products, a tiered aggregate exposure assessment was conducted. At tier 1: simple deterministic addition of individual product exposures using the SCCS 2012 exposure values for the individual products in the EU population, and tier 2: a probabilistic person-orientated method incorporating product specific phenoxyethanol concentration and chemical occurrence data in the female population, using 2 models: Creme Care and Cosmetics, and PACEM. The female population was chosen at this more refined tier 2 in this instance to ensure that the exposure estimate was relevant for the population of cosmetic and personal care users, as it is known that females are higher users of these products. This study demonstrated the advantages of refining the exposure using subject-level probabilistic analysis, and specifically by incorporating chemical occurrence data. Using the deterministic simple addition with basic aggregation (tier 1) the P95 internal exposure is 2.19 mg/kg/day. By utilising the

tier 2 approach the P95 internal exposure is refined to 1.38 in PACEM and 0.38 mg/kg/day in Creme Care and Cosmetics.

Comparing the outcomes of the higher tier aggregate exposure models with the first tier method for aggregate exposure should demonstrate that the incorporation of realistic information on use and co-use and the chemical occurrence of the substance lead to a reduction of the exposure estimate. Indeed, the higher tier Creme aggregate results at the P95 level range from about 40 – 114% of the highest screening level prediction for a single use (0.99 mg/kg/day, Table 6).

However, in the case of the PACEM assessment, the reduction is less than was observed in previous applications (Gosens et al, 2013, Dudzina et al, 2015) where the estimated exposure in proceeding from a low tier to a more realistic assessment was typically in the order of a factor 100. This could be due to the fact that this phenoxyethanol study looked at only a female population from the Netherlands, where exposure is mainly driven by the exposure to body lotion, (which accounts for about half of the total exposure estimated in the tier 1 assessment) and is not as much the result of a total aggregate assessment contributions from different sources of the aggregate exposure estimate.

In the case of PACEM, the first two refinement scenarios in the tier 2 assessment even lead to comparable estimate (even somewhat higher) as the SCCS approach used in Tier 1. There are several different reasons for this. The source of the exposure data in the two approaches is completely different; The SCCS data is based on European wide probabilistic exposure studies from the male and female population (Hall et al, 2007 & 2011), as compared to the PACEM input data which is from a survey in the Dutch population (Biesterbos et al, 2015).

In the case of the Creme Care and Cosmetics Tier 2 assessment, the exposure input data includes the same European data on amounts per use for the products, derived from Hall et al, (2007, 2011), but also included in the tier 2 assessment is the product co-use data at the subject level (is true for PACEM product use database), explaining why the exposure output is refined – through the use of a probabilistic model with which to assess consumer exposure that is based on real consumer habits and practices, as opposed to deterministically summing the contribution from each product category. All other assumptions regarding substance presence, concentration, product retention and penetration remain consistent.

In both the PACEM and Creme probabilistic exposure assessments the inclusion of product-specific concentration estimates and chemical occurrence data have considerable impact on refining the exposure estimate.

Household Products

To advance to a tier 2 estimation of aggregate exposure to phenoxyethanol from household products further data are required. The realism in the assessment can be increased by incorporating data on co-use patterns of product usage and the chemical occurrence of the ingredient. Some publicly available databases do exist that contain substance-specific information such as prevalence in products however this information is usually limited and important data required for the aggregation of exposure are missing for example, co-use data at

an individual user level. Recently work completed under the CEFIC-LRI-B7 project has highlighted the paucity of co-use data for household products.

3.3.3 Conclusion

As this case study shows, aggregate exposure assessments can be quite complex, particularly if the material of interest is ubiquitous, being present for example in several consumer products, foods and the environment.

