Chemicals Alternatives Assessment (CAA): Tools for Selecting Less Hazardous Chemicals

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ABSTRACT

Chemicals alternatives assessment (CAA) is a form of alternatives assessment that focuses on finding alternative chemicals, materials or product designs to substitute for the use of hazardous chemicals. Chemical hazard assessment (CHA) or comparative CHA is a method for comparing chemicals based on their inherent hazard properties. CAA is inclusive of CHA. However, a comprehensive CAA can be much broader and include information such as cost, availability, performance and social and environmental life-cycle attributes. CHA/CAA provides users with hazard-based information to make informed decisions when selecting less hazardous chemical alternatives. There are multiple CAA methods in use around the world and these methods share a common goal, namely, to support the intelligent design, use and substitution of chemicals to benefit humankind in a manner that will not harm our environment and its inhabitants. Ideally, a CAA/CHA will completely characterize a chemical's intrinsic human health and environmental hazards, in the process promoting the selection of less hazardous chemical ingredients, in addition to avoiding unintended consequences of switching to a poorly characterized chemical substitute.

CHA methods typically share common hazard endpoints related to human toxicity, environmental toxicity and environmental fate. The

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endpoints are evaluated based on criteria that allow for the use of measured or predicted data. Human health criteria in CHA evaluate endpoints such as potential carcinogenicity, mutagenicity, reproductive and developmental toxicity, endocrine disruption, acute and chronic or repeat dose toxicity, dermal and eye irritation and dermal and respiratory sensitization. Acute and chronic aquatic toxicity, terrestrial toxicity, persistence and bioaccumulation are commonly evaluated to predict a chemical's environmental toxicity and fate. Finally, some CHAs (such as GreenScreen™) also evaluate a chemical's physical characteristics such as flammability and reactivity.

Of the CAA methods listed, only the US Environmental Protection Agency (EPA)'s DfE program, CPA's GreenScreen™ and MBDC's Cradle to Cradle® paradigms are fully transparent and publicly available methods of assessment. Most other CAAs in use around the world do not fully disclose all of their reasoning or resources used for establishing threshold values for hazard criteria, prioritization of hazard endpoints and life-cycle concerns. Some CAA methods are limited to a focus on CHA whereas others such as MBDC's Cradle to Cradle® expand the focus to consider some life-cycle attributes. Whether the CAA method includes additional attributes or not, CHA can be used in a modular way, combining with other needed information to inform decision-making.

CAA provides a powerful means to improve upon the *status quo* by establishing methods to inform chemical substitution in a scientifically rigorous and defensible manner. Recognizing the value of CAA and fostering greater adoption of CAA methods provide stakeholders with much-needed tools to address a serious deficiency in the way in which chemicals are used in society, as maintaining the *status quo* is analogous to giving up. As humankind's understanding of the full costs and benefits of chemicals matures, it is critical that we cease using those chemicals that can permanently impair human health or the environment.

1.1 Introduction to Chemicals Alternatives Assessments

Chemicals alternatives assessment (CAA) is a form of alternatives assessment that focuses on finding alternative chemicals, materials or product designs to substitute for the use of hazardous chemicals in products. Chemical hazard assessment (CHA) or comparative CHA is a method for comparing chemicals based on their inherent hazard properties. CAA is inclusive of CHA. CHA/CAA provides users with hazard-based information to make informed decisions when selecting less hazardous chemical alternatives. The approach is used to assess a chemical's impact on human health and the environment. Hazard can be defined as the way in which a chemical, object or situation may cause harm. The degree of a chemical's capacity to harm depends on its intrinsic properties, such as its capacity to interfere with normal biological processes and

its capacity to burn, explode or corrode (*e.g.*, non-life-threatening allergic skin reaction to nickel jewelry, lethal egg-shell thinning in avian species attributed to exposure to the organochlorine pesticide DDT).[1] The goal of a CAA is to find a science-based solution that identifies and completely characterizes chemical hazards, promoting the selection of less hazardous chemical ingredients, in addition avoiding unintended consequences of switching to a poorly characterized chemical substitute.

Hazard assessment is a systematic process of assessing and classifying hazards across an entire spectrum of endpoints and levels of severity It involves a characterization of the nature and strength of the evidence of causation.[2] A comparative CHA is a type of hazard assessment that evaluates hazards from two or more agents, with the intent to guide decision-making toward the use of the least hazardous options via a process of informed substitution, as illustrated in Figure 1.1.

