EXPOSURE-BASED PRIORITIZATION OF CHEMICALS FOR RISK ASSESSMENT

Peter P. Egeghy[*†], *Daniel A. Vallero*[†], *and Elaine A. Cohen Hubal*[‡]

† National Exposure Research Laboratory, U.S. Environmental Protection Agency, Research Triangle Park, NC 27711; ‡ National Center for Computational Toxicology, U.S. Environmental Protection Agency, Research Triangle Park, NC 27711.

* Corresponding author e-mail: egeghy.peter@epa.gov.

ABSTRACT

Manufactured chemicals are used extensively to produce a wide variety of consumer goods and are required by important industrial sectors. Presently, information is insufficient to estimate risks posed to human health and the environment from the over ten thousand chemical substances currently in use and the hundreds more that are introduced each year. The vast majority of chemicals in products with wide commercial use are not measured in the environment, and potential for human exposure is not quantified. Regulatory agencies in North America and Europe have increased calls to address exposure to these chemicals. New, more reliable approaches are needed to characterize thousands of environmental chemicals on the basis of both hazard and exposure in a rapid and efficient manner, and to prioritize chemicals based on potential risk. Various approaches for prioritization based on exposure potential are summarized and compared. Knowledge gaps and research needed to facilitate rapid exposure-based prioritization for chemical evaluation are highlighted.

KEYWORDS. Chemical screening, Rapid prioritization, Risk assessment, Chemical exposure, Chemicals management

Introduction

Manufactured chemicals are used extensively in consumer goods, such as plastics, electronics, and cosmetics and in numerous industrial sectors including energy, agriculture, and pharmaceuticals. Both the manufacture and use of chemicals have significantly increased. Synthetic chemicals are integrated into nearly all industrial processes and commercial products. Whereas the social benefits, such as contributions to life expectancy and public health, and economic benefits, such as employment and economic growth, of the chemical industry are well documented (Wilson and Schwarzman, 2009: American Chemical Council, 2009), information regarding risks posed to human health and the environment from the growing dependence on chemicals is inadequate (Judson et al., 2009; Dellarco, et al., 2010). To evaluate these tradeoffs, new approaches are immediately required to evaluate environmental chemicals rapidly and efficiently to prioritize testing and assess potential for risk to human health (Dix, et al., 2007), based on both hazard and exposure dimensions (Sheldon and Cohen Hubal, 2009).

Development of a new generation of toxicity-based efforts to rapidly prioritize chemicals for further, more comprehensive evaluation is well underway. Currently, data from state-of-the-art high-throughput screening (HTS) bioassays combined with computational chemistry and other advanced tools are being applied to build statistical and computational models with a goal of forecasting potential toxicity in humans (Dix et al., 2007; Collins, et al., 2008).

Recognizing the critical need for exposure-based prioritization approaches on par with those for toxicity, the U.S. Environmental Protection Agency (EPA) has initiated the ExpoCast™ program to better evaluate and prioritize chemicals based on biologically relevant human exposures. The research program employs systematic and comprehensive approaches to consolidate existing exposure information and generate new tools to inform chemical design, evaluation, and risk management. Current research seeks robust approaches that use human exposure data, product use information, and

modeled human behavior to systematically prioritize potential for exposure, based on chemical properties, product life cycle, and individual and population characteristics (Cohen Hubal et al., 2010). This paper explores mandates for addressing human exposure in chemical prioritization in the U.S. and beyond. An assortment of available tools for evaluating exposure potential is identified, and additional needs to facilitate rapid exposure-based prioritization for chemical evaluation are suggested.

CHALLENGES TO ENSURING THE SAFETY OF CHEMICALS

Nearly 100,000 chemicals in commerce have been inventoried in the U.S. (Muir and Howard, 2006); these include about 82,000 TSCA-regulated substances as well as 8,600 food additives, 3,400 cosmetic ingredients, 1,800 pharmaceuticals, and 1,000 pesticide active ingredients. The total continues to increase as between 500 and 1,000 Notices of Commencement of Manufacture or Import are submitted each year (EPA, 2010a). About 2,750 organic chemicals were manufactured or imported in the U.S. in volumes exceeding 450 MT y^{-1} (Nguyen and Fehrenbacher, 2008). These High Production Volume (HPV) chemicals make up an estimated 95% of the total U.S. chemical production and are found in a wide array of consumer goods, cosmetics, medications, motor fuels, and building materials (Landrigan, 2010). Roughly 4,000 chemicals are Moderate Production Volume (MPV) chemicals produced at between 11 and 450 MT y^{-1}. Approximately 30,000 substances are believed to be in wide commercial use, marketed in volumes above 1 MT y^{-1} (Muir and Howard, 2006).

The principal objective of chemicals management is to ensure protection of human health and the environment. Although it has contributed to a cleaner and safer environment for humans and ecosystems (Fung and O'Rourke, 2000), the public is increasingly confronted with reports of chemicals measured in their homes, schools, and even bodies that are associated with chronic disease. As examples, persistent organic pollutants are readily measured in breast milk (Wolff, 1983; LaKind, et al., 2009), and flame retardants and pesticides in infant cord blood (Fukata, et al., 2005; Frederiksen, et al., 2009).

Biomonitoring results from the National Health and Nutrition Examination Survey show widespread human exposure to industrial chemicals.

Human or ecologic toxicity has been sufficiently assessed on only a small subset of chemicals. Of nearly 10,000 HPV and MPV chemicals, pesticide ingredients, and drinking water contaminants identified for the EPA ToxCast screening and prioritization program, high-quality toxicology evaluation is unavailable for about three-quarters and even limited toxicity information is lacking for one-third (Judson et al., 2009). This has improved since 1998, when only seven percent of 3,000 HPV chemicals had the full OECD Screening Information Data Set and about 43% lacked any toxicity testing data (EPA, 1998). Likewise, a 1999 analysis of 2,465 EU HPV chemicals in the International Uniform Chemical Information Database (IUCLID) (Allanou, et al., 1999) found only 14% to have the EU "base set" data relevant for risk assessment and 21% to have no data at all.

The vast majority of chemicals in wide commercial use are not monitored in environmental media, and their environmental fate and potential for human exposure are unknown. For contaminants of emerging concern, even basic occurrence information is unavailable (Muir and Howard, 2006). Production volume has served as the main surrogate of exposure, and evaluation efforts have been restricted to HPV or MPV chemicals. Under TSCA, EPA has also relied on additional surrogates, including chemical release, product formulation, use category, physical and chemical properties, and estimates of persistence and bioaccumulation potential. Under the Canadian Environmental Protection Act (CEPA) of 1999, Health Canada used a tiered system to categorize chemicals by exposure; relying on production volume, number of producers, and use categories for the first tier, and consumer use scenarios, chemical properties, and bioavailability for the second tier. Under the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) Regulation in Europe, the level of exposure information required from manufacturers varies with production volume, but with extensive exposure assessments required for all substances with a hazard level classified as "dangerous." REACH

was intended to directly address a fundamental barrier to effective assessment of exposure by encouraging communication between chemical manufacturers and downstream users.

The EPA recently laid out principles for fundamental reform of U.S. chemicals management. Characterizing TSCA as inadequate for protecting the public, Congress was asked to overhaul U.S. regulation of new and existing chemicals (EPA, 2009a) to shift the burden of demonstrating safety to industry, to give EPA authority to require that manufacturers provide sufficient exposure, hazard, and use data for risk characterization, and management in the face of uncertainty. The principles were largely endorsed by the American Academy of Pediatrics (Council on Environmental Health, 2011). The chemical manufacturing industry, already working with EPA to make chemical information public and preparing hazard and exposure information for ECHA, has also publically supported reform of U.S. laws. Altogether, reform appears to be backed by industry, U.S. states, the medical community, and the environmental community.

Methods

We identified prominent developers and users of exposure-based chemical prioritization tools through the EPA Exposure Science Community of Practice (http://www.epa.gov/ncct/exposure_science.html). Information on prioritization mandates and strategies was elicited through personal communications and with a global stakeholder workshop held in Research Triangle Park, NC (EPA, 2010b). The tools currently available for comprehensively evaluating exposure potential were identified and tabulated in order to compare and contrast relevant qualitative indicators (Table 1).

Results

PRIORITIZATION EFFORTS IN THE U.S.

Chemical risk assessment provides the foundation for regulating hazardous chemicals, and several laws in the U.S. (e.g., Clean Air Act of 1970, Clean Water Act of 1972) address pollutants that are

released into the environment. To a lesser extent, potentially hazardous chemicals have also been regulated based on their intentional use in manufactured products. In the U.S., the product categories are: (1) pesticides regulated under the Federal, Insecticide, Fungicide and Rodenticide Act (FIFRA); (2) food, drugs and cosmetics regulated under the Federal Food, Drugs and Cosmetics Act, which was amended as the Food Quality Protect Act (FQPA) in 1996; and (3) the remainder of industrial chemicals are regulated under the Toxic Substances Control Act (TSCA).

