Consumer Product Ingredient Safety

Exposure and Risk Screening Methods for Consumer Product Ingredients

2nd Edition

american cleaning institute℠
for better living

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Preface to the Second Edition

In 2004, The Soap and Detergent Association (SDA; now the American Cleaning Institute) published *Exposure and Risk Screening Methods for Consumer Product Ingredients* as a guide for companies engaged in stewardship of consumer products with repeated human exposures or environmental releases, especially via down-the-drain disposal. Included in the publication were several examples based on SDA's experience in the US EPA and OECD high production volume (HPV) chemical programs. Since the initial publication, several of the submissions for particular chemical categories sponsored by SDA have been completed and accepted by the relevant HPV chemical program, and peer-reviewed journal articles have been published for those cases. The second edition, re-titled *Consumer Product Ingredient Safety: Exposure and Risk Screening Methods for Consumer Product Ingredients* to highlight the broader applicability of the publication, contains updated information on exposure assessment methodology as well as finalized case studies and the final manuscripts of the peer-reviewed articles as appendixes.

The following contributed significantly to the development of this document: The SDA High Production Volume Chemicals Task Force; the Personal Care Products Council (formerly the Cosmetic, Toiletry, and Fragrance Association); the Consumer Specialty Products Association; the European Cosmetic Toiletry and Perfumery Association; the Human and Environmental Risk Assessment project; Exponent; and the Danish National Environmental Research Institute. A panel of international experts conducted a peer review which provided very helpful input in finalizing the document.

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GLOSSARY

ACI: American Cleaning Institute, formerly the Soap and Detergent Association (SDA)

acute exposure: Human - one exposure or multiple exposures occurring within a short time (24 hours or less). Environmental - exposures lasting far less than a reproductive cycle of an organism, generally 24 to 96 hours but species dependent.

aggregate exposure: Total exposure to all individual products containing the same chemical or similar chemicals from the same category to which a consumer is likely exposed.

AIHC: American Industrial Health Council

AISE: *Association Internationale de la Savonnerie de la Détergence et des Produits d'Entretien*, or International Association for Soaps, Detergents and Maintenance Products. Represents the European soap, detergent, and maintenance product industries.

allowable daily intake (ADI): Estimate of the amount of a substance in food or drinking water, expressed on a body mass basis (usually mg/kg body weight), which can be ingested daily over a lifetime by humans without appreciable health risk.

APAG: The European Oleochemicals and Allied Products Group

assessment factors: Numbers used to extrapolate available toxicity data to predict actual toxicity. Available toxicity data are divided by numbers generally ranging from 1 to 1,000 to address uncertainties in the use of the toxicity data to protect human health and the environment.

CESIO: Comité Européen des Agents de Surface et de Leurs Intermédiaires Organiques, or European Committee of Organic Surfactants and Their Intermediaries

Chemical Abstract Service (CAS) number: A unique number for each chemical issued by the Chemical Abstract Service; used to search for a specific chemical regardless of the choice of chemical name.

Chemical Awareness (CA): Formerly the Alliance for Chemical Awareness; a voluntary initiative by chemical and consumer product manufacturers to enhance the accessibility to the public of information pertaining to major chemicals in commerce.

chronic effect: An effect that is manifested due to repeated exposure over time. See also *chronic exposure*.

chronic exposure: Multiple exposures occurring over an extended period of time or over a significant fraction of the animal's or individual's lifetime.

Concentration-response: A relationship between the exposure concentration and the biological response (effect) to that exposure.

Dose-response: A correlation between a quantified exposure (dose) and the proportion of a population that demonstrates a specific effect (response).

EC_x: The effective concentration or concentration of the substance causing an x% decline in the biological parameter of interest (e.g., reproduction, growth). Similar to the LC_x, or concentration causing x% mortality. Typically calculated using concentration response statistics; avoids some of the interpretation problems associated with NOECs.

exposure: Contact between a chemical, physical, or biological agent and the outer boundary of an organism. Exposure is quantified as the amount of an agent available at the exchange boundaries of the organism (e.g., skin, lungs/gills, gut).

exposure assessment: The process of measuring or estimating the intensity, frequency, and duration of exposures to an agent currently present in the environment or of estimating hypothetical exposures that might arise from the release of new chemicals into the environment.

exposure concentration: The concentration of a chemical in its transport or carrier medium to the point of contact.

exposure pathway: The physical course a chemical or pollutant takes from the source to the organism exposed.

exposure route: The way a chemical or pollutant enters an organism after contact – for example, by ingestion, inhalation/respiration, or dermal exposure.

exposure scenario: A set of facts, assumptions, and/or inferences about how exposure takes place that aids the exposure assessor in evaluating, estimating, or quantifying exposures.

fabric density (FD): A parameter used in the screening-level exposure equation for the indirect dermal laundry detergent/fabric conditioner scenario. This parameter refers to the weight of the fabric per square centimeter and is used to calculate the PR factor. The value used in this assessment, 10 mg/cm^2, represents a medium blend fabric. A nylon or polyester fabric has a fabric density of 1 mg/cm^2, whereas a terry cloth fabric has a fabric density of 20 to 30 mg/cm^2 (SDA, 2003).

HERA: Human and Environmental Risk Assessment; A voluntary European industry program that standardizes risk assessment of ingredients in household cleaning products.

high end: a plausible estimate at the upper end of a distribution of values, conceptually above the 90th percentile.

high-end exposure (dose) estimate: A plausible estimate of individual exposure or dose for those persons at the upper end of an exposure or dose distribution, conceptually above the 90th percentile, but not higher than the individual in the population who has the highest exposure or dose.

high production volume (HPV): Chemicals produced in quantities greater than 1 million pounds annually.

ICCA: International Council of Chemical Associations

JSDA: Japan Soap and Detergent Association

K_{ow}: The octanol:water partition coefficient. A measure of the potential for a molecule to occur in a nonpolar phase, such as a lipid membrane, or a more polar phase, such as water.

lowest observed adverse effect level (LOAEL): The lowest exposure level at which a statistically significant increase in observed frequency or severity of adverse effects between the exposed population and its appropriate control occurs (mammalian system).

lowest observed effect concentration (LOEC): The lowest exposure concentration at which a statistically significant increase in observed frequency or severity of effects between the exposed population and its appropriate control occurs (environmental system).

margin of exposure (MOE): The ratio of the no observed adverse effect level (NOAEL) to the estimated exposure dose (EED); MOE is unitless.

mesocosm/microcosm: A subset of the natural environment contained, controlled, and manipulated for experimental purposes. Mesocosms and microcosms are used to investigate interactions among the physical, chemical, and biological components of the ecosystem in a controlled environment. Mesocosms are larger experimental systems than microcosms and thus can support more species complexity.

no observed adverse effect level (NOAEL): The highest exposure level in a study or a group of studies at which no statistically significant increase in the frequency or severity of adverse effects between the exposed population and its appropriate control occurs (mammalian system).

no observed effect concentration (NOEC): The exposure concentration below which no statistically significant increase in the frequency or severity of adverse effects between the exposed population and its appropriate control occurs (environmental system).

OECD: Organization for Economic Co-operation and Development

percent deposition (PD): A parameter used in the screening-level exposure equation for the indirect dermal laundry detergent/fabric conditioner scenario. This parameter refers to the percentage of product that is deposited on the fabric during the wash cycle and is based on the amount of water used during the spin cycle and the amount of water remaining on the fabric after the spin cycle. The PD parameter is used to calculate the value of the percent retained.

percent retained (PR): A parameter used in some of the screening-level exposure equations. When used in the indirect dermal laundry detergent/fabric conditioner scenario, PR refers to the percentage of product that remains on the fabric after the fabric has been washed. When used in direct dermal personal care product (e.g., shampoo, soap, lotions) scenarios, PR refers to the percentage of product that remains on the body after use of the product. When used in the indirect oral dish detergent scenario, PR refers to the percentage of product that remains on the dish after the dish has been washed but not rinsed with clean water.

percent transferred (PT): A parameter used in the screening-level exposure equation for the indirect dermal laundry detergent/fabric conditioner scenario. This parameter refers to the percentage of product remaining on the fabric that is transferred to the skin.

predicted no-effect concentration (PNEC): The environmental concentration at which there would be no observable adverse effects on naturally occurring biological communities.

product exposure (PE): An estimate of exposure to an end-use product typically expressed as $mg_{product}/kg_{body\ weight}/day$.

quantitative structure activity relationship (QSAR): A mathematical expression used to relate physical or chemical parameters to biological or chemical activity of a molecule.

R (product retained on skin): A parameter used in the screening-level exposure equation for the direct dermal baby bath liquid scenario. This parameter refers to the amount of product remaining on the baby's skin after use of the product. This parameter is very similar to the PR parameter; however, it is presented in terms of $mg_{product\ remaining}/cm^2_{body\ surface\ area}$.

reasonable worst case: A semi-quantitative term referring to the lower portion of the high end of the exposure, dose, or risk distribution. The reasonable worst case has historically been loosely defined, including synonymously with *maximum exposure* or *worst case*. As a semi-quantitative term, it is sometimes useful to refer to individual exposures, doses, or risks that, while in the high end of the distribution, are not in the extreme tail.

reference dose (RfD): An estimate of the daily exposure to the human population that is likely to be without appreciable risk of deleterious non-cancer effects during a lifetime.

screening information data set (SIDS): A data set consisting of general information on a chemical's production, use patterns, physical and chemical characteristics (particularly those that might suggest how and to what extent people might become exposed,) and its fate in the environment. A basic set of toxicology data is included: acute-dose (single-dose) toxicity, repeated-dose toxicity, genetic toxicity, reproductive toxicity, and developmental toxicity. Similar testing requirements exist for harmful (non-human) effects in the environment.

SDA: The Soap and Detergent Association (United States), now the American Cleaning Institute

SIAR: SIDS Initial Assessment Report

SIC: Standard Industrial Classification code

threshold dose: The dose or exposure below which no deleterious effect is expected to occur.

time scaling factor (TF): A parameter used in the direct dermal scenario exposure equations. This factor refers to the amount of time actually spent performing an activity (e.g., hand-washing clothes, hand-washing dishes, using cleaning products). The values used for these factors are based on the number of minutes performing the specific activity divided by the total number of minutes in one day.

tolerable daily intake (TDI): Estimate of the amount of a substance (usually expressed in mg/person, assuming a body weight of 60 kg) which can be ingested daily over a lifetime by humans without appreciable health risk.

worst case: A semi-quantitative term referring to the maximum possible exposure, dose, or risk, that can conceivably occur, regardless of whether this exposure, dose, or risk actually occurs in a specific population.

REFERENCE

SDA (The Soap and Detergent Association). 2003. SDA Member Company Data, 2002-2003. Washington, DC.

1. INTRODUCTION

1.1. Aim and Audience

The consumer products industry has exposure information and screening methods that can be of value in viewing chemical hazard data from an exposure perspective and thereby facilitate prioritization of chemicals for further risk evaluation, as appropriate. The industry's unique consumer exposure information, which is based on the formulation and use of consumer products, is presented in this book and is recommended for use in risk screening analysis.

The main purpose of this book is to present methodologies and specific consumer exposure information that can be used for screening-level risk assessments of environmental and human exposures to high production volume (HPV) chemicals through the manufacturing and use of consumer products, mainly laundry, cleaning, and personal care products. The approach can be applied generally to other consumer products when information on how consumers use the products is available. These methodologies allow hazard information to be put into context by using exposure information to characterize risk. Screening-level risk assessments are useful for prioritizing the need for further work.

Several ongoing chemical management programs globally are focusing on both legacy and HPV chemicals. This book compiles data and methods, illustrated using examples from these global programs, that can be a useful resource for prioritizing compounds. Because of the large numbers of chemicals under investigation in global chemical management programs, a specific need for category assessments – the main focus of this book – exists. The intended audience is chemical risk assessors in government agencies, businesses, and stakeholder groups who have experience in the area of consumer product exposure (PE) and risk assessment and are responsible for prioritizing chemical safety reviews.

The book is produced by the American Cleaning Institute (ACI; formerly, the Soap and Detergent Association) in collaboration with its partners and member companies. ACI is a U.S. national trade association representing the formulators of household, institutional, and industrial cleaning products and the manufacturers of the ingredients and finished packaging used to bring these products to the marketplace. Under a major SDA/ACI program, the Association manages the efforts of over 60 companies within ten U.S. and global HPV chemical consortia to meet their commitment to compile and make publicly available a baseline set of health and environmental effects data covering almost 300 chemicals. SDA/ACI prepared more than 6,100 study summaries from existing hazard data. Only eight of the study summaries were based on new testing (about 0.13% of the total number of studies); the rest were provided by the companies and the scientific literature.

1.2. Background on the SDA/ACI HPV Chemical Program

Soaps, detergents, and personal care products, like other consumer products, are sold in large quantities across the globe. Consequently, the main chemical ingredients in these products are often high volume chemicals. The products are used either directly (e.g., bar soap, body moisturizers) or indirectly (e.g., via washing and laundry) on the consumer's skin. After these products are used, residual ingredients are washed directly down the drain toward the municipal wastewater treatment plant and from there are released into the aquatic environment with the wastewater treatment plant effluent. This use-and-release pattern places an extraordinary responsibility on producers to understand and document the consumer and environmental exposure and safety of the products and their ingredients. ACI represents its more than 60 member and non-member companies in voluntary HPV chemical programs, and has coordinated the preparation of the Organization for Economic Co-operation and Development's (OECD's) Screening

Information Data Set (SIDS) program Initial Assessment Reports (SIARs) for seven categories of chemicals for the global industry:

1. Aliphatic acids (sponsored by Italy)
2. Amine oxides (sponsored by the United States)
3. Fatty acid methyl esters (industry sponsored)
4. Hydrotropes (sponsored by Australia)
5. Aliphatic alcohols (sponsored by the United Kingdom)
6. Alkyl sulfates, alkane sulfonates and α-olefin sulfonates (sponsored by Germany)
7. Glycerides (industry sponsored)

In addition, SDA/ACI sponsored three categories of chemicals under the U.S. EPA HPV Challenge Program:

1. Aluminum alkoxides
2. Linear and branched alkylbenzene sulfonic acids and derivatives
3. Triclocarban

These chemicals have a wide range of uses, including, for example, soaps and detergents; disinfectants, sanitizers, and household pest controls; cosmetics, fragrances, and personal care products; food and food additives; automotive care products; and polishes. The scope of the SIARs includes both human and environmental health exposure and hazard evaluations as each relates to the production and use of nearly 300 chemicals grouped into ten categories that SDA/ACI manages. It is generally recognized that during the chemical manufacturing, product formulation, and use and disposal of these products, some human exposures and environmental releases will occur. Human exposure can be both direct and indirect. There can be both occupational exposure and exposure due to use of consumer products. Environmental releases to air, water, and land might occur during the manufacture, processing or formulating, and use of the chemical or product.

Multiple steps are required to prepare a SIAR. The initial step in the SIAR process involves assembling the available hazard data (i.e., physicochemical properties, environmental fate, ecotoxicity, and mammalian toxicity) and preparing a summary document for each chemical category as well as an Assessment Plan, as prescribed by the U.S. Environmental Protection Agency (EPA) HPV Challenge Program (http://www.epa.gov/HPV/index.htm) and by the EPA Chemical Management Program (http://www.epa.gov/oppt/existingchemicals/index.html); exposure and risk screening methods presented in this book can be used to prioritize further assessment of chemicals under these programs. The second step is a global effort to gather and summarize available production, use, and exposure information for the same families of chemicals. The information gathered includes:

- annual production volumes by region (North America, Europe, Asia/Pacific);
- use categories and/or functions;
- pounds/kilos of chemical for each use category and/or function;
- physical form of the product(s);
- likely sources of exposure, including occupational (manufacturing and commercial use), consumer use, and indirect (via food, water, and air);

- recommended workplace exposure limits and/or controls in place;
- sources of potential releases to the environment;
- relevant routes of human exposure by use category and/or function; and
- modeling and/or monitoring data on human exposure and on releases to air, water, and land.

The hazard information, along with the use and exposure information, is summarized in the SIAR, which includes a recommendation that either (1) the chemical (or category) is currently a low priority for follow-up work, except for periodic review, or (2) the chemical is a candidate for further work.

In recognition of the extra responsibility of the cleaning products industry in being stewards of the chemicals used in their products – in terms of the volumes, direct consumer application, and down-the-drain disposal pathway – ACI created this book to describe screening-level methodologies that assist in the priority-setting process by integrating exposure information with chemicals hazard data to characterize the risks posed by exposures. The approaches may be considered for use in national, regional, and intergovernmental chemicals management programs. For further data and information, please visit the ACI Science website at http://www.aciscience.org/.

1.3. Background on Screening-Level Risk Assessments for Priority Setting

Screening-level risk assessments are typically used to prioritize chemicals for future work on the basis of their hazards and exposure potential. These screens use readily available exposure information and simple models based on first-principle equations that are generally used by the scientific and regulatory communities. Conservative default assumptions are integrated into the screens to compensate for gaps in the data and uncertainties. The assumptions are deliberately designed to be conservative in order to avoid risk decisions based on "false negatives."[1] Consequently, screening estimates of releases, exposure, and risks are conservative and often higher than actual values reported (Pittinger et al. 2003).

More refined assessments can be conducted, if warranted. The refined assessments are designed to closely simulate a particular exposure scenario and thus require more detailed chemical-, site-, and receptor-specific data and use fewer default conservative assumptions.

Screening tools that prioritize chemicals for further work can include:

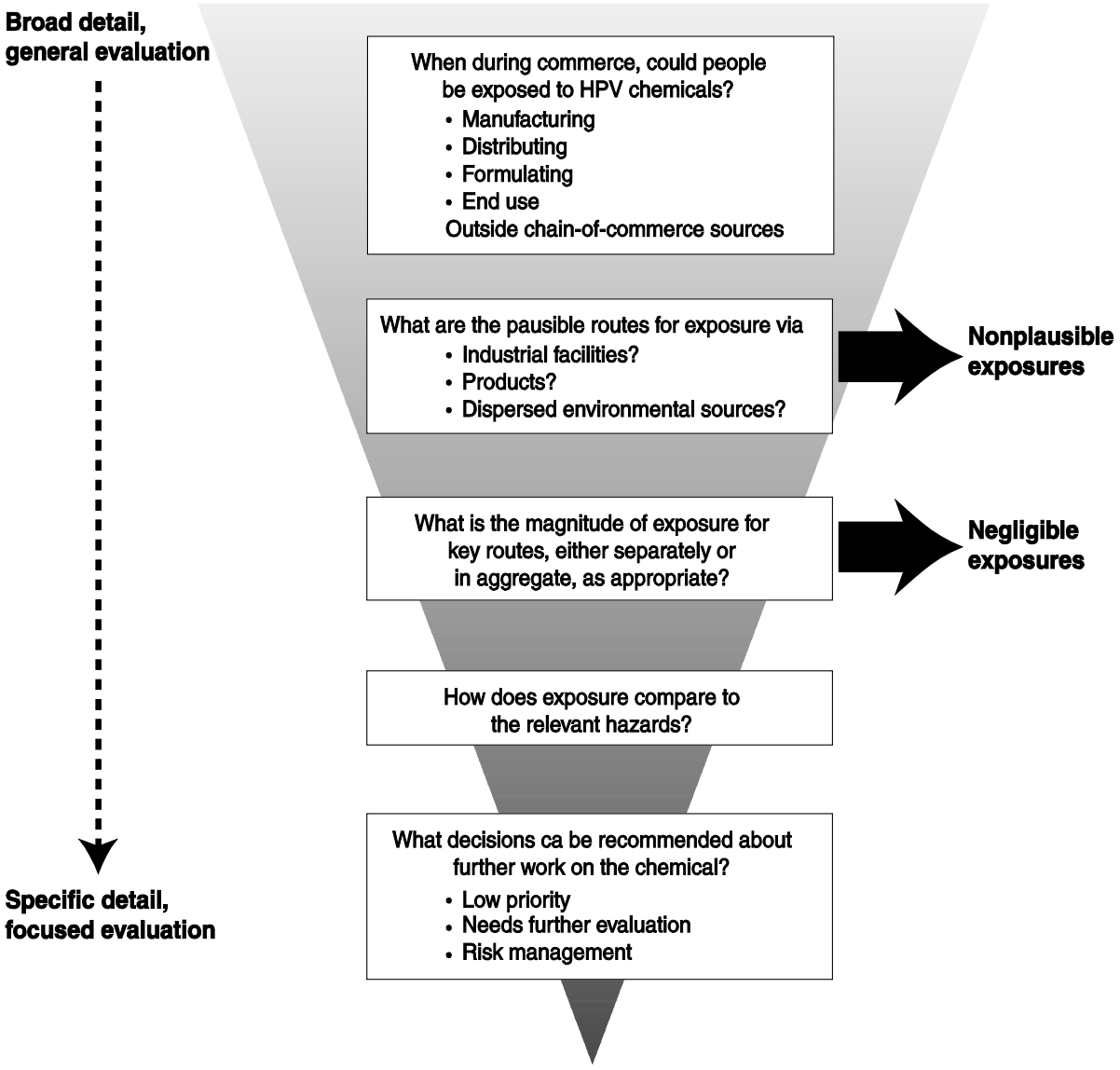
- those based on readily available information on the intrinsic properties of the chemical (e.g., physicochemical properties and toxicity; see the EPA's Estimation Programs Interface (EPI) Suite, http://www.epa.gov/oppt/exposure/pubs/episuite.htm, and the OECD's (Q)SAR toolbox, http://www.oecd.org/document/23/0,3343,en_2649_34377_33957015_1_1_1_37465,00.html),
- databases of quantities of chemicals released into the environment (e.g., Toxic Release Inventory, http://www.epa.gov/tri/), and
- a combination of these two as well as assessments that integrate the available hazard data with more sophisticated exposure estimates based on mathematical model predictions. In general, because screening-level risk assessments are less resource intensive or costly, they serve as an efficient means of categorizing and prioritizing those chemicals that either warrant more tailored and detailed assessments or are of no concern and can be put aside.

The group Chemical Awareness (CA) developed two assessment frameworks that focus on a screening-level approach to inform priority setting for HPV chemicals: *Framework for Evaluation of High*

[1] In this context, *false negative* means that exposure and risk estimates are lower than their actual levels.

Production Volume (HPV) Chemicals for Human Exposure and Risk (2002) and *Framework for Evaluation of High Production Volume (HPV) Chemicals for Potential Ecological Exposure and Risk* (2002); for a summary of the two frameworks, see Appendix IV. The frameworks provide a stepwise approach for assessing potential exposure and risks posed by HPV chemicals to relevant human and ecological receptors. Figure 1-1 presents the CA generic exposure framework, starting with a broad general evaluation and, as appropriate, proceeding to a more specific detailed evaluation.

Figure 1-1. Generic Exposure Framework



The following questions are addressed in the framework:

- When, during commerce, could people or the environment be exposed to chemicals – manufacturing, distributing, formulating, end use, disposal?
- What are the plausible routes for exposure via industrial facilities, products, and/or dispersed environmental sources?

- What is the magnitude of exposure for key routes, either separately or in aggregate, as appropriate? How does the exposure level or concentration compare to the relevant hazard effect level or concentration? What decisions can be recommended about further work on the chemical – low priority, needs further evaluation, risk management?

This book presents more specific exposure information and methodologies that can be used for screening-level risk assessments for human and environmental exposures to HPV chemicals resulting from the manufacturing and use of consumer products, mainly laundry, cleaning, and personal care products. For screening purposes, both environmental and human exposures are typically established using models based on conservative assumptions and readily available information. For environmental screening assessment, conservative assumptions are usually made about characteristics of the chemical, its manufacture and use, and its environmental fate. Similarly, in a screening assessment of consumer exposures via direct use of products, exposure factors such as frequency of use and amount of product use are conservatively estimated.

The screening assessment methodologies presented in this document are based on the CA generic exposure framework. Three exposure scenarios are of primary interest as they relate to use of chemicals in consumer products discussed in this book:

1. Human exposures (dermal, oral, and inhalation) to chemicals via use of consumer products
2. Environmental releases of chemicals at a manufacturing facility
3. Environmental releases of chemicals following use and down-the-drain disposal of consumer products

For human exposure scenarios involving the direct use of consumer products, the main objective of the risk screening methodology is to identify product categories and associated use scenarios that present the greatest potential for exposure. In the environmental release scenarios (i.e., from manufacturing sites and down-the-drain disposal), potential exposures to both ecological (e.g., fish, wildlife) and human receptors (e.g., drinking water, fish for consumption) are considered. On the basis of this information and appropriate hazard information, uses that warrant detailed evaluation can be identified. This prioritization is done by comparing the estimated human exposure to the appropriate no observed adverse effect level (NOAEL) for the most sensitive human toxicity endpoint. In this comparison, if a margin of exposure (MOE, the quotient of the NOAEL divided by the estimated human exposure) is adequate, no further evaluation is needed. However, because this initial evaluation process relies on conservative high-end exposure assumptions, if the MOE is not adequate, more refined analyses can be conducted by replacing high-end assumptions with more detailed, scenario-specific exposure information.

For the environmental release scenarios, the main objective of the environmental exposure screening methodology is to provide reasonable estimates that are based on predicted environmental concentrations (PECs). PECs are chemical (or chemical category) specific and, by design, are intended to be representative of conditions in a given geographic region. When data are available, refined analyses are conducted by replacing standard, conservative defaults with more chemical-specific and local or regional information. PECs can be used in screening-level risk evaluations by comparing the exposure estimate to a concentration expected to have no effect on organisms in the environment (i.e., the predicted no effect concentration, or PNEC) and determining the margin by which the ratio between the predicted exposure level and the level determined to not cause adverse effects (PEC/PNEC) is less than 1.0.

The screening methodology to evaluate human health risks from exposure to chemicals via use of consumer products is presented in Section 2 of this book. The environmental screening methodology addressing environmental release scenarios is described in Section 3. Integrated case studies based on the

OECD use and exposure format (as shown in Appendix III) are provided to illustrate how both screening methodologies are applied to produce initial exposure and risk characterization outputs.

1.4. References

CA (Chemical Awareness, formerly Alliance for Chemical Awareness). 2002. Framework for evaluation of high production volume (HPV) chemicals for human exposure and risk.

CA (Chemical Awareness, formerly Alliance for Chemical Awareness). 2002. Framework for evaluation of high production volume (HPV) chemicals for potential ecological exposure and risk.

Pittinger CA, Brennan TH, Badger DA, Hakkinen PT, Fehrenbacher MC. 2003. Aligning chemical assessment tools across the hazard continuum. Risk Anal. 23(3):529–535.

SDA (The Soap and Detergent Association). 2003. SDA Member Company Data, 2002-2003. Washington, DC.

2. RISK SCREENING METHODOLOGY FOR EXPOSURE TO HIGH PRODUCTION VOLUME CHEMICALS VIA CONSUMER PRODUCTS

2.1. Background and Scope

Consumer products may have multiple forms, uses, and exposure scenarios. Their uses are often associated with a range of exposure frequencies, durations, and pathways. Given the large number of products and possible associated consumer exposure scenarios, a priority-setting process is needed to identify consumer products and use scenarios for which more detailed exposure and risk assessment may be needed to adequately characterize consumers' exposures and risks and to set aside those that represent low concern. Screening-level risk assessments provide the basis for that process.

The Organization for Economic Co-operation and Development (OECD) Screening Information Data Set (SIDS) program provides the following guidance with respect to characterization of potential human exposure to chemicals:

> *The human population for which there is a potential exposure to the chemical should be identified with specific consideration of occupational exposure, consumer exposure and indirect exposure via the environment. These considerations should be based on readily available general information on exposure, the use pattern, and physicochemical properties of the chemical* (OECD, 2003).

Consistent with these guidelines, exposure can be estimated for priority-setting purposes without the need for either monitoring or sophisticated modeling data. Rather, for priority-setting purposes, estimates of exposure can be based on simple, first-principle exposure equations that are regularly used in the scientific and regulatory communities; conservative default assumptions about exposure; and readily available information about the characteristics of the chemical category, the consumer product type, and the nature of product use. Although the use of conservative assumptions would clearly lead to overestimation of exposure, the conservatism is appropriate for screening-level assessments that are purposely designed to avoid making "false negative" decisions.[2] This section of the book proposes a screening methodology for evaluating potential human exposures and risk from chemicals as a result of their use in consumer products. Indirect exposures via releases to the environment from manufacturing facilities and disposal of consumer products down the drain are discussed in Section 3 of this document.

Chemical Awareness (CA) developed a screening-level assessment as part of a framework for a stepwise approach for risk characterization that provides for the opportunity, on an as-needed basis, to replace conservative exposure assumptions with more realistic data prior to deciding whether additional toxicology information needs to be gathered or risk management actions need to be taken. By design, one advances to the next step in the process only if there is reason to believe that the refinement will likely result in a different decision about the priority for further work on the chemical. The key steps in the screening-level process, as described in the CA framework (CA, 2002), are as follows:

1. Identify product categories and product(s) in which the chemical is used, the concentration (%) of the chemical in the product(s), the physical and chemical properties of the chemical and the

[2] False negative decisions are based on exposure and risk estimates that are lower than their true levels—for example, a decision not to conduct further tests because risk estimates were falsely estimated to be low.

product(s), available SIDS hazard data, related products that could be evaluated as a category, and so forth.

2. Estimate, qualitatively or quantitatively, exposure to the chemical for each product category, initially by using highly conservative assumptions about the circumstances of product(s) use.
3. Identify the relevant SIDS endpoint and a no observed adverse effect level (NOAEL) or a lowest observed adverse effect level (LOAEL) from an epidemiology study or animal toxicology study.
4. Determine, for each product category, whether or not the margin of exposure to the chemical is adequate.
5. If necessary, sequentially develop more detailed and realistic exposure information.
6. Make the decision about the need for further evaluation or risk management.

In general, the risk screening methodology described in this book mirrors the key steps identified in the CA framework. It includes an initial assessment of the products that contain a given chemical category and their uses in order to identify those products that, on the basis of the circumstances of their use, are most likely to contribute significantly to the overall exposure. Related chemicals may be grouped by shared exposure scenarios to simplify the analysis and to maximize the use of available hazard information.

The described methodology addresses non-cancer SIDS endpoints and is focused on a screening-level assessment. Because the SIDS program focuses on initial prioritization of chemicals for further work and non-cancer endpoints, exposure and risk assessments beyond screening approaches and cancer risk assessment are beyond the scope of this methodology. Additionally, the scope of this risk screening methodology is limited to the exposure scenarios that fall within the intended or labeled use of products. Although it is recognized that foreseeable misuses of products occur – for example, washing the side of a house with dishwashing liquid – this scenario is a minor use and does not constitute high exposure.

2.2. Objectives

Chemical hazard information is required under the OECD SIDS program. However, to effectively prioritize chemicals for further work, it is necessary to put the hazard information in the context of exposure and risks. Toward this goal, the objective of the exposure and risk screening methodology outlined below is to provide relevant information regarding human exposure to consumer products and a transparent process for putting the hazard information in the context of the estimated human exposure. The process involves identifying the product categories and associated use scenario(s) with the greatest exposure potential and then integrating the potential exposures with the hazard data so that uses that may warrant more detailed exposure characterization can be identified.

It should be emphasized that this identification process is only an initial screening assessment, which relies on conservative, high-end toxicity and exposure assumptions (e.g., using the most toxic chemical in the category of chemicals, assuming maximum absorption of the chemical) that are designed to overestimate exposures and risks. When necessary, refined risk analyses can be conducted by replacing high-end assumptions with more detailed scenario and chemical-specific information.

2.3. General Framework

A general approach to screening-level risk assessment is to develop exposure and risk estimates for the chemical or category of chemicals for each product category; those estimates are based on default high-end exposure and conservative dose–response parameters. These screening-level risk estimates would

represent reasonable high-end estimates of exposure and risks for a given product. The following human health screening-level risk characterization algorithm is applied:

Margin of Exposure (MOE) =

Dose–Response Threshold/[Product Exposure (PE) × Ingredient Concentration (IC)]

or

MOE = NOAEL/(PE × IC)

For screening purposes, the selection of the appropriate NOAEL or LOAEL for non-cancer risks is based on the following considerations:

- The most sensitive repeated-exposure toxicity endpoints (i.e., lowest NOAEL of all the repeated-dose endpoints evaluated when a range of values is available)
- Routes of exposure relevant to the product exposure scenarios (i.e., dermal, oral, or inhalation)
- The quality of available experimental study data

Using a screening analysis, product categories with the lowest margins of exposure can be identified for more detailed characterization if the MOE is not adequate. In the subsequent refined assessment of these product categories, a more detailed evaluation could be pursued to identify both the most appropriate NOAEL for the chemical in the product and exposure scenarios and more realistic exposure information beyond the screening approach described above.

Conceptually, PE × IC is the surrogate high-end exposure to the chemical substance, also called the *screening-level chemical exposure*. The PE component is an estimate of exposure to the consumer product ($mg_{product}$/kgBW/day), and the IC component is the concentration (%) of the chemical ingredient in that product. More details on these components of the screening risk characterization are described in the exposure data matrix in Sections 2.4 and 2.5 where applicable examples and data for a chemical category are provided.

2.4. Screening-Level Exposure Data

As indicated above, the screening-level chemical exposure estimate is based on two components: the product exposure (PE) estimate and the chemical ingredient concentration (IC, %) in that product. The PE estimates are based on several screening exposure equations. The equation input parameters have been derived from a number of government and nongovernment sources. (See Appendix I-A for a list of sources for PE models and input parameters. See Appendix I-B for their relevance to the exposure scenarios addressed in this document.) The IC estimates are based on a survey of companies that produce these products sponsored by The Soap and Detergent Association (SDA) and the Personal Care Product Council (PCPC; formerly known as the Cosmetic, Toiletry, and Fragrance Association; SDA, 2003). In the following sections, detailed descriptions of these components of the screening chemical exposure estimate are provided.

2.4.1. PE Estimates – Data Matrix

To facilitate the implementation of this risk screening methodology, a PE data matrix has been constructed for several categories of consumer products. The data matrix provides exposure factors (e.g.,

frequency of use, duration of use, amount of use per occasion) and equations used to estimate oral, inhalation, and dermal exposures for the key scenarios of each consumer product category. It should be noted that the exposure estimates are provided in terms of product, not specific chemical substance. To estimate exposures to the chemical, these exposures would be combined with formulation data. This matrix does not account for indirect exposures (e.g., environmental, dietary, drinking water). Estimated exposures from those routes are developed separately and integrated into the assessment.

Several first-principle equations (models) are used to estimate exposure to consumer products. Although most models are generic and based on general parameters and high-end values[3] providing conservative estimates of exposure, some are based on chemical-specific and scenario-specific parameters. Table 2-1 provides an overview of the model equations and parameters included in the data matrix.

For a screening-level assessment, high-end exposure factors (e.g., high-end frequency of product use, longer duration of product contact, largest amount of product use per occasion) would be used. The default high-end screening PE data matrix and associated references and documentation can be found in Appendix II-A. For transparency and comprehensiveness, the readily available ranges of values (minimum-maximum, or min-max) and associated references and documentation are also summarized in Appendix II-B. If it is determined that further refinement is necessary as the result of a screening assessment, the typical values from the data range could be used in a refined analysis when exposure condition and hazard information are available to support such refinement.

In general, the PE estimates are based on a 60 kg body weight for women. For products designed for a specific target population, however, the representative body weights for those populations are used. For example, if the product is developed for use by men, then the exposure estimates are based on a male body weight of 70 kg, or if the exposure estimates are made for baby care products, the default body weight used for children is 15 kg. Also, when a product may be used by multiple subcategories (e.g., both adults and children use toothpaste), the PEs are calculated on the basis of the subcategory resulting in the greatest exposure. For example, for the toothpaste-ingestion scenario, the default subpopulation is based on children. The U.S. Environmental Protection Agency (EPA) issued a child-specific exposure handbook in 2008 containing child-specific exposure scenarios that may be used to more accurately assess child exposures (e.g., in relation to *consumer products,* here under *personal care products*; EPA, 2008).

In continuing work with regard to exposure to consumer product ingredients, the European Union (EU) is working on the European Information System (EIS) toolbox on risks from chemicals released from consumer products and articles (EIS-ChemRisks). The aim is, among other things, to configure the toolbox standard to the implementation needs of the Registration, Evaluation, Authorisation, and Restriction of Chemicals (REACH) regulation regarding consumer exposure to chemicals released from consumer products and preparations and articles (http://web.jrc.ec.europa.eu/eis-chemrisks/toolbox.cfm). The work with EIS-ChemRisk began in 2008. Development of exposure scenarios (particularly descriptions of conditions of use), are in Chapters R12 and R13 of the European Chemicals Agency guidance (http://guidance.echa.europa.eu/docs/guidance_document/information_requirements_en.htm). Supporting guidance on exposure estimations for consumers, estimation of exposures from articles and environmental exposure estimation is in Chapters R12 to R18.

Regional exposure factor handbooks beyond North America, Japan, and Europe may also be relevant (e.g., for Korea, http://www.kefh.or.kr/new/main/main.php). Often, specific regional and subpopulation exposure data are uncommon; in such situations conservative default values from other regions are used.

[3] *High-end values* refer to values in the upper percentile range of the distribution—that is, above the 90th percentile.

Table 2-1. Summary of Model Equations Used to Calculate Product Exposure (PE)

Exposure Route	PE Scenario	PE Model	Parameters
Dermal: Indirect	*Exposure after activity/use:* Laundry detergents: wearing clothing Fabric conditioners: wearing clothing	**North American (NA) approach:** $\frac{A \times PR \times PT \times CF \times DA}{BW}$ where, PR = 1% based on SDA data **European Union (EU) approach:** $\frac{A \times PR \times PT \times CF \times DA}{BW}$ where $PR = (PD \times FD) / W) \times CA$ and $PD = Sw / Tw$	A: amount used (g/day) PR: percent retained on clothing (%) PT: % transferred from clothing to skin CF: conversion factor (1,000 mg/g) DA: dermal absorption (100%) BW: female body weight (60 kg) PD: percent deposition (%) FD: fabric density (mg/cm^2) W: total wash weight (mg) CA: body surface contact area (cm^2) Sw: Mass of water after spin cycle (kg) Tw: Mass of water per spin cycle (kg)
Dermal: Direct	*Exposure during activity/use of:* Laundry detergent: hand-washing clothes Laundry detergent: laundry pretreatment Dish detergent: hand-washing dishes Dish detergent: washing hands Dilutable hard surface cleaners Nondilutable hard surface cleaners Dilutable all-purpose cleaners Nondilutable all-purpose cleaners	**NA and EU approach:** $\frac{FQ \times CA \times PC \times FT \times CF \times TF \times DA}{BW}$	FQ: frequency of use (use/day) CA: body surface contact area (cm^2) PC: product concentration (g/cm^3) FT: film thickness on skin (cm) CF: conversion factor (1,000 mg/g) TF: time scaling factor (unitless) DA: dermal absorption (100%) BW: female body weight (60 kg)

Table 2-1. Summary of Model Equations Used to Calculate Product Exposure (PE)

Exposure Route	PE Scenario	PE Model	Parameters
Dermal: Direct	*Exposure after activity/use (residual):* *Adult rinse-off products:* Body washes Bath foam/bubble baths Hair conditioners Hair rinses Hand/body/face soaps Shaving cream Shampoos *Adult leave-on products:* Antiperspirants Aftershave Face/eye cosmetics Fragrances Facial cream Hand/body moisturizer Hair Spray Styling/tonic gel Styling mouse Sun cream/lotions *Baby care rinse-off products:* Baby bath liquids Kid shampoos *Baby care leave-on products:* Baby lotion and cream	**NA and EU approach:** $\frac{FQ \times A \times PR \times CF \times DA}{BW}$	FQ: frequency of use (use/day) A: amount used (g/use) PR: percent retained (%) CF: conversion factor (1,000 mg/g) DA: dermal absorption (100%) BW: female body weight (60 kg); male body weight (70 kg) (shaving products); child body weight (15 kg) (baby care products)
Oral: Indirect	*Exposure after activity/use:* Dish detergents (hand-washed)	**NA and EU approach:** $\frac{C' \times Ta' \times Sa \times CF}{BW}$	C': product concentration (mg/cm^3) Ta': amount of water on dish after rinse (mL/cm^2) Sa: area of dish contacting food (cm^2/day) CF: conversion factor (1 cm^3 water/1 mL water) BW: female body weight (60 kg)
Oral: Direct	*Exposure during activity/use:* Mouthwash Lipstick Toothpaste Food additives Over-the-counter (OTC) medicine/ pharmaceuticals	**NA and EU approach (except additives and OTC medicine):** $\frac{FQ \times A \times FI \times CF}{BW}$ **NA and EU approach (additives and OTC medicine only):** $\frac{FI \times C}{BW}$	FQ: frequency (use/day) A: amount used (g/day) FI: fraction ingested (%) CF: conversion factor (1,000 mg/g) BW: female body weight (60 kg); child body weight (15kg) (toothpaste) C: food consumption of pharmacological dose *Note:* FI and C will vary by food types. Default screening values have not been established.

Table 2-1. Summary of Model Equations Used to Calculate Product Exposure (PE)

Exposure Route	PE Scenario	PE Model	Parameters
Inhalation: Direct	*Exposure during activity/use:* Hairspray Antiperspirants – aerosols Fragrances Paints	**NA and EU approach:** $\frac{FQ \times A \times IR \times ED \times F \times CF}{V \times BW}$	FQ: frequency (use/day) A: amount used (g/use) IR: inhalation rate (m^3/hr) ED: exposure duration (hr/day) F: respirable fraction (%) CF: conversion factor (1,000 mg/g) V: effective breathing air space (2 m^3) (*Note:* This value is not appropriate for paints.) BW: female body weight (60 kg)
Inhalation: Direct	*Exposure during activity/use:* Laundry detergent – powders	**NA and EU approach:** $\frac{FQ \times A \times F}{BW}$	FQ: frequency (use/day) A: amount used (g/use) (*Note:* A is the amount of dust/scoop × 1 scoop/use) F: respirable fraction (%) BW: female body weight (60 kg)
Inhalation: Direct	*Exposure during activity/use:* Trigger spray cleaners	**NA and EU approach:** $\frac{FQ \times RPC \times IR \times ED \times BA}{BW}$	FQ: frequency (use/day) RPC: respirable product concentration in breathing zone (mg/m^3) IR: inhalation rate (m^3/hr) ED: exposure duration (hr/day) BA: bioavailability fraction (100%) BW: female body weight (60 kg)

2.4.1.1. Product Exposure Data Sources

The exposure equations and parameters were extracted from a variety of sources, including government agency documents, use surveys involving consumer product manufacturers, SDA companies' in-house habits-and-practices data obtained from product development studies, and the published literature. Because the resulting screening exposure assessments are to be submitted to OECD and/or EPA under the High Production Volume (HPV) Challenge Program, it was necessary to select model equations and parameters that are used or would be accepted by the appropriate regulatory authorities. Thus, the prevailing North American and EU equations and exposure factors compiled in the data matrix are based on guidance and practices previously provided by the European Union, EPA, and OECD. The sources of data were selected in the following order:

1. Government documents written by regulatory authorities (e.g., EPA's *Exposure Factors Handbook* [1997], the European Union's 2003 *Technical Guidance Document*)
2. Documents written for submission to regulatory authorities (e.g., International Association for Soaps, Detergents and Maintenance Products [AISE] Human and Environmental Risk Assessment [HERA] project risk assessments, American Industrial Health Council exposure initiative assessments)
3. Survey data collected by industry associations (i.e., PCPC and the European Cosmetics Association cosmetic use surveys, AISE HERA Habits and Practices Survey for cleaning products)
4. SDA member company data
5. Data found in the published literature.

Much of the data in the published literature have been captured in source categories 1 and 2. In most cases, data were found in source categories 1 through 4, and exhaustive searches of the published literature were limited to exposure parameters that were not found among those sources. Generally, the selection process followed the above hierarchy; however, there were some minor exceptions. For example, in some cases, such as the cosmetic use pattern parameters, data from association surveys (e.g., PCPC's use survey for body lotion, hairspray, face cream, lipstick, perfume, and foundation) were selected over data found in EPA's *Exposure Factors Handbook* (1997). The *Exposure Factors Handbook* refers to older PCPC data. Therefore, it was reasonable to select PCPC use data from a more recent survey (May 2000). If available, region-specific data were used for North America and the European Union; if not, the references are identified in footnotes in Appendixes II-A and II-B.

Appendixes I-A and I-B provide descriptions of references, detailed mapping of documents reviewed for each exposure scenario, relevant secondary references within the primary source, and documents selected as the source information for the habits-and-practices data presented in Appendixes II-A and II-B. Each selected document may be used as source information for several parameters and equations, and Appendixes II-A and II-B provide more specific source identification for each individual equation and input parameter.

2.4.2. Screening-Level IC Data

The IC data presented in this document are based on a 2001 SDA survey of manufacturers, importers, processors, and formulators of chemicals used in soaps, detergents, and related consumer, commercial, and industrial products for up to 10 families of chemicals (aliphatic acids, aliphatic alcohols, amine oxides, anionic surfactants, fatty acid distillation residues, glycerides, hydrotropes, linear alkylbenzene sulfonate/alkylbenzene sufonate [LAS/ABS], methyl esters, and triclocarban). SDA conducted this survey

to provide information on chemical production, uses, and exposures for these chemical families managed by SDA at a regional level for North America,[4] Europe, and Asia and the Pacific.

The survey was administered in two parts. The first part collected general information about company activities for each of the listed chemicals to determine whether each company was a manufacturer/importer, processor, or formulator of the respective chemicals and to determine focus areas for follow-up surveys. The following definitions were used for the survey:

- *Manufacturer/importer:* Produces the subject chemical, including importation and toll manufacturing, as a commodity or intermediate
- *Processor:* Uses the subject chemical in the production of derivatives or other intermediates but not end-use products
- *Formulator:* Uses the subject chemical or intermediates derived from a subject chemical in formulation of end-use products.

The second part of the survey involved collection of specific data and information on:

- chemical production and/or importation amounts,
- chemical use by product type,
- chemical releases to the environment,
- conditions under which potential worker exposures are mitigated with personal protective equipment and/or engineering controls, and
- chemical concentrations in formulated products.

The information collected from the survey was compiled to develop a minimum and maximum IC for each product category. For conducting a screening-level assessment, minimum and maximum ICs for an entire category of chemicals were generated for each product use category. Table 2-2 shows the information that was collected on one HPV category, amine oxides (AO). In screening-level assessments, both the minimum and maximum IC values would be used to develop screening exposure estimates encompassing the range of ingredient concentrations; see Appendix III for further details on the AO assessment.

Table 2-2. Ingredient Concentration (IC) Data Matrix for the HPV Chemical Category Amine Oxide (AO)*

Product Type	Range of Concentration in Products (%)
Dishwashing detergents (liquid)	0.1 – 10
Hard surface cleaners (liquid spray)	1 – 5
Hard surface cleaners (liquid)	0.1 – 5
Laundry detergents (liquid)	1 – 5
Hand/face soaps (bar)	0.1 – 5
Shampoos	0.09 – 5
Hair conditioners	0.6 – 0.7
Hair styling tonic/gel	0.1 – 2
Cleansing products	0.04 – 9
Skin creams/moisturizers	0.2 – 0.6

[4] For the purposes of this survey, *North America* included only the United States and Canada.

Table 2-2. Ingredient Concentration (IC) Data Matrix for the HPV Chemical Category Amine Oxide (AO)*

Product Type	Range of Concentration in Products (%)
Aftershaves	0.5 – 1
Home dry cleaning products	0.1 – 0.5
Douches	1 – 2
Face/eye foundations (liquid)	<0.1
Hair coloring preparations	<0.1
Permanent waves preparations	1 – 2

Note: HPV = high production volume.

* The product concentration ranges indicate active AO concentration in the formulated products and do not take into account any dilution prior to or during use. Many products on the market in these categories do not contain AO, and not all the products listed are available in all regions of North America, the European Union, and Asia and the Pacific.

2.5. Selecting NOAELs for Screening-Level Risk Characterization

The OECD (2003) guidance for the preparation of a SIDS Initial Assessment Report (SIAR) for Hazard Assessment indicates that the results of the following toxicity tests and other information should be summarized and discussed in the SIAR:

- Toxicokinetics, metabolism, and mechanism of action (if known)
- Acute toxicity
- Repeated-dose toxicity
- Reproductive/developmental toxicity
- Genetic toxicity
- Any other information that is available (e.g., experience with human exposure).

The OECD guidance document also indicates that a judgment on the NOAEL and LOAEL be made and presented in the context of the adverse effects, information on the dose–response relationship, and an assessment of whether any adverse effects are considered compound related on the basis of the test results of repeated-dose and reproductive/developmental toxicity. In addition, the toxicological significance of breakdown products or metabolites (if any) and relevant available data on non-SIDS elements such as irritation, skin sensitization, and carcinogenicity are to be stated and the associated results, discussion, and conclusions summarized in a similar manner.

The OECD SIDS program provides the option to put the hazard information into perspective by reporting the exposure information along with the hazard data. The primary focus of the SDA methodology is to put repeated-dose studies in an exposure-risk context. Most chemicals with substantial consumer product use have relatively low acute toxicity; oral or dermal LD_{50}s are greater than 2,000 mg/kg and classifiable as Category 5 (the least acutely toxic classification) under the OECD Harmonized Integrated Classification System for Human Health and Environmental Hazards of Chemical Substances and Mixtures. However, in less common situations, in which a chemical has oral or dermal LD_{50} of less than 50 mg/kg (Categories 1 and 2 under the OECD Harmonized Integrated Classification System), risks from acute toxicity would be evaluated. Moreover, if non-SIDS elements such as metabolites, irritations, and carcinogenicity are noted and described in the hazard assessment, they would also be discussed accordingly and put in an exposure context in the screening-level assessments.

Given the number of chemicals that may be grouped into an SDA chemical category, the hazard data set for a chemical category is expected to comprise one or more chemicals with NOAELs and/or LOAELs for various SIDS endpoints and routes of exposure. For the initial screening-level risk characterization, a default approach would be to select the most sensitive endpoint (i.e., the toxicity endpoint with the lowest NOAEL). Table 2-3 displays a hypothetical, but typical, hazard data matrix in which different chemicals within a category have different NOAELs for different SIDS endpoints. For this hypothetical data matrix, the lowest NOAEL value would be selected as the default NOAEL for the entire category.

Table 2-3. Hypothetical Hazard Data Matrix

Toxic Endpoints	NOAEL (X)				Selected NOAEL for Chemical Category
	Chemical #1	Chemical #2	Chemical #3	Chemical #4	
A. Reproductive	X_{1A}	No data	No data	No data	**X_{1C}**
B. Developmental	No data	No data	No data	X_{4B}	
C. Repeated	*X_{1C}	X_{2C}	X_{3C}	X_{4C}	

Note: NOAEL = no observed adverse effect level; X = NOAEL value. Subscripts A, B, and C indicate the endpoints, and subscripts 1, 2, 3, and 4 indicate the corresponding chemical number.

*Lowest NOAEL value.

This default approach adds conservatism to the screening-level analysis because all products would not necessarily contain this specific chemical; some may actually contain a chemical that is less toxic. When applying this default strategy, the following additional considerations could lead to a decision to choose a NOAEL other than the lowest one:

- *Experimental data quality.* The default approach of selecting the lowest relevant NOAEL would be examined when the quality of the underlying study is poor. In such cases, a higher NOAEL from a better quality study would be used.
- *Use of a LOAEL from a higher quality study,* which could improve consistency in data quality across chemicals and category of chemicals.
- *Relevance of experimental routes of exposure to the use of the chemicals.* When a dermal NOAEL is available, it should be used for comparison with dermal exposure data. If an oral NOAEL from a gavage study is used for comparison with dermal exposure, then dermal absorption factors should be used to adjust estimates of exposure. Note that if dermal absorption is taken into consideration to determine systemic exposure, then oral absorption must also be considered and expressed on a systemic exposure basis. Published guidelines such as the *European Commission Guidance Document on Dermal Absorption* should be used as a reference for dermal absorption factors (European Commission 2004).

Table 2-4 presents an example of a hazard data matrix for the HPV category AO. For this chemical category, a NOAEL for the repeat-dose study of 80 mg/kgBW/day was selected as the most relevant and representative for the AO category and used to determine the MOE. This NOAEL was chosen because of the high quality of the study from which it is derived and its consistency with the NOAELs from the other toxicity endpoints.

Table 2-4. HPV Chemical Category AO Hazard Data Matrix

Toxic Endpoints	NOAEL (mg/kgBW/day)				Representative NOAEL for AO (mg/kgBW/day)
	Chemical #1	Chemical #2	Chemical #3	Chemical #4	
A. Reproductive	>40*	No data	No data	No data	80
B. Developmental	25**	100	No data	No data	
C. Repeated	80	No data	No data	No data	
D. Chronic	52.6***	No data	No data	No data	

Note: AO = amine oxide; HPV = high production volume; NOAEL = no observed adverse effect level.

*Effect was not observed at any dose level in the experiment, including the highest dose level; 40 mg/kgBW/day was the lowest dose category in the experiment, and no effect was observed at this lowest dose.

**Maternal toxicity was observed at a lowest observed adverse effect level (LOAEL) = 100 mg/kgBW/day. However, no effect was observed at 25 mg/kgBW/day.

***The chronic NOAEL of 52.6 mg/kgBW/day is consistent with the result in the reproductive study (i.e., NOAEL <40mg/kgBW/day) and with the developmental study because it falls in the range between the NOAEL (25 mg/kgBW/day) and the LOAEL (100 mg/kgBW/day).

2.6. Screening-Level Assessments

Using the outline described in Section 2.3, screening-level assessments can be carried out for chemical categories. Two approaches for applying this framework are described in this section:

1. Screening based on exposures can be conducted to identify product categories and use scenarios that result in the highest exposures in the chemical category.
2. Screening risk characterization can be conducted by comparing screening exposure estimates with appropriately selected hazard data. (Appropriate selection of hazard data is described in Section 2.5.)

Where necessary, refinements can be made to provide more realistic estimates of exposure and risk. The initial screening assessments are described below. Section 2.7 describes the refinement process in more detail.

2.6.1. Screening Based on Exposures

The purpose of screening based on exposures is to identify the product categories with the most significant consumer exposure potential before considering the hazard data. In this assessment, the screening-level estimate of exposures (in $mg_{chemical}$/kgBW/day) is based on PE × IC. The output of this exposure assessment is a list of PE scenarios and their corresponding screening-level exposure estimates for the oral, dermal, and inhalation routes for each product category in which the chemical is used. By sorting screening exposure estimates for each route (i.e., dermal, oral, and inhalation) from high to low, PE scenarios with the highest potential exposures to the chemical can be identified, as can those that pose negligible exposure.

As an example, screening-level exposure to the category AO from consumer uses of products was estimated using this methodology. The default high-end PE estimates were based on the habits-and-practices data provided in Appendix II-A, and the IC for AO was obtained from the SDA survey work as previously described and summarized in Table 2-2. The exposure estimates of this screening-level assessment are shown in Table 2-5.

Table 2-5. HPV Chemical Category AO Screening-Level Exposures by PE Scenarios

Product Exposure Scenarios	Screening-Level Exposure Estimates (mg_{AO}/kgBW/day)	
	Dermal (minimum to maximum)	Inhalation (minimum to maximum)
Cleaning Products (direct exposure)		
Laundry pretreatment (undiluted)	1.0E-3 to 5.0E-3	
Hard surface cleaner (undiluted)	1.0E-4 to 5.0E-3	
Hand-wash laundry (diluted)	4.7E-5 to 2.3E-4	
Hand-wash dishes (diluted)	9.0E-6 to 9.0E-4	
Hand-wash hands (dish liquid, diluted)	3.0E-6 to 3.0E-4	
Hard surface cleaner (diluted)	9.4E-6 to 4.7E-4	
Spray cleaner		1.6E-6 to 8.2E-5
Laundry product (residual on clothing)		
Liquid detergent	2.0E-3 to 1.0E-2	
Personal care product (residual after use)		
Hair conditioner	4.1E-3 to 4.7E-3	
Shampoo	2.5E-3 to 1.4E-1	
Bar soap, hand	3.6E-4 to 1.8E-2	
Cleansing products	2.3E-4 to 5.1E-2	
Bar soap, face	4.5E-5 to 2.2E-3	
Personal care product (leave-on)		
Aftershave	7.0E-2 to 1.4E-1	
Hair styling tonic/gel	4.7E-3 to 9.3E-2	
Body moisturizer	1.1 to 3.2	

Note: AO = amine oxide; HPV = high production volume; NOAEL = no observed adverse effect level.

2.6.1.1. Screening Aggregate Exposures – Within Product Categories

Screening-level exposure estimates for the various PE scenarios could be aggregated within each product category to identify the product category with the highest potential exposure to the chemical. This aggregation by product category could be based simply on adding the scenario exposures within a product category. In the case of AO, for the liquid detergents product category, this could be done by simply adding the screening estimates from the three modeled scenarios – hand-washing, pretreatment, and residual on clothing.

Table 2-6 provides a summary of the screening exposure estimates for various product categories based on aggregation within a product category. For AO, neither inhalation nor indirect exposures shown above contribute significantly to the overall exposure. As indicated in the table, at maximum screening exposure level, three of the products – body moisturizers, hair care (hair conditioner, shampoo, styling tonic/gel), and aftershave – are the primary drivers of the exposure, and exposures from all other product categories are one to three orders of magnitude lower.

Table 2-6. Exposures to AO by Product Category

Product Category	Estimated Exposure (mg_{AO}/kgBW/day), (minimum to maximum)
Body moisturizer	1.1 to 3.2
Hair care	1.1E-2 to 2.4E-1
Aftershave	7.0E-2 to 1.4E-1
Laundry detergent (liquid)	3.0E-3 to 1.5E-2
Bar soap	4.1E-4 to 2.0E-2
Cleansing products	2.3E-4 to 5.1E-2
Dish detergent (liquid)	1.2E-5 to 1.2E-3
Hard surface cleaner (liquid)	1.1E-4 to 5.5E-3

Note: AO = amine oxide.

2.6.1.2. Screening Aggregate Exposures – Relevant Product Combination

An estimate of total aggregate exposures can be obtained by simply adding the exposures from all the individual products. For AO, the use of all consumer products by a single consumer is plausible because no duplicate product types exist within a category. If there were duplicate types of product (e.g., both liquid and granule laundry detergents), as a conservative approach, the product resulting in the higher exposure would be used, but not both forms of the same product. It could be argued that consumers using aftershave (primarily men) would be less likely to use body moisturizers and cleansing products (users of which are primarily women). However, adding these exposures with other uses would be appropriate for a conservative screening approach.

For AO, which have fairly widespread uses across household cleaning and personal care categories, the simple addition of multiple exposures did not change the order of magnitude of the total exposure. In fact, the total aggregate exposure estimate is not significantly different from the exposures estimated for two product categories (hair care and aftershave) because the use of these two products contributes 80% to 85% of the total aggregate exposure. Table 2-7 provides a summary of the percent of total exposure by each product type.

Table 2-7. Contribution of Total Exposure by Product Type (%)

	Estimated AO Exposure (mg_{AO}/kgBW/day)	
	Minimum	**Maximum**
Aggregate Exposure	1.21	3.68
Product Type	**Percentage of Total Exposure**	
Body moisturizer	90.8	86.9
Hair care	0.9	6.5
Aftershave	5.8	3.8
Laundry detergent (liquid)	2.5	0.4
Bar soap	0.0	0.5
Cleansing products	0.0	1.4
Dish detergent (liquid)	0.0	0.3
Hard surface cleaner (liquid)	0.0	0.1

2.6.2. Screening-Level Human Health Risk Characterization

Screening risk characterization is conducted by estimating MOE using the formula

$$MOE = NOAEL/(PE \times IC),$$

where IC is converted from percent to a fraction during the calculation

By using the screening aggregate exposure estimate for each product category and screening total aggregate exposure estimate for all relevant product category combination, as previously described, screening MOEs for each product category and combined product categories, respectively, can be developed. The following sections describe these steps in more details.

2.6.2.1. Screening Risk Characterization by Product Categories

For each product category, a number of screening-level MOEs can be developed for all possible routes of exposure (dermal, oral, inhalation). (The approach to select a default conservative NOAEL is described in Section 2.5). Table 2-8 illustrates a hypothetical output from the screening risk characterization.

Table 2-8. Hypothetical Outputs from a Screening Risk Characterization

Product Category	Screening Risk Characterization		
	MOE_{Dermal}	MOE_{Oral}	$MOE_{Inhalation}$
A	$NOAEL_{dermal}/PE_A \times IC_A$	$NOAEL_{oral}/PE_A \times IC_A$	$NOAEL_{inh}/PE_A \times IC_A$
B	$NOAEL_{dermal}/PE_B \times IC_B$	$NOAEL_{oral}/PE_B \times IC_B$	—
C	$NOAEL_{dermal}/PE_C \times IC_C$	—	$NOAEL_{inh}/PE_C \times IC_C$

Note: MOE = margin of exposure; NOAEL = no observed adverse effect level.

Table 2-9 provides the screening-level MOEs for various products with AO as an ingredient. AO exposure estimates for various PE scenarios described in Section 2.6.1.1 were compared to a NOAEL of 80 mg/kgBW/day to develop the MOEs.

Table 2-9. Screening-Level MOEs from AO Exposures by Product Category

Product Type	MOEs	
	Minimum	Maximum
Body moisturizer	72.7	25
Aftershave	1,109	570
Hair care	7,268	332
Laundry detergent (liquid)	26,650	5,329
Bar soap	195,005	3,997
Cleansing products	347,667	1,567
Hard surface cleaner (liquid)	726,836	14,537
Dish detergent (liquid)	6,662,666	66,626

Note: AO = amine oxide; MOE = margin of exposure; NOAEL = no observed adverse effect level.

2.6.2.2. Determination of Products and Routes of Exposure Requiring Further Evaluation Based on MOE

The purpose of the screening risk characterization is to identify product-specific and route-specific exposures that can be set aside with high confidence as well as those that are of potential concern and

warrant more in-depth evaluation. Identification of products with high or low potential risks is based on the screening-level MOEs. If MOE is 1,000 or greater, an initial default decision of "not of concern and no further refinement" is considered adequate for two reasons:

1. Conservative approaches are used to develop the screening-level exposure estimates.
2. The use of the lowest NOAEL of all the toxicity studies conducted deliberately errs on the side of protection (i.e., conservative estimates).

In general, the following "default" filtering process would be applied:

- For product categories with MOEs larger than 1,000, there would be no need for further consideration or assessment.
- For product categories with MOEs greater than 100 but less than 1,000, a decision for refined assessment would be dependent upon the specifics of the study conducted (e.g., a 90-day vs. a 6-month or longer study, the severity of the response, the quality and comprehensiveness of the data set) and the particular product and its uses.
- For product categories with low screening MOE estimates (i.e., less than 100), refinement of the NOAEL and/or the exposure estimates would be warranted.