In practical terms, comparative CHA is a term that describes the practice of assessing hazards for specific items (such as chemicals, materials, products or technologies) and then comparing these hazards following a structured approach. Ideally, CHA minimizes subjectivity in hazard classification since a

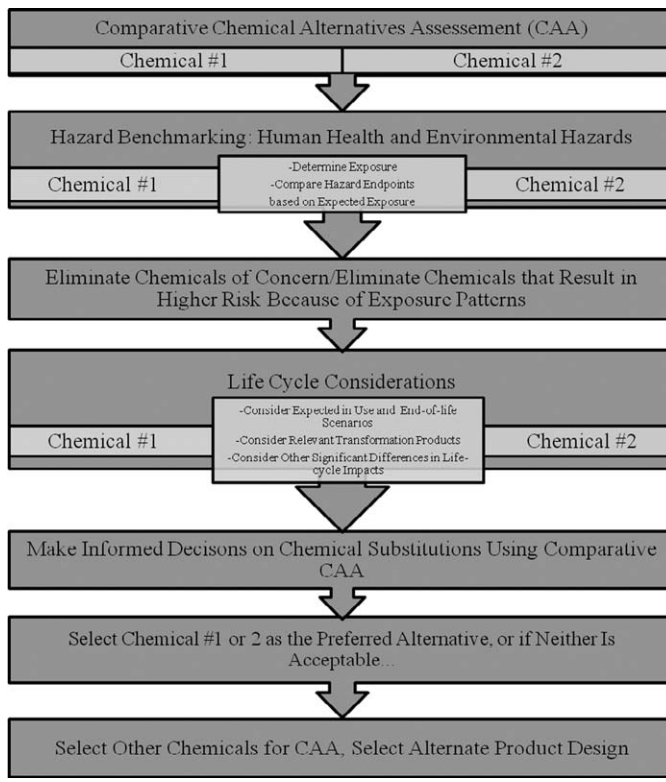

Figure 1.1 Comparative chemical alternatives assessments.

structured approach is used to assign hazards. Over the past 10 years, the number of comparative hazard tools has continued to increase. The Toxics Use Reduction Institute (TURI) at the University of Massachusetts presented a collection of over 100 tools for comparing hazard characteristics of different chemicals.[3] CAAs have numerous applications, including the following:

- Enabling the prioritization of chemicals for reduction or phase-out:
  - from any phase in product life-cycle (*e.g.*, manufacturing, product design);
  - from the whole supply chain.
- Assisting in the selection of alternatives for the following:
  - banned or restricted chemicals or materials;
  - chemicals that are perceived as hazardous by the public;
  - identifying and classifying Restricted Use Materials (RUMs);
  - developing environmentally preferred products.

Some CHA methods, such as GreenScreen™, focus solely on individual chemicals or materials and their subsequent health or environmental impacts while other CAA methods such as Cradle to Cradle® incorporate CHA in addition to certain life-cycle-based considerations such as energy use, water quality and efficiency, social responsibility and potential for material reuse.

To date, various CAA partnerships have brought together environmental agencies, such as the US EPA, industry organizations such as the Phosphorus, Inorganic and Nitrogen Flame Retardants Association (pinfa), academia (such as the University of Massachusetts at Lowell) and non-governmental organizations such as the United States Green Chemistry and Commerce Council (GC3) and Europe's ChemSec to evaluate environmental and health impacts of potential alternatives to problematic chemicals and chemical classes, such as phthalate esters (ubiquitously used in flexible plastics), flame retardants in furniture and printed circuit boards and nonylphenol ethoxylate surfactants (which are commonly used in laundry detergents and are exceedingly toxic to aquatic organisms). Such partnerships demonstrate that CAA can be employed to benefit both producers and users of the chemical to the improvement of ecological and human health.

The purpose of this collection of chapters in the *Issues in Environmental Science and Technology* series is to describe and exemplify several existing CAA methodologies currently being used in North America, Europe and China and to make suggestions on how to improve the overall CAA process, fostering the greater adoption of CAA around the world. This introductory chapter identifies a number of common themes among CAA methods and provides a broad overview of such methods.

1.2 Common Traits Among CAA Paradigms

CAA paradigms share a number of similarities that are implemented as part of a CAA and all have the common goal of identifying less hazardous chemicals. CAAs use standardized procedures to assess whether alternatives have the

potential for an improved health and environmental profile. CAAs assess whether the adoption of an alternative chemical is likely to result in lasting environmental or public health improvement. Ideally, a CAA will also address whether chemical alternatives are commercially available, perform well and are cost-effective.

1.2.1 Step One: Hazard Assessment Through Literature Search and Data Identification

As a first step towards characterizing the human health and/or environmental hazards of a chemical, a CHA is performed. The practitioner assesses hazards for each chemical alternative across a range of health effects and environmental endpoints. Such endpoints generally include the following: acute and repeat dose toxicity, endocrine activity, carcinogenicity and mutagenicity, reproductive and developmental toxicity, neurotoxicity, respiratory and dermal sensitization, skin and eye irritation, acute and chronic aquatic toxicity, terrestrial toxicity and persistence and bioaccumulation. When measured data are not available or adequate for an endpoint, a hazard concern level can be assigned based on quantitative structure–activity relationships (QSARs or SARs) and expert judgment. This practice ensures that all endpoints are considered as part of the hazard assessment and that alternatives are evaluated based on a complete understanding of their potential human health and environmental hazards. A level of confidence associated with studies is often assigned.