Such assessments are, by necessity, an iterative process, which should be conducted using a tiered strategy, where the lowest tier (0) consists of a rough sum of exposure to each product, the mid-tier (1) tends to be a semi quantitative estimate, such as a deterministic estimate with conservative assumptions, and the higher tier (2) is a more realistic estimation of population exposure that is modelled using probabilistic methods and a person-orientated approach. The rough or low tier estimates can be calculated quickly yielding conservative exposure values, and if this approach is lower than the “safe” toxicological exposure dose, then it may not be necessary to move to a higher tier. While exposure assessments at tier 2, using person orientated probabilistic approaches to estimate exposure in populations, can be data-intensive and time consuming, they produce more refined and accurate estimates of population exposure, enabling the risk assessor to feel confident that the risk assessment is applicable to the population of interest.

The estimated refined internal exposures can be compared with the experimental biomonitoring data estimated from urine excretion. As discussed in Troutman et al, 2015, three human biomonitoring studies (Fromme et al, 2013; Goeen et al, 2001; Garlantézec et al, 2012) that include a total of 637 subjects report levels of the major metabolite of phenoxyethanol, PhAA, in urine ranging from 0.12 to 47.4 mg/L, with the highest values reported by Fromme et al (2013). In the Fromme study, the measured concentration of PhAA in urine collected from 44 subjects was 0.80 mg/L (median), 23.6 mg/L (95th percentile) and 47.4 mg/L (maximum). From this the corresponding external dose level of phenoxyethanol was estimated at 0.015 (median), 0.43 (P95) and 0.86 (maximum) mg /kg/day by assuming that the urine samples were collected under steady-state conditions from the general population with corresponding body weight and urine output values of 70 kg and 1.4 L urine/day, respectively (Davies and Morris, 1993). This estimated P95 internal exposure value of 0.43 mg/kg/day from biomonitoring data, can be compared to the tier 2 P95 internal exposure estimates from the PACEM and Creme Care and Cosmetics assessment tools (1.3 mg/kg/day and 0.38 mg/kg/day) and are similar. However, aggregation of the exposure from household products yields an internal exposure value of 9.67 mg/kg/day. Comparison of this value with the internal exposure value from biomonitoring data demonstrates that the lower tier tools do not provide a realistic estimate of general population exposure that can be aggregated with other exposures. Investment is needed in the collation/generation of data (e.g. co-use and chemical occurrence data) for household products to facilitate the development of higher tier more realistic aggregate exposure estimates across consumer product categories.

4. DISCUSSION AND CONCLUSION

The landscaping exercise demonstrated that tools and data exist to estimate exposures from consumer products but the amount of data and tools available varies per applicability domain and tier of exposure assessment. The tabulated information provides a useful resource for individuals seeking to perform consumer exposure estimation. An evergreen version of this or a similar reference resource would be useful for the exposure assessment community in general.

In practice, the purpose of the exposure assessment and the required level of detail define the framework and algorithm of exposure modelling and, in particular, the strategy of aggregation of exposure (e.g. sum of worst-cases, or consideration of more refined data like products co-use and chemical occurrence of the chemical). This information should be borne in mind at all points in an exposure assessment, in turn informing what tools and data are best used for a given purpose. Different models and data are best suited for specific purposes, and knowing what tier given tools can to be used for is a vital consideration when performing exposure estimations. Said otherwise, the exposure assessment should be fit-for-purpose.

At lower tiers, for chemicals with a large margin of exposure, it may be sufficient to simply sum worse case consumer exposures, bearing in mind that the output will not be realistic. Lower tier models are purposefully designed estimates of exposure considered to be conservative, that is a high estimate of exposure potential so that they can quickly prioritise where more detailed exposure estimation may be useful. Thus, adding individual low tier estimates will provide a quantitative value that is not likely to reflect an actual exposure, but rather an inflated exposure estimate. At higher tiers, aggregation ideally should adhere to a person-oriented approach (Delmaar et al, 2006) to maintain consistency and to avoid unreasonable overestimation of exposure. If exposure potentially occurs via different sources/pathways, the combination of the pathways considered in the assessment should represent a realistic situation for the considered individual. Sources/pathways that in reality would never co-occur should not be combined (for example, the occupational exposure of an industrial worker should not be combined with the hand-mouth contact exposure of an infant).