Various factors need to be taken into consideration when determining whether an initial default MOE of less than 1,000 but greater than 100 is adequate. Those factors include:

- the quality and comprehensiveness of the database available on the chemical/category of chemicals,
- the duration of the study (28 days vs. 90 days vs. 6 months or greater),
- the quality of the study upon which the MOE is based,
- the seriousness of the effect observed,
- the steepness of the dose-response curve, and
- what is known about the toxicokinetics and toxicodynamics of the chemical in animals vs. humans.

With respect to study duration, for repeat-dose toxicity studies, an initial default of 10 is generally used when extrapolating a 90-day repeat-dose study to lifetime exposures. If the repeat-dose study is 6 months or greater, then an uncertainty factor of 10 is not necessary because a study of this duration is considered predictive of non-cancer chronic toxicity. With respect to consideration of the seriousness of the adverse effect, if the effect that is observed is minor and/or reversible, if the MOE is based on a high-quality 90-day study and if the database for the chemical category is of high quality and comprehensive with respect to studied endpoints, then a MOE of less than 1,000 may be adequate for making the decision that no further refinement of the assessment is needed.

Numerous documents have been written about risk assessment and application of appropriate uncertainty factors to studies or data sets when deriving appropriate guidance values for exposure limits for humans. It is not the intent of this book either to list all those documents or to discuss in depth the various factors. However, a key document that one can consult in making a decision about the adequacy of the MOE is "Assessing Human Health Risks of Chemicals: Derivation of Guidance Values for Health-Based Exposure Limits" (WHO 1994).

In the case of AO, with the exception of the body moisturizers, hair care, and aftershave products, all products have MOEs greater than 1,000 and thus are not subject to further assessment. Although the MOEs for body moisturizers, hair care, and aftershave use are below 1,000, refinements are not necessary because:

- the MOE was based on a high-quality, repeat-dose toxicity study;
- chemical category AO has a comprehensive toxicity data set that includes developmental toxicity, reproductive toxicity, and chronic toxicity as well as carcinogenicity data (beyond SIDS endpoint requirements); and
- the MOE is greater than 100 and thus is sufficient to account for the 10-fold uncertainty factor for interspecies variability and the 10-fold uncertainty factor for intraspecies variability (Health Canada 1994; Kodell and Gaylor 1999).

2.6.2.3. Screening Aggregate Human Health Risk Characterization — Relevant Product Combination

The main purpose of developing screening-level aggregate exposure by summing exposures for the relevant combination of product uses by an individual (described in Section 2.6.1.1) is to identify PE scenarios that are the drivers for total exposures and that may warrant more detailed and refined exposure assessments.

Taking this a step further and comparing this screening-level aggregate exposure to the default lowest NOAEL from the hazard dataset of an entire chemical category to characterize risks (i.e., MOEs) would amount to a comprehensive risk assessment, with an explicit assumption of equivalent toxicity for all chemicals within a category. Clearly, this is not the case. However, if one uses this conservative approach and the resulting MOE is adequate (see discussion above on adequacy of MOE), then a conclusion of "no concern and no further work needed" for the use of the entire chemical category in consumer products could be made with a high degree of confidence. Conversely, if this "no concern" conclusion cannot be made, refined assessments for the product uses that were identified as exposure/risk drivers would be carried out using more chemical-specific information. The following section describes such refinements in more detail.

2.7. Consideration for Refinements

Similar to most screening-level assessment methodologies, the methodology described above is purposely designed to prevent false negative decisions by making the worst-case assumptions about toxicity and exposure, including default assumptions of high-end PE estimates, ingredient concentration ranges for the category applied to all product types irrespective of the actual chemical concentration, and the use of the lowest NOAEL. As such, there is a high level of confidence in the classification of product types and use scenarios – and/or combinations thereof – as "of no concern and no further work is necessary" on the basis of this screening-level assessment. Conversely, using this screening methodology would lead to the high likelihood of false positives.[5] Thus, refinements of exposures and risks for the product use scenarios that have been classified as "potential concern" would be necessary.

Consequently, it is important that a continual refinement process, as outlined in Figure 2-1, be implemented. This process begins with the initial screening, which is based on high-end default assumptions (described in this methodology), and continues with the loop of refining exposure estimates and selecting NOAELs that are more appropriate for the product use scenarios of concern.

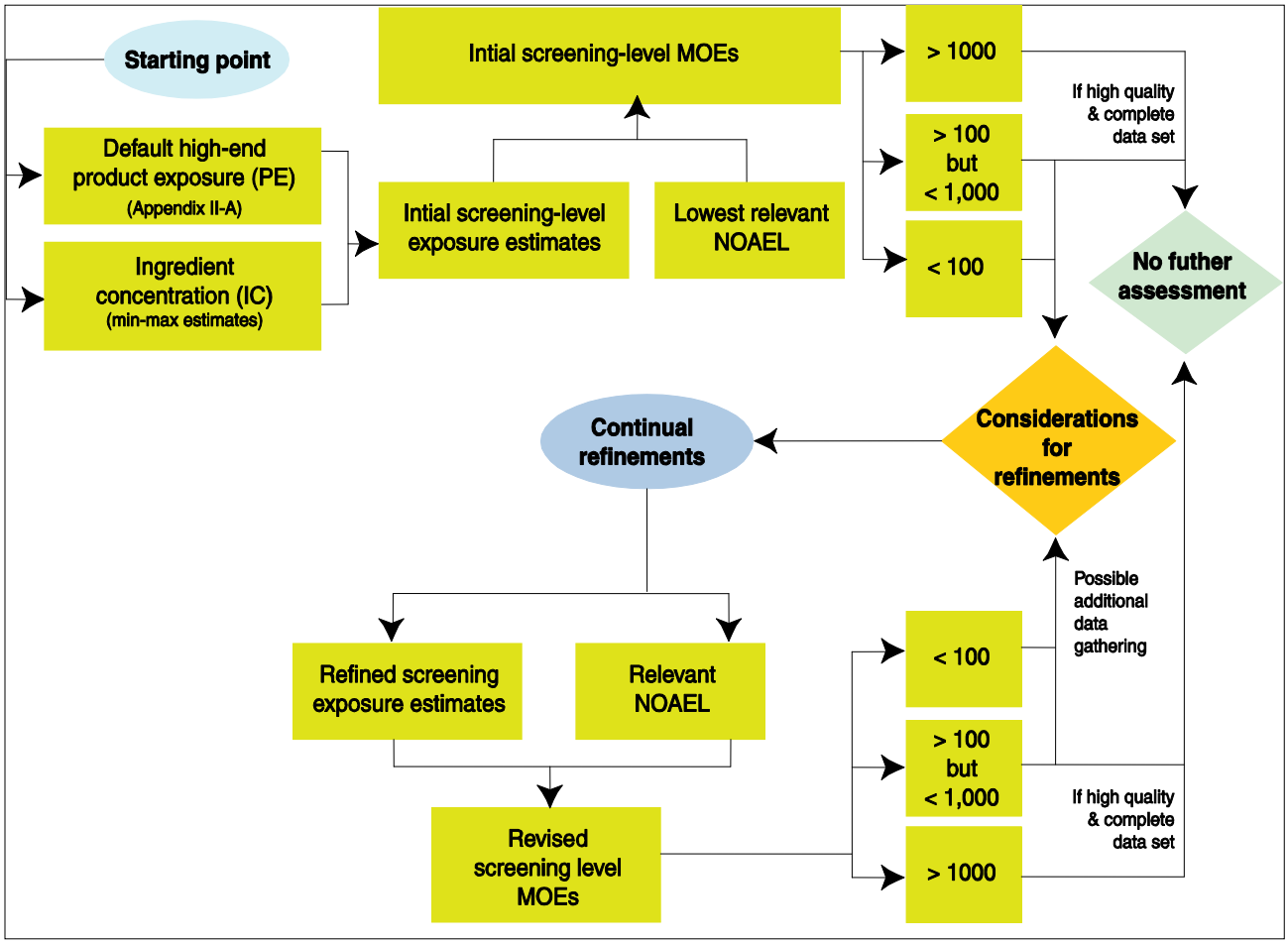
[5] In this context, screening estimates of exposures and risks are higher than in reality.

2.7.1. Refining Exposures

Conservative exposure factors were selected as defaults to yield high-end initial exposure estimates in this screening methodology. Combinations of average and high-end values for exposure model input parameters (e.g., frequency of product use, amount of product use, product retention factors) could be used to develop more realistic high-end exposure estimates than estimates based on combination of high-end values assumed in this screening methodology (EPA, 1992). Examples of approaches to further refining the screening exposure estimates could include the following:

- *Refining the dermal penetration default value.* The default value of 100% dermal penetration in the screening exposure assessment models can be modified according to measured or modeled dermal penetration/absorption values (e.g., the Dermal Permeability Coefficient Program [DERMWIN] under EPA's Estimation Programs Interface [EPI] Suite). If dermal exposure is modified and dermal exposure is being compared to an oral toxicity study NOAEL, actual oral absorption of the chemical must also be taken into consideration when determining the MOE. An example is the HERA alcohol ethoxysulfates assessment (HERA 2003).

Figure 2-1. Screening-Level Assessment – Continual Refinement Process



- *Refining surface area estimates.* For skin creams and other consumer products that are applied to the skin, the specific habits and practices data for these products can be used to refine exposure. For example, with skin creams, total body application is assumed. However, if the chemical of

interest is used only in facial cream, this surface area is not appropriate. Refinement from total body surface area to just facial surface area would significantly reduce exposure estimates.

- *Refining the frequency and/or duration of product use on the basis of more detailed product category information.* This process can provide more realistic estimates.

2.7.2. Identifying Relevant NOAELs

Refinements of the NOAEL can be carried out through a reexamination of the appropriateness of selecting the lowest repeated-dose NOAEL as the representative dose–response threshold for an entire chemical category. Sorting chemicals within each chemical category by toxicological potency would be more appropriate in a refined assessment. One option could be to select a NOAEL for the specific chain length(s) that are typically used in the product category. For example, if the lowest NOAEL selected in the screening assessment is based on a short chain length (e.g., C6) and the shorter chain chemicals have been shown to be more toxic than the longer chain chemicals, but the actual ingredient or chemical in the products that is subject to refined assessments are of the longer chain length and of lower toxicity (e.g., C14, C16, and C18), then refining the risk characterization using the higher NOAEL is appropriate. Moreover, if toxicities were different for the different routes of exposure, toxicity equivalents would be considered in the aggregation. Sophisticated aggregate assessments requiring more detailed specification of input parameters, including distribution and probabilistic assessment methodology like those required under the Food Quality Protection Act (FQPA, 1996) are beyond the scope of screening-level assessment.

2.8. Minor Exposure Scenarios Not Considered in Screening Assessment

The purpose of the screening exposure assessment and screening risk characterization is to identify any products and use scenarios of potential concern. Each consumer product may have many possible exposure scenarios; however, only one or a few scenarios usually are relevant in contributing the dominant exposure for each product. By comparison, the other scenarios are insignificant in the assessment of most chemicals because they do not contribute appreciably to estimated exposures and risks. For example, previous assessments have shown that human exposure to household cleaning product ingredients is very low for a number of product scenarios in which ingredients of interest comprise up to 30% of the product. For soaps, LAS, and alkyl sulfates, combined exposures for all household cleaning scenarios are less than 6 μg/kgBW/day (HERA, 2007). Dermal exposures during hand dishwashing and household surface cleaning, from detergent residue on laundered clothes, and from inhalation exposure to laundry powder dust and aerosol cleaning products contribute less than one-third of the total household cleaning PE (<2 μg/kgBW/day). Dermal exposure during hand laundering and laundry pretreatment and ingestion of detergent residue on dinnerware contributes to the remainder (<4 μg/kgBW/day) (See www.heraproject.com). In general, these minor scenario uses do not need to be included in the screening-level exposure assessment when exposures due to other uses are expected to greatly exceed exposures due to these uses and when the MOE is expected to be very large.

2.9. Summary

As stated in the general approach section of this document, this risk screening methodology is based on default high-end PE estimates and conservative dose-response data (i.e., lowest NOAEL and route-specific data when available). The main purpose of this methodology is to serve as a priority-setting tool. The screening exposure and risk characterization outputs from the application of this methodology can help focus resources to develop more refined risk assessments where refinement is needed, and to assist in deciding where exposures and risks are of minimal concern and refined assessment is not warranted.

In Appendix III, case studies that use this consumer exposure/risk screening method with initial exposure and risk characterization results are provided. The case studies are for AO and long-chain alcohols, both of which are based on the format of the OECD use/exposure pilot project.

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3. EXPOSURE, EFFECTS, AND RISK SCREENING METHODOLOGIES FOR HIGH PRODUCTION VOLUME CHEMICALS VIA ENVIRONMENTAL RELEASES

3.1. Background and Scope

This section provides a methodological approach for screening environmental exposures of high production volume (HPV) chemicals sponsored by The Soap and Detergent Association (SDA), European Oleochemicals and Allied Products Group (APAG), European Committee of Organic Surfactants and Their Intermediaries (CESIO), and Japan Soap and Detergent Association (JSDA). These chemicals are used primarily in laundry, cleaning, and personal care products. Screening-level assessment is often sufficient to provide an adequate characterization of exposure and resulting risk. Conservatively high exposure estimates that are well below toxicological threshold levels support a determination that harm to the environment is unlikely.

Chemicals can be evaluated separately or as categories of related substances. Two exposure scenarios are of primary interest:

- Environmental releases of chemicals at a manufacturing facility (including production, processing, and formulation facilities)
- Environmental releases during and following product use and as a consequence of down-the-drain disposal.

Because of the physicochemical nature of these chemicals and their primary uses, the environmental medium of most interest and the focus of this assessment is the freshwater aquatic environment. However, exposure in other media, including air, soil, and biota, and in other aquatic environments, such as estuary and marine systems (see Section 3.8, Related Compartments), can also be considered either as part of the screening process or in subsequent assessments. It must also be recognized that some of the exposure assessment models discussed later in this section (e.g., E-FAST) do not estimate exposure in these other media. Therefore, additional work would be required to estimate exposure in environmental media beyond the freshwater aquatic environment.

Chemical Awareness (CA) has prepared an assessment framework entitled *Framework for Evaluation of Chemicals for Potential Ecological Exposure and Risk* (2002). It consists of a stepwise approach for conducting assessments of potential exposure and risk to relevant ecological and human receptors posed by chemicals released to the environment. In addition to ecological receptors (e.g., fish and wildlife), environmental releases from both manufacturing sites and down-the-drain disposal can result in human exposure (e.g., drinking water and fish for consumption). The CA framework is a screening-level approach that can inform priority setting. It is a generic yet detailed framework that is well suited to the wide range of chemicals and product uses covered by the International Council of Chemical Associations (ICCA) initiative and the interests of the SDA, JSDA, APAG, and CESIO consortia.

The CA exposure and risk assessment framework consists of four phases:

1. *Description of the flow in commerce and resulting emissions to the environment.* The goal of this step is to gain an understanding of where, how, and at what gross levels the chemical is likely to reach the environment.
2. *Assessment formulation.* The goal of this step is to determine the need for risk characterization and level of exposure on the basis of the available use and exposure information along with the

hazard profile of the chemical. Key exposure pathways and receptors are identified as part of this step.

3. *Screening exposure/risk assessment.* The goal of this step is to prepare quantitative estimates of exposure and risk on the basis of modeled information and, where available, monitoring information.

4. *Higher-level/refined assessment.* This step can be deemed necessary depending on the outcome of Step 3 or the status of the substance as persistent, bioaccumulative, and toxic (PBT). Step 4 is used to refine/expand the screening-level assessment using chemical-specific information and/or site- and situation-specific information.

The framework has established the pathways by which chemicals can lead to exposure to environmental and human receptors. The guidance proposes a process for coupling environmental exposure and effects assessments into a decision-making framework. However, the framework does not specify the methods to be used to conduct the exposure and effects assessments, which is the primary objective of this book.

The framework and this book were written to help assessors estimate exposure for PBT and non-PBT chemicals. However, because of their persistence and the possibility that concentrations can build up in the environment over time, PBT chemicals may require a higher-level assessment. This document assumes that the route chemicals follow from consumer use and disposal into municipal wastewater treatment plants (WWTPs) and subsequent release into the environment occurs primarily in the form of liquid effluents. Assuming degradation, the highest environmental concentration will occur in the effluent immediately after dilution. Assuming no degradation, continued use will result in accumulation in soil, sediment, or surface waters. Hence, this accumulation may need to be considered in a higher-level assessment if the degradation rate is extremely slow. Criteria for determining whether a substance is a PBT can be found in the Stockholm Convention on Persistent Organic Pollutants (POPs; see http://www.pops.int/) and in national regulations such as the Canadian Toxic Substance Management Policy[6] and the U.S. Environmental Protection Agency's (EPA's) rules for PBT chemicals.[7] Japan's "Monitoring Report on the Persistent Organic Pollutants in Japan" can be found at http://www.env.go.jp/en/chemi/pops/Appendix/00report/00top.pdf, and specific laws can be found at http://www.env.go.jp/en/chemi/pops/Appendix/05-LawsPOPs.htm. The European Union (EU) defines POPs using the United Nations 1998 Protocol to the 1979 convention on Long-Range Transboundary Air Pollution on Persistent Organic Pollutants;[8] and an additional commission proposal was adopted in August 2004.[9]

The approach discussed in this book is intended to be applied to surface waters. Thus, exposure models and procedures for assessment of effects focus on estimated exposure and effects in this compartment. This approach is consistent with the intent of the HPV process. Data relevant to determining exposure and effects in the terrestrial compartment or in estuarine and marine systems may be provided in chemical data summaries; where available, these data can be used, but this area is beyond the scope of the HPV process and the method described here.

This book's approach also does not directly address exposure to impurities or degradation products, although similar methods can be used if the data required for this assessment are available or can be estimated for the impurity or degradation products of interest. Moreover, toxicity data are likely to help address the toxicity of impurities and degradation products to the extent that these compounds were present in tests conducted on the parent compound.

[6] available at http://www.ec.gc.ca/CEPARegistry/policies/
[7] available at http://www.epa.gov/tri/lawsandregs/pbt/pbtrule.htm
[8] available at http://www.unece.org/env/lrtap/full%20text/1998.POPs.e.pdf
[9] see http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=COM:2004:0537:FIN:EN:PDF

3.2. Assessment Tiers versus Levels

A tiered process is typically followed in a traditional risk assessment. In the lower tiers, risks are assessed using relatively little data and conservative assumptions. If a decision can be made on the basis of a lower-tier assessment, then the assessment is stopped. However, if a decision cannot be made and additional data are needed, the assessment proceeds to the higher tiers. Thus, the word *tier* implies an iterative process. Within the context of screening-level assessments as described in this book, assessments are performed after all available data are collected and collated. Thus, most assessments will not be iterative, and the concept of a tiered process does not typically apply. Hence, this book uses the term *assessment level* to describe different amounts and types of data that are available for estimating exposure corresponding to different degrees of sophistication in the exposure and effects assessments.

With increasing assessment levels, standard conservative defaults are replaced with more chemical-specific and local/regional information and thus progress from a conservative to a more realistic exposure estimate. In effect assessments, assessment factors are reduced as more ecologically relevant data are used to establish the predicted no-effect concentration (PNEC; see Section 3.6). In screening-level risk evaluations, predicted environmental concentrations (PECs) are compared to an effect benchmark (i.e., the PNEC) to determine the margin between the predicted exposure level and the level determined to be "safe," or not pose significant risk to the biological receptor(s) of interest.

3.3. Exposure Assessment

The following sections present a toolbox of methodologies for use in environmental assessments of chemicals. The goal is to identify those environmental exposure methods that are both widely used and accepted by regulatory agencies to place within this toolbox. Case study examples of how to take a chemical or category through the screening process presented in the draft Organization for Economic Co-operation and Development (OECD) format for chemical use and exposure assessments are provided in Appendix III.

3.3.1. Objectives

The main objective of the environmental exposure screening methodology is to provide reasonable estimates of PECs using the best available data and widely accepted models. PECs are chemical (or chemical category) specific and, by design, are intended to be representative of conditions in a given geographic region.

3.3.2. Chemical Use and Exposure Information

As part of the hazard profile developed for each chemical (or chemical category), physicochemical data are provided that can be used in the exposure modeling process. These data minimally include

- water solubility,
- octanol:water partition coefficient (K_{ow}),
- vapor pressure,
- stability in water – hydrolysis,
- photodegradation, and
- biodegradability test results.

The Level 1 assessment approach assumes that these data will be available. For many of these chemicals, however, additional data that can be used to support higher-level exposure assessments are included in the assessment summary.

As described in Section 2.4.2, SDA conducted a survey of producers and consumer product formulators to obtain information on the annual production/importation volume of individual chemicals (identified by Chemical Abstract Service [CAS] number) by geographic region and the percentage of that volume that was sold or used as a final product, exported outside the region, or further processed to an intermediate (and whether that intermediate is site limited). These data can be used to obtain initial environmental emissions estimates, which are necessary to conduct the environmental exposure assessment. In addition, when available, region-specific information was collected to determine the likelihood and location of manufacturing releases and off-site transfer (e.g., stack releases, discharge to wastewater treatment, landfill disposal, incineration); requests were also made for available environmental monitoring data (e.g., wastewater treatment removal efficiency and/or surface water concentrations) and for facility classification (e.g., Standard Industrial Classification [SIC] codes for U.S. facilities and Main and Industrial categories for EU facilities). Among the "Beyond SIDS[10] Data" collected in this survey that would be useful in the exposure assessments are the following:

- Wastewater treatment plant removal
- Sorption onto soils and sediments
- Realistic (i.e., beyond screening) degradation test results and estimates of half-lives
- Effluent/emission or environmental monitoring

3.3.3. General Framework

Consumer product chemicals generally enter the environment through water discharges (see Figure 3-1) during production, formulation, and consumer use, although for some products, significant proportions of environmental releases are to air or soil as a result of use. Industrial discharges are also generally to water, although emissions can occur to the air and soil environments, depending on the process operations and the physicochemical properties of the chemical. The SDA-sponsored HPV chemicals generally have low volatility, so air releases are relatively limited. The sponsored chemicals range from *highly water soluble* to *much less water soluble* and have a corresponding affinity to partition to solids and/or lipids, indicating that they are most likely to be in water discharges. Because most of the volume of the chemicals produced for use in consumer products for cleaning, beauty, and personal care is disposed to the environment after use of the product and little is released during production or formulation of the product, the main focus of models that estimate fate and exposure for consumer product chemicals is on disposal in household wastewater that is discharged to surface waters after treatment in a WWTP.

3.3.4. Basic Equations

The fate model and the exposure model use similar approaches and equations to estimate chemical concentrations in surface water due to chemical disposal in household wastewater. For clarity, this section describes the basic approach and equations. The assessor should read user manuals and publications that describe the models to understand the specific details of the models described in this section.

The basic equation is

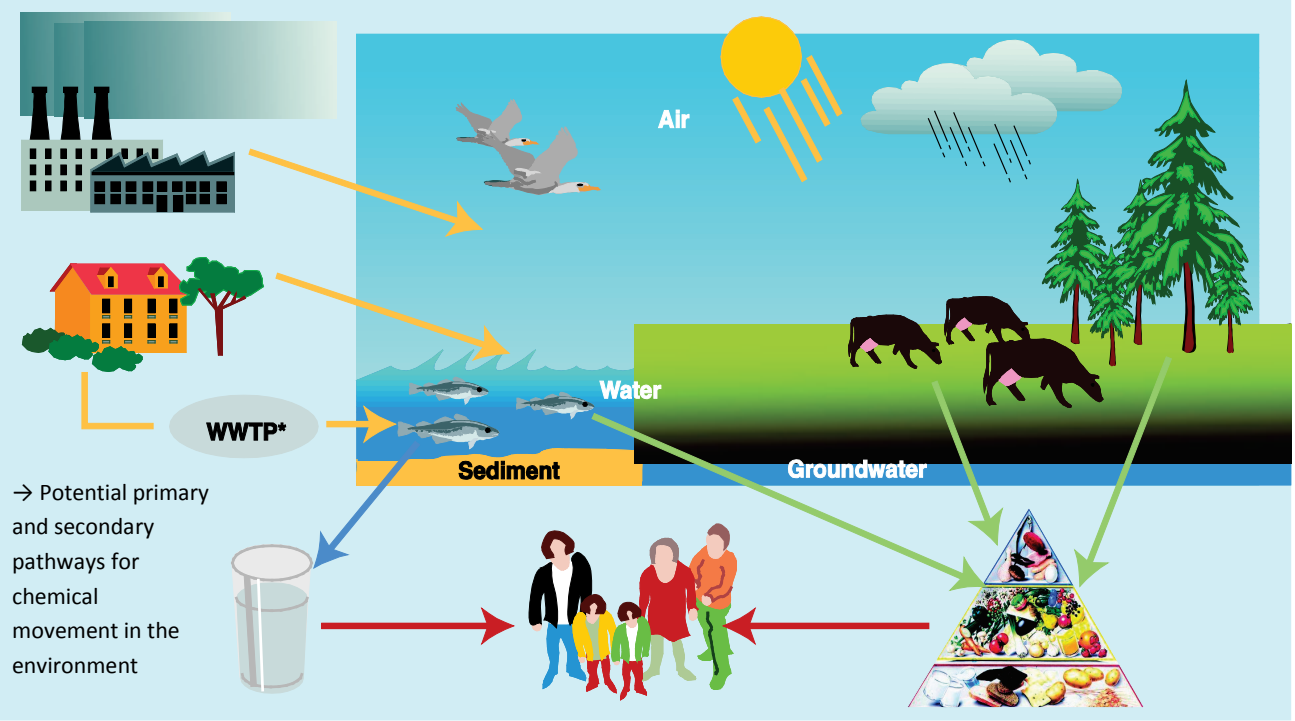
$$PEC = (Q \times Cf\,(1 - R)) / (365 \times WW \times POP \times DF)$$

where *PEC* (mg/L) is the predicted exposure concentration, *Q* (kg/yr) is the quantity of the substance used in consumer products in the relevant geography, *Cf* is the conversion factor for kg to mg, *R* is the fraction of the chemical removed in wastewater treatment (%), 365 is the conversion factor from year to days, *WW* (L/day) is the amount of wastewater produced by one person per day, *POP* is the population size in the

[10] SIDS = Screening Information Data Set

relevant geography that uses the consumer product, and *DF* (unitless) is the dilution factor for the wastewater in the surface water. The values for these factors are generally region specific.

Figure 3-1. Pathways to the Environment of Chemicals Produced and Used in Consumer Products



*WWTP = wastewater treatment plant; there could be alternative treatment technology

Going the next step beyond exposure assessment, a media-specific PEC (e.g., in surface water) can be compared with an established safe exposure threshold for a chemical (e.g., PNEC). This comparison forms the basis for an initial risk evaluation. For chemically related materials (i.e., those with similar physico-chemical and toxicological properties and fates), a PEC can be derived for the chemical category or cate-gories. A conservative estimate of environmental exposure would begin with the assumption that the total production volume (e.g., metric tons per year) of the chemical, or the combined production volume for the chemical category, is released into the environment following consumer use and down-the-drain disposal. If the PEC derived in this manner is less than the PNEC for a chemical or category of chemicals, biological receptors (e.g., people, fish) are not likely to be injured. Section 3.6 provides specific guidance for the derivation of a PNEC.

If it cannot be concluded with confidence that injury is unlikely, then the assessor must determine whether additional work to refine the PEC value to reflect actual-use conditions is possible. Refinement for PEC includes, for example, subtracting that portion of the total volume that does not go down the drain after use or, for manufacturing facilities, refining estimates of the amount of chemical released to the environment on the basis of the total process loss amount and/or the amount removed during on-site wastewater treatment or in a municipal plant that receives wastewater from the facility. If it is not possible to refine the PEC value, the risk characterization is based on a comparison of the conservative PEC with the PNEC.

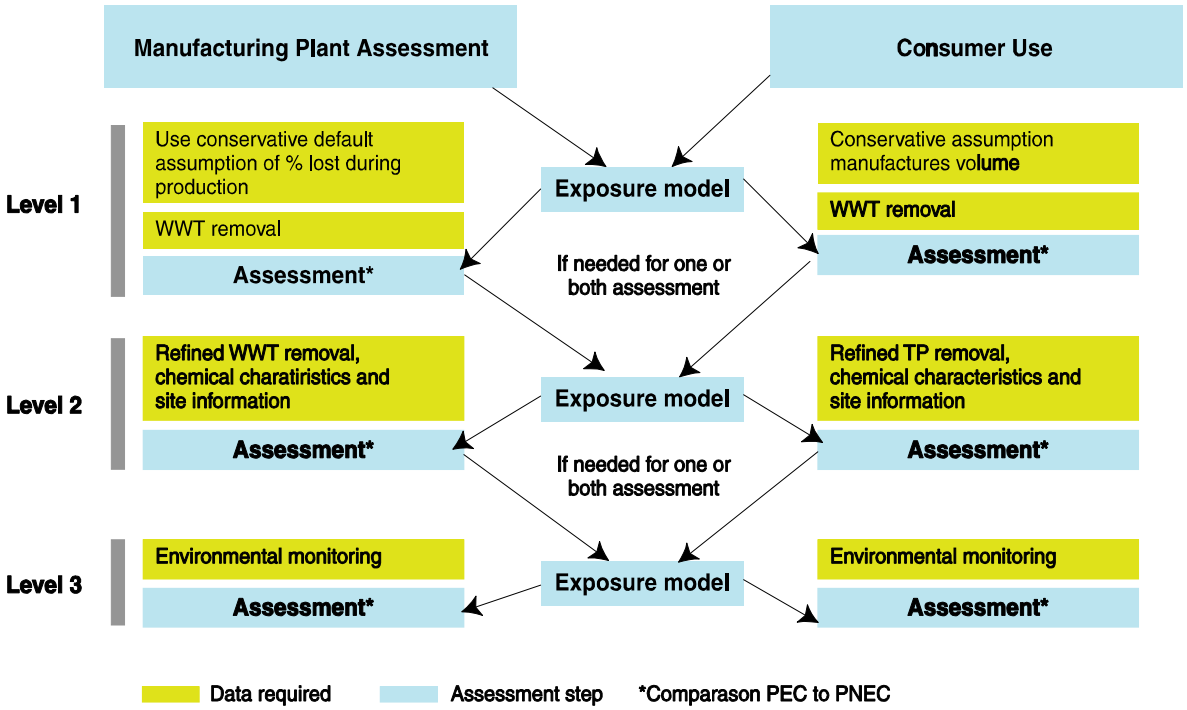
Reasons to undertake higher-level/refined assessments include any of the following three conditions:

1. The screening-level assessment indicates that the chemical may cause adverse effects.
2. The screening-level assessment indicates the chemical is persistent and/or bioaccumulative such that longer-term exposures are likely.
3. The screening-level assessment indicates that environmental compartments beyond the aquatic compartment may be exposed (e.g., terrestrial biota or, perhaps, humans via their diet).

At the discretion of the assessor, a refined assessment can also be performed to more fully and/or accurately describe environmental exposures (and risks). Higher-level exposure (and risk) assessments are tailored to a specific chemical and use scenario, and the components need to be quite varied and flexible. Because various methodologies exist for conducting higher-level exposure assessments, which can be very detailed, these higher-level approaches are not covered in this book.

For the screening-level assessments, the exposure assessment can be based on the approach outlined in Figure 3-2, where the assessments can be refined from screening-level assessments by using more accurate data on either the chemical's properties or the locations of likely release and environmental exposure. For chemicals, the recommended approach is to conduct the assessment at the highest level possible given the available data.

Figure 3-2. Exposure Assessment Approach



The environmental exposure methodologies described above and the case studies for amine oxides (AO) and long-chain alcohols (LCOH) provided in Appendix III are focused at the "screening level" – that is, a first approximation of exposures calculated on the basis of generally recognized and accepted estimation techniques. Discussion of approaches, data and model requirements, and case studies can also be found in

published guidance documents and articles. The OECD website on environmental exposure assessment[11] and the EU *Technical Guidance Documents on Risk Assessment* (EU, 2003)[12, 13] are good starting points for identifying methods and case studies for higher-level/refined environmental exposure assessments.

3.3.5. Key Methodologies

As indicated above, different geographic regions and their regulatory agencies have established methods for estimating environmental exposures, especially at the initial screening levels of the assessment. The methods share underlying chemical fate and transport principles but contain region-specific aspects to reflect, for example, regional habits and practices, average stream flows, initial chemistry of the stream, and typical dilutions of wastewater discharges. Regional differences in product use, wastewater treatment practices, and regulatory frameworks dictate which region-specific data and modeling procedures are recommended for the United States, European Union, and Asia and the Pacific regions.

3.3.6. Identifying Relevant Environmental Compartments and Fate Processes

A "universal" tool that is often used as a first step to ensure that the subsequent exposure assessment is focused on the most relevant environmental compartments and fate processes for a given chemical is the chemical partitioning, or fugacity, model (Mackay et al. 1996), which goes by numerous names (e.g., the *Mackay model;* the *multimedia equilibrium criterion model;* or the *EQC model,* which is the name used in this book). The EQC model is well established and has undergone numerous refinements over the years. EPA's Office of Pollution Prevention and Toxics (OPPT) recommends the EQC model and discusses its application on its exposure website.[13] The EQC model can be viewed and downloaded from the Canadian Environmental Modeling Centre (Trent University) website.[14]

The EQC model allows the user to progress through a sequence of levels (I, II, and III) that have increasing data requirements, introduce greater complexity, and reveal progressively more about the distribution and fate of a chemical in the environment. At a minimum, the model requires information on the chemical's water solubility, vapor pressure, Henry's law constant (which can be calculated from the water solubility and vapor pressure), and octanol:water partition coefficient. The EQC model output includes the percentage of the chemical predicted to reside in the air, water, soil, and sediment compartments under equilibrium or steady-state conditions (with or without degradation and advection occurring). The output identifies the environmental compartments in which a chemical is most likely to reside and, therefore, where exposure is most likely to occur following the chemical's use and release. The model results can also be used to identify which transport, exchange, and degradation processes should be included in subsequent fate and exposure modeling.

EPA's Estimation Programs Interface suite of models (EPI Suite™)[15] contains a multimedia model; however, it is not recommended that the assessor use this model at this stage of the assessment because the assessor cannot view all the input parameters and output needed to understand the environmental distribution and processes that affect this distribution.

3.3.7. Exposure Models Used in U.S. Assessments

Numerous environmental exposure models have been developed and used in chemical assessments performed in the United States. A partial list of these can be viewed (and in many cases downloaded) from the EPA OPPT exposure website.[13] The most relevant screening-level model for the purposes of the

[11] http://www.oecd.org/document/63/0,3343,en_2649_34373_1908991_1_1_1_1,00.html
[12] Available at: http://ecb.jrc.ec.europa.eu/tgd/
[13] Available at the EPA OPPT exposure website (http://www.epa.gov/opptintr/exposure/)
[14] http://www.trentu.ca/cemc/welcome.html
[15] Available at http://www.epa.gov/opptintr/exposure/pubs/episuitedl.htm

chemicals is the Exposure and Fate Assessment Screening Tool (E-FAST). E-FAST was developed as a screening-level tool to support EPA's assessment of the potential (human and aquatic) exposures to new chemicals, which is submitted to EPA for review before manufacturing (the submission is called the *premanufacture notification*).

E-FAST provides screening-level estimates of the concentration of chemicals released to the environment via air, water, and land from manufacturing facilities as well as from use and down-the-drain disposal of consumer products. The model estimates environmental concentrations using default assumptions. For example, in the down-the-drain module, the model assumes that consumer products are disposed of in household wastewater and treated before being released in surface water, and surface concentration is estimated under the assumption of average and low-flow conditions. To calculate exposures using the modeled concentrations, E-FAST incorporates either a combination of upper-percentile and mean exposure parameter values (e.g., breath rates, water intake rates) or all upper-percentile parameter values as defaults. Thus, E-FAST exposure estimates are considered high end. The following exposure scenarios are provided by E-FAST:

- *Human exposure scenarios.* Inhalation exposure from fugitive/vent releases from manufacturing facilities, ingestion exposure from drinking water as a result of releases to groundwater (via landfill) from manufacturing facilities, ingestion exposure from consuming water and fish contaminated by releases to surface water by manufacturing facilities, and ingestion exposure from consuming water and fish contaminated by disposal of consumer products down the drain.
- *Aquatic exposure scenarios.* Surface water releases from manufacturing facilities to freshwater streams and rivers as well as to bays, lakes, and estuaries, if the industrial facility discharges to these types of environments; down-the-drain exposure from disposal of consumer products.

E-FAST can be viewed and downloaded from EPA website.[16] The EPA OPPT exposure website,[17] as well as the EPA HPV website,[18] provides links to case studies for down-the-drain chemical releases and ecological and human exposure following environmental releases. In addition, assessors should read the user manual for E-FAST[19] before using the model to ensure that they have an adequate understanding of the equations and assumptions used in the model. There has been no formal validation or verification of the E-FAST model; however, it is based on first principles, so it is expected to be valid and conservative.

3.3.8. Exposure Models Used in European Assessments

Numerous environmental exposure models have been developed and used in chemical assessments performed in Europe. A partial list of models can be viewed (and in many cases, downloaded) from the Consumer Products Safety & Quality (CPS&Q) Unit,[20] formerly known as European Chemicals Bureau (http://ecb.jrc.ec.europa.eu/). The most relevant screening-level model for purposes of the chemicals assessment initiative is the European Union System for the Evaluation of Substances (EUSES). EUSES is based on the European Union (2003) technical guidance document on risk assessment for new and existing substances. EUSES, which can be purchased online, includes a scenario to evaluate exposure and risk as a result of release of cleaning and washing agents into the environment.

EUSES can be used to carry out screening, intermediate, or refined tiers of assessment by replacing the default data, estimated parameter values, or intermediate results with more accurate estimates or

[16] http://www.epa.gov/oppt/exposure/pubs/efast.htm
[17] http://www.epa.gov/opptintr/exposure/
[18] http://www.epa.gov/chemrtk/
[19] http://www.epa.gov/oppt/exposure/pubs/efast2man.pdf
[20] The CPS&Q unit is part of the Institute for Health and Consumer Protection, one of seven scientific institutes in the European Commission's Joint Research Centre.

measured data. It is not specifically designed to conduct site-specific assessments, but it does allow evaluations for both local (i.e., in the vicinity of a large hypothetical point source) and regional (i.e., from all sources in the region) exposure scenarios. The continental (i.e., sum of all EU member states) scale is also included to provide background information for the regional-scale model. For the local scale, the environment is characterized by a "standard environment" that includes a combination of average values or reasonable high-end values, depending on the parameter in question. The generic regional environment is used to assess the release from point and diffuse sources in a larger area using the same "standard environment" characteristics. Regional concentrations are used as background concentrations in the calculation of the local exposure concentrations. The chemical concentrations are estimated for fresh surface water, freshwater sediments, soil resulting from the application of sewage sludge, and releases to groundwater and air. Moreover, marine environments were added to EUSES 2.1[21] in 2008. Some verification/validation studies have been conducted for EUSES, including Jager (1995), who discussed the EUSES 1.0 validation status, and Verdonck et al. (2005), who discussed EUSES 2.0.

Another source of relevant environmental exposure methodologies (and case studies) for the European Union can be found on the website for the Human and Environmental Risk Assessment (HERA) project, which addresses ingredients of European household cleaning products (www.heraproject.com.) The HERA initiative's objective is to provide a common risk assessment framework for the European household cleaning products industry. Therefore, the focus is on conducting exposure and risk assessments for releases that occur during and after product use; it does not include guidance on industrial facility discharges. The environmental exposure and risk assessment for down-the-drain disposal of these types of products incorporates the use of EUSES, among other exposure and risk characterization methodologies. In addition, HERA identifies the modifications to EUSES that are recommended for assessing down-the-drain ingredients such as those in detergents (Fox et al. 2002.).

As part of Registration, Evaluation, Authorisation, and Restriction of Chemicals (REACH), a new EU Exposure Assessment Toolbox has been launched as part of the EIS-ChemRisk (European Information System on risks from chemicals released from consumer products and articles), including exposure data, factors, and algorithms for scenario-based exposure assessments.[22] A description of the toolbox may be found at http://web.jrc.ec.europa.eu/eis-chemrisks/doc/12NovemberToolboxDraft.pdf.

Recommendations from the European Chemicals Agency (ECHA) regarding requirements for chemical safety assessments in REACH, including the development of exposure scenarios (particularly descriptions of conditions of use), are in Chapters R12 and R13 of the ECHA guidance documents.[23] Supporting guidance on exposure estimations for consumers, estimation of exposures from articles and environmental exposure estimation is in Chapters R12 to R18.

3.3.9. Exposure Models Used in Asia and the Pacific

Japan follows general OECD principles and practices for environmental exposure assessment. That is, PECs are derived using a combination of modeling and monitoring. These PEC values are then compared to their toxicology counterpart, PNEC, to provide a risk characterization. Yoshimura (2001) provided brief descriptions of these practices and examples of their use. The JSDA engages in ongoing efforts regarding environmental exposure assessment, including water quality surveys in which surface waters are monitored for concentrations of high-priority chemicals using chemical-specific analyses (e.g., liquid chromatography–mass spectrometry for cationic and nonionic surfactants). Yamamoto et al. (1997) provided a good example of environmental exposure and risk characterization using the Tamagawa River model as a basis for establishing exposure concentrations for consumer product chemicals. The situation

[21] http://ecb.jrc.ec.europa.eu/euses/
[22] http://web.jrc.ec.europa.eu/eis-chemrisks/index.cfm
[23] http://guidance.echa.europa.eu/docs/guidance_document/information_requirements_en.htm

in Japan is different from that in the U.S. and European environments because Japan permits direct discharge of gray water[24] to the environment.

3.3.10. Other International Exposure Modeling Resources

Additional international efforts aimed at harmonized methodologies for environmental exposure assessment can be viewed at the website on OECD Activities on Environmental Exposure Assessment.[25] There one will find links to numerous additional resources for exposure modeling and use of monitoring data. It also links to organizations in the United States, Europe, and Japan that are conducting environmental exposure assessments.

Several other countries provide their own guidance for conducting environmental exposure assessment relevant to chemicals. For example, Environment Canada (1997) provided methodology that was applied to a consumer product chemical by Canada Chemicals Evaluation Division (2001).

3.3.11. Use of Monitoring Data

Monitoring data available for a chemical should be considered in an assessment. OECD (2000) has written guidance on how to judge and use available monitoring data in the exposure assessment of industrial chemicals, including HPV chemicals. In the context of screening-level assessments, the location and characteristics of the monitoring sites should be an important consideration in whether the data can be used. Also, the monitoring data can be used to verify estimated exposures derived from models.

3.4. Instructions for Generating PECs in the United States, European Union, and Japan

This section provides guidance on estimating surface water chemical exposure concentrations in the United States, the European Union, and Japan after the EQC model has confirmed that the aquatic environment is the most likely exposure media for a chemical of interest. For each geographic region, the guidance is split into separate approaches on the basis of consumer use and manufacturing.

3.4.1. United States

In the United States, the environmental exposure assessment approach is quite advanced and has been used for many years within the EPA to determine the acceptability of new and existing chemicals that are released to fresh surface waters. The scheme is shown in Figure 3-3.

3.4.1.1. Consumer Product Use and Disposal

Level 1

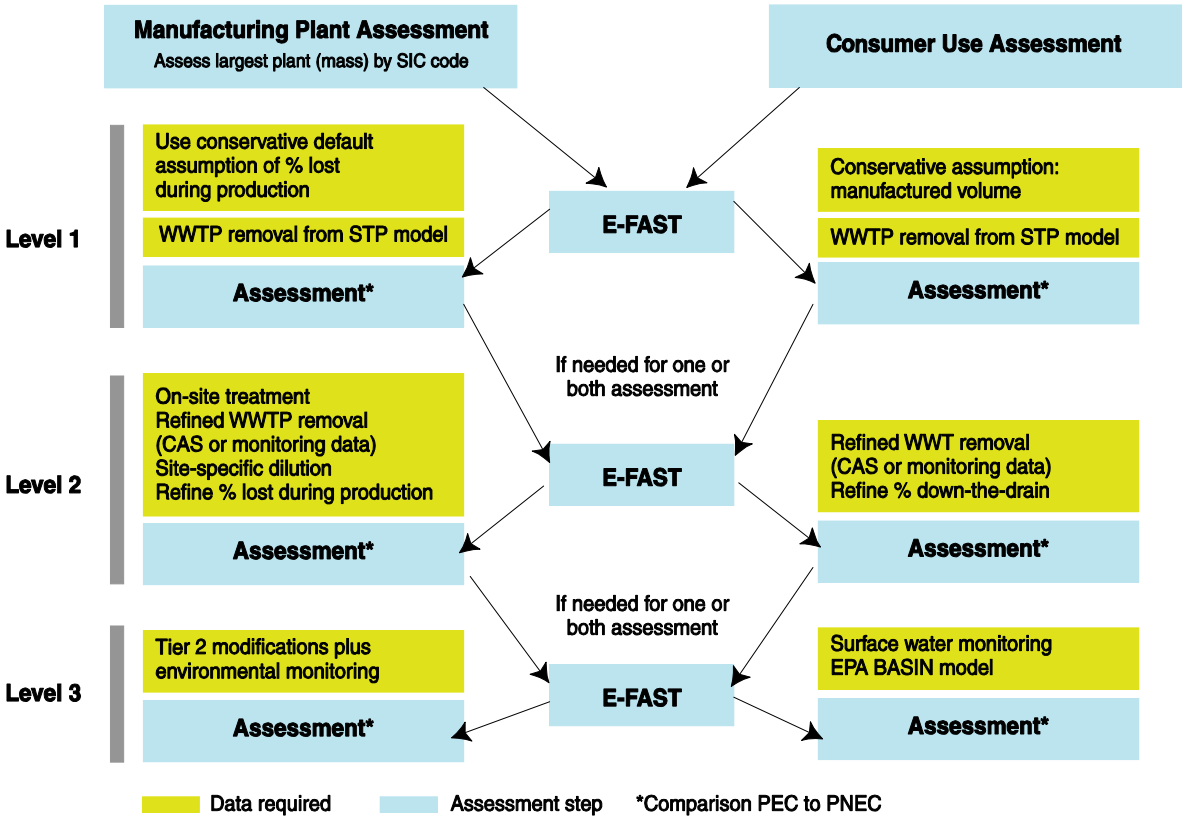
Use the EPA's E-FAST model to estimate surface water concentrations from consumer use and disposal after sewage treatment. Select the module "Models for Screening Level Exposure Assessments," and within that, select the "Down the Drain" module. It is necessary to select the CAS number and replace default values wherever actual physical and chemical data exist before running any module. The following input parameters are required:

1. *Annual production volume*.
2. *Years of use.* This input parameter does not affect surface water concentrations but is needed to estimate human exposures via consumption of drinking water and fish.

[24] Any water that has been used in the home, except water from toilets, is called *gray water*. Dish, shower, sink, and laundry water comprise 50% to 80% of residential wastewater. This water may be reused for other purposes, especially landscape irrigation.
[25] http://www.oecd.org/document/63/0,3343,en_2649_34373_1908991_1_1_1_1,00.html

3. *Bioconcentration factor (BCF).* This input parameter does not affect the surface water concentrations. It is used to estimate human exposures via fish consumption. If a measured value is not available, one can be estimated with the BCFWIN model in EPI Suite. EPI Suite Version 4.00 is a series of structure activity and structure property prediction tools produced by the EPA and widely accepted by the scientific community. This tool can be found at http://www.epa.gov/oppt/exposure/pubs/updates_episuite_v4.00.revised.htm.
4. *Percent removal*. Estimated or measured removal by sewage treatment; the STP model can be downloaded at http://www.trentu.ca/academic/aminss/envmodel/models/STP211.html. Use of the STP model results from the EPI Suite is not recommended because the model allows for the use only of estimated property data and because a direct link between the BIODEG model results and the degradation rates has not been developed.

Figure 3-3. U.S. Exposure Assessment Process



E-FAST's down-the-drain module will produce median (50th percentile) and high-end (10th percentile) surface water concentrations for various flow regimes. The 10th percentile surface water concentration indicates that 90% of the surface water will have concentrations less than this value. The high-end surface water concentration should be used as the environmental exposure concentration for screening purposes.

If additional data are available to estimate the exposure in the aquatic environment or if the exposure concentration exceeds the PNEC, then a Level 2 assessment should be considered.

Level 2

In the second level are two options for including additional or refined data:

1. *Percent removal* during sewage treatment can be further refined by continuous activated sludge[26] testing or by conducting a monitoring study to generate a WWTP removal percentage. These studies could require the use of radiolabeled compounds or development of appropriate analytical methods to analyze the concentrations of the specific chemical ingredient in influents and effluents.
2. *Down-the-drain volume* can be better estimated to reflect the total mass going down the drain. This will require sound data on the use of an ingredient in different product categories and its disposal pathways.

With these input parameters, the assessor should run E-FAST to estimate the environmental exposure concentration. If additional data are available to better estimate exposure in the aquatic environment or if the PEC exceeds the PNEC at this level of assessment, a Level 3 assessment should be considered.

Level 3

In the third level are three options for including additional or refined data or using additional approaches:

1. *Using a river basin or national surface water model to estimate the concentrations in relevant surface waters.* These types of models include the EPA BASINS model,[27] the GIS-ROUT model[28] (Wang et al. 2004) and SDA's iSTREEM model.[29]
2. Using WWTP removal data obtained by field monitoring of WWTPs. Chemical-specific analytical methods are needed to analyze the concentrations of the ingredient in influent and effluent.
3. *Using concentrations in surface waters measured during field monitoring.* Chemical-specific analytical methods are needed to analyze the concentrations of the ingredient in surface water. The locations to be monitored should be selected to represent conditions downstream of a range of sewage treatment plant types (i.e., activated sludge, trickling filter, lagoon, oxidation ditch, rotating biological contactor) that operate properly.

The environmental exposure concentration is estimated using refined input parameters developed by these approaches.

3.4.1.2. Manufacturing Plant Releases

Level 1

The E-FAST model can be used to estimate surface water concentrations from manufacturing releases from a particular industry, as identified by its SIC, after wastewater treatment. Select "General Population and Ecological Exposure from Industrial Releases" as the module after data on the chemical of interest have been selected. Within this module, select the average probabilistic dilution model (PDM) analysis (SIC) on the right-hand side. Then go to the "select SIC Code" tab and choose the appropriate code. This step will populate the data on the "General Release Info" tab. Once any data or comments have been entered, select the "Release activities completed?" button on the bottom, and the exposure factors page for human exposure will appear. Finally, after the "Calculate, Save results and Display results" button is clicked, the exposure will be calculated.

[26] Continuous activated sludge testing uses a bench-scale simulated sewage treatment system.
[27] http://www.epa.gov/OST/BASINS/
[28] http://proceedings.esri.com/library/userconf/proc02/pap1259/p1259.htm
[29] http://gis2.uc.edu/iSTREEM/login.aspx

The required input values are as follows:

1. *SIC*. An input selected from a pick list provided by this E-FAST module. The recommendation would be Soap, Detergent etc. Manufacturers.
2. *Release data*.The choice of SIC will indicate which data are needed. When choosing data to represent the emissions to the environment, facilities of different sizes should be examined to determine whether any trend exists in percentage releases with the size of the manufacturing or formulation facility.

E-FAST's PDM SIC module will produce median (50th percentile) and high-end (upper 10th percentile) surface water concentrations as a result of discharges to wastewater from this type of industry across the United States under the "SIC Code" tab. Use the high-end surface water concentration as the environmental exposure concentration. If additional data are available to better estimate exposure in the aquatic environment, or if a conclusion that the use of the chemical is unlikely to harm the environment is unsupported, then a Level 2 assessment is recommended.

Level 2

In Level 2, exposure is assessed at one site using the probabilistic dilution model and a realistic worst-case estimate of the volume produced at the largest site. To conduct a Level 2 assessment, some information will need to be obtained from the company owning the site producing the greatest volume. The best available data (e.g., CAS unit, monitoring) should be used to estimate removal during wastewater treatment.

- Among chemical manufacturers, formulators, and processors, the chemical manufacturers are most likely to discharge the largest amounts to wastewater which narrows down the number of facilities to be considered to chemical manufacturers of the chemical under consideration.
- Industry associations whose members are sponsoring the chemical can help compile site-specific information about members' facilities.
- The Permit Compliance System database, maintained by the EPA's Office of Wastewater, tracks information about facilities that are regulated by the National Pollutant Discharge Elimination System. The database can be used to identify and locate the major dischargers of any particular chemical.

The following information about the high-end manufacturing sites (those that will result in the highest surface water concentrations) will need to be obtained:

- *On-site treatment (yes/no) and percent removal* by on-site treatment, if any
- *Amount released (kg/day)* after any type of on-site treatment but before treatment by municipalities or publicly owned treatment works (POTW). When choosing data to represent emissions to the environment, facilities of different sizes should be examined to determine any trend in percent releases associated with the size of the manufacturing or formulation facility.
- *Wastewater flow from the site* (volume/day)
- *Wastewater flow through the POTW* (volume/day) that treats the wastewater from the site
- *Ratio of sewage-treated effluent to river flow* at the point of discharge

For each manufacturing site that is analyzed, E-FAST's site-specific PDM module will produce median (50th percentile) and high-end (10th percentile) surface water concentrations. The high-end surface water

concentration should be used as the environmental exposure concentration in screening risk assessments. If additional data are available to better estimate the exposure in the aquatic environment, or if a conclusion that use of a chemical is unlikely to harm the environment cannot be supported, then a Level 3 assessment is recommended.

Level 3

The third level for assessing manufacturing releases requires obtaining site-specific information from field monitoring. The manufacturing facilities to be included in the monitoring should be carefully selected to represent good operating conditions at the on-site treatment units and any POTW, if appropriate. Great care should be taken to make sure the facilities' operations are representative of "typical" manufacturing operations at the time of sampling. High-end facilities – from the standpoint of discharge amounts, on-site treatment, number of release days per year, and downstream dilution factors – should be included in the monitoring.

Three criteria are used to select sites: volume of material processed, presence of wastewater treatment of the effluent, and final dilution in the river. Using the criteria, the goal is to end up with sites that are realistic but representative of locations where environmental concentrations can reasonably be expected to be the greatest.

With the refined or additional input parameters, estimate the environmental exposure concentration. If potential concerns with environmental safety remain, additional monitoring of the surface waters downstream of the industrial facility should be considered.

3.4.2. European Union

The European Union has a long history of conducting environmental exposure assessments for new and existing ingredients. As mentioned previously, it has also developed tools to use in these assessments. The EU-recommended approach uses the EUSES model and recommended refinements from the HERA project. The general procedure is similar to that described above for the United States; however, key differences in both the consumer-use and the manufacturing-release scenarios exist (see Figure 3-4).

3.4.2.1. Consumer Product Use and Disposal

Level 1

The Level 1 exposure assessment is obtained by EUSES, the most relevant screening-level model for purposes of assessing chemicals in Europe. For the assessment of exposure resulting from widespread consumer use in densely populated areas, the regional model is used.

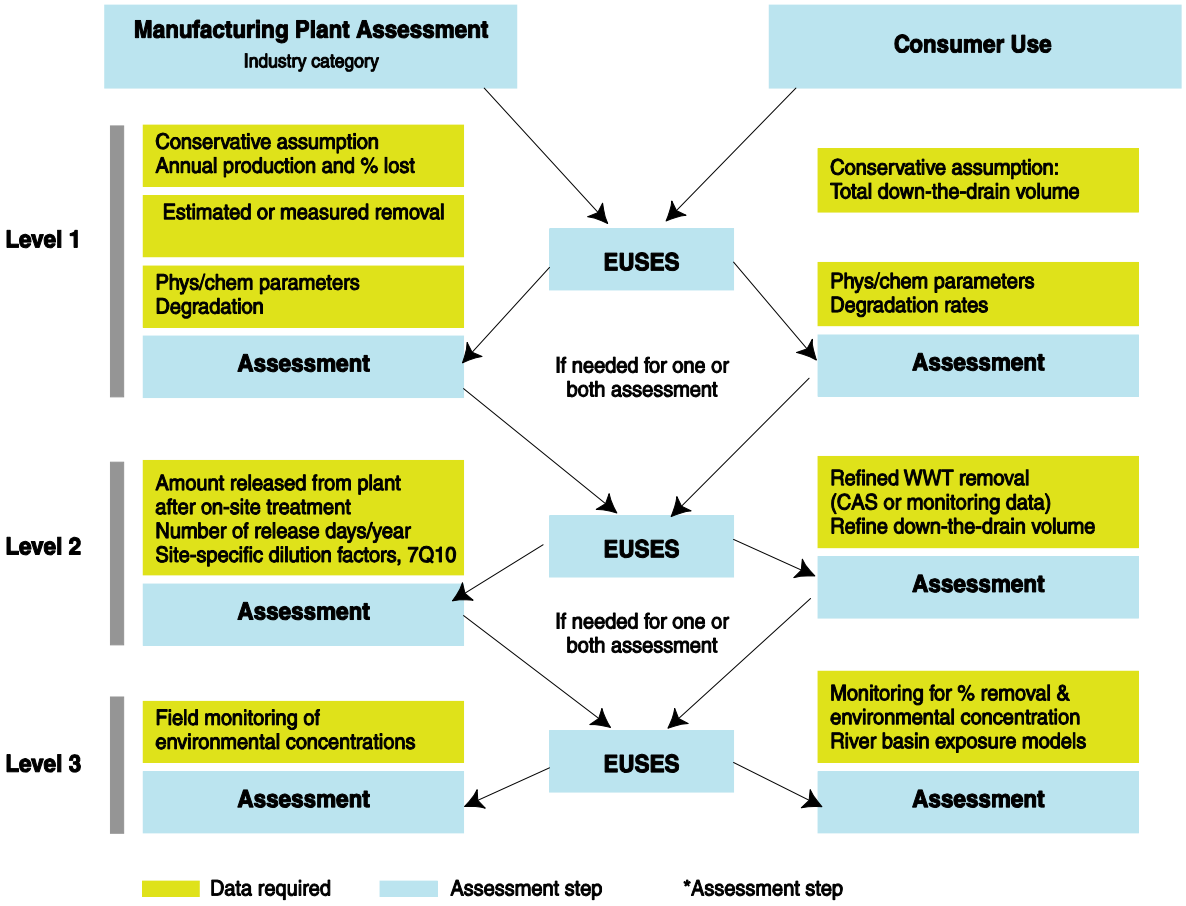
The following chemical-specific input parameters are needed for a Level 1 assessment using EUSES:

- Molecular weight (g/mol)
- Melting point (°C)
- Boiling point (°C)
- Vapor pressure (Pa)
- Water solubility (g/m^3)
- Octanol:water partition coefficient (unitless)
- Degradation half-life in air or photooxidation half-life (days)
- Degradation half-life in water (days)

- Degradation half-life in soil (days)
- Degradation half-life in sediment (days)

The degradation rates are estimated from pass/fail "ready" biodegradation test results.

Figure 3-4. EU Exposure Assessment Process



In addition, the *total down-the-drain volume,* or *environmental emission rate,* in EUSES terminology, of the ingredient (metric tons/year) is needed. Note that for detergent product chemicals, HERA has recommended that changes be made in the default scenario parameters in EUSES (see www.heraproject.com and Fox et al. 2002), which should be considered when conducting these analyses.

EUSES' local module will produce the following four results:

- PEC_{air} (µg/m^3) — usually very low for down-the-drain consumer product ingredients; typically an assessment in air is not necessary
- $PEC_{surface\ water}$ (µg/L)
- PEC_{soil} (µg/kg dry weight)
- $PEC_{sediment}$ (mg/kg dry weight).

The high-end surface water concentration should be used as the environmental exposure concentration in an assessment. If additional data are available to better estimate exposure in the aquatic environment, or if

a conclusion that using the chemical is unlikely to cause harm to the environment cannot be supported, then a Level 2 assessment is recommended.

Level 2

In a second-level assessment, the following additional or refined data can be used in the assessment to override defaults:

- Percent removal in sewage treatment can be further refined by measuring it in laboratory units that mimic WWTPs (e.g., continuous activated sludge testing). Specific analytical methods or radiolabeled compounds may be needed for this testing to analyze the concentrations of a chemical ingredient in influent and effluent.
- In addition, it may be possible to refine the volume or release information.

With the refined input parameter for percent removal and/or volume or release information, the EUSES regional module can be rerun using the high-end surface water concentration as the environmental exposure concentration. If additional data are available to better estimate exposure in the aquatic environment, or if a conclusion that the chemical is unlikely to harm the environmental cannot be supported, then a Level 3 assessment is recommended.

Level 3

In the third level, additional or refined data on the percent removal in sewage treatment and/or the concentrations in surface waters from field monitoring or from river basin exposure modeling can be used in the assessment.

- River Basin models, such as GREAT-ER (http://www.great-er.org/pages/home.cfm), can be used to better estimate the surface water concentrations in rivers of interest.
- Field monitoring of selected WWTPs and/or river waters can be performed. The river water sites and the sewage treatment plants to be monitored should be selected on the basis of their operating conditions and the range of sewage treatment types (i.e., activated sludge, trickling filter, lagoon, oxidation ditch, rotating biological contactor) in the country.

These revised surface water concentrations can be used as the environmental exposure concentration in a Level 3 assessment. If additional perspective is still needed and no monitoring or limited monitoring has been conducted, then a more extensive field monitoring program should be considered.

3.4.2.2. Manufacturing Plant Releases

Level 1

Estimates of environmental exposures from manufacturing discharges are obtained with EUSES, the most relevant screening-level model for purposes of the assessment initiative in Europe. The following input values are needed for a Level 1 assessment:

- *Industry category:* Select the appropriate industry category in EUSES. For each of the industry categories that are represented, EUSES contains release estimates for a generic point source (before treatment) and estimates of the number of days per year that these releases are expected to occur; both estimates are based on industry averages. These parameter estimates for generic point sources in EUSES are based on surveys of facilities in EU member countries.
- *Annual production/processing volume* or *environmental emission rate,* in EUSES terminology, of the chemical ingredient (metric ton/year). When choosing data to represent the emissions to the

environment, facilities of different sizes should be examined to determine any trend in percent releases with the size of the manufacturing or formulation facility.

- Estimated or measured removal by sewage treatment *(percent removal)*
- The following chemical-specific input parameters are also required:
  - Molecular weight (g/mol)
  - Melting point (°C)
  - Boiling point (°C)
  - Vapor pressure (Pa)
  - Water solubility (g/m^3)
  - Octanol:water partition coefficient (unitless)
  - Degradation half-life in air or photooxidation half-life (days)
  - Degradation half-life in water (days)
  - Degradation half-life in soil (days)
  - Degradation half-life in sediment (days)

The degradation rates are estimated from pass–fail "ready" biodegradation test results.