Sources of information to evaluate and characterize human health and environmental hazards in a CAA include one of more of the following:

- Publicly available experimental data obtained from a literature review
  - Sources of such toxicological and environmental fate and effects data include online databases indexing scientific literature, such as:
    - ChemIDplus: http://www.cleanproduction.org/library/greenscreen-translator-benchmark1-possible%20benchmark1.pdf
    - EPA High Production Volume Information System (HPVIS): http://www.epa.gov/hpvis/index.html
    - UNEP OECD (Organisation for Economic Co-operation and Development) Screening Information Datasets (SIDS): http://www.chem.unep.ch/irptc/sids/OECDSIDS/sidspub.html
    - European Chemical Substances Information System IUCLID Chemical Data Sheets (ESIS): http://esis.jrc.ec.europa.eu/index.php?PGM = dat
    - United States National Toxicology Program (NTP): http://ntp.niehs.nih.gov/
    - International Agency for the Research on Cancer (IARC): http://www.inchem.org/pages/iarc.html
    - Human and Environmental Risk Assessment on ingredients of household cleaning products (HERA): http://www.heraproject.com/RiskAssessment.cfm

  - European Chemicals Agency (ECHA): http://echa.europa.eu/
  - ExPub (Expert Publishing): http://www.expub.com
- Experimental data that are not publicly available (such as industry- or trade association-sponsored studies)
- SAR-based estimations from predictive methods such as US EPA models (*e.g.*, EpiSuite, Ecosar), European Union (*e.g.*, VEGA, ToxTree) or OECD (*e.g.*, OECD Toolbox), Derek, Topkat, among other predictive software algorithms.

1.2.2 Step Two: Hazard Classification and Benchmarking of Relevant Data

Once the literature search has been performed, relevant studies have been retrieved and data collected, the second step of a CHA generally entails assigning hazard scores for the criteria evaluated. For example, a GreenScreen™ will assign hazard scores of low, moderate, high (and, for some endpoints, very low or very high) for 18 health and environmental fate and toxicity endpoints, as illustrated for an example chemical in Figure 1.2.[4] Criteria for assigning hazard scores in a CAA are often based on the Global Harmonized System of Classification and Labeling of Chemicals (GHS) criteria,[1] in addition to criteria from other authoritative lists. As an example, a complete version of GreenScreen™'s hazard criteria for each endpoint can be found at the CPA's website.[4]

For several endpoints, such as acute mammalian toxicity, systemic toxicity, acute and chronic aquatic toxicity, persistence and bioaccumulation, hazard scores are often assigned based on specific dose thresholds and/or ranges. For example, the US EPA's Design for the Environment (DfE) Alternatives Assessment Criteria for Hazard Evaluation will assign a chemical a hazard

DEHT was assigned a GreenScreen™ Benchmark Score of 3_{DG} as it does not meet the data gap requirements for a GreenScreen™ Benchmark score of 4. Data gaps (dg) exist for Neurotoxicity (N) and Respiratory Sensitization (SnR).[16]

Green Screen Hazard Ratings: Di(2-ethylhexyl) terephthalate (DEHT)																		
Group I Human					Group II and II* Human									Ecotox		Fate		Physical	
C	M	R	D	E	AT	ST		N		SnS*	SnR*	IrS	IrE	AA	CA	P	B	Rx	F
						single	repeat*	single	repeat*										
L	**L**	*L*	**L**	*L*	*L*	dg	**L**	dg	dg	*L*	dg	*L*	*L*	*L*	*L*	*vL*	*L*	*L*	*L*

Note: Hazard levels [Very High (vH), High (H), Moderate (M), Low (L), Very Low (vL)] in *italics* reflect estimated values and lower confidence. Hazard levels in **Bold** font reflect values based on test data.[16]

AA	Acute Aquatic Toxicity	E	Endocrine Activity	P	Persistence
AT	Acute Mammalian Toxicity	F	Flammability	R	Reproductive Toxicity
B	Bioaccumulation	IrE	Eye Irritation/Corrosivity	Rx	Reactivity
C	Carcinogenicity	IrS	Skin Irritation/Corrosivity	SnS	Sensitization-Skin
CA	Chronic Aquatic Toxicity	M	Mutagenicity and Genotoxicity	SnR	Sensitization-Respiratory
D	Developmental Toxicity	N	Neurotoxicity	ST	Systemic/Organ Toxicity

Figure 1.2 Example GreenScreen™ hazard ratings: di(2-ethylhexyl) terephthalate (DEHT).

score of Low for acute mammalian toxicity based on an oral LD_{50} of 2000 mg kg^{-1} or greater and a hazard score of Moderate for persistence based on a half-life in water that falls between 16 and 60 days.

For other endpoints, such as carcinogenicity, mutagenicity and reproductive and developmental toxicity, professional judgment and a clear understanding of the available data are necessary to draw a conclusion and assign a hazard classification. If a 2 year carcinogenicity study performed by the US National Toxicology Program (NTP) shows a statistically significant increase of hepatic tumors in rats, US EPA DfE and GreenScreen™ alternatives assessment criteria would assign a hazard score of High for carcinogenicity. In contrast, if a reproductive toxicity study reports a Lowest Observed Adverse Effect Level (LOAEL) of 250 mg kg-bw^{-1} d^{-1} in mice based on an effect such as decreased weight gain, US EPA and GreenScreen™ alternatives assessment criteria may or may not consider this effect relevant for purposes of assigning a hazard for reproductive toxicity depending on the chemical's mechanism of action. Ultimately, the hazard classification may come down to the professional opinion of the scientist performing the CAA. It is imperative to the integrity of a CAA that all hazard scores are based on sound scientific knowledge and can be properly supported and defended, if necessary.