TSCA

In the U.S., TSCA authorizes EPA to gather information from manufacturers and importers to determine whether chemical substances pose unacceptable risks to human health and the environment. In 1977, EPA promulgated the Inventory Update Rule (IUR) to obtain volumetric information on non-polymeric organic chemicals manufactured at any single site in volumes exceeding 4.5 MT y^{-1} (Giannotto and Pechulis, 2004). In 2006, EPA amended the IUR, raising the threshold to 11 MT y^{-1}, but requiring more extensive reporting on a broader range of chemical substances. Further, information relating to downstream use of substances was required at 136 MT y^{-1}. This amendment was intended to facilitate screening of chemicals to which large numbers of workers and consumers are exposed.

In 2007, EPA implemented an IUR-based prioritization program that was designed to broaden EPA's screening-level characterizations for MPV and HPV chemicals to prioritize for additional data collection or risk reduction measures. Although now replaced with an enhanced chemical management program utilizing available information on exposure, hazard, uses, persistence, bioaccumulation, and toxicity to identify potential human and environmental concerns and potential risk management actions, the program did indeed conduct exposure and risk characterizations and risk-based prioritizations (RBPs) on over 200 chemicals (EPA, 2009b,c).

The RBPs are qualitative evaluations that (1) summarize basic hazard and exposure information collected through EPA's HPV Challenge Program and the Organisation for Economic Cooperation and

Development HPV Programme; (2) identify potential risks; (3) note scientific uncertainties; and (4) identify initial priority for future action. They indicate whether hazard, exposure, and risk elements are low, medium, or high, according to specified criteria. Figure S-1 depicts the process for developing RBPs. The RBPs explain scientific rationale and regulatory considerations factored into the assigned low, medium, or high priority. Screening-level exposure and hazard characterizations are provided except for substances determined to be low hazard. However, these characterizations are qualitative and based largely on surrogates for exposure such as use, production volume, environmental releases, physical and chemical properties, and environmental fate. All available information, including Confidential Business Information (CBI), is used in developing prioritization rankings. Most of this consists of general chemical manufacturing, importation, processing, and broad category-of-use information. Qualitative exposure characterizations are provided for the environment and for the general population, workers, adult consumers, and children. Rankings for potential exposures to children relate specifically to products intended for children and consumer products that may result in exposures through household use, even if not specifically intended for children.

Superfund

The Comprehensive Environmental Response, Compensation and Liability Act of 1980 (known as Superfund) established the Priority List of Hazardous Substances for the Agency for Toxic Substances and Disease Registry (ATSDR) (Fay and Mumtaz, 1996). ATSDR analyzes risks to communities near 1,300 Superfund hazardous waste sites. Exposure investigations are part of the public health assessment process or in response to requests from the public. The agency uses this information to prepare a priority list of substances determined to pose the most significant potential threat to human health to support regulatory action by other agencies. Prioritization is based on a combination of frequency, toxicity, and potential for human exposure.

Endocrine Disruptor Screening Program

The 1996 FQPA and the 1996 amendment to the Safe Drinking Water Act directed EPA to test ~87,000 compounds and formulations for their estrogen modulating capacity (subsequently expanded to modulators of androgens and thyroid hormones). The Endocrine Disruptor Screening and Testing Advisory Committee adopted a tiered approach that includes a prioritization stage to consider such aspects as potency and likelihood of exposure (Gierthy, 2002). Existing data were evaluated to categorize chemicals based on the quality and quantity of evidence supporting health effects. These categories were chemicals: (1) with sufficient data (primarily polymers) indicating that they are not likely to interact with hormone systems, (2) having insufficient data and therefore require Tier 1 screening for hormonal activity, (3) with sufficient evidence of hormonal interaction and therefore require Tier 2 testing, and (4) having sufficient evidence of hormonal interaction and hormone-related effects, thus requiring hazard assessment. Chemicals placed in the second category were to be prioritized for screening on the basis of both exposure- and effects-related information and then phased into the screening program (NRC, 1999). EPA's approach for selecting the initial 50–100 chemicals for Tier 1 screening focuses on human exposure but also considers widespread ecological exposures. The first group of chemicals identified for testing includes pesticide active ingredients and inerts (EPA, 1995). EPA also constructed an Endocrine Disruptor Priority-Setting Database for combining diverse sets of information in key areas, including data on human and ecological effects, production volume, and fate and exposure.

Pesticides

All pesticides in the United States must be registered by EPA under FIFRA, based on scientific data showing no unreasonable risks to human health, workers, or the environment when used as directed on product labeling. The EPA Office of Pesticide Programs determines the safety of pesticides by conducting multi-pathway and multi-chemical exposure risk assessments. EPA implements

prioritization in several programs. As an example, the Conventional Reduced Risk Pesticide Program expedites the review and regulatory decision-making process of conventional pesticides that pose less risk to human health and the environment than existing conventional alternatives. Reduced risk criteria include low use rates (thus minimizing exposures) and low potential for groundwater contamination, as well as lower toxicity to humans and non-target organisms (birds, fish, plants), low pest resistance potential, and compatibility with integrated pest management practices (Miller and Evans, 2009).

Water

The Safe Drinking Water Act requires EPA to list unregulated contaminants (known or anticipated to occur in public water systems) and which may require regulation in the future. Every five years, EPA must publish a list of contaminants called the Contaminant Candidate List (CCL). EPA uses the CCL to prioritize research and data collection efforts to inform Agency's decisions on whether to regulate a specific contaminant.

The current (i.e., third) CCL (Donohue, 2009) established the universe of contaminants from publicly available data sources from which contaminants for a preliminary CCL (PCCL) were selected. For the initial screen, toxicity was ranked numerically (1–5) based on both quantitative (acute and chronic toxicity endpoints) and qualitative (expert judgment) criteria. Occurrence was ranked into six categories based hierarchically on measured or modeled concentrations in water, estimated releases to environment, and production volume. A toxicity-by-occurrence matrix was used to select contaminants.

A refining process was used to select chemicals from the PCCL for the CCL. Toxicity was scored for both potency (1–10) and severity (1–9). Then, a compendium of terms and scores was developed using expert judgment (e.g., 1= No critical effect; 7 = reproductive effects; 9 = increased mortality). Occurrence was scored for both prevalence (1–10) and magnitude (1–10). Prevalence was based on the number of systems, number of states, or environmental fate. Scores were processed using linear, decision-tree, and neural network computer models. Post model refinements were applied to remove

contaminants screened on low confidence data (mainly LD_{50} values and production data) and to consider the relationship between health-based values and concentrations in water, when available.

Office of Resource Conservation and Recovery

EPA's Office of Resource Conservation and Recovery developed a list of 53 PBT chemicals and categories that may be found in hazardous wastes regulated under the Resource Conservation and Recovery Act (RCRA). The list was developed in the late 1990s to promote voluntary waste minimization efforts to reduce PBT hazardous waste generation. Thousands of chemicals were screened based on persistence, bioaccumulation, and human and ecological toxicity and their presence in hazardous waste. A preliminary set of 156 chemicals were ranked based on (1) PBT scores, (2) environmental presence, (3) quantities in hazardous wastes, (4) number of generators, and (5) RCRA concern. Thirty chemicals were eventually chosen from the draft list of 53, with EPA later adding an additional family of chemicals (i.e., polychlorinated biphenyls). These 31 chemical classes form the basis of the National Partnership for Environmental Priorities, a voluntary partnership program for reducing the use of potentially hazardous chemicals from products and processes (Portoghese Kollar and Powell, 2009).

Other U.S. Federal Programs

Several other regulatory programs in the U.S., both within the EPA (e.g., Office of Pesticide Programs' Antimicrobials Division, Integrated Risk Information System [IRIS], Design for the Environment [DfE], Great Lakes National Program Office) and in other agencies (e.g., U.S. Food and Drug Administration's Center for Food Safety and Applied Nutrition [CFSAN], U.S. Consumer Product Safety Commission [CPSC]) have developed chemical prioritization programs to reduce or eliminate the use of potentially hazardous chemicals.

The CPSC Chronic Health Advisory Panel on phthalates originated out of the recognition of widespread human exposure to the compounds and is an example of an effort to gather critical exposure information. CPSC is also attempting to prioritize thousands of products used in and around the home (Thomas 2010), but is hindered by a lack of data on product ingredients and consumer use scenarios (especially unintended and off-label uses). To overcome these challenges, CPSC is reaching out for international cooperation in the development of probabilistic models to estimate exposure. Emerging technologies, especially nanotechnologies, present even greater prioritization difficulties, since exposure pathways and routes may vary from those for the conventional chemical substance (Seager and Linkov, 2008). These materials highlight the need for predictive models and novel tools for decision making under extreme uncertainty.

States within the U.S.