The EUSES local module will produce the following output:

- PEC_{air} ($\mu g/m^3$) (PEC in air)
- $PEC_{surface\ water}$ ($\mu g/L$)
- PEC_{soil} (μg/kg dry weight)
- $PEC_{sediment}$ (mg/kg dry weight).

The high-end surface water concentration can be used as the environmental exposure concentration. If additional data are available to better estimate exposure in the aquatic environment, or if a conclusion that use of a chemical is unlikely to harm the environment cannot be supported, then a Level 2 assessment is recommended.

Level 2

For a Level 2 assessment, additional or refined data for site-specific scenarios are used. The greatest challenge in conducting these site-specific assessments is selecting which available data should be used or which sites should be monitored in planned studies. Even though no general formula exists for site selection, some guidelines can be offered:

- Among chemical manufacturers, formulators, and processors, the chemical manufacturers are most likely to discharge the largest amounts of a chemical into municipal wastewater. This probability narrows down the number of facilities to be considered to chemical manufacturers of the chemical under consideration.
- Industry associations whose members are sponsoring the chemical can help compile site-specific information about members' facilities.

The following information will need to be obtained about the high-end manufacturing sites (those that will result in the highest surface water concentrations):

- *Amount released (kg/day)* after any type of on-site treatment but before treatment by municipalities or POTW. When choosing data to represent emissions to the environment, facilities of different sizes should be examined to determine any relationship between percentage releases and size of the manufacturing or formulation facility.
- *Number of release days per year,* typically less than 365 because of maintenance days.

- *Dilution factors* of POTW effluent into receiving surface water under median flow, low flow, and flood conditions.

With the refined input parameters, the assessor should run EUSES (local module) with these parameters replacing the model defaults and using the high-end surface water concentration as the environmental exposure concentration. If additional data are available to better estimate exposure in the aquatic environment, or if a conclusion that use of a chemical is unlikely to harm the environment cannot be supported, then a Level 3 assessment is recommended.

Level 3

In the third level for manufacturing releases, data from field monitoring, if available or conducted, is used to refine the concentrations immediately downstream from where industrial effluents enter surface waters. For sampling during routine production, great care should be taken to make sure that the facilities' operations are representative of "typical" manufacturing operations at the time of sampling. At the same time, reasonable high-end considerations from the standpoint of discharge amounts, on-site treatment, number of release days per year, and downstream dilution factors should be included in the monitoring.

3.4.3. Japan

In Japan, the assessment approach has not yet been clearly defined. No defined and accepted regulatory approach to environmental exposure assessment is available for either consumer products or manufacturing releases. However, two projects on chemical exposure modeling have recently started. One is the Virtual World Project led by the National Institute for Environmental Studies in Japan.[30] This approach is focused on the evaluation of the ambient concentration of endocrine-disrupting chemicals using a GIS modeling technique.[31]

Another approach is led by the Research Center for Chemical Risk Management, National Institute for Advanced Industrial Science and Technology. In this approach, the emission amounts of chemicals are estimated on the basis of national statistics or data obtained from the Japanese Pollutant Release and Transfer Register.[32] Also, the Research Center has conducted estuarine modeling of Tokyo Bay.[33]

Level 1

One approach is to conduct the exposure assessment using the river model developed for the Tama River and its tributaries which is based on actual river flow, POTW discharge flow, and water abstraction flow data measured in 1992. The following nine input parameters are needed:

1. *Consumer ingredient usage* (mg/person × day)
2. *Untreated gray water flow* (L/person × day)
3. *In-stream removal degradation rate* (1/day)
4. *Fraction of ingredient removed in conveyance systems* (assume 0 if no data)
5. *Fraction of gray water reaching the river*
6. *Fraction of ingredient removed in sewage treatment, by type:*
7. percent $\text{removal}_{\text{primary}}$
8. percent $\text{removal}_{\text{activated sludge}}$
9. percent $\text{removal}_{\text{trickling filter}}$

[30] http://www.niehs.nih.gov/index.cfm
[31] http://www.nies.go.jp/gaiyo/panf2002/edc/edc-e.html
[32] Available from http://www.env.go.jp/en/chemi/prtr/prtr.html
[33] Available from http://www.riskcenter.jp/RAMTB/ and http://www.aist-riss.jp/main/modules/groups_emg/

The Tama River model produces a range of PECs in surface water (µg/L) for each section of the Tama River and its tributaries. The high-end surface water concentration can be used as the environmental exposure concentration in an assessment. If additional data are needed to better understand exposure in the aquatic environment, continue with a Level 2 assessment.

Level 2

The Level 2 assessment can use field monitoring to further refine the estimates of exposure concentrations immediately downstream of the discharge points for the consumer products or where industrial effluents join surface waters. Specific analytical methods should be used to analyze the concentrations of a chemical ingredient in influent, effluent, and river water. The consumer product discharge points and/or the manufacturing facilities included in the monitoring should be carefully selected to represent good operating conditions of the on-site treatment units and the public sewage treatment plants. Great care should be taken to make sure the facilities' operations are representative of "typical" manufacturing operations at the time of sampling. High-end facilities – from the standpoint of discharge amounts, on-site treatment, number of release days per year, and downstream dilution factors – should be included in the monitoring.

3.5. Exposure Assessment Summary

The following sections of this document present a basic framework and widely used methods to assess the exposure (and potential risk) to ecological receptors (non-target organisms) and humans as a result of contact with consumer product chemicals released into the environment. Specific screening-level models are identified, and links to websites where those models can be obtained are provided. Examples are provided (following the draft format of the OECD use/exposure pilot project) for SDA-sponsored categories of HPV chemical categories AO and LCOH. The case studies use screening-level exposure models and present initial exposure and risk characterization results. Screening-level assessment is often sufficient to provide an adequate characterization of exposure and risk. That is, conservative (generally high) exposure estimates are well below toxicological threshold levels. Refinements to the initial assessment, including more data intensive models and more location-specific data, can be made as warranted. Such refinements are discussed in the CA (2002) framework document and at most of the websites listed in this book.

3.6. Effects Assessment

Much has been written about the development of Quantitative Structure Activity Relationship ([Q]SAR)[34] (EPA 1999a) and empirical (EPA 1999b; OECD 2003) aquatic effects data on chemicals. Toxicity, or effects, data are frequently gathered in order to understand the relative toxicity of chemicals, assess the need for hazard labeling, and evaluate the potential for effects on the environment. Because most toxicity data are developed in the laboratory with relatively few species, the data must be extrapolated to protect the environ-ment in general. This extrapolation is intended to address uncertainties arising from the fact that structure activity or laboratory toxicity data on a limited number of species are used to attempt to understand effects on organisms in the environment.

The usual procedure is to divide the effects value by an assessment or uncertainty factor or to use a statistical extrapolation technique to generate a PNEC. Although generation of a PNEC is not required under the OECD program, it "might nevertheless be useful for the interpretation of available toxicity data" (OECD 2003). The PNEC is generated once all relevant aquatic toxicity data on the chemical have been collated and evaluated for quality. Because much has been written about the summary and evaluation of data (AISE 2002; European Union 2003; OECD 2003) and the extrapolation process

[34] (Q)SAR is a mathematical expression used to relate physical or chemical parameters to biological or chemical activity of a molecule.

(Cowan et al. 1995; European Union 2003; OECD 2003; Solomon et al. 2008), the intent of this section is to summarize this guidance and facilitate the development of PNECs for chemicals.

3.6.1. Objective

Environmental effects data may be available for different organisms tested under a variety of conditions. To be useful within the chemicals assessment process, a consistent approach to interpreting and valuing this data is needed to help reach conclusions supported by the available information. The objective of this section is to provide a uniform approach for using the variety of effects data on a compound to generate a concentration expected to have no effect on organisms in the environment – that is, the PNEC.

3.6.2. Data Evaluation

Toxicity data are typically generated on a wide variety of aquatic organisms and, occasionally, on sediment-dwelling and terrestrial organisms. However, because of the sensitivity of aquatic organisms, the likelihood of exposure, and the possibility of wide distribution of chemicals released into the environment, effects assessments are limited to a focus on the aquatic organisms within the OECD HPV chemical program; the minimum requirement is three acute studies – on fish, algae, and invertebrates.

The most relevant data for setting the PNEC are reliable chronic toxicity data obtained under field or mesocosm conditions (assuming those systems are well controlled and the studies are operated and evaluated well; see Level 3 below). However, some level of consistency should exist within the entire data set, from acute data up to the highest level data. Although higher-level data are preferred and do take precedence, all toxicity data should be used to help evaluate the appropriateness of the higher-level information and to ensure data consistency. When an inconsistency exists, it should be evaluated and explained (e.g., acute toxicity LC_{50} data at a concentration lower than chronic no observed effect concentration [NOEC] values for the same species).

Information may be available on a variety of organisms tested acutely and/or chronically in the laboratory, microcosm, mesocosm, or field. As data are collated, they should be separated by their method of collection (acute, chronic, microcosm, mesocosm). When few data points exist, the assessment factor approach is used. When six or more chronic toxicity values are available for relevant organisms, a statistical or probabilistic extrapolation process may be used.

In acute and chronic toxicity tests, various statistics (e.g., LC_{50}, NOEC) on a variety of endpoints (growth, survival) can be calculated. At the acute level, the LC_{50} or the EC_{50} should be used and should be based on mortality (LC_{50}) or immobility (EC_{50}). Death is readily determined in fish but can be difficult to assess in some invertebrates, so immobility is typically used with these organisms. At the chronic level, the NOEC is conventionally determined on the basis of growth, survival, and/or reproduction. In some cases, an EC_x value such as the EC_{20} may be available instead of the NOEC. When an EC_{10} or EC_{20} value is available, it can be used as the appropriate statistic in the risk assessment. EC_{10} and EC_{20} values are not equivalent to the NOEC but provide an acceptable endpoint for risk assessment. As with the NOEC, the EC_{10} and EC_{20} values should be based on adverse effects on growth, survival, or reproduction. For a discussion of the relative merits of EC_x and NOEC values, please refer to Bruce and Versteeg (1992).

3.6.3. Assessment Factors Approach

The extrapolation process attempts to use existing data to protect biological community structure and function. When limited data are available, assessment or extrapolation factors (see Table 3-1) are used to account for uncertainties in extrapolating from acute to chronic, few to many species, lab to field, and so forth. These factors have a long history of use, and their development and applicability to aquatic effects assessments are discussed in multiple publications (Cowan et al. 1995; European Union 2003; OECD 2003; Solomon et al. 2008).

Table 3-1. Assessment Factors for the Derivation of PNECs from Aquatic Toxicity Data

Level	Data	Assessment Factor
1	Acute LC_{50} and EC_{50} values for fish, algae, and invertebrates	100–1,000
2	Chronic EC_{20} or NOEC values for fish, algae, and invertebrates	10–100
3	Mesocosm or field data	1–5

All toxicity values should be compared with the solubility limit prior to applying assessment factors. If the toxicity endpoint exceeds the solubility limit, the solubility limit is used as a conservative estimate of the endpoint. If multiple values are available for an individual species and the values are of similar quality and technical merit, the geometric mean should be used as the best estimate of the toxicity value for that species.

Level 1
Acute LC_{50} or EC_{50} values for fish, algae, and invertebrates are divided by 100 to 1,000. If only one or two species are available, the factor of 1,000 should be used. The PNEC is the lowest value. The factor of 1,000 is conservative and protective but may be reduced to 100 when all three categories are included and when

- data from related chemicals suggests the acute to chronic ratio will be less than 10, or
- data suggest the chemical acts via a nonspecific or narcotic mode of action.

For compounds with a log $K_{ow} > 5$, the factor of 1,000 should be used.

Level 2
Chronic EC_{20} or NOEC values for fish, algae, and invertebrates can be divided by 10 to 100. The Level 3 PNEC is the lowest of these values. If data on all three species are available or convincing evidence is provided that the most sensitive species has been tested (i.e., Level 2 data for that species is well below five times that of the other tested species), 10 may be used. When EC_{20} or NOEC values for one or two among fish, algae, and invertebrate are available, a factor of 50 or 100 may be used. In this case, the chronic PNEC is compared with the Level 2 PNEC, and the lowest PNEC is used. If microcosm data exist, such data should be compared with the available acute and chronic toxicity data. The data should be used qualitatively to support or refute the single-species toxicity data. If the microcosm data refute the single-species toxicity data, additional effects data may be required.

Level 3
Mesocosm and field data will exist for a small subset of chemicals. When high-quality data are available from a well-operated mesocosm or field study, an assessment factor of 1 to 5 can be applied to the NOEC value (Brock et al. 2006). Criteria used to evaluate the rigor of a mesocosm or field study were discussed at a workshop in 2007 (http://www.systemecology.eu/AMPERE/Start.html) and in several publications (Brock et al. 2006; Giddings et al. 2002; Hill et al. 1994; Okkerman et al. 1993; Scholz et al. 1997); these criteria recognize the need for flexibility in design and interpretation by practitioners and regulators. Data should be evaluated on a case-by-case basis and should be compared with the acute and chronic toxicity data.

No universal definition of a mesocosm (in terms of size, level of biological complexity required, experimental design details) exists. Particular attention should be given to the type of mesocosm used and the route of exposure. After bioavailability is considered, if the mesocosm or field data refute the single-species toxicity data, additional effects data may be needed to ensure protection of appropriate species and communities. Mesocosm studies vary considerably in their ability to discern differences between

biological responses in the control and treated categories. Hence, care is needed in accepting mesocosm NOECs as the sole value for use in a risk assessment. Selection of high-quality studies is important, as is comparison of mesocosm NOECs with single-species data.

3.6.4. Statistical Extrapolation Process

When chronic toxicity values (NOEC, EC_{10}, or EC_{20} values) from six or more species are available, the statistical or probabilistic extrapolation process may be used to establish the PNEC (Aldenberg and Slob 1993; Posthuma et al. 2002; Solomon et al. 2008; Stephan et al. 1985; Versteeg et al. 1999). This approach, called the *probabilistic approach,* uses all the available chronic toxicity data to construct a species sensitivity frequency distribution. Statistical tools are then used to determine the concentration where 5% of the distribution is lower and 95% of the distribution is greater. In theory, at this concentration, only 5% of the species will have a lower chronic toxicity value.

The minimum number of toxicity values needed to estimate the PNEC using the statistical approach is being debated. The EPA uses a minimum of eight species with at least one representative from eight different taxonomic categories. The European Union (2003) recommends a minimum of 10 (preferably 15) from eight taxonomic categories, whereas OECD (2003) appears to support eight species from among fish, crustaceans, insects, algae, higher plants, and another category not previously tested. van Leeuwen (1990) and Scott-Fordsmand and Jensen (2002) suggested a minimum of five species. Versteeg et al. (1999) used as few as six and observed good agreement between the statistically derived PNEC and the mesocosm NOEC. Inclusion of toxicity data from the family *Daphnidae* improves the ability of limited single-species toxicity data to predict the probabilistic PNEC (Host et al., cited in Pennington, 2003). Moreover, increasing the sample size from six to eight species results in a small change in the probabilistic PNEC (Pennington 2003). Given the practical demonstration of the utility of the statistical approach with six species and the use of five species in ecological risk methods supported by the Danish environmental authorities (Scott-Fordsmand and Jensen, 2002), a minimum of six species, including a daphnid species (e.g., member of the genus *Daphnia* or *Ceriodaphnia*), should be used to estimate the PNEC using the statistical extrapolation approach. Clearly, the more data available, the better. However, the statistical approach using all the available data can provide a useful perspective on the PNEC when six or more chronic single-species effects values are available.

The concentration, which is lower than 95% of single-species toxicity values, is calculated statistically and visualized graphically using a cumulative species sensitivity plot (see Figure 3-5). Chronic toxicity values (e.g., EC_{20}, EC_{10}, NOEC values) are ranked from low to high, and a probability value is assigned to each rank according to the Van Waerde equation (Erickson and Stephan 1988):

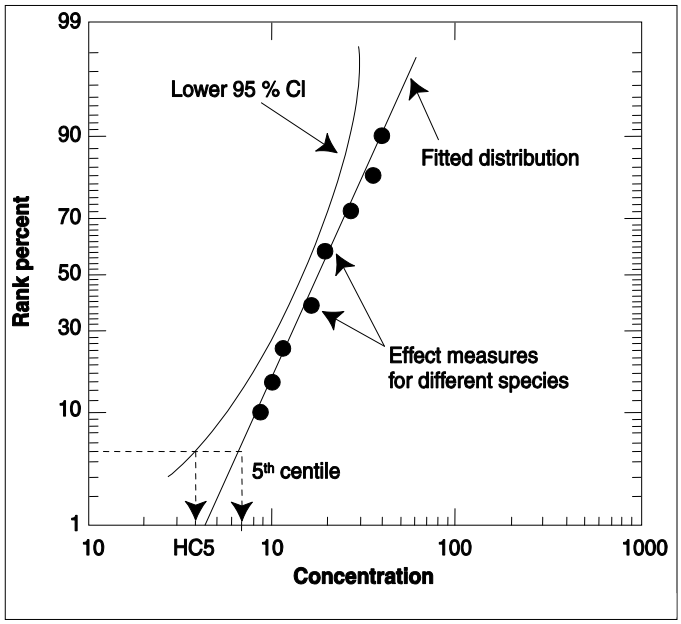
$$P(r) = r/(n+1)$$

Where $P(r)$ is probability of observing values less than or equal to the rank r, r is the rank of each species sensitivity, and n is number of species in the dataset.

The probability values and associated toxicity values are fit to a log-logistic, log-normal, or other distribution using maximum likelihood procedures to estimate distribution parameters (Aldenberg and Slob, 1993; McCullagh and Nelder 1989). The goodness-of-fit of the distribution can be evaluated using Cramér von Mises or related tests (e.g., Kolmogorov–Smirnoff statistical test; Stephens 1986).

From the plot of the cumulative probability distribution, it becomes relatively easy to calculate the concentration that is lower than 95% of the data (i.e., the value protective of 95% of the species from adverse chronic effects). This value is considered to be the probabilistic PNEC. As a probability value, it provides a margin of safety; thus, no application factor is applied in the derivation of the PNEC.

Figure 3-5. Extrapolation from a Species-Sensitivity Distribution (Recreated from Posthuma et al., 2002)



3.7. Comparison of PEC and PNEC

The voluntary chemicals management programs are designed to provide a level of familiarity with the fate and effects of HPV chemicals. The EPA Test Plan and the OECD SIDS Initial Assessment Report (SIAR) are intended to communicate available environmental fate and effects data to regulators and the public and are not intended to provide a comprehensive risk assessment for the compounds being studied. However, much of the data that might be used in a risk characterization is provided in robust summaries. Moreover, the SIAR does provide guidance on the calculation of surface water PECs downstream of manufacturing plants and municipal WWTPs and on the PNEC, which can be used to understand the potential for effects in surface waters. Although it is not the intent of these HPV programs to calculate and report a risk ratio (PEC/PNEC), an exposure annex may be included in the report to provide reliable information on monitored and/or estimated surface water PECs. The PECs can be brought forward into the SIAR and compared with the PNEC(s) for aquatic organisms to support insights about whether hazard levels are reached in the aquatic environment and to assist in drawing conclusions as to whether additional data are needed and the priority for further work on the compound.

The environmental screening assessment process leads to one of two decisions for each chemical category: (1) no further testing or (2) priority for additional testing. The decision is based on several criteria: completeness of data relevant to deriving the PEC and PNEC, quality of data, the compounds for which data are available, and the factor separating the PEC and PNEC values.

Completeness of data. Much of the environmental data reported in the SIAR can be used to estimate the PEC and/or PNEC for a chemical in the aquatic environment. Not all endpoints, however, must be available for all chemicals. For example, in understanding volatility, availability of data on vapor pressure and Henry's law constants are more useful than data on boiling point. If data are available on either vapor pressure or Henry's law constant, data on boiling point are not needed.

Data quality. Chemical categories comprise several or many toxicologically similar compounds. Data for some compounds can be used to predict the value of endpoints for others. The precision of these predictions depends on the appropriateness of the prediction tool (e.g., [Q]SAR) and the similarity between the compounds with data and those for which data are estimated. Both the number and the

quality of the data predictions and the relevance of the data in predicting the PEC and PNEC should be considered.

Factor separating the PEC and PNEC. Safety is ensured when the concentration to which organisms are exposed in the environment (PEC) is below the maximum concentration at which effects will not be observed (PNEC). The larger the factor separating the PEC and the PNEC, the greater the confidence that there will be no effects in the environment. The estimation of the PEC and PNEC values in the environment typically applies conservative approaches when little data are available (Levels 1 and 2) and uses approaches leading to more realistic values but greater certainty at higher levels (Levels 3 and 4.) The relative importance of data completeness and data quality should be balanced with the relative separation of the PEC and PNEC. Simply put, when the PNEC is orders of magnitude above the PEC, modest increases in the uncertainty in the PEC and/or PNEC will not affect conclusions regarding the potential for harm to the environment.

The following discussion helps to incorporate these criteria into the decisions about each chemical. The key considerations are the level of comfort with the derived PEC and the PNEC values and whether, after considering uncertainty, the PNEC is less than the PEC. Clearly, judgment calls must be made, and it is not possible to consider every situation. Therefore, the following summary is intended as guidance describing conditions that support the OECD decisions.

I. No further testing decision

a. *When the PEC equals zero.* In this case there is no need to investigate.

b. *When the PEC and the PNEC are based on complete sets of environmental data such that further study of fate and effects are unlikely to cause a reduction in their uncertainty or a change in these values.* In this case, if the PNEC > PEC, no additional work is needed. If the PNEC < PEC, however, then risk management options need to be considered.

c. *When environmental fate and effects data are relatively complete for the chemicals within a chemical category, or the methods used to read across are likely to provide an accurate estimate of environmental properties.* The available data are sufficient to establish good estimates of the PEC in the aquatic environment after consumer use and manufacturing, and an order of magnitude or more exists between the maximum PEC and the PNEC. If some of the critical fate or effects data are missing or the predictions are uncertain, no further testing would be necessary so long as this data is replaced by conservative estimates and those estimates support an order of magnitude between the PEC and PNEC.

II. Priority for further testing

a. *When the PEC is greater than the PNEC, regardless of data uncertainty.* Further investigation is always necessary in such cases.

b. When the environmental data are incomplete leading to inaccurate estimates of the PEC and/or PNEC, and conservative estimates of the PEC and PNEC are either impossible or result in a PEC greater than PNEC.

3.8. Related Compartments

Although the current HPV process focuses on fresh surface waters as the primary environmental compartment, exposure to organisms also occurs in the marine compartment. Because of dilution factors in freshwater systems, the highest environmental concentrations of consumer product ingredients are expected in those systems. The marine compartment also receives effluents directly and is the ultimate sink for nonvolatile, nondegradable materials via rivers and streams, but dilution factors in marine

systems are generally greater than in freshwater systems (European Union 2003). Therefore, exposure concentrations will be less than those occurring in freshwater systems.

The available data suggest that marine and freshwater organisms are similar in sensitivity to the toxic effects of chemicals (European Centre for Ecotoxicology and Toxicology of Chemicals 2000). Hence, risk (i.e., PEC/PNEC) to marine organisms resulting from the release of a chemical into the environment is likely similar to the risk to freshwater organisms. For perspective, the technical guidance document (European Union 2003) uses a factor of 10 to account for the possibility of increased susceptibility of marine organisms but adds another factor of 10 dilution to account for lower exposure in marine systems.

3.9. Summary

This section provides guidance on the derivation of the PEC and PNEC and the use of fate and effects data in decision making. The types of data considered range from information predicted from structure activity relationships to environmental monitoring and field testing. As with any scientific endeavor, when new methods are developed and as additional data become available, these approaches can be refined and improved. That said, these approaches have a long and successful history of use in protecting the environment and are appropriate for evaluating the effects of chemicals.

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4. APPENDIXES

Appendix I-A

Sources of Product Exposure (PE) Models and Model Inputs Parameters

Numerous documents were reviewed in compiling the exposure equations and input parameters provided in the product exposure factor data matrix. The emphasis in this effort was on identifying screening-level factors and calculation approaches. The identified sources include the following:

AISE Human & Environmental Risk Assessment (HERA). 2002. *Table of Habits and Practices for Consumer Products in Western Europe*. Developed within the HERA project using consolidated company data.

AISE Human & Environmental Risk Assessment (HERA) on Ingredients of European Household Cleaning Products. 2005. *Guidance Document Methodology* (http://www.heraproject.com/files/HERA%20TGD%20February%202005.pdf).

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(2003) Ingredients of European household cleaning products: fluorescent brightener FWA-5 (CAS 27344-41-8).

(2005) Ingredients of European household cleaning products: sodium carbonate CAS No. 497-19-8.

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(2007) Linear alkylbenzene sulphonate: LAS. CAS No. 68411-30-3.

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(March 15, 2000) *Exposure Assessment Program Team Exposure Initiative.* Appendix 1: Glucose amides case study aggregate human exposure assessment case example–glucose amides.

(March 15, 2000) *Exposure Assessment Program Team Exposure Initiative.* Appendix 2: Amine oxides case study aggregate human exposure assessment case example–alkyldimethylamine oxides.

(March 15, 2000) *Exposure Assessment Program Team Exposure Initiative.* Appendix 3: Dimethyl ether case study aggregate human exposure assessment case example–dimethyl ether (DME).

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(1998) *CICADS 10.* 2-Butoxyethanol.

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(1999) *CICADS 15*. Ethylenediamine.

(1999) *CICADS 16*. Azodicarbonamide.

(1999) *CICADS 17*. Butyl benzyl phthalate.

(1999) *CICADS 18*. Cumene.

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Dimethyldicotandecylammomonium chloride (CAS No. 107-64-2)

Dodecanedioic acid (CAS No. 693-23-2)

N,N-dimethyl-2-aminoethanol (CAS No. 108-01-0)

L-Ascorbic acid (CAS No. 50-81-7)

Nicotinic acid (CAS No. 59-67-6)

Sodium dodecyl sulfate (SDS) (CAS No. 151-21-3)

Stearyl alcohol (CAS No. 112-92-5)

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Appendix I-B

Primary, Secondary and Selected References for Exposure Models and Factors

Appendix I-B

Primary, Secondary, and Selected References for Exposure Models and Factors

Exposure Scenario	Documents Reviewed	Secondary References (Documents referenced within reviewed document)	Documents Selected [Secondary Reference]
NA Dermal: laundry detergent Pretreatment Hand washing clothes Wearing clothes	ACA, Oct 2001		AIHC glucose amides SDA data U.S. EPA, 1997 and 2001 AISE/HERA, 2002 Habits and Practices Table AIHC alkyldimethylamine oxides
	ACA, Jan 2002		
	ACA, Feb 2002		
	AISE/HERA, 2002 Habits and Practices Table		
	AIHC glucose amides	U.S. EPA, 1997 SDA data, 2002-2003	
	AIHC alkyldimethylamine oxides	U.S. EPA, 1997 SDA internal data,2002-2003	
	U.S. EPA, 1997		
	U.S. EPA, 1997 and 2001		
	Multiple OECD SIDS/SIARS		
	SDA data		
NA Dermal: Dish detergent: washing hands Dish detergent: washing dishes Hard surface and all purpose cleaner	ACA, Oct 2001		AIHC alkyldimethylamine oxides SDA internal data, 2002-2003 U.S. EPA, 1997 and 2001 AISE/HERA, 2002 Habits and Practices
	ACA, Jan 2002		
	ACA, Feb 2002		
	AISE/HERA 2002 Habits and Practices Table		
	AIHC glucose amides	U.S. EPA, 1997; SDA data	
	AIHC alkyldimethylamine oxides	U.S. EPA, 1997; SDA data	
	AIHC Dipropylene glycol n-butyl (DPnB)ether	U.S. EPA, 1997 U.S. EPA EFAST model	
	CSPA		
	U.S. EPA, 1997		
	U.S. EPA, 1997 and 2001		
	Multiple OECD SIDS/SIARS		
	SDA data		

Appendix I-B

Primary, Secondary, and Selected References for Exposure Models and Factors (Cont'd)

Exposure Scenario	Documents Reviewed	Secondary References (Documents referenced within reviewed document)	Documents Selected [Secondary Reference]
NA Dermal: Personal care (hair care, skin care, antiperspirants, deodorants) Cosmetics Baby products Fragrances	ACA, Oct 2001		K.S. Crump Group, 1999 [ECA, 1997] K.S. Crump Group, 1999 [CTFA, 1983; COLIPA, 1981] CTFA, 2002 CTFA, 2003 SDA internal data, 2002-2003 EU TGD, 2003 U.S. EPA, 1997 and 2001
	ACA, Jan 2002		
	ACA, Feb 2002		
	AIHC alkyldimethylamine oxides	U.S. EPA, 1997 SDA internal data, 2002-2003	
	CTFA, 2002		
	CTFA, 2003		
	K.S. Crump Group, 1999	ECA, 1997 MRI, 1995 MRI, 1996 U.S. EPA, 1997 U.S. EPA, 1989 CTFA, 1983 COLIPA, 1981	
	Multiple OECD SIDS, SIARS		
	Sciences International, 2001		
	SDA internal data		
	EU TGD, 2003		
	U.S. EPA, 1997		
	U.S. EPA, 1997 and 2001		

Appendix I-B

Primary, Secondary, and Selected References for Exposure Models and Factors (Cont'd)

Exposure Scenario	Documents Reviewed	Secondary References (Documents referenced within reviewed document)	Documents Selected [Secondary Reference]
EU Dermal: Laundry detergent Pretreatment Hand wash clothes Wearing clothes	AISE/HERA 2002 Habits and Practices Table		AISE/HERA Zeolite A, 2001 [Lally, 2001; EU TGD] AISE/HERA Sodium Carbonate, 2002 AISE/HERA Fluorescent Brightener, 2001 [U.S. EPA AISE/HERA, 2002 Habits and Practices Table SDA internal data, 2002-2003 EU TGD, 2003
	AISE/HERA, April 2002		
	AISE/HERA LAS, 2002	P&G unpublished data Vermeire, 1993 HERA, 2002 EU TGD	
	AISE/HERA Alcohol sulphates, 2002	EU TGD, 2003 HERA, 2002	
	AISE/HERA Sodium Carbonate, 2002	Lally, 2001 HERA, 2002 U.S. EPA, 1997	
	AISE/HERA Fluorescent Brightener, 2001	EU TGD, 2003 HERA, 2002 U.S. EPA, 1997	
	AISE/HERA Zeolite, 2001	Lally, 2001 U.S. EPA, 1989 HERA, 2002 EU TGD,2003	
	AISE/HERA Fatty acid salts, 2002	EU TGD, 2003 HERA, 2002 Vermeire, 1993	
	AISE/HERA Alcohol ethoxysulphates, 2003	HERA, 2002 EU TGD, 2003	
	EU TGD, 2003		
	IPCS, 1994		
	Multiple IPCS CICADS (see appendix I-A)		
	Multiple OECD SIDS/SIARS (see appendix I-A)		
	SDA internal data, 2002-2003		

Appendix I-B

Primary, Secondary, and Selected References for Exposure Models and Factors (Cont'd)

Exposure Scenario	Documents Reviewed	Secondary References (Documents referenced within reviewed document)	Documents Selected [Secondary Reference]
EU Dermal: Dish detergent: washing hands Dish detergent: washing dishes Hard surface and all purpose cleaner	AISE/HERA, 2002 Habits and Practices Table		AIHC alkyldimethylamine oxides AISE/HERA Sodium Carbonate, 2002 AISE/HERA, 2002 Habits and Practices Table AISE/HERA Fluorescent Brightener, 2001 [U.S. EPA] AISE/HERA Zeolite A, 2001 [Lally, 2001; EU TGD] SDA internal data, 2002-2003 EU TGD, 2003
	AISE/HERA, April 2002		
	AIHC alkyldimethylamine oxides	U.S. EPA, 1997 SDA internal data, 2002-2003	
	AISE/HERA LAS, 2002	HERA, 2002 EU TGD	
	AISE/HERA Alcohol sulphates, 2002	EU TGD HERA, 2002	
	AISE/HERA Alcohol ethoxysulphates, 2003	HERA, 2002 EU TGD	
	AISE/HERA Fluorescent Brightener, 2001	EU TGD HERA, 2002 U.S. EPA, 1997	
	AISE/HERA Zeolite, 2001	Lally, 2001 HERA, 2002 EU TGD	
	EU TGD, 2003		
	IPCS, 1994		
	Multiple IPCS CICADS		
	Multiple OECD SIDS/SIARS (see appendix I-A)		
	SDA data		

Appendix I-B

Primary, Secondary, and Selected References for Exposure Models and Factors (Cont'd)

Exposure Scenario	**Documents Reviewed**	**Secondary References** (Documents referenced within reviewed document)	**Documents Selected** [Secondary Reference]
EU Dermal: Personal care (hair care, skin care, antiperspirants, deodorants) Cosmetics Baby products Fragrances	AISE/HERA, April 2002		EU TGD, 2003 COLIPA, 2002 K.S. Crump Group, 1999 [ECA, 1997] SDA internal data, 2002-2003 CTFA, 2003 U.S. EPA, 1997
	K.S. Crump Group, 1999	ECA, 1997 MRI, 1995 MRI, 1996 U.S. EPA, 1997 U.S. EPA, 1989 CTFA, 1983 COLIPA, 1981	
	Cadby, 2002	COLIPA, 1987	
	COLIPA, 2002		
	CTFA, 2003		
	EU SCCNFP, 2000	COLIPA, 1997	
	IPCS, 1994		
	Multiple IPCS CICADS (see appendix I-A)		
	Multiple OECD SIDS, SIARS (see appendix I-A)		
	SDA internal data, 2002-2003		
	EU TGD, 2003		
	U.S. EPA, 1997		

Appendix I-B

Primary, Secondary, and Selected References for Exposure Models and Factors (Cont'd)

Exposure Scenario	Documents Reviewed	Secondary References (Documents referenced within reviewed document)	Documents Selected [Secondary Reference]
NA Oral: Dishwashing liquid deposition Personal care products (toothpaste, mouthwash, lipstick)	ACA, Oct 2001		AISE/HERA LAS, 2002 [Schmitz, 1973; Official French legislation 1990]) EU SCCNFP, 2003 EU TGD, 2003 K.S. Crump Group, 1999 [ECA, 1997] Barnhart, 1974 CTFA, 2002 and 2003 SDA internal data, 2002-2003 U.S. EPA, 1997 and 2001
	ACA, Jan 2002		
	ACA, Feb 2002		
	AIHC glucose amides	U.S. EPA, 1997 SDA internal data, 2002-2003	
	AIHC alkyldimethylamine oxides	U.S. EPA, 1997 SDA Internal data, 2002-2003	
	AISE/HERA LAS, 2002	Schmitz, 1973 Official French legislation, 1990 HERA, 2002 EU TGD	
	Barnhart, 1974		
	CTFA, 2002		
	CTFA, 2003		
	EU SCCNFP, 2000		
	EU SCCNFP, 2003	Beltran, 1998; Bently, 1999; Barnhart, 1974; Baxter, 1980; Bently, 1997; Brunn, 1988; Dowel, 1981; Ericcson, 1969; Levy, 1993; Naccache, 1992; Naccache, 1990; Simard, 1989; Simard, 1991	
	K.S. Crump Group, 1999	ECA, 1997; MRI, 1996 U.S. EPA, 1997; CTFA, 1983 COLIPA, 1981	
	Multiple OECD SIDS, SIARs (see appendix I-A)		
	OECD SDS SIAR	Ekstrand, 1980	
	Sciences International, 2001		
	SDA internal data, 2002-2003		
	EU TGD, 2003		
	U.S. EPA, 1997		
	U.S. EPA, 1997 and 2001		

Appendix I-B

Primary, Secondary, and Selected References for Exposure Models and Factors (Cont'd)

Exposure Scenario	Documents Reviewed	Secondary References (Documents referenced within reviewed document)	Documents Selected [Secondary Reference]
EU Oral: Dishwashing liquid deposition Personal care products (toothpaste, mouthwash, lipstick)	AISE/HERA, April 2002		AISE/HERA LAS, 2002 [Schmitz, 1973; Official French legislation, 1990]) EU SCCNFP, 2003 EU TGD, 2003 Barnhart, 1974 SDA internal data, 2002-2003
	AISE/HERA LAS, 2002	Schmitz, 1973 Official French legislation, 1990 HERA, 2002 EU TGD, 2003	
	Barnhart, 1974		
	EU SCCNFP, 2000		
	EU SCCNFP, 2003	Beltran, 1998; Bently, 1999 Barnhart, 1974; Baxter, 1980 Bently, 1997; Brunn, 1988 Dowel, 1981; Ericcson, 1969 Levy, 1993; Naccache, 1992 Naccache, 1990; Simard, 1989 Simard, 1991	
	Multiple OECD SIDS, SIARs (see appendix I-A)	Ekstrand, 1980	
	IPCS, 1994		
	Multiple IPCS CICADS (see appendix I-A)		
	SDA internal data, 2002-2003		
	EU TGD, 2003		

Appendix I-B

Primary, Secondary, and Selected References for Exposure Models and Factors (Cont'd)

Exposure Scenario	**Documents Reviewed**	**Secondary References** (Documents referenced within reviewed document)	**Documents Selected** [Secondary Reference]
NA Inhalation: Laundry detergent dust Spray cleaners Paints	ACA, Oct 2001		AISE/HERA LAS, 2002 [Van de Plassche, 1998]) CSPA, 2002 SDA internal data, 2002-2003 Battelle, 1999 EU TGD, 2003 U.S. EPA, 1997 U.S. EPA, 1997 and 2001
	ACA, Jan 2002		
	ACA, Feb 2002		
	AIHC DPnB	EPA CHEMSTEER	
	Battelle, 1999		
	CSPA, 2002		
	AISE/HERA LAS, 2002	Van de Plassche, 1998 HERA, 2002 EU TGD, 2003	
	U.S. EPA, 1997		
	U.S. EPA, 1997 and 2001		
	EU TGD, 2003		
	Multiple OECD SIDS/SIARS (see appendix I-A)		
	SDA internal data, 2002-2003		
NA Inhalation: Personal care products (hair sprays, fragrances, antiperspirants, deodorants)	ACA, Oct 2001		AIHC DME K.S. Crump Group, 1999 [ECA, 1997] [MRI, 1995]) CTFA, 2002 CTFA, 2003 SDA internal data, 2002-2003 U.S. EPA, 1997 and 2001 EU TGD, 2003
	ACA, Jan 2002		
	ACA, Feb 2002		
	K.S. Crump Group, 1999	ECA, 1997; MRI, 1995 and 1996; U.S. EPA, 1989 and 1997; CTFA, 1983; COLIPA, 1981	
	AIHC DME		
	CTFA, 2000		
	CTFA, 2003		
	U.S. EPA, 1997		
	U.S. EPA, 1997 and 2001		
	Multiple OECD SIDS/SIARS (see appendix I-A)		
	EU TGD, 2003		
	SDA internal data, 2002-2003		

Appendix I-B

Primary, Secondary, and Selected References for Exposure Models and Factors (Cont'd)

Exposure Scenario	**Documents Reviewed**	**Secondary References** (Documents referenced within reviewed document)	**Documents Selected** [Secondary Reference]
EU Inhalation: Laundry detergent dust Spray cleaners Paints	AISE/HERA, April 2002		AISE/HERA LAS, 2002 [Van de Plassche, 1998] CSPA, 2002 SDA internal data, 2002-2003 Battelle, 1999 EU TGD, 2003 U.S. EPA, 1997
	AISE/HERA LAS, 2002	Van de Plassche, 1998 HERA, 2002 EU TGD, 2003	
	Battelle, 1999		
	CSPA, 2002		
	IPCS, 1994		
	Multiple IPCS CICADS (see appendix I-A)		
	U.S. EPA, 1997		
	EU TGD, 2003		
	Multiple OECD SIDS/SIARS (see appendix I-A)		
	SDA internal data, 2002-2003		
EU Inhalation: Personal care products (hair sprays, antiperspirants, deodorants, fragrances)	AISE/HERA, April 2002		K.S. Crump Group, 1999 [ECA, 1997 COLIPA, 2002 SDA internal data, 2002-2003 EU TGD, 2003
	K.S. Crump Group, 1999	ECA, 1997 MRI, 1995 and 1996 U.S. EPA, 1989 and 1997 CTFA, 1983 COLIPA, 1981	
	COLIPA, 2002		
	IPCS, 1994		
	Multiple IPCS CICADS (see appendix I-A)		
	Multiple OECD SIDS/SIARS (see appendix I-A)		
	EU TGD, 2003		
	SDA internal data		

Appendix II-A

Screening Product Exposure Data Matrix: Default High-End Values

Appendix II-A

Screening Product Exposure Data Matrix: Default High-End Values

Appendix II-A presents the default high-end input values for the exposure parameters and the associated references/documentation. In cases where the maximum value was not selected as the "high-end" default value, an "*" notation and rationale are provided in the numeric footnotes.

Appendix II-A-1: Dermal Exposure Parameters to Estimate Screening Exposures to Consumer Products – North America

(References, abbreviations and special notes are described in footnotes at end of table)

	Product Use Freq. [FQ]		Product Amount Used per Use [A]		Product Amount Used per Day [A']		Product Use Conc.		Product Use Conc. [PC]		Contact Area [CA]		Product Retained [R]		Film Thickness [FT]	Product Retained [PR]		Percent Transfer [PT]		Dermal Abs. [DA]	Body Weigh t [BW]		Scaling: Duration of Exposure [TF]		Product Exposure (mg/kg-day)	Model/Equation Reference	Model/Equation Formula
	(use/day)		(g/use)		(g/day)		(%)		(g/cm^3)		(cm^2)		(mg/cm^2)		(cm) (E)	(%)		(%)		(%)	(kg)						note: CF refers to conversion factor of 1000mg/g; assumed 100% dermal absorption
Soaps and Detergents																											
Laundry detergent – Wearing clothes			121	A												1.00%	A	1%	A	100%	60	F			0.2017	SDA data; AIHC Exposure Initiative: Glucose amides	A x PR x PT x DA x CF / BW
Laundry detergent (tablets) -- Wearing clothes			135	G												1.00%	A	1%	A	100%	60	F			0.2250	SDA data; AIHC Exposure Initiative: Glucose amides	A x PR x PT x DA x CF / BW
Fabric conditioners, rinse added – wearing clothes			112	A												1.00%	A	1%	A	100%	60	F			0.1867	SDA data; AIHC Exposure Initiative: Glucose amides	A x PR x PT x DA x CF / BW
Fabric conditioners, dryer sheets – wearing clothes			3	A												10.00%	A	1%	A	100%	60	F			0.0500	SDA data; AIHC Exposure Initiative: Glucose amides	A x PR x PT x DA x CF / BW
Laundry detergent/fabric conditioner handwash	1	A					1%	A	0.01	A'	1680	C			0.0024					100%	60	F	0.007	G	0.0047	AIHC Exposure Initiative: Glucose amides	FQ x PC x CA x FT x DA x TF x CF / BW
Laundry detergent pretreatment (powder paste)	1	A					60%	G	0.6	A'	360	H			0.0024					100%	60	F	0.007	G	0.0600	AIHC Exposure Initiative: Glucose amides	FQ x PC x CA x FT x DA x TF x CF / BW
Laundry detergent pretreatment (liquid neat/non-dilutable)	1	A					100%	Q	1.0	A'	360	H			0.0024					100%	60	F	0.007	G	0.1000	AIHC Exposure Initiative: Glucose amides	FQ x PC x CA x FT x DA x TF x CF / BW
Dishwashing liquids-handwash (hands)	0.14	E							0.9	E	1680	C			0.0024					100%	60	F	0.00035	A	0.0030	AIHC Exposure Initiative: Amine Oxides	FQ x PC x CA x FT x DA x TF x CF / BW
Dishwashing liquids-handwash (dishes)	3	A					0.15%	A	0.0015	A'	1680	C			0.0024					100%	60	F	0.03	G	0.0095	AIHC Exposure Initiative: Amine Oxides	FQ x PC x CA x FT x DA x TF x CF / BW
Hard surface cleaner-powder	1	A	51	A			1%	P	0.01	A'	1680	C			0.0024			100%	N	100%	60	F	0.014	G	0.0095	AIHC Exposure Initiative: Amine Oxides	FQ x PC x CA x FT x PT x DA x TF x CF / BW
APC liquid	1	A	76	A			1.5%	P	0.015	A'	1680	C			0.0024			100%	N	100%	60	F	0.014	G	0.0143	AIHC Exposure Initiative: Amine Oxides	FQ x PC x CA x FT x PT x DA x TF x CF / BW
APC gel (neat/non-dilutable)	1	G					100%	Q	1.0	A'	180	D			0.0024			100%	N	100%	60	F	0.014	G	0.1000	AIHC Exposure Initiative: Amine Oxides	FQ x PC x CA x FT x PT x DA x TF x CF / BW
APC spray (neat/non-dilutable)	1	G					100%	Q	1.0	A'	180	D			0.0024			100%	N	100%	60	F	0.0104	B,*,6	0.0504	AIHC Exposure Initiative: Amine Oxides	FQ x PC x CA x FT x PT x DA x TF x CF / BW
Personal Care and Cosmetics																											
Shampoos	1	B	16.4	B												1%	K			100%	60	F			2.73	AIHC/D4	FQ x A x PR x DA x CF / BW
Hair rinses	1	B	12.7	B												1%	K			100%	60	F			2.12	AIHC/D4	FQ x A x PR x DA x CF / BW
Styling tonic/gel	1	A	5.6	K												5%	K			100%	60	F			4.67	AIHC/D4	FQ x A x PR x DA x CF / BW
Hair sprays – aerosol	2	*, J, 2	5.33	*, J, 2												5%	K			100%	60	F			8.88	AIHC/D4	FQ x A x PR x DA x CF / BW
Hair spray (pump)	2	*, J, 2	7.81	*, J, 2												5%	K			100%	60	F			13.02	AIHC/D4	
F&H liquid soap – hand	8	A	1.7	A												1.0%	N			100%	60	F			2.27	AIHC/D4 (skin care)	FQ x A x PR x DA x CF / BW
F&H Bar Soap – Hand	6	A	0.36	A												1.0%	N			100%	60	F			0.36	AIHC/D4 (skin care)	FQ x A x PR x DA x CF / BW
Liquid Soap – Body	0.57	B	11.8	B*, 1												1.0%	N			100%	60	F			1.12	AIHC/D4 (skin care)	FQ x A x PR x DA x CF / BW
F&H Bar Soap – Body	3	B	8.6	A												1.0%	N			100%	60	F			4.30	AIHC/D4 (skin care)	FQ x A x PR x DA x CF / BW
Cleansing products	2	B	1.7	B*, 1												1.0%	N			100%	60	F			0.57	AIHC/D4 (skin care)	FQ x A x PR x DA x CF / BW
Body Wash	1	A	12	A												1.0%	N			100%	60	F			2.00	AIHC/D4 (skin care)	FQ x A x PR x DA x CF / BW
Bath Foam/Bubble Bath	0.29	M	17	A												1.0%	N			100%	60	F			0.82	AIHC/D4 (skin care)	FQ x A x PR x DA x CF / BW
F & H Bar Soap – Face	1.00	A	0.27	A												1.0%	N			100%	60	F			0.05	AIHC/D4 (skin care)	FQ x A x PR x DA x CF / BW

Appendix II-A-1: Dermal Exposure Parameters to Estimate Screening Exposures to Consumer Products – North America (cont'd)

(References, abbreviations and special notes are described in footnotes at end of table)

	Product Use Frequency [FQ]		Product Amount Used per Use [A]		Product Amount Used per Day [A']		Product Use Conc.		Product Use Conc. [PC]		Contact Area [CA]		Product Retained [R]		Film Thickness [FT]	Product Retained [PR]		Percent Transfer [PT]		Dermal Abs. [DA]	Body Weight [BW]		Scaling: Duration of Exposure [TF]		Product Exposure (mg/kg-day)	Model/Equation Reference	Model/Equation Formula
Shave Cream	1.00	A	4	*, N, 3												1%	A			100%	70	F			0.57	AIHC/D4 (skin care);	FQ x A x PR x DA x CF / BW
Body moisturizer					16.1	*, J, 2										100%	L			100%	60	F			268.33	AIHC/D4 (skin care);	FQ x A x PR x DA x CF / BW
Antiperspirants – roll-ons	1	A*, 5	1.22	K												100%	L			100%	70	F			17.43	AIHC/D4 (male data)	FQ x A x PR x DA x CF / BW
Antiperspirant aerosols	1	A*, 5	2.2	A												75%	N			100%	60	F			27.50	AIHC/D4	FQ x A x PR x DA x CF / BW
Antiperspirant solid/bar	1	A*, 5	1.2	A												100%	L			100%	60	F			20.00	AIHC/D4	FQ x A x PR x DA x CF / BW
Lipstick	3	*, J, 2	0.024	*, J, 2												100%	L			100%	60	F			1.20	AIHC/D4	FQ x A x PR x DA x CF / BW
Face/eye cosmetics foundation liquid	2	J	1.2	*, J, 2												100%	L			100%	60	F			40.00	AIHC/D4 (skin care)	FQ x A x PR x DA x CF / BW
Other – Makeup remover	2	M	2.5	M												5%	I			100%	60	F			4.17	AIHC/D4	FQ x A x PR x DA x CF / BW
Baby Care Products																											
Baby/Bath liquid	1	A	0.873	O							9000	A	0.097	A		100%				100%	15	F			58		FQ x A x PR x DA x CF / BW
Baby Lotions and creams	2	B	2	N												100%	L			100%	15	F			267	AIHC/D4	FQ x A x PR x DA x CF / BW
Kids shampoos	0.43	B	10	A												1%	K			100%	15	F			3	AIHC/D4	FQ x A x PR x DA x CF / BW
Fragrances																											
Fine fragrances	1.67	*, J, 4	0.68	*, J, 2												100%	L			100%	60	F			18.93	AIHC/D4 (skin care)	FQ x A x PR x DA x CF / BW
Aftershave	1	A	1	A												100%	L			100%	70	F			14.29	AIHC/D4 (skin care)	FQ x A x PR x DA x CF / BW
Miscellaneous Products																											
Paints																											
Lubricants																											
Paper products and processing																											
Other – Pharmaceuticals																											
Other – Metal working fluid																											

Appendix II-A-1: Dermal Exposure Parameters to Estimate Screening Exposures to Consumer Products - North America (cont'd)

(References, abbreviations and special notes)

Abbreviations:

AIHC	American Industrial Health Council
AISE	International Association for Soaps, Detergents and Maintenance Products
APC	All purpose cleaners
CTFA	Cosmetic, Toiletry and Fragrance Association
D4	Octamethylcyclotetrasiloxane Exposure Assessment prepared by K.S. Crump Group (1999)
EFH	U.S. EPA's Exposure Factors Handbook, 1997
F & H	Face and Hand
HERA	Human & Environmental Risk Assessments (subcommittee within AISE)
SRTC	CTFA's Safety and Regulatory Toxicology Committee
TGD	EU Technical Guidance Document, 2003

References:

A	SDA Internal Data
A'	PC (%) was converted to PC (g/cm^3); where (X g product/ 100 g water) x (1g water/1cm^3 water)
B	U.S. EPA, 1997 (EFH)
C	AIHC alkyldimethylamine oxide assessment: hands and forearms
D	EFH&SDA 2/03 and 4/03 resolutions – one palm, average females
E	AIHC alkyldimethylamine oxide assessment: internal data
F	U.S. EPA, 1997 and 2001 (OPP Residential SOPs)
G	AISE/HERA, 2002 (Table of Habit and Practices for consumer products in Western Europe) (No NA specific data identified)
H	EFH: both palms (average female) – SDA 2/03 resolution
I	Data on % product retained (PR) was not available for make-up remover scenario; 5% was assumed to be a reasonable high-end estimate
J	CTFA, 2002
K	AIHC/K.S. Crump Group, 1999 (D4 assessment)
L	Leave-on product; assumed 100%
M	EU TGD, 2003 (No NA-specific data identified)
N	CTFA's SRTC comments on SDA Exposure Assessment Methodology, April 2003
O	Derived based on CA x R/1000 (recommended by SDA-HPV consortium for consistency with adult dermal scenarios at Feb 2003 meeting)
P	PC (%) was calculated by assuming product will be diluted in 5 L of water; PC (%) = (X g/use) / (5L/use) x (1000g/L)
Q	Non-diluted products use 100% product concentration

*** Value other than maximum selected, see additional numbered notes below:**

1. Full data range not provided; only averages were available
2. Selected value at 90th percentile of data range
3. Selected reasonable average value as recommended by CTFA's SRTC
4. Selected average value from CTFA 2002 which is in the upper range of data provided in EFH
5. Selected reasonable value based on outcome of discussions among SDA member companies
6. Selected value based on mean estimate of 15 minute a day, which was based on the sum of EPA-EFH estimates for cleaning bathroom sinks/tubs (average 44 hours/year) and cleaning kitchen sinks (average 41 hours/yr)

Appendix II-A-2: Dermal Exposure Parameters to Estimate Screening Exposures to Consumer Products – Europe

(References, abbreviations and special notes are described in footnotes at end of table)

	Product Use Freq [FQ]		Product Amount Used per Use [A]		Product Amount Used per Day [A']		Product Use Conc.		Product Use Conc. [PC]		Contact Area [CA]		Product Retained [R]		Product Retained [PR]		Film Thick-ness [FT]		Transfer to Skin [PT]		Dermal Abs. [DA]	Body Weight [BW]		Scaling: Duration of Exposure [TF]		Product Exposure	Model/Equation Reference	Model/Equation Formula
	(use/day)		(g/use)		(g/day)		(%)		(g /cm^3)		(cm²)		(mg/cm²)		(%)		(cm)		(%)		(%)	(kg)				(mg/kg-day)		note: CF refers to conversion factor of 1000mg/g; assumed 100% dermal absorption
Soaps and Detergents																												
Laundry detergents-indirect: powder			290	B											0.95%	A'			10%	A	100%	60	H			4.59	HERA RA for Sodium Aluminum Silicate	A x PR x PT x DA x CF / BW
Laundry detergents-indirect: liquid			230	B											0.95%	A'			10%	A	100%	60	H			3.64	HERA RA for Sodium Aluminum Silicate	A x PR x PT x DA x CF / BW
Laundry detergent-indirect: tablet			135	B											0.95%	A'			10%	A	100%	60	H			2.14	HERA RA for Sodium Aluminum Silicate	A x PR x PT x DA x CF / BW
Fabric conditioners indirect: liquid regular			140	B											0.95%	A'			10%	A	100%	60	H			2.22	HERA RA for Sodium Aluminum Silicate	A x PR x PT x DA x CF / BW
Fabric conditioners indirect: liquid Concentrate			90	B											0.95%	A'			10%	A	100%	60	H			1.43	HERA RA for Sodium Aluminum Silicate	A x PR x PT x DA x CF / BW
Handwashing: powder	2.57	B					1%	B	0.01	D	1980	C					0.01	A			100%	60	H	0.007	B	0.06	HERA RA for Sodium Carbonate	FQ x PC x CA x FT x DA x TF x CF / BW
Handwashing: liquid laundry and fabric conditioners	1.43	B					1%	B	0.01	D	1980	C					0.01	A			100%	60	H	0.007	B	0.03	HERA RA for Sodium Carbonate	FQ x PC x CA x FT x DA x TF x CF / BW
Pretreatment (powder paste)	1.00	E					60%	B	0.6	D	840	H					0.01	A			100%	60	H	0.007	B	0.58	HERA RA for Sodium Carbonate	FQ x PC x CA x FT x DA x TF x CF / BW
Pretreatment (liquid neat)	1.00	E					100%	M	1	D	840	H					0.01	A			100%	60	H	0.007	B	0.97	HERA RA for Sodium Carbonate	FQ x PC x CA x FT x DA x TF x CF / BW
Dishwashing liquids – handwash (hands)	0.14	G							0.9	G	1680	G					0.01	A			100%	60	H	0.00035	E	0.01	AIHC Exposure Initiative: Amine Oxides	FQ x PC x CA x FT x DA x TF x CF / BW
Dishwashing liquids – handwash (dishes)	3.0	B	28	H			0.93%	I	0.009	D	1980	C					0.01	A			100%	60	H	0.03	B	0.29	AIHC Exposure Initiative: Amine Oxides	FQ x PC x CA x FT x DA x TF x CF / BW
APC liquid	1.0	B	110	B			2.20%	B'	0.022	D	1980	C					0.01	A			100%	60	H	0.014	B	0.10	HERA RA for Sodium Carbonate (detergents)	FQ x PC x CA x FT x DA x TF x CF / BW
APC powder	1.0	B	40	B			0.80%	B'	0.008	D	1980	C					0.01	A			100%	60	H	0.014	B	0.04	HERA RA for Sodium Carbonate (detergents)	FQ x PC x CA x FT x DA x TF x CF / BW
APC spray (neat) diluted	1.0	B	30	B			0.60%	B'	0.006	D	1980	C					0.01	A			100%	60	H	0.007	B	0.01	HERA RA for Sodium Carbonate (detergents)	FQ x PC x CA x FT x DA x TF x CF / BW
APC gel (neat) diluted	1.0	B	40	B			0.80%	B'	0.008	D	1980	C					0.01	A			100%	60	H	0.014	B	0.04	HERA RA for Sodium Carbonate (detergents)	FQ x PC x CA x FT x DA x TF x CF / BW
APC spray (neat) undiluted	1.0	B					100%	M	1	D	1980	C					0.01	A			100%	60	H	0.007	B	2.29	HERA RA for Sodium Carbonate (detergents)	FQ x PC x CA x FT x DA x TF x CF / BW
APC gel (neat) undiluted	1.0	B					100%	M	1	D	1980	C					0.01	A			100%	60	H	0.014	B	4.58	HERA RA for Sodium Carbonate (detergents)	FQ x PC x CA x FT x DA x TF x CF / BW
Personal Care and Cosmetics																												
Shampoos	1	O	8	O, *, 1											1%	G					100%	60	H			1.33	TGD	FQ x A x PR x DA x CF / BW
Hair conditioners	0.29	H	14	H											1%	G					100%	60	H			0.68	TGD	FQ x A x PR x DA x CF / BW
Styling Mousse	2	H	5	H											5%	G					100%	60	H			8.33	TGD	FQ x A x PR x DA x CF / BW
Hair sprays – aerosol	2	O	5	O											10%	O					100%	60	H			16.67	No EU data; AIHC/D4	FQ x A x PR x DA x CF / BW
F&H liquid soap – hand	7	E	1.6	E											0.5%	E					100%	60	H			0.93	TGD	FQ x A x PR x DA x CF / BW
F&H Bar Soap – Hand (Toilet soap)	6	O	0.8	O											10.0%	O					100%	60	H			8.00	TGD	FQ x A x PR x DA x CF / BW
Liquid Soap – Body (Shower gel)	1.07	O	5	O											10.0%	O					100%	60	H			8.92	TGD	FQ x A x PR x DA x CF / BW

F&H Bar Soap – Body	1	E	10	E											0.5%	E					100%	60	H			0.83	TGD	FQ x A x PR x DA x CF / BW
F &H Bar Soap – Face	1	E	0.27	E											0.5%	E					100%	60	H			0.02	No EU data: AIHC/D4 (skin care)	FQ x A x PR x DA x CF / BW
Body Wash	1	E	9.2	E											0.5%	E					100%	60	H			0.77	TGD	FQ x A x PR x DA x CF / BW
Bath Foam/Bubble Bath	0.29	H	17	E											0.5%	E					100%	60	H			0.41	TGD	FQ x A x PR x DA x CF / BW
Shaving Lubricant	1	H	2	H											1%	E					100%	70	H			0.29	TGD	FQ x A x PR x DA x CF / BW
Skin lotions and creams (body lotion)	0.71	O, *, 1	8	O											100%	O					100%	60	H			94.67	TGD	FQ x A x PR x DA x CF / BW
Hand moisturizer	7	E	0.8	E											100%	K					100%	60	H			93.33	TGD	FQ x A x PR x DA x CF / BW
Fragrance cream (include makeup and foundation)	0.29	O	5	O											100%	O					100%	60	H			24.17	TGD	FQ x A x PR x DA x CF / BW
Facial moisturizer	2	O	0.8	O											100%	O					100%	60	H			26.67	TGD	FQ x A x PR x DA x CF / BW
Antiperspirants – aerosols	3	H	3	H											100%	K					100%	60	H			150.00	TGD	FQ x A x PR x DA x CF / BW
Antiperspirant – roll-ons	1	O	0.5	O, *, 1											100%	O					100%	60	H			8.33	TGD	FQ x A x PR x DA x CF / BW
Antiperspirant solid/bar	1	O	0.5	O, *, 1											100%	O					100%	60	H			8.33	TGD	FQ x A x PR x DA x CF / BW
Lipstick	6	H	0.01	H											100%	K					100%	60	H			1.00	TGD	FQ x A x PR x DA x CF / BW
Face/Eye Cosmetics	3	H	0.025	H											100%	K					100%	60	H			1.25	TGD	FQ x A x PR x DA x CF / BW
Other – Makeup remover	2	H	2.5	H											5%	L					100%	60	H			4.17	TGD	FQ x A x PR x DA x CF / BW
Baby Care Products																												
Baby shampoo					5	E									1%	G					100%	15	H			3.33	SDA data	A' x PR x DA x CF / BW
Baby/Bath liquid	1	E	0.873	J							9000	E	0.097	E							100%	15	H			58.20	SDA data	FQ x R x CA x DA x CF / BW
Baby Lotions and creams	2	N	2	F											100%	K					100%	15	H			266.67	No EU data: AIHC/D4	FQ x A x PR x DA x CF / BW
Skin wipes																												
Fragrances																												
Fine fragrances -pour form	5	E	1.2	E											100%	K					100%	60	H			100.00	TGD	FQ x A x PR x DA x CF / BW
Aftershave	1	E	1	E											100%	K					100%	70	H			14.29	No EU data; AIHC/D4 (skin care)	FQ x A x PR x DA x CF / BW
Eau de toilette (including perfume and aftershave)	1	O	0.75	O											100%	O					100%	60	H			12.50	TGD	FQ x A x PR x DA x CF / BW

Appendix II-A-2: Dermal Exposure Parameters to Estimate Screening Exposures to Consumer Products – Europe (cont'd)

(References, abbreviations and special notes)

Abbreviations:	AIHC	American Industrial Health Council
	AISE	International Association for Soaps, Detergents and Maintenance Products, (Association Internationale de la Savonnerie, de la Détergence et des Produits d'Entretien)
	APC	All purpose cleaners
	COLIPA	European Cosmetic, Toiletry, and Perfumery Association
	CTFA	Cosmetic, Toiletry and Fragrance Association
	D4	Octamethylcyclotetrasiloxane Exposure Assessment, K.S. Crump Group (1999)
	EFH	U.S. EPA's Exposure Factors Handbook, 1997
	HERA	Human & Environmental Risk Assessments (subcommittee within AISE)
	F & H	Face and Hand
	SRTC	CTFA-Safety Regulatory Toxicology Subcommittee
	TGD	EU Technical Guidance Document