Points to consider when determining the validity of available data include whether a study was performed following Good Laboratory Practices (GLP) or whether a study was conducted following a specific test guideline (*e.g.*, OECD test guidelines). The level of detail reported in a study is also important, as is the source of the study. Primary sources such as peer-reviewed studies are preferred; however, high-quality secondary sources are acceptable, particularly when supported by a Klimisch score of 1 or 2 (1 = reliable without restrictions; 2 = reliable with restrictions), which provides an indication as to the reliability of the actual data.[5]

In the case of conflicting data, weight of evidence should be used to assign the ultimate hazard score for a specific health effect/environmental endpoint. All professional judgments must be fully justified within the section of that endpoint. The justification for a final hazard score must be transparent and easily understood by all who may read the CAA.

1.2.3 Step Three: CAA Report Preparation

Once the hazard assessment and classification portion of the CAA has been completed, a CAA report is written to provide contextual and supplemental information designed to aid in decision-making and may include descriptions of manufacturing processes, use patterns and life-cycle stages that may pose special exposure concerns. The CAA report may contain a description of the cost of use and the potential economic impacts associated with the selection of alternatives and may also contain information on alternative technologies that might result in safer chemicals, manufacturing processes and practices.

Examples of alternatives assessments can be found for numerous types and classes of chemicals, including nonylphenol ethoxylate surfactants, flame

retardants in furniture and printed circuit boards, diethylhexyl phthalate and perchloroethylene.[6,7]

1.3 Life-cycle Assessment and Chemicals Alternatives Assessment

In comparing alternatives, it is important to consider life-cycle impacts in order to avoid shifting burdens between stages of a material's life-cycle. Life-cycle assessment (LCA) is a standardized and quantifiable approach to assessing life-cycle impacts, such as ISO Standard 14040 (Environmental Management: Life Cycle Assessment-Principles and Framework).[8,9] Production of all chemicals or substances requires the extraction of resources from the earth, including water, energy and other raw materials. Energy and other resources are used for manufacture, transportation and during the use phase. At the end of a product's useful life, the product may be released into the environment. This can be problematic if the product contains hazardous materials. As climate change becomes more of a global concern, manufacturers are beginning to assess how their processes affect the environment. Many businesses have responded by identifying 'greener' raw materials and using 'greener' processes to manufacture their products. They are able to reduce the environmental impact their actions have by utilizing LCA. There are four main phases of an LCA:

1. *Defining the goals and scope of the LCA* – Define and describe the product, process or activity.
2. *Performing a life-cycle inventory* – Identify and quantify energy, water and materials usage and environmental releases (*e.g.*, air emissions, solid waste disposal, waste water discharges);
3. *Performing a life-cycle impact assessment* – Assess the potential human and ecological effects of energy, water and material usage and the environmental releases identified in the inventory analysis;
4. *Interpretation* – Evaluate the results of the inventory analysis and impact assessment to select the preferred product, process or service with a clear understanding of the uncertainty and the assumptions used to generate the results.

LCA helps to avoid shifting environmental burdens from one step in a product's life-cycle to another. For example, when choosing between two materials, Option 1 may appear environmentally beneficial because it is more easily biodegradable. However, after conducting an LCA, it may become obvious that Option 2 will produce less of an environmental impact because it uses less energy to manufacture and its breakdown products may pose less of a risk to aquatic ecosystems. An ideal CAA paradigm will take into account life-cycle thinking when evaluating a chemical or material and seek to reduce hazard across the life-cycle. Commercially available LCA software packages such as GaBi and SimaPro are commonly used for LCA, with growing interest in the freeware OpenLCA, which requires inputting of life-cycle inventory data.

1.4 Chemical Alternatives Assessment Paradigms in Use: a Critical Evaluation

Currently, there are a number of CAA paradigms in use around the world to evaluate environmental and human health impacts of potential alternatives to problematic chemicals, as presented in Table 1.1. Often, CAAs employ life-cycle considerations to predict and understand specific phases, from development to manufacture, where industry can make changes to realize environmental and health benefits.[6,10]

Table 1.1 North American and European Alternatives Assessment Paradigms.

Name of Alternative Assessment	*Organization*	*Endpoints*
DfE Alternatives Assessment Criteria	Design for the Environment (DfE)	Acute mammalian toxicity, carcinogenicity, mutagenicity/genotoxicity, reproductive/developmental toxicity, neurotoxicity, repeat dose toxicity, sensitization, eye/skin irritation, endocrine activity, aquatic toxicity, persistence, bioaccumulation
GreenScreen™	Clean Production Action (CPA)	Carcinogenicity, mutagenicity/genotoxicity, reproductive/developmental toxicity, endocrine disruption, neurotoxicity, acute toxicity (inhalation, dermal, oral toxicity), corrosion/irritation of the skin or eye, sensitization of the skin or respiratory system, immune system effects, systemic toxicity/organ effects, acute and chronic aquatic toxicity, persistence, bioaccumulation, explosivity, flammability
Cradle to Cradle® (C2C)	McDonough Braungart Design Chemistry, LLC (MBDC)	Material health [*i.e.* carcinogenicity, endocrine disruption, mutagenicity, reproductive toxicity, teratogenicity, acute and chronic toxicity, irritation of the skin or mucous membranes, sensitization, other (carrier function, skin penetration potential, *etc.*), vertebrate toxicity (fish), invertebrate toxicity (daphnia), aquatic plant toxicity (algae), persistence/biodegradation, bioaccumulation, contents of halogenated organics, metal content, climate relevance/ozone depletion] Material reutilization/design for environment; energy; water; social responsibility

Table 1.1 Continued.