In the U.S., a coalition of 13 states released their own principles for TSCA reform in December of 2009. While the principles largely mirror those of the EPA Administrator in asserting that manufacturers should be required to develop and provide sufficient toxicity, exposure, and use information to regulators to ensure that chemicals in commerce do not endanger public or environmental health, they also assert that government should establish protocols for evaluating potential alternatives to chemicals of concern. Alluding to the precautionary principle, the coalition declares that emerging chemicals should be assessed before they go into widespread commerce. States acknowledge the need for strong Federal regulation, while expressly preserving authority of state and localities to implement measures to manage chemicals of concern (Stone and Delistraty, 2010).

Numerous states are enacting their own chemical legislation. In response to public concern regarding chemical use and potential risk to sensitive populations, particularly from products marketed to children, Washington State enacted the Children's Safe Product Act (CSPA) in 2008. It directs the state Department of Ecology to identify High Priority Chemicals (HPCs) and Chemicals of High Concern to

Children. The legislation included specific criteria on toxicity and potential human exposure to identify chemicals posing a risk to children. The initial methodological step was compiling a list of HPCs based on toxicity information. A smaller set of chemicals was then identified based on potential exposure among children, namely, detection in biomonitoring studies and presence in residential exposure media or consumer products (Stone and Delistraty, 2010).

Similar legislation has been passed in Maine, Connecticut, Minnesota, Michigan, Massachusetts, and California. As in Washington State, the legislation in Maine, Minnesota, and Connecticut is primarily focused on the impact of chemicals on children's health. Legislation in California, Michigan, and Massachusetts is more broadly based, directed toward developing a more comprehensive chemical management policy. Not all of these state efforts include exposure in addition to hazard (Stone and Delistraty, 2010).

DOMESTIC SUBSTANCES LIST CATEGORIZATION IN CANADA

CEPA provides the framework for identification, prioritization, assessment, and management of existing substances that pose a risk to human health or the environment. The Act required Ministers of Health and of the Environment to set priorities for risk assessment and management for ~23,000 existing substances listed on the Domestic Substances List (DSL). Existing substances were defined as chemicals used, imported, or manufactured in Canada for commercial purposes in excess of 100 kg in any calendar year from 1984 through 1986. Substances introduced later are assessed under the new substances provisions of CEPA (Meek and Armstrong, 2007). CEPA mandates exposure and hazard "categorization" and then, if necessary, screening assessments. Categorization identified either those substances that present the greatest potential for exposure or those that are persistent or bioaccumulative and inherently toxic. It considered consumer and environmental (but excludes occupational) exposures for all age groups through a transparent, peer-reviewed, and well documented process (Meek and Armstrong, 2007). The categorization and screening process is detailed in Figure S-2.

Categorization sets the stage for human health screening assessments. These determine further action as: (1) no further action, (2) further in-depth assessment, or (3) risk management. General population exposures are typically compared with toxicological benchmark estimates. Using an iterative approach for multiple levels of exposure and effects, upper bounding estimates of exposure are first compared with lowest reported effect levels to estimate margins of exposure. If margins of exposure are small or if some probability of harm exists at all levels of exposure, comparisons of exposure and effects are refined, increasingly taking into account weight of evidence for hazard and mode of action, as necessary (Environment Canada, 2007).

A simple exposure tool (SimET) was developed for DSL categorization and prioritization based on three factors: (1) quantity in commerce, (2) number of companies involved, and (3) expert judgment of potential for human exposure from identified uses. SimET analysis resulted in both binning and relative ranking of substances. Although not used in this categorization/prioritization, a more complex tool (ComET) was also developed that can provide quantitative plausible maximum age-specific estimates of environmental and consumer exposure based on use scenario (using sentinel products), physical and chemical properties, and bioavailability. In addition, a set of simple (SimHaz) and complex (ComHaz) hazard tools have been developed to complement the exposure tools (Meek and Armstrong, 2007).

Categorization was performed on the entire DSL and a draft "maximal list" of priorities was released in October 2004. This list contains ~1,900 substances prioritized for more comprehensive evaluation and grouped according to their level of concern as high, moderate, or low. In 2007, the CEPA DSL project was completed, identifying 4,300 chemicals for further scrutiny. The 200 substances presenting greatest risk are currently being assessed in the Ministerial Challenge Program, which requires industry to provide relevant information on each substance. About 1,200 substances at the next level of concern were selected by Environment Canada for rapid screening. The rapid screening exercise identified about 750 substances that are unlikely to cause environmental harm, and about 450 substances that will require further assessment. To address the remaining CEPA DSL substances, Environment Canada and

Health Canada will assess about 900 high- and medium-priority substances by grouping together classes of chemicals and undertaking joint reviews with other countries. The remaining 1,085 substances will be assessed at a pace of about 110 assessments a year between 2010 and 2020 (OAG, 2008).

The DSL categorization exercise highlighted the importance of direct consumer exposure relative to indirect environmental exposure. Specifically, the results indicate that persistence and bioaccumulation potential, which are used to estimate concentrations in the various environmental compartments, do not necessarily reflect the major sources of exposure, particularly for those compounds formulated into consumer products and articles but not discharged into the environment at high levels (Jayjock et al., 2008). Moreover, use profiling was far more influential than production volume in determining exposure rankings (Meek, 2008). This emphasizes the importance of the acquisition of downstream production and consumer use information for prioritizing chemicals.

THE EUROPEAN UNION

Arguably, the most ambitious effort to develop and apply prioritization schemes is found in the European Union. REACH Regulation provides significant impetus for industry to conduct exposure-based prioritization for chemical risk management. Under REACH, all substances (existing and new) produced or imported in volumes greater than 1 MT y^{-1} must be registered by 2018. Registration includes information on physiochemical, toxicological and ecotoxicological properties and identified uses throughout the supply chain. At production >10 MT y^{-1}, registrants must provide a Chemical Safety Report assessing risks and proposing risk management measures for manufacture and all identified uses. Registration ensures that all chemicals undergo basic health and safety testing (Bodar et al., 2002; van der Wielen, 2007).

A crucial feature of REACH is the shift of responsibility for data generation and risk assessment from governmental authorities to industry. Under REACH, industry prepares the risk assessments, which are then reviewed and evaluated by ECHA (Bodar et al., 2002; van der Wielen, 2007; Applegate and Baer,

2006). Responsibility of manufacturers or importers includes ascertainment of all relevant uses and better characterization of the entire chemical life cycle through communication with downstream users (van der Wielen, 2007). Evaluation of prioritized substances is the task of the Member States.

Under REACH, manufacturers/importers must develop exposure scenarios for substances with properties of very high concern; namely, those classified as dangerous or designated as PBT (persistent, bioaccumulative and toxic) or vPvB (very persistent and very bioaccumulative). Exposure scenarios describe conditions of use by industries, downstream users, and consumers as well as measures to control exposure to humans and the environment. Estimates for each exposure scenario must contain three elements: (1) emissions during all relevant parts of the life-cycle; (2) evaluation of chemical fate and environmental distribution through potential degradation, transformation, or reaction processes; and (3) estimation of exposure levels for all human populations (i.e. workers, consumers, and humans exposed indirectly via the environment) wherever exposure is reasonably foreseeable (ECHA. 2010).

Registered substances will be prioritized for evaluation by ECHA and EU Member States. Prioritized substances will be placed on a "Community Rolling Action Plan," with evaluations divided between Member States. Identified substances of very high concern (i.e., carcinogenic, mutagenic or toxic to reproduction or PBT/vPvB) may require authorization before they can be manufactured or imported. These substances will only be authorized for specific uses if the registrant can demonstrate that the risk from the use of the substance is adequately controlled or that socio-economic benefits of the chemical outweigh risks and no safe alternatives exist. If a viable alternative exists, the company must present a plan for gradual replacement (van der Wielen, 2007). Proposals to restrict use of a substance also can be made by the Commission or by Member States.

CHEMICAL MANUFACTURING INDUSTRY

Important initiatives have been taken in the industrial community that are not chemical prioritization and evaluation efforts, *per* se, but that supply information that may support such efforts. Notable

examples include the introduction of programs such as “Responsible Care” (Givel, 2007), an autonomous global initiative by chemical manufacturers to improve health, safety, and environmental performance, and “Product Stewardship,” in which all participants in the life cycle of a product partner with government to share responsibility for reducing human exposure and environmental impacts. An example of a stewardship program is EPA’s 2010/15 PFOA Stewardship Program (http://www.epa.gov/opptintr/pfoa/), in which eight major fluoropolymer and telomer manufacturers have committed to reducing facility emissions and product content of PFOA and related chemicals, with a goal of total elimination by 2015. Furthermore, the sector has provided funding for international research into exposure to and long-term effects of substances, particularly those produced in large quantities (ICCA, 2009). Many global businesses have very publically embraced “green” programs. Most key initiatives by these consumer businesses deal with reducing carbon footprint, but phasing out ingredients and materials deemed hazardous is also addressed. For example, in October 2006, Wal-Mart Stores announced implementation of a product screening tool to identify and reduce use of potentially hazardous chemicals found in various household products (Wal-Mart, 2011).