Another important aspect for consideration when aggregating exposure is the toxicity of the chemical under study. The timescale on which the exposure is assessed should be consistent with the exposure durations for which health effects are observed. If acute toxicity is a critical endpoint, the assessment should estimate exposures on acute timescales (e.g. one day). Here, details on the temporal and spatial correlations of single exposure events become important, since e.g. two or more exposures occurring simultaneously along different pathways may in combination lead to a peak exposure exceeding some tolerable level, although each exposure event individually may remain below this level. If longer (e.g. one year) timescales are considered, adding the average exposures from different pathways without explicit reference to the temporal correlations between the exposure events can be acceptable. However, in the case of a highly variable profile, the time-averaged value may not only depend on the length of the averaging interval but also on the commencement and termination of this interval (e.g. a weekly average from Monday to Monday or from Sunday to Sunday).

Besides the timescale, the aggregation strategy is very much determined by exposure route(s), which in turn is also governed by the chemical toxicity profile. Generally, when the health effects differ among exposure routes, aggregation should be performed for each individual route separately (ECHA, 2016), followed by the integration of the commonly expressed route-specific aggregate exposures into a ‘collective aggregate

exposure'. To accurately aggregate the route-specific doses e.g. to derive the total systemic dose, one needs to calculate the uptake, i.e. the amount of substance that can penetrate the outer barrier of the body (such as skin, lung or gut). Therefore, it is essential to distinguish between the exposure that describes the situation when the human body gets in contact with a chemical and the (internal) dose that actually describes the amount of chemical taken up into the human body as a result of exposure event. The route-specific uptake rates, which are usually measured by means of *in vitro* or *in vivo* animal studies, may not necessarily reflect the true absorption or penetration, since realistic exposure scenarios typically differ from the experimental conditions of these studies. The differences may arise due to studying of the pure substance instead of product mixtures, application of high/infinite doses, translating *in vitro* results to *in vivo* situations (Blaauboer, 2010; Yoon et al, 2012).

In conclusion, doing aggregate exposure in a meaningful way, using higher tier approaches, requires a high level of detail, in both exposure and hazard aspects, to support the development of realistic summed estimates of exposure via multiple sources. This level of information can be resource intensive to collect. The literature examples provide cases where this has been done for select product categories. Few studies provide aggregation on a total level from all sources, which would require an even greater level of information on co-exposure patterns and likelihood of those patterns, covering the entire range of possible exposure sources for a substance.

This evaluation of the state of science suggests that a most useful first effort might be further development of guidelines for understanding when the additional information provided by an aggregate estimate is most warranted. For example, if population level biomonitoring data are available for a substance and that substance is shown to have low risk potential, that substance may be a lower priority for directing resources to obtain detailed information needed to support aggregate modelling. If, however that substance is considered to have a risk potential that suggests exposure reductions may be appropriate and a specific exposure source is not recognised to be dominant, then it may be appropriate to perform an aggregate assessment to identify key source contributions that could be acted upon. Other types of criteria, such as those mentioned earlier, could be considered for inclusion in a systematic approach to identifying when the level of resources needed to perform aggregate exposure estimation will provide information needed to adequately characterise risk or safety potential, depending upon the purposes of the assessment being performed.

4.1 Areas of Opportunity for Exposure Science in the next 2-5 years

Exposure science is an ebullient and ever-developing area of research driven in part by the number and volume of chemicals being produced. Advances in analytical capabilities, increased public awareness and access to information on chemical hazard and exposure, as well as consumer market development also warrant continuous advancement of research in exposure assessment. With respect to cosmetic and personal care products in Europe, the regulatory bans on animal testing has resulted in exposure becoming more important, as it is increasingly recognised exposure and toxicokinetics are far more discriminating determinants of risk than is hazard. Scientists routinely work to develop *in vitro, in silico* and modelling approaches as alternatives to more traditional toxicology methods for use in safety assessments. Good exposure modelling is essential so

that *in vitro* doses can be translated to realistic exposure scenarios in consumers, and in reverse to allow safety assessments going forward in the new paradigm.