Name of Alternative Assessment	*Organization*	*Endpoints*
Pollution Prevention Options Analysis System (P2OASys)	Massachusetts Toxics Use Reduction Institute (TURI)	Acute human effects (*i.e.* dermal/ocular/respiratory irritation, skin absorption, inhalation LC_{50}, oral/dermal LD_{50}); Chronic human effects (*i.e.* carcinogenicity, mutagenicity, reproductive/developmental toxicity, neurotoxicity, respiratory sensitivity/disease, other organ effects); Aquatic hazards (*i.e.* water quality criteria, aquatic LC_{50}, plant EC_{50}, fish NOAEC, observed ecological effects); persistence, bioaccumulation; atmospheric hazards (*i.e.*, ozone depletor, greenhouse gas, acid rain formation); chemical hazards (*i.e.*, volatile organic compounds, flammability, reactivity/instability, pH); disposal hazard; energy/resource use; product hazard; exposure potential
Chemical Scoring and Ranking Assessment Model (SCRAM)	Michigan Department of Environmental Quality, Surface Water Quality Division (SWQD) and Michigan State University, National Food Safety and Toxicology Center	Subchronic/chronic toxicity (based on repeat dose toxicity, general organ toxicity, carcinogenicity, mutagenicity, neurotoxicity, immunotoxicity, reproductive and developmental toxicity, endocrine disruption), acute aquatic toxicity, acute terrestrial toxicity, persistence, bioaccumulation
Chemicals Assessment and Ranking System (CARS)	Zero Waste Alliance	Proprietary, but may include carcinogenicity, teratogenicity, endocrine disruption, persistence, bioaccumulation (PBT status), aquatic toxicity, impact on climate, ozone; considers frequency of use, human health, safety impacts, ecological and global impacts, costs
GreenList™	SC Johnson	Proprietary, but may include acute human toxicity, carcinogenicity, mutagenicity and reproductive toxicity, persistence, bioaccumulation (PBT status), aquatic toxicity, biodegradability
PRIO	Swedish Chemicals Agency	Phase-out substances: carcinogenicity, mutagenicity, reproductive toxicity, endocrine disruption, hazardous metals, ozone depletion, persistence, bioaccumulation. Priority risk-reduction substances: acute and chronic toxicity (inhalation, dermal, oral toxicity, sensitization, mutagenicity) persistence, bioaccumulation

Table 1.1 Continued.

Name of Alternative Assessment	*Organization*	*Endpoints*
Quick Scan	Dutch Ministry of Housing, Spatial Planning and the Environment	Persistence, bioaccumulation, ecotoxicity, carcinogenicity, mutagenicity, reproductive toxicity, inhalation or dermal toxicity, hormone disruption
Column Model and GHS Column Model	German Institute for Occupational Safety (BIA)	Acute and chronic health hazards (including inhalation, dermal, oral toxicity, sensitization; carcinogenicity and mutagenicity, reproductive toxicity, bioaccumulation), environmental hazards, explosivity, flammability, exposure potential, hazards caused by procedures
Evaluation Matrix	German Federal Environmental Agency	Inclusion in lists of problematic substances, physico-chemical properties, human toxicity, problematic properties related to the environment, mobility within the environment, origin of raw materials, greenhouse gas emission, resource consumption, persistence, bioaccumulation

As mentioned above, CAAs are inclusive of CHA and share common endpoints. CAA methods evaluate chemicals based on their measured or predicted human and ecological hazards, in addition to their environmental fate. Human health criteria in a CAA evaluate endpoints such as potential carcinogenicity, mutagenicity, reproductive and developmental toxicity, endocrine disruption, acute and chronic or repeat dose toxicity, irritation and sensitization. Acute and chronic aquatic toxicity, terrestrial toxicity, persistence and bioaccumulation are commonly evaluated to predict a chemical's environmental toxicity and fate. Finally, some CAAs (such as GreenScreen™) also evaluate a chemical's physical characteristics. such as flammability and reactivity.

Of the CAA methods listed, only the US EPA's DfE program and CPA's GreenScreen™ are fully transparent and publicly available methods of assessment. A number of the other CAA methods identified in Table 1.1 do not fully disclose all of their reasoning or resources used for establishing threshold values for hazard criteria, prioritization of hazard endpoints and life-cycle concerns.

This section describes a number of CAA methods. Although each method uses its own set of criteria when evaluating the hazards of a chemical, the most commonly used benchmarks used when assigning a hazard for a specific endpoint mirror those developed by the US EPA, the OECD, and/or the Globally Harmonized System of Classification and Labeling of Chemicals (GHS). Tables 1.2 and 1.3 provide an overview of how each

Table 1.2 Comparison of human health hazard evaluation criteria among CAA methods.