Chemical trade associations, such as the Soap and Detergent Association, Consumer Specialty Products Association, and Canadian Consumer Specialty Products Association, have developed a Consumer Product Ingredient Communication Initiative to provide consumers with information about ingredients in products in four major areas: hair care, automotive care, cleaning, and floor maintenance. Many companies, such as the Clorox Company and SC Johnson, have begun listing all ingredients for their companies’ products on their Web sites. Nonetheless, there remains a large information gap for product ingredients. For example, obtaining information on fragrance and phthalate ingredients remains particularly problematic.

SUMMARY REVIEW OF RAPID PRIORITIZATION APPROACHES

To be most useful, approaches (tools, schemes or models) for prioritizing chemicals based on exposure should consider potential for exposure across the full life cycle of chemical substances and should address both near field (from consumer products) and far field (from the greater environment) exposure. Figure 1 illustrates a framework for assessing exposure that follows the life cycle of a chemical from manufacture, through product use scenarios, to disposal or recovery and considers pathways at all stages of the life-cycle which ultimately lead to contact with humans. Exposure can occur in any the stages of the life cycle of a substance: manufacture (including production and processing); transportation and storage; product formulation; product use; and finally product disposal including waste treatment. Thus, chemical prioritization must consider how each of these stages presents a possibility for environmental release to one or several environmental compartments (including air, water, soil and food). Based on the fate and transport of the chemical through these media, concentrations can be derived for each compartment to quantify the exposure associated with typical human activities. This approach is applied at each life cycle stage for the product, reaction products, degradates and metabolites. Prioritization requires tiered approaches and tools to address key drivers in this framework based on limited data and the need for rapid assessment.

Eleven currently available tools designed to rapidly prioritize large numbers of chemicals were identified (Table 1), namely, DSL Categorization, CEPST, IUR-Based Prioritization, ECETOC TRA, ConsExpo, EUSES, GExFRAME, USETox, RAIDAR/FHX, IMPACT, and MENTOR. Sponsors are typically governmental organizations such as Health Canada, the European Commission, the Dutch National Institute for Public Health and the Environment (RIVM), and the EPA, but also include universities (University of Michigan, Trent University), the European Chemical Trade Association, and a nonprofit organization (Lifeline Group). Several of the tools have characteristics in common, such as a tiered approach and consideration of use/functional categories, exposure scenarios, and multiple exposure pathways. The tools differ in scope with respect to near field and far field exposure sources. The tools also differ in the specifics of their algorithms, including the types of data sources utilized and

consideration of activity patterns. While the degree of reliance on expert or professional judgment varies, few are explicit in documenting the number of professional judgment parameters used. Quantification of exposure levels also varies greatly, ranging from exposure tiers, to relative rankings, to quantified exposure estimates (point or distribution) or characterization factors. The numbers of compounds previously evaluated ranges across two orders of magnitude, but the cost per chemical has not been quantified by any of the tools.

Discussion

Rapid and efficient risk assessment is needed to address both large inventories of existing chemicals and newly proposed chemicals. Such assessment requires predictive, high-throughput tools and strategies to integrate toxicity and exposure pathways using systems approaches, with consideration of the entire life cycle of the chemical (Dellarco, et al., 2010). Determining the likelihood of exposure to environmental chemicals among workers, consumers, and ecological receptors is a tremendous challenge. Exposure is influenced not only by the physical and chemical properties of the chemical but also by a multitude of factors, including human activities, acting jointly to produce or control emissions along the entire life cycle. Further, characteristics of the environment and of the individual/organism (e.g., the life stage-related exposure vulnerabilities) influence exposures.

This review has identified eleven currently available tools for exposure-based prioritization. Only three (CEPST, ConsExpo, and GExFRAME) rely purely on exposure as the basis of prioritization; the remainder incorporate hazard and employ risk as the basis. CEPST provides quantitative estimates of the upper bound of exposure potential based only on the physical chemical properties of the chemical and a description of the general type of products that contain the chemical. CEPST is designed to require only minimal information on uses (Jayjock et al., 2008). ConsExpo comprises a number of mechanistic, source-to-dose models that simulate single exposure events which are averaged over a year based on assumptions on the frequency at which these exposure events take place. The included

database compiles information on exposure factors for various categories of consumer products (Delmaar et al., 2005). GExFRAME is designed as a generic environment for housing models and data (Kephalopoulos et al., 2008). It not only accommodates the algorithms of ConsExpo, but also includes algorithms to estimate risk from dietary and non-dietary residential exposure to pesticides. Of the three, only ConsExpo is readily accessible. While these three are focused on near field exposures from consumer products (the middle row of Figure 1), GExFRAME begins to expand to far field exposures.

Among the five that consider both near and far field exposures, two (IUR-Based Prioritization and DSL Categorization) are better described as approaches than as tools. It is hoped that the experience gained through the implementation of these approaches by EPA and Health Canada, respectively, will inform refinement of existing tools and development of new tools. MENTOR is more of a framework linking predictive models of exposure and dose with links to databases of available occurrence, exposure factor, and activity information to facilitate source-to-dose linkages (Georgopoulos and Lioy, 2006). In contrast, EUSES (Vermeire et al, 2005) and ECETOC TRA (http://www.ecetoc.org) are both "turnkey" tools currently widely used to register chemicals under REACH. Both rely heavily on standardized production and use scenarios and have modules for estimating exposures to consumers, to workers, and to the environment. The key metric is the "margin of safety" ratio of a health benchmark dose divided by anticipated exposure. Both appear to require detailed information on processing and use, which is more suited to a large number of manufacturers each modeling a relatively small number of chemicals for which they can obtain detailed information (as under REACH), than it would be to a centralized evaluation of a very large number of chemicals with relatively little available information (as under TSCA).

RAIDAR/FHX, USETox, and IMPACT are all multimedia mass balance models that combine fate processes and food web bioaccumulation processes to assess exposure and risk, similar to the environmental exposure module of EUSES. All three can process large numbers of chemicals with minimal inputs, namely, easily obtainable estimates of physical and chemical properties. Fugacity-based

partitioning into various environmental compartments is estimated from these properties. Treatment of food webs is more sophisticated in RAIDAR, while USETox and IMPACT appear to give more attention to the life cycle of the chemical (Arnot, 2009; Rosenbaum et al., 2008; Humbert et al., 2009). Exposure is estimated as population-averaged intake as a fraction of total emissions to the environment, and rankings can be performed based on a scalable unit emission rate. Only indirect exposure via the environment is considered, and all three thus rely heavily on estimates of persistence (likelihood to persist after release) and bioaccumulation (likelihood to build up in the food chain).

The emphasis on persistent and bioaccumulative chemicals seems reasonable given the association of many chemicals of this class with adverse human health effects (including effects on the nervous system, endocrine dysfunction, reproductive and developmental toxicities, and cancer). These properties, however, are typically estimated rather than directly measured, often with little regard to "domains" of knowledge and predictability (Vallero, 2010). As a result, predictions of these properties from different methods may deviate considerably (Arnot and Mackay, 2008; Zhang et al., 2010). Moreover, relying exclusively on persistence and bioaccumulation in the outdoor environment neglects near field exposure from consumer products, which may be considerable for many chemicals, and ignores persistence in the indoor environment.

An important limitation on application of existing exposure-based prioritization tools centers on the type and quality of information needed, especially in light of the predominance of data-poor chemicals. The tools that require minimal information provide only a partial assessment of exposure, namely, indirect exposure via the environment. The tools that also estimate direct exposure require information on processes and uses that is not readily accessible for the majority of chemicals. While the Substances in Preparations in Nordic Countries (SPIN) database (http://195.215.251.229/Dotnetnuke/) goes a long way towards providing information on functions and uses for those chemicals in the Nordic Product Registers, more complete information on functions, processes, uses, product formulations, product use patterns, indoor emission rates, and indoor persistence is required. REACH addresses this need by

requiring chemical producers to perform their own assessments. Without meaningful TSCA reform that shifts the burden of generating sufficient exposure information from government to producers (as laid out in EPA Principles for TSCA Reform) (EPA, 2009a), these tools will have limited utility for exposure-based prioritization in the U.S.

In the meantime, there is a need for benchmarking of results across models as well as evaluation against measured environmental concentrations and biomarker levels. One approach for benchmarking is to bring model developers together to standardize some output metrics, followed by the development and evaluation of a suite of consistent approaches to assess metrics at different levels. This could provide the additional benefit of an assessment of the relative importance of parameters and intermediary steps in the screening results (see for example Hauschild, et al., 2008). Another critical step is the development of a methodology for merging different types of limited data (e.g., monitoring, biomarker, and modeling) in order to grade relative rankings and to extrapolate exposure potentials from chemicals with less uncertainty to the data-poor chemicals.