Attempts have been made by the scientific community to prioritise chemicals based on *in vitro* high-throughput screening assays and focus research on those substances that need to be further tested for potential toxicity (http://www2.epa.gov/chemical-research/toxicity-forecasting). Alongside chemical hazard characterisation, developing companion methods for high-throughput exposure assessment is also receiving much attention (http://www2.epa.gov/chemical-research/rapid-chemical-exposure-and-dose-research). Models like SHEDS-HT, developed and used under ExpoCast framework by the U.S. EPA, provide estimates of multi-source and multi-route exposure for thousands of chemicals. Combining large-scale exposure estimations with high-throughput hazard predictions provides the capability to develop rapid risk-based screening for chemicals, which are most in need of additional testing. However, the improvement of modelling tools for realistic exposure assessment is still an ongoing process, which attempts to identify and address existing challenges.

For refined/sophisticated exposure modelling, detailed knowledge about the actual sources of chemical exposure, related pathways and uptake mechanisms is essential. Assessment of aggregate exposure, i.e. exposure occurring via multiple (equally important) sources/routes, requires a systematic approach. Numerous research efforts have been directed towards accumulating raw input data for comprehensive exposure modelling in residential and consumer settings, as well as towards the development of validated modelling approaches for realistic exposure predictions (PACEM, Merlin-Expo, INTEGRA, CARES, Creme Care & Cosmetics). The first aspect encompasses data collection, e.g. information on products composition and co-use, chemical concentrations in consumer products and contact media, activity records and product use patterns, population biometric details, etc. It is also important to account for the ingredient's prevalence or frequency of occurrence (chemical occurrence) in a specific product category. Should reliable data on the market fraction of a specific product category containing the substance of interest be available, the exposure predictions could be much more accurate compared to the estimates obtained assuming 100% prevalence. To date, the exposure input data are only available for certain types of consumer products (e.g. cosmetics and personal care, cleaning products) and are scattered across various consumer product databases and scientific literature. It would be useful to develop a narrative for each exposure assessment to indicate when obtaining additional information would be of greatest use. For example, in some cases where the lower tier exposure estimate associated with a single source are very conservative, they might exceed higher tier aggregate estimates (for multiple sources) that use more realistic data. In such instances the lowest tier single source value might be sufficient to account for aggregate sources as well, due to the conservative assumptions. In these cases, the narrative should detail areas of conservatism in the exposure assumptions enabling the assessor to focus refinement efforts on areas that would have the greatest impact, if required. Wider engagement of industry, public and regulators into generation, harmonising and management of input data related to consumer exposure will foster the advances and predictive power of aggregate exposure models. One example where this has been successfully carried out is the ongoing effort by the Research Institute for Fragrance Materials (RIFM), who routinely gather fragrance use levels of fragrance materials in a variety of personal care products and cosmetics using an online data portal, ultimately for integration into the Creme RIFM aggregate exposure model.

Validation of predicted exposure is another important aspect to be considered while developing and advancing exposure tools. Validation normally involves the verification of the modelling assumptions and the input parameters ('model verification'), as well as the evaluation of the magnitude and ranges of the estimated exposure against real world values ('assessment verification'). The validity of the individual models with regard to their applicability for modelling exposure scenarios should be checked along with the verification of the integrated system of separate models. Addressing verification issues throughout the whole modelling chain from source to dose and for various building blocks of the model guarantees that coincidental correspondence between predictions and measurements at the end of the chain is avoided.