	Human health endpoint criteria								
Method	*Acute mammalian toxicity*	*Carcinogenicity*	*Mutagenicity/ genotoxicity*	*Reproductive/developmental toxicity*	*Repeat dose toxicity (also referred to as systemic/organ effects)*	*Irritation/corrosion*	*Sensitization*	*Neurotoxicity*	*Endocrine disruption*
DfE Alternatives Assessment Criteria[12]	*Low:* • LD_{50} >2000 mg kg^{-1} (oral) • LD_{50} >2000 mg kg^{-1} (dermal) • LC_{50} >20 mg L^{-1} (gas/vapor) • LC_{50} >5 mg L^{-1} d^{-1} (dust/mist/fume) *Moderate:* • LD_{50} ≥ 300–2000 mg kg^{-1} (oral) • LD_{50} ≥ 1000–2000 mg kg^{-1} (dermal) • LC_{50} ≥ 10–20 mg L^{-1} (gas/vapor) • LC_{50} 1–5 mg L^{-1} d^{-1} (dust/mist/fume) *High:* • LD_{50} >50–300 mg kg^{-1} (oral) • LD_{50} ≥ 200–1000 mg kg^{-1} (dermal) • LC_{50} ≥ 2–10 mg L^{-1} (gas/vapor) • LC_{50} ≥ 0.5–1 mg L^{-1} d^{-1} (dust/mist/fume) *Very High:* • LD_{50} ≤50 mg kg^{-1} (oral) • LD_{50} ≤2000 mg kg^{-1} (dermal)	*Low:* • Negative studies • Negative robust mechanism-based SAR *Moderate:* • Limited or marginal evidence of carcinogenicity in animals • Inadequate evidence in humans *High:* • Suspected human carcinogen (GHS Cat. 2) *Very High:* • Known or presumed human carcinogen (GHS Cat. 1A and 1B)	*Low:* • Negative for chromosomal aberrations and gene mutations • No structural alerts *Moderate:* • Evidence of mutagenicity supported by positive results in in vitro or in vivo somatic cells of humans or animals *High:* • Substances causing concern for humans due to possible induction of heritable mutations in the germ cells of humans • OR Evidence of mutagenicity supported by positive results in *in vitro* AND *in vivo* somatic cells and/or germ cells of humans or animals (GHS Cat. 2) *Very High:* • Substances known to	*Very Low:* • NOAEL >1000 mg kg-bw^{-1} d^{-1} (oral) • NOAEL >2000 mg kg-bw^{-1} d^{-1} (dermal) • NOAEC >20 mg L^{-1} d^{-1} (gas/vapor) • NOAEC >5 mg L^{-1} d^{-1} (dust/mist/fume) *Low:* • NOAEL >250–1000 mg kg-bw^{-1} d^{-1} (oral) • NOAEL >500–2000 mg kg-bw^{-1} d^{-1} (dermal) • NOAEC >2.5–20 mg L^{-1} d^{-1} (gas/vapor) • NOAEC >0.5–5 mg L^{-1} d^{-1} (dust/mist/fume) *Moderate:* • NOAEL 50–250 mg kg-bw^{-1} d^{-1} (oral) • NOAEL 100–500 mg kg-bw^{-1} d^{-1} (dermal) • NOAEC 1–2.5 mg L^{-1} d^{-1} (gas/vapor) • NOAEC 0.1–0.5 mg L^{-1} d^{-1} (dust/mist/fume) *High:* • NOAEL <50 mg kg-bw^{-1} d^{-1} (oral) • NOAEL <100 mg kg-bw^{-1} d^{-1} (dermal) • NOAEC <1 mg L^{-1} d^{-1} (gas/vapor) • NOAEC <0.1 mg L^{-1} d^{-1} (dust/mist/fume)	• All values based on 90 day study, triple for 28 day study: *Low:* • NOAEL >100 mg kg-bw^{-1} d^{-1} (oral) • NOAEL >200 mg kg-bw^{-1} d^{-1} (dermal) • NOAEC >1 mg L^{-1} (6 h)$^{-1}$ d^{-1} (gas/vapor) • NOAEC >0.2 mg L^{-1} (6 h)$^{-1}$ d^{-1} (dust/mist/fume) *Moderate:* • NOAEL 10–100 mg kg-bw^{-1} d^{-1} (oral) • NOAEL 20–200 mg kg-bw^{-1} d^{-1} (dermal) • NOAEC 0.2–1 mg L^{-1} (6 h)$^{-1}$ d^{-1} (gas/vapor) • NOAEC 0.02–0.2 mg L^{-1} (6 h)$^{-1}$ d^{-1} (dust/mist/fume) *High:* • NOAEL <10 mg kg-bw^{-1} d^{-1} (oral) • NOAEL <20 mg kg-bw^{-1} d^{-1} (dermal) • NOAEC <0.2 mg L^{-1} (6 h)$^{-1}$ d^{-1} (gas/vapor)	*Very Low:* • Not irritating (eye and skin) *Low:* • Clearing in less than 24 h, mildly irritating (eye) • Mild or slight irritation at 72 h (skin) *Moderate:* • Clearing in 7 d or less, moderately irritating (eye) • Moderate irritation at 72 h (skin) *High:* • Clearing in 8–21 d, severely irritating (eye) • Severe irritation at 72 h (skin) *Very High:* • Irritation persists for >21 d or corrosive (eye) • Corrosive (skin)	*Low:* • Adequate data available and not GHS Cat. 1A or 1B (skin) • Adequate data available indicating lack of respiratory sensitization *Moderate:* • Low to moderate frequency of sensitization in humans and/or low to moderate potency in animals (GHS Cat. 1B) (skin) • EC3 >2% (local lymph node assay) • ≥ 30–60% responding at ≤0.1–≤1% intradermal dose or ≥ 30% at >1% dermal dose (guinea pig maximization test) • ≥ 15–<60% responding at >0.2–≤20% topical dose or ≥ 15% at >20% topical dose (Buehler assay) • Limited evidence, including presence of structural alerts (respiratory) *High:* • High frequency of sensitization in humans and/or high potency in animals (GHS Cat. 1A) (skin) • EC3 ≤2% (local lymph node assay)	• All values based on 90 day study, triple for 28 day study: *Low:* • NOAEL >100 mg kg-bw^{-1} d^{-1} (oral) • NOAEL >200 mg kg-bw^{-1} d^{-1} (dermal) • NOAEC >1 mg L^{-1} (6 h)$^{-1}$ d^{-1} (gas/vapor) • NOAEC >0.2 mg L^{-1} (6 h)$^{-1}$ d^{-1} (dust/mist/fume) *Moderate:* • NOAEL 10–100 mg kg^{-1} bw^{-1} d^{-1} (oral) • NOAEL 20–200 mg kg-bw^{-1} d^{-1} (dermal) • NOAEC 0.2–1 mg L^{-1} (6 h)$^{-1}$ d^{-1} (gas/vapor) • NOAEC 0.02–0.2 mg L^{-1} (6 h)$^{-1}$ d^{-1} (dust/mist/fume) *High:* • NOAEL <10 mg kg-bw^{-1} d^{-1} (oral) • NOAEL <20 mg kg-bw^{-1} d^{-1} (dermal) • NOAEC <0.2 mg L^{-1} (6 h)$^{-1}$ d^{-1} (gas/vapor) • NOAEC <0.02 mg L^{-1} (6 h)$^{-1}$ d^{-1} (dust/mist/fume)	Evidence of a chemical having endocrine activity will be summarized in a narrative