References:	A	AISE HERA RA Sodium Aluminum Silicate
	A'	AISE HERA RA Sodium Aluminum Silicate where PR = (PD x FD1)/WI x CA; Product deposition (5%); FD1 = fabric density (10 mg/cm^2); WI = total wash weight (1kg); CA = body contact area (cm^2)
	B	AISE HERA Habits and Practices, 2002 (developed by AISE within the HERA project)
	B'	AISE HERA Habits and Practices (diluted in 5 L of water)
	C	AISE HERA Florescent Brightener FWA-5
	D	PC (%) was converted to PC (g/cm^3); where (X g product/100 g water) x (1g water/1cm^3 water)
	E	SDA internal data
	F	Based on CTFA-SRTC comments on SDA Exposure Assessment Methodology April 2003 (no EU specific data)
	G	AIHC/D4, K.S. Crump Group (1999)
	H	EU TGD, 2003
	I	SIAR triethanolamine: dilute in 3000 cm^3 water
	J	Derived based on CA x R/1000 (SDA-HPV consortium's recommendation for consistency with adult dermal scenarios, Feb 2003)
	K	Leave-on product; assumed 100%
	L	No available data
	M	Non-diluted products use 100% product concentration
	N	U.S. EPA, 1997 (EFH) (No EU specific data)
	O	COLIPA, 2002

***Value other than maximum selected, see additional numbered notes below:**

´Selected value based COLIPA, 2002 data

Appendix II-A-3: Oral Exposure Parameters to Estimate Screening Exposures to Consumer Products -- North America

(References, abbreviations and special notes are described in footnotes at end of table)

	Product Use Frequency [FQ]		Product Amount Used per Use [A]		Product Use Conc. [C']		Product Retained [Ta']		Dish Area Contacting Food [Sa]		Fraction Ingested [FI]		Body Weight [BW]		Product Exposure	Model/Equation Reference	Model/Equation Formula
	(use/day)		(g/use)		(g/cm^3)		(ml/cm^2)		(cm^2)		(%)		(kg)		(mg/kg-day)		note: CF refers to conversion factor of 1000mg/g; assumed 100% dermal absorption
Soaps and Detergents																	
Dishwashing liquids – hand-wash (dishware deposition)			5	B	0.001	B'	5.50E-05	C	5400	A			60	G	0.0050	HERA-LAS	C' x Ta' x Sa x CF/BW
Personal Care and Cosmetics																	
Toothpaste	3	A, *, 1	0.8	F, *, 2							35%	F, *, 3	15	G	56.0	SCNNFP, 2003	FQ x A x FI x CF / BW
Mouthwash adult	2	A	30	A							8.5%	A	60	G	85.0	TGD	FQ x A x FI x CF / BW
Lipstick	2.6	E, *, 4	0.024	E, *, 4							100%	D	60	G	1.0	AIHC/D4	FQ x A x FI x CF / BW
Food and Food Additives																	
Foods																	
Flavors																	

Abbreviations:

AIHC	American Industrial Health Council
AISE	International Association for Soaps, Detergents and Maintenance Products
CTFA	Cosmetic, Toiletry and Fragrance Association
D4	Octamethylcyclotetrasiloxane Exposure Assessment prepared by K.S. Crump Group (1999)
EFH	U.S. EPA's Exposure Factors Handbook, 1997
HERA	Human & Environmental Risk Assessments (subcommittee within AISE)
TGD	EU Technical Guidance Document, 2003
SCCN FP	The Scientific Committee on Cosmetic Products and Non-food Products Intended for Consumers
SRTC	CTFA-Safety Regulatory Toxicology Subcommittee

References:

A	SDA internal data
B	AISE HERA-LAS
B'	AISE HERA-LAS: based on 5g product per task divided by 5L (5000 cm^3) water = 1 mg/cm^3 = 0.001 g/cm^3
C	AISE HERA-LAS: amount of water on dishes after rinsing = 10% water left on non-rinsed dish x 5.5 $x10^{-4}$ ml/cm^2 = 5.5$x10^{-5}$ ml/cm^2
D	No data; assumed 100%
E	Based on SRTC comments, April 2003 and CTFA, 2002
F	Barnhart, 1974
G	U.S. EPA, 1997 and 2001 (OPP Residential SOPs)

* **Value other than maximum selected, see additional numbered notes below:**

1 Selected value is at 95th percentile of range in EFH data

2 Selected 0.8 g/use value because it is the high end value from SCCNP (2003) and agrees with the 0.86 g/use average value presented in Barnhart, 1974

3 Selected 35% as an upper estimate based on Barnhart, 1974

4 Selected value based on CTFA-SRTC comments and at the 90th percentile of the CTFA 2002 survey data range

Appendix II-A-4: Oral Exposure Parameters to Estimate Screening Exposures to Consumer Products – Europe

(References, abbreviations and special notes are described in footnotes at end of table)

	Product Use Frequency [FQ]		Product Amount Used per Use [A]		Product Use Conc. [C']		Product Retained [Ta']		Dish Contacting Food [Sa]		Fraction Ingested [FI]		Body Weight [BW]		Product Exposure	Model/Equation Reference	Model/Equation Formula
	(use/day)		(g/use)		(g/cm^3)		(ml/cm^2)		(cm^2)		(%)		(kg)		(mg/kg-day)		note: CF refers to conversion factor of 1000mg/g; assumed 100% dermal absorption
Soaps and Detergents																	
Dishwashing liquids—hand-wash dishware deposition			5	C	0.001	C'	5.50E-05	D	5400	A			60	F	0.0050	HERA-LAS	C' x Ta' x CD x CF/BW
Personal Care and Cosmetics																	
Toothpaste	3	A	0.8	E							35%	*, G, 1	15	F	56.0	SIAR for Na dodecyl sulfate; SCCNFP (2003)	FQ x A x FI x CF / BW
Mouthwash adult	5	F	10	F							8.5%	A	60	F	70.8	TGD	FQ x A x FI x CF / BW
Lipstick	6	F	0.01	F							100%	B	60	F	1.0	TGD; AIHC/D4 Assessment	FQ x A x FI x CF / BW
Food and Food Additives																	
Foods																	
Flavors																	

Abbreviations:

AIHC	American Industrial Health Council
AISE	International Association for Soaps, Detergents and Maintenance Products
D4	Octamethylcyclotetrasiloxane Exposure Assessment prepared by K.S. Crump Group (1999)
HERA	Human & Environmental Risk Assessments (subcommittee within AISE)
TGD	EU Technical Guidance Document, 2003
SCCNFP	The Scientific Committee on Cosmetic Products and Non-food Products Intended for Consumers

References:

A	SDA internal data
B	Assumed 100%
C	AISE HERA-LAS
C'	AISE HERA-LAS: based on 5g product per task divided by 5L (5000 cm^3) water = 1mg/cm^3 = 0.001g/cm^3
D	AISE HERA-LAS: amount of water on dishes after rinsing = 10% water left on non-rinsed dish x $5.5x10^{-4}$ ml/cm^2 = $5.5x10^{-5}$ml/cm^2
E	SCCNFP: The Safety of Fluorine Compounds in Oral Hygiene Products for Children Under the Age of 6 Years (2003)
F	EU TGD, 2003
G	Barnhart, 1974

***Value other than maximum selected, see additional numbered notes below:**

1 Selected 35% as an upper estimate based on Barnhart, 1974

Appendix II-A-5: Inhalation Exposure Parameters to Estimate Screening Exposures to Consumer Products – North America

(References, abbreviations and special notes are described in footnotes at end of table)

	Product Use Frequency [FQ]		Product Amount Used per Use [A]		Air-space Volume [V]		Respirable Product Conc. in Breathing Zone [RPC]		Inhalation Rate [IR]		Exposure Duration [ED]		Respirable Fraction [F]		Bio-available Fraction [BA]		Body Weight [BW]		Product Exposure	Model/Equation Reference	Model/Equation Formula
	(use/day)		(g/use)		(m^3)		(mg/m^3)		(m^3/hr)		(hr)		(%)		(%)		(kg)		(mg/kg-day)		note: CF refers to conversion factor of 1000mg/g; assumed 100% dermal absorption
Soaps and Detergents																					
Laundry detergent—powder	1	A	2.70E-07	A'									100%	A			60	G	4.50E-09	HERA LAS	FQ x A x F x CF / BW
Triggers–spray cleaners	1	A					0.72	H	0.8	C	0.25	C, *, 4			100%	A	60	G	0.0032	CSPA	FQ x RPC x IR x ED x BA / BW
Personal Care and Cosmetics																					
Hair spray (aerosol)	2	F, *, 1	5.33	F, *, 1	2	B			0.8	C	0.25	B	50%	A			60	G	8.88	AIHC Exposure Initiative: DME	FQ x A x IR x ED x F x CF / V x BW
Hair spray (pump)	2	F, *, 1	7.81	F, *, 1	2	B			0.8	C	0.25	B	50%	A			60	G	13.0	AIHC Exposure Initiative: DME	FQ x A x IR x ED x F x CF / V x BW
Antiperspirants—aerosols	2	D	2.2	A	2	B			0.8	C	0.78	D	25%	E			60	G	5.7	AIHC/D4 Assessment	FQ x A x IR x ED x F x CF / V x BW
Fine fragrances	1.67	F, *, 2	0.68	F, *, 1	2	B			0.8	C	0.78	D	50%	A			60	G	2.95	AIHC/D4 Assessment	FQ x A x IR x ED x F x CF / V x BW
Miscellaneous Products																					
Paints	0.0116	C, *, 3	206.6	C, *, 3	2	B			0.8	C	1.52	C, *, 3	1%	I			60	G	0.24	SDA; Assumes exposure to 1% of spray	FQ x A x IR x ED x F x CF / V x BW
Lubricants																					
Paper products and processing																					
Other—Pharmaceuticals																					
Other–Metal-working fluid																					

Abbreviations:

AIHC	American Industrial Health Council
AISE	International Association for Soaps, Detergents and Maintenance Products
CTFA	Cosmetic, Toiletry and Fragrance Association
D4	Octamethylcyclotetrasiloxane Exposure Assessment prepared by K.S. Crump Group (1999)
EFH	U.S. EPA's Exposure Factors Handbook, 1997
HERA	Human & Environmental Risk Assessments (subcommittee within AISE)
SRTC	CTFA-Safety Regulatory Toxicology Subcommittee
TGD	EU Technical Guidance Document, 2003

References:

A	SDA internal data
A'	AISE HERA LAS assessment: 0.27ug dust/scoop x 1 scoop/load
B	EU TGD, 2003
C	EFH
D	D4 assessment
E	SRTC Comments on the SDA HPV Exposure Assessment Methodology April, 2003
F	CTFA, 2002
G	U.S. EPA, 1997 and 2001 (OPP Residential SOPs)
H	Battelle, 1999
I	No available data, SDA

*** Value other than maximum selected, see additional numbered notes below:**

1 Selected value at the 90th percentile of range

2 Selected CTFA value is in the upper range of EFH data source

3 Selected mean value

4 Selected value based on mean estimate of 15 minute a day, which was based on the sum of EPA-EFH estimates for cleaning bathroom sinks/tubs (average 44 hours/year) and cleaning kitchen sinks (average 41 hours/yr)

Appendix II-A-6: Inhalation Exposure Parameters to Estimate Screening Exposures to Consumer Products – Europe

(References, abbreviations and special notes are described in footnotes at end of table)

	Product Use Frequency [FQ]		Product Amount Used per Use [A]		Airspace Volume [V]		Respirable Product Conc. in Breathing Zone [RPC]		Inhalation Rate [IR]		Exposure Duration [ED]		Bio-available Fraction [BA]		Respirable Fraction [F]		Body Weight [BW]		Product Exposure	Model/Equation Reference	Model/Equation Formula
	(use/day)		(g/use)		(m^3)		(mg/m^3)		(m^3/hr)		(hr)		(%)		(%)		(kg)		(mg/kg-day)		note: CF refers to conversion factor of 1000mg/g; assumed 100% dermal absorption
Soaps and Detergents																					
Laundry detergent-powder	1	D	2.70E-07	D'											100%	D	60	A	4.50E-09	HERA LAS	FQ x A x F x CF / BW
Trigger Spray Cleaners	1	D					0.72	B	0.8	A	0.33	D	100%	D			60	A	0.0032	CSPA	FQ x RPC x IR x ED x BA / BW
Personal Care and Cosmetics																					
lair sprays—aerosol	2		5	G	2	A			0.8	A	0.25	A			50%	D	60	A	8.33	TGD/D4 Assessment	FQ x A x IR x ED x F x CF / V x BW
Antiperspirants—aerosols	3	A	3	A	2	A			0.8	A	0.78	C			50%	D	60	A	23.4	TGD/D4 Assessment	FQ x A x IR x ED x F x CF / V x BW
Fragrances																					
Fine fragrances	5	A	1.2	A	2	A			0.8	A	0.78	C			50%	D	60	A	15.6	D4 Assessment	FQ x A x IR x ED x F x CF / V x BW
Miscellaneous Products																					
Paints	0.012	A	206.6	E, *, 1	2	A			0.8	A	1.52	E, *, 1			1%	F	60	A	0.251	No EU data; SDA Assumes exposure to 1% of spray	FQ x A x IR x ED x F x CF / V x BW
Lubricants																					
Paper products and processing																					
Other—Pharmaceuticals																					
Other—Metal working fluid																					

Abbreviations:

AIHC	American Industrial Health Council
AISE	International Association for Soaps, Detergents and Maintenance Products
COLIPA	European Cosmetic, Toiletry, and Perfumery Association
D4	Octamethylcyclotetrasiloxane Exposure Assessment prepared by K.S. Crump Group (1999)
EFH	U.S. EPA's Exposure Factors Handbook, 1997
HERA	Human & Environmental Risk Assessments (subcommittee within AISE)
TGD	EU Technical Guidance Document, 2003

References:

A	TGD, 2003
B	Battelle, 1999
C	D4 assessment
D	SDA internal data
D'	AISE HERA LAS assessment: 0.27 ug dust/scoop x 1 scoop/load
E	EFH
F	No available data
G	COLIPA, 2002

* **Value other than maximum selected, see additional numbered notes below:**

1 Selected mean value

Appendix II-B

Screening Product Exposure Data Matrix: Min-Max Values

Appendix II-B

Screening Product Exposure Data Matrix: Min-Max Values

Appendix II-B presents the range of data input values. The range includes the minimum and maximum values identified in various sources. In some cases, the minimum and maximum values came from two different sources. In these situations, the associated sources are identified in the footnotes. It should be noted that although there are several sources of data for a particular value, only the sources that contain the minimum and maximum are reported in Appendix II-B.

Appendix II-B-1: Data Ranges (Min-Max) of Dermal Exposure Parameters to Estimate Screening Exposures to Consumer Products – North America

(References, abbreviations and special notes are described in footnotes at end of table)

	Product Use Frequency [FQ]		Product Amount Used per Use [A]		Product Amount Used per Day [A']		Product Use Conc.		Product Use Conc. [PC]		Contact Area [CA]		Product Retained [R]		Film Thickness [FT]	Product Retained [PR]		Percent Transfer [PT]		Dermal Absorption [DA]	Body Weight [BW]		Scaling: Duration of Exposure [TF]	
	(use/day)		(g/use)		(g/day)		(%)		(g /cm^3)		(cm²)		(mg/cm²)		(cm) (E)	(%)		(%)		(%)	(kg)			
Soaps and Detergents																								
Laundry detergent--Wearing clothes			76—121	A												0.1—1%	A	1%	A	100%	60	F		
Laundry detergent (tablets) -- Wearing clothes			45—135	G												0.1—1%	A	1%	A	100%	60	F		
Fabric conditioners, rinse added -- wearing clothes			56–112	A												0.1–1%	A	1%	A	100%	60	F		
Fabric conditioners, dryer sheets -- wearing clothes			3	A												10.00%	A	1%	A	100%	60	F		
Laundry detergent/fabric conditioner handwash	1	A					0.1–1%	A	0.001–.01	A'	1680	C			0.0024					100%	60	F	0.007	G
Laundry detergent pretreatment (powder paste)	1	A					50–60%	G	0.5–0.6	A'	360	H			0.0024					100%	60	F	0.007	G
Laundry detergent pretreatment (liquid neat/non-dilutable)	1	A					100%	Q	1.0	A'	360	H			0.0024					100%	60	F	0.003–0.007	G
Dishwashing liquids-handwash (hands)	0.1–0.14	E							0.9	E	1680	C			0.0024					100%	60	F	0.00035	A
Dishwashing liquids-handwash (dishes)	1.0–3.0	A–E					0.03–0.15%	A	0.0003–0.0015	A'	1680	C			0.0024					100%	60	F	0.007–0.03	G
Hard surface cleaner-powder	0.14–1	A	20–51	A			0.4–1%	P	0.004–0.01	A'	1680	C			0.0024			100%	N	100%	60	F	0.007–0.014	G
APC liquid	0.14–1	A	41–76	A			0.8–1.5%	P	0.008–0.015	A'	1680	C			0.0024			100%	N	100%	60	F	0.007–0.014	G
APC gel (neat/non-dilutable)	0.14–1	G					100%	Q	1.0	A'	180	D			0.0024			100%	N	100%	60	F	0.007–0.014	G
APC spray (neat/non-dilutable)	0.14–1	G					100%	Q	1.0	A'	180	D			0.0024			100%	N	100%	60	F	0.0014–0.014	G, A
Personal Care and Cosmetics																								
Shampoos	0.48–1	B	5–16.4	E, B												0.5–1%	A, K			100%	60	F		
Hair rinses	0.064–1	B	7–12.7	A, B												0.5–1%	A, K			100%	60	F		
Styling tonic/gel	0.5–1	A	1.5–5.6	A, K												0.5–5%	A, K			100%	60	F		
Hair sprays–aerosol	1–5.36	*, J, 1	0.05 -14.08	*, J, 1												0.5–5%	A, K			100%	60	F		
Hair spray (pump)	1–4.22	*, J, 1	0–21.4	*, J, 1												0.5–5%	A, K			100%	60	F		
F&H liquid soap–hand	5.0–8.0	A	1.6–1.7	A												0.5–1%	A, N			100%	60	F		
F&H Bar Soap -Hand	1.0–6.0	A	0.36	A												0.5–1%	A, N			100%	60	F		
Liquid Soap-Body	0.088–0.57	B	11.8	B*, 2												0.5–1%	A, N			100%	60	F		
F&H Bar Soap -Body	0.95–3	B	2.6–8.6	B, A												0.5–1%	A, N			100%	60	F		
Cleansing products	0.54–2	B	1.7	B*, 2												0.5–1%	A, N			100%	60	F		
Body Wash	1	A	8.0–12.0	A												0.5–1%	A, N			100%	60	F		
Bath Foam/Bubble Bath	0.14–0.29	M	14–17	A												0.5–1%	A, N			100%	60	F		
F &H Bar Soap–Face	1.00	A	0.27	A												0.5–1%	A, N			100%	60	F		
Shave Cream	0.3–1	A	1.0–9.0	*, N, 3												1%	A			100%	70	F		
Body moisturizer					0.05–36.3	*, J, 1										100%	L			100%	60	F		
Antiperspirants–roll-ons	0.8–2.0	B*, 6	0.52–1.22	B, K												100%	L			100%	70	F		
Antiperspirant aerosols	0.8–2.0	B*, 6	0.52–2.2	B, A,												75%	N			100%	60	F		
Antiperspirant solid/bar	0.8–2.0	B*, 6	0.5–1.2	A												100%	L			100%	60	F		
Lipstick	1.0–4.0	B, 5	0–0.2	*, J, 1												100%	L			100%	60	F		
Face/eye cosmetics foundation liquid	1.0–2.0	J	0–2.65	*, J, 1												100%	L			100%	60	F		
Other–Makeup remover	1.0–2.0	M	2.5	M												5%	I			100%	60	F		
Baby Care Products																								
Baby/Bath liquid	1	A	0.873	O							9000	A	0.097	A		100%				100%	15	F		
Baby Lotions and creams	0.38–2	B	1.4–2	B, N												100%	L			100%	15	F		
Kids shampoos	0.11–0.43	B	0.5–10	B, A												0.5–1%	A. K			100%	15	F		
Fragrances																								
Fine fragrances	1.0–11.6	B, J *, 4	0.1–5.08	*, J, 1												100%	L			100%	60	F		
Aftershave	0.66–1	A	0.65–1	A												100%	L			100%	70	F		

Appendix II-B-1: Data Ranges (Min-Max) of Dermal Exposure Parameters to Estimate Screening Exposures to Consumer Products – North America (Cont'd)

(References, abbreviations and special notes are indicated in grey columns and described in footnotes at end of table)

Abbreviations:	AIHC	American Industrial Health Council
	AISE	International Association for Soaps, Detergents and Maintenance Products
	APC	All purpose cleaners
	CTFA	Cosmetic, Toiletry and Fragrance Association
	D4	Octamethylcyclotetrasiloxane Exposure Assessment, K.S. Crump Group (1999)
	EFH	U.S. EPA's Exposure Factors Handbook, 1997
	F&H	Face and Hand
	HERA	Human & Environmental Risk Assessments (subcommittee within AISE)
	SRTC	CTFA-Safety Regulatory Toxicology Subcommittee
	TGD	EU Technical Guidance Document, 2003

References:	A	SDA data
	A'	PC (%) was converted to PC (g/cm^3); where (X g product/ 100 g water) x (1g water/$1cm^3$ water)
	B	U.S. EPA, 1997 (EFH)
	C	AIHC alkyldimethylamine oxide assessment: hands and forearms
	D	EFH&SDA 2/03 and 4/03 resolutions -- one palm average females
	E	AIHC alkyldimethylamine oxide assessment: internal data
	F	U.S. EPA, 1997 and 2001 (OPP Residential SOPs)
	G	AISE/HERA, 2002 (Table of Habit and Practices for consumer products in Western Europe) (No NA-specific data identified)
	H	EFH: both palms (average female)-- SDA 2/03 resolution
	I	No available data
	J	CTFA, 2002
	K	AIHC/K.S. Crump Group, 1999 (D4 assessment)
	L	Leave-on product; assumed 100%
	M	EU TGD, 2003 (No NA specific data identified)
	N	Based on CTFA-SRTC comments on SDA Exposure Assessment Methodology April 2003
	O	Derived based on CA x R/1000
	P	PC (%) was calculated by assuming product will be diluted in 5 L of water; PC (%) = (X g/use) / (5L/use) x (1000g/L)
	Q	Non-diluted products use 100% product concentration
		***Value other than maximum selected; see additional numbered notes below:**
		1 Selected 90th percentile from data range
		2 Full data range not provided; only averages were available
		3 Selected reasonable average value as recommended by CTFA-SRTC
		4 Selected average value from CTFA 2002 which is in the upper range of data provided in EFH
		5 Selected value based on CTFA-STRC comment and at the 90th percentile of the CTFA 2002 survey data range
		6 Selected reasonable value based on outcome of discussions among SDA member companies

Appendix II-B-2: Data Ranges (Min-Max) of Dermal Exposure Parameters to Estimate Screening Exposures to Consumer Products – Europe

(References, abbreviations and special notes are described in footnotes at end of table)

	Product Use Frequency [FQ]		Product Amount Used per Use [A]		Product Amount Used per Day [A']		Product Use Conc.		Product Use Conc. [PC]		Contact Area [CA]		Product Retained [R]		Product Retained [PR]		Film Thickness [FT]		Transfer to Skin [PT]		Dermal Absorption [DA]	Body Weight [BW]		Scaling: Duration of Exposure [TF]	
	(use/day)		(g/use)		(g/day)		(%)		(g/cm^3)		(cm^2)		(mg/cm^2)		(%)		(cm)		(%)		(%)	(kg)			
Soaps and Detergents																									
Laundry detergents-indirect: powder			55–290	B											0.95%	A'			10%	A	100%	60	H		
Laundry detergents-indirect: liquid			78–230	B											0.95%	A'			10%	A	100%	60	H		
Laundry detergent-indirect: tablet			45–135	B											0.95%	A'			10%	A	100%	60	H		
Fabric conditioners indirect: liquid regular			50–140	B											0.95%	A'			10%	A	100%	60	H		
Fabric conditioners indirect: liquid concentrate			11.0–90	B											0.95%	A'			10%	A	100%	60	H		
Hand-washing: powder	0.14–2.57	B					0.1–1%	B		D	1980	C					0.01	A			100%	60	H	0.007	B
Hand-washing: liquid laundry and fabric	0.26–1.43	B					0.1–1%	B		D	1980	C					0.01	A			100%	60	H	0.007	B
Pretreatment (powder paste)	1.00	E					50–60%	B		D	840	H					0.01	A			100%	60	H	0.007	B
Pretreatment (liquid neat)	1.00	E					100%	M		D	840	H					0.01	A			100%	60	H	0.007	B
Dishwashing liquids-hand wash (hands)	0.14	G							0.9	G	1680	G					0.01	A			100%	60	H	0.00035	E
Dishwashing liquids-hand wash (dishes)	0.43–3.0	B	3.0–28	B, H			0.1–0.9 %	I	0.001–0.009	D	1980	C					0.01	A			100%	60	H	0.007 -0.03	B
APC liquid	0.14–1	B	30–110	B				B'		D	1980	C					0.01	A			100%	60	H	0.007–0.014	B
APC powder	0.14–1	B	20–40	B				B'		D	1980	C					0.01	A			100%	60	H	0.007–0.014	B
APC spray (neat) diluted	0.14–1	B	5.0–30	B				B'		D	1980	C					0.01	A			100%	60	H	0.0014–0.007	B
APC gel (neat) diluted	0.14–1	B	20–40	B				B'		D	1980	C					0.01	A			100%	60	H	0.007–0.014	B
APC spray (neat) undiluted	0.14–1	B					100%	M	1	D	1980	C					0.01	A			100%	60	H	0.0014–0.007	B
APC gel (neat) undiluted	0.14–1	B					100%	M	1	D	1980	C					0.01	A			100%	60	H	0.007–0.014	B
Personal Care and Cosmetics																									
Shampoos	0.29–1	H, O	8.0–12	O, H, *, 1											0.5–1%	E, G					100%	60	H		
Hair conditioners	0.14–0.29	H	14	H											0.5–1%	E, G					100%	60	H		
Styling mousse	1.0–2.0	H	4.0–5.0	E, H											0.5–5%	E, G					100%	60	H		
Hair sprays–aerosol	2	O	5	O											0.5–10%	E, O					100%	60	H		
F&H liquid soap–hand	5.0–7.0	E	1.6	E											0.5%	E					100%	60	H		
F&H bar soap -hand (toilet soap)	6	O	0.8	O											10.0%	O					100%	60	H		
Liquid soap-body (shower gel)	1.07	O	5	O											10.0%	O					100%	60	H		
F&H bar soap –body	1	E	5.0–10	E											0.5%	E					100%	60	H		
F &H bar soap–face	1	E	0.27	E											0.5%	E					100%	60	H		
Body wash	1	E	9.2	E											0.5%	E					100%	60	H		
Bath foam/bubble bath	0.14–0.29	H	14–17	E											0.5%	E					100%	60	H		
Shaving lubricant	1	H	2	H											1%	E					100%	70	H		
Skin lotions and creams (body lotion)	0.71–2	O, H, *, 1	7.5–8	H, O											100%	O					100%	60	H		
Hand moisturizer	1.0–7.0	E	0.5–0.8	E											100%	K					100%	60	H		
Fragrance cream (including makeup and foundation)	0.29	O	5	O											100%	O					100%	60	H		
Facial moisturizer	1.0–2.0	E, O	0.8	O											100%	O					100%	60	H		
Antiperspirants–aerosols	1.0–3.0	H	0.5–3.0	E, H											100%	K					100%	60	H		
Antiperspirant -- roll-ons	1	O	0.5–1.0	O, E, *, 1											100%	O					100%	60	H		
Antiperspirant -- solid/bar	1	O	0.5–1.0	O, E, *, 1											100%	O					100%	60	H		
Lipstick	2.0–6.0	H	0.01	H											100%	K					100%	60	H		
Face/Eye Cosmetics	0.5–3	H	0.005–0.025	H											100%	K					100%	60	H		
Other–Makeup remover	1.0–2.0	H	0.5–2.5	H											5%	L					100%	60	H		
Baby Care Products																									
Baby shampoo					5	E									1%	G					100%	15	H		
Baby/Bath liquid	1	E	0.873	J							9000	E	0.097	E							100%	15	H		
Baby Lotions and creams	0.38–2	N	1.4–2	N, F											100%	K					100%	15	H		
Skin wipes																									
Fragrances																									
Fine fragrances -pour form	0.66–5	E	0.1–1.2	E											100%	K					100%	60	H		
Aftershave	0.66–1	E	0.65–1	E											100%	K					100%	70	H		
Eau de toilette (including perfume and aftershave)	1	O	0.75	O											100%	O					100%	60	H		

Appendix II-B-2: Data Ranges (Min-Max) of Dermal Exposure Parameters to Estimate Screening Exposures to Consumer Products – Europe (Cont'd)

(References, abbreviations and special notes are described in footnotes at end of table)

Abbreviations:	AIHC	American Industrial Health Council
	AISE	International Association for Soaps, Detergents and Maintenance Products
	APC	All purpose cleaners
	COLIPA	European Cosmetic, Toiletry, and Perfumery Association
	CTFA	Cosmetic, Toiletry and Fragrance Association
	D4	Octamethylcyclotetrasiloxane Exposure Assessment, K.S. Crump Group (1999)
	EFH	U.S. EPA's Exposure Factors Handbook, 1997
	F&H	Face and Hand
	HERA	Human & Environmental Risk Assessments (subcommittee within AISE)
	TGD	EU Technical Guidance Document
References:	A	AISE HERA RA Sodium Aluminum Silicate
	A'	AISE HERA RA Sodium Aluminum Silicate where PR = (PD x FD1) / WI x CA; Product deposition (5%); FD1 = fabric density (10mg/cm^2); WI = total wash weight (1kg); CA = body contact area (cm^2)
	B	AISE HERA Habits and Practices (developed by AISE within the HERA project in 2002)
	B'	AISE HERA Habits and Practices (diluted in 5L of water)
	C	AISE HERA Florescent Brightener FWA-5
	D	PC (%) was converted to PC (g/cm^3); where (X g product /100 g water) x (1g water / 1 cm^3 water)
	E	SDA internal data
	F	Based on SRTC comments on SDA Exposure Assessment Methodology April 2003 (no EU specific data)
	G	AIHC/D4, K.S. Crump Group (1999)
	H	EU TGD, 2003
	I	SIAR triethanolamine: dilute in 3000cm^3 water
	J	Derived based on CA x R/1000 (recommended by SDA-HPV consortium for consistency with adult dermal scenarios at Feb 2003 meeting)
	K	Leave on product; assumed 100%
	L	No available data
	M	Non-diluted products use 100% product concentration
	N	U.S. EPA, 1997 (EFH) (No EU specific data)
	O	COLIPA, 2002
	*	**Value other than maximum selected, see additional numbered notes below:**
	1	Selected value based COLIPA, 2002 data

Appendix II-B-3: Data Ranges (Min-Max) of Oral Exposure Parameters to Estimate Screening Exposures to Consumer Products – North America

(References, abbreviations and special notes are described in footnotes at end of table)

	Product Use Frequency [FQ]		Product Amount Used Per Use [A]		Product Use Conc. [C']		Product Retained [Ta']		Dish Area Contacting Food [Sa]		Fraction Ingested [FI]		Body Weight [BW]	
	(use/day)		(g/use)		(g/cm^3)		(ml/cm^2)		(cm^2)		(%)		(kg)	
Soaps and Detergents														
Dishwashing liquids – handwash (dishware deposition)			2.0–5.0	B	0.0004–0.001	B'	5.50E-05	C	697–5400	A			60	H
Personal Care and Cosmetics														
Toothpaste	0.67–4.0	G, *, 1	0.05–2.4	F, A, *, 2							3–40%	A, F, *, 3	15	H
Mouthwash (adult)	0.4–2	A	30	A							8.5%	A	60	H
Lipstick	1.0–4.0	G, *, 5	0–0.2	E, *, 4							100%	D	60	H
Food and Food Additives														
Foods														
Flavors														

Abbreviations:

AIHC	American Industrial Health Council
AISE	International Association for Soaps, Detergents and Maintenance Products
CTFA	Cosmetic, Toiletry and Fragrance Association
D4	Octamethylcyclotetrasiloxane Exposure Assessment prepared by K.S. Crump Group (1999)
EFH	U.S. EPA's Exposure Factors Handbook, 1997
HERA	Human & Environmental Risk Assessments (subcommittee within AISE)
TGD	EU Technical Guidance Document, 2003
SCCNFP	The Scientific Committee on Cosmetic Products and Non-food Products Intended for Consumers
SRTC	CTFA-Safety Regulatory Toxicology Subcommittee

References:

A	SDA internal data
B	AISE HERA-LAS
B'	AISE HERA-LAS: product amount per use divided by 5L (5000 cm^3) water
C	AISE HERA-LAS: amount of water on dishes after rinsing = 10% water left on non-rinsed dish x $5.5x10^{-4}$ ml/cm^2=$5.5x10^{-5}ml/cm^2$
D	No data; assumed 100%
E	Based on CTFA-SRTC comments and CTFA, 2002 survey data
F	SCCNFP: The Safety of Fluorine Compounds in Oral Hygiene Products for Children Under the Age of 6 Years (2003)
G	EFH
H	U.S. EPA, 1997 and 2001 (OPP Residential SOPs)

*** Selected value other than maximum; see additional notes below:**

1 Selected value at the 95th percentile of range
2 Selected 0.8 g/use value because it is the high end value from SCCNP and agrees with the 0.86 g/use (average) value presented in Barnhart, 1974
3 Selected 35% as an upper estimate based on Barnhart, 1974
4 Selected value at the 90th percentile of range
5 Selected value based on CTFA-SRTC comments and at the 90th percentile of CTFA 2002 survey data range

Appendix II-B-4: Data Ranges (Min-Max) of Oral Exposure Parameters to Estimate Screening Exposures to Consumer Products – Europe

(References, abbreviations and special notes are described in footnotes at end of table)

	Product Use Frequency [FQ]		Product Amount Used per Use [A]		Product Use Conc. [C']		Product Retained [Ta']		Dish Contacting Food [Sa]		Fraction Ingested [FI]		Body Weight [BW]	
	(use/day)		(g/use)		(g/cm^3)		(ml/cm^2)		(cm^2)		(%)		(kg)	
Soaps and Detergents														
Dishwashing liquids – handwash (dishware deposition)			2.0–5.0	C	0.0004–0.001	C**	5.50E-05	D	697–5400	A			60	F
Personal Care and Cosmetics														
Toothpaste	1.0–3.0	F, A	0.05–0.8	E							3–40%	A, E, *, 1	15	F
Mouthwash adult	1.0–5.0	F	10	F							8.5%	A	60	F
Lipstick	2.0–6.0	F	0.01	F							100%	B	60	F
Food and Food Additives														
Foods														
Flavors														

Abbreviations:

AIHC	American Industrial Health Council
AISE	International Association for Soaps, Detergents and Maintenance Products
D4	Octamethylcyclotetrasiloxane Exposure Assessment prepared by K.S. Crump Group (1999)
HERA	Human & Environmental Risk Assessments (subcommittee within AISE)
TGD	EU Technical Guidance Document, 2003
SCCNFP	The Scientific Committee on Cosmetic Products and Non-food Products Intended for Consumers

References:

A	SDA data
B	Assume 100%
C	AISE HERA-LAS:
C**	AISE HERA-LAS: product amount per use divided by 5 L (5000 cm^3) water
D	AISE HERA-LAS: amount of water on dishes after rinsing = 10% water left on non-rinsed dish x 5.5 x 10-4 ml/cm^2 = 5.5 x 10-5 ml/cm^2
E	SCCNFP: The Safety of Fluorine Compounds in Oral Hygiene Products for Children Under the Age of 6 Years (2003)
F	EU TGD, 2003

***Selected value other than maximum; see additional notes below:**

1 Selected 35% as an upper estimate based on Barnhart, 1974

Appendix II-B-5: Data Ranges (Min-Max) of Inhalation Exposure Parameters to Estimate Screening Exposures to Consumer Products – North America

(References, abbreviations and special notes are described in footnotes at end of table)

	Product Use Frequency [FQ]		Product Amount Used per Use [A]		Airspace Volume [V]		Respirable Product Conc. in Breathing Zone [RPC]		Inhalation Rate [IR]		Exposure Duration [ED]		Respirable Fraction [F]		Bioavailable Fraction [BA]		Body Weight [BW]	
	(use/day)		(g/use)		(m^3)		(mg/m^3)		(m^3/hr)		(hr)		(%)		(%)		(kg)	
Soaps and Detergents																		
Laundry detergent-powder	1	A	2.7E-07	A'									100%	A			60	G
Triggers spray cleaners	0.14–1	J, A					0.13–0.72	H	0.8	C	0.03–0.33	J, A			100%	A	60	G
Personal Care and Cosmetics																		
Hair spray (aerosol)	1–5.36	F, *, 1	0.05–14.08	F, *, 1	2	B			0.8	C	0.25	B	50%	A			60	G
Hair spray (pump)	1–4.22	F, *, 1	0–21.4	F, *, 1	2	B			0.8	C	0.25	B	50%	A			60	G
Antiperspirants – aerosols	0.8–2	C, D	0.52–2.2	C, A	2	B			0.8	C	0.78	D	25%	E			60	G
Fine fragrances	1–11.6	C, F, *, 2	0.1–5.08	F, *, 1	2	B			0.8	C	0.78	D	50%	A			60	G
Miscellaneous Products																		
Paints	0.003–1	C, *, 3	0.13–1612	C, *, 3	2	B			0.8	C	0.0003–5	C, *, 3	1%	I			60	G
Lubricants																		
Paper products and processing																		
Other – pharmaceuticals																		
Other – metal-working fluid																		

Abbreviations:
- AIHC American Industrial Health Council
- AISE International Association for Soaps, Detergents and Maintenance Products
- CTFA Cosmetic, Toiletry and Fragrance Association
- D4 Octamethylcyclotetrasiloxane Exposure Assessment, K.S. Crump Group (1999)
- EFH U.S. EPA's Exposure Factors Handbook, 1997
- HERA Human & Environmental Risk Assessments (subcommittee within AISE)
- SRTC CTFA's toxicology subcommittee
- TGD EU Technical Guidance Document, 2003

References:
- A SDA internal data
- A' AISE HERA LAS assessment: 0.27ug dust/scoop x 1 scoop/load
- B EU TGD, 2003
- C EFH
- D D4 assessment
- E SRTC Comments on the SDA HPV Exposure Assessment Methodology April, 2003
- F CTFA 2002
- G U.S. EPA, 1997 and 2001 (OPP Residential SOPs)
- H Battle, 1999
- I No available data
- J Table of Habit and Practices for consumer products in Western Europe, Developed by AISE within the HERA project in 2002

***Selected value other than maximum; see additional notes below:**

1 Selected value at the 90th percentile of range
2 Selected CTFA value is in the upper range of EFH data source
3 Selected mean value

Appendix II-B-6: Data Ranges (Min-Max) of Inhalation Exposure Parameters to Estimate Screening Exposures to Consumer Products – Europe

(References, abbreviations and special notes are described in footnotes at end of table)

	Product Use Frequency [FQ]		Product Amount Used per Use [A]		Airspace Volume [V]		Respirable Product Conc. in Breathing Zone [RPC]		Inhalation Rate [IR]		Exposure Duration [ED]		Bioavailable Fraction [BA]		Respirable Fraction [F]		Body Weight [BW]	
	(use/day)		(g/use)		(m^3)		(mg/m^3)		(m^3/hr)		(hr)		(%)		(%)		(kg)	
Soaps and Detergents																		
Laundry detergent – powder	1	D	2.7E-07	D'											100%	D	60	A
Trigger spray cleaners	0.14–1	B, D					0.13–0.72	H	0.8	A	0.03–0.33	B, D	100%	D			60	A
Personal Care and Cosmetics																		
air sprays – aerosol	2	G	5	G	2	A			0.8	A	0.25	A			50%	D	60	A
Antiperspirants – aerosols	1.0–3.0	A	0.5–3	D, A	2	A			0.8	A	0.78	C			50%	D	60	A
Fragrances																		
Fine fragrances	0.66–5	D, A	0.1–1.2	D, A	2	A			0.8	A	0.78	C			50%	D	60	A
Miscellaneous Products																		
Paints	0.012	A	0.13–1612	E, *, 1	2	A			0.8	A	0.0003–5	E, *, 1			1%	F	60	A
Lubricants																		
Paper products and processing																		
Other – pharmaceuticals																		
Other – metal-working fluid																		

Abbreviations:

AIHC	American Industrial Health Council
AISE	International Association for Soaps, Detergents and Maintenance Products
COLIPA	European Cosmetic, Toiletry, and Perfumery Association
D4	Octamethylcyclotetrasiloxane Exposure Assessment prepared by K.S. Crump Group (1999)
EFH	U.S. EPA's Exposure Factors Handbook, 1997
HERA	Human & Environmental Risk Assessments
TGD	EU Technical Guidance Document, 2003

References:

A	EU TGD, 2003
B	Table of Habit and Practices for consumer products in Western Europe, Developed by AISE within the HERA project in 2002
C	D4 assessment
D	SDA internal data
D'	AISE HERA LAS assessment; 0.27 ug dust/scoop x 1 scoop/load
E	EFH
F	No available data
G	COLIPA, 2002
H	Battle, 1999
*	**Selected value other than maximum; see additional notes below:**
1	Selected mean value

Appendix III

Case Studies

Appendix III

Case Studies

The OECD has adopted "formats" (or templates) for reporting use and exposure information for the HPV chemicals initiative. The OECD exposure information template provides a standardized way to summarize and present exposure data in much the same way as the OECD IUCLID template provides a standardized and accepted way to summarize and present physicochemical, environmental fate, and toxicological data for HPV chemicals. The template is presented as chapters covering general information, exposure modeling, and exposure monitoring.

SDA, APAG and CESIO participated in the OECD Use/Exposure Pilot Project. As part of this initiative, the OECD draft template procedure was applied to the two categories Amine Oxides (AO) and Long Chain aliphatic Alcohols (LCOH). These chemicals are surfactants, used as the primary cleaning agent in a variety of laundry and cleaning products. While the OECD reporting formats would be comparable, some additional effort would be required to provide relevant use and exposure estimates for other geographies (e.g., Europe or Japan) taking into account their production volumes, local habits and practices, and exposure models.

Herein is presented the resulting peer-reviewed human and environmental safety assessments for both AO and LCOH. The exposure and risk assessments followed the methods outlined in this book and serve here as examples of the implementation of the methods.

Appendix III-A

Amine Oxides (AO) - Human Health

Sanderson H, Counts JL, Stanton KL, Sedlak RI. 2006. Exposure and prioritization – human screening data and methods for high production volume chemicals in consumer products: amine oxides, a case study. Originally published in *Risk Analysis*, 26:1637–1657 (DOI: 10.1111/j.1539-6924.2006.00829.x); *Risk Analysis* is a journal of The Society for Risk Analysis. The definitive version is available at www.blackwell-synergy.com.

Exposure and Prioritization – Human Screening Data and Methods for High Production Volume (HPV) Chemicals in Consumer Products: Amine Oxides, a Case-Study

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1.0 Introduction

Consumer and personal care products may have multiple forms, uses and exposure scenarios. Their uses are often associated with a range of intended and unintended exposure routes (e.g. oral, dermal, and inhalation), frequencies and durations. Given the large number of products and possible associated consumer exposure scenarios to chemical ingredients, a priority setting process is needed to identify consumer product ingre-dients and use scenarios for which more detailed exposure and risk assessment may be needed to adequately characterize consumers' exposures and risks to product ingredients. This is especially important for the compounds with widespread use in industry, including in consumer and personal products. These compounds can be referred to as High Production Volume (HPV) chemicals. HPVs are receiving increasing regulatory attention due to lack of information and the chemical right-to-know initiative in the U.S.A (http://www.epa.gov/chemrtk/) (Hansson and Ruden, 2006). Screening-level exposure and risk assessments provide the basis for that process. Recommendations and/or requirements for further work due to concerns based on the hazard profile should also consider the findings of screening level exposure and/or risk assessments.

While several regulatory bodies have programs to assess "new chemicals," some are also focusing attention to existing chemicals, i.e., those recognized as being in commerce prior to a particular date. The Canadian Domestic Substances Lists (DSL) (http://www.ec.gc.ca/substances/ese/eng/dsl/pilpro.cfm) process relies heavily on exposure assessment of categorization and prioritization of compounds registered before 1986 (~23,000 compounds), and the European Registration Evaluation Authorization of Chemicals (REACH) (http://europa.eu.int/comm/environment/chemicals/reach.htm) program also will rely on exposure assess-ments for registration of compounds marketed before 1981 (~ 100,000 compounds).

The Organization for Economic Co-operation and Development (OECD) already has indicated approaches in relation to HPVs that can be used as a globally recognized methodology by contributing to development of regional and national HPV screening and prioritization procedures and generating initial data sets to those programs such as the U.S. EPA Challenge program, Canadian Domestic Substances List, OECD HPV pro-gram (OECD, 2003), and REACH. The OECD (2003) Screening Information Data Set (SIDS) program provides the following guidance with respect to characterization of potential human exposure to HPV chemicals (e.g., consumers exposure via consumer product ingredients): The human population for which there is a potential exposure to the chemical should be identified with specific consideration of occupational exposure, consumer exposure and indirect exposure via the environment. These considerations should be based on readily available general information on exposure, the use pattern, and physicochemical properties of the chemical. The concluding OECD recommendations based on the hazard information results in either a recommendation for further work (typically refined exposure assessment and/or risk assessment), or low priority for further work that member countries may consider (http://www.oecd.org/document/7/0,2340,en_2649_34379_1947463_1_1_1_1,00.html).

Consistent with these guidelines, exposure can be estimated for priority-setting purposes without the need for either monitoring or sophisticated modeling data. Rather, for screening and priority-setting purposes, conservative estimates of exposures can be based on the following: simple, first principle exposure equations that are regularly used in the scientific and regulatory communities; conservative assumptions

about exposure; and readily available information about the characteristics of the HPV chemical category, the consumer product type, and the nature of product use. Although the use of conservative assumptions would lead to over-estimation of exposure, the conservatism is appropriate for screening-level assessments that are purposely designed to avoid making false negative decisions (decisions that are based on exposure and risk estimates that are lower than their true levels; for example, decision not to conduct further tests because risk estimates were falsely estimated to be low).

The most significant limiting factor to accurate exposure screening and subsequent prioritization for further risk screening has been the lack of readily available specific use and exposure data as these data are generally considered competitively sensitive information by companies. This paper provides detailed use and exposure data that is based upon a consolidation of information shared by many consumer and personal product companies, and a proposed exposure screening methodology for evaluating potential chronic human exposures and risk from HPV chemicals due to their use in consumer products in North America (Canada and the United States) and the European Union (EU).

The Alliance for Chemical Awareness (ACA) suggested a screening level assessment as part of a framework for a stepwise approach for risk characterization that provides the opportunity, on an as-needed basis, to replace conservative exposure assumptions with more realistic data prior to deciding whether additional toxicology information should be generated or risk management actions need to be taken. By design, one only advances to the next step in the process if there is reason to believe that the refinement will likely result in a different decision about the priority for further work (such as more detailed exposure assessment or risk assessment) on the HPV chemical. The following are the key steps in the screening level process for human health endpoints as described in the ACA framework (ACA, 2002):

1. Identify the product type(s) where the HPV chemical is used, the concentration (%) of the HPV chemical in the product(s), the physical and chemical properties of the HPV chemical
2. Estimate, qualitatively or quantitatively, exposure to the HPV chemical for each product category, initially by using highly conservative assumptions about the circumstances of product(s) use.
3. Identify the relevant SIDS endpoint and a “no observed adverse effect level” (NOAEL) or a “lowest observed adverse effect level” (LOAEL) from animal toxicology or epidemiological studies
4. Determine, for each product category, whether or not the margin of exposure (MOE) to the HPV chemical is adequate.

In general, the risk screening methodology described in this paper mirrors the key steps identified in the ACA framework mentioned above. The described methodology addresses chronic non-cancer SIDS endpoints and is focused on a screening-level assessment (OECD, 2003). The scope of this risk screening methodology in this paper is limited to the exposure scenarios that fall within the intended/labeled use of products. The HPV category Amine Oxides (AO) is used as a case-study to illustrate the described stepwise methodology (AO SIDS Initial Assessment Report (SIAR), 2006).

Commercial AO are either alkyl dimethyl amine oxides or alkyl dihydroxyethyl amine oxides which contain 2 methyl groups or 2 hydroxyethyl groups, respectively, attached to the tertiary nitrogen. Alkyl chain lengths range from 8 to 20 with 12 and 14 being predominant. For the AO Category as a whole, current production is approximately 26,000 metric tonnes in the U.S., 16,000 tonnes in Europe and 6,800 tonnes in Japan (AO SIAR, 2006). Amine oxides are amphoteric surfactants used at active concentrations between 0.1 and 10% in consumer cleaning and personal care products, usually in conjunction with other surfactants. They function as foam stabilizers, thickeners and emollients, emulsifying and conditioning agents in liquid dishwashing and laundry detergents, liquid hard surface cleaners, shampoos, hair

conditioners, creams, moisturizers, bar soaps, cleansing and other personal care products (AO SIAR, 2006).

2.0 Methods

2.1 Exposure Screening

To facilitate the implementation of this risk screening methodology, a product exposure data matrix has been constructed for many categories of consumer products. Several first principle equations (models) are used to estimate consumer exposure. Although most are generic equations based on general parameters and maxi-mum or target values (maximum values refers to values in the upper percentile range of the distribution, i.e. above the 90th percentile; target refers to the value recommended on the product labels), some are based on chemical and scenario-specific parameters. Taken together, these equations provide for a conservative esti-mate of consumer exposure by a particular route. Appendix Table 1 provides an overview of the model equa-tions and parameters included in the appropriate screening level exposure assessment. The equations are standard international equations and conservative default assumptions as described in section 2.2 (SDA, 2005).

For a screening-level assessment, maximum exposure factors (e.g., maximum frequency of product use, longer duration of product use/contact, largest amount of product use per occasion) would be used. For transparency and comprehensiveness, the readily available ranges (minimum-maximum) of values for North America and the EU and associated references/documentation are also summarized in the Appendix Tables 2-4AB. Tables 2A, 3A, and 4A contain factors for North America (NA), and Tables 2B, 3B, and 4B contain factors for the EU. The data matrix provides use factors (e.g., frequency of use, duration of use, amount use per occasion) and equations used to estimate oral, inhalation, and dermal exposures directly resulting from use of the product for the key scenarios of each consumer product category. It is possible and appropriate to further refine the screening assessment based upon more relevant exposure parameters. The average or median values from the data range could be utilized in a refined analysis, when exposure conditions and hazard information are available to support such refinement. It should be noted that the exposure estimates are provided in terms of product types – not specific chemical substances. To estimate exposures to the ingredient, these exposures would be combined with formulation data. The presented data matrix does not account for indirect exposures (e.g., environmental, dietary or drinking water). Estimated exposures from all exposure routes are developed and integrated into the overall assessment.

In general, conservative exposure assessments for consumer and personal care products can be based on an adult female with a body weight of 60 kg. However, for products designed for a specific target population (e.g., children at 15 kg or adult men at 70 kg) the representative body weights for those populations are employed (SDA, 2005). Also, in those instances where a product may be used by multiple subgroups (e.g. both adults and children use toothpaste), a screening conservative assessment would consider the product exposures based on the subgroup resulting in the greatest exposure. For example, for the toothpaste ingestion scenario, the default sub-population is based on children (Beltran and Szpunar, 1998).

2.2 Data Sources and Collection Methodology for Exposure Parameters

The exposure equations and input values were extracted from a variety of sources, including governmental agency documents, product use surveys of consumer product manufacturers, in-house habits and practices data obtained from company product development studies, and the published literature. The sources of data were selected in the following order: 1) governmental documents written by regulatory authorities (e.g., U.S. EPA's *Exposure Factors Handbook (*1989-1997*)*, EU *Technical Guidance Document (*2003); 2) documents written for submission to regulatory authorities (e.g., AISE HERA risk assessments (www.heraproject.com), AIHC exposure initiative assessments (2000-2001); 3)

survey data collected by industry associations (i.e., CTFA and COLIPA cosmetic use surveys; AISE HERA Habits and Practices Survey for cleaning products; SDA member company data); and; 4) data found in the published literature (SDA, 2005).

Much of the data in the published literature have been captured in the source categories 1 and 2 described above. In most cases, data were found in source categories 1-3 and exhaustive searches of the published literature were limited to exposure parameters that were not found among these sources. Generally, the selection process followed the above hierarchy; however, there were some minor exceptions. For example, in some cases, such as the cosmetic use pattern parameters, data from association surveys (e.g., CTFA use survey for body lotion, hairspray, face cream, lipstick, perfume, and foundation) were selected over the data found in EPA's *Exposure Factors Handbook* (EFH). The EFH (EPA, 1997) refers to older CTFA data. Therefore, it was reasonable to select CTFA use data from a more recent survey (CTFA, 2000).

The ingredient concentration data presented in this document are based on an SDA survey of manufacturers, importers, processors, and formulators in 2001 regarding the use of HPV chemicals in soaps, detergents and related consumer, commercial, and industrial products for a number of different families of chemicals (aliphatic acids, aliphatic alcohols, amine oxides, anionic surfactants, glycerides, hydrotropes, linear alkylbenzene sulfonate/alkylbenzene sufonate (LAS/ABS), methyl esters, and triclocarban (TCC)). SDA conducted this survey to provide information on chemical production, uses, and exposures for these chemical families managed by SDA consortia in two regions; North America and the EU. The survey was administered in two parts.

The first part of the survey was directed toward collecting very general information about company activities for each of the listed chemicals; to determine if the surveyed companies were a manufacturer, importer, processor, or formulator of the respective chemicals and to determine focus areas for follow up surveys. The following definitions were used for the survey: Manufacturer or Importer: Those who produces the subject chemical, including importation and toll manufacturing, as a commodity or intermediate; Processor: Those who utilize the subject chemical in the production of derivatives or other intermediates, but not end-use products; Formulator: Those who utilize the subject chemical or intermediates derived from a subject chemical in formulation of end use products.

The second part of the survey involved collection of specific data and information on: chemical production and/or importation amounts; chemical use by product type; chemical releases to the environment; conditions under which potential worker exposures are mitigated with personal protective equipment and/or engineering controls; and chemical concentrations in formulated products.

The information collected from the survey was compiled to develop a minimum and maximum ingredient concentration (IC) for each product category. For conducting a screening-level assessment, the range of minimum to maximum IC for an entire group of HPV chemicals was generated for each product use category (SDA, 2005).

2.3 Risk Screening

A general approach to screening-level risk assessment is to develop exposure and risk estimates for the chemical or group of chemicals for each product category based on default maximum exposure (see Appendix Table 2-4AB) and conservative dose-response parameters. These screening-level risk estimates would represent reasonable worst-case estimates of exposure and risks for a given product. The following screening-level risk characterization algorithm (1) (SDA, 2005) is applied:

$$MOE = \frac{NOAEL}{PE \times IC} \quad (1)$$

where,

MOE = Margin of Exposure
NOAEL = No Observed Adverse Effect Level (the dose-response threshold)
PE = Product Exposure
IC = Ingredient Concentration

For screening purposes, when a range of reliable values are available, the most relevant NOAEL/LOAEL for non-cancer risks is the highest NOAEL below the lowest LOAEL.

Conceptually, [PE x IC] is the surrogate maximum exposure to the chemical substance, also called the screening-level chemical exposure. The PE component is an estimate of exposure to the consumer product ($mg_{product}$/kg/day) and the IC component is the concentration (%) of the chemical ingredient in that product. The PE estimates are based on screening exposure equations appropriate for the consumer product end use (see Appendix Table 1).

2.4 Amine Oxides Case-Study

The HPV category Amine Oxides (AO) can be used to illustrate the screening process (AO SIAR, 2006). Both European and North American exposure assessment equations were used and the most conservative results were reported. The Japanese product formulation and usage are comparable to those of the EU and North America. Table 1 shows the IC information collected on consumer products containing AO. In screening-level assessments, both the minimum and maximum IC values would be used to develop screening exposure estimates encompassing the range of ingredient concentrations.

Table1. Product Ingredient Concentration Data Matrix for AO

Product Type	AO Concentration range*
Dishwashing detergents (liquid)	0.1 – 10%
Hard surface cleaners (liquid spray)	0.05 – 5%
Hard surface cleaners (liquid)	0.5 – 5%
Laundry detergents (liquid)	1 – 5%
Hand/face soaps (bar)	0.1 – 5%
Shampoos	0.09 – 5%
Hair conditioners	0.6 – 0.7%
Hair styling tonic/gel	0.1 – 2%
Cleansing products	0.04 – 9%
Skin creams/moisturizers	0.2 – 0.6%
Aftershaves	0.5 – 1%
Home dry cleaning products	0.1 – 0.5%
Douches	1 – 2%
Face/eye foundations (liquid)	< 0.1 %
Hair coloring preparations	< 0.1 %
Permanent waves preparations	1 – 2%

* The product concentration ranges indicate AO concentration in the formulated products and do not take into account any dilution by the end user prior to or during use. Many products on the market in these categories do not contain AO and not all the products listed are available in both NA and EU www.sdahq.org/amineoxides.

The first stage of this assessment is to identify the product category or categories with the most significant exposure potential prior to consideration of the hazard data. In this assessment, the screening-level estimate of exposures (in mg_{AO}/kg BW/day) is based on product exposure (PE) x ingredient concentration

(IC). The output of this exposure assessment is a list of product exposure scenarios and their corresponding screening-level exposure estimates for the oral, dermal, and inhalation routes for each product category where AO is used. By sorting screening exposure estimates for each route (i.e. dermal, oral, and inhalation) from high to low, product exposure scenarios with the highest potential exposures to AO can be identified, as well as those that present negligible exposure.

Screening-level exposure to AO from consumer uses of products were estimated using this methodology. The default maximum product exposure estimates (PE) in North America and EU for AO were calculated using the information obtained from the survey as previously described and summarized in Appendix Table 2-4AB (SDA, 2005) in combination with the AO ICs. Appendix Table 1 includes a summary of the model equations used to derive the exposure estimates. The exposure estimates of this screening level assessment are shown in Table 2.

Table 2. AO Aggregate Screening-Level Exposures to AO by Product Category

Product Exposure Scenarios	***Screening-Level Exposure Estimates (mg AO/kg BW/day)***	
	Dermal (Minimum to Maximum)	**Inhalation (Minimum to Maximum)**
Cleaning Products (direct exposure)		
Laundry pre-treatment (undiluted)	1.0E-3 to 5.0E-3	NA
Hard surface cleaner (undiluted)	1.0E-4 to 5.0E-3	NA
Hand wash laundry (diluted)	4.7E-5 to 2.3E-4	NA
Hand wash dishes (liquid dish detergent – diluted)	9.0E-6 to 9.0E-4	NA
Hand wash hands (liquid – diluted)	3.0E-6 to 3.0E-4	NA
Hard surface cleaner (diluted)	9.4E-6 to 4.7E-4	NA
Hard surface cleaner (liquid (spray cleaner))	NA	1.6E-6 to 8.2E-5
Laundry product (residual on clothing)		
Liquid detergent	2.0E-3 to 1.0E-2	NA
Personal Care product (residual after use)		
Hair conditioner	4.1E-3 to 4.7E-3	NA
Shampoo	2.5E-3 to 1.4E-1	NA
Bar soap – hand	3.6E-4 to 1.8E-2	NA
Cleansing products	2.3E-4 to 5.1E-2	NA
Bar soap – face	4.5E-5 to 2.2E-3	NA
Personal Care product (leave on materials)		
Body moisturizer	1.1 to 3.2	NA
Aftershave	7.0E-2 to 1.4E-1	NA
Hair styling tonic/gel	4.7E-3 to 9.3E-2	NA

Screening-level exposure estimates for the various product exposure scenarios could be aggregated within each product category. This aggregation by product category could be simply based on adding the scenario exposures within a product category. An example would be in the case of AO, to add the screening estimates from the three modeled scenarios; hand-washing laundry, laundry pre-treatment, and residual laundry product on clothing to estimate the aggregate exposure for the liquid detergent product category.

Table 3 provides a summary of the screening exposure estimates for various product categories based on aggregation within a product category. For AO, inhalation does not contribute significantly to the overall exposure (vapor pressure = 2.6 E-7 to 4.6 E-5 Pa), and since AO is not present in products intended to be

eaten (oral exposure), dermal is the principle exposure route. As indicated in Table 3, at maximum screening exposure level, for a particular exposure, body moisturizer, hair care products (hair conditioner, shampoo, styling tonic/gel) and aftershave are the primary drivers of the exposure, with exposures from all other product categories being one to three orders of magnitude lower.

Table 3. Dermal Exposures to AO by Product Category

Product Category	Estimated Dermal Exposure (mg AO/kg BW/day)
	Minimum to Maximum
Body Moisturizer	1.1 to 3.2
Hair Care	1.1E-2 to 2.4E-1
Aftershave	7.0E-2 to 1.4E-1
Laundry Detergent – liquid	3.0E-3 to 1.5E-2
Bar Soap	4.1E-4 to 2.0E-2
Cleansing Products	2.3E-4 to 5.1E-2
Dish Detergent – liquid	1.2E-5 to 1.2E-3
Hard Surface Cleaner – liquid	1.1E-4 to 5.5E-3

An estimate of total aggregate exposures can be obtained by adding the exposures from all the individual products. In the case of AO, the use of all of consumer products by a single consumer is plausible since there are no duplicate product types within a category. If there were duplicate types of product (e.g., both liquid and granule laundry detergents), as a conservative approach, the product resulting in the higher exposure would be used. However, it could be reasonable to assume that consumers using aftershave (men) would be less likely to use body moisturizers and cleansing products (primarily women). However, adding these exposures with other uses would be appropriate for an initial conservative screening approach. In the case of AO, which has fairly widespread uses across household cleaning and personal care categories, the simple addition of multiple exposures did not change the order of magnitude of the total exposure. In fact, the total aggregate exposure estimate is not significantly different from the exposures estimated for three product categories (body moisturizers, hair care and aftershave) since the use of these three products contribute 80-85% of the total aggregate exposure.

2.4.1 AO Screening Risk Characterization

Using the screening aggregate exposure estimate for different product category and screening total aggregate exposure estimate for all relevant product category combinations, as previously described, screening MOE's for each product category can be developed. For each product category, a number of screening-level MOEs can be developed for all possible routes of exposure (dermal, oral, inhalation.).