Validation of human exposure predictions normally includes quantitative relation and comparison of the modelling results (i.e. 'target dataset') to independent measurements (i.e. 'verification dataset') with a specific care given to the verification dataset coming from a representative and comparable population. The exposure estimates can be compared e.g. to human biomonitoring (HBM) data or chemical concentrations measured in different microenvironments (e.g. residential indoor air, house dust), provided that these measurements were collected under similar conditions, i.e. the conditions reflected in exposure model. A physiologically based pharmacokinetic (PBPK) or mechanistic multi-media fate models can then be used to convert/bridge the exposure predictions to either body tissues and fluids or environmental media concentrations, respectively. Thus, it may be worth looking at collecting relevant measurement data in order to substantiate models' validity in their application risk management purposes. To date, biomonitoring studies have greatly improved understanding of population level exposures, but their usefulness for evaluating exposure model predictions remains limited due to lack of contextual information. The incremental effort of including surveys to help understand exposure sources of biomonitoring participants would enable this information to be better used for exposure model validation and development. Ideally these surveys would include information on dietary patterns, activity patterns, locations, and consumer product use so that total exposures estimated from biomonitoring data could then be compared to the sum of model predictions across all sources.

Further directions for improvement of aggregate exposure models are foreseen from the perspective of model validation with spot sample biomonitoring data. It is deemed appropriate to increase temporal resolution of the consumer exposure model and calculate aggregate individual exposures not on a daily basis but within shorter time intervals (e.g. 6 hours). This approach would be primarily advantageous for validation of aggregate exposure predictions for those compounds that have very short elimination half-lives relative to in-between exposure intervals (e.g. parabens, phthalates), as many of these compounds demonstrated substantial intra-individual, within-day variation in biomarker concentration (Preau et al, 2010). For such analytes direct use of the spot samples from an individual over a single day in reverse dosimetry approaches may result in up to three orders of magnitude variation of the external dose estimates for the same day and individual (Aylward et al, 2012). A highly-resolved consumer exposure model could significantly facilitate interpretation of observed variability in cross-sectional epidemiological studies and assist in design of studies utilising biomonitoring data as markers for exposure.

Linking external dose-based exposure models to biomonitoring data requires the use of physiologically-based pharmacokinetic (PBPK) models, in order to establish the link between the externally applied dose and the resulting concentration measured in a bodily fluid. Additionally, with the advent of alternative non-animal based methods in toxicology, it is likely that PBPK models again will be vital in linking safe-levels derived from *in vitro* cell systems to doses from external exposure. This is also the case in reverse dosimetry. Therefore,

greater effort needs to be placed upon linking PBPK models with more “conventional” exposure models to facilitate better risk assessment in the future.

The probabilistic person-oriented approaches to aggregate consumer exposure modelling can also improve chemical risk assessments. It is, however, challenging to implement probabilistic models when input data are scarce or not available, and the generation of required inputs is both laborious and expensive. It might therefore be worth exploring modern statistical tools that can help in the situations of data paucity, for instance the Bayesian approach (Herring and Savitz, 2005; Crépet and Tressou, 2011). The concept is based on Bayes’ theorem and provides a sound mathematical framework for incorporating prior statistical knowledge (in the form of a probability distribution) about model parameters and updating this knowledge with new data (likelihood). Bayesian analysis could be useful if e.g. one would want to estimate the blood concentration distribution of a specific biomarker in a given population having only few data points (likelihoods). Consideration of a large monitoring dataset available for a similar population (prior distribution) makes it possible to derive a posterior distribution for the former population assuming that the exposure circumstances in both populations are comparable. Such an assumption should be a subject to additional verification utilising (cross-sectional) socioeconomic data, time activity patterns, consumer behavioural information to allow conclusions on exposure similarity. The derived posterior distribution can then be used as an approximation of the "true” concentration distribution of the investigated substance in the population of interest, enabling rigorous validation of exposure modelling. Additionally, and as mentioned previously, approaches should be considered or developed that address whether aggregate exposure assessment is in fact necessary or of use, such as by considering an analogy to the Maximum Cumulative Ratio used in mixture assessment (Price and Han, 2011).