Building confidence in model predictions will also require extrapolation from existing experience in the evaluation of a limited number of chemicals to inform efficient evaluation of the rest. In particular, this may help to identify chemicals for quantitative anchoring of surrogate chemicals (i.e., those screened to represent larger chemical structure, manufacturing or use classes). This may also allow for the selection of the simplest, most discriminating determinants of exposure and drive toward safer (i.e., lower exposure potential) chemical substitutes.

Exposure-based prioritization ideally should consider both human exposure and ecological exposure, as is required for risk-based prioritization (Bodar et al., 2002). However, the methodology for ecological exposure assessment, including identification of ecological receptors of concern, is not well articulated in most of the prioritization approaches reviewed here, and human exposure or health appears to be the

dominant driver for prioritization decisions. We are not aware of any process proposed in the scientific literature for weighting human exposure and ecological exposure in the context of prioritization.

Hazard-based chemical screening and prioritization approaches have advanced substantially in recent years. The EPA with partners and stakeholders has recently initiated research to enhance exposure-based prioritization, recognizing that regulators need reliable approaches to screen and prioritize chemicals based on their likelihood of exposure. Regulators are also increasingly requiring that human and ecosystem exposure research be linked based on a chemical's persistence, transformation, bioaccumulation and other inherent and environmentally conditional properties to predict biological dose within human tissues and exposure in ecosystems. These relationships should inform chemical prioritization, reducing uncertainties due to spatial and temporal scale and complexities within systems.

ACKNOWLEDGMENT

We thank participants in the exposure-based chemical prioritization workshop held April 6–7, 2010, for their recommendations and insights. The workshop presentations can be found online (EPA, 2010b). We thank Olivier Jolliet (University of Michigan), Jon Arnot (Trent University), Yuri Bruinen de Bruin (RIVM), Michael Jayjock (The Lifeline Group), Nhan Nguyen (EPA), Rosemary Zaleski (ExxonMobil Biomedical Sciences), Sastry Isukapalli (EOHSI), Muhilan Pandian (Infoscientific.com), and Heather Patterson (Health Canada) for information on current models. We thank Jade Mitchell-Blackwood (EPA) for helpful comments and discussions. We are grateful to several anonymous reviewers for their insightful comments and suggestions. The United States Environmental Protection Agency through its Office of Research and Development funded and managed the research described here. It has been subjected to Agency’s administrative review and approved for publication.

References

ACC (American Chemistry Council). 2009. 10 Principles for Modernizing TSCA, August 4, 2009. Available: http://www.americanchemistry.com/s_acc/sec_article_acc.asp?CID=2178&DID=9939

Allanou R, Hansen B, van det Bilt Y. 1999. Public Availability of Data on EU High Production Volume Chemicals. European Chemicals Bureau, Joint Research Center, Ispra, Italy, EUR18996EN.

Applegate J, Baer K. 2006. Strategies for Closing the Data Gap. Available: http://www.progressivereform.org/articles/Closing_Data_Gaps_602.pdf

Arnot JA, Mackay D. 2008. Policies for chemical hazard and risk priority setting: can persistence, bioaccumulation, toxicity, and quantity information be combined? Environ Sci Technol. 42(13):4648-54.

Arnot JA. 2009. Mass Balance Models for Chemical Fate, Bioaccumulation, Exposure and Risk Assessment. In: Simeonov LI, Hassanien MA (eds.). Exposure and Risk Assessment of Chemical Pollution – Contemporary Methodology, Springer, The Netherlands.

Bodar C, de Bruijn J, Vermeire T, van der Zandt P. 2002. Trends in risk assessment of chemicals in the European Union. Hum Ecol Risk Assess. 8(7):1825-43.

Canadian Centre for Environmental Modelling and Chemistry. 2011 Model index. http://www.trentu.ca/academic/aminss/envmodel/models/models.html; accessed May 15, 2011.

Cohen Hubal EA, Richard A, Aylward L, Edwards S, Gallagher J, Goldsmith M-R, et al. 2010. Advancing exposure characterization for chemical evaluation and risk assessment. J Toxicol Environ Health, Part B. 13(2):299-313.

Collins FS, Gray GM, Bucher JR. 2008. Transforming environmental health protection. Science 319(5865):906-7.

Council on Environmental Health. 2011. Chemical-Management Policy: Prioritizing Children's Health. Pediatrics. 127(5):983-90.

Dellarco V, Henry T, Sayre P, Seed J, Bradbury S. 2010. Meeting the common needs of a more effective and efficient testing and assessment paradigm for chemical risk management. J Tox Environ Health, Part B. 13(2):347-360.

Delmaar JE, Park MVDZ, van Engelen JGM. 2005. ConsExpo 4.0: Consumer Exposure and Uptake Models Program Manuel. Bilthoven, The Netherlands: National Institute for Public Health and the Environment (RIVM). Report 320104004/2005.

Dix DJ, Houck KA, Martin MT, Richard AM, Setzer RW, Kavlock RJ. 2007. The ToxCast program for prioritizing toxicity testing of environmental chemicals. Toxicol Sci. 95(1):5-12.

Donohue JM. 2009. Chemical Prioritization Example: Contaminant Candidate List 3. Agency Partner Meeting on Exposure Prioritization for Chemical Management, 3 December 2009.

EC. 2004. European Union System for the Evaluation of Substances 2.0 (EUSES 2.0). Prepared for the European Chemicals Bureau by the National Institute of Public Health and the Environment (RIVM), Bilthoven, The Netherlands (RIVM Report no. 601900005).

ECHA. 2010. REACH Navigator. Available: http://guidance.echa.europa.eu/

Environment Canada. 2007. Domestic Substances List Categorization and Screening Program. Available: http://www.ec.gc.ca/substances/ese/eng/dsl/dslprog.cfm

EPA (U.S. Environmental Protection Agency). 1995. Endocrine Disruptor Screening Program; Chemical Selection Approach for Initial Round of Screening. 70 Federal Register 186 (27 September 2005), pp. 56449-65.

EPA. 1998. Chemical Hazard Data Availability Study. Office of Pollution Prevention and Toxics. Available: http://www.epa.gov/HPV/pubs/general/hazchem.pdf

EPA. 2009a. Essential Principles for Reform of Chemicals Management Legislation. Available: http://www.epa.gov/oppt/existingchemicals/pubs/principles.html

EPA. 2009b. Methodology For Risk-Based Prioritization Under ChAMP, Office of Pollution Prevention & Toxics, U.S. Environmental Protection Agency, April 2009. Available: http://www.epa.gov/champ/

EPA. 2009c. High Production Volume (HPV) Challenge. Available: http://www.epa.gov/hpv/

EPA. 2010a. What Is the TSCA Chemical Substance Inventory? Available: http://www.epa.gov/oppt/newchems/pubs/invntory.htm

EPA. 2010b. ExpoCast™ Exposure-Based Chemical Prioritization Workshop: Exploring Opportunities for Collaboration. Available: http://www.epa.gov/ncct/expocast/workshop.html

European Centre for Ecotoxicology and Toxicology of Chemicals. 2011. Targeted risk assessment tools. http://www.ecetoc.org/; accessed May 15, 2011.

Fay RM, Mumtaz MM. 1996. Development of a priority list of chemical mixtures occurring at 1188 hazardous waste sites, using the HazDat database. Food and Chemical Toxicology. 34(11-12):1163-1165.

Frederiksen M, Vorkamp K, Thomsen M, Knudsen LE. 2009. Human internal and external exposure to PBDEs--a review of levels and sources. Int J Hyg Environ Health. 212(2):109-34.

Fukata H, Omori M, Osada H, Todaka E, Mori C. 2005. Necessity to measure PCBs and organochlorine pesticide concentrations in human umbilical cords for fetal exposure assessment. Environ Health Perspect. 113(3):297-303.

Fung A, O'Rourke D. 2000. Reinventing Environmental Regulation from the Grassroots Up: Explaining and Expanding the Success of the Toxics Release Inventory. Environ Manage. 25(2):115-127.

Georgopoulos PG, Lioy PJ. 2006. From a theoretical framework of human exposure and dose assessment to computational system implementation: the Modeling ENvironment for TOtal Risk Studies (MENTOR). J Toxicol Environ Health B Crit Rev. 9(6):457-83.

Giannotto MS, Pechulis KP. 2004. New TSCA Requirements Present Substantial Challenge to Manufacturers that Produce or Import Chemical Substances. Goodwin Proctor Environmental Law Advisory, December 2004. Available: http://www.goodwinprocter.com/Publications/Listing.aspx?key=tsca

Gierthy JF. 2002. Testing for endocrine disruption: how much is enough? Toxicol Sci. 68(1):1-3.