Table 4 provides the screening level MOEs for various products with AO as an ingredient. AO exposure estimates for various product exposure scenarios described in the Table 3 were compared to the most relevant reported NOAEL of 80 mg/kg BW/day (AO SIAR, 2006) to develop the MOEs.

Table 4. Screening-Level MOEs from AO Exposures by Product Category

Product Type	MOE*	
	Maximum	Minimum
Body Moisturizer	363	41.6
Aftershave	1,109	570
Hair Care	7,268	332
Laundry Detergent – liquid	26,650	5,329
Bar Soap	195,005	3,997
Cleansing Products	347,617	1,567
Hard Surface Cleaner – liquid	726,836	14,537
Dish Detergent – liquid	6,662,666	66,626

* NOAEL = 80 mg/kg BW/day

In conclusion, amine oxides (AO) in consumer cleaning and personal care products may be used as is, or diluted prior to or during use. Dermal contact, during or after product use, is expected with these products. There is potential for incidental or accidental ingestion or eye contact with products during handling and use, however, these would be acute exposures and are not addressed in the scope of the screening level evaluation presented in this paper. Exposure to formulated consumer products is mitigated by following use and precaution instructions on product labels. Product labels reflect the hazard potential of the summation of the chemical ingredients in the product.

These product labels may also include first aid instructions accompanying each hazard warning. For example, products may include eye and skin irritancy warnings along with instructions to rinse thoroughly if dermal or other exposure occurs. Human exposure will be mitigated by the fact that residues from many of these products are washed or rinsed off. Dermal exposure modeling for use of products containing amine oxide estimates exposures ranging from 0.000009 to 1.4 mg/kg/day, based on an assumption of 100% absorption. This is an overestimate of exposure as actual dermal absorption of AO is < 1% of product (Rice, 1977). Inhalation modeling of trigger-spray products provides an estimated exposure of 0.000016 to 0.00032 mg/kg/day. For a particular exposure, body moisturizer, hair care products and aftershave (all 'leave on materials') are the primary exposure drivers for AO, and the resulting MOEs for AO ranges from 42 (maximum exposure via body moisturizer) to 6,662,666 (minimum exposure via liquid dish detergent).

3.0 Discussion

The main purpose of developing screening-level aggregate exposure for the relevant combination of product uses is to identify product-exposure scenarios that are the drivers for total exposures and that may warrant more detailed and refined exposure assessments. Taking this a step further, comparing screening-level aggregate exposure to the default lowest NOAEL from the hazard dataset of an entire HPV chemical category to characterize risks (i.e., MOEs), would amount to a cumulative risk assessment, with an explicit conservative assumption that there is equivalent toxicity (lowest NOAEL) for all chemicals within a HPV category. Chemicals in the HPV program can, and should when possible, be grouped into categories based upon similar physico-chemical and toxicological properties to facilitate their assessment and avoid unnecessary testing (http://www.oecd.org/dataoecd/20/62/30029029.pdf). Clearly, this is not the case. However, if one uses this conservative approach and the resulting MOE is acceptable or adequate, then a conclusion of "low concern and no further work needed" for the use of the entire HPV chemical category in consumer products could be made with confidence. On the other hand, if this "low concern" conclusion cannot be made, refined assessments for the product uses that were identified as either exposure or hazards drivers could be carried out using more chemical specific information. Application of a category approach would also require additional consideration of refinements such as the probability of co-occurrence of category constituents in a given consumer product (in which case the maximum exposure concentration could be adjusted).

Similar to most screening-level assessment methodologies, the methodology described above is purposely designed to prevent false negative decisions by making the worst-case assumptions about toxicity and exposure, including default assumptions of maximum product exposure estimates, ingredient concentration ranges for the group applied to all product types irrespective of the actual chemical concentration, and the use of the most relevant NOAEL. As such, this warrants a high level of confidence in the recommendation of product types and use scenarios, and/or combination thereof for chemical categories that is of "low concern and no further work is needed" based on this screening level assessment. Conversely, using this screening methodology would lead to the high likelihood for false positives, in this context, screening estimates of exposures and risks are higher than their true estimates. Thus, refinements of exposures and risks for the product-use scenarios that have been considered of "potential concern" would be necessary.

Conservative exposure factors were selected as defaults to yield maximum initial exposure estimates in this screening methodology. Combinations of average and maximum values for exposure model input parameters (e.g., frequency of product use, amount of product use, product retention factors) could be used to develop more realistic maximum exposure estimates rather than those based on combination of worst-case values assumed in this screening methodology (U.S. EPA, 1992). Some example approaches to further refine screening exposure estimates could include:

1) Refining the dermal penetration default value, e.g. actual dermal penetration information on the chemical of interest or via the DERMWIN model in the EPI Suite provided by the U.S. EPA (http://www.epa.gov/oppt/exposure/docs/episuite.htm). The SkinPerm model also represents a refinement model (http://home.wxs.nl/~wtberge/skinperm.html). If dermal exposure is modified and dermal exposure is being compared to an oral toxicity study NOAEL, actual oral absorption of the chemical must also be taken into consideration when determining the MOE. An example of this is the HERA alkyl ethoxy sulfates assessment (HERA, 2003).

2) Refining skin surface area estimates. For skin creams and other consumer products that are applied to the skin, the specific habits and practices data for these products can be used to refine exposure. For example, with skin creams total body application is assumed in this assessment. However, if the HPV chemical of interest is only used in a facial cream, this surface area is not appropriate. Refinement from total body surface area to just facial surface area would significantly reduce exposure estimates.

3) Refinements to the frequency and/or duration of product use based on more detailed product category information can provide more realistic estimates. For example, if a skin cream is only to be used at night and washed off in the morning then assuming a 24 hr exposure is not appropriate.

4) Re-assessment of actual chemical concentration used in the product form to ensure an accurate representation is being made. As well as assessment of the ingredients specific presence in different product types within a product category and between the categories.

As mentioned, the purpose of the screening exposure assessment and screening risk characterization is to identify any products and use scenarios of potential concern. For each consumer product there may be a large number of possible exposure scenarios. However, there are usually only one or a few scenarios that are relevant in contributing the dominant exposure for each product. By comparison, the others are insignificant in the assessment of most chemicals since they do not contribute appreciably to estimated exposures and risks. For example, previous assessments have shown that human exposure to household cleaning product ingredients is very low for a number of product scenarios in which ingredients of interest comprise up to 30% of the product (www.heraproject.com). For their use in one category of products, such as household cleaning products, ingredients such as soap, LAS and alkyl sulfates produce aggregate exposures of less than 6 micrograms per kg body weight per day (<6 μg/kg BW/day) (www.heraproject.com). Dermal exposures during hand dishwashing, household surface cleaning and from detergent residue on laundered clothes, and inhalation exposure to laundry powder dust and aerosol cleaning products contribute less than one-third of the total household cleaning product exposure (<2 μg/kg BW/day). Dermal exposure during hand laundering and laundry pretreatment and ingestion of detergent residue on dinnerware contributes to the remainder (<4 μg/kg BW/day) (www.heraproject.com). In general, these minor scenario uses do not need to be included in the screening level exposure assessment when exposures due to other uses are expected to greatly exceed exposures due to these uses and when the MOE is expected to be very large.

4.0 Conclusions

Use and exposure data have been compiled and provided for HPV ingredients in consumer products allowing exposure screening. Indeed the general equations and habits and practices data can be reapplied

to any chemical of interest in these product types, as long as estimates of IC could be developed. As stated in the general approach section of this document, this risk screening methodology is based on default maximum product exposure estimates and conservative dose-response data (i.e. the most relevant NOAEL and route-specific data when available), with the option to refine the assessment. The main purpose of this methodology is to serve as a priority-setting tool. The screening exposure and risk characterization outputs from the application of this methodology can help focus resources to develop more refined risk assessments where such refinement is needed, and assist in deciding where exposures/risks are of minimal concerns and refined assessment is not warranted. In deterministic screening-level assessments as described in here, uncertainty, often in the form of conservative bias, can confound the ability to discretize or prioritize scenarios/product categories. Refinement to avoid this bias could include, where enough data is available and the data supports it, probalistic screening level calculations on an individual basis rather than on a population basis. Aggregate probabilistic analyses (where conditional probabilities such as the percentage of population using a given product, and other product use probabilities such as the month of year or day of week probabilities that reflect frequency of use, can be incorporated into a time series (calendar-based modeling). The probabilistic approach combined with exposure metric (e.g. daily, seasonal, annual, lifetime averages) relevant to the toxicological endpoints of interest and the effects underlying dose-response conditions (e.g. acute, sub-chronic, chronic, and time to effect if known) are potentially useful refinement approaches beyond the scope of screening.

Finally, we have demonstrated the methodology with Amine Oxides (AO) as a case-study, with resulting MOEs of 42 to 6,662,666 depending upon use scenario. Body moisturizer, hair care and aftershave were the primary exposure drivers and liquid dish detergent was the minimum exposure route.

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APPENDIX TABLES:

Appendix Table 1 presents the summary of Model Equations used to calculate the product Exposure (PE).

Appendix Table 1: Summary of Model Equations Used to Calculate Product Exposure (PE)

Exposure Route	Product Exposure Scenario	Product Exposure Model	Parameters
Dermal: Indirect	*Exposure after activity/use of:*		A: amount used (g/day)
	Laundry detergents: wearing clothing	**NA approach:**	PR: percent retained on clothing (%)
	Fabric conditioners: wearing clothing	$\frac{A \times PR \times PT \times CF \times DA}{BW}$	PT: percent transferred from clothing to skin
			CF: conversion factor (1000 mg/g)
		where:	BW: female body weight (60 kg)
		PR = 1% based on SDA data.	DA: dermal absorption (100%)
		EU approach:	
		$\frac{A \times PR \times PT \times CF \times DA}{BW}$	PD: percent deposition (%)
			FD: fabric density (mg/cm^2)
		where:	W: total wash weight (mg)
		PR = (PD x FD) / W) x CA	CA: body surface contact area (cm^2)
		and PD = Sw / Tw	Sw: Mass of water after spin cycle (kg)
			Tw: Mass of water per spin cycle (kg)
Dermal: Direct	*Exposure during the activity/use of: product*		FQ: frequency of use (use/day)
	Laundry detergent: hand-washing clothes	**NA and EU approach:**	CA: body surface contact area (cm^2)
	Laundry detergent: laundry pretreatment	$\frac{FQ \times CA \times PC \times FT \times CF \times TF \times DA}{BW}$	PC: product concentration (g/cm^3)
	Dish detergent: hand washing dishes		FT: film thickness on skin (cm)
	Dish detergent: washing hands		CF: conversion factor (1000 mg/g)
	Dilutable hard surface cleaners		TF: time scaling factor (unitless)
	Non-dilutable hard surface cleaners		BW: female bodyweight (60 kg)
	Dilutable all-purpose cleaners		DA: dermal absorption (100%)

Appendix Table 1: Summary of Model Equations Used to Calculate Product Exposure (PE) cont'd

Exposure Route	Product Exposure Scenario	Product Exposure Model	Parameters
Dermal: Direct	*Exposure after the activity/use (residual):* *Adult rinsed-off products:* Body washes Bath foam/bubble baths Hair conditioners Hair rinses Hand/body/face soaps Shaving cream Shampoos *Adult leave-on products:* Antiperspirants Aftershave Face/eye cosmetics Fragrances Facial cream Hand/body moisturizer Hair Spray Styling/tonic gel Styling mouse Sun cream/lotions *Baby care rinsed-off products:* Baby bath liquids Kid Shampoos *Baby care leave-on products:* Baby lotion and cream	**NA and EU approach:** $\frac{FQ \times A \times PR \times CF \times DA}{BW}$	FQ: frequency of use (use/day) A: amount used (g/use) PR: percent retained (%) CF: conversion factor (1000 mg/g) DA: dermal absorption (100%) BW: female bodyweight (60 kg) male bodyweight (70kg) (shaving products) child bodyweight (15 kg) (baby care products)

Appendix Table 1: Summary of Model Equations Used to Calculate Product Exposure (PE) cont'd

Exposure Route	Product Exposure Scenario	Product Exposure Model	Parameters
Oral: Indirect	*Exposure after activity/use:* Dish detergents (hand washed)	**NA and EU approach:** $\frac{C' \times Ta' \times Sa \times CF}{BW}$	C': product concentration (mg/cm^3) Ta': amount of water on dish after rinse (ml/cm^2) Sa: area of dish contacting food (cm^2/day) CF: conversion factor (1 cm^3 water/ 1 ml water) BW: female bodyweight (60 kg)
Oral: Direct	*Exposure during activity/use:* Mouthwash Lipstick Toothpaste Food additives Over the counter (OTC) pharmaceuticals	**NA and EU approach (except additives and OTC medicine):** $\frac{FQ \times A \times FI \times CF}{BW}$ **NA and EU approach (additives and OTC pharmaceuticals only):** $\frac{FI \times C}{BW}$	FQ: frequency (use/day) A: amount used (g/day) FI: fraction ingested (%) CF: conversion factor (1000 mg/g) BW: female bodyweight (60 kg) child bodyweight (15kg) (toothpaste) C: food consumption of pharmacological dose Note: FI and C will vary by food types. Default screening values have not been established.
Exposure Route		Product Exposure Model	Parameters
Inhalation: Direct	*Exposure during activity/use:* Hairspray Antiperspirants–aerosols Fragrances Paints	**NA and EU approach:** $\frac{FQ \times A \times IR \times ED \times F \times CF}{V \times BW}$	FQ: frequency (use/day) A: amount used (g/use) IR: inhalation rate (m^3/hr) ED: exposure duration (hr/day) F: respirable fraction (%) CF: conversion factor (1000 mg/g) V: effective breathing air space (2 m^3); (Note: this value is not appropriate for paints) BW: female body weight (60 kg)
	Exposure during activity/use: Laundry Detergent - powders	NA and EU approach: $\frac{FQ \times A \times F}{BW}$	FQ: frequency (use/day) A: amount used (g/use); (Note: A is the amount of dust/scoop x 1 scoop/use) F: respirable fraction (%) BW: female body weight (60 kg)
	Exposure during activity/use: Trigger Spray Cleaners	**NA and EU approach:** $\frac{FQ \times RPC \times IR \times ED \times BA}{BW}$	FQ: frequency (use/day) RPC: respirable product concentration in breathing zone (mg/ m^3) IR: inhalation rate (m^3/hr) ED: exposure duration (hr/day) BA: bioavailability fraction (100%) BW: female body weight (60 kg)

Appendix Tables

2-4AB present ranges of product use factors. The range for each product category includes the minimum and maximum (min-max) values identified in various sources. In some cases, the minimum and maximum values came from two different sources. The associated sources for these values are identified in the footnotes. It should be noted that although there are several sources of data for a particular value, only the sources that contain the minimum and maximum are reported in the footnotes to each Table. Tables 2A and 2B present ranges of product use factors used for dermal exposure estimation, 3A and 3B oral, and 4A and 4B inhalation exposure estimation.

Appendix Table 2A: Data Ranges (Min-Max) of Dermal Exposure Parameters to Estimate Screening Exposures to Consumer Products – North America

(References, abbreviations and special notes are indicated in grey columns and described in footnotes at end of table)

	Product Use Frequency [FQ]		Product Amount Used per Use [A]		Product Amount Used per Day [A']		Product Use Conc.		Product Use Conc. [PC]		Contact Area [CA]		Product Retained [R]		Film Thickness [FT]	Product Retained [PR]		Percent Transfer [PT]		Dermal Absorption [DA]	Body Weight [BW]		Scaling: Duration of Exposure [TF]	
	(use/day)		(g/use)		(g/day)		(%)		(g /cm^3)		(cm²)		(mg/cm²)		(cm) (E)	(%)		(%)		(%)	(kg)			
Soaps and Detergents																								
Laundry detergent – wearing clothes			76 - 121	A												0.1 - 1%	A	1%	A	100%	60	F		
Laundry detergent (tablets) – wearing clothes			45 - 135	G												0.1 - 1%	A	1%	A	100%	60	F		
Fabric conditioners, rinse added – wearing clothes			56 - 112	A												0.1 - 1%	A	1%	A	100%	60	F		
Fabric conditioners, dryer sheets – wearing clothes			3	A												10.00%	A	1%	A	100%	60	F		
Laundry detergent/fabric conditioner handwash	1	A					0.1 - 1%	A	0.001 - .01	A'	1680	C			0.0024					100%	60	F	0.007	G
Laundry detergent pretreatment (powder paste)	1	A					50 - 60%	G	0.5 - 0.6	A'	360	H			0.0024					100%	60	F	0.007	G
Laundry detergent pretreatment (liquid neat/non-dilutable)	1	A					100%	Q	1.0	A'	360	H			0.0024					100%	60	F	0.003 - 0.007	G
Dishwashing liquids – handwash (hands)	0.1 - 0.14	E							0.9	E	1680	C			0.0024					100%	60	F	0.00035	A
Dishwashing liquids –handwash (dishes)	1.0 - 3.0	A - E					0.03 - 0.15%	A	0.0003 - 0.0015	A'	1680	C			0.0024					100%	60	F	0.007 - 0.03	G
Hard surface cleaner – powder	0.14 - 1	A	20 - 51	A			0.4 - 1%	P	0.004 - 0.01	A'	1680	C			0.0024			100%	N	100%	60	F	0.007 - 0.014	G
APC liquid	0.14 - 1	A	41 - 76	A			0.8 - 1.5%	P	0.008 - 0.015	A'	1680	C			0.0024			100%	N	100%	60	F	0.007 - 0.014	G
APC gel (neat/non-dilutable)	0.14 - 1	G					100%	Q	1.0	A'	180	D			0.0024			100%	N	100%	60	F	0.007 - 0.014	G
APC spray (neat/non-dilutable)	0.14 - 1	G					100%	Q	1.0	A'	180	D			0.0024			100%	N	100%	60	F	0.0014 - 0.014	G, A
Personal Care and Cosmetics																								
Shampoos	0.48 - 1	B	5 - 16.4	E, B												0.5 - 1%	A, K			100%	60	F		
Hair rinses	0.064 - 1	B	7 - 12.7	A, B												0.5 - 1%	A, K			100%	60	F		
Styling tonic/gel	0.5 - 1	A	1.5 - 5.6	A, K												0.5 - 5%	A, K			100%	60	F		
Hair sprays – aerosol	1 - 5.36	*, J, 1	0.05 -14.08	*, J, 1												0.5 - 5%	A, K			100%	60	F		
Hair spray (pump)	1 - 4.22	*, J, 1	0 - 21.4	*, J, 1												0.5 - 5%	A, K			100%	60	F		
F&H liquid soap – hand	5.0 - 8.0	A	1.6 - 1.7	A												0.5 - 1%	A, N			100%	60	F		
F&H Bar Soap – Hand	1.0 - 6.0	A	0.36	A												0.5 - 1%	A, N			100%	60	F		
Liquid Soap – Body	0.088 - 0.57	B	11.8	B*, 2												0.5 - 1%	A, N			100%	60	F		
F&H Bar Soap – Body	0.95 - 3	B	2.6 - 8.6	B, A												0.5 - 1%	A, N			100%	60	F		
Cleansing products	0.54 - 2	B	1.7	B*, 2												0.5 - 1%	A, N			100%	60	F		
Body Wash	1	A	8.0 - 12.0	A												0.5 - 1%	A, N			100%	60	F		
Bath Foam/Bubble Bath	0.14 - 0.29	M	14 - 17	A												0.5 - 1%	A, N			100%	60	F		
F &H Bar Soap – Face	1.00	A	0.27	A												0.5 - 1%	A, N			100%	60	F		
Shave Cream	0.3 - 1	A	1.0 - 9.0	*, N, 3												1%	A			100%	70	F		
Body moisturizer					0.05–36.3	*, J, 1										100%	L			100%	60	F		
Antiperspirants – roll-ons	0.8 - 2.0	B*, 6	0.52 - 1.22	B, K												100%	L			100%	70	F		
Antiperspirant aerosols	0.8 - 2.0	B*, 6	0.52 - 2.2	B, A,												75%	N			100%	60	F		
Antiperspirant solid/bar	0.8–2.0	B*, 6	0.5 - 1.2	A												100%	L			100%	60	F		
Lipstick	1.0 - 4.0	B, 5	0 - 0.2	*, J, 1												100%	L			100%	60	F		
Face/eye cosmetics foundation liquid	1.0 - 2.0	J	0 - 2.65	*, J, 1												100%	L			100%	60	F		
Other – Makeup remover	1.0 - 2.0	M	2.5	M												5%	I			100%	60	F		
Baby Care Products																								
Baby/Bath liquid	1	A	0.873	O							9000	A	0.097	A		100%				100%	15	F		
Baby Lotions and creams	0.38 - 2	B	1.4 - 2	B, N												100%	L			100%	15	F		
Kids shampoos	0.11 - 0.43	B	0.5 - 10	B, A												0.5 - 1%	A. K			100%	15	F		
Fragrances																								
Fine fragrances	1.0 - 11.6	B, J *, 4	0.1 - 5.08	*, J, 1												100%	L			100%	60	F		
Aftershave	0.66 - 1	A	0.65 - 1	A												100%	L			100%	70	F		

Abbreviations:	AIHC	American Industrial Health Council
	AISE	International Association for Soaps, Detergents and Maintenance Products
	APC	All purpose cleaners
	CTFA	Cosmetic, Toiletry and Fragrance Association (Loretz et al. 2005; 2006)
	D4	Octamethylcyclotetrasiloxane Exposure Assessment, K.S. Crump Group (1999)
	EFH	U.S. EPA's Exposure Factors Handbook, 1997
	F&H	Face and Hand
	HERA	Human & Environmental Risk Assessments (subcommittee within AISE)
	SRTC	CTFA-Safety Regulatory Toxicology Subcommittee (Loretz et al. 2005; 2006)
	TGD	EU Technical Guidance Document, 2003

References:	A	SDA Data
	A'	PC (%) was converted to PC (g/cm^3); where (X g product/ 100 g water) x (1g water/$1cm^3$ water)
	B	U.S. EPA, 1997 (EFH)
	C	AIHC alkyldimethylamine oxide assessment: hands and forearms
	D	EFH&SDA 2/03 and 4/03 resolutions -- one palm average females
	E	AIHC alkyldimethylamine oxide assessment: internal data
	F	U.S. EPA, 1997 and 2001 (OPP Residential SOPs)
	G	AISE/HERA, 2002 (Table of Habit and Practices for consumer products in Western Europe) (No NA-specific data identified)
	H	EFH: both palms (average female)-- SDA 2/03 resolution
	I	No available data
	J	CTFA, 2002
	K	AIHC/K.S. Crump Group, 1999 (D4 assessment)
	L	Leave-on product; assumed 100%
	M	EU TGD, 2003 (No NA specific data identified)
	N	Based on CTFA-SRTC comments on SDA Exposure Assessment Methodology April 2003
	O	Derived based on CA x R/1000
	P	PC (%) was calculated by assuming product will be diluted in 5 L of water; PC (%) = (X g/use) / (5L/use) x (1000g/L)
	Q	Non-diluted products use 100% product concentration
		***Value other than maximum selected; see additional numbered notes below:**
		1 Selected 90th percentile from data range
		2 Full data range not provided; only averages were available
		3 Selected reasonable average value as recommended by CTFA-SRTC
		4 Selected average value from CTFA 2002 which is in the upper range of data provided in EFH
		5 Selected value based on CTFA-STRC comment and at the 90th percentile of the CTFA 2002 survey data range (Loretz et al. 2005; 2006)
		6 Selected reasonable value based on outcome of discussions among SDA member companies

Appendix Table 2B: Data Ranges (Min-Max) of Dermal Exposure Parameters to Estimate Screening Exposures to Consumer Products – Europe

(References, abbreviations and special notes are indicated in grey columns and described in footnotes at end of table)

	Product Use Frequency [FQ]		Product Amount Used per Use [A]		Product Amount Used per Day [A']		Product Use Conc.		Product Use Conc. [PC]		Contact Area [CA]		Product Retained [R]		Product Retained [PR]		Film Thickness [FT]		Transfer to Skin [PT]		Dermal Absorption [DA]	Body Weight [BW]		Scaling: Duration of Exposure [TF]	
	(use/day)		(g/use)		(g/day)		(%)		(g/cm^3)		(cm^2)		(mg/cm^2)		(%)		(cm)		(%)		(%)	(kg)			
Soaps and Detergents																									
Laundry detergents – indirect: powder			55 - 290	B											0.95%	A'			10%	A	100%	60	H		
Laundry detergents – indirect: liquid			78 - 230	B											0.95%	A'			10%	A	100%	60	H		
Laundry detergent – indirect: tablet			45 - 135	B											0.95%	A'			10%	A	100%	60	H		
Fabric conditioners – indirect: liquid regular			50 - 140	B											0.95%	A'			10%	A	100%	60	H		
Fabric conditioners – indirect: liquid concentrate			11.0 - 90	B											0.95%	A'			10%	A	100%	60	H		
Hand-washing: powder	0.14 - 2.57	B					0.1 - 1%	B		D	1980	C					0.01	A			100%	60	H	0.007	B
Hand-washing: liquid laundry and fabric conditioners	0.26 - 1.43	B					0.1 - 1%	B		D	1980	C					0.01	A			100%	60	H	0.007	B
Pretreatment (powder paste)	1.00	E					50 - 60%	B		D	840	H					0.01	A			100%	60	H	0.007	B
Pretreatment (liquid neat)	1.00	E					100%	M		D	840	H					0.01	A			100%	60	H	0.007	B
Dishwashing liquids-hand wash (hands)	0.14	G							0.9	G	1680	G					0.01	A			100%	60	H	0.00035	E
Dishwashing liquids-hand wash (dishes)	0.43 - 3.0	B	3.0 - 28	B, H			0.1 - 0.9 %	I	0.001 - 0.009	D	1980	C					0.01	A			100%	60	H	0.007 -0.03	B
APC liquid	0.14 - 1	B	30 - 110	B				B'		D	1980	C					0.01	A			100%	60	H	0.007 - 0.014	B
APC powder	0.14 - 1	B	20 - 40	B				B'		D	1980	C					0.01	A			100%	60	H	0.007 - 0.014	B
APC spray (neat) diluted	0.14 - 1	B	5.0 - 30	B				B'		D	1980	C					0.01	A			100%	60	H	0.0014 - 0.007	B
APC gel (neat) diluted	0.14 - 1	B	20 - 40	B				B'		D	1980	C					0.01	A			100%	60	H	0.007 - 0.014	B
APC spray (neat) undiluted	0.14 - 1	B					100%	M	1	D	1980	C					0.01	A			100%	60	H	0.0014 - 0.007	B
APC gel (neat) undiluted	0.14 - 1	B					100%	M	1	D	1980	C					0.01	A			100%	60	H	0.007 - 0.014	B
Personal Care and Cosmetics																									
Shampoos	0.29 - 1	H, O	8.0 - 12	O, H, *, 1											0.5 - 1%	E, G					100%	60	H		
Hair conditioners	0.14 - 0.29	H	14	H											0.5 - 1%	E, G					100%	60	H		
Styling mousse	1.0 - 2.0	H	4.0 - 5.0	E, H											0.5 - 5%	E, G					100%	60	H		
Hair sprays – aerosol	2	O	5	O											0.5 - 10%	E, O					100%	60	H		
F&H liquid soap – hand	5.0 - 7.0	E	1.6	E											0.5%	E					100%	60	H		
F&H bar soap – hand (toilet soap)	6	O	0.8	O											10.0%	O					100%	60	H		
Liquid soap – body (shower gel)	1.07	O	5	O											10.0%	O					100%	60	H		
F&H bar soap – body	1	E	5.0 - 10	E											0.5%	E					100%	60	H		
F &H bar soap – face	1	E	0.27	E											0.5%	E					100%	60	H		
Body wash	1	E	9.2	E											0.5%	E					100%	60	H		
Bath foam/bubble bath	0.14 - 0.29	H	14 - 17	E											0.5%	E					100%	60	H		
Shaving lubricant	1	H	2	H											1%	E					100%	70	H		
Skin lotions and creams (body lotion)	0.71 - 2	O, H, *, 1	7.5 - 8	H, O											100%	O					100%	60	H		
Hand moisturizer	1.0 - 7.0	E	0.5 - 0.8	E											100%	K					100%	60	H		
Fragrance cream (including makeup and foundation)	0.29	O	5	O											100%	O					100%	60	H		
Facial moisturizer	1.0 - 2.0	E, O	0.8	O											100%	O					100%	60	H		
Antiperspirants – aerosols	1.0 - 3.0	H	0.5 - 3.0	E, H											100%	K					100%	60	H		
Antiperspirant – roll-ons	1	O	0.5 - 1.0	O, E, *, 1											100%	O					100%	60	H		
Antiperspirant – solid/bar	1	O	0.5 - 1.0	O, E, *, 1											100%	O					100%	60	H		
Lipstick	2.0 - 6.0	H	0.01	H											100%	K					100%	60	H		
Face/Eye Cosmetics	0.5 - 3	H	0.005 - 0.025	H											100%	K					100%	60	H		
Other – Makeup remover	1.0 - 2.0	H	0.5 - 2.5	H											5%	L					100%	60	H		
Baby Care Products																									
Baby shampoo					5	E									1%	G					100%	15	H		
Baby/Bath liquid	1	E	0.873	J							9000	E	0.097	E							100%	15	H		
Baby Lotions and creams	0.38 - 2	N	1.4 - 2	N, F											100%	K					100%	15	H		
Skin wipes																									
Fragrances																									
Fine fragrances -pour form	0.66 - 5	E	0.1 - 1.2	E											100%	K					100%	60	H		
Aftershave	0.66 - 1	E	0.65 - 1	E											100%	K					100%	70	H		
Eau de toilette (including perfume and aftershave)	1	O	0.75	O											100%	O					100%	60	H		

Abbreviations:	AIHC	American Industrial Health Council
	AISE	International Association for Soaps, Detergents and Maintenance Products
	APC	All purpose cleaners
	COLIPA	European Cosmetic, Toiletry, and Perfumery Association
	CTFA	Cosmetic, Toiletry and Fragrance Association (Loretz et al. 2005; 2006)
	D4	Octamethylcyclotetrasiloxane Exposure Assessment, K.S. Crump Group (1999)
	EFH	U.S. EPA's Exposure Factors Handbook, 1997
	F&H	Face and Hand
	HERA	Human & Environmental Risk Assessments (subcommittee within AISE)
	TGD	EU Technical Guidance Document

References:	A	AISE HERA RA Sodium Aluminum Silicate
	A'	AISE HERA RA Sodium Aluminum Silicate where PR = (PD x FD1) / WI x CA; Product deposition (5%); FD1 = fabric density (10mg/cm^2); WI = total wash weight (1kg); CA = body contact area (cm^2)
	B	AISE HERA Habits and Practices (developed by AISE within the HERA project in 2002)
	B'	AISE HERA Habits and Practices (diluted in 5L of water)
	C	AISE HERA Florescent Brightener FWA-5
	D	PC (%) was converted to PC (g/cm^3); where (X g product /100 g water) x (1g water / 1 cm^3 water)
	E	SDA internal data
	F	Based on SRTC comments on SDA Exposure Assessment Methodology April 2003 (no EU specific data)
	G	AIHC/D4, K.S. Crump Group (1999)
	H	EU TGD, 2003
	I	SIAR triethanolamine: dilute in 3000cm^3 water
	J	Derived based on CA x R/1000 (recommended by SDA-HPV consortium for consistency with adult dermal scenarios at Feb 2003 meeting)
	K	Leave on product; assumed 100%
	L	No available data
	M	Non-diluted products use 100% product concentration
	N	U.S. EPA, 1997 (EFH) (No EU specific data)
	O	COLIPA, 2002
		***Value other than maximum selected, see additional numbered notes below:**
		[1]Selected value based COLIPA, 2002 data

Appendix Table 3A: Data Ranges (Min-Max) of Oral Exposure Parameters to Estimate Screening Exposures to Consumer Products – North America

(References, abbreviations and special notes are indicated in grey columns and described in footnotes at end of table)

	Product Use Frequency [FQ]		Product Amount Used Per Use [A]		Product Use Conc. [C']		Product Retained [Ta']		Dish Area Contacting Food [Sa]		Fraction Ingested [FI]		Body Weight [BW]	
	(use/day)		(g/use)		(g/cm^3)		(ml/cm^2)		(cm^2)		(%)		(kg)	
Soaps and Detergents														
Dishwashing liquids – hand-wash (dishware deposition)			2.0 - 5.0	B	0.0004 - 0.001	B'	5.50E-05	C	697 - 5400	A			60	H
Personal Care and Cosmetics														
Toothpaste	0.67 - 4.0	G, *, 1	0.05 - 2.4	F, A, *, 2							3 - 40%	A, F, *, 3	15	H
Mouthwash (adult)	0.4 - 2	A	30	A							8.5%	A	60	H
Lipstick	1.0 - 4.0	G, *, 5	0 - 0.2	E, *, 4							100%	D	60	H

Abbreviations:	AIHC	American Industrial Health Council
	AISE	International Association for Soaps, Detergents and Maintenance Products
	CTFA	Cosmetic, Toiletry and Fragrance Association (Loretz et al. 2005; 2006)
	D4	Octamethylcyclotetrasiloxane Exposure Assessment prepared by K.S. Crump Group (1999)
	EFH	U.S. EPA's Exposure Factors Handbook, 1997
	HERA	Human & Environmental Risk Assessments (subcommittee within AISE)
	TGD	EU Technical Guidance Document, 2003
	SCCNFP	The Scientific Committee on Cosmetic Products and Non-food Products Intended for Consumers
	SRTC	CTFA-Safety Regulatory Toxicology Subcommittee

References:	A	SDA internal data
	B	AISE HERA-LAS
	B'	AISE HERA-LAS: product amount per use divided by 5L (5000 cm^3) water
	C	AISE HERA-LAS: amount of water on dishes after rinsing = 10% water left on non-rinsed dish x $5.5x10^{-4}$ ml/cm^2 = $5.5x10^{-5}ml/cm^2$
	D	No data; assumed 100%
	E	Based on CTFA-SRTC comments and CTFA, 2002 survey data (Loretz et al. 2005; 2006)
	F	SCCNFP: The Safety of Fluorine Compounds in Oral Hygiene Products for Children Under the Age of 6 Years (2003)
	G	EFH
	H	U.S. EPA, 1997 and 2001 (OPP Residential SOPs)
	*	**Selected value other than maximum; see additional notes below:**
	1	Selected value at the 95th percentile of range
	2	Selected 0.8 g/use value because it is the high end value from SCCNP and agrees with the 0.86 g/use (average) value presented in Barnhart, 1974
	3	Selected 35% as an upper estimate based on Barnhart, 1974
	4	Selected value at the 90th percentile of range
	5	Selected value based on CTFA-SRTC comments and at the 90th percentile of CTFA 2002 survey data range

Appendix Table 3B: Data Ranges (Min-Max) of Oral Exposure Parameters to Estimate Screening Exposures to Consumer Products – Europe

(References, abbreviations and special notes are indicated in grey columns and described in footnotes at end of table)

	Product Use Frequency [FQ]		Product Amount Used per Use [A]		Product Use Conc. [C']		Product Retained [Ta']		Dish Contacting Food [Sa]		Fraction Ingested [FI]		Body Weight [BW]	
	(use/day)		(g/use)		(g/cm^3)		(ml/cm^2)		(cm^2)		(%)		(kg)	
Soaps and Detergents														
Dishwashing liquids – hand-wash (dishware deposition)			2.0 - 5.0	C	0.0004 - 0.001	C**	5.50E-05	D	697 - 5400	A			60	F
Personal Care and Cosmetics														
Toothpaste	1.0 - 3.0	F, A	0.05 - 0.8	E							3 - 40%	A, E, *, 1	15	F
Mouthwash adult	1.0 - 5.0	F	10	F							8.5%	A	60	F
Lipstick	2.0 - 6.0	F	0.01	F							100%	B	60	F

Abbreviations:

AIHC	American Industrial Health Council
AISE	International Association for Soaps, Detergents and Maintenance Products
D4	Octamethylcyclotetrasiloxane Exposure Assessment prepared by K.S. Crump Group (1999)
HERA	Human & Environmental Risk Assessments (subcommittee within AISE)
TGD	EU Technical Guidance Document, 2003
SCCNFP	The Scientific Committee on Cosmetic Products and Non-food Products Intended for Consumers

References:

A	SDA internal data
B	Assume 100%
C	AISE HERA-LAS:
C**	AISE HERA-LAS: product amount per use divided by 5 L (5000 cm^3) water
D	AISE HERA-LAS: amount of water on dishes after rinsing = 10% water left on non-rinsed dish x 5.5 x 10-4 ml/cm^2 = 5.5 x 10-5 ml/cm^2
E	SCCNFP: The Safety of Fluorine Compounds in Oral Hygiene Products for Children Under the Age of 6 Years (2003)
F	EU TGD, 2003
*	**Selected value other than maximum; see additional notes below:**
1	Selected 35% as an upper estimate based on Barnhart, 1974

Appendix Table 4A: Data Ranges (Min-Max) of Inhalation Exposure Parameters to Estimate Screening Exposures to Consumer Products – North America

(References, abbreviations and special notes are indicated in grey columns and described in footnotes at end of table)

	Product Use Frequency [FQ]		Product Amount Used per Use [A]		Airspace Volume [V]		Respirable Product Conc. in Breathing Zone [RPC]		Inhalation Rate [IR]		Exposure Duration [ED]		Respirable Fraction [F]		Bioavailable Fraction [BA]		Body Weight [BW]	
	(use/day)		(g/use)		(m^3)		(mg/m^3)		(m^3/hr)		(hr)		(%)		(%)		(kg)	
Soaps and Detergents																		
Laundry detergent – powder	1	A	2.7E-07	A'									100%	A			60	G
Triggers spray cleaners	0.14 - 1	J, A					0.13 - 0.72	H	0.8	C	0.03 - 0.33	J, A			100%	A	60	G
Personal Care and Cosmetics																		
Hair spray (aerosol)	1 - 5.36	F, *, 1	0.05 - 14.08	F, *, 1	2	B			0.8	C	0.25	B	50%	A			60	G
Hair spray (pump)	1 - 4.22	F, *, 1	0 - 21.4	F, *, 1	2	B			0.8	C	0.25	B	50%	A			60	G
Antiperspirants – aerosols	0.8 - 2	C, D	0.52 - 2.2	C, A	2	B			0.8	C	0.78	D	25%	E			60	G
Fine fragrances	1 - 11.6	C, F, *, 2	0.1 - 5.08	F, *, 1	2	B			0.8	C	0.78	D	50%	A			60	G
Miscellaneous Products																		
Paints	0.003 - 1	C, *, 3	0.13 - 1612	C, *, 3	2	B			0.8	C	0.0003 - 5	C, *, 3	1%	I			60	G

Abbreviations:

AIHC	American Industrial Health Council
AISE	International Association for Soaps, Detergents and Maintenance Products
CTFA	Cosmetic, Toiletry and Fragrance Association (Loretz et al. 2005; 2006)
D4	Octamethylcyclotetrasiloxane Exposure Assessment, K.S. Crump Group (1999)
EFH	U.S. EPA's Exposure Factors Handbook, 1997
HERA	Human & Environmental Risk Assessments (subcommittee within AISE)
SRTC	CTFA's toxicology subcommittee
TGD	EU Technical Guidance Document, 2003

References:

A	SDA data
A'	AISE HERA LAS assessment: 0.27ug dust/scoop x 1 scoop/load
B	EU TGD, 2003
C	EFH
D	D4 assessment
E	SRTC Comments on the SDA HPV Exposure Assessment Methodology April, 2003
F	CTFA 2002 (Loretz et al. 2005; 2006)
G	U.S. EPA, 1997 and 2001 (OPP Residential SOPs)
H	Battle, 1999
I	No available data
J	Table of Habit and Practices for consumer products in Western Europe, Developed by AISE within the HERA project in 2002
*	**Selected value other than maximum; see additional notes below:**
1	Selected value at the 90th percentile of range
2	Selected CTFA value is in the upper range of EFH data source
3	Selected mean value

Appendix Table 4B: Data Ranges (Min-Max) of Inhalation Exposure Parameters to Estimate Screening Exposures to Consumer Products – Europe

(References, abbreviations and special notes are indicated in grey columns and described in footnotes at end of table)

	Product Use Frequency [FQ]		Product Amount Used per Use [A]		Airspace Volume [V]		Respirable Product Conc. in Breathing Zone [RPC]		Inhalation Rate [IR]		Exposure Duration [ED]		Bioavailable Fraction [BA]		Respirable Fraction [F]		Body Weight [BW]	
	(use/day)		(g/use)		(m^3)		(mg/m^3)		(m^3/hr)		(hr)		(%)		(%)		(kg)	
Soaps and Detergents																		
Laundry detergent – powder	1	D	2.7E-07	D'											100%	D	60	A
Trigger spray cleaners	0.14 - 1	B, D					0.13 - 0.72	H	0.8	A	0.03 - 0.33	B, D	100%	D			60	A
Personal Care and Cosmetics																		
air sprays – aerosol	2	G	5	G	2	A			0.8	A	0.25	A			50%	D	60	A
Antiperspirants – aerosols	1.0 - 3.0	A	0.5 - 3	D, A	2	A			0.8	A	0.78	C			50%	D	60	A
Fragrances																		
Fine fragrances	0.66 - 5	D, A	0.1 - 1.2	D, A	2	A			0.8	A	0.78	C			50%	D	60	A
Miscellaneous Products																		
Paints	0.012	A	0.13 - 1612	E, *, 1	2	A			0.8	A	0.0003 - 5	E, *, 1			1%	F	60	A

Abbreviations:

AIHC	American Industrial Health Council
AISE	International Association for Soaps, Detergents and Maintenance Products
COLIPA	European Cosmetic, Toiletry, and Perfumery Association
D4	Octamethylcyclotetrasiloxane Exposure Assessment prepared by K.S. Crump Group (1999)
EFH	U.S. EPA's Exposure Factors Handbook, 1997
HERA	Human & Environmental Risk Assessments
TGD	EU Technical Guidance Document, 2003

References:

A	EU TGD, 2003
B	Table of Habit and Practices for consumer products in W. Europe, Developed by AISE within the HERA project in 2002
C	D4 assessment
D	SDA internal data
D'	AISE HERA LAS assessment; 0.27 ug dust/scoop x 1 scoop/load
E	EFH
F	No available data
G	COLIPA, 2002
H	Battle, 1999
*	**Selected value other than maximum; see additional notes below:**
1	Selected mean value

Appendix III-B

Amine Oxides (AO) - Environmental Safety

Sanderson H, Tibazarwa C, Greggs W, Versteeg DJ, Kasai Y, Stanton K, Sedlak RI. 2009. High production volume chemical amine oxides [C8–C20] category environmental risk assessment. Originally published in *Risk Analysis,* 29:857–867 (DOI: 10.1111/j.1539-6924.2009.01208.x), *Risk Analysis* is a journal of The Society for Risk Analysis. The definitive version is available at www.blackwell-synergy.com.

High Production Volume Chemical Amine Oxides [C_8-C_{20}] Category Environmental Risk Assessment

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1. INTRODUCTION

Most High Production Volume (HPV) chemicals have been on the market for decades, but it has only been in the last 10 years or so that efforts have been made to develop comprehensive datasets on their physicochemi-cal and ecotoxicological properties and make them publicly available. In the absence of these publicly avail-able datasets, HPV chemicals are under increasing regulatory scrutiny globally. In 1990, member countries of the Organisation for Economic Co-operation and Development (OECD) decided to undertake the investi-gation of HPV chemicals in a co-operative way. These HPV chemicals include all chemicals reported to be produced or imported at levels greater than 1,000 tonnes per year in at least one member country or in the European Union region. The OECD HPV program proceeds under the agreement that member countries will: co-operatively select the chemicals to be investigated; collect, review and characterize effects and exposure information from government and public sources; encourage industry to provide information from their files; complete the agreed dossier for the Screening Information Data Set (SIDS); and make an initial assessment of the potential hazard of each chemical investigated. When a full SIDS dossier on a chemical is available, an initial assessment of the information is developed and conclusions are drawn on the potential hazard(s) and exposure information. Since 1999, the work in OECD has concentrated on data gathering, testing, and initial hazard assessment. Detailed exposure information gathering and assessment of risk is no longer re-quired as part of the SIDS initial assessment, but can be carried out in follow-up at the national (or regional) level, as appropriate. The global chemical industry, through the International Council of Chemical Associa-tions (ICCA), launched a global initiative on HPV chemicals in 1998 to accelerate progress on the OECD HPV program. The cost of generating data and the work to draft the assessments has been borne by industry - and shared, whenever possible, by companies in international consortia. Industry thus aims to ensure a sound scientific basis for any subsequent regional, national, or global risk assessments while ensuring re-source efficiency, especially on the need for animal testing (CEFIC, 2007).

This paper presents the relevant information provided to the OECD by the global industry Amine Oxide (AO) Consortium needed to perform an environmental risk assessment of AO. The Sponsor country presenting the amine oxides category to the OECD was the United States, with U.S. Environmental Protection Agency (EPA) as the lead government agency.

Surfactants known as amine oxides (AO) contain even numbered linear alkyl chains ranging from C_8 to C_{20}. AOs are amphoteric, as they change from net cationic to zwitterionics and nonionics going from low to high pH (Singh et al., 2006). AO are also known as fatty alkyl dimethyl amine oxides, they are usually produced by reacting alkyl dimethyl amines with hydrogen peroxide in water. AO have been known and studied for more than a century, but it wasn't until the 1960s that their utility in liquid household formulations was developed and globally commercialized (Singh et al. 2006). The amine oxides are produced and used either as single chain length substances (e.g., C_{12}) or as a mixture of different chain lengths (e.g., C_{12} to C_{18}) (Table I). The most common amine oxide in commerce is the alkyl dimethyl amine oxide, where the alkyl group contains 10 to 16 carbon atoms, predominately C_{12} and C_{14}, and the average chain length is $C_{12.9}$. The chemicals of the amine oxides category do not typically exist as 'pure' substances, but are produced and distributed as aqueous solutions, typically at a 25-35% AO level.

Impurities, such as hydrogen peroxide (trace levels) and free amine (<1%), may be present. The tonnages considered in the HPV assessment were as follows: 26,000 metric tonnes in the U.S.; 16,000 tonnes in Europe, and 6,800 tonnes in Japan (OECD, 2008). Amine oxides are typically used at active concentrations between 0.1 and 10% in consumer cleaning and personal care products, usually in conjunction with other surfactants. The majority of AO used in North America (95% of total volume) are used in household cleaning products including liquid dishwashing and laundry detergents and liquid hard surface cleaners. Much smaller volumes (<5%) are used in personal care (i.e., shampoos, hair conditioners, creams, moisturizers, bar soaps), and in industrial, institutional and commercial applications (Sanderson et al., 2006). They function in products as foam stabilizers, thickeners and emollients, emulsifying and conditioning agents.

The SIAR for the AO category was reviewed and approved by the OECD on April 2006, as a global hazard dataset. Due to the elimination of the risk assessment from the OECD HPV program in 1999, hazard data collected for the purposes of the program are not publicly presented in a risk context. The human exposure and risk estimates for the AO HPV category was published in *Risk Analysis* by Sanderson et al. (2006). Hence, this paper focuses on the environmental fate, effects and risk assessment of AO. The bulk of the data needed for this assessment are found in the category's SIDS Initial Assessment Report (SIAR) (OECD, 2008).

2. METHODS

2.1. Compounds

The justification for grouping the amine oxides (AO) into a category is based on their structural and functio-nal similarity (Table I). All of the substances in this category are surfactants, consisting of a polar "head" (the amine oxide) and a relatively inert, hydrophobic "tail" (the long alkyl substituent). The structural varia-tions in the category are three-fold: 1) the nature of the second and third substituents on the amine are either methyl groups or hydroxyethyl groups; 2) the long alkyl chain ranges in length from 8 to 20 carbons; and 3) the long alkyl chain may contain one or two double bonds (i.e. unsaturation) as in $C_{18:1}$ (oleyl) or $C_{18:2}$ (lino-leyl). Alkyl chain lengths range from 8 to 20 with 12 and 14 being predominant. Average chain lengths for these multi-component substances are 12.9 to 13.5, with the exception of one tallow-derived compound. The presence of methyl- vs. hydroxyethyl-substituents affects the basicity of the nitrogen only marginally, and the hydroxyethyl group lends more bulk to the hydrophilic head-group of the surfactant. The length of the longest alkyl substituent does not alter the chemical reactivity of the molecule, but does affect its physical properties. The influence of unsaturation in the alkyl chain (as in CAS Nos. 93962-62-0 (Ethanol, 2,2'-[(9Z)-9-octadecenyloxidoimino]bis-) and 61791-46-6 (Ethanol, 2,2'-iminobis-, N-tallow alkyl derivs., N-oxides)) is expected to make the molecule prone to reactions as typical for unsaturated fatty alkyl chains. Nevertheless, their overall chemical behavior fits within that of the group of $C_{8\text{-}20}$ alkyl dihydroxy ethyl amine oxides. Amine oxides molecular formula is: $CH_3{\cdot}(CH_2)_R{\cdot}N(CH_3)_2{:}O$, where R is 7-19. Commercial amine oxides are either alkyl dimethyl amine oxides or alkyl dihydroxyethyl amine oxides which contain 2 methyl groups or 2 hydroxyethyl groups, respectively, attached to the tertiary nitrogen.

The chemical behavior of amine oxides are expected to be very similar. Differences relate to the alkyl substituents, their nature (methyl, hydroxyethyl) and the number of carbon atoms in the alkyl chain. These structural variances impact the physical and chemical properties of these substances. The AO category is best represented by $C_{12\text{-}14}$, or by the average $C_{12.9}$, in terms of commercial use in the United States and, thus, these will be the focus of the potential environmental exposure and risk assessment presented in this paper. As indicated above, the U.S. tonnage considered in the HPV assessment was 26,000 metric tonnes. This tonnage is based on the U.S. EPAs Inventory Update Reporting (IUR) data and therefore covers 100% of the total tonnage in the country (OECD, 2008). Thus, a $C_{12.9}$ AO reflects an average chain length and the bulk (>95%) of the 26,000 metric tonnes of different AO mixtures in commercial use in the U.S.

Table I. Amine Oxides Category, CAS number and Alkyl Chain Length Distribution (%).

CAS No.	Chemical Name	Avg. Chain Length	C_8	C_{10}	C_{12}	C_{14}	C_{16}	C_{18}	C_{20}
1643-20-5	1-Dodecanamine, N,N-dimethyl-, N-oxide	12.0		0-1	98-100	0-1			
70592-80-2	Amines, C10-16-alkyldimethyl, N-oxides	12.9		<1	41-75	22-51	4-9	<1	
68955-55-5	Amines, C12-18-alkyldimethyl, N-oxides	13.5		0-3	50-64	18-26	9-17	6-14	0-2
3332-27-2	1-Tetradecanamine, N,N-dimethyl-, N-oxide	14.0			2-6	86-97	1-10		
2605-79-0	1-Decanamine, N,N-dimethyl-, N-oxide	10.0		96-100	0-4				
61788-90-7	Amine oxides, cocoalkyldimethyl	13.0		<1-3	64-74	21-30	2-13	<1-9	
85408-48-6	Amines, C10-18-alkyldimethyl, N-oxides	13.2		2	58	24	10	6	
85408-49-7	Amines, C12-16-alkyldimethyl, N-oxides	13.4		0-3	40-62	20-50	9-13	5-9	
7128-91-8	1-Hexadecanamine, N,N-dimethyl-, N-oxide	16.0				<3	>94	<2	
2571-88-2	1-Octadecanamine, N,N-dimethyl-, N-oxide	18.0					<5	>94	<5
2530-44-1	Ethanol, 2,2'-(dodecyloxidoimino)bis-	12.0			> 98				
61791-47-7	Ethanol, 2,2'-iminobis-, N-coco alkyl derivs., N-oxides	13.1	5	6	50	19	10	10	
61791-46-6	Ethanol, 2,2'-iminobis-, N-tallow alkyl derivs., N-oxides	17.2			1	4	31	64	
14048-77-2	Ethanol, 2,2'-(octadecyloxidoimino)bis-	18.0						> 95	
93962-62-0	Ethanol, 2,2'-[(9Z)-9-octadecenyloxidoimino]bis-	18.0						> 80	

2.2. Physicochemical Behavior Characteristics

The vast majority (> 95%) of AO in consumer products is used in household cleaning products and therefore enters the environment via treated wastewater. Amine oxides are not volatile. Predicted vapor pressure values for the dimethylamine oxides are in the range 2.6×10^{-7} to 4.6×10^{-5} Pa for increasing chain length moving from C_{10} to C_{16} while the predictions for the C_{12} to C_{18} dihydroxyethyl amine oxides range between 3.4×10^{-12} to 7.5×10^{-15} Pa for increasing chain length (EPI Suite v3.20). Amine oxides are known to be highly water-soluble ($C_{10\text{-}16}$ AO = 409.5 g L^{-1}) (EPI Suite v3.20; USEPA, 2007). Moreover, based on Level III fugacity modeling (EQC version 2.8, 2002), water is quantitatively the most important receiving compartment for amine oxides with approximately 99.5% predicted to partition to water (OECD, 2008). Hence, the greatest likelihood of environmental exposures is the aquatic compartment. Accurate measurement of surfactant partitioning is challenging due to their amphoteric nature. Although a measured log Kow value exists for $C_{10\text{-}16}$ AO, with a result of –1.08 (OECD, 2008), the accurate measurement of octanol-water partitioning for surface active substances is difficult, because they tend to accumulate at the octanol/water interface, forming octanol-water emulsions. Log Kow values ranging between 0.95-2.7 have also been predicted by comparing published Critical Micellar Concentration (CMC) values (Singh et al., 2006) of C_{10} to C_{14} amine oxides, in water, with measured octanol solubility values (CMC's can be considered as a conservative measure of water solubility for surface active substances (Mukerjee and Mysels, 1971)). Thus, amine oxides with alkyl chain length less than C_{14} can be considered as having Log Kow < 2.7. Consequently, based purely on hydrophobicity, AO chain lengths less than C_{14} are expected to have a low potential to bioconcentrate (BCF < 87 L kg^{-1}) (OECD, 2008; Sanderson et al., 2006).

2.3. Amine Oxides Fate, Exposure Modeling, and Environmental Monitoring

AOs are highly removed by conventional sewage treatment systems and biodegrade rapidly and completely under aerobic (Garcia et al., 2007) and anaerobic conditions (OECD, 2008). Commercial AOs are regarded as being ready biodegradable according to OECD criteria (OECD, 2008). In ready aerobic biodegradation OECD screening studies, up to 93% theoretical oxygen (ThO_2) consumption and 97% dissolved organic carbon (DOC) removal was observed (OECD, 2008). A removability simulation study in the presence of activated sludge on amines $C_{10\text{-}16}$ alkyldimethyl N-oxides (CAS No. 70592-80-2) (GLP conditions and radiolabel detection), resulted in greater than 99.8% removal with a mineralization rate of 125 hr^{-1} (OECD, 2008), or more than 100 times faster than the 1 hr^{-1} default for a ready biodegradable material used in the E-FAST model. These rapid measured biodegradation rates suggest mineralization is the main removal mechanism during wastewater treatment. Parent amine oxide molecules reaching surface waters are expected to undergo further mineralization. Based on $^{14}CO_2$ measurements, amine

oxides present in effluent derived from a Continuous Activated Sludge simulation study underwent extensive mineralization in river water, as indicated by the measured 63% CO_2 production in 14 days, and a mineralization half life of ~4 days (OECD, 2008). During an anaerobic mineralization study, C_{10-16} AO produced 78.9% of the theoretically expected biogas (CO_2/ CH_4) in 28 days (greater than 85% was measured after 62 days). These rates support the conclusion that AOs degrade readily under anaerobic conditions (OECD, 2008). Garcia et al. (2007) further found that AOs are readily and easily converted into CO_2, H_2O and biomass under aerobic conditions, and that AOs containing an amide-bond can be regarded as readily and ultimately biodegradable under anaerobic conditions due to enzymatic hydrolysis.

An AO (C_{12-14}) monitoring study at ten U.S. sewage treatment plants of different types (oxidation ditch (n=2), activated sludge (n=3), trickling filter (n=2), lagoon (n=2), rotating biological contactor (n=1)) was conducted in 2001. The 10 plants were located in nine principal drainage basins in the U.S. Samples consisted of 24-hr composite samples of influent and effluent collected from each STP during 3 days. Daily samples were composited based on treatment plant flow to form a 3-day, flow-based composite of each sample type. Influent (raw sewage), primary effluent (settled sewage) and final effluent samples were extracted using a chloroform/methanol/formic acid/water solvent. Extracted samples were subsequently analyzed by flow injection/mass spectrometry/mass spectrometry (FI/MS/MS). Quality control samples were analyzed simultaneously using the same protocol. Average total amine oxide levels in raw sewage influent ranged from 2.3 to 27.8 μg L^{-1} while treated effluent concentrations ranged from 0.4 to 2.91 μg L^{-1}. Effluent concentrations were greatest at oxidation ditch and trickling filter sewage treatment plants. Average removal of amine oxide in activated sludge secondary treatment facilities was > 96%. Although surface water concentrations of AO have not been measured in the U.S., they can be predicted from the effluent concentrations that were measured. Assuming a dilution factor of 3 into the receiving surface waters (Rapaport, 1988), and given the measured effluent concentrations of 0.4 to 2.9 μg L^{-1}, total AO surface water concentrations of 0.13 to 0.97 μg L^{-1} are estimated (OECD, 2008; Amine Oxide Consortium, 2006).

A less well understood mechanism that appears to contribute significantly to elimination of parent amine oxide molecules from the environment is dissipation in the sewers prior to wastewater treatment, also referred to as “pipe-loss” (Matthijs et al., 1995). The mechanisms may involve settling and/or flocculation of the substances with other waste components followed by biodegradation of the parent molecules. Since pipe-loss is difficult to measure it is calculated based on the amount of a compound disposed down the drain and the amount reaching wastewater treatment plants. Comparisons of amine oxide based on the monitoring data with theoretically expected concentrations of amine oxides in wastewater treatment influent (based on national consumption volume) indicate that pipe-losses account for pre-wastewater treatment losses of ~98% of parent based on data obtained for 10 locations in the U.S.

In a monitoring study in The Netherlands, samples of raw and treated sewage were collected during three consecutive days at six municipal activated sludge sewage treatment plants (STPs) between May and July 1996 (OECD, 2008). Samples for the analysis of AO were taken by automatic samplers – hourly samples were taken over each 24-hr period. Portions of the 24 hourly samples were mixed to generate 24-hr flow proportional composite samples. Collected samples were frozen and lyophilized prior to analysis. Analysis was preceded by a solvent extraction procedure (mixture of chloroform/methanol/formic acid/water, 80/20/1/3) and subsequent FI/MS/MS detection of C_{12-14} AO. Measured influent concentrations of AO ranged from 9 to 130 μg L^{-1} and average AO concentrations in effluents ranged from < 0.3 to 0.43 μg L^{-1}. Most STP (4 of 6) effluent concentrations were below the detection limit of the analytical method (0.3 μg L^{-1}). The average total removal of AO during sewage treatment was 98% (removal at individual STPs removals ranged from >94.9 to >99.5). An average pipe-loss of 92% of AO was calculated from the monitoring data in The Netherlands. As in the U.S., downstream surface water concentrations of AO were not measured in The Netherlands. With mean measured effluent

concentrations of < 0.3 to 0.43 μg L^{-1}, surface water concentrations of < 0.1 to 0.14 μg L^{-1} are predicted by assuming a dilution factor of 3 into receiving waters (Rapaport, 1988; OECD, 2008; Amine Oxides Consortium, 2006).

A monitoring study of AO in Japanese rivers was undertaken in 1998-2006 (Miura et al., 2008). Grab river water samples (200 mL) were collected at 7 locations in 4 urban rivers (Tamagawa, Edogawa, Arakaw, and Yodogawa) that receive sewage treatment effluent and untreated household wastewater. Three of the sites were located near drinking water intake sites; two were just below municipal wastewater effluent discharge points and, two were near ditches containing untreated household wastewaters. Sampling was carried out 4 times during the year at 3-month intervals at each location. The sampling period took place between June 1998 and March 2007. The river water was extracted on a solid phase extraction column. Analyses of C_{10},

C_{12}, C_{14} and C_{16} AO were performed by LC/Electron Spray Ionization (ES)/MS (LC-ES-MS (detection limit 0.01 μg L^{-1}). The measured 95th percentile AO river water was 0.15 μg L^{-1} with a geometric mean concentration of 0.013 μg L^{-1} (n = 140) (Miura et al., 2008; OECD, 2008).

Surface water concentrations have also been predicted using the U.S. EPA exposure tool E-FAST (U.S. EPA, http://www.epa.gov/oppt/exposure/pubs/efast.htm). High-end to bounding estimates of surface water concen-tration due to daily consumer usage of cleaning and personal care products containing amine oxides was modelled assuming down-the-drain release of total U.S. annual production volume (26,000 tonnes) into the total volume of U.S. municipal wastewater system and accounting for wastewater treatment and in-stream dilution. Wastewater treatment removal was set to 98% but pipe loss was ignored. The model outputs were: Mean stream flow concentration = 0.066 μg L^{-1} and 7Q10 stream flow concentration = 0.34 μg L^{-1} (7Q10 is the lowest 7-day average flow in a year that occurs during 7 consecutive days on an average once every 10 years) (OEDC, 2008). If pipe loss were included, predicted surface water concentrations would be far less.

Measured and modelled AO concentrations in receiving surface water at a model U.S. manufacturing sites ranged from 0.007 to 0.19 μg L^{-1} (OECD, 2008). All the derived predicted environmental concentrations (PEC) are summarized in Table II.

Table II. Summary of Environmental Exposure Scenarios.

AO Aquatic Exposure Scenario	Surface Water Concentration (μg L^{-1})
Measured Surface Water Concentrations	
United States (effluent concentrations)	<0.13 to <0.97
Netherlands (effluent concentrations)	<0.1 to 0.14
Japan (measured downstream river concentrations)	0.15*
Modeled Surface Water Concentrations for Consumer down-the-drain Release (E-FAST)	
Mean stream concentration.	0.066
7Q10 stream concentration	0.34
Measured U.S. Manufacturing Site	
Low end (estimated from effluent concentration)	0.007
High end (estimated from effluent concentration)	0.04
Modeled U.S. Manufacturing Site (E-FAST)	
Mean stream concentration	0.046
7Q10 stream concentration	0.19

* 95th percentile concentration, the geometric mean = 0.013 μg L^{-1}

Of all regions monitored, the greatest surface water PEC (predicted environmental concentration) for AO would be < 0.97 μg L^{-1} – this value is based on measured STP effluent concentrations with oxidation ditch and trickling filter as treatment technologies, and assumes a conservative 3-fold dilution of wastewater treatment effluents into receiving surface waters in the U.S. The 0.97 μg L^{-1} represents the maximum modelled PEC value. The more realistic 95th percentile and geometric mean measured concentrations (0.15 and 0.013 μg L^{-1}, respectively) are used in Table V for the risk quotient analysis.