Additionally, there is a potential to enhance predictive power of aggregate exposure models by reducing the model uncertainty due to inappropriate or incomplete reflection of true exposure mechanisms. For example, the potential adsorption of airborne chemicals to interior surfaces can be included, should the information on chemical‘s air: surface partitioning be available (Hodgson et al, 2003). Failure to include these additional sinks and potential secondary emission sources may result in inaccurate estimation of the population inhalation exposure. Furthermore, the development and implementation of computational algorithms for aggregate dermal exposure and risk assessments of the product ingredients identified as potential contact allergens/sensitisers is needed. Here, potency is defined as the relative ability of a chemical to induce sensitisation, which is determined by the quantity of a chemical per unit surface area required for the acquisition of skin sensitisation in a previously immunologically naive individual (induction phase) (van Loveren et al, 2008). Nevertheless, the question remains whether and under which circumstances using external dermal load is the correct way to proceed in a quantitative risk assessment (QRA) of sensitisers, as dermal absorption may be a crucial step in skin sensitisation. There are some, not yet quantifiable, exposure factors that may influence the internal exposure, among others being e.g. the concentration of Langerhans cells (at specific skin sites) that transport the allergen (as hapten) to regional lymph nodes, where it is presented to responsive T-lymphocytes inducing an immune response (sensitisation) (Api et al, 2008). A subsequent exposure will provoke a dermal inflammatory (allergic) reaction. The challenge is therefore to mechanistically model the internal process of sensitisation, including dermal absorption, hapten formation, Langerhans cell transport to the lymph nodes, repeated aggregate exposures from application of multiple consumer products under different scenarios and apply this in QRA.

Another area of opportunity for exposure science is the plethora of devices that are being used to monitor consumer health. On the consumer side, there are a large number of self-reporting smartphone apps and wearable technologies that monitor key exposure determinants such as activity, diet and other health parameters that are relevant to consumer health and potentially exposure. On the more scientific side, there sensor technologies have improved in quality and reduced in size, enabling a greater volume of data to be generated and gathered in order to monitor and assess consumer exposure via controlled studies, by e.g. examining inhaled air in various locations and scenarios. The volume of data generated from either approach is potentially huge, and would require computational platforms capable of handling what is now commonly termed Big Data.

4.2 Conclusions

While being a well-established component of risk assessment, exposure assessment is still an often-overlooked step in establishing the safety of a chemical. Greater emphasis needs to be placed upon exposure assessment if purely hazard-driven approaches are to be avoided in the safety assessment of chemicals. This is particularly the case in light of the current trend that considers alternative techniques like *in vitro* assays and *in silico* models for establishing a safe dose of a chemical for humans, which are becoming more and more common place as we move towards alternatives to animal testing. Such methods are used as both screening techniques for the prioritisation of chemicals for risk assessment and as a complete alternative to animal testing to establish safe doses protective of human health. Also, it should always be borne in mind that once a safe level or health based guidance value is established for a chemical, the exposure aspect is often the only avenue available to the risk assessor and risk manager in terms of analysing and affecting human exposure and therefore safety.

Despite the importance of exposure assessment, challenges still remain and have been highlighted in this report. The first is access to the appropriate tools and data for conducting consumer exposure assessment. While many sources of information are available, no centralised repository exists where all sources are catalogued for use, detailing domain of applicability and the nature of the data. Additionally, it is not always clear what level of detail or what tier of exposure assessment various data sources and tools are appropriate for. Some efforts have been made to create a resource providing an overview of available tools and data sources for consumer exposure assessment, as well as detailing the nature of the data and tools. While this represents an important first step, it should be recognised that the resource is not exhaustive. A resource of available tools and data sources for consumer exposure assessment should always be a dynamic resource that is continually updated, ideally housed in a web-based platform that can be interactively accessed and refreshed as new tools and data sources become available.

In terms of gaps identified for data sources and tools, key amongst these were a lack of a database on the chemical composition of consumer products based on actual use levels. Such a resource is important for developing realistic exposure estimates, as it is often the first port of call when refining an exposure assessment which is often based on maximum authorised use levels. Such a database often raises the issue of access to proprietary data; however specific use levels are not always required as ranges or estimates of statistical distributions of concentration are often all that is required. Similarly, resources that determine the frequency of occurrence of a chemical in consumer products or the chemical occurrence (often derived from

market survey databases) are a key resource that should be greater developed owing to the refinement they offer in an exposure assessment.