Givel M. 2007. Motivation of chemical industry social responsibility through Responsible Care. *Health Policy* **81** (1): 85–92

Hauschild MZ, Huijbregts M, Jolliet O, MacLeod M, Margni M, van de Meent D, Rosenbaum, RK and McKone, TE. 2008. Building a model based on scientific consensus for Life Cycle Impact Assessment of chemicals: the search for harmony and parsimony. Environ Sci Technol. 42(19):7032-7.

Health Canada. 2011. Environmental and workplace health. http://www.hc-sc.gc.ca/ewh-semt/pubs/contaminants/final_framework-int-cadre-eng.php; accessed May 15, 2011.

Humbert S, Manneh R, Shaked S, Wannaz C, Horvath A, Deschênes L, Jolliet O, Margni M.. 2009. Assessing regional intake fractions in North America. Sci Tot Env 407(17):4812-20.

ICCA (International Council of Chemical Associations). 2009. Annual Review 2008-09. Available: http://www.cefic.be/Files/Publications/Icca-Review_2008-2009.pdf

Jayjock MA, Chaisson CF, Franklin CA, Arnold, S and Price PSW. 2008. Using publicly available information to create exposure and risk-based ranking of chemicals used in the workplace and consumer products. J Expos Sci Environ Epidemiol 19(5): 515-24.

Judson R, Richard A, Dix DJ, Houck K, Martin M, Kavlock R, Dellarco V, Henry T, Holderman T, Sayre P, Tan S, Carpenter T, Smith E. 2009. The toxicity data landscape for environmental chemicals. Environ Health Perspect. 117(5):685-95.

Kephalopoulos SD, Arvanitis A and Pandian, MdR. 2008. GExFRAME – a Web-Based Framework for Accommodating Global Consumer Exposure Data, Scenarios and Models. Epidemiology 19(6):S182-S183.

LaKind JS, Berlin CM Jr, Sjödin A, Turner W, Wang RY, Needham LL, et al. 2009. Do human milk concentrations of persistent organic chemicals really decline during lactation? Environ Health Perspect. 117(10):1625-31.

Landrigan PJ. 2010. What causes autism? Exploring the environmental contribution. Curr Opin Pediatr. 22(2):219-25.

Meek ME, Armstrong VC. 2007. The assessment and management of industrial chemicals in Canada. In: Van Leeuwen CJ, Vermeire TG (eds.). Risk Assessment of Chemicals: An Introduction, 2nd Ed. Springer, Dordrecht, The Netherlands.

Meek ME. 2008. Considering Exposure in Priority Setting – Categorization of the Domestic Substances List under the Canadian Environmental Protection Act (CEPA). USEPA Exposure Community of Practice, 8 June 2008.

Miller DJ, Evans J. 2009. Exposure Prioritization at US EPA's Office of Pesticide Programs – Registration and Registration Review. Agency Partner Meeting on Exposure Prioritization for Chemical Management, 3 December 2009.

Muir DCG, Howard PH. 2006. Are there other persistent organic pollutants? A challenge for environmental chemists. Environ Sci Technol. 40:7157-7166.

National Institute for Public Health and the Environment. 2011. Product safety. http://www.rivm.nl/en/healthanddisease/productsafety/Kopie_van_ConsExpo.jsp; accessed May 15, 2011.

Nguyen N, Fehrenbacher C. 2008. Prioritization of HPV Chemicals under the Chemical Assessment and Management Program (ChAMP). EPA Office of Pollution Prevention and Toxics. Available: http://www.epa.gov/ncct/practice_community/exposure_science/120808_Fehrenbacher.pdf

NRC. 1999. Hormonally Active Agents in the Environment. National Academies Press, 1999.

OAG (Office of the Auditor General). 2008. Status Report of the Commissioner of the Environment and Sustainable Development. Available: http://www.oagbvg.gc.ca/internet/English/parl_cesd_200803_e_30125.html

Portoghese Kollar T, Powell S. 2009. ORCR's Efforts in Prioritizing Chemicals. Agency Partner Meeting on Exposure Prioritization for Chemical Management, 3 December 2009.

Rosenbaum R, Bachmann T, Swirsky Gold, L, Huijbregts, MAJ, Jolliet, O, Jaraske, R, Koehler, A, Larsen, HF, MacLeod, M, Margni, M, McKone, TE, Payet, J, Schuhmacher, M, van de Meent, D and Hausdchild, MZ. 2008. "USEtox—the UNEP-SETAC toxicity model: recommended

characterisation factors for human toxicity and freshwater ecotoxicity in life cycle impact assessment. Int J Life Cycle Assess 13(7): 532-546.

Seager TP, Linkov I. 2008. Coupling multicriteria decision analysis and life cycle assessment for nanomaterials. J Ind Ecol 12(3):282-5.

Sheldon LSS, Cohen Hubal EA. 2009. Exposure as part of a systems approach for assessing risk. Environ Health Perspect. 117(8):1181-1184.

Stone A, Delistraty D. 2010. Sources of toxicity and exposure information for identifying chemicals of high concern to children. Environ Impact Assess Rev. Prepub DOI: 10.1016/j.eiar.2009.11.002.

The Lifeline Group. 2011. Chemical exposure priority setting tool™ (CEPST™ / ComET©) and assessing exposures to chemicals in consumer products - Library of associated documentation, http://www.thelifelinegroup.org/CEPTS/library.htm; accessed May 15, 2011.

Thomas T. 2010. Consumer Product Exposure Assessment. US EPA Exposure-Based Chemical Prioritization Workshop, RTP, NC, 6-7 April, 2010.

USEtox Team. 2011. Usetox model. http://www.usetox.org/; accessed May 15, 2011.

Vallero DA. 2010. *Environmental biotechnology: A biosystems approach*. Elsevier Academic Press: Burlington, MA.

van der Wielen A. 2007. REACH: next step to a sound chemicals management. J Expo Sci Environ Epidemiol. 17(Suppl 1):S2-6.

Vermeire T, Rikken M, Attias L, Boccardi P, Boeije G, Brooke D, de Bruijn J, Comber M, Dolan B, Fischer S, Heinemeyer G, Koch V, Lijzen J, Muller B, Murray-Smith R, Tadeo J. 2005. European Union system for the evaluation of substances: the second version. Chemosphere 59(4):473-485.

Wal-Mart, 2011. Sustainable products: chemicals. http://walmartstores.com/sites/sustainabilityreport/2007/environmentSustainableChemicals.html; accessed May 15, 2011

Wilson MP, Schwarzman MR. 2009. Toward a new U.S. chemicals policy: rebuilding the foundation to advance new science, green chemistry, and environmental health. Environ Health Perspect. 117(8):1202-9.

Wolff MS. 1983. Occupationally derived chemicals in breast milk. Am J Ind Med. 4(1-2):259-81.

Zhang X, Brown TN, Wania F, Heimstad ES, Goss KU. 2010. Assessment of chemical screening outcomes based on different partitioning property estimation methods. Environ Int. 36(6):514-20.

Table1. Exposure prioritization approaches evaluated.

Name	DSL Categorization	IUR-Based Prioritization[1]	CEPST	ConsExpo 4.1	ECETOC TRA	EUSES 2.03
Expanded Name	Domestic Substances List Categorization	IUR-Based Prioritization	Chemical Exposure Priority Setting Tool (formerly Complex Exposure Tool)	RIVM Consumer Exposure Model	European Centre for Ecotoxicology and Toxicology of Chemicals Targeted Risk Assessment	European Union System for the Evaluation of Substances
Sponsor	Health Canada	USEPA OPPT	The Lifeline Group, Health Canada	Dutch National Institute for Public Health and the Environment (RIVM)	European Chemical Trade Association	RIVM, European Commission
Prioritization Basis	Risk (exposure and hazard)	Risk (exposure and hazard)	Exposure only	Exposure only	Risk (exposure and hazard)	Risk (exposure and hazard)
Source Distance	Near field and far field	Near field and far field	Near field	Near field	Near field (worker and consumer), and far-field	Near field and far field
Chemical Classes	Organic, inorganic, UVCBs, polymers	High and Medium Production Volume chemicals	Various	Cleaning products, cosmetics, pesticides, paint, children's toys	Targeted to organic chemicals	Industrial chemicals (including consumer products) and biocides
Use/Functional Categories	Functional and industrial use codes	Particularly products intended for children	Functional categories	Types of consumer products	Use categories and handling procedures	Production and use categories

[1] Program has been replaced with an enhanced chemical management program that is utilizing available information/data on exposure, hazard, uses, persistence, bioaccumulation, and toxicity to identify potential human and environmental concerns and potential risk management actions.