2.4. Environmental Predicted No Observed Effect Concentration (PNEC)

Data on a variety of endpoints for aquatic effects are available for a wide range of taxonomic groups and include dimethyl-, as well as dihydroxyethyl- amine oxides. Acute toxicity data are available for forty-one single chain length amine oxides, as well as mixtures. Twenty-one chronic toxicity studies were conducted with fish, daphnid (invertebrates) and algal species provided by the Consortia members (OECD, 2008).

2.4.1. Acute Toxicity

Acute toxicity is affected by chain length for fish and invertebrates (Table III). Chain length affects hydrophobicity, which likely increases the rate of uptake and decreases depuration in these species. Both the acute and chronic data suggest that freshwater green algae are the most sensitive species. Interestingly, the available data do not support an influence of chainlength on toxicity to algae.

2.4.1.1. Fish Acute Toxicity

AO acute toxicity data to fish range from 600 to 32,000 μg L^{-1} (Table III). Acute toxicity increases as a function of alkyl chain length but is only a marginal influenced by other substituents on the nitrogen (whether methyl or hydroxyethyl groups), hence, data for dimethyl and dihydroxyethyl AOs are summarized together. For AOs with average chain lengths ≤14, the 96h LC_{50} values were in the 1,000 to 32,000 μg L^{-1} range. AOs with chain lengths >14 were more toxic, with LC_{50} values from 600 to 1400 μg L^{-1}.

2.4.1.2. Acute toxicity to invertebrate

AO acute toxicity data on invertebrates are only available for Daphnia magna (Table 3). As with fish, the acute toxicity of AOs to invertebrates increases as a function of chain length and the nature of the substituents on the nitrogen (whether methyl or hydroxyethyl groups) only marginally affects toxicity. For AOs with average chain lengths ≤14, the 48h EC_{50} values ranged from 1000 to 11,000 μg L^{-1}. Amine oxides with chain lengths greater than 14 were more acutely toxic to daphnids, with LC_{50} values ranging from 500 to 700 μg L^{-1}. Garcia et al. (2007) found acute 48h EC_{50} values of 14,000 and 6800 μg L^{-1}, for AO C_{12} and C_{14}, respectively.

2.4.1.3. Acute toxicity to algae

Based on the hazard data, the most acutely sensitive freshwater species is the green algae (Desmodesmus) among the species tested. As described above, data for dimethyl and dihydroxyethyl AOs have been combined in this assessment. The results of testing different algal species suggest that amine oxide toxicity to algae is not influenced by alkyl chain length (Table III). Given that the algal studies have been conducted in a variety of ways on different mixtures of AOs, all effect concentration values (ECx) were recalculated using the same statistical model, Bruce and Versteeg (1992). This model assumes a sigmoidal dose response curve, which adequately fits the data. For Desmodesmus and Pseudokirchneriella, the biomass-based EC_{50} values range between 10 and 400 μg L^{-1} for C_{12} and longer chain length amine oxides. For Anabaena and Diatoma, the biomass-based EC_{50} values range between 2000 and 5000 μg L^{-1} (data based on a $C_{10\text{-}16}$ AO, a mixture of predominantly C_{12} and C_{14} amine oxides, of average chain length $C_{12.6}$).

Table III. Acute Aquatic Toxicity Values for Amine Oxides (OECD, 2008).

Average Chain length	Species	48-96h LC_{50} ($\mu g\ L^{-1}$)	CAS No.
C8 ≥ x <C13	*Danio rerio, n=2*	10,500 – 32,000	1643-20-5 2530-44-1
	Oryzias latipes, n=1	29,900	1643-20-5
	Pimephales promelas, n=1	2600 – 3500	70592-80-2
	Daphnia magna, n=5	1000 –10,800	1643-20-5 2530-44-1 70592-80-2
	Pseudokirchneriella subcapitata, n=5	10 – 400	1643-20-5 2530-44-1 70592-80-2
	Desmodesmus, n=2	40 – 280	1643-20-5 70592-80-2
	Chlorella, n=1	1700	70592-80-2
	Diatoma, n=1	2160	70592-80-2
	Anabaena, n=1	5300	70592-80-2
C13 ≤ x ≤ C14	*Danio rerio, n=4*	1000 – 3400	61788-90-7 68955-55-5 3332-27-2 61791-47-7
	Oncorhynchus, n=1	13,000	61788-90-7
	Daphnia magna, n=3	1100 – 2900	61788-90-7 3332-27-2 61791-47-7
	Pseudokirchneriella subcapitata, n=3	80 – 290	61788-90-7 3332-27-2 61791-47-7
C16 ≥ x < C20	*Danio rerio, n=4*	600 – 1400	7128-91-8 2571-88-2 61791-46-6 93962-62-0
	Daphnia magna, n=3	500 – 700	7128-91-8 61791-46-6 93962-62-0
	Pseudokirchneriella subcapitata, n=4	80 – 300	7128-91-8 2571-88-2

2.4.5. Chronic toxicity

Toxicity test data are available on a variety of amine oxides of varying chain lengths for fish, algae and invertebrates. As with the acute toxicity data, chain length affects the chronic toxicity of AO to fish and invertebrates, but not to the algae Pseudokirchneriella subcapitata. At present, there are chronic toxicity data for a variety of different amine oxides on eight aquatic species. Since the environmental risk assessment is based on the use of chronic data and the average alkyl chain length in North America is 12.9 carbon atoms, all available fish and invertebrate chronic toxicity data were normalized to this chain length using the method outlined by Fendinger et al. 1994. Normalization to a single chain length allows all data to be used in the effects assessment. Algae data were not normalized since chain length does not appear to influence amine oxide toxicity. Extrapolation from C12.6 to C12.9 equals an increase in chronic toxicity by 26%. The resulting, geometric mean values per species are shown in Table IV.

2.4.2.1. Chronic toxicity fish

A chronic study was conducted on fathead minnows (Pimephales promelas) with $C_{12.6}$ amine oxide (OECD, 2008). This study includes a 302-day survival, growth and reproduction study as well as a 60-day larval survival and growth study on larvae produced during the 302-day study. The result was a measured

NOEC of 420 µg L^{-1} based on the most sensitive endpoints, growth and hatchability. Normalization of the data to a $C_{12.9}$ amine oxide resulted in a predicted NOEC of 310 µg L^{-1} (Table IV).

2.4.2.2. Chronic toxicity to invertebrates

Two chronic studies are available for Daphnia magna, one with an amine oxide of average chain length of 12.6 (Maki, 1979), and the second with average chain length of 12.0 (OECD, 2008). Based on the available data, reproduction was observed to be the most sensitive indicator of chronic toxicity in both studies. Normalization of the data to a $C_{12.9}$ amine oxide resulted in a geometric mean predicted EC_{10} value of 280 µg L^{-1}. This finding is consistent with the anticipated similarity between invertebrates and fish in terms of their sensitivity to amine oxides, which has also been described in Maki (1979).

Table IV. Chronic Toxicity of Amine Oxide to Fish, Invertebrates and Algae. Data on fish and invertebrates are normalized to $C_{12.9}$ alkyl chain length (OECD, 2008).

Chain length normalized	Species	Endpoint	Chronic geometric mean (µg L^{-1})	CAS Number
$C_{12.9}$	*Pseudokirchneriella subcapitata, n*=12*	(72h EC_{20}, EC_{10})	52	70592-80-2 1643-20-5 2530-44-1 61788-90-7 3332-37-2 61791-47-7 7128-91-8 2571-88-2 93962-62-0 61791-46-6
	Desmodesmus, n=2	(72h EC_{20})	45	70592-80-2 1643-20-5
	Anabaena,n=1	(240h EC_{10})	1900	70592-80-2
	Diatoma, n=1	(240h EC_{20})	180	70592-80-2
	Navicula, n=1	(120h, NOEC)	75	70592-80-2
	Chlorella, n=1	(120h, EC_{20})	770	70592-80-2
	Daphnia magna, n=2	(21d EC_{10}, NOEC)	280	1643-20-5 70592-80-2
	Pimephales promelas, n=1	(302d NOEC-hatchability)	310	70592-80-2

* n = number of tests performed

2.5. Environmental Risk Assessment (PEC/PNEC)

Based on use pattern, the predominant disposal route of these substances is down-the-drain with concomitant transport via the wastewater collection system to a wastewater treatment plant. Greater than 90% pipe loss occurs during transport in the sewers, and ~98% of the remaining amine oxide is removed by wastewater treatment systems. This has been confirmed by field monitoring studies in the United States, The Nether-lands and Japan where amine oxide concentrations in sewage treatment plant effluents were found to be in the <0.3 to 3.0 µg L^{-1} range. In concurrence with the field monitoring results, E-FAST, a U.S. EPA model used to predict environmental concentrations (U.S. EPA, http://www.epa.gov/oppt/exposure/pubs/efast.htm), estimated a mean and 7Q10 surface water concentrations of 0.066 and 0.34 µg L^{-1}, respectively, for the high-end to bounding consumer use scenario. E-FAST modeling of manufacturing facility effluent discharges resulted in estimated mean and low flow (7Q10) stream concentrations of 0.046 µg L^{-1} and 0.19 µg L^{-1}, respectively for bounding conditions. In order to be conservative a worst-case effluent PEC of 0.97 µg L^{-1} was considered for the risk assessment, in addition a more realistic measured 95th percentile river PEC of 0.15 µg L^{-1} was

considered. For perspective, a geometric mean measured river water PEC of 0.0013 µg L^{-1} has been measured in four rivers in Japan downstream wastewater treatment plants over eight years (n = 140) (Miura et al. 2008) was also considered as the most realistic average PEC (Table II).

2.5.1. PNEC derivation

The PNEC was derived using two approaches, one based on a species sensitivity distribution (SSD) derived from all available single species chronic toxicity data, and another based on higher tier microcosm data.

2.5.2. SSD PNEC

A statistical extrapolation method was used to derive a predicted no effect concentration (PNEC) for a $C_{12.9}$ amine oxide, following the methodology described in Versteeg et al. (1999) and Posthuma et al. (2002) and following the guidelines laid out by the OECD. In this approach, single species chronic toxicity data were fitted to a cumulative log-logistic distribution and the PNEC derived from the single species sensitivity distribution at the concentration predicted to protect 95% of species HC_5 (hazardous concentration, 5%) (Figure 1). As noted above, fish and invertebrate data were normalized to $C_{12.9}$ while algal data were used without normalization. The 5% indicates that 95% of laboratory generated chronic single species values (e.g. NOECs) were greater than the HC_5. Using this approach, a PNEC of 23 µg L^{-1} was derived for a $C_{12.9}$ amine oxide, and is believed to be protective of at least 95% of species from adverse chronic effects (OECD, 2008). As a probability value, based on 21 studies of 8 species, it provides a margin of safety. Since the size of the application factor which could be applied to the HC5 is subjective, not globally harmonized and the SSD based PNEC has been found to be conservative relative to mesocosm NOEC values (Versteeg et al. 1999), we ascribed a factor of one in the derivation of the PNEC from the HC5.

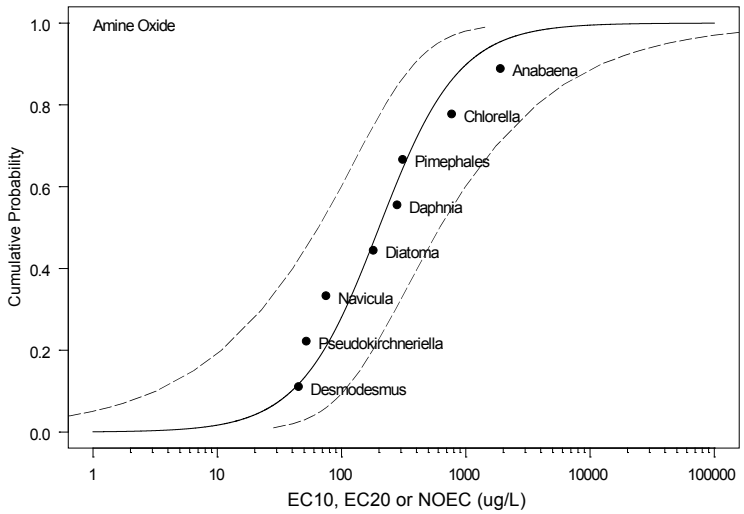

Figure 1. Species sensitivity distribution for aquatic species exposed to amine oxide in chronic toxicity tests. Toxicity data from Table IV are shown in a cumulative log-logistic distribution.

2.5.3. Microcosm PNEC

Given that AOs have different sensitivities to different taxa with freshwater green algae being the most sensitive (Table III), a 28-day freshwater periphyton microcosm assay was conducted for a $C_{10\text{-}16}$ AO (with an average chain length of $C_{12.6}$). This microcosm was composed of a complex consortia of bacterial, cyano-bacterial, algal, and fungal species, and included 110 taxa of algae (notably 87 diatom, 12 green, 7 blue-green, 2 euglenoid, 1 chrysophyte and 1 red). The study was conducted by allowing tiles and cobble to naturally colonize for two months in two different rivers in Ohio, the Little Miami River

and Big Darby Creek. After colonization, the tiles were moved to the laboratory where exposures occurred up to a maxi-mum measured concentration of 67 µg L^{-1}. Periphyton samples were collected on days 0, 12, 21, and 28 and were scraped, fixed, and prepared for detailed taxonomic analysis as dscribed in Belanger et al. (1996). Dominant populations and community metric data were subjected to one-way ANOVA or the non-parame-tric Kruskal-Wallis to determine effects. A NOEC value of 67 µg L^{-1} was derived, protective of all auto-trophic and heterotrophic periphyton communities tested (OECD, 2008). When the measured chronic NOEC value of 67 µg L^{-1} for a $C_{12.6}$ average chain length amine oxide is normalized to $C_{12.9}$ amine oxide, the PNEC becomes 50 µg L^{-1}. Again an assessment factor of 1 was ascribed as this microcosm contained the most sensitive taxa, the exposure was chronic in nature, functional and structural community level metrics derived for multiple different endpoints were used, and there is currently no globally harmonized AF for microcosm studies.

2.5.4. Risk Quotient (RQ)

The data above allows two different scenarios of risk characterization with different degrees of precaution and realism. The most precautionary, but also less realistic calculations are the PECs based on estimated from STP effluent concentrations with a dilution factor of 3 and E-FAST 7Q10 modeled concentrations ranging from 0.34 to 0.97 µg L^{-1}. For this assessment, we use the highest PEC (0.97 µg L^{-1}). In addition, we consider the worst-case measured downstream surface water concentration of 0.34 µg L^{-1} and the mean measured concentration of 0.04 µg L^{-1} (JSDA, 2003). These are then compared to PNEC values to derive the most conservative RQs for the two scenarios. For the statistical extrapolation NOEC based on SSD algae the PNEC = 23 µg L^{-1} the RQ = 0.04 (Scenario 1), and the most realistic PNEC from microcosm testing PNEC = 50 µg L^{-1} yielding a RQ = 0.02 (Scenario 2). If we consider the same PNECs but compare these with the 95th percentile measured surface water concentration of 0.15 µg L^{-1} we derive RQs of 0.007 (Scenario 3) and 0.003 (Scenario 4). The last scenarios (5 and 6) are based on the geometric mean measured PEC of 0.0013 µg L^{-1} yielding RQs of 0.0006 and 0.0003, respectively (Table V).

Table V. Risk Quotient for Six Exposure Scenarios

Scenario	PEC worst-case µg L^{-1}	PNEC µg L^{-1}	PEC/PNEC (RQ)
1	0.97 (max. model)	23 (SSD)	0.04
2	0.97 (max. model)	50 (Microcosm)	0.02
3	0.15 (95th percentile measured)	23 (SSD)	0.007
4	0.15 (95th percentile measured)	50 (Microcosm)	0.003
5	0.013 (geo mean measured)	23 (SSD)	0.0006
6	0.013 (geo mean measured)	50 (Microcosm)	0.0003

These data, with RQ ranging from 0.04 to 0.0003 depending upon assessment methodology, indicate that aquatic hazard levels for amine oxides are not likely to be reached with normal conditions of manufacture and use, under mean and low river flow conditions. This assessment applies immediately below oxidation ditch and trickling filter wastewater treatment plants before biodegradation in surface waters as well as further down stream and assuming all of the AO to be biologically available to aquatic organisms for toxi-city. RQs below other wastewater treatment plants (e.g. activated sludge) would be lower since environmen-tal concentrations at these sites are lower. The measured worst-case most realistic and empirically derived RQ = 0.003, and the geometric mean measured PEC compared to the microcosm PNEC (most empirically realistic) RQ of 0.0003, further suggest low aquatic risk. There were no assigned assessment factors for the risk analysis, which typically would range from 1-5 for these types of data. Even at the highest assessment factor that might be assigned, 5, the potential risk would still be insignificant. Using these conservative assumptions and the rich empirical data material it can be concluded that the risk of substances in the AO category in the environment is acceptable.

3. CONCLUSIONS

Sanderson et al. (2006) concluded that industry have compiled a comprehensive data package on the AO category (OECD, 2008) which was approved by the OECD member countries for the OECD HPV programme, and that AOs in the category do not pose a risk to human safety with conservative margin of exposures (MOEs) of 42 to 6,662,666 depending upon use scenario. The data presented in this risk assessment indicate that aquatic hazard levels for amine oxides are not likely to be reached in normal conditions of neither manufacture nor use under mean and low flow conditions, as reasonable worst case RQs range from 0.04 to 0.0003 depending upon assessment scenario. As AO degrades in the environment, risk will be further reduced, and it can thus be concluded that the AO category will not pose an unacceptable risk to the aquatic environment.

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Appendix III-C

Long Chain Alcohols (LCOH) – Category Overview

Sanderson H, Belanger SE, Fisk PR, Schäfers C, Veenstra G, Nielsen AM, Kasai Y, Willing A, Dyer SD, Stanton K, Sedlak RI. 2009. An overview of hazard and risk assessment of the OECD high production volume chemical category – Long chain alcohols [C6--C22] (LCOH). Originally published in *Ecotoxicology and Environmental Safety*, 72:973–979. Available at http://www.elsevier.com/locate/ecoenv. DOI:10.1016/j.ecoenv.2008.10.006.

An Overview of Hazard and Risk Assessment of the OECD High Production Volume Chemical Category – Long Chain Alcohols [C_6–C_{22}] (LCOH)

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Abstract

This review summarizes the findings of the assessment report for the category, long chain alcohols (LCOH) with a carbon chain length range of C_6-C_{22} covering 30 substances, and >1.5 million tons/year consumed globally. The category was evaluated under the Organization for Economic Co-operation and Development (OECD) high production volume chemicals program in 2006. The main findings of the assessment include: (1) no unacceptable human or environmental risks were identified; (2) these materials are rapidly and readily biodegradable; (3) a parabolic relationship was demonstrated between carbon chain length and acute and chronic aquatic toxicity; (4) category specific (Quantitative) Structure-Activity Relationships were developed enabling prediction of properties across the entire category; (5) LCOH occur naturally in the environment in an equilibrium between synthesis and degradation; (6) industry coming together and sharing resources resulting in minimizes the need for additional animal tests, produces cost savings, and increases scientific quality of the assessment.

1. Introduction

The aim of this paper is to summarize and introduce the assessment of the long chain alcohols (LCOH) category, and also to give a brief review of ongoing national and international assessment frameworks addressing non-assessed or high production volume chemicals. Most High Production Volume (HPV) chemi-cals have been on the market for decades but rarely have comprehensive datasets on their physicochemical and toxicological properties been publicly available. Therefore HPV chemicals are under increasing regula-tory scrutiny globally. In 1990, member countries of the Organisation for Economic Co-operation and Deve-lopment (OECD) decided to undertake the investigation of HPV chemicals in a co-operative way. These HPV chemicals include all chemicals reported to be produced or imported at levels greater than 1,000 tonnes per year in at least one member country or in the European Union region. The most recent OECD HPV Chemicals List compiled in 2004 contains 4,843 substances based on submissions of nine national invento-ries and that of the European Union. The OECD HPV program proceeds by the agreement that member countries will co-operatively select the chemicals to be investigated, collect and characterize effects and ex-posure information from government and public sources and encourage industry to provide information from their files, complete the agreed dossier for the Screening Information Data Set (SIDS), and make an initial assessment of the potential hazard of each chemical investigated. When a full SIDS dossier on a chemical is available, an initial assessment of the information is undertaken and conclusions are drawn on the potential hazard(s) and exposure information to put the hazard information into context (e.g., based on use in the Sponsor country). Since 1999, the work in OECD has concentrated on data gathering, testing, and initial hazard assessment. Detailed exposure information gathering and assessment of risk is no longer required as part of the SIDS initial

assessment, but can be carried out in follow-up at the national (or regio-nal) level, as appropriate, following national (or regional) priority setting as post-SIDS work. Detailed inter-national as-sessment of risks to human health and/or the environment is also no longer carried out under the SIDS initial assessments. In the policy bodies of OECD, member countries discuss and agree on any fol-low-up actions on chemicals for which further work is recommended. Finalized SIDS dossiers and initial assessment reports are made available worldwide through UNEP Chemicals website (http://www.chem.unep.ch/). Protocols were established for close co-operation with the industry in the various stages of the Programme, which is undertaken in co-ordination with national, regional and other international existing chemicals programmes (OECD, 2004).

The global chemical industry, through the International Council of Chemical Associations (ICCA), launched a global initiative on HPV chemicals in 1998 to expedite the OECD HPV program. Through this commit-ment, the chemical industry has undertaken to provide, as a first step, harmonized data sets on the intrinsic hazards of and initial hazard assessments for approximately 1,000 HPV substances by the end of 2004. The information consisting of a SIDS Dossier, a SIDS Initial Assessment Report (SIAR); and the SIDS Initial Assessment Profile (SIAP), are submitted to the OECD for international agreement as part of its refocused HPV Chemicals Programme. The cost of generating data and the work to draft the assessments will be borne by industry – and shared, whenever possible, by companies in international consortia. The main features of the ICCA HPV chemicals initiative are for voluntary action by the world chemical industry to speed up the process under existing regional and/or global programmes with a clear target date, provide globally harmo-nized, internationally agreed data sets and initial hazard assessments under the refocused HPV Chemicals Programme of the OECD, and the elimination of duplication of testing and assessment efforts. The main expected benefits of these actions are to restore public confidence in chemicals and to foster a positive reputation of the chemical industry on a global basis, to establishment of a sound scientific basis for any subsequent regional, national, or global risk assessment need, to minimize the cost for the industry and to reduction in the number of animals needed for testing (CEFIC, 2007).

There are, of course, other ongoing or planed national and international HPV initiatives with different regulatory objectives, but a common feature among them is the desire for increased transparency regarding the properties of chemicals. The OECD datasets complement these other initiatives, some of which are described in the following paragraphs.

The United States Environment Protection Agency (U.S. EPA) initiated their HPV Challenge program in 1999, challenging industry to provide data on some 2860 HPVs. This was done under the chemical rights-to-know program (http://www.epa.gov/chemrtk/). Of these substances, U.S. EPA found that 43% have no publicly available data on basic toxicity, and only 7% have a full set of basic test data publicly available. EPA also found that only 55% of the chemicals reported in the Toxics Release Inventory had full basic toxicity testing data publicly available. Only about one quarter of chemicals in consumer products had basic testing information publicly available. This lack of publicly available toxicity data compromised, in the Administration’s view, the public's right to know about chemicals in their homes, their workplaces, and the products they buy (Goldman, 1998). Hence the U.S. EPA HPV Challenge Program. The results are made publicly available via the USEPA HPV Information System (HPVIS) (http://www.epa.gov/hpvis/).

The Canadian Environment Protection Act (CEPA) was revised in 1999 and required that all existing chemicals on the market and identified the Domestic Substances List (DSL) would need review based on their properties and likelihood of exposure to humans or the environment. The compounds would then be categorized based on their Persistence (P), Bioaccumulation (B), and Toxic (T) (PBT) properties and likelihood of exposure. The DSL includes ~23,000 substances that were in Canadian commerce, used for manufacturing purposes, or manufactured in or imported into Canada in a quantity of 100 kg or more in

any calendar year between January 1, 1984, and December 31, 1986. The aim here is prioritize which chemicals to categorize for and risk assessment (CEPA, 1999).

The European Union (EU) Existing Chemicals Program, initiated in the mid 1990s mandated industry to provide all available data for EU priority chemicals in two priority phases. The first phase included compounds on the EU market >1000 tonnes/year with known hazardous properties, and the second phase included all other compounds >1000 tonnes/year. Subsequently the authorities were to prioritise the substances according to their environmental relevance (exposure) and hazard properties. Starting with the substances of highest concern, comprehensive risk assessments were to be conducted. If relevant data gaps were identified, industry had to conduct and provide data from additional studies. However, the progress of the program was rather slow so that after 10 years only for a minor fraction of the substances at >1000 tonnes/year final risk were assessment available. As a consequence of this the EU issued a white-paper on the future chemicals policy (EU, 2001), and initiated the European Registration Evaluation Authorization of Chemicals (REACH) process in 2001 (EU, 2001b). This policy will address registration of compounds marketed before 1981 in volumes greater than 1 ton (~30,000 compounds). Priority is given to high production volume chemicals under REACH (>1000 tonnes/year). The deadline for registration of chemicals used at these tonnages is three years after full implementation of REACH (~2011). For feasibility purposes (minimizing animal tests, time, costs), assessment of chemical categories as well as use of read-across and (Q)SARs (Quantitative Structure Activity Relationships) play important roles in the implemen-tation of REACH. The bottom-line of REACH has been summarized as: No data – No market.

In 2005, the Japanese government started its voluntary HPV program for substances produced or imported in Japan in volumes greater than 1000 tonnes/year. The program focuses on HPV chemicals on the Japanese market which are not evaluated by any other HPV program, such as the OECD and U.S. challenge programs. A total of 652 HPV chemicals appear on the Japanese market today, 140 of which are not covered by any of the other international HPV programs and have no data specific for Japan. Hence, these substances need as-sessment under the Japanese HPV challenge program. Roughly half of these have voluntarily been sponsored by the Japanese industry and are currently being assessed. The required endpoints are the OECD SIDS data package. The initial assessment phase of the program will be completed by March of 2009 (Japan MOE, 2005).

In concert with these national and international chemical management programs the United Nations Economic and Social Council adopted the Globally Harmonized System (GHS) for Chemicals Classification and Labeling in 2003 (UN, 2003), which will allow the intrinsic hazard properties of to be translated into hazard classes that are readily interpretable worldwide for hazard communication. Thus, HPV datasets support national and regional efforts to improve the safe handling and use of chemicals.

The purpose of this special issue of Ecotoxicology and Environmental Safety is to review the SIAR for one of the best documented and largest categories of substances evaluated under the OECD HPV programme in terms of number of chemicals (30) and global production volume (>1.5 million metric tons/year). The category is the long chain alcohols (LCOH) with a carbon chain length range of C_6-C_{22}. A global Aliphatic Alcohols Consortium was formed and managed by The Soap and Detergent Association (U. S.) in 1999 (consortia are defined under HPV programs as a group of companies working together to mutually provide data and expertise from their respective companies for the purpose of HPV submissions). The Consortium is comprised of 13 international companies from three different continents, representing both up- and downstream users of the substances. The United Kingdom was the sponsor country and Shell International was the lead company. The issue address properties of LCOH covering: 1) Description of the physicochemical properties and acute aquatic toxicity (Fisk et al., 2009); 2) Chronic toxicity (Schäfers et al. 2009); Mammalian toxicity (Veenstra et al., 2009); and Environmental risk assessment (Belanger et al. 2009). The aim of this review is to summarize, with an emphasis on the

environmental compartment, the findings of the SIAR (OECD, 2006), which will be outlined in greater detail in the following papers.

2. Materials and methods

2.1 Chemicals

This case-study addresses a category of long chain alcohols [C_6-C_{22}]. It covers 30 LCOH (pure substances and commercially available complex mixtures) CAS number entries. The commercially available products generally include several LCOH components, with a range of carbon chain lengths and various compositions and structures. The composition depends on the production method and the related feedstocks. Most of the alcohols have linear carbon chains but certain manufacturing processes create linear and essentially linear structures. Long chain alcohols are manufactured by a number of processes, but these can be divided into two general categories by feedstock. 1) Oleochemical - include; coconut, palm, kernel oil, and tallow fat or other triglycerides. 2) Various processes use petrochemical - the most commonly being olefins (alpha and internal) and ethylene. Some commercially available products are blends of two or more specific chain length alcohols to produce mixtures. Moreover, the commercial industrial processes used to produce alcohols in some cases necessarily result in a spread of carbon number, and some alkyl chain branching. In addition, a limited number of unsaturated substances very similar to the saturated analogues are included. The total annual global usage in 2004 was 1,580,429 metric tons. A significant portion of these substances are used in personal and household care products ultimately disposed of down-the-drain, and enter the environment at low levels via wastewater treatment plant effluent.

2.2 Chemical Category Rationale

Key attributes that the category members share are, comparable structural features, similar metabolic pathways, a common mode of ecotoxicological action, and common levels and mode of human health related effects. Grouping of the long chain alcohols into a common category is possible because the group is a homologous series of structures that impart the predictable pattern of properties. In addition, certain branched and unsaturated structures are considered to have such similar properties that their inclusion in the category is justified. Commercial products contain a range of alcohols, including unsaturated alcohol components, essentially linear (mono-alkyl branched) components, and linear alcohols. All components of all commercial products relevant to this category are primary alcohol structures. This allows multi-compo-nent reaction products to be considered within the Category by the application of validated models of expo-sure and effects, on the basis of detailed knowledge of the composition. For the environmental end-point assessment, this has been done by read across and modelling. The read-across approach was applied to biodegradability where sufficient data existed to allow interpretation of degradation patterns across the entire category to fill data gaps directly. For algae, read-across-based expert judgement was applied, taking into account measured and predicted effects in daphnids and fish for the substance of interest. Modelling of the ideal solubility of the components of the substances was developed, allowing component and total solubility at any loading rate to be calculated. By using knowledge of the properties of each component, ecotoxicological effects have been predicted.

The mammalian biotransformation of LCOH involves an oxidation step of the alcohol function to the corres-ponding aliphatic carboxylic acid, with the aldehyde being a transient intermediate. These carboxylic acids (i.e., fatty acids) are subsequently broken down by stepwise removal of one or several C_2 units from the ali-phatic carbon chain through β-oxidation. The stepwise breakdown of LCOH results in common intermediate metabolites with shorter chain lengths which provides additional justification that the alcohols under consi-deration can be regarded as a single category. The observation also explains the similarity in toxico-logical profile for systemic effects. LCOH are generally metabolized in a highly efficiently manner and limited potential exists for retention or bioaccumulation for the parent alcohols and their biotransformation products.

3. Results

3.1 Physicochemical properties

While (Q)SAR techniques are developed using reported and measured data, they may also be confirmed and useful across many other structural types. Their success in predicting properties for category members for which measured data exist suggests that the members do not possess any particularly unusual features. The physicochemical properties vary across members of the category (Fisk et al., 2009; OECD, 2006).

Table 1: Ranges of measured physicochemical and biological properties.

End point	Melting point, ^{o}C	Boiling point, ^{o}C	Density, g cm^{-3}	Log Kow	Water solubility, mg L^{-1}	Vapour pressure, hPa	BCF
Range	-47.5 – 72.5*	158 – > 400*	0.8 – 0.85*	2.03 – > 7 $^{\Omega}$	0.001 – 5,900 $^{\Delta}$	8.2 x 10^{-8} – 1.22*	7 – 46,000 $^{\Phi}$

*C_6-C_{22}; $^{\Omega}C_6$-C_{20}; $^{\Delta}C_{18}$-C_6; $^{\Phi}C_6$-C_{16}

3.2 Biodegradation

Long chain alcohols with chain lengths up to C_{18} (docosanol) are readily biodegradable in tests that conform most closely to ready test biodegradability methods (OECD 301 series). At carbon chain lengths greater than C_{14}, most tests showed that pass levels for ready biodegradation were reached within the 10-day window. Chain lengths of $C_{16\text{-}18}$ achieved ready test pass levels, although not within the 10-day window. The one test on a single carbon chain length greater than C_{18} showed degradation of 37% most likely due to the interplay of de-sorption, solubility, and biodegradbility. These rates are in accord with field data for measured concentrations in waste-water treatment plant influent and effluent showing greater than 99% removal for carbon numbers 12 to 18. This summary of degradation is applicable to both linear and essentially linear components of substances in the category. Therefore, the whole category is considered to show very high levels of biodegradability. The substances are susceptible to atmospheric degradation by hydroxyl radicals, with half-lives ranging between ca. 10 to 30 hours (based on measured and estimated rate constants, for a hydroxyl radical concentration of 5 x 10^5 molecules/cm^3). Predictions from the SRC BIOWIN v4.00 program (part of the EPI Suite v3.12) supports the conclusion of rapid degradation for the linear alcohols, but cannot be used quantitatively (Fisk et al., 2009).

Moreover, Federle and Itrich (2006) have studied the fate of free and linear alcohol-ethoxylate-derived fatty alcohols in activated sludge. Radiolabelled (^{14}C) C_{12}; C_{14}; and C_{16} alcohols were used. The study was a batch-mode activated sludge die-away system, where disappearance of parent, formation and disappearance of metabolites, uptake into biomass and mineralization to ^{14}C CO_2 were monitored over time. The activated sludge from a municipal waste water treatment plant was obtained, and used at 2500 mg L^{-1}. The degradation of LCOH involved two principle pathways, which were oxidation to a fatty acid, which was then β-oxidized to CO_2, and Ω-oxidation of the methyl group to yield dioic acids, which then undergo β-oxidation. In conclusion, Federle and Itrich (2006) found that long chain alcohols are extensively and rapidly mineralized to carbon dioxide and water, with half-lives in sewage treatment being less than one minute.

3.3 Environmental exposure

The published and grey literature on the environmental occurrence, fate and behavior of LCOH has been reviewed (Mudge et al., 2008). The principal focus of that review was on the natural production of alcohols, which occurs in all living organisms from bacteria to man, and the profiles and concentrations of these compounds in water, soils and sediments. The major production mechanism is from the reduction of fatty acids, through aldehyde intermediates, to fatty alcohols and in many organisms to esters with fatty

acids to form waxes (Metz et al., 2000). Due to the nature of the synthetic pathway using acetyl-CoA, most long chain alcohols are of an even numbered chain length. Terrestrial plants utilize fatty alcohols as a waxy coating and these compounds are dominated by long chain moieties, with chain lengths from C_{22} to C_{32}. In contrast, marine organisms synthesize smaller compounds with peak chain lengths of C_{14} to C_{16}. Bacteria also produce fatty alcohols but these can also be odd chain lengths and contain branching. The alcohols are ubiquitous and occur in most environments around the world, including the deep ocean and in sediment cores. The rates of production of long chain alcohols from natural waxes and fatty acids in environmental conditions are not known (Mudge et al., 2008). These include release rates and mass contributions from microbial senescence, household consumption of animal and vegetable matter, and the like. For example, Leeming et al. (1994) established that long chain alcohols (C_{14-32}) are measurable components of human faeces in wastewater. The sum of C_{14} to C_{18} chain lengths ranged from 217-1825 $\mu g\ g^{-1}$ in human waste sent to sewage treatment. It is clear that measurements of long chain alcohol in environmental matrices will reflect the combination of both natural and anthropogenic sources. The concentration of individual free alcohols in the environment ranges from low values in old (several thousand year) deep cores from the open ocean floor (undetectable to 12 $ng\ g^{-1}$ dry weight for C_{16}) to high values near natural sources and especially in suspended particulate matter (2.7 $mg\ g^{-1}$ dry weight for C_{16}) (Mudge et al., 2008).

Several methods that measure long chain alcohols in environmental matrices are available. Dunphy et al. (2001) devised and executed a method whereby alcohols present in an environmental sample can be detected at extremely low concentrations, often less than 10 $ng\ L^{-1}$. The method involves extraction of wastewater effluent and associated solids followed by derivatization with 2-fluoro-N-methylpyridinium p-toluenesulfonate to a permanent cation for quantitation by HPLC/MS.

Influent levels of long chain alcohols have been reported for 12 wastewater treatment plants across the United States (MRI, 2004; Morrall et al., 2006). Average influent concentrations for C_{12}–C_{15} ranged from 64.0 (C_{13}) to 117.5 (C_{12}) $\mu g\ L^{-1}$. The sum of C_{12-15} long chain alcohols averaged 394.5 $\mu g\ L^{-1}$ across all influents that were sampled. For treatment plant effluents monitored within the U.S., the weighted average concentrations were ordered as C_{12} (0.255 $\mu g\ L^{-1}$) > C_{14} > C_{15} > C_{13} (0.035 $\mu g\ L^{-1}$). For treatment plant effluents monitored in Canada, the average concentrations were greatest for C_{15} (0.619 $\mu g/L$) > C_{14} > C_{18} > C_{12} > C_{13} (0.209 $\mu g\ L^{-1}$). For treatment plant effluents monitored within Europe, the average concentrations were greatest for C_{12} (0.281$\mu g\ L^{-1}$) > C_{14} > C_{15} > C_{13} (0.165 $\mu g\ L^{-1}$). The overall trend appears to be that effluents have higher concentrations of longer LCOH than shorter chain lengths (OECD, 2006; Belanger et al., 2009). This is also consistent with the expected chain length distributions found in the waters association with primarily natural sources of LCOH (USEPA, 1997). For example, activated sludge (AS) treatment accounts for 80.6% of total U.S. wastewater flow versus 7.1% for trickling filters. Therefore, individual measurements can be weighted to achieve a national average concentration. For the U.S., Canada, and Europe, the average total long chain alcohol concentrations (C_{12} to C_{15}) in effluent are 0.572; 1.711; and 0.910 $\mu g\ L^{-1}$, respectively. The 90^{th} percentile (all measurements at this concentration or lower) for individually monitored effluent measurements worldwide, not accounting for treatment type and flow, is 1.979 $\mu g\ L^{-1}$ and the global average for the three regional measurements is 1.064 $\mu g\ L^{-1}$. These values include both free and bound alcohol to wastewater solids. For the U.S., Canada and Europe, the average total LCOH concentrations (C_{12} to C_{15}) following adjustment due to sorption are 0.417; 1.487; and 0.654 $\mu g\ L^{-1}$, respectively, yielding a global average of 0.739 $\mu g\ L^{-1}$. Note that the focus from a toxicological and risk assessment point of view is on the chain lengths < C_{15}, as the longer chain lengths are not bioavailable (OECD, 2006; Belanger et al., 2009).

Dyer et al. (2006) recently documented the appropriateness of adapting the Dunphy et al. (2001) analytical method for measuring alcohol ethoxylate in coarse sediments. The method was applied at three sites of varying sediment composition. Further refinements to the methods were instituted to potentially

measure free long chain alcohols and alcohol ethoxylates in pore water, surface waters, and chemical sorbed to coarse and fine sediments. Long chain alcohols were ubiquitous and primarily associated with fine particulate matter in river sediments. Measurements by chain length and location were variable with the highest measurements (up to 12 μg g^{-1}) recorded far downstream of sewage treatment plant inputs (above that recorded in the mixing zones and discharge proper). Levels of alcohols upstream of sewage inputs highly overlapped those in discharge and mixing zone samples (circa 0.1 to 1 μg g^{-1}) (Dyer et al. 2006). These observations are indicative of and consistent with the widespread natural presence of alcohols in sediments reviewed by Mudge et al. (2008).

3.4 Environmental toxicology

3.4.1 Acute

Alcohols, with the exception of some propargylic alcohols (Veith et al., 1989) which are excluded from this category, act by non-polar narcosis (Lipnick et al., 1985). As chain length increases, hydrophobicity increases resulting in greater toxicity, and in parallel, solubility decreases. At a critical point, solubility becomes lower than expected toxicity and longer chain lengths show no acute toxicity. Chronic effects for such substances are also known; data indicate that effects are anticipated up to C_{15}. For alcohols with carbon numbers higher than C_{15}, there are significant experimental difficulties in producing, maintaining and quantifying exposures of the test substance. Even so, it is unlikely that they would exhibit chronic toxicity because the relationship between carbon number and chronic toxicity suggests that the solubility of the alcohol would limit the bioavailable dissolved fraction to sub-toxic concentrations (Schäfers et al., 2009). In this assessment, trends between aquatic toxicity and carbon chain length are based on normal (non-propargylic) alcohols.

Acute toxicity is predicted well by category specific (Q)SARs. Their success in predicting toxicity for Category members suggests that the members do not possess any particularly unique features. Substances comprising a range of carbon chain lengths can be dealt with by appropriate addition of their individual toxic unit contributions to the whole (Dyer et al., 2006). Effect concentrations vary across members of the category (Table 2).

Table 2: Representative ranges of measured ecotoxicological effect concentrations (μg/L).

Fish acute LC_{50}	D. magna acute EC_{50}	D. magna chronic NOEC	Algae growth rate
480 – 97,000*	800 – 200,000 $^{\Delta}$	10 - 1000$^{\Omega}$	100 – 80,000$^{\Phi}$

* C_{14}-C_6; $^{\Delta}$ C_{11}-C_6; $^{\Omega}$ C_{14}-C_8; $^{\Phi}$ $C_{10\text{-}16}$-C_6

No effects up to the limit of water solubility for single chain lengths >$C_{13\text{-}14}$ and for some multi-component substances are observed. Moreover, no chronic effects are expected for single chain lengths >C_{15} up to limit of aqueous solubility. For Daphnia magna which has the steepest dose-response relative to chain length and is generally recognized as the most sensitive of the three trophic levels tested, the subsequent acute (Q)SAR developed (r^2 = 0.98) is thus:

$EC_{50\ \text{Daphnia magna}}$ (mmol L^{-1}) = 1.92 – 0.83 Log Kow (1) (Fisk et al., 2009).

3.4 Chronic Daphnia magna reproduction

Theory and practice in aquatic toxicology are established for testing that occurs at or below the level of solu-bility. At concentration above the limit of solubility, physical effects enter into observed responses of the organism, but do not reflect the influence of the chemical entering the body, target tissues or cells (ECETOC, 1996; Ruffli et al., 1996). A Daphnia magna chronic toxicity value for C_8 exists in the open literature (Kuhn et al. 1989). Further studies have been conducted for $C_{10,\ 12,\ 14,\ 15}$. Studies with C_{14} and C_{15}

were especially difficult as the predicted water solubilities for these alcohols are very low and very close to expected chronic effect concentrations. Thus, interpretation of the responses can potentially be confounded due to a combina-tion of both physical effects (e.g., entrapment of particles in feeding structures, oil droplets and microemul-sions coating organism surfaces) and toxicity. It is a reality that separating these physical effects and those responses associated with chemical uptake or ecotoxicity is not possible. However, it is possible to evaluate whether test observations adhere to theory and thus allow the results to assist in the inference of solubility being exceeded or not. An example of this would be the expectation that a monotonic increase in toxicity would be observed as hydrophobicity of a chemical series increases. Great care was taken with analytical preparations for the chronic 21-day Daphnia magna tests. Measurements of solubilities, particularly for alcohols of higher chain length (>C_{13}), become increasingly difficult to conduct and increasingly variable. Predicted solubilities then become useful to reduce the importance of variability in the data and its interpre- tation, and to provide grounds for comparison across all compounds. Due to the extensive and rapid bio- degradation of alcohols during the conduct of aquatic toxicity tests, extreme care was taken to minimize the loss of test substances during the tests. Thus, slight modifications of the OECD 211 test guideline were in- troduced. The vessels containing the D. magna were closed to reduce entry of bacteria from the atmosphere, and gently aerating the test vessels top layer to prevent unacceptably low dissolved oxygen levels due to degradative losses of alcohol. Figure 1 represents the measured chronic reproduction toxicity values as a function of hydrophobicity (i.e., log K_{ow}). The data reveal a deflection in the toxicity-hydrophobicity (carbon chain length-dependent) relationship with C_{14} as the most toxic chain length.

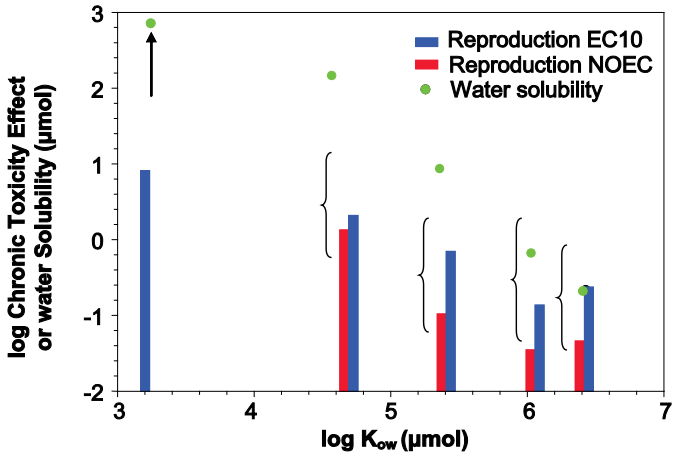

Figure 1. Chronic toxicity of long chain alcohols to Daphnia magna. Both 21-d NOEC and EC10 for reproduction are indicated relative to water solubility. Brackets indicate the range of measured exposure concentration in chronic toxicity studies described in Schäefers et al., 2009. Deflection in the structure-activity relationship occurs as effects are observed at the limit of water solubility with maximum toxicity observed at the C_{14} chain length.

The resulting chronic reproduction (Q)SAR (r^2 = 0.96) with a cut-off at C_{14} is thus: Log $NOEC_{Daphnia\ magna}$ (µmol L^{-1}) = 4.28 – 1.03 Log Kow (2) (OECD, 2006; Schäfers et al., 2009). Emphasis in the risk assessment was placed on 21-d EC10 values as opposed to NOECs due to the greater technical defensibility of EC10s to represent the exposure-response relationship (OECD, 1998).

3.5 Mammalian toxicity

A review of the toxicological database for the category of the LCOH demonstrates that these materials are of a low order of toxicity upon single or repeated exposure. Overall, the data show an inverse relationship between chain length and toxicity. The shorter chain alcohols tend to induce more pronounced effects when compared to materials with a longer chain length. This is illustrated most clearly by the degree of local irritation in studies involving single or repeat administration. LCOH have no skin sensitisation potential, are not mutagenic and have not shown any adverse effects on fertility, development and reproduction. The key human health hazards identified for this category are the irritative properties for skin and eye of the alcohols with chain lengths of C_{11} or below. These hazards are well characterized and do not to lead tissue destruction or irreversible changes. They should nevertheless be noted by chemical

safety professionals and users. On the basis that a clear relationship exists between chain length and toxicological properties, substances with chain lengths exceeding the upper range tested can be expected to possess toxicological properties similar to those tested. The hydroxyl group in alcohols confers upon the hydrocarbon chain a considerable degree of polarity, and hence affinity for water. It is susceptible to oxidation by metabolic processes. Linear or essentially linear hydrocarbon chains are also readily oxidised metabolically. No highly branched structures are included in the Category reviewed in this paper. Substances that contain a number of homologous components can be expected to behave in a way consistent with the carbon number distribution present (Fisk et al., 2009; Veenstra et al., 2009; OECD, 2006).

The typical NOAEL's (No Observed Adverse Effect Levels) recorded for this category range between ca. 200 mg/kg body weight (BW)/day and 1000 mg/kg BW/day in the rat upon sub-chronic administration via the diet. The dermal NOAEL is >2000 mg/kg BW/day. The maximum consumer exposure (dermal) is via body moisturisers (28 mg/kg BW/day). The representable dermal absorption percentage is 32%, yielding a worst-case margin of exposure (MOE) = 2000/28 mg/kg BW/day* 32% absorbed equals a MOE factor of 333 (Veenstra et al., 2009; OECD, 2006). The exposure assessment was conducted according to the methods outlined by Sanderson et al. (2006) and (SDA, 2005).

4. Discussion

The recommendation from the OECD SIDS Initial Assessment Meeting (SIAM) in April of 2006 regarding human health hazards of long chain alcohols was that the key hazards identified for the category are the local irritative properties for skin and eye of alcohols with chain lengths of C_{11} or below. The category is thus of low priority for further work (OECD, 2006; Veenstra et al., 2009).

The recommendation regarding the environmental hazards concluded that all of the category members are rapidly biodegradable, especially at environmentally relevant concentrations. Alcohols are metabolized and/or biotransformed in living organisms. This biotransformation suggests that bioaccumulation potentials based on octanol-water partition coefficients may be overestimates. Measured BCF data on a related alcohols category supports the concept that the bioaccumulation potential of these substances will be lower than estimated from log K_{ow}. Sixteen out of the 30 compounds had an acute aquatic toxicity below 1 mg L^{-1}, which leads to a default recommendation for further work by the OECD, if the compound is not an intermediate, regardless of any other property associated to the compound (e.g. rapid biodegradation). Hence, member states, and others, are invited to conduct an exposure assessment and, if necessary, a risk assessment (OECD, 2006). The papers provided in this journal issue provide that risk assessment.

LCOH tend to sorb to sediments after release to the environment via wastewater treatment effluent. Trickling filter treatment facilities have the least effective removal rate of alcohols (98.8%) and also the relatively highest effluent concentrations (maximum total (C_{12-15}) measured = 4.92 μg L^{-1}). Hence, the expected worst-case exposure scenario would be the sediments downstream a trickling filter treatment plant. Dyer et al. (2006) reported a sediment dependent organism PEC/PNEC = 0.03-0.07 for the combined mixture of LCOH C_{12-18} downstream of a trickling filter plant (total sediment concentration = 0.546 μg L^{-1}), indicative of low environmental risk (Belanger et al. 2009). In this relation it is important to recall Federle and Itrich (2006) results on the rapid degradation of long chain alcohols, with half-lives in sewage treatment being less than one minute. The conditions downstream the trickling filter plant will also incur rapid degradation in situ and it is thus unlikely that LCOH will accumulate to levels that would cause physical stress to biota in or above the sediment under normal environmental conditions. The focus on the C_{12-18} homologue range was chosen because this is range of greatest commercial interest to the detergent industry and this range overlaps the compounds that were recommended for further work by the OECD. Hazard screening is certainly an important first tier in evaluating the safety of chemicals. However, regulatory decision-making and risk management based on hazard information only, and

ignoring exposure and risk aspects, is relying on information fraught with significant scientific and extrapolation uncertainties. To a large extent, these uncertainties are the very same uncertainties a sound and science based risk assessment aim to elucidate.

5. Conclusion

The main findings of the HPV long chain alcohol (LCOH) category case-study are:

- No unacceptable human or environmental risks were identified
- LCOH occur naturally in the environment in a fluctuating equilibrium between synthesis and degradation by natural processes.
- A parabolic relationship exists between carbon chain length (hydrophobicity) and toxicity as a demonstrated in chronic testing of the very rapidly biodegradable compounds in this category - very close to the compounds' limit of water solubility.
- Category specific read-across and (Q)SARs were developed enabling prediction of key properties across the entire category (C_{6-22}).
- The overall conclusions from this case-study relative to the global HPV activities are that industry can come together and form international consortia to share resources resulting in minimizing the need for additional animal tests, producing cost savings, and increasing transparency and the scientific quality of the work even for large and very complex categories of chemicals.

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Appendix III-D

Long Chain Alcohols (LCOH) - Human Health Risk Assessment

Veenstra G, Webb C, Sanderson H, Belanger SE, Fisk P, Nielsen A, Kasai Y, Willing A, Dyer S, Penney D, Certa H, Stanton K, Sedlak R. 2009. Human health risk assessment of long chain alcohols. Originally published in *Ecotoxicology and Environmental Safety*, 72:1016–1030. Available at http://www.elsevier.com/locate/ecoenv. DOI:10.1016/j.ecoenv.2008.07.012.

Human Health Risk Assessment of Long Chain Aliphatic Alcohols

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Abstract

Representative chemicals from the long chain fatty alcohols category have been extensively tested to define their toxicological hazard properties. These chemicals show low acute and repeat dose toxicity with high dose effects (if any) related to minimal liver toxicity. These chemicals do not show evidence of activity in genetic toxicity tests or to the reproductive system or the developing organism. These chemicals also are not sensitizers. Irritation is dependant on chain length; generally, alcohols in the range $C_{6\text{-}11}$ are considered as irritant, intermediate chain lengths (C_{12-16}) alcohols are considered to be mild irritants and chain lengths of C_{18} and above are considered non-irritants. These chemicals are broadly used across the consumer products industry with highest per person consumer exposures resulting from use in personal care products. Margins of exposure adequate for the protection of human health are documented for the uses of these chemicals.

1.0 Introduction

The long chain aliphatic alcohol category is based upon a homologous series of increasing carbon chain lengths sharing common and predictable physical-chemical properties within the family covering a carbon (C) chain length range of C_6 to C_{22} (Fisk et al., 2009). The raw materials and the commercial industrial processes used for the manufacture of these alcohols necessarily result in a distribution of homologous chain lengths and, therefore, commercial long chain aliphatic alcohols usually contain a range of carbon chain lengths. The components of all industrial products relevant to this category are primary alcohols. Some products may include components that are unsaturated; essentially linear (mono-alkyl branched) and linear alcohols with carbon chain length that are odd, even or both. The two subcategories (linear and essentially linear) as defined in OECD (2006) are noted after each CAS number as this distinction becomes important for segments of the risk assessment.

The long chain aliphatic alcohols are used in a wide variety of industrial, commercial and institutional uses (Modler et al., 2004). Many of the applications utilize the alcohol backbone as a synthetic intermediate which is then ethoxylated, propoxylated, sulfated or both to derive anionic (alcohol sulfate, alcohol ethoxysulfate) and nonionic (alcohol ethoxylate or propoxylate) surfactants. A number of

applications also use the free alcohols as such. Most of these latter applications involve their lubricating, emollient, solubilizing or emulsifying properties. These include cosmetics and toiletries, surface lubricants and pharmaceutical preparations.

Based on a survey in 2002, the estimated total production of long chain alcohols (C_6 to C_{22}) is *ca*. 1550 million metric tones per annum with North America, Europe and Asia-Pacific regions accounting for *ca.* 40%, 45%, and 15% of the total production, respectively (OECD, 2006).

The primary data set presented here was endorsed by the Organisation for Economic Co-operation and Development (OECD) high production volume (HPV) chemicals programme as a category of substances at the SIDS Initial Assessment Meeting (SIAM) 22, in which data for individual members are presented as part of a whole set, rather than substance-by-substance (long chain aliphatic alcohol category SIAR; OECD, 2006). Additional data have been included when their availability post dates the OECD submission or when data were not relevant to the OECD hazard-based submission for the designated substances in the category, but are relevant to the risk assessment. A chemical category is defined as "a group of chemicals whose physicochemical and toxicological properties are likely to be similar or follow a regular pattern as a result of structural similarity" (OECD, 2006). Fisk et al. (2009) present data which establishes such a pattern for this homologous series of alcohols.

2.0 Methods

Details of the chemicals belonging to the category of the long-chain aliphatic alcohols, the rational for the formation of this category and their physico-chemical properties are presented by Sanderson et al. (2009) and Fisk et al. (2009).

In this paper an overview of the hazard data available for the long chain alcohols (LCOH) category is presented. The test methods and protocols are not described in detail in this paper; further details are presented in the SIAR and its Annexes for this category (OECD, 2006).

Any studies referred to in this overview article were conducted in accordance to national and/or international guidelines for protection of human subjects and animal welfare.

2.1 Consumer Exposure Scenarios

The use of consumer laundry detergents, fabric conditioners and personal care products have been modelled using screening level inputs for an initial consumer exposure assessment. These inputs can be based on simple, first principle exposure equations, conservative assumptions about exposure, and readily available information about the characteristics of the chemical group, the consumer product type, and the nature of the products used. Additional data to refine the assessment have been included as needed depending on the margin of exposure consistent with the general principles of an iterative risk assessment. The skin is the predominant route of exposure associated with the use of these products, but a scenario addressing potential inhalation exposure through the use of sprays is also included in this assessment.

2.1 Tools and Models

The modeling presented here uses simple, first principle equations, which, when combined with conservative (protective) input values, err on the side of being protective.

These exposure calculations use the principle equations and are mathematically consistent with the Exposure Guidelines of the U.S. EPA (1992) with regard to modeling dermal and inhaled exposures.

In general terms, human exposure to a chemical can be characterized as a function of the level of exposure to a particular product or product type and the concentration of the chemical of concern found therein. Mathematically, this can be expressed as:

Equation 1:
Potential Chemical Exposure (PE) = Exposure to Product (EXP) x Chemical Concentration in Product Formulation (PF)

More specific forms of this generalized model can be formulated for dermal and inhalation routes of exposure as described below.

Dermal exposure models for example, would be appropriate for exposure during the activity or use of diluted and undiluted laundry and diluted or undiluted hard surface cleaning products as characterized in Equation 2:

Equation 2: $$\frac{[FQ \times CA \times PC \times FT \times CF \times TF \times DA]}{BW} \times PF$$

A modification of the equation would be appropriate for exposure to laundry products and fabric conditioners which leave a potential residual chemical on clothing as expressed in Equation 3:

Equation 3: $$\frac{[FQ \times A \times PR \times PT \times DA \times CF]}{BW} \times PF$$

A third modification would be suitable for exposure to a residual chemical after using personal care products where the chemical is intentionally applied in a way that results in exposure to skin as in Equation 4:

Equation 4: $$\frac{[FQ \times A \times PR \times DA \times CF] \times PF}{BW}$$

In all the above cases (Equations 2, 3, and 4) the relevant variables are below:

FQ: Frequency of use (use/day)
CA: Body surface contact area (cm^2)
PC: Product concentration (g/cm^3)
FT: Film thickness on skin (cm)
TF: Time scaling factor (unit less)
DA: Dermal absorption (%)
BW: Body weight (kg)
PF: LCA concentration in product formulation (%)
A: Amount per use (g/day or g/wash)
PR: Percent retained on clothing or on skin (%)
PT: Percent transferred from clothing to skin (%)
CF: Conversion factor (g conversion to mg)

Another exposure scenario which was considered is by inhalation. This exposure scenario would be relevant for inhalation exposure (non-volatile components) to spray cleaning products during use as described in Equation 5:

Equation 5: $$\frac{[FQ \times RPC \times IR \times ED \times BA]}{BW} \times PF$$

Where:
FQ: Frequency of Use (use/day)

RPC: Respirable Product Concentration in breathing zone (mg/m^3)
IR: Inhalation rate (m^3/hr)
ED: Exposure duration (hr/day)
BA: Weight fraction absorbed or bioavailable (%)
BW: Body weight (kg)
PF: Concentration in product formulation (%)

3.0 Results

3.1 *Toxicokinetics, metabolism and distribution*

The initial step in the mammalian metabolism of primary alcohols is the oxidation to the corresponding carboxylic acid, with the corresponding aldehyde being a transient intermediate. These carboxylic acids are susceptible to further degradation via acyl-CoA intermediates by the mitochondrial β-oxidation process. This mechanism removes C_2 units in a stepwise process; linear acids are more efficient in this process than the corresponding branched acids. In the case of unsaturated carboxylic acids, cleavage of C_2-units continues until a double bond is reached. Since double bonds in unsaturated fatty acids are in the cis-configuration, whereas the unsaturated acyl-CoA intermediates in the β-oxidation cycle are trans, an auxiliary enzyme, enoyl-CoA isomerase catalyses the shift from cis to trans. Thereafter, β-oxidation continues as with saturated carboxylic acids (WHO, 1998).

An alternative metabolic pathway for the degradation of aliphatic acids exists through microsomal degradation via ω-or ω–1 oxidation followed by β-oxidation. This mechanism provides an efficient stepwise chain-shortening pathway for branched aliphatic acids (Verhoeven et al., 1998).

The acids formed from the longer chain aliphatic alcohols can also enter the lipid biosynthesis and may be incorporated in phospholipids and neutral lipids (Bandi et al., 1971a, 1971b; Mukherjee et al., 1980). A small fraction of the aliphatic alcohols may be eliminated unchanged or as the glucuronide conjugate (Kamil et al., 1953).

Mudge et al. (2008) presents a detailed overview of the metabolic pathways involved in the degradation of long-chain aliphatic alcohols.

Aliphatic alcohols have a potential for absorption at varying degrees by all common routes of exposure. Based on comparative *in vitro* skin permeation data and dermal absorption studies in hairless mice, aliphatic alcohols show an inverse relationship between absorption potential and chain length with the shorter chain alcohols having a higher absorption potential than the longer chain alcohols (Iwata et al., 1987) consistent with the established relationship between skin penetration and physico-chemical properties. However, quantitative dermal absorption data were not available from the literature.

To address this data gap, the following study was conducted (P&G, 2007). The study was a non-GLP which conformed to OECD test methods (OECD, 2004). An *in vitro* skin permeation study of radiolabeled tetradecanol from a 2% tetradecanol containing oil-in-water prototype emulsion, formulated to be representative of a typical body lotion, was conducted to assist in an estimation of the systemic exposure of tetradecanol in particular, and long chain fatty alcohols in general from topically applied personal care products. Tetradecanol was chosen as the model alcohol because it is the shortest chain length alcohol reported to be used in personal care products (SDA, 2002). Given that skin penetration is anticipated to decline with increasing chain length (due to decreasing water solubility and increasing molecular weight), testing the shortest chain length alcohol provides an estimate of the maximum

potential absorption of fatty alcohols used in personal care products. For comparison, hexadecanol, using the DERMWIN model (U.S. EPA, Epi Suite v. 3.12, SRC, 2005), would be projected to have a 2.7-fold lower skin penetration coefficient than tetradecanol and the larger alcohols would have even lower skin penetration rates. The intradermal and transdermal permeation of radiolabeled tetradecanol was assessed using split-thickness cadaver skin from three donors over emulsion application times ranging from three to 48 hr following application of 2 mg/cm2 product containing 2% tetradecanol. The data generated in this study show that the *in vitro* skin permeation of radiolabeled tetradecanol can be modeled as a square-root-of-time function as described in the literature. The derived penetration percentage which is applicable only until residual product is removed from the skin translates to 32% over 24-hours under the conditions of this *in vitro* study.