Knowing then what data and tools are available, an immediate question posed is what is the appropriate use of different data for different types of exposure assessments? This question was addressed by examining the nature of different types of data and tools and via two case studies in aggregate exposure. It was established that low tier tools are not appropriate for determining aggregate exposure, due to their inherent conservatism. This is particularly true for tools and data sources for industrial chemicals in consumer products outside of the cosmetics and personal care products domain. Should aggregate exposure be required for that area, greater work and effort is required to gather the appropriate data on product co-use. What may be of greater benefit is to place resources into techniques that establish whether aggregate exposure is required at all. For example, the case studies indicated that the additional resources dedicated to aggregate exposure predictions could result in exposures similar to maximum screening level predictions for single products. For domains where higher-tier tools are available (namely cosmetics), the considerable refinements that can be introduced by data on consumer habits and practices, product co-use, refined concentration values and presence probabilities was demonstrated using the examples of triclosan and phenoxyethanol. These case studies re-establish an important point; if the margin of safety initially established in a screening level exposure assessment is unacceptable, the next steps could be either a more refined exposure assessment or a risk management measure. Factors such as uncertainty, variability, and initial skew or bias in the original estimation should be considered to assist in decision making as to which of these steps is appropriate.

ABBREVIATIONS

AISE	International Association for Soaps, Detergents and Maintenance Products
C&PCPs	Cosmetics and personal care products
Cefic	European Chemical Industry Council
Cefic-LRI	Cefic Long-range Research Initiative
COLIPA	Cosmetic trade association now called Cosmetics Europe
CONCAWE	European Oil Company Organisation for Environment, Health and Safety
CPCat	EPA Chemical/Product Categories Database
CPSC	(US) Consumer Product Safety Commission
D5	Decamethylcyclopentasiloxane
Danish EPA	Danish Environmental Protection Agency
DIY	Do-it-yourself
DNEL	Derived no effect level
DPGME	Dipropylene glycol methyl ether
DUCC	Downstream Users of Chemicals Co-ordination Group
EFSA	European Food Safety Authority
EGBE	Ethylene glycol butyl ether
EGRET	The European Solvents Industry Group (ESIG) Generic Exposure. Scenario (GES) Risk and Exposure Tool
EHMC	Ethylhexyl methoxycinnamate
EPHECT	European collaborative action: Emissions, Exposure Patterns and Health Effects of Consumer Products in the EU
ESR	Existing substances regulation
GES	Generic Exposure Scenarios
GNPD	Global new products database
HBM	Human biomonitoring
HERA	(AISE) Human and environmental risk assessment project
INTEGRA	Integrated external and internal exposure modelling platform
IPCS	International Programme on Chemical Safety
LPG	Liquid petroleum gas
LOAEL	Lowest observed effect level
MAR	Maximum aggregate ratio
MCR	Maximum cumulative ratio
ME	Microenvironmental
Merlin	Modelling **e**xposure to chemicals for **R**isk assessment: a comprehensive **L**ibrary of multimedia and PBPK models for **I**ntegration, Prediction, u**N**certainty and Sensitivity analysis Expo tool
MOA	Mode of action
NHANES	(US) National health and nutrition examination survey
NOAEL	No observed adverse effect level

PACEM	Probabilistic aggregate consumer exposure model
PBPK	Physiologically based pharmacokinetic
PC	Product category
PCP	Personal care products
PhAA	Phenoxyacetic acid
PHE	Phenoxyethanol
QRA	Quantitative risk assessment
RCR	Risk characterisation ratio
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals
REACT	REACH Exposure assessment consumer tool
RIFM	Research Institute of Fragrance Materials
RIVM	National Institute for Public Health and the Environment in the Netherlands
SCCS	(EU) Scientific Committee on Consumer Safety
SCEDs	Specific consumer exposure determinants
SKU	Stock Keeping Unit
TRA	(ECETOC) Targeted risk assessment tool
WHO	World Health Organization

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