Name	DSL Categorization	IUR-Based Prioritization[1]	CEPST	ConsExpo 4.1	ECETOC TRA	EUSES 2.03
Exposure Categories	General population	Gen. population, environmental, occupational, consumer, children	Acute, short term, or long term; Six age groups; Applied or Absorbed Dose	Consumer exposure	Worker, consumer, and environmental Modules	Human (worker, via environment, consumer) and environmental exposure
Media Focus / Exposure Routes	All routes	Releases to all media including land, water and air; exposures by main routes (inhalation, dermal, and ingestion)	Oral, dermal, inhalation, and systemic (total)	Inhalation, dermal and oral routes	Far field: releases to all media. Near field: inhalation and dermal for worker, inhalation, dermal, oral for consumers	Humans: all routes Environment: emissions to air, water and soil
Scenarios	Use scenario for sentinel products	Used for qualitative assessments	At least 1 scenario per functional category, defined as an explicit exposure circumstance	Limited number of categories of similar products defined. Also allows for custom scenarios.	Consumer: Product use categories Worker: Process categories. Environmental: Releases by sector of use	Consumers: limited scenarios Workers: ~ 150 scenarios Environment: at least 1 per production/use scenario
Exposure Algorithm	Based on three factors: quantity in use, number of submitters/users, and reported use codes	Production volume and use information are extracted from IUR (masked for CBI). Chemical properties and transport information used to characterize potential exposures	Each scenario translated into specific exposure predicting algorithms and parameters for each relevant route. Provides quantitative exposure estimate in mg/kg	Program is based on relatively simple exposure and uptake models	Env. exposure potential is based on spreadsheet version of EUSES; worker based upon EASE; consumer based upon linear algorithms from REACH guidance document	Each scenario translated into specific exposure predicting algorithms and parameters

Name	DSL Categorization	IUR-Based Prioritization[1]	CEPST	ConsExpo 4.1	ECETOC TRA	EUSES 2.03
Tiered Approach	Yes (SimET, SimHaz, ComHaz)	No	Yes	Yes, progressively advances from very simple to refined mechanistic models	Yes. Also tiered entry to ConsExpo (higher tier consumer exposure model)	Yes
Activity Patterns	No	No	Yes	Frequency and duration of product use	Consumer: frequency and duration of product use	Consumers/ workers: frequency and duration of product use Environment: local and regional exposure per emission event
Data Sources	Used industry data submitted during compilation of the DSL	Screening-level exposure characterization considers a selected number of public sources (HSDB, HPV, SIDS, Test Rule), Households Product db, EMAP, NEI) but is primarily based on information from IUR	Publically available data	European Exposure Factors (ExpoFacts) Sourcebook (2004), EPA Exposure Factors Handbook (1989), Statistics Netherlands, scientific literature and other public sources, own research. Compiled and summarized in supporting fact sheets.	Multiple sources: documented in ECETOC TRA manual posted on ECETOC site.	See ECHA Guidance Document R16 and EUSES Background Documentation

Name	DSL Categorization	IUR-Based Prioritization[1]	CEPST	ConsExpo 4.1	ECETOC TRA	EUSES 2.03
Professional Judgment	Used to rank potential exposure use codes and to determine cut-offs for exposure tiers	Yes	Displays the number of professional judgment parameters used in deriving dose	No	No	No judgments
Quantification Level	Exposure tiers (GPE/IPE/LPE)	Relative rankings	Ranking	Provides distribution of exposure endpoints	Quantified exposure estimate	Risk characterization ratios
Numbers of Chemicals Evaluated	23,000 substances	220 Risk-Based Prioritizations and 83 Hazard-Based Prioritizations performed	39 compounds on demonstration spreadsheet	N/A	N/A	At least 140 existing substances and 1000 new chemicals in the EU
Regulatory Context	Yes	Yes	No	No	Yes	Yes
References and Links	Health Canada (2011) (http://www.hc-sc.gc.ca/ewh-semt/pubs/contaminants/final_framework-int-cadre-eng.php)	EPA (2009b,c)	Jayjock et al. (2008) and The Lifeline Group (2011) (http://www.thelifelinegroup.org/CEPTS/library.htm)	National Institute for Public Health and Environment (2011) (http://www.rivm.nl/en/healthanddisease/productsafety/Kopie_van_ConsExpo.jsp)	European Centre for Ecotoxicology and Toxicology of Chemicals (2011) (http://www.ecetoc.org/)	ECHA (2010) (http://guidance.echa.europa.eu/)

Table1 (continued). Exposure prioritization approaches evaluated.

Name	GExFRAME	MENTOR	USETox	RAIDAR / FHX	IMPACT
Expanded Name	Generic Consumer Exposure Modelling Software Framework	Modeling ENvironment for TOtal Risk studies	UNEP-SETAC Toxicity Model	Risk Assessment, IDentification And Ranking / Far-field Human Exposure	IMPact Assessment of Chemical Toxics
Sponsor	European Commission Joint Research Centre	USEPA and the Environmental & Occupational Health Sciences Institute, NJ	United Nations Environment Program SETAC Lifecycle Initiative	Environment Canada, Health Canada, Industry	University of Michigan, Ecole Polytechnique Montreal
Prioritization Basis	Exposure only	Risk (exposure and hazard)	Risk (exposure and hazard)	Risk (exposure and hazard)	Risk (exposure and hazard)
Source Distance	Near field	Near and far field	Far field	Far field	Far field and regional
Chemical Classes	Chemicals and pesticides	Air pollutants and multimedia contaminants	Non polar non ionic organic chemicals and metals	Organic chemicals	Non polar non ionic organic chemicals and metals
Use/ Functional Categories	Functional category is one descriptor for chemical type	Use, production, new products in commerce	Various products and services over their life cycle	No	Various products and services over their life cycle
Exposure Categories	Consumer exposure	General population, sensitive subpops, occupational; acute, short-, or long-term	Increase in amount of compound transferred into population per kg increases in emissions	FHX includes various demographic categories	Chronic exposure per kg emission and for product over life cycle

Name	GExFRAME	MENTOR	USETox	RAIDAR / FHX	IMPACT
Media Focus / Exposure Routes	Dermal, food and water ingestion, incidental ingestion, inhalation	Inhalation, dermal, ingestion, infusion; drinking water, food, nondietary, dermal	Inhalation and multimedia ingestion through drinking water, vegetables, meat, milk and fish	Inhalation, ingestion: air, water, soil, vegetation, fish, meat products	Inhalation and multimedia ingestion through drinking water, vegetables, meat, milk and fish
Scenarios	Allows custom scenarios (e.g., "trigger spray scenario")	Custom scenarios defined based on the chemical class and product use	Production and emission scenarios	No product use scenarios, but includes chemical release scenarios	Production and emission scenarios
Exposure Algorithm	Algorithms based on RIVM's ConsExpo; EPA's Residential SOPs; CARES; EPA's MCCEM (Multiple Chamber Consumer Exposure Model)	Source-to-dose linkage of exposure-relevant processes. Modules can be customized based on data availability and the objective of study	Mass balance modeling framework for estimating intake fraction, combined with linear dose-responses based on ED50s and with severity in DALY	Combined fate and food web mass balance models for estimating exposure and ranking, includes bioaccumulation, biomagnifications, and biotransformation	Spatialized mass balance to calculate intake fraction for 831 airsheds and 523 watersheds in North America.
Tiered Approach	Both lower tier screening assessments and higher tier probabilistic Monte Carlo assessments	Screening to complex; individual-level to population; deterministic to probabilistic	No	Deterministic and stochastic exposure estimates, sensitivity and uncertainty analyses	Yes, lower tier generic (non spatialized) versus spatialized assessment
Activity Patterns	Yes. CHAD data.	CHAD or user-specified profiles	No	No	No

Name	GExFRAME	MENTOR	USETox	RAIDAR / FHX	IMPACT
Data Sources	Framework houses exposure related data and models. New databases and models added continuously. Data can be imported by users	Linkages to multiple databases. Examples include EPA's air and water databases, product-related, CHAD, USGS, NHANES, NHEXAS and site-specific, databases	Physical-chemical data and environmental fate parameters from EPI Suite. Several other existing datasets used, particularly for eco and human toxicological data	Physical-chemical data and degradation half-life parameters from databases or QSARs, e.g., EPI Suite.	Physical-chemical data and environmental fate parameters from EPI Suite. Several other existing datasets used for eco and human toxicological data (CPDM database)
Professional Judgment	Yes, to determine type of modeling	Yes, to validate data before input	No	No	No
Quantification Level	Categorical and quantified intake in mass per body weight per day	Exposure distributions (mass per body weight per day), including rankings, dose endpoints	Characterization factors per kg emitted (function of intake fraction and ED50)	Ranking of human exposure potential using daily intake, intake fraction, or internal dose; ranking by scaling unit emission rate	Characterization factors per kg emitted in each air/watershed (function of intake fraction and ED10)
Numbers of Chemicals Evaluated	N/A	Evaluated many compound classes (nanoparticles, VOCs, organics), but not yet used for prioritization	Recommended or interim factors for 1000 human tox and 2500 eco tox substances.	Applied to several thousand chemicals, used to screen substances on Canadian DSL	Characterization factors for 859 human tox and 393 eco tox. Can run with all USEtox substances
Regulatory Context	Yes	No	No	No	No
References and Links	Kephalopoulos et al. (2008)	Georgopoulos and Lioy (2006)	Rosenbaum et al. (2008)	Canadian Centre for Environmental Modelling and Chemistry (2011) (http://www.trentu.ca/academic/aminss/envmodel/models/models.html)	Humbert et al. (2009)