In order to apply skin penetration coefficients as an adjustment to oral bioavailability when using oral toxicology data for the risk assessment it is important to understand the oral bioavailability of the test material. Oral absorption of aliphatic fatty alcohols appears to be good (Friedberg, 1976). Using doubly labeled hexadecanol as a model compound Friedberg found that up to 23% was found in plasma as unchanged fatty alcohol (similar to other reports of 25%) and that significant radioactivity was also seen in phospholipid, triglyceride and diacyl glyceryl ether fractions with smaller amounts as free fatty acids and wax esters consistent with other reports that metabolites of these chemicals enter normal lipid metabolism pathways. Total mass balance is not presented by Friedberg, but based on the author's reference to earlier studies that showed 25% of oral hexadecanol is absorbed as the unchanged fatty alcohol and the reported results that show that fatty alcohol was only from 3-23% of the total plasma radioactivity, it appears that overall absorption of administered hexadecanol as the sum of unchanged and metabolized compound represents the majority of the dosed material.

With regards to the blood-brain barrier, a chain-length dependant absorption potential exists with the lower aliphatic alcohols and acids more readily being taken up than aliphatic alcohols/acids of longer chain-length (Gelman and Gilbertson, 1975).

Aliphatic alcohols are unlikely to have tissue retention or bioaccumulation potential (Bevan, 2001). Longer chain aliphatic alcohols within this category may enter common lipid biosynthesis pathways and, if so, could be indistinguishable from the lipids derived from other sources (including dietary glycerides) (Kabir and Kimura, 1993; 1995; Mudge et al. (2008).

3.2 *Acute Toxicity*

3.2.1 Oral

The category of the long chain alcohols is of a low order of acute toxicity with oral LD_{50} values in excess of 2,000 to well over 10,000 mg/kg across the whole category. Most reported values represent the highest dose tested instead of lethality. 1-Hexanol is also of a low order of acute oral toxicity. However the data suggest that its LD_{50} value (ca. 3000–4000 mg/kg) is somewhat lower than that of the linear alcohols with a chain length of C_8 and higher (OECD, 2006).

In line with current testing guidelines, more recent studies report oral LD_{50} values >2,000 mg/kg, the limit dose. No significant signs of toxicity were noted in these studies and a high degree of consistency was observed within the long chain alcohol category for this endpoint. Acute oral toxicity data in species other than the rat are limited, but confirm the very low acute human toxicity of this category of alcohols (OECD, 2006).

Few, if any signs of toxicity were reported following oral administration of the aliphatic alcohols ranging from C_6 to C_{22} alcohols. At doses approaching acute lethality loss of appetite, lethargy and diarrhea was

reported for some of the alcohols. Animals surviving a large oral dose showed no evidence of any delayed or irreversible effects following acute administration. In decedents irritation of the gastro-intestinal tract and typical agonal changes were observed. However no substance specific observations could be recognized for any of the materials. Animals surviving a large oral dose showed no evidence of any delayed or irreversible effects following acute administration of any of these alcohols. There are no observations reported to suggest a potential for CNS depression following administration of a single oral dose (OECD, 2006).

Intratracheal installation studies in rats suggested that linear aliphatic alcohols with chain lengths up to C_{13} may have an aspiration potential. In these studies alcohols with a chain length up to C_{10} induced immediate respiratory or cardiac arrest. Alcohols in the range C_{10-13} induced significant pneumonitis (Gerarde and Ahlstrom, 1966).

Conclusion: The category of the long chain aliphatic alcohols is of a low order of acute toxicity upon oral administration.

3.2.2 Inhalation

The volatility of the category of aliphatic alcohols as a whole is low. Saturated vapour pressures for the higher chain alcohols are extremely low; for example the calculated concentration of a saturated atmosphere of 1-dodecanol and 1-octadecanol at ambient conditions is in the order of 10^{-2} and 10^{-5} mg/L, respectively. Most experimental studies used the maximum achievable vapor concentrations or aerosols for the assessment of the acute lethal concentration. For all substances tested, the LC_{50} values exceeded the maximum achievable vapor concentrations. The more volatile members of this category (e.g. 1-hexanol, C_{6-12} alcohols, 1-heptanol and 1-undecanol) showed no evidence of toxicity after a single exposure for 1to 6 hours. None of the acute inhalation studies provided any evidence of CNS depression. This conclusion is further supported by data in mice indicating that inhalation of high concentrations (up to ca. 10,000 ppm) of 1-heptanol for short periods of time did not induce anaesthesia (OECD, 2006).

Conclusion: Inhalation of vapours of long chain alcohols in the range C_6-C_{22} at levels up to the saturated vapour pressure is unlikely to be associated with significant toxicity.

3.2.3 Dermal

The reported dermal LD50 values are >2000 mg/kg, all representing the maximum dose tested (limit dose). For some of the aliphatic alcohols the reported acute dermal LD_{50} values were 8000 mg/kg or higher. Although some incidental LD_{50} values below 2000 mg/kg were reported, these data generally represented the maximum dose tested, and were without evidence of any systemic toxicity (OECD, 2006).

Occluded exposure for 24 hours generally caused local dermal irritation. There was a clear (inverse) relationship between the chain length and the severity of the dermal effects. The severity of the irritation was graded as moderate–severe for the lower members of this category; typical observations included erythema, oedema, wrinkling, desquamation and cracking. The grading of the local effects for the aliphatic alcohols with a longer carbon chain was reported as slight-moderate. Animals showing signs of significant local irritation displayed signs of toxicity such as general weakness, anorexia, lethargy; it is not possible to ascertain if these findings were secondary to the irritation or evidence of direct systemic toxicity (OECD, 2006).

Conclusion: The category of the long chain aliphatic alcohols is of a low order of acute toxicity upon dermal administration.

3.3 Irritation and sensitisation

3.3.1 Skin Irritation Studies in Animals

The lower members of the aliphatic alcohols (C_{6-11}) have a skin irritancy potential ranging from mild to irritant, when applied undiluted for 4–24 hours. Application of diluted materials resulted in a lower grade irritation. The skin irritation potential of aliphatic alcohols in the range C_{12} and C_{16} is graded as mild - essentially non-irritant. Alcohols with a carbon chain length C_{18} and above were generally without evidence of a skin irritation potential.

Unsaturated alcohols have a potential for mild skin irritation (Guillot et al., 1977; Motoyoshi et al., 1979).

For read-across, alcohols in the range C_{6-11} are considered as irritant, representing the worst-case response within this range. Similarly, the intermediate chain lengths $C_{12–16}$ alcohols are considered to be mild irritants and non-irritant for chain lengths of C_{18} and above.

3.3.2 Skin Irritation Studies in Humans

Comparative studies have shown that the cutaneous responses following a single topical application of aliphatic alcohols in the range $C_{6–22}$ decreased in the order rabbit, guinea pig, hairless mouse and human, with the human responses being categorised as virtually non-irritant (Kaestner, 1977; Motoyoshi et al., 1979). Human skin contact for periods up to 4 hours showed that alcohols in the range $C_{6–10}$ were not classifiable as a skin irritant when compared to SLS (sodium lauryl sulphate, SLS; a positive control – classifiable- substance) (Griffiths et al., 1997).

Alcohols in the range C_{12-18}, including unsaturated alcohols, caused at most a mild transient erythema following an open application test according to Burckhardt, or in a 4- hour semi-occluded patch test (comparable to OECD 404, OECD, 2002) or an open application test. The responses recorded in these assays were well below those observed for a positive control substance (20% SLS) and justify no classification for skin irritation for these alcohols (OECD, 2006; Griffiths et al., 1997). Sato et al. (1996) reported a low irritancy in the range $C_{12–18}$ alcohols. However 1-octanol was of a slightly higher order of irritation.

In scarified human skin slight to marked responses were reported following daily applications over a period of 3 days. The degree of irritation was inversely related with the carbon chain length with a marked response reported for C_{10} and C_{12} alcohol, a moderate response for C_{14} alcohol and a slight response for C_{16} alcohol (Frosch and Kligman, 1976).

Overall, human data indicate that the irritation responses for the category of the long chain aliphatic alcohols are of a lower order than that observed in rabbits.

3.3.3 Eye Irritation

The available eye irritation data indicate that the members of category of alcohols induce varying degrees of irritation within the lower chain lengths [$C_{6–11}$]. The eye irritation potential for the long chain alcohols with a chain length of C_{12} and above is minimal (OECD, 2006).

For read-across purposes alcohols in the range C_{6-11} are regarded eye irritant, representing the worst case within this range. Alcohols with a chain length of C_{12} and above are expected to be non-irritant.

3.3.4 Respiratory Tract Irritation

In mice, RD_{50} (concentration required to evoke a 50 % reduction in respiration rate) values in the order of 50–100 ppm were recorded for 1-heptanol and 1-octanol, suggesting a potential sensory irritation for some of the lower alcohols (Hansen and Nielsen, 1994; Muller and Greff, 1984; Bos et al., 1991). On the

basis of the limited volatility especially at higher chain lengths, higher aliphatic alcohols are unlikely to be of concern for sensory irritation. For example, the saturated vapour concentration for C_9 alcohols is ca. 30 ppm (25°C), whereas for $C1_2$ alcohol it is calculated to be ca. 1 ppm (25°C) (Fisk et al., 2009).

3.3.5 Skin Sensitisation

No skin sensitisation reactions were observed for the category of the aliphatic alcohols, with the exception of a single report (OECD 2006). In a modified (non-adjuvant) Draize test 1-decanol [a commercial sample of unknown isomeric composition] did not show any responses in guinea pigs following an intra-dermal induction and a topical and/or an intradermal challenge. However after a re-induction (intra-dermal) and re-challenge a weak response was reported (Sharp, 1978). The significance of this single weakly positive result is very limited on the basis that the result was obtained in a non-standard test assay applying a material of unknown composition and origin. U.S. EPA (2006a) reports that decanol was not a sensitizer when tested at 37.98% or at 79% in guinea pigs. The weight of the evidence indicates that this category does not have significant skin sensitisation potential in guinea pigs.

Human volunteer studies showed no evidence of any sensitising properties following a repeated insult patch tests for C_{16} and C_{18} alcohol (Gloxhuber, 1983). Patch testing of patients with contact dermatitis showed that several long chain aliphatic alcohols were implicated in contact allergies. Considerable variation in the incidence of responders was reported in these studies (range ca. 1–25%). There is evidence to suggest that some of the responders were atopics (Auth et al., 1984; Blondeel et al., 1978; Fisher et al., 1971; Goossens et al., 1999; Hjorth and Trolle-Lassen, 1963; Tosti et al., 1996; Van Ketel, 1984).

Given the wide dispersive use in consumer and occupational applications and the relatively low numbers of reported cases of allergy, it can be concluded that long chain alcohols have a very low allergenic potency.

3.4 Repeated Dose Toxicity

3.4.1 Studies in rats

3.4.1.1 Inhalation

Inhalation of saturated vapours $C_{9\text{-}11}$ alcohols (CAS 66455-17-2, containing mainly C_9, C_{10}, C_{11} Alcohols, linearity > 80%) for 9-days caused no adverse effects (OECD, 2006).

3.4.1.2 Oral

The following section summarizes a large series of studies on related members of the long chain alcohol category with respect to repeat oral dose toxicity.

Iso-amyl alcohol [CAS 123-51-3 essentially linear]: This alcohol was administered daily by gavage for 17 weeks to rats with interim laboratory assessments at 3 and 6 weeks. No adverse effects, other than reduced body weight gain and food consumption were recorded at 1000 mg/kg (Carpanini et al., 1973).

1-Hexanol [CAS 111-27-3]: Rats exposed to 1-hexanol via the diet for 13 weeks showed no signs of statistically significant toxicity when administered at nominal concentrations up to 1% (with staged increases at concentrations up to 6% during the last phase of the exposure period). There were no microscopic alterations recorded in the animals receiving concentrations of 1-6% (equivalent to 1127 mg/kg/day). Examination of testes and the ovaries did not show any abnormalities (OECD, 2006).

Exposure of male rats to high dietary concentrations (up to 8%) of 1-hexanol for 2 weeks did not produce evidence of peroxisome proliferation (Moody and Reddy, 1978, 1982).

C_{6-12} Alcohol [CAS 68603-15-6, essentially linear]: A 2-week study showed no potential for peroxisomal proliferation for a C_{6-12} alcohol. There were no effect on liver and testes weight and indications of peroxisome proliferation and hypolipidaemic activity in male rats was absent; an equivocal increase in palmityl CoA oxidase activity was noted in an *in vitro* assay (Rhodes et al., 1984). In sub-acute studies, essentially linear alcohols in the range C_{7-9}; when administered orally for 2 weeks did not show evidence of systemic toxicity, including effects on the liver and testes or signs of peroxisomal proliferation or hypolipidaemia (Rhodes et al., 1984). Administration (5 ml/kg/day) of C_6 to$_{12}$ alcohol (containing mainly C_7, C_8 and C_9 alcohols or mainly C_9, C_{10}, C_{11} alcohols) to rats resulted in local irritation of the GI-tract and equivocal evidence of slight liver toxicity in some rats (Brown et al., 1970).

C_{7-11} Alcohols [CAS 85566-14-9 essentially linear]: In a developmental toxicity study the surrogate C_{7-11} alcohol was administered by daily oral gavage of rats during days 6-15 of pregnancy at dose levels of 0, 144, 720 or 1440 mg/kg/day. There were no treatment-related effects noted in body weight development, food consumption or adverse clinical observations during the study. No further detailed assessment of maternal toxicity was included in the design of this developmental toxicity study (Hellwig and Jäckh, 1997).

1-Octanol [CAS 111-87-5]: In a developmental toxicity study administration of 1-octanol by daily gavage of doses in the range 130 – 1300 mg/kg to pregnant rats caused dose-related clinical signs of toxicity, including nasal discharge, pneumonia, and signs consistent with slight, transient CNS depression at levels of 650, 975 and 1300 mg/kg/day. Slight decreases in body weight gain and food consumption were observed. The severity of these effects may have been exacerbated by the pregnancy of the test animals. 1-Octanol induced respiratory distress upon repeated administration of a bolus dose. No detailed assessment of the maternal toxicity was included in the design of this developmental toxicity study (Hellwig and Jäckh, 1997).

Fatty alcohol blend (56.7% 1-decanol 112-30-1, 42.7% octanol 111-87-5): This alcohol blend was tested in an oral developmental toxicity study in rats (U.S. EPA, 2006a). In this study a developmental toxicity NOAEL was established at 1,000 mg/kg/day (highest dose tested), while a maternal NOAEL of 375 mg/kg/day was defined based on an increased incidence of salivation at the 1,000 mg/kg/day dose. Within the same research program (U.S. EPA, 2006a), a 90-day dermal application study in rats was also performed which demonstrated primarily changes to the skin indicative of irritation. According to the summary, systemic effects were limited to marginally increased adrenal glands in high-dose animals, slightly reduced RBC counts, hematocrit, and increased WBC and platelet counts in high-dose animals. No gross or histological alterations other than severe irritation. Based on these observations at 1,000 mg/kg, U.S. EPA defined 300 mg/kg as the NOAEL. It is plausible that the non-skin effects noted reflect the consequences of the severe skin effects and the resultant inflammatory response and stress.

1-Dodecanol [CAS 112-53-8]: This C_{12} alcohol was tested in rats in a combined repeated-dose and reproductive / developmental toxicity screen. Animals received dietary concentrations of 1500, 7500 or 30,000 ppm during all phases in the production of a single generation; the composition of the diet was adjusted to take account of the caloric incorporation of the test material. Male animals were exposed for a total of 37 days including the mating period. Females were allowed to litter naturally and were terminated at day 5 post-natally. In males, there were no effects recorded other than a reduction in mean white blood cell count (15, 38 and 32% reduction for the low mid or high dose group, respectively) and changes in free cholesterol (38% reduction in the mid dose group) and triglycerides (46% reduction at the top dose level). In the absence of any changes in the differential white cell count, the observed reduction in total WBC is considered of uncertain significance. A reduction in plasma cholesterol was observed in the middle dose group; this was considered a chance finding associated with 2 outlying values. Although the reduction in plasma triglycerides and cholesterol levels may be indicative of marginal effects in the liver,

the differences in composition of the test diets between control and the treatment groups may have confounded some of the parameters measured in this study. The NOEL was <1500ppm (<100 mg/kg/day) based on the haematological (WBC) changes; the NOAEL was 30,000 ppm (2000 mg/kg/day) (Hansen, 1992a).

C_{10-16} Alcohol [CAS 67762-41-8 essentially linear]: In a 28-day oral toxicity study in rats C_{10-16} alcohol induced slight body weight reductions in males receiving 1000 mg/kg/day (ca. 10% reduction in overall body weight gain). Further changes at 1000 mg/kg/day were consistent with slight liver toxicity: elevated levels of ALT, AP and cholesterol (increases of *ca* 50, 40, 30% respectively) in females but without any concurrent histopathological findings. There was a dose-related increased in relative kidney weights in males at 300 and 1000 mg/kg/day. However there were no toxicological findings associated with the renal weight changes and, therefore, the kidney weight changes were considered not of toxicological significance. The level of 300 mg/kg is therefore regarded to be without adverse effects (NOAEL) based the body weight changes and liver effects at 1000 mg/kg/day. No changes were noted in testis and ovaries at 1,000 mg/kg/day, the highest dose tested. At 100 mg/kg/day no changes were observed (OECD, 2006).

C_{14-16} alcohol [CAS 68333-80-2 essentially linear]: In a 13-week rat study C_{14-16} alcohol was administered via the diet at concentrations of 0, 0.2, 1 and 5%. The top and intermediate dose level (5 and 1%, respectively) had limited palatability and induced a considerable reduction in growth (> 30% and ca. 15% reduction in body weight in high and mid dose males, respectively). Biochemistry showed changes in AP, ALT and protein ratios at the 1 and/or 5% level. Organ weight changes were consistent with an increased liver weight. No treatment-related microscopic changes were observed, including both the testis and ovaries at this same dose level. Based on the effect on body weight a NOAEL was established at the 0.2% dietary incorporation level (ca. 200 mg/kg/day). The results of the clinical chemistry and the organ weight analysis are consistent with slight liver toxicity, however there were no correlating histopathological changes in the liver. These changes in the liver enzyme profile may well have been confounded by inanition (Ito et al., 1978).

1-Tridecanol [CAS 112-70-9]: 1-tridecanol was shown to be without a potential for peroxisomal proliferation or hypolididaemia. No histological or weight changes were observed in the liver and testes after oral administration of 184 mg/kg/day for 2 weeks (Rhodes et al., 1984).

1-Hexadecanol [CAS 36653-82-4]: The C_{16} alcohol was without toxic effects in a 28-day study in rats receiving daily oral [gavage] doses of 0 (control), 100, 500 and 1000 mg/kg/day (OECD, 2006).

In a 13-week study in rats 1-hexadecanol was administered in the diet at concentrations of 0 (control), 1, 2.5 or 5%; the level in the highest dose group being increased stepwise to 10% during the last 3 weeks of the study. Reductions in body weight gain (82-90% of control values) and food consumption (76–90% of control values) in the highest dose group and, occasionally, at the 2.5% level were the main findings of this study. Relative liver weights were increased in males at the top dose level (124% of control values) but in the absence of any microscopic findings the significance of this change is uncertain. A NOAEL was established at a dietary concentration of 1% (equivalent to *ca.* 750 mg/kg/day) based on the reductions in body weight gain and food consumption (OECD, 2006).

C_{16-18} and C_{18} unsaturated alcohols [CAS 68002-94-8]: These alcohols were without adverse effects in rats upon daily administration of 1 ml/kg/day (*ca.* 850 mg/kg/day) for 4 weeks (OECD, 2006).

1-Octadecanol [CAS 112-92-5]: C_{18} alcohol was tested in Wistar rats in a combined repeated dose and reproductive/developmental screen. Animals received dietary concentrations of 1500, 7500 or 30,000 ppm during all phases in the production of a single generation; the composition of the diet was adjusted to

take into account the caloric value due to the incorporation of the test material. Male animals were exposed for 37 days including the mating period. Females were allowed to litter and were terminated at post-natal day 5. In male animals (females were not investigated) reductions were recorded in the levels of plasma glucose (>15% reduction in all treatment groups) and triglycerides (>37% reduction all treated level); free cholesterol levels were increased 25% or more in all treated groups; these changes were without a clear dose-response. No treatment-related histopathological changes were recorded. Although the clinical chemical changes may be indicative of mild effects in the liver, the differences in the composition of the test diets may have contributed to these results. The NOAEL was 30,000ppm (2000 mg/kg/day); the NOEL was <1500 ppm (<100 mg/kg/day) based on the changes in the clinical chemistry (Hansen, 1992b).

In a 4-week oral study 1-octadecanol was administered daily (5 times/week) in olive oil to groups of 10 male and female Sprague-Dawley rats at levels of 0 (control), 100, 500 and 1000 mg/kg/day. There were no adverse effects reported in this study during all stages of the study (OECD, 2006).

1-Docosanol [CAS 661-19-8; C22 alcohol]: Docosanol was administered daily to groups of rats at levels up to 1000 mg/kg for 26 weeks. Body weight and food consumption was not affected by treatment. Haematology, clinical chemistry and gross necropsy investigations showed no evidence of toxicity. There were no treatment related microscopic changes (OECD, 2006).

C_{24}-C_{34} Alcohols [CAS 123607-66-9]: These very long chain alcohols were dosed daily by oral gavage of rats for periods up of 12 months. No adverse effects were recorded in any of these studies. The NOAEL was 1000 mg/kg/day (highest dose tested) following a 52-week exposure period (Rodeiro et al., 1998a).

3.4.1.3 Other routes of exposure

1-Hexanol [CAS 111-27-3]: No potential for peripheral neuropathy was identified in rats upon i.p. administration of 1-hexanol at levels of 102.5 mg/kg for 30 weeks (6 days/week) (Perbellini et al., 1978).

3.4.2 Studies in dogs

1-Hexanol [CAS 111-27-3]: Daily administration of capsules containing 1000 mg/kg/day 1-hexanol to male and female dogs resulted in post-dose salivation, transient but marked CNS effects (ataxia, tremors and narcosis) and mortality. One animal died after the first dose (not examined microscopically); 3 of 5 animals after 3-5 weeks. In all decedents death was attributed to aspiration while the animals were under substance-induced narcosis. Macroscopic and microscopic examination of the decedents showed severe inflammation of the upper gastro-intestinal tract and testicular atrophy and decreased oogenesis. The single surviving female showed signs of gastro-intestinal irritation; however there were no adverse effects on the ovaries.

Other groups of 2 dogs/sex received 1-hexanol incorporated in the daily ration at nominal concentrations of 0 (control), 0.5 or 1.0%. Apart from local irritation of the gastro-intestinal tract in the 1.0% dose group, no adverse systemic effects were observed in these animals.

The testicular effects observed in the early decedents were attributed to the general ill health of these animals caused by the severe gastro-intestinal irritation. This likelihood is supported by the lack of gonadal effects in dogs exposed to 1% and 0.5% 1-hexanol in the dietary portion of the study that showed greatly diminished or absence of the gastro-intestinal irritation, respectively. No other significant effects were noted at the 0.5% dietary level. The threshold for local irritative effects was 190 mg/kg/day (0.5%). The NOAEL for systemic effects was established at 1.0%, equivalent to 370 mg/kg/day (the highest dose tested in this portion of the study) (OECD, 2006).

1-Hexadecanol [CAS 36653-82-4]: In a 13-week study groups of 2 dogs/sex/dose received dietary concentrations of 0 (control), 0.5, 1.0 or 3% 1-hexadecanol. There no were adverse effects reported except for elevations of AST at week 13 at all incorporation levels, without evidence of a clear dose response relationship. The small groups sizes used in this study preclude a definitive conclusion about the significance of these changed enzyme levels, especially in the absence of any further corroborating evidence of liver toxicity (liver weight and histology). A NOAEL of 1000 mg/kg (highest dose tested) is therefore proposed (OECD, 2006).

1-Docosanol [CAS 661-19-8; C_{22} alcohol]: In this study docosanol was administered daily to groups of dogs at levels up to 2000 mg/kg for 26 weeks. Body weight and food consumption was not affected by treatment. Haematology, clinical chemistry and gross necropsy investigations showed no evidence of toxicity. There were no treatment related microscopic changes (OECD, 2006).

C_{24}-C_{34} Alcohols [CAS 123607-66-9]: Daily oral administration of 50 or 250 mg/kg to dogs (4 animals/group/sex) for 52 week was without effects. A NOAEL was established at 250 mg/kg/day (highest dose tested for 52 weeks) (Aleman et al., 2001)

3.4.3 Conclusions regarding repeated dose toxicity

The repeat dose toxicity of the category of long chain alcohols with chain lengths ranging from C_6 to C_{22} indicates a low order of toxicity upon repeated exposure. Typical NOAEL's recorded for this category range between ca. 200 mg/kg/day to 1000 mg/kg/day in the rat upon sub-chronic administration via the diet; a detailed overview of the NOAEL's and the effects at the LOAEL for each of the repeated dose toxicity studies is further details are presented in the SIAR and its Annexes of this category (OECD, 2006). At the lower end, members of this category induce local irritation at the site of first contact. Other notable findings observed for several members within this group suggest mild changes consistent with low-grade liver effects. Typical findings include: slightly increased liver weight, in some cases accompanied by clinical chemical changes but generally without concurrent histopathological effects. As noted in OECD (2006) members of the essentially linear aliphatic alcohols subcategory appear to have NOAELs for liver effects at the lower end of this range compared to members of the linear aliphatic alcohols subcategory. These materials have not shown evidence of a potential for peroxisome proliferation. A potential for CNS depression as observed for short chain aliphatic alcohols (C_1 to C_4; not included in this category) was also identified for 1-hexanol and 1-octanol.

3.5 *Mutagenicity*

Bacterial mutagenicity (Ames test) data for a representative number of aliphatic alcohols show a consistent lack of mutagenic activity across the whole range within this category. Further *in vitro* data include negative chromosomal aberration tests in RL1 cells for C_{10-16} alcohols and in CHO cells for C_{10-16} alcohols (OECD, 2006). In addition to these *in vitro* results, 1-dodecanol, 1-octadecanol, 1-docosanol and C_{24-34} alcohols were consistently negative in an *in vivo* mouse bone marrow micronucleus test (Hachiya et al., 1982; Iglesias et al., 2002a; Rodeiro et al., 1998b; OECD, 2006). Further support for a lack of mutagenicity of this category is provided by substances below the minimal chain length considered in this category (e.g. n-butanol; OECD SIDS, 2004). Additional details about the mutagenicity data of this category are presented in the supplemental information.

Data to support the assessment for the potential genotoxicity of the alcohols category can also be derived from data of a series of Alkyl Acetates including C_{6-8}, C_{7-9}, C_{8-10}, C_{9-11} and C_{11-14} branched alkyl esters. These alkyl acetates are manufactured from the corresponding aliphatic primary –branched- alcohols and cover a carbon chain length of C_6 to C_{14}. The standard protocol of *in vitro* mutagenicity test routinely applies a mammalian metabolic activation system (S9); the esterases present in this activation system produce acetic acid and the corresponding (branched) aliphatic alcohol. The mutagenicity tests for these

esters have, therefore, included the corresponding alcohols and the mutagenicity data available for these esters can be applied to further assess the mutagenic potential for the sub-category of the essentially linear alcohols (OECD, 2006). A summary of the data for these acetates as shown in the text table below has shown a clear absence of mutagenic activity for the alkyl acetates and the corresponding aliphatic branched alcohols with a carbon chain length ranging from C_6 to C_{14}.

Summary of the mutagenicity data for branched alkyl acetates

Chain length branched alcohol	C_6	C_{6-8}	C_{7-9}	C_{11-14}
CAS No.	88230-35-7	90438-79-2	108419-32-5	108419-35-8
In Vitro Assay				
Gene mutation	Negative	Negative	Negative	Negative
Chromosomal Aberration	Negative	Negative	Not Performed	Not Performed
In vivo Assay				
Mouse Micronucleus	Not Performed	Not Performed	Negative	Negative

It is important to note that the category of long chain aliphatic alcohols under consideration does not contain any structural elements that are of concern for potential mutagenic activity (Ashby and Tenant, 1991). Furthermore, primary alcohols (linear and branched) in the range C_1 to C_5 do not have a mutagenic potential (Bevan, 2001; OECD SIDS butanol, 2004). Furthermore, in a review by WHO-JECFA a series of 22 saturated aliphatic branched-chain primary alcohols and the corresponding aldehydes and acids in the range C_4 to C_8 showed no activity in a battery of *in vitro* and *in vivo* mutagenicity tests (WHO, 1998). On this basis it is concluded that the category of long chain alcohols does not have a mutagenic potential and that read-across within the category of long chain alcohols can be justified.

3.6 *Carcinogenicity*

Hexanol-1, 1-octanol, 1-decanol, 1-dodecanol, 1-tetradecanol, 1-hexadecanol and 1-octadecanol have been tested as control substances in one or more skin painting studies or in experiments in mice that had been initiated or were co-exposed with carcinogens such as 7, 12-dimethylbenz[a]-anthracene or benzo[a]pyrene (B[a]P). The data show that none of aliphatic alcohols tested have a potential to induce local skin tumours upon repeated dermal application at or above the maximum tolerated (irritant) dose (Sicé, 1966; Bingham and Falk, 1969; Van Duuren and Goldschmidt, 1976). These data are unsuitable to assess properties such as co-carcinogenicity or tumour promotion for this category of alcohols. Most of the study protocols considered here have almost certainly induced considerable local effects, however details of the irritation responses are limited and were reported only in a few cases. Irrespective of the causative agent, irritation at the site of application is a significant confounder in skin painting studies and its role in the tumour development of non-genotoxic chemicals has been well established (for examples see Nessel et al., 1998, 1999; Argyris, 1985).

In other assays 1-octanol, 1-dodecanol or 1-octadecanol were repeatedly injected into the peritoneal cavity or implanted in the bladder of mice. No induction of primary lung tumours was recorded, however a low incidence of benign bladder tumours was reported (Stoner et al., 1973; Bryan et al., 1966). Ando et al. (1972) published a study in which small groups of mice (n = 4-6), implanted intra-peritoneally with Ehrlich ascites tumour cells, were exposed i.p. to different doses of 1-decanol, 1-dodecanol, 1-tetradecanol, 1-hexadecanol and 1-octadecanol once daily for 5 consecutive days. Although a prolongation of survival time was observed, these experiments do not allow any conclusions regarding the carcinogenic potential of these alcohols.

Long chain alcohols are non-genotoxic and lack structural elements of concern for interaction with DNA (Ashby and Tenant, 1991). Together with the lack of response upon repeated application the skin painting studies long chain alcohols are regarded to be of little concern regarding carcinogenicity.

3.7 *Toxicity for Reproduction*

3.7.1 Effects on Fertility

Dodecanol-1 and 1-octadecanol have been tested for potential reproductive toxicity in a combined repeat dose reproductive/developmental toxicity screening study in rats. The materials were administered to male and female rats via the diet at concentrations up to 30,000 ppm (2,000 mg/kg/day) during pre-mating, mating and gestation. Pregnancy rates, uterine parameters, time to pregnancy and gestation length indicated that fertility was not affected by exposure to dodecanol or octadecanol. There were no microscopic changes observed in the reproductive organs (Hansen, 1992 a,b). Docosanol (C_{22}) did not affect reproductive parameters when administered orally at levels up to 1000 mg/kg/day to male and female rats during pre-mating (10 weeks for males and 2 weeks for females), mating and gestation (Iglesias et al., 2002b).

Literature supports a conclusion of an absence of toxicity to reproductive organs at significant doses for long chain alcohols. As noted previously, testicular atrophy observed in dogs following a 13 week repeated dose exposure to 1000 mg/kg/day 1-hexanol administered via gelatin capsule was attributed to the general ill health, including severe gastrointestinal irritation, of the animals likely due to the manner in which the substance was administered. No effects on reproductive organs were observed in dogs that were exposed to the same test substance in the dietary portion of the study at both the 1% and 0.5% level of exposure (OECD, 2006). Similarly, rats receiving 1-hexanol in the diet at concentrations of 1% (with step-wise increases to 6%) showed no testicular weight changes or microscopic changes in the gonads (OECD, 2006). In a separate study the potential for testicular toxicity in rats was investigated for C_{6-12} alcohol by oral administration of 1.0 mM/kg for 14 days (Rhodes et al., 1984). In a dedicated 2-week study it was shown that C_{6-12} alcohols and C_{10-16} alcohol and 1-tridecanol did not induce adverse testicular effects (Rhodes et al., 1984).

Administration of high doses (up to 1000 mg/kg/day) of 1-hexadecanol, 1-octadecanol, 1-docosonol or C_{24-34} alcohols to rats and/or dogs for periods up to one year was without adverse effects on the reproductive organs. Overall, these data justify the conclusion that linear alcohols have no potential for adverse effects on the reproductive organs.

Similarly, the 90-day dietary repeat dose study on C_{14-16} alcohol showed an absence of effects on reproductive organs (Ito et al., 1978). In this study relative testes and ovary weights were increased at the 1% and/or 5% incorporation level, but at these levels a considerable reduction in bodyweight gain due to inanition was induced. The effects on relative organ weights were considered to be associated with the effects on body weight rather than a direct toxic effect. More importantly, there was no evidence of microscopic changes in the gonads.

A lack of effect on reproductive organs was also observed, as noted previously, in the 28-day repeated dose study of C_{10-16} alcohol at the highest dose tested, 1,000 mg/kg/day (OECD, 2006).

Conclusion: Fertility assays did not reveal any adverse reproductive effects. Furthermore, there was no evidence indicative of adverse changes in the reproductive organs in a number of repeated-dose studies. Overall, there are no concerns that the category of Long Chain Aliphatic Alcohols might adversely affect fertility.

3.7.2 Developmental Toxicity

3.7.2.1 Inhalation

Iso-amyl alcohol (IAA) is a C5 alcohol just below the lower end of the category of the aliphatic alcohols.

A developmental toxicity study for IAA in rats was without any developmental effects upon exposure to atmospheres of 10 mg/l [highest dose tested] (6 hours daily) during days 6-15 of gestation. Maternal effects consisted of a slight depression of body weight gain (ca. 75% of the growth in controls) at the highest exposure group during the initial phases (days 6-9) of the exposure period. The maternal NOEC was 2.5 mg/l (Klimisch and Hellwig, 1995).

Rats inhaled 1-hexanol at concentrations of 3.5 mg/L (the maximum vapour concentration achievable; 7 hours/day) throughout the gestation period without any adverse effects in dams and foetuses. There was a slight increase of questionable significance in the number of resorptions (1.3/litter; a value at the upper range of the spontaneous incidence, the corresponding control incidence was 0.4/litter, an unexpectedly low value) (Nelson et al., 1989). In another developmental toxicity study in the rat using the oral route of exposure (Rodwell et al., 1988) the number of resorptions was unaffected by treatment even at dose level up to 1000 mg/kg, supporting the conclusion that this finding represents a chance observation.

Inhalation of 1-octanol, 1-nonanol or 1-decanol at the maximum achievable vapour concentrations (0.4, 0.14 and 0.10 mg/L, respectively) from days 1-19 of gestation did not result in any treatment-related changes in rats on maternal, uterine and foetal parameters. Although these exposure levels are below the concentrations inducing adverse effects, they represent a worst-case scenario for potential human exposure (Nelson et al., 1990a, b).

A developmental toxicity study for iso-amyl alcohol in rabbits caused depression maternal body weight during days 6-15 of gestation in the group exposed to atmospheres of 10 mg/L without any evidence for developmental effects in the offspring upon exposure to atmospheres of 10 mg/l [highest dose tested] (6 hours daily) during organogenesis. The maternal NOAEC was 2.5 mg/L based on the reduction in maternal animals; the developmental NOAEC was 10 mg/L (highest dose tested (Klimisch and Hellwig, 1995).

3.7.2.2 Oral

Hexanol-1 was administered orally to rats during day 6-15 of gestation (Rodwell et al., 1988). At the 1000 mg/kg dose level a decreased maternal body weight gain and a minimal reduction in foetal body weights was recorded. The foetal weights at this treatment level were within the range of the historical data and this finding is not considered to represent an adverse developmental effect. There were no treatment-related changes in the incidence of visceral and skeletal variations and malformations.

Administration of 1-octanol to rats at daily gavage doses of 0, 130, 650, 975 or 1300 mg/kg resulted in significant, dose-related maternal toxicity, including clinical signs (CNS depression, nasal discharge and pneumonia), and slight decreases in body weight gain and food consumption at 650, 975 or 1300 mg/kg/day. No adverse effects were recorded on foetal and developmental parameters (Hellwig and Jäckh, 1997).

$C_{7\text{-}11}$ alcohols [CAS 85566-14-9 essentially linear] was tested in rats that received daily oral doses up to 1440 mg/kg/day during days 6-15 of pregnancy. No treatment related adverse effects were noted in maternal, uterine and foetal parameters (Hellwig and Jäckh, 1997).

In a screening study for developmental toxicity, dietary administration of 1-dodecanol to pregnant rats throughout the gestation period at nominal concentrations up to 2000 mg/kg/day was without adverse maternal or developmental effects (Hansen, 1992a). Similarly, the longer chain alcohols did not show any maternal or developmental toxicity in rats based on a reproductive/developmental toxicity screening study with 1-octadecanol (Hansen, 1992b), or a developmental toxicity studies with 1-docosanol and C_{24}-C_{34} alcohols (Iglesias et al., 2002b; Rodriguez et al., 1998).

A developmental toxicity studies in rabbits with 1-docosanol and C_{24}-C_{34} alcohols was without adverse maternal and developmental effects (Iglesias et al., 2002b, Rodriguez et al., 1998).

Overall, the category of the aliphatic alcohols has shown a chain length dependant response with maternal toxicity in rats observed only at chain lengths of C_6 and C_8. No embryotoxicity or foetotoxicity was noted in any of the studies for the aliphatic alcohols.

3.7.3 Discussion of developmental toxicity of Long Chain Aliphatic Alcohols

The available data for developmental toxicity for the category LCOH as a whole does not raise any indication of adverse developmental effects including clearly negative developmental toxicity studies based on studies with rats for C_5 alcohol, 1-hexanol, C_{7-11} alcohols and 1-octanol (Hellwig and Jäckh, 1997; Klimisch and Hellwig, 1995).

On the other hand developmental toxicity studies with 2-ethyl hexanol (2-EH) (not a member of the category) gave indications of developmental toxicity, and might raise a potential concern regarding the develop-mental toxicity at the lower end of the category of the LCOH (WHO, 1993). U.S. EPA (2006b) has reviewed the developmental toxicity of 2-EH and notes that while effects have been reported following high dose oral exposure (1525 mg/kg bw/day over gestation days 6-13), no adverse foetal outcomes were found following dermal application (6 hours daily occluded dermal application of 3mL/Kg/day over gestation days 6-15).

Aliphatic carboxylic acids are key metabolic products of the biotransformation of LCOH and aliphatic carboxylic acids conforming to specific structural characteristics and are known developmental toxicants. By extension, aliphatic alcohols that are metabolized to carboxylic acids that are known to be developmental toxicants, or that fall within the SAR rules for carboxylic acids with known developmental toxicity, could be anticipated to be potential developmental toxicants depending on the kinetics of formation and elimination of the carboxylic acids. First, it is important to recognize that only branched chain carboxylic acids with branches corresponding to very specific structural requirements have been shown to exhibit these effects. The majority of the LCOH materials are exempt from this category of concern because they are either linear or have branch chains that are too short. If the starting alcohol is not branched, or does not have a branch in the appropriate position, or of sufficient length, a corresponding acid with a structure of potential concern will not be produced by metabolism.

The alcohols under consideration in this category consist of aliphatic alcohols that are primarily linear with some members of the category containing branched components. The branched components have a single side chain, consisting predominantly of a methyl group (see OECD, 2006 for details of the structures).

The Structure Activity Relationships for the developmental toxicity of aliphatic carboxylic acids have been well established. Aliphatic carboxylic acids with a single alkyl-branch at the C_2 position and the side chain length being C_2 or higher have a potential for developmental toxicity. Carboxylic acids with a single methyl-branch at the C_2 position or acids branched at a position other than C_2, irrespective of the length of the side chain or the backbone, lack a potential for developmental toxicity. For the branched carboxylic acids, the fo-etoxicity appears to be associated in particular with carboxylic acids with a total carbon chain length in the range of C_{7-9} (DiCarlo et al., 1986; Narotsky et al., 1994; Scott et al., 1994; Bojic, et al., 1996; Ambroso et al., 1999). Furthermore, SAR for the carboxylic acids indicates that developmental toxicity is mainly associ-ated with chain lengths of C_{7-9}, for which good quality data showing no developmental toxicity for the ali-phatic alcohols exist (Hellwig and Jäckh, 1997). For higher chain lengths category members there is no con-cern for developmental toxicity based on SAR for the aliphatic acids with a chain length of C10 and higher (DiCarlo et al., 1986; Narotsky et al., 1994; Scott et

al., 1994; Bojic, et al., 1996; Ambroso et al., 1999). Finally it is noted that linear alcohols (not branched) are used in applications with the highest consumer exposures, and those exposures are dermal (personal care products).

Conclusion. The available information confirms the absence of a potential for developmental toxicity for the category of the aliphatic alcohols.

3.8 Initial Assessment for human health

A review of the toxicological database for the category of the LCOH demonstrates that members of the category of the fatty alcohols are of a low order of toxicity upon single or repeated exposure. Overall, the data show an inverse relationship between chain length and toxicity. The shorter chain alcohols tend to induce more pronounced effects when compared to materials with a longer chain length. This is illustrated most clearly by the degree of [local] irritation in studies involving single (acute) or repeat administration. Aliphatic alcohols do not have a skin sensitisation potential, are not mutagenic and have not shown any adverse effects on fertility, development and reproduction. There is a clear relationship between the chain length and the toxicological properties justifying read-across of potential toxicological properties between members of this category.

The key human health hazards for this category are skin and eye irritation. For the aliphatic alcohols in the range $C_{6–11}$ a potential for skin and eye irritation exists, without concerns for tissue destruction or irreversible changes. Aliphatic alcohols in the range $C_{12–16}$ have a low degree of skin irritation potential; alcohols with chain lengths of C_{18} and above are non-irritant to skin. The eye irritation potential for alcohols with a chain length of C_{12} and above has been shown to be minimal.

3.9 Exposure Assessment for human health

3.9.1 Product Function and Use Categories

Long Chain Aliphatic Alcohols (C_6-C_{22}) are used in the manufacture of some major classes of ionic and anionic surfactants (ca. 50% of the manufactured volume). The remainder of the volume of the LCOH finds use as in a wide range of applications relying on the lubricating, emollient, solubilising or emulsifying properties of the LCOH.

Aliphatic Alcohols of the category LCOH (C_6-C_{22}) are applied in industry and by professionals in paints, lubricants, emulsifiers, flotation agents, rolling and formwork oils. They also are used as an additive in certain plastics, paper products and plaster and used in processing of textiles, leather and plastics. The LCOH can also be found in some pharmaceutical products and agrochemical formulations (Modler et al., 2004).

Aliphatic alcohols are also extensively used in consumer products, household cleaning and personal care products. Typically, aliphatic alcohols with a chain-length of C_{10} and higher are applied in products such as laundry powder, general/hard surface cleaners, and fabric conditioners. Another important suite of uses include personal care products such as shampoos, hair conditioners, styling gel and mousse, cleaners, body washes, skin lotions and creams, antiperspirants, face and eye cosmetics, make up remover and hair dyes, fragrances and fragrance ingredients. The personal care products typically make use of the longer chain linear alcohols, e.g. products containing C_{14}, C_{16} and C_{18} alcohols. The distinction that these products use materials from the linear aliphatic alcohols subcategory that are distinct from the essentially linear aliphatic alcohols subcategory as defined in OECD (2006) becomes important for the subsequent risk assessment discussion. These two subcategories show substantial similarity in their toxicological effects and for the majority of the applications addressed in this paper they can be treated as a single group. However, as detailed in OECD (2006), members of the essentially linear aliphatic alcohols

subcategory have somewhat lower NOAELs for liver effects than do the members of the linear aliphatic alcohols subcategory which becomes important when defining the margin of exposure for the personal care products with the highest exposure tier.

The exposure media considered in more detail in this publication are the consumer products containing Long Chain Aliphatic Alcohols. The concentrations of LCOH's in specified product types used in these assessments are based on a survey of use and exposure information provided by the member companies of the Long Chain Aliphatic Alcohols Consortium and industry groups representing downstream producers of finished products (SDA, 2002).

Table 1 presents the results of the survey based on the responses from regions North America, Europe and Asia-Pacific regions; in the table the minimum and maximum of the range(s) for each product category containing LCOH are shown. These ranges were utilized as inputs for the exposure models.

Table 1. Summary of typical levels and ranges of aliphatic alcohols in use in consumer products

Product Category	**Product Formulations (%)**					
	USA		EU		AP	
	Mean	Range	Mean	Range	Mean	Range
House Hold Products						
Laundry detergents: Powder	3	1 - 5	3	1 - 5	3	1 - 5
Fabric softener	3	1 - 5	3	1 - 5	0.75	0.5 - 1
General and Hard Surface Cleaners	3	1 - 5	-	-	3	1 - 5
Personal Care and Cosmetic products						
Hair: Conditioners gel, Mousse Dye	3	1 - 5	3	1 - 5	1.88 3 7.5	0.5 - 5 1 - 5 5-10
Skin lotions, creams, cleaners	3	1 - 5	3	1 - 5	1.88	0.5 - 5
Antiperspirants (solid)	17.5	10 - 25	17.5	10 - 25	17.5	10 - 25
Face/Eye Cosmetics: Liquid Powder Mascara	 3 3	 1 - 5 1 - 5	 3	 1 - 5	 3 0.75 3	 1 - 5 1 - 5

3.9.2 Description of Modelled Exposure Scenarios

On the basis of the information presented above the following consumer activities and uses were modelled to support the development of chronic exposure estimates for comparison to chronic effect levels (e.g., developmental and reproductive toxicity, carcinogenicity):

Dermal exposure scenarios were developed for various activities or use phases of cleaning products. These included pre-treatment with laundry detergents, hand-washing of laundry, and use of diluted and undiluted hard surface cleaners. Table 2 provides input scenarios for modeled situations, Table 3 provides input scenarios for exposure to residual laundry products on fabrics, and Table 4 provides input scenarios for a range of relevant personal care products and their uses. Table 5 provides an inhalation exposure scenario inputs for the non-volatile components for spray cleaning products.

Table 2. Exposure during the activity/use of diluted and undiluted laundry and diluted and undiluted hard surface cleaning products

$$\frac{[FQ \times CA \times PC \times FT \times CF \times TF \times DA] \times PF}{BW}$$

	Laundry Pre-treatment (undiluted)	Hand-wash of Laundry (diluted)	Hard Surface Cleaners (diluted)	Hard Surface Cleaners (undiluted)
Frequency (FQ) (use/day)*	1	1	1	1
Contact Area (CA) (cm^2)*	360	1680	1680	180
Product Concentration (PC) (g/cm^3)*	0.6	0.01	0.015	1
Film Thickness (FT) (cm)*	0.0024	0.0024	0.0024	0.0024
Conversion Factor (CF) (g → mg)*	1000	1000	1000	1000
Time Scaling Factor (TF) (unitless)	0.007	0.007	0.014	0.014
Dermal Absorption (DA) (%)*	100	100	100	100
Female body weight (BW)(kg)*	65.4	65.4	65.4	65.4
LCOH concentration in product formulation (PF) (%)**	1-5%	1-5%	1-5%	1-5%

Table 3. Exposure to laundry product residual on clothing

$$\frac{[FQ \times A \times PR \times PT \times DA \times CF] \times PF}{BW}$$

	Laundry Detergent	Fabric Conditioner
Amount Per Use (A) (g/day or g/wash)*	121	112
Use Frequency (FQ) (use/day)*	1	1
Percent Retained on Clothing (PR) (%)*	1	1
Percent Transferred from Clothing to Skin (PT) (%)*	1	1
Dermal Absorption (DA) (%)*	100	100
Conversion Factor (CF) (g → mg)	1000	1000
Female body weight (BW) (kg)*	65.4	65.4
LCOH concentration in product (PF)**	1-5%	1-5%

* *Exposure and Risk Screening Methods for Consumer Product Ingredients* (SDA, 2005), N. America
** LCAA Consortium survey; Min-Max values (SDA, 2002)

Table 4. Exposure to personal care products residual after use

$$\frac{[FQ \times A \times PR \times DA \times CF] \times PF}{BW}$$

	Hair conditioner	Hair styling tonic/gel**	Anti perspirants	Face/Eye cosmetics	Body Moisturiser	Cleansing products
Frequency of Use (FQ) (use/day)*	0.282	1	2	2	1-2	2
Amount Per Use (A) (g/use)*	142	5.6	0.51	2.65	7.82 - 7.23	1.7
Percent Retained on Skin (PR) (%)*	1	5	100	100	100	1
Dermal Absorption (DA) (%)	32	32	32	32	32	32
Conversion Factor (CF) (g → mg)	1000	1000	1000	1000	1000	1000
Body weight (BW) (kg)*	65.4	65.4	65.4	65.4	65.4	65.4
LCOH concentration in product (PF) (%)**	0.5 - 5%	0.5 - 5%	10 - 25%	1 - 5%	0.5 - 5%	0.5 - 5%

Exposure values preferentially referenced from Loretz et al. (2005 and 2006) and SCCP (2006) when available. When no category data available from these sources, values taken from:
* *Exposure and Risk Screening Methods for Consumer Product Ingredients* (SDA, 2005), N. America
** LCAA Consortium survey; Min-Max values (SDA, 2002)

Table 5. Inhalation exposure (non volatile components) to spray cleaning products during use.

$$\frac{FQ \times RPC \times IR \times ED \times BA}{BW} \times PF$$

	Spray Cleaner
Frequency of Use (FQ) (uses/day)*	1
Respirable Product Concentration in air (RPC) (mg/m^3)*	0.72
Inhalation Rate (IR) (m^3/hr)*	1.0
Exposure Duration (ED) (hr)*	0.33
Weight fraction absorbed or bioavailable (BA)*	100
Female body weight (BW) (kg)*	65.4
LCA concentration in product formulation (PF) (%)**	0.1 - 5%

* *Exposure and Risk Screening Methods for Consumer Product Ingredients* (SDA, 2005), N. America
** LCAA Consortium survey; Min-Max values (SDA, 2002)

The exposure during application and use of personal care products is not modeled due to the short use period (minutes); the resulting exposures are very small in comparison to the exposures associated with the residual amounts that remain on the skin until the next use. The exposure modeling examples shown below include the use of LCOH in body moisturizers; this use is considered to be representative of all skin lotions and creams applications. In fact, the exposure potential associated with the use of body moisturizers represents the worst-case exposure within the category of skin lotions and creams.

The exposure scenarios encompass conservative, screening-level inputs including: the high-end frequency of product use, the high-end amount of product per use, the high-end percent of product retained on skin or clothes following use; typically the 90^{th} percentile is used as a high end value. Initially, all modeled exposures include a default assumption of 100% dermal absorption and bioavailability. The use of multiple conservative input parameters results in exposure estimates that are at least 1–2 orders of magnitude above the true exposure of a typical consumer.

In some cases, the initial exposure assessment afforded exposure estimates that indicated an inadequate margin of exposure for the use of some applications. The estimated dermal absorption was refined in these cases to reflect a more realistic estimate of the dermal absorption.

The parameters for all the scenarios considered in this paper have been evaluated by the U.S. Soap and Detergent Association (SDA, 2005). In addition, for the personal care product use scenarios recent data developed by the Scientific Commission on Consumer Products (SCCP, 2006) and by the CTFA (Cosmetics Toiletries and Fragrance Association) (Loretz et al., 2005, 2006) have been used to estimate exposure.

3.9.3 Exposure Estimates

The exposure estimates were calculated for each of the scenarios using the input parameters as described previously. Table 6 presents the modeled exposure

estimates from the use of laundry detergents and surface cleaners. Overall, these screening level exposure estimates indicate dermal exposures below 1 μg/kg bodyweight per day. Scenario's involving potential inhalation exposure, the screening levels exposure estimate are at least 2 orders of magnitude below that of the scenario's involving dermal exposures.

Table 6. Summary of the exposure estimates of the scenario's laundry detergents and cleaning products and the margins of exposure

Exposure Scenario	Exposure Estimate[a] (mg/kgBW/day)	Margin of Exposure
Dermal Modelling		
Cleaning Products		
Laundry pre-treatment (undiluted)	$5.5x10^{-4}$ - $2.8x10^{-3}$	>10,000
Hand-wash of laundry (diluted)	$4.3x10^{-5}$ - 2.2 $x0^{-4}$	>10,000
Hard surface cleaner (diluted)	1.3 x 0^{-4} - 6.5 x 10^{-4}	>10,000
Hard surface cleaner (undiluted)	9.2 x 10^{-4} - 4.6 x 10^{-3}	>10,000
Laundry product residual on clothing		
Liquid detergent	1.9 x 10^{-3} - 9.2 x 10^{-3}	>10,000
Fabric Conditioner	1.7x 10^{-3} - 8.6 x 10^{-3}	>10,000
Inhalation Modelling		
Cleaning Products		
Spray cleaner	3.6 x 10^{-6} - 1.8 x 10^{-5}	>10,000

[a] Range based on minimum and maximum product concentration values (SDA, 2002)

The exposure estimates from the use of personal care and cosmetic products are shown in Table 7.

Table 7. Summary of exposure estimates from the use of personal care and cosmetic products

Exposure Scenario	Absorbed Exposure Estimate[a] (mg/kg/day)	Worst Case Margin of Exposure[a]
Antiperspirants	0.5 – 1	1,000
Body moisturizer	0.3 – 3	333
Cleansing products	8.x 10^{-3} – 8 x 10^{-4}	125,000
Face/Eye cosmetics	0.3 – 1	1,000
Hair conditioner	1 x10^{-2} – 0.1	10,000
Hair styling tonic/gel	7x 10^{-2} – 7 x 10^{-1}	1,428

[a]Based on maximum formula concentration, maximum use amount, maximum skin penetration and conservative interpretation of NOAEL.

4.0 Human Health Risk Assessment

The approach used for the human health risk assessment for the LCOH category consists of the ratio of the most relevant No-Adverse Effect Level (NOAEL) involving repeated exposure and the screening level exposure estimates to calculate the Margin of Exposure (MOE).

4.1 Laundry detergent and cleaning products

The starting point for the assessment is the most relevant NAOEL for the group of alcohols that finds applications in household cleaning products. Alcohols typically used in these applications are of a chain length of C_{10} and above. In this case the NAOEL for the sub-chronic toxicity in rats for $C_{14\text{-}16}$ alcohols was considered as the most relevant value for the risk assessment. The NOAEL (200 mg/kg/day) is based on a depression of the body weight observed and changes in biochemistry values at a dose level of *ca.* 1000 mg/kg/day. The data suggest that the effects observed in this study may well have been confounded by inanition due to poor palatability of the diets and the selected NOAEL is therefore considered a conservative estimate of the threshold of the adverse effects for the LCOH with an intermediate chain length.

All MOE's calculated for the use of laundry detergents and cleaning products are well in excess of 10,000 (see Table 6). Taking into account the overall data base for this category including the lack of concern regarding developmental and reproductive toxicity, genotoxicity and carcinogenicity for this category it is concluded that the use of the LCOH in household products is without concern for human health.

4.2 Personal Care Exposure Scenarios

The point of departure for the risk assessment of the personal care scenarios is the most relevant NAOEL for the alcohols used for these applications. Examining the product use scenario that results in the highest exposure (body lotion) and using the product application data from SCCP (2006) (body lotion applied to 15670 cm^2 and 8 grams of product applied at the maximum reported formulation level of 5%) would result in a dose/unit area application of alcohol of 0.5 mg product/cm^2 or 25 µg of alcohol/cm^2. It can be anticipated that parts of the application area will receive higher unit area doses. Under the *in vitro* study conditions, 40 µg of alcohol/cm^2 were applied making it a reasonable approximation of a worst case dose/unit area application rate for a single daily application. Based upon the measured penetration of 32% (also used in exposure models, Table 4) the worst case body lotion scenario application of 25 µg/cm^2/day, and 8 µg X 15670 cm^2 application area results in a worst case estimate of material penetrating into and through the skin of 125 mg/day or approximately 2 mg/kg/day for a 65.4 kg person. Skin penetration of hexadecanol is estimated to be 2.5-fold lower or 0.8 mg/kg/day. Of note, CTFA (Loretz et al., 2005) reports similar body lotion application rates, but reports that at the 90th percentile consumers apply product twice per day. While a second product application is anticipated to increase the amount absorbed over 24 hours it is not anticipated that the second application would result in a doubling of the amount absorbed given that there would still be residual alcohol in the skin from the first application. Using the value of 14.1 gm/day (Loretz et al., 2005) as the sum of two daily applications (50 µg/cm^2) and assuming that the two daily applications don't influence each other would result in a worst case penetration estimate (into and through the skin) of 225 mg/day or 3.4 mg/kg/day.

The NOAEL values for repeat dose studies are all in a similar range and all reflect minimal effects at the highest doses tested. The NOAEL selected for this assessment is 1000 mg/kgBW/day based on hexadecanol as a representative of the linear aliphatic alcohols subcategory in the chain length range used in personal care product applications which result in the greatest exposure to be assessed for its risk. This dose takes into account a transient slight depression in body weight gain and food consumption in rats receiving diets containing 2.5% hexandecanol (*ca*. 2000 mg/kgBW/day) for 13 weeks. Although the next lower dose in the same study was 1% (equivalent to ca. 750 mg/kgBW/day), other studies with hexadecanol in rats and dogs have established unequivocal NOAEL's at 1000 mgBW/kg/day. Taking into account the overall weight of the evidence the selection of 1000 mg/kg/day as the threshold for assessing risk can be justified. Supporting data are reflected in the NOAEL values summarized previously for other members of the linear, aliphatic alcohols subcategory.

For the subcategory of essentially linear aliphatic alcohols C_{14-16} alcohol [CAS 68333-80-2 essentially linear] could be used as a representative material to define a level at which this category of substances do not cause chronic effects. In a 13-week rat study C_{14-16} alcohol was administered via the diet at concentrations of 0, 0.2, 1 and 5%. The top and intermediate dose level (5 and 1%, respectively) had limited palatability and induced a considerable reduction in growth (>30% and ca. 15% reduction in body weight in high and mid dose males, respectively). Biochemistry showed changes in AP, ALT and protein ratios at the 1 and/or 5% level. Organ weight changes were consistent with an increased liver weight. No treatment-related microscopic changes were observed, including both the testis and ovaries at this same dose level. Based on the effect on body weight a NOAEL was established at the 0.2% dietary incorporation level (ca. 200 mg/kgBW/day) (Ito et al., 1978). For essentially linear aliphatic alcohol exposures with small MOEs it would be conservative to use the same NOAEL (i.e., 200 mg/kgBW/day). For the purposes of this risk assessment, separate values are not calculated for the essentially linear alcohols versus the linear alcohols since the MOEs for the applications where the essentially linear materials may be used are so large that the factor of 5-fold is insignificant.

The reasonableness of this route to route extrapolation is supported by a dermal study on shorter chain length fatty alcohols (anticipated to show better dermal penetration). Specifically, U.S. EPA (2006a)

summarized a 90-day dermal application study in rats exposed to a fatty alcohol blend (56.7% 1-decanol 112-30-1, 42.7% octanol 111-87-5). The primary responses observed were changes to the skin indicative of irritation. "Systemic effects were limited to marginally increased adrenal glands in high-dose animals, slightly reduced RBC (red blood cell) counts, hematocrit, and increased WBC (white blood cell) and platelet counts in high-dose animals. No gross or histological alterations other than severe irritation." Based on these observations at 1,000 mg/kg/d, U.S. EPA defined 300 mg/kgBW/d as the NOAEL. It is plausible that the non-skin effects noted reflect the consequences of the severe skin effects and the resultant inflammatory response and stress. Note that dermal penetration is higher in rodents than in humans and is generally considered to overestimate human dermal absorption by at least a factor of 3 (Poet, 2000). Absorption would have been further enhanced by skin barrier disruption due to the significant irritant effects of topical treatment. These factors combined suggest that in reality the NOAEL for systemic effects following dermal exposure that is relevant to humans is likely >1,000 mg/kgBW/d.

In Table 7 the calculated MOE's are shown calculated for the ranges of the minimum and maximum product concentration values, according to SDA (2002).

Inspection of this Table indicates that all MOE's are in excess of 1000 with the exception of the exposure scenario for body moisturizers when a high product concentration (up to 5%) is used; in this case the calculated margin of exposure is 167 for hexadecanol.

The exposure estimates used in the assessment of the exposure of personal care and the cosmetic products take into account several parameters that have given prevalence to values ensuring that the exposure estimates represent a worst-case value. Even after a refinement of the skin penetration estimate, the true exposure associated with these applications is expected to be at least one order of magnitude below the values calculated in these scenarios. A further complication in the assessment of these MOE's is the fact that the primary biotransformation products of the aliphatic alcohols are indistinguishable from those derived from common dietary sources (triglycerides), with the human intake from dietary sources being several orders of magnitude above those arising from the use of LCOH in personal care and cosmetic products.

Taking into account the overall data base for this category, no concerns exist regarding developmental and reproductive toxicity, genotoxicity and carcinogenicity for this category justifying the conclusion that the use LCOH in personal care and cosmetic products is safe.

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Appendix III-E

Long Chain Alcohols (LCOH) - Environmental Risk Assessment

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Assessment of the Environmental Risk of Long Chain Aliphatic Alcohols

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Abstract

An environmental assessment of long chain alcohols (LCOH) has recently been conducted under the OECD SIDS High Production Volume (HPV) Program via the Global ICCA (International Council of Chemical Associations) Aliphatic Alcohols Consortium. LCOH are used primarily as intermediates, as a precursor to alcohol-based surfactants and as alcohol per se in a wide variety of consumer product applications. Global production volume is approximately 1.58 million metric tonnes. The OECD HPV assessment covers linear to slightly branched LCOH ranging from 6 to 22 alkyl carbons (C). LCOH biodegrade exceptionally rapidly in the environment (half-lives on the order of minutes); however, due to continuous use and distribution to wastewater treatment systems, partitioning properties, biodegradation of alcohol-based surfactants, and natural alcohol sources, LCOH are universally detected in wastewater effluents. An environmental risk assessment of LCOH is presented here by focusing on the most prevalent and toxic members of the linear alcohols, specifically, from $C_{12\text{-}15}$. The assessment includes environmental monitoring data for these chain lengths in final effluents of representative wastewater treatment plants and covers all uses of alcohol (i.e., the use of alcohol as a substance and as an intermediate for the manufacturing of alcohol-based surfactants). The 90th percentile effluent discharge concentration of 1.979 µg/L ($C_{12\text{-}15}$) was determined for wastewater treatment plants in 7 countries. Chronic aquatic toxicity studies with *Daphnia magna* demonstrated that between C_{13} and C_{15} LCOH solubility became a factor and that the structure-activity relationship was characterized by a toxicity maximum between C_{13} and C_{14}. Above C_{14} the LCOH was less toxic and become un-testable due to insolubility. Risk quotients based on a Toxic Units (TU) approach were determined for various scenarios of exposure and effects extrapolation. The global average TU ranged from 0.048 – 0.467 depending on the scenario employed suggesting a low risk to the environment. The fact that environmental exposure calculations include large fractions of naturally derived alcohol from animal, plant, and microbially mediated biotransformations further supports a conclusion of low risk.