	• LC_{50} $\leq$2 mg L^{-1} (gas/vapor) • LC_{50} $\leq$0.5 mg L^{-1} d^{-1} (dust/mist/fume)	induce heritable mutations or to be regarded as if they induce heritable mutations in the germ cells of humans (GHS Cat. 1A or 1B)	• NOAEC $<$0.02 mg L^{-1} (6 h)$^{-1}$ d^{-1} (dust/mist/fume)	• $\geq$ 30% responding at $\leq$0.1% intradermal dose or $\geq$ 60% at $>$0.1–$\leq$1% intradermal dose (guinea pig maximization test) • $\geq$ 15% responding at $\leq$0.2% topical dose or $\geq$ 60% at $>$0.2–$\leq$20% topical dose (Buehler assay) • Occurrence in humans or evidence of sensitization in humans based on animal or other tests (GHS Cat. 1A and 1B) (respiratory)				
GreenScreen version 1.2[4]	*Low:* • No basis for concern identified • LD_{50} $>$2000 mg kg^{-1} (oral) • LD_{50} $>$2000 mg kg^{-1} (dermal) • LC_{50} $>$20 mg L^{-1} (gas/vapor) • LC_{50} $>$5 mg L^{-1} (dust/mist/fume) or • GHS Category 5 *Moderate:* • LD_{50} $>$300–2000 mg kg^{-1} (oral) • LD_{50} $>$1000–2000 mg kg^{-1} (dermal) • LC_{50} $>$10–20 mg L^{-1} (gas/vapor) • LC_{50} $>$1–5 mg L^{-1} (dust/mist/fume) or • GHS Category 4 *High:* • LD_{50} $>$50–300 mg kg^{-1} (oral)	*Low:* • No basis for concern identified • IARC Group 4 *Moderate:* • Limited or marginal evidence of carcinogenicity in animals • Analog data • Chemical class known to produce toxicity • IARC Group 2B • EU Category 3 or • GHS Category 2 *High:* • Evidence of adverse effects in humans	*Low:* • No basis for concern identified *Moderate:* • Suggestive animal studies • Analog data • Chemical class known to produce toxicity • EU Category 3 or • GHS Category 2 *High:* • Evidence of adverse effects in humans • Weight of evidence demonstrates potential for adverse effects in humans • EU Category 1 or 2 or	*Low:* • No basis for concern identified *Moderate:* • Suggestive animal studies • Analog data • Chemical class known to produce toxicity • GU Category 3 or GHS Category 2 *High:* • Evidence of adverse effects in humans • Weight of evidence demonstrates potential for adverse effects in humans • NTP Center for the Evaluation of Risks to Human Reproduction • California Prop 65 • GHS Category 1A or 1B	*Low:* • No basis for concern identified • NOAEL $>$50 mg kg-$bw^{-1}$$d^{-1}$ (oral) • NOAEL $>$200 mg kg-$bw^{-1}$$d^{-1}$ (dermal) • NOAEC $>$1 mg L^{-1} (6 h)$^{-1}$ day (gas/vapor) • NOAEC $>$0.2 mg L^{-1} (6 h)$^{-1}$ day (dust/mist/fume) *Moderate* • NOAEL $>$10–100 mg kg-bw^{-1} d^{-1} (oral) • NOAEL $>$20–200 mg kg-bw^{-1} d^{-1} (dermal) • NOAEC $>$0.2–1 mg L^{-1} (6 h)$^{-1}$ d^{-1} (gas/vapor) • NOAEC $>$0.02–0.2 mg L^{-1} (6 h)$^{-1}$ d^{-1} (dust/mist/fume) • GHS Category 3 single exposure or	*Low:* • No basis for concern identified *Moderate:* • Evidence of reversible effects in humans or animals • GHS Category 3: mild irritant (skin) • GHS Category 2B: mildly irritating (eye) *High:* • GHS Category 2: irritant (skin) • GHS Category 2A: irritating (eye) *Very High:* • Evidence of irreversible effects in studies of human populations • Weight of evidence of irreversible effects in animal studies or • GHS Category 1: corrosive and/or irreversible (skin or eye)	*Low:* • No basis for concern identified *Moderate:* • Suggestive animal studies • Analog data or • Chemical class known to produce toxicity • GHS Category 1B (low to moderate frequency of occurrence) *High:* • Evidence of adverse effects in humans • Weight of evidence demonstrates potential for adverse effects in humans • GHS Category 1A (high frequency of occurrence)	*Low:* • No basis for concern identified *Moderate:* • Suggestive animal studies • Analog data or • Chemical class known to produce toxicity • GHS Category 3 single exposure or • Category 2 repeated exposure *High:* • Evidence of adverse effects in humans or • Weight of evidence demonstrates potential for adverse effects in humans • GHS Category 2 single exposure or • Category 1 repeated exposure	*Low:* • No basis for concern identified • EU Category 3a *Moderate:* • Evidence of endocrine activity • Suggestive animal studies • Analog data • Chemical class known to produce toxicity • EU Draft List – Category 1 or 2 *High:* • Evidence of endocrine activity and adverse effects in humans or