FIGURES

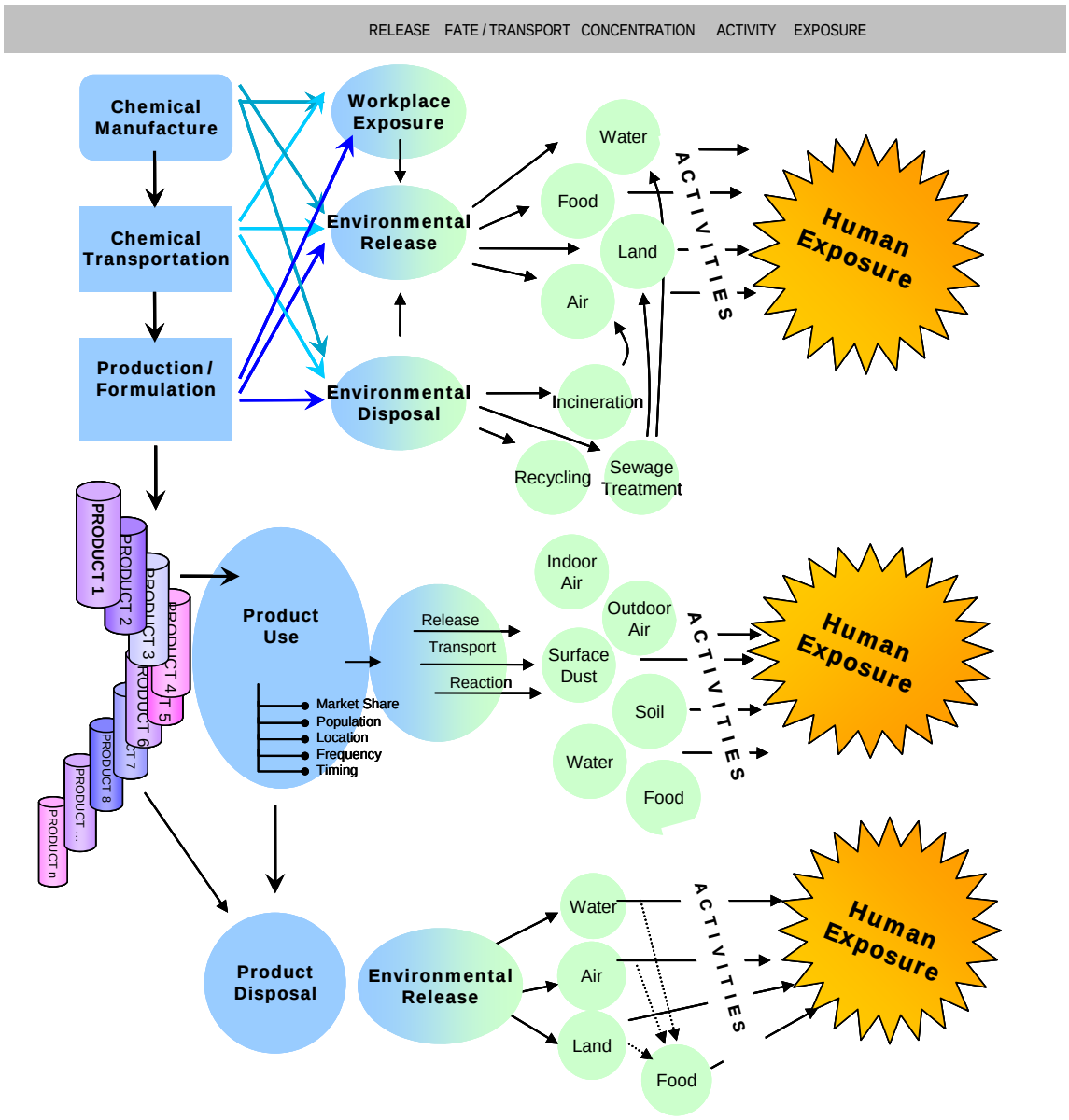

Figure 1. Human exposure framework that follows life cycle of a chemical from manufacture, through product use scenarios, and ultimately to contact with humans. Figure developed by Linda Sheldon, US EPA.

Supplemental Information

Schematic representations of the process used by EPA for developing risk-based prioritizations under the Chemical Assessment and Management Program (Figure S-1) and the process used by Health Canada for categorization of the Domestic Substances List under the Canadian Environmental Protection Act (CEPA) of 1999 (Figure S-2).

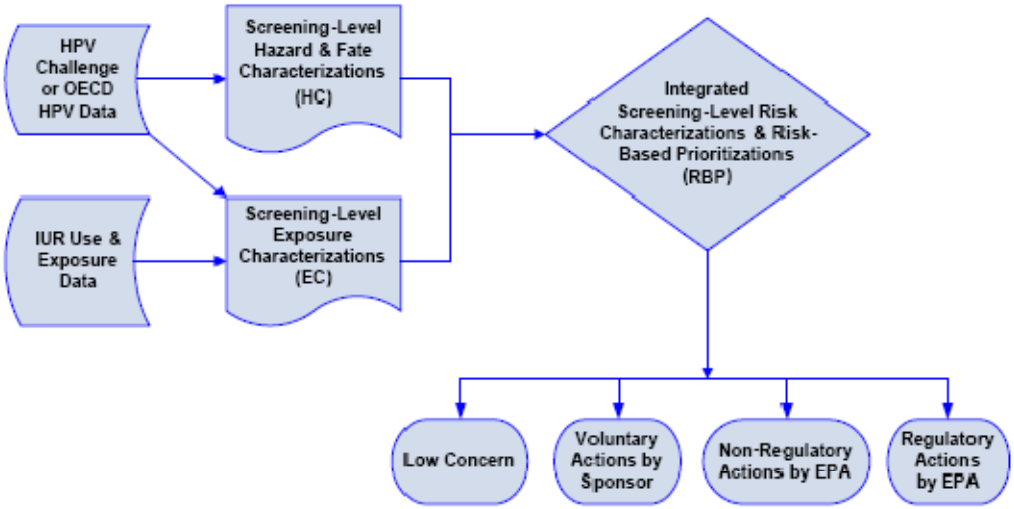

Figure S-1. Process for developing risk-based prioritizations (Source: EPA. 2009b)

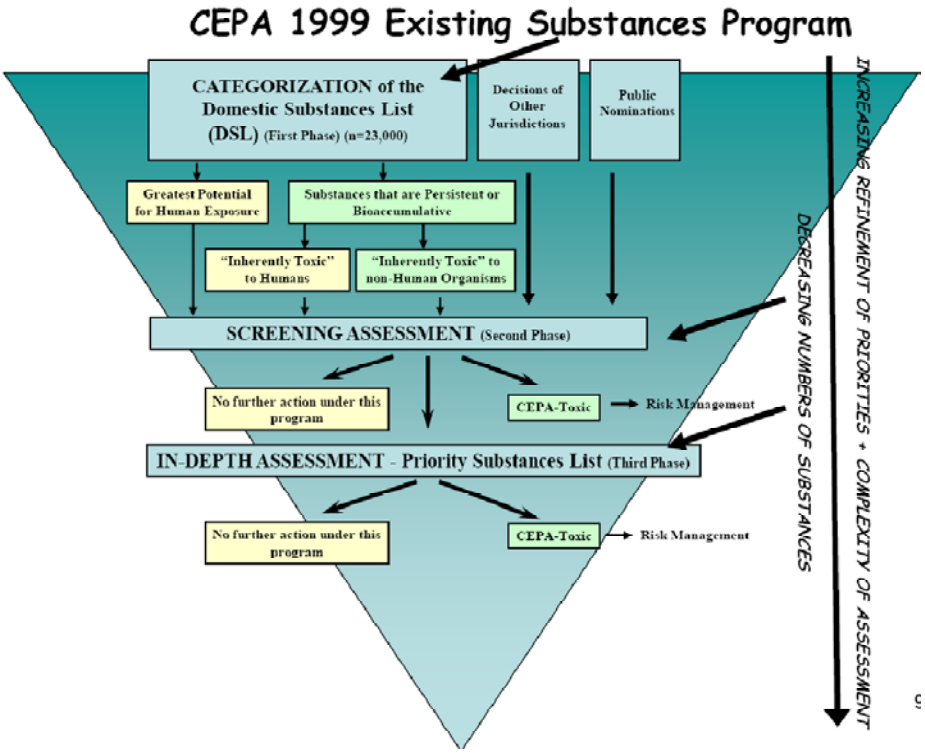

Figure S-2. CEPA categorization and screening process (Source: Meek, 2008).