1.0 Introduction

Long chain alcohols (LCOH) are a family of structurally related compounds sharing common and predictable physical-chemical properties covering a carbon (C) chain length range of C_6 to C_{22} (Fisk et al., 2009). LCOH are used in a wide variety of commercial industrial applications including household laundry powders and liquids, dishwashing liquids, other household cleaners, personal care products

(including shampoos and soaps) and a variety of industrial, commercial and institutional uses (Modler et al., 2004). Many of the detergent applications utilize the alcohol backbone as a synthetic intermediate which is then ethoxylated, propoxylated, or sulfated to derive anionic (alcohol sulfate, alcohol ethoxysulfate) and nonionic

(alcohol ethoxylate or propoxylate) detergents. A number of applications also use the free alcohols as such. Most of these applications involve their lubricating, emollient, solubilizing or emulsifying properties. These include cosmetics and toiletries, surface lubricants and pharmaceutical preparations. Total production of long chain alcohols (C_6 to C_{22}) is 1.580 million metric tonnes per annum with North America, Europe and Asia-Pacific regions accounting for 0.624, 0.710, and 0.245 million metric tonnes, respectively (OECD, 2007).

Sources of the alcohol in the environment are varied and include those of natural origin, from direct use, or as degradation products from alcohol-containing compounds (Figure 1). Wind et al. (2006) demonstrated that approximately 34% of LCOH (C_{12} to C_{18}) in wastewater treatment effluents is accounted for by the degradation of alcohol ethoxylate to LCOH leaving open the question as to additional LCOH sources. Federle and Itrich (2006) demonstrated exceptionally high biodegradation rates of alcohols in activated sludge treatment and that these were so rapid it is unlikely that the remainder of the alcohol measured in effluents is solely from down-the-drain disposal. Natural production of LCOH occurs in all living organisms from bacteria to humans, and the profiles and concentrations of these compounds in water, soils and sediments have not been systematically investigated (Mudge, 2005). The major production mechanism is from the reduction of fatty acids, through aldehyde intermediates, to fatty alcohols and in many organisms to esters with fatty acids to form waxes (Metz et al., 2000). These waxes are used for a variety of purposes from the prevention of desiccation in the terrestrial environment to energy reserves in the marine environment (Sargent et al., 1976; Buckner et al., 1996; Nelson et al., 1999; Ishige et al., 2003; Dahl et al., 2005). They are ubiquitous and occur in most environments around the world, including the deep ocean and in sediment cores (Mudge, 2005).

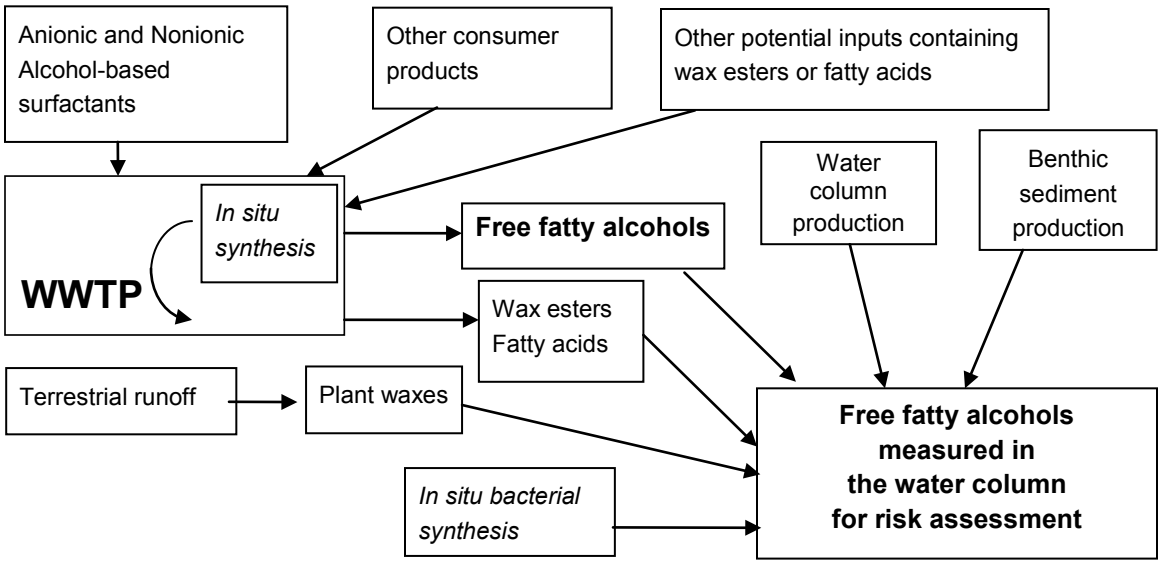


Figure 1. Potential sources of fatty (long chain) alcohols in the aquatic environment.

The ecotoxicology of LCOH is summarized by Fisk et al. (2009) and Schäfers et al. (2009). Acute toxicity was least for algae, followed by fish and *Daphnia magna*. Therefore, chronic toxicity focused on *Daphnia magna*. Toxicity was driven by a combination of hydrophobicity and solubility. Chronic

toxicity, summarized as 21-d EC_{10} using mean measured concentrations for reproduction (the most sensitive endpoint), ranged from 210 µg/L (1.33 µmol) for C_{10} to 12 µg/L (0.05 µmol) for C_{15}. Because LCOH are rapidly metabolized, Schäfers et al. (2009) undertook all efforts to minimize this influence on toxicity tests. Best practices were employed, but substantial losses still occurred. Thus, when expressed based on initial measured exposure concentrations the 21-d EC_{10}s were 630 µg/L (3.97 µmol) to 74 µg/L (0.32 µmol) for C_{10} to C_{15}, respectively. The structure-activity relationship indicated solubility of the higher C_{14} and C_{15} chain lengths affected toxicity interpretation. Beginning near C_{14}, and more clearly at C_{15}, water solubility becomes too low for toxic effects to be exerted. Overall, a non-polar narcotic (baseline toxicity) mode of action was concluded with acute:chronic ratios (ACR) in the range of 2-5 supporting the conclusion.

Testing at chain lengths above C_{15} has not been performed. Maximum solubility of hexadecanol and octadecanol in pure water (i.e., absent ions found in surface water) has been measured at 13 and 1.1 µg/L, respectively (OECD, 2007; Fisk et al., 2009). These levels are below concentrations which could exert chronic effects (Fisk et al., 2009; Schäfers et al., 2009). Morrall et al. (2006), Eadsforth et al. (2006) and Dyer et al. (2006) provided environmental monitoring data for C_{12} to C_{18} alcohols in wastewater treatment plant effluents in the U.S., Canada, and across Europe. Although the C_{16}-C_{18} alcohols are present in the environment at measurable concentrations, probably because of their slightly slower kinetics of biodegradation due to limited bioavailability (Federle and Itrich, 2006), these chain lengths are from an ecotoxicological point of view of less relevance because of their solubility-limited (low) toxicity. This approach is consistent with scientific and regulatory schemes for testing difficult substances (Ruffli et al., 1998; Hooftman et al., 1995).

A recent risk assessment of alcohol ethoxylates (AE) employed the concept of mixture toxicity with environmental monitoring of homologous structures to assess risk based on Toxic Units (Belanger et al., 2006). In that study, AE with an ethoxylation of 0 is equivalent to LCOH. Additional monitoring and new aquatic toxicity data allows the completion of a global environmental risk assessment of the long chain alcohols. Particular emphasis is placed on those chain lengths with the greatest potential for toxicity and highest volumes based on use in cleaning applications, namely, C_{12} to C_{15}.

2.0 Materials and Methods

2.1 Environmental Monitoring

LCOH have been quantified by the method of Dunphy et al. (2001), which is used in the evaluation of alcohol ethoxylates in the environment. Alcohols were derivatized with 2-fluoro-N-methylpyridinium p-toluenesulfonate (Fluka Chemical) to a permanent cation for analysis by HPLC/MS. Morrall et al. (2006) and Dyer et al. (2006) described the environmental monitoring of U.S. wastewater treatment plants (the same process was used by both investigators). A total of 12 sites in the U.S. have been monitored spanning the range of treatment types including activated sludge, lagoon, oxidation ditch, trickling filter and rotating biological contactor technologies. Samples consisted of 24-hr flow-weighted composites of influent and final effluent (composited separately) at each site. Details per location can be found in the cited papers. Because LCOH are universally the most abundant homologue in the AE distribution, all LCOH concentrations were measured above the limit of quantification (usually less than 10 ng/L).

Eadsforth et al. (2006) provided similar information to Morrall et al. (2006) for final wastewater treatment plant effluents located in Canada and across Europe (United Kingdom, Netherlands, Germany, Italy, and Spain). Sampling was somewhat different than occurred in the U.S. in that samples consisted of grab collections of effluent, but otherwise sample preservation, derivatization, and quantification were the same. A total of 8 effluent samples were from plants in four different Canadian provinces and included three types of treatment systems (activated sludge, trickling filter, and rotating biological contactor).

European effluent samples were all from activated sludge treatment facilities (12 sites). The distribution (number of different wastewater treatment plant types and their discharge columes) are only quantitatively known for U.S. facilities (Rapaport, 1988; USEPA, 1996). Therefore, the regional (U.S.) average discharge for each chain length can be calculated and properly weighted by the amount of wastewater by treatment type (Morrall et al., 2006). However, the relative effluent flow for each treatment type in Canada and Europe are not known, therefore simple averages were calculated ignoring treatment or wastewater volume.

2.2 Bioavailability, Dilution, and In-Stream Loss of LCOH

The LCOH concentration to which organisms in the environment are exposed via wastewater effluents is dependent on the LCOH concentration in the effluent, the effluent dilution rate, bioavailability, and further biodegradation in the river. Therefore, to establish site-specific predicted exposure concentrations (PEC) for LCOH, total measured concentrations were serially refined incorporating bioavailability and conservative in-stream dilution and parent mineralization scenarios.

Van Compernolle et al. (2006) reported on the sorption of alcohol ethoxylates to wastewater solids, including new LCOH-specific data. The authors constructed a generic model to understand the sorptivity (K_d and K_{oc}) of AE as a function of hydrophobicity as indicated by the octanol-water partition coefficient (K_{ow}). Based on data reported in Van Compernolle et al. (2006), Fisk et al. (2008, *this issue*) described LCOH-specific quantitative structure activity relationships (QSARs) (Equation 1, below).

Equation 1: $\text{Log } K_d = \text{Chain Length} \times 0.235 + 0.642 \qquad (R^2 = 0.99, n = 4)$

The use of a bioavailability adjustment is especially required in this evaluation due to some limitations of the analytical method. Because the environmental monitoring was performed to capture extremely small concentrations of homologues across the entire distribution of alcohol ethoxylates, relatively large volumes were sampled (4L) and concentrated. The extraction steps necessarily include both bound and sorbed alcohol in the measurement. Thus, by a bioavailability correction based on measured K_ds, the initial concentration of LCOH in the liquid phase was estimated.

Dilution of waste water treatment plant effluent was incorporated into the exposure assessment. For U.S. locations, site-specific dilution information was obtained by combining U.S. Geological Survey (USGS) stream flow data with daily effluent release parameters from NPDES (National Pollutant Discharge Elimination System) discharge permits. Dilution factors were applied that represent 7Q10 low flow conditions, or the 7-day low stream flow recorded once every ten years. Mean dilution for U.S. sites was 1.8 and ranged from 1 to 6.2. Similar data are not available for Canada or Europe so a conservative dilution factor of 2 was applied to all sites.

In-stream loss of LCOH was based on a conservative first order decay model (equation 2, Holman et al., 1981).

Equation 2: $C_{downstream} = C_{mixing\ zone}\, e^{-kt}$

Where:

C = LCOH concentration,
t = travel time for 1000 m at 1 m/s river velocity (therefore t = 1000 s for the scenario estimation)
k = first order mineralization or parent loss rate

Federle and Itrich (2006) demonstrated that first order loss rates for C_{12} to C_{16} linear alcohols ranged from 86-113 hr^{-1} for parent loss and 1.8 to 11.0 hr^{-1} for mineralization determined in activated sludge die away studies. Solids concentrations used in the die-away studies of Federle and Itrich (2006) were 100 fold

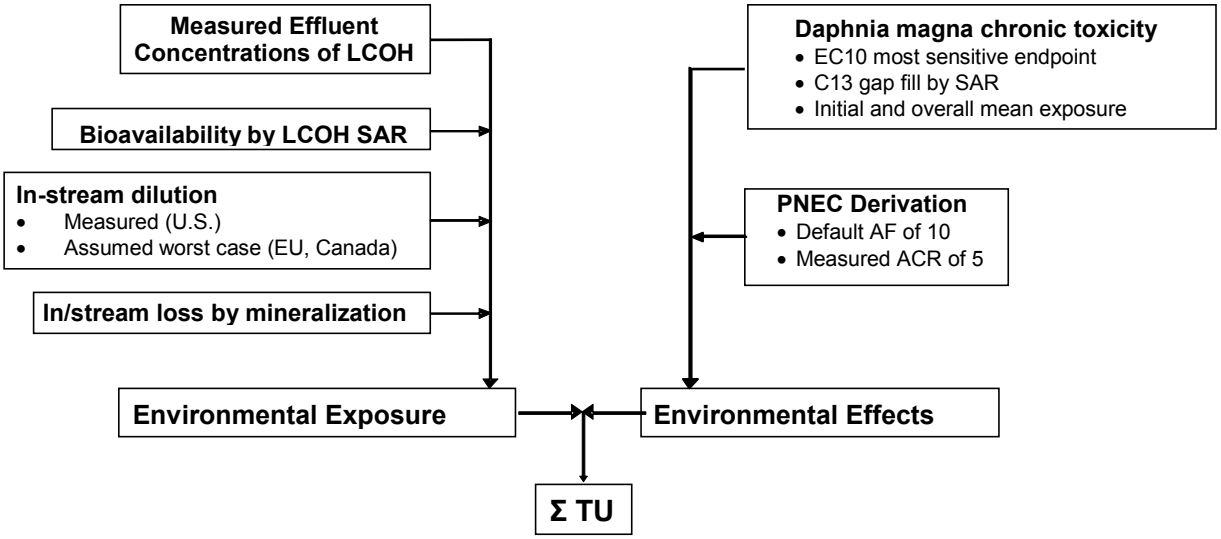
higher than in effluent. Direct use of these loss rates are not justified for effluent diluted in river water. Therefore, the loss rates were assumed to be no greater than those observed for anionic alcohol-based surfactants such as alcohol sulfate and alcohol ethoxysulfate (Federle et al., 1997) which were assayed in river water conditions. Thus to be conservative, k was set at 0.1 hr^{-1}.

2.3 Effects and Toxic Unit Predictions

Schäfers et al. (2009) presented the chronic toxicity of several pure LCOH homologues to *Daphnia magna* in 21-d reproduction and survival tests. The 21-d EC_{10} for reproduction inhibition was the most sensitive endpoint. Effects for C_{10}, C_{12}, C_{14}, and C_{15} were measured and EC_{10}s for C_{13} were predicted based on structure activity summarized in Schäfers et al. (2009). Effects were expressed based on overall mean measured exposure concentrations as well as initial mean measured concentrations. Predicted No Effect Concentration (PNECs) in the environment can be conservatively extrapolated by applying an application factor of 10, but a factor of 5 is more appropriate for this group of non-polar narcotics (Schäfers et al., (2009). Toxic unit (TU) summations of LCOH at each site were then calculated by combining PNECs with predicted exposures following adjustments for bioavailability, dilution, and in-stream biodegradation. Table 1 presents the *Daphnia magna* toxicity data for specific LCOH homologues and Figure 2 summarizes the overall process. A simple similar concentration addition model (Nirmalakhandan et al., 1994) can be used for assessing the environmental mixtures of LCOH because they act by a general nonpolar narcotic mode of action and are a structurally homologous series of compounds (see also Belanger et al., 2006; Boeije et al., 2006 for alcohol ethoxylates).

Table 1. Response of *Daphnia magna* to long chain alcohols in 21-d, chronic reproduction and survival test (from Schäfers et al., 2009). Measured EC_{10}s were used when available and predictions for untested chain lengths (C_{13}) were based on (Q)SAR.

Reproduction EC_{10} Chain Length	**µg/L**	**µmol**
	Based on overall mean measured concentrations	
10	210	1.33
12	12.8	0.07
13	17.2	0.09
14	6.3	0.03
15	12	0.05
	Based on mean initial measured concentrations	
10	630	3.97
12	150	0.81
13	148	0.74
14	70	0.33
15	74	0.32



$$TU\ \Sigma = \frac{C12OH\ Exposure}{C12OH\ PNEC} + \frac{C13OH\ Exposure}{C13OH\ PNEC} + \frac{C14OH\ Exposure}{C14OH\ PNEC} + \frac{C15OH\ Exposure}{C15OH\ PNEC}$$

Figure 2. Conceptual diagram of developing TU (toxic unit) prediction for LCOH environmental risk characterizations.

3.0 Results

3.1 Monitoring of LCOH in Influent and Effluent

A complete set of monitoring data for C_{12}-C_{15} LCOH was collected for the U.S. under five different forms of wastewater treatment. Influent concentrations (total) ranged from 91.4 to 1209.8 µg/L, which probably reflects diversity in LCOH consumption and disposal, distance from sewage treatment works, and water usage patterns (Table 2). Final effluent concentrations ranged from 0.063 to 4.921 µg/L. The highest concentrations were recorded at locations employing trickling filter treatment. Site-specific removals were all very high and ranged from 98.4 to nearly 100% (high removals at several locations would require reporting 5 significant digits with little practical significance). Removal was similar across all chain lengths, with C_{12} being the least effectively removed homologue at 99.6%.

Final effluent was monitored in Canadian and European wastewater treatment plants. The range of effluent concentrations in Canada was 0.158 to 8.823 µg/L and in Europe was 0.074 to 4.634 µg/L (Table 3). The single highest concentration in the study was from a fixed film, rotating biological contactor facility in Cardston, Alberta, Canada at 8.823 µg/L. The average concentration of LCOH across regions was 0.572, 0.910, and 1.711 for the U.S., Europe, and Canada, respectively with a global mean of 1.064 µg/L. Because the sample size is substantial (a total of 32 sites) the monitoring data can be assessed using distributional statistics. The 90^{th} percentile effluent concentration, based on the entire data set, is 1.979 µg/L and a total of 4 of 32 sites exceed or equal this value.

Total final effluent concentrations were re-evaluated using a bioavailability correction to represent the amount of LCOH initially present in the samples (Table 4). This method is used because analytical determinations of LCOH can only be made by simultaneously extracting the analytes from both solid and liquid phases, therefore, LCOH in the liquid is estimated following a bioavailability correction (see also Belanger et al., 2006; Federle and Itrich, 2006; and van Compernolle et al., 2006). Adjustments are chain length dependent in accordance with the known (Q)SAR, thus, the contributions of C_{12}, C_{13}, C_{14} and C_{15}

Table 2. Measured long chain alcohols in sewage treatment plant influents, effluents and removal from monitoring studies in the U.S. (concentrations expressed in µg/L) (data from Morrall et al., 2006[a] and MRI, 2004[b]). AS=activated sludge; L=lagoon; OD=oxidation ditch; RBC=rotating biological contactor; TF=trickling filter.

	Location	Treatment Type	C_{12}	C_{13}	C_{14}	C_{15}	Total
Influent	San Benito, Texas[a]	L	40.1	39.9	51.2	165.6	296.8
	Rockaway Valley, New Jersey[a]	OD	82.1	25.4	83.7	57.6	248.8
	St. Clairsville, Ohio[a]	RBC	51.5	15.0	55.6	34.7	156.8
	Oskaloosa, Iowa[a]	TF	139.2	68.5	168.7	122.7	499.1
	Sedalia, Missouri[a]	TF	201.3	64.5	163.6	102.7	532.1
	Rosehill, Kansas[a]	L	26.1	4.25	26.6	10.49	67.44
	Lodi, California[a]	AS	69.2	12.3	71.8	52.0	205.3
	Durham, Oregon[a]	AS	23.2	5.0	31.8	32.9	92.9
	Opelika, Alabama[a]	OD	124.7	90.8	83.8	403.1	702.4
	Lowell, Indiana[b]	AS	409.6	268.5	277.4	254.3	1209.8
	Wilmington, Ohio[b]	AS	30.0	19.5	21.1	20.8	91.4
	Bryan, Ohio[b]	AS	213.1	154.2	143.4	119.9	630.6
	Average		117.5	64.0	98.2	114.7	394.5
Effluent	San Benito, Texas	L	0.958	0.067	0.626	0.329	1.980
	Rockaway Valley, New Jersey	OD	0.603	0.025	0.093	0.021	0.742
	St. Clairsville, Ohio	RBC	0.023	0.008	0.025	0.007	0.063
	Oskaloosa, Iowa	TF	0.965	0.134	0.448	0.422	1.969
	Sedalia, Missouri	TF	1.892	0.499	1.952	0.578	4.921
	Rosehill, Kansas	L	0.552	0.067	0.406	0.062	1.087
	Lodi, California	AS	0.134	0.015	0.041	0.026	0.216
	Durham, Oregon	AS	0.132	0.007	0.057	0.027	0.223
	Opelika, Alabama	OD	0.140	0.128	0.032	0.010	0.310
	Lowell, Indiana	AS	0.160	0.004	0.004	0.385	0.553
	Wilmington, Ohio	AS	0.097	0.004	0.056	0.086	0.243
	Bryan, Ohio	AS	0.051	0.004	0.004	0.004	0.063
	Weighted Average		0.255	0.035	0.147	0.135	0.572
Removal (%)	San Benito, Texas	L	97.6	99.8	98.8	99.8	99.3
	Rockaway Valley, New Jersey	OD	99.3	99.9	99.9	100.0	99.7
	St. Clairsville, Ohio	RBC	100.0	99.9	100.0	100.0	100.0
	Oskaloosa, Iowa	TF	99.3	99.8	99.7	99.7	99.6
	Sedalia, Missouri	TF	99.1	99.2	98.8	99.4	99.1
	Rosehill, Kansas	L	97.9	98.4	98.5	99.4	98.4
	Lodi, California	AS	99.8	99.9	99.9	100.0	99.9
	Durham, Oregon	AS	99.4	99.9	99.8	99.9	99.8
	Opelika, Alabama	OD	99.9	99.9	100.0	100.0	100.0
	Lowell, Indiana	AS	100.0	100.0	100.0	99.8	100.0
	Wilmington, Ohio	AS	99.7	100.0	99.7	99.6	99.7
	Bryan, Ohio	AS	100.0	100.0	100.0	100.0	100.0
	Average		**99.6**	**99.9**	**99.8**	**99.8**	**99.8**

Table 3. Summary of measured long chain alcohols in sewage treatment effluents cited from monitoring studies in the United States (Morrall et al., 2006[a], Dyer et al., 2006[b]), Canada, and Europe (Eadsforth et al., 2006[c]) (all concentrations expressed in µg/L). L = lagoon; OD = oxidation ditch; TF = trickling filter; AS = activated sludge; RBC = rotating biological contactor. The U.S. average is not a simple arithmetic mean, but reflects the national distribution of each form of waste treatment based on flow.

Location	Treatment	C_{12}	C_{13}	C_{14}	C_{15}	Total
USA						
San Benito, Texas[a]	L	0.958	0.067	0.626	0.329	1.980
Rockaway Valley, New Jersey[a]	OD	0.603	0.025	0.093	0.021	0.742
St. Clairsville, Ohio[a]	RBC	0.023	0.008	0.025	0.007	0.063
Oskaloosa, Iowa[a]	TF	0.965	0.134	0.448	0.422	1.969
Sedalia, Missouri[a]	TF	1.892	0.499	1.952	0.578	4.921
Rosehill, Kansas[a]	L	0.552	0.067	0.406	0.062	1.087
Lodi, California[a]	AS	0.134	0.015	0.041	0.026	0.216
Durham, Oregon[a]	AS	0.132	0.007	0.057	0.027	0.223
Opelika, Alabama[a]	OD	0.140	0.128	0.032	0.010	0.310
Lowell, Indiana[b]	AS	0.160	0.004	0.004	0.385	0.553
Wilmington, Ohio[b]	AS	0.097	0.004	0.056	0.086	0.243
Bryan, Ohio[b]	AS	0.051	0.004	0.004	0.004	0.063
Average		0.255	0.035	0.147	0.135	0.572
Canada						
Vernon, British Columbia[c]	TF	0.393	0.174	0.428	0.886	1.881
Kelowna, British Columbia[c]	AS	0.243	0.102	0.107	0.181	0.633
Toronto, Ontario[c]	AS	0.027	0.235	0.548	0.312	1.122
La Prairie, Quebec[c]	AS	0.070	0.030	0.029	0.041	0.170
Victoriaville, Quebec[c]	AS	0.069	0.019	0.014	0.048	0.150
Paris, Ontario[c]	AS	0.036	0.030	0.033	0.059	0.158
Cardston, Alberta[c]	RBC	1.251	0.961	3.354	3.257	8.823
Waterloo, Ontario[c]	AS	0.301	0.122	0.156	0.172	0.751
Average		0.299	0.209	0.584	0.619	1.711
Europe						
Northwich, United Kingdom[c]	AS	0.468	0.319	0.305	0.154	1.246
Cannock, United Kingdom[c]	AS	0.104	0.087	0.069	0.084	0.344
Rushmoor, United Kingdom[c]	AS	0.134	0.104	0.095	0.125	0.458
Kralingse Veer, Netherlands[c]	AS	0.410	0.147	0.138	0.125	0.820
De Meern, Netherlands[c]	AS	0.282	0.208	0.174	0.155	0.819
Horstermeer, Netherlands[c]	AS	0.360	0.211	0.212	0.136	0.919
Estepona, Spain[c]	AS	0.214	0.073	0.182	0.148	0.617
La Vibora, Spain[c]	AS	1.179	0.533	1.741	1.181	4.634
Munich, Germany[c]	AS	0.010	0.023	0.007	0.034	0.074
Torino, Italy[c]	AS	0.070	0.094	0.057	0.058	0.279
Robecco, Italy[c]	AS	0.092	0.130	0.072	0.206	0.500
Ratingen, Germany[c]	AS	0.046	0.052	0.033	0.083	0.214
Average		0.281	0.165	0.257	0.207	0.910
Global Average		0.278	0.136	0.329	0.320	1.064

Table 4. Summary of measured long chain alcohols in sewage treatment effluents following adjustment for bioavailability using the long chain alcohol (Q)SAR (all concentrations expressed in µg/L). L = lagoon; OD = oxidation ditch; TF = trickling filter; AS = activated sludge; RBC = rotating biological contactor. The U.S. average is not a simple arithmetic mean, but reflects the national distribution of each form of waste treatment based on flow.

Location	Treatment	C_{12}	C_{13}	C_{14}	C_{15}	Total
USA						
San Benito, Texas[a]	L	0.821	0.052	0.419	0.178	1.470
Rockaway Valley, New Jersey[a]	OD	0.517	0.019	0.062	0.011	0.609
St. Clairsville, Ohio[a]	RBC	0.020	0.006	0.017	0.004	0.047
Oskaloosa, Iowa[a]	TF	0.827	0.104	0.300	0.229	1.460
Sedalia, Missouri[a]	TF	1.621	0.388	1.308	0.313	3.630
Rosehill, Kansas[a]	L	0.473	0.052	0.272	0.034	0.831
Lodi, California[a]	AS	0.115	0.012	0.027	0.014	0.168
Durham, Oregon[a]	AS	0.113	0.005	0.038	0.015	0.171
Opelika, Alabama[a]	OD	0.120	0.099	0.021	0.005	0.245
Lowell, Indiana[b]	AS	0.137	0.003	0.003	0.209	0.352
Wilmington, Ohio[b]	AS	0.083	0.003	0.038	0.047	0.171
Bryan, Ohio[b]	AS	0.044	0.003	0.003	0.002	0.052
Average		0.219	0.027	0.098	0.073	0.417
Canada						
Vernon, British Columbia[c]	TF	0.337	0.135	0.287	0.480	1.239
Kelowna, British Columbia[c]	AS	0.208	0.079	0.072	0.098	0.457
Toronto, Ontario[c]	AS	0.023	0.183	0.367	0.169	0.742
La Prairie, Quebec[c]	AS	0.060	0.023	0.019	0.022	0.124
Victoriaville, Quebec[c]	AS	0.059	0.015	0.009	0.026	0.109
Paris, Ontario[c]	AS	0.031	0.023	0.022	0.032	0.108
Cardston, Alberta[c]	RBC	1.072	0.747	2.247	1.765	5.831
Waterloo, Ontario[c]	AS	0.258	0.095	0.105	0.093	0.551
Average		0.256	0.162	0.391	0.335	1.487
Europe						
Northwich, United Kingdom[c]	AS	0.401	0.248	0.204	0.083	0.936
Cannock, United Kingdom[c]	AS	0.089	0.068	0.046	0.046	0.249
Rushmoor, United Kingdom[c]	AS	0.115	0.081	0.064	0.068	0.328
Kralingse Veer, Netherlands[c]	AS	0.351	0.114	0.092	0.068	0.625
De Meern, Netherlands[c]	AS	0.242	0.162	0.117	0.084	0.605
Horstermeer, Netherlands[c]	AS	0.309	0.164	0.142	0.074	0.689
Estepona, Spain[c]	AS	0.183	0.057	0.122	0.080	0.442
La Vibora, Spain[c]	AS	1.010	0.414	1.167	0.640	3.231
Munich, Germany[c]	AS	0.009	0.018	0.005	0.018	0.050
Torino, Italy[c]	AS	0.060	0.073	0.038	0.031	0.202
Robecco, Italy[c]	AS	0.079	0.101	0.048	0.112	0.340
Ratingen, Germany[c]	AS	0.039	0.040	0.022	0.045	0.146
Average		0.241	0.128	0.172	0.112	0.654
Global Average		0.239	0.106	0.220	0.173	0.739

alcohols to the final concentrations declined by approximately 14, 23, 33, and 46%, respectively. The predicted bioavailable concentration per site reflects the site-specific distributions. The total concentrations declined 17.8% (Bryan, Ohio U.S.) to 36.4% (Lowell, Indiana, U.S.) following correction for bioavailability. Regional total AE average concentrations were reduced 24.6, 28.2, and 30.3% for the

U.S., Europe, and Canada, respectively. The 90th percentile effluent concentration following bioavailability correction is 1.469 µg/L.

Final effluent entering receiving waters is often diluted immediately upon entry. A conservative scenario using site-specific dilution data for U.S. monitored sites and a similarly conservative dilution factor for non-U.S. sites was combined with projected in-stream loss of LCOH due to mineralization. Figure 3 presents cumulative frequency distributions of environmental concentrations of LCOH with perspective on total unadjusted, following bioavailability adjustment, and accounting for bioavailability, dilution, and in-stream mineralization of parent. The 90th percentile line is drawn indicating the influence of increasing realism on the exposure assessment, particularly for the highest exposure concentration sites. The 90th percentile in-stream concentrations following accounting for dilution and in-stream mineralization of parent are 1.334 and 1.298 µg/L, respectively.

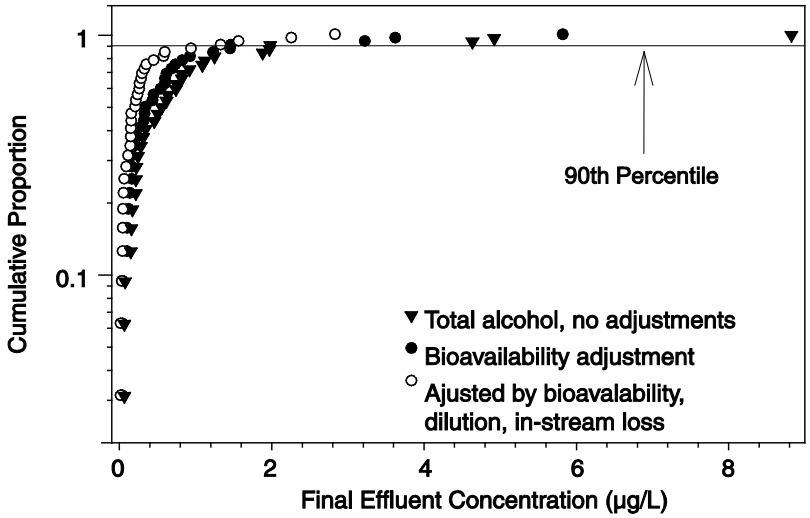


Figure 3. Cumulative frequency distribution of final effluent concentrations before (total, unadjusted) and after (total adjusted) correcting for bioavailability dilution and in-stream mineralization of parent alcohol.

3.2 Toxic Unit Characterizations

Predictions of Toxic Units summed for C_{12} to C_{15} alcohol chain lengths were made using mean measured (initial and final) concentrations and mean initial concentrations from *Daphnia magna* chronic studies. TU summations ranged from 0.002 to 0.587 with a global average of 0.048 when based on initial measured concentrations, an application factor of 10 to derive the PNEC and use of the adjusted in-stream concentrations (bioavailability, dilution, in-stream loss) for the PEC (Table 5). In this case all sites had risk characterization ratios (TU) below 1, even when conservative assumptions are employed. TU summations when considering overall mean measured concentrations and the same PEC ranged from 0.021 to 3.071 with a global average of 0.467 (Table 6). Four sites had risk characterization ratios exceeding 1 in the most conservative scenario. The 90th percentile TUs when PNECs were based on initial versus overall mean concentrations in the chronic *D. magna* studies were 0.125 and 1.305 (Figure 4).

Three of the four sites with the highest TU estimates were wastewater treatment plants that employed fixed film treatment technologies or had indications they may have otherwise been treating poorly (high BOD, ammonia or suspended solids in the effluent discharged). In general, TU estimates based on mean initial concentrations determined in the *D. magna* chronic studies were a factor of 10.3 less than when based on overall mean (initial and final concentrations) (range of 8.8 to 13.2 times). Overall, TUs associated with LCOH following activated sludge treatment were significantly lower than all other treatment types (t-test, $p < 0.05$ for TUs based on either mean initial concentration or mean of initial and final concentrations in *Daphnia magna* chronic toxicity tests).

Table 5
Summary of Toxic Unit predictions for all sites based on refined exposure (bioavailability, dilution, and in-stream removal accounted for) and effect assessments using mean initial exposure concentration data from *Daphnia magna* chronic toxicity assessments (with an assessment factor of 10); United States (Morrall et al., 2006[a], Dyer et al., 2006[b]), Canada, and Europe (Eadsforth et al., 2006[c]).

Location	Treatment Type	C_{12}	C_{13}	C_{14}	C_{15}	Total
USA						
San Benito, Texas[a]	L	0.045	0.003	0.054	0.022	0.129
Rockaway Valley, New Jersey[a]	OD	0.033	0.001	0.008	0.001	0.044
St. Clairsville, Ohio[a]	RBC	0.001	0.001	0.001	0.001	0.002
Oskaloosa, Iowa[a]	TF	0.036	0.005	0.028	0.020	0.088
Sedalia, Missouri[a]	TF	0.067	0.016	0.117	0.026	0.227
Rosehill, Kansas[a]	L	0.010	0.001	0.013	0.001	0.026
Lodi, California[a]	AS	0.007	0.001	0.004	0.002	0.014
Durham, Oregon[a]	AS	0.007	0.001	0.005	0.002	0.014
Opelika, Alabama[a]	OD	0.001	0.001	0.001	0.001	0.004
Lowell, Indiana[b]	AS	0.006	0.001	0.001	0.020	0.027
Wilmington, Ohio[b]	AS	0.005	0.001	0.005	0.005	0.015
Bryan, Ohio[b]	AS	0.003	0.001	0.001	0.001	0.004
Average		0.019	0.002	0.020	0.008	0.033
Canada						
Vernon, British Columbia[c]	TF	0.015	0.008	0.045	0.039	0.107
Kelowna, British Columbia[c]	AS	0.010	0.005	0.011	0.008	0.033
Toronto, Ontario[c]	AS	0.001	0.011	0.057	0.014	0.083
La Prairie, Quebec[c]	AS	0.003	0.001	0.003	0.002	0.009
Victoriaville, Quebec[c]	AS	0.003	0.001	0.001	0.002	0.007
Paris, Ontario[c]	AS	0.001	0.001	0.003	0.003	0.009
Cardston, Alberta[c]	RBC	0.049	0.043	0.351	0.143	0.587
Waterloo, Ontario[c]	AS	0.012	0.005	0.016	0.008	0.041
Average		0.008	0.005	0.027	0.022	0.063
Europe						
Northwich, United Kingdom[c]	AS	0.013	0.008	0.014	0.005	0.041
Cannock, United Kingdom[c]	AS	0.003	0.002	0.003	0.003	0.011
Rushmoor, United Kingdom[c]	AS	0.004	0.003	0.004	0.004	0.015
Kralingse Veer, Netherlands[c]	AS	0.011	0.004	0.006	0.004	0.026
De Meern, Netherlands[c]	AS	0.008	0.005	0.008	0.005	0.027
Horstermeer, Netherlands[c]	AS	0.010	0.005	0.010	0.005	0.030
Estepona, Spain[c]	AS	0.006	0.002	0.008	0.005	0.022
La Vibora, Spain[c]	AS	0.033	0.014	0.081	0.042	0.170
Munich, Germany[c]	AS	0.001	0.001	0.001	0.001	0.002
Torino, Italy[c]	AS	0.002	0.002	0.003	0.002	0.009
Robecco, Italy[c]	AS	0.003	0.003	0.003	0.007	0.017
Ratingen, Germany[c]	AS	0.001	0.001	0.001	0.003	0.007
Average		0.008	0.004	0.012	0.007	0.031
Global Average		0.0117	0.0040	0.0196	0.0126	0.048

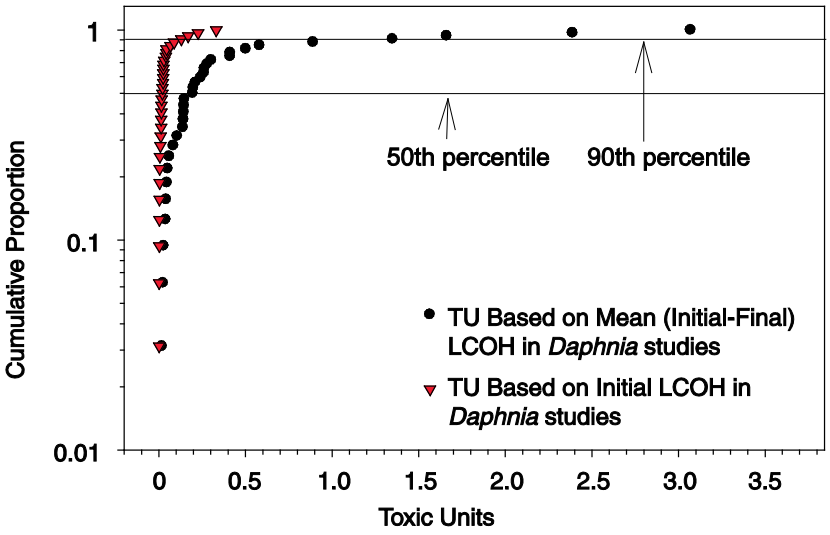


Figure 4. Cumulative frequency distribution of TU determinations for LCOH for the 32 monitored sites in Europe, Canada and the U.S.

4.0 Discussion

The environmental risk of LCOH is best thought of as probable range of risk characterization ratios. Precise determination of risk quotients is exceptionally difficult due to a variety of factors. Among these are the complications of natural sources of alcohol contributing to measured environmental concentrations. A recent risk assessment of alcohol ethoxylate (AE) non-ionic surfactants encountered a similar problem which was solved by identifying the fraction of alcohol that was directly associated with the production of AE or as a result of AE biodegradation (Wind et al., 2006; Belanger et al., 2006). In this case, approximately one-third of the LCOH (C_{12} to C_{18}) measured in wastewater treatment plant effluents could be experimentally tied to AE and the balance was non-AE derived and was appropriately not included in the AE risk assessment.

However, this observation did beg the question, "where does all other alcohol come from?" Federle and Itrich (2006) and others (OECD, 2006) have clearly demonstrated exceptionally short half-lives of alcohol in the environment and the preponderance of LCOH measured in environmental matrices seems inconsistent with anthropogenic origin. Many sources of LCOH exist, including microbial biotransformation and *in situ* production, from terrestrial plant waxes, and from other sources of wax esters and fatty acids. The presence of LCOH of the same chain lengths as those evaluated in this study are ubiquitous around the globe and have been found in deep sedimentary cores from freshwater and marine systems (Hottham, 2001; Mohd Ali, 2003). Cores described in these studies were taken before the geologic period of human influence. Quantitative studies are still lacking to understand the role of natural processes that contribute to the presence of LCOH in sewage treatment effluents as well as proximate surface sediments and receiving surface waters. Environmental half-lives in compartments such as river water and sediment appear to be controlled by the measured de-sorption of LCOH on solids to water where they are rapidly attacked by bacteria (Federle and Itrich, 2006; Van Compernolle et al., 2006).

TU that were determined from the combined exposure and effects data for LCOH range across an order of magnitude depending on the assumptions applied. The greatest contributor to differences in the various permutations is how exposures to LCOH were expressed in the *Daphnia magna* chronic effect studies. Because LCOH degraded so rapidly during the tests reported by Schäfers et al. (2009), in spite of extreme precautions to prevent test material losses, test material was usually completely degraded during the 24-hr time span of solution renewals. Note that flow through studies were attempted that only exacerbated the problem as biodegradation losses were faster than test material could be renewed and bacterial inocula only acclimated more and more. Thus, expression of exposure based on mean initial concentrations and the mean of initial and 24-hr old test solution concentrations were about a factor of 10 apart. This is also

Table 6. Summary of Toxic Unit predictions for all sites based on refined exposure (bioavailability, dilution, and in-stream removal accounted for) and effect assessments using overall mean exposure concentration data from *Daphnia magna* chronic toxicity assessments (with an assessment factor of 10).

Location	Treatment Type	C_{12}	C_{13}	C_{14}	C_{15}	Total
USA						
San Benito, Texas[a]	L	0.583	0.027	0.605	0.135	1.351
Rockaway Valley, New Jersey[a]	OD	0.389	0.011	0.095	0.009	0.504
St. Clairsville, Ohio[a]	RBC	0.008	0.002	0.014	0.002	0.026
Oskaloosa, Iowa[a]	TF	0.419	0.039	0.309	0.124	0.891
Sedalia, Missouri[a]	TF	0.790	0.141	1.295	0.163	2.389
Rosehill, Kansas[a]	L	0.121	0.010	0.141	0.009	0.281
Lodi, California[a]	AS	0.087	0.007	0.042	0.011	0.147
Durham, Oregon[a]	AS	0.080	0.003	0.055	0.011	0.149
Opelika, Alabama[a]	OD	0.015	0.009	0.005	0.001	0.023
Lowell, Indiana[b]	AS	0.075	0.001	0.003	0.122	0.201
Wilmington, Ohio[b]	AS	0.057	0.002	0.052	0.034	0.145
Bryan, Ohio[b]	AS	0.033	0.002	0.004	0.002	0.041
Average		0.222	0.021	0.218	0.052	0.513
Canada						
Vernon, British Columbia[c]	TF	0.128	0.038	0.222	0.195	0.583
Kelowna, British Columbia[c]	AS	0.079	0.022	0.056	0.040	0.197
Toronto, Ontario[c]	AS	0.009	0.052	0.283	0.068	0.413
La Prairie, Quebec[c]	AS	0.023	0.006	0.015	0.009	0.053
Victoriaville, Quebec[c]	AS	0.022	0.004	0.007	0.010	0.044
Paris, Ontario[c]	AS	0.012	0.006	0.017	0.013	0.048
Cardston, Alberta[c]	RBC	0.408	0.211	1.736	0.716	3.071
Waterloo, Ontario[c]	AS	0.098	0.027	0.081	0.038	0.244
Average		0.097	0.046	0.302	0.136	0.581
Europe						
Northwich, United Kingdom[c]	AS	0.152	0.070	0.158	0.034	0.414
Cannock, United Kingdom[c]	AS	0.034	0.019	0.035	0.019	0.107
Rushmoor, United Kingdom[c]	AS	0.044	0.023	0.049	0.028	0.144
Kralingse Veer, Netherlands[c]	AS	0.133	0.032	0.071	0.028	0.264
De Meern, Netherlands[c]	AS	0.092	0.046	0.090	0.034	0.262
Horstermeer, Netherlands[c]	AS	0.117	0.046	0.110	0.030	0.304
Estepona, Spain[c]	AS	0.067	0.016	0.094	0.032	0.212
La Vibora, Spain[c]	AS	0.384	0.117	0.901	0.260	1.662
Munich, Germany[c]	AS	0.003	0.005	0.004	0.007	0.020
Torino, Italy[c]	AS	0.023	0.021	0.029	0.013	0.085
Robecco, Italy[c]	AS	0.030	0.029	0.037	0.045	0.141
Ratingen, Germany[c]	AS	0.015	0.011	0.017	0.018	0.061
Average		0.091	0.036	0.133	0.046	0.306
Global Average		0.137	0.034	0.218	0.078	0.467

reflected in the calculated 21-d EC_{10}s (Table 1). These differences translate directly into the PNEC and TU determinations. Reality of exposure in tests is likely somewhere between these extremes, but is logistically impossible to confirm with the amount of sampling that would have been required.

The difficulty of interpreting pulsed exposures in aquatic toxicology is well known (Diamond et al., 2006; Stoughton et al. 2008). In the case of LCOH which are discharged as components of wastewater treatment plant effluents, concentrations would be expected to oscillate with both consumer and industrial use and discharge volumes on a daily cyclical basis (Fendinger et al., 1992). The response of organisms to peak versus average exposures was discussed by Diamond et al. (2006) in the context of wastewater permit limits and the authors concluded that peak concentrations often drive toxicological outcomes. Pulsed contaminant exposures for metals (zinc, copper - Diamond et al., 2008; selenium- Hoang and Klaine, 2008), inorganic or simple organic compounds (sodium chloride, nitric acid, ammonia - Diamond et al., 2005, 2008), pharmaceuticals (imidacloprid - Stoughton et al. 2008), and many pesticides (Reinert et al. 2002) often show peak concentrations drive effects on aquatic biota. It seems likely that LCOH would behave similarly and that basing effects on mean initial concentrations from Daphnia magna chronic toxicity studies is a reasonable assumption with resulting PNECs derived from these observations also being representative.

The highest measurements of LCOH in effluents from wastewater treatment plants occur from facilities that do not employ activated sludge treatment. Importantly, non-activated sludge treatment plants discharge most often at lower volumes and are sited on smaller river systems thereby restricting their overall environmental impact (Dyer and Wang, 2002; De Zwart et al., 2006). In general, the total dilution available for non-activated sludge treatment plants can be low, hence flow dilution factors often approach 1 (USEPA, 1996).

Few chronic fish studies have been performed on LCOH and none in the range of LCOH considered in these studies (OECD, 2006); however, some algal acute and chronic studies have been performed and when combined with a full analysis of the acute data available it is a sound conclusion that *Daphnia magna* represents a most sensitive species to which an application factor of 10 for risk assessment can be justified (Fisk et al. (2009), Schäfers et al., (2009)). This remains a conservative approach based on demonstrated acute-chronic ratios of the LCOHs (range of 2-5) consistent with a non-polar narcotic mode of action. Studies by Dyer et al. (2006) and Lange et al. (1998) quantitatively explored inter-species toxicity correlations using large data bases and demonstrated that daphnid species were consistently among the more sensitive taxa. Additional application factors for the purpose of extrapolation might not be needed considering the high biodegradability of the substances.

Other factors also influenced the TU determinations and in order of greatest apparent influence (other than the discussion above) were the dilution scenario employed, bioavailability adjustment, and incorporation of in-stream loss via biodegradation. The dilution scenarios used were conservative (i.e., based on known or presumed low flow) as were losses due to biodegradation. For the latter, stream flow rates of 1 m/s and a first order loss rate for mineralization were assumed. It is interesting to note that biodegradation and biotransformation play prominent roles in this risk assessment and influence the perception of the hazard posed by LCOH which appear relatively toxic compared to many other organic compounds. Formation of natural alcohol in the environment by microbial process, use of LCOHs by many animals for physiological and metabolic purposes (for example, as energy reserves, as a buoyancy mechanisms, and as insulation), and ubiquitous presence in the environment suggest that caution should be used to not over interpret the measured levels in environmental matrices as these are confounded by these other factors (Mudge, 2005). Many of the LCOH have relatively high log K_{ow}s (Fisk et al., 2009), which suggest high bioaccumulative potential. Metabolic biotransformation of alcohols though is very high as has been demonstrated by assays of analogous alcohol-based surfactants (Bernhard and Dyer,

2005) and several, branched long chain alcohols (de Wolf and Parkerton, 1999 unpublished presentation and industry reports submitted for the categorization of the Canadian Domestic Substances List to Environment Canada; Weisbrod et al., 2005; and Environment Canada, 2005). Calculated bioconcentration factors (BCF) are usually 1 to >2 log units higher than measured BCFs incorporating metabolism.

In summary, the environmental risk of LCOH based on new aquatic toxicity, fate and monitoring data indicates a low likelihood of risk. Fully definitive assessments are made difficult by the presence of natural sources of LCOH in the environment as well as by the inherently rapid biodegradation of chemicals in this family of compounds.

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Appendix IV-A

Summary of Chemical Awareness Framework for Evaluation of High Production Volume (HPV) Chemicals for Human Exposure and Risk

High Production Volume (HPV) Chemicals for Human Exposure and Risk

The Framework illustrated in Figure 1 was developed by Chemical Awareness (formerly, the Alliance for Chemical Awareness) for evaluating the human exposure and risk associated with high production volume (HPV) chemicals in commerce.

Phase I: Describing the flow of chemicals in commerce

There are a variety of stages in the lifecycle of a chemical which need to be taken into consideration when estimating exposure. Elaborating the flow of a chemical in commerce helps identify both sources of information, as well as sources of potential exposure. For simplicity, boxes 1-7 describe the essential flows of chemicals throughout commerce. These lead into two basic categories of potential exposure: (a) those related to industrial facilities where an individual chemical is manufactured, used, handled or processed, or (b) those related to the use of products containing a chemical. Boxes in the diagram are elaborated on in the paragraphs below.

Phase II: Identifying and qualitatively evaluating potential human exposure

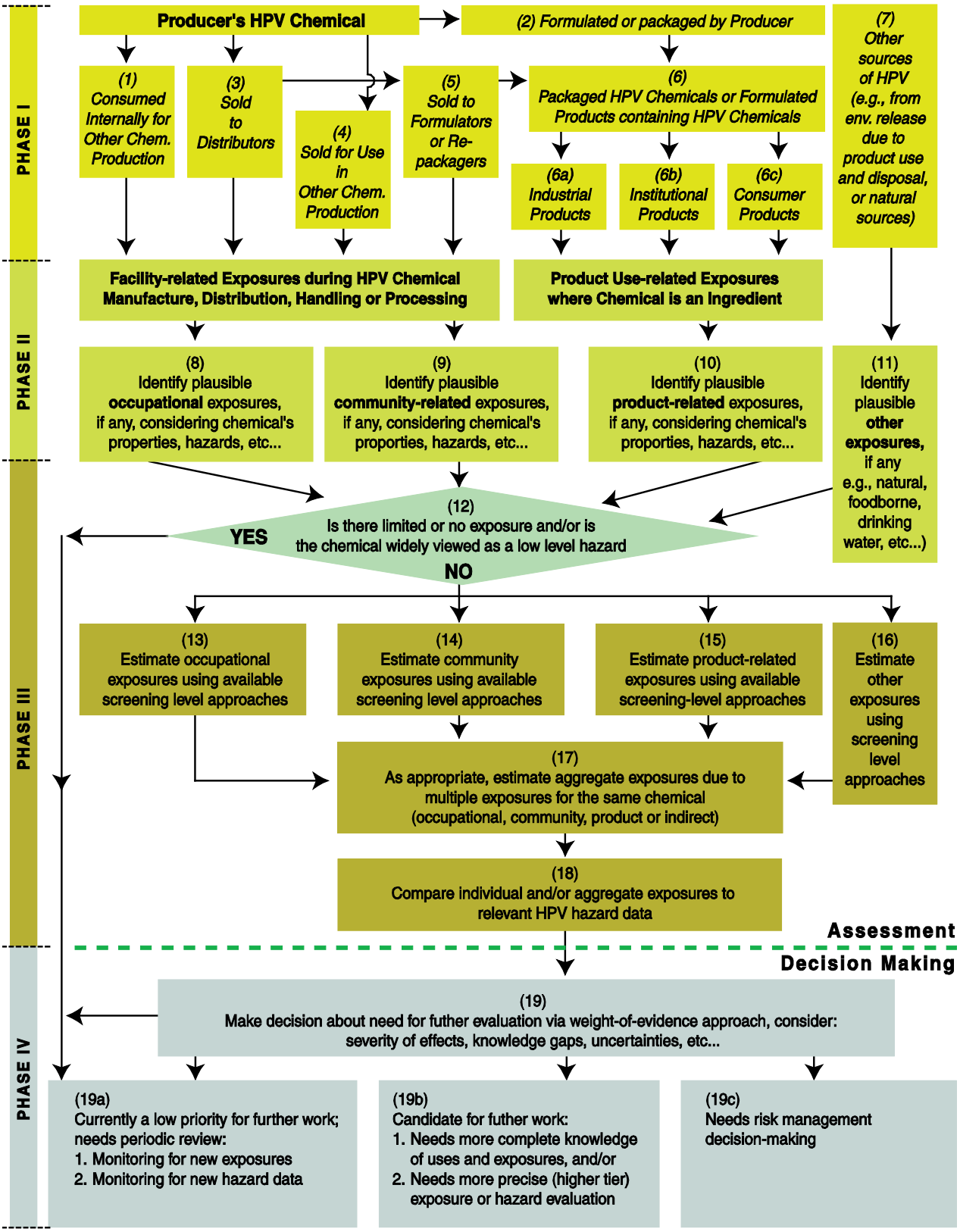
The potential exposures to chemicals are generally the result of two basic scenarios: (a) those related to industrial facilities where an individual chemical is manufactured, used, handled or processed, resulting in occupational exposure to workers, and/or community exposure via local environmental emissions; and (b) those related to the use of end products. Boxes 8-11 describe a qualitative process for identifying and preliminarily evaluating potential human exposures each of the sources outlined above, taking off from information on where and how the flows through commerce.

Phase III: Estimation of human exposure for comparison to hazard data

For each of the scenarios described in Figure 1, there are a wide range of approaches available for estimating exposure. Some are general; others are specifically designed for well-described industrial settings or product uses. The estimation of exposure can include predictive models, and/or direct observations (e.g., monitoring data, habits and practices, etc.). Careful selection of appropriate approaches is essential, and HPV chemical sponsors will need to consider both the level of analysis that will be sufficient to support decision-making, as well as the need to make timely, practical evaluations that will be relevant for public communications. Boxes 12-18 illustrate generally the information and analyses needed under the different scenarios outlined.

Phase IV: Making decisions about further evaluation of the studied uses

The comparison of both hazard and exposure data is essential for understanding the effects of chemicals on human health and the environment. Neither factor alone is normally sufficient. A weight-of-evidence approach is normally used, taking into account the severity of effects, dose response, precision and accuracy of data, reliability, statistical significance, and biological relevance of the hazards. This last factor may be especially important. For example, in carcinogenicity studies, adverse findings may be due to genetic harm by the test chemical, or they may be a consequence of the very high doses that are often used in long-term animal studies, which can lead to physiological responses that indirectly cause cancer, but that are not biologically relevant under normal exposure conditions to humans. The boxes in Step 19 describe the basic options available to decision-makers after a screening level evaluation.



Chemical Awareness Framework for Evaluation of High Production Volume (HPV) Chemicals for Human Exposure and Risk.

Appendix IV-B

Summary of Chemical Awareness Framework for Evaluation of High Production Volume (HPV) Chemicals for Potential Ecologic Exposure and Risk

The Framework illustrated in Figure 2 was developed by Chemical Awareness to help sponsors evaluate and prioritize chemicals based on their potential for adverse effects on relevant ecological receptors.

Phase Ia. Describing the Flow of the HPV Chemical in Commerce

There are a variety of stages in the lifecycle of a chemical which need to be taken into consideration when estimating exposure. Elaborating the flow of a chemical in commerce helps identify both sources of exposure information, as well as sources of potential emissions and thus of ecological exposure. Boxes 1-6 describe the essential flows of chemicals throughout commerce. These lead to two categories of potential releases to the environment: (a) those related to industrial facilities and (b) those related to the use and disposal of products containing a chemical. This phase of the ecological assessment is identical to, and uses the same information as, Phase 1 of the human exposure assessment framework.

Phase Ib. Identifying and evaluating potential environmental releases

Boxes 7-9 represent qualitative decision logic for identifying and conducting a preliminary evaluation of potential releases to the environment, using information on handling and use of chemicals in commerce. Data on emissions gathered in this phase will be used in conjunction with physical chemical data in the following phase to focus the assessment on emission sources that are most likely to result in exposure of relevant ecological receptors.

Phase II: Identifying the need for or scope of subsequent assessment

The purpose of this phase (Box 10) is to determine the level of assessment relative to potential ecological exposures and the scope of the evaluation based on data collected in Phases 1 and 2. Based on the results of this assessment formulation, one of three decisions might be made: a) the chemical is of sufficiently low priority to warrant no further evaluation at the time, b)the chemical warrants further assessment as a screening-level assessment, or c) the chemical warrants a higher tiered assessment directly.

Phase III: Estimation of ecological exposures and comparison to hazard data

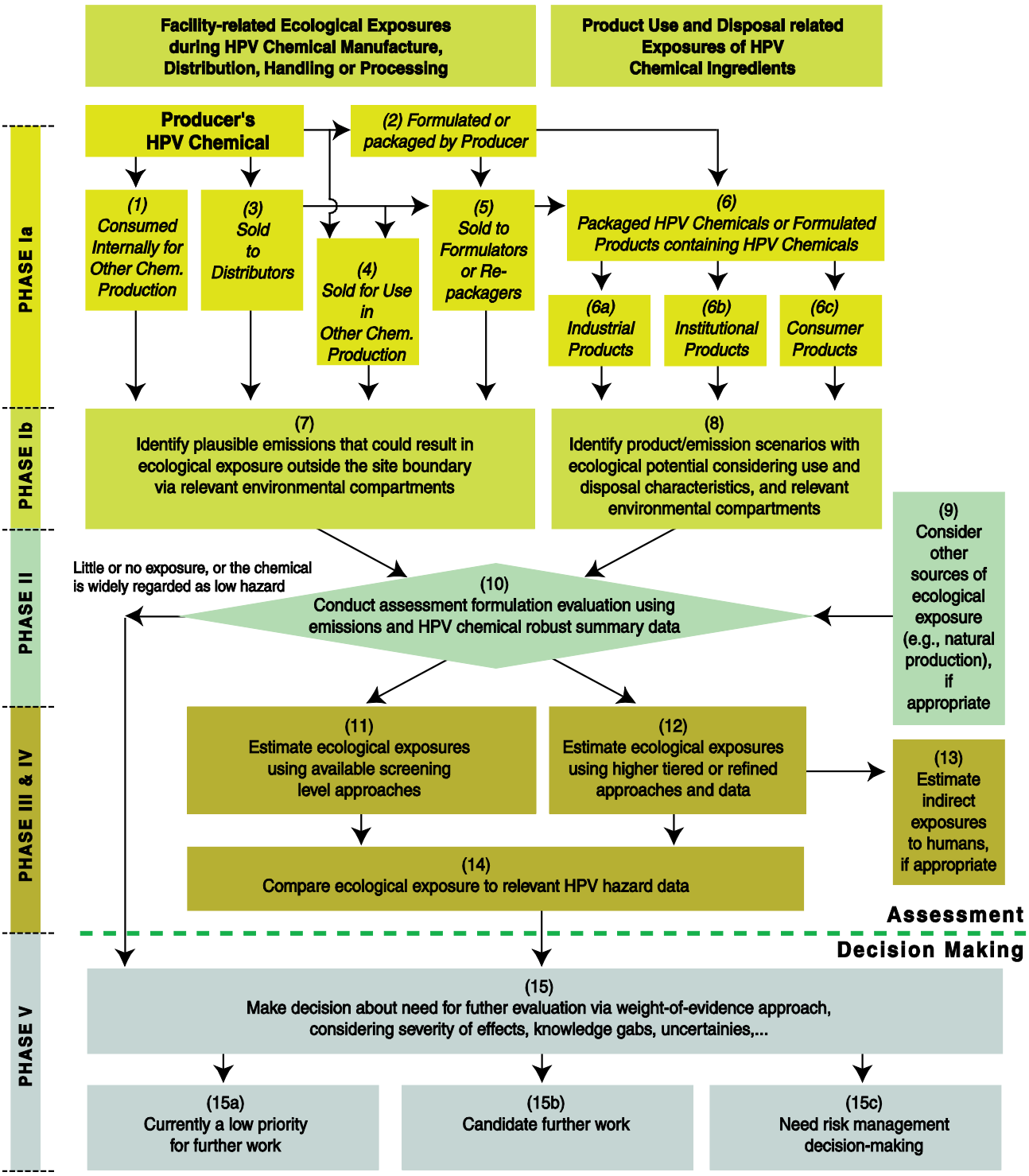
Using available screening-level approaches, ecological exposures for key products and emissions scenarios are estimated (Box 11), beginning with those that potentially have the most significant exposure potential and based on the initial qualitative analysis. The exposure information is integrated with previously collected hazard data to assess the need for further work or risk management.

Phase IV: Higher Tier/Refined Assessment

Higher tier/refined assessments are conducted as necessary (Box 12). The higher tier exposure information is integrated with previously collected hazard data to assess the need for further work or risk management (Box 14). Data on indirect exposure to humans as a result of environmental releases may be developed for incorporation in the human exposure assessment (Box 13).

Phase V: Making Decisions about Further Evaluation of the Studied Uses

The comparison of both hazard and exposure data is essential for understanding the potential for adverse effects of chemicals on the environment. In general, a weight-of-evidence approach is advocated as the basis for determining the need for further study or risk management. The weight-of-evidence approach would take into account the magnitude of a hazard quotient, the severity of effects, limited versus widespread nature of the emissions, dose response, precision and accuracy of data, reliability, statistical significance, and biological relevance of the hazards. These deliberations can have one of three basic outcomes shown in Box 15a, 15b, or 15c.



Chemical Awareness Framework for Evaluation of High Production Volume (HPV) Chemicals for Potential Ecologic Exposure and Risk.

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