Table 1.2 Continued.

	Human health endpoint criteria								
Method	*Acute mammalian toxicity*	*Carcinogenicity*	*Mutagenicity/ genotoxicity*	*Reproductive/develop-mental toxicity*	*Repeat dose toxicity (also referred to as systemic/organ effects)*	*Irritation/corrosion*	*Sensitization*	*Neurotoxicity*	*Endocrine disruption*
	• LD_{50} >200–1000 mg kg^{-1} (dermal) • LC_{50} >2.0–10 mg L^{-1} (gas/vapor) • LC_{50} >0.5–1 mg L^{-1} (dust/mist/fume) • US EPA Extremely Hazardous Substance List or • GHS Category 3 *Very High:* • LD_{50} ≤50 mg kg^{-1} (oral) • LD_{50} ≤200 mg kg^{-1} (dermal) • LC_{50} ≤2 mg L^{-1} (gas/vapor) • LC_{50} ≤0.5 mg L^{-1} (dust/mist/fume) • US EPA Extremely Hazardous Substance List or • GHS Category 1 or 2	• Weight of evidence demonstrates potential for adverse effects in humans • NTP known or reasonably anticipated to be human carcinogen • OSHA carcinogen • California Prop 65 • IARC Group 1 or 2A • EU Category 1 or 2 or • GHS Category 1A or 1B	• GHS Category 1A or 1B		• Category 2 repeated exposure *High:* • NOAEL ≤10 mg kg-bw^{-1} d^{-1} (oral) • NOAEL ≤20 mg kg-bw^{-1} d^{-1} (dermal) • NOAEC ≤0.2 mg L^{-1} $(6\ h)^{-1}$ d^{-1} (gas/vapor) • NOAEC ≤0.02 mg L^{-1} $(6\ h)^{-1}$ d^{-1} (dust/mist/fume) • GHS Category 2 single exposure or • Category 1 repeated exposure *Very High:* • GHS Category 1 single exposure			*Very High:* • GHS Category 1 single exposure	• Weight of evidence demonstrates that mechanisms of action lead to adverse effects • EU Draft List – Category 1 or 2
C2C version 3.0 (Includes only Ingredient Characterization Criteria)[19]	*Green:* • LD_{50}>2000 mg/kg (oral/dermal) • LC_{50}>2000 ppmV (gas) • LC_{50}>20mg/L (4 h vaper) • LC_{50}>5mg/L (4 h dust/mist) *Yellow:* • LD_{50} 300–2000 mg/kg (oral) • LD_{50} 1000–2000 mg/kg (dermal)	*Green:* • Not known or suspected carcinogen *Yellow:* • Not classifiable as a human carcinogen *Red:* • Known or suspected carcinogen	*Green:* • Product has been tested and is not mutagenic or clastogenic invitro at concentration up to 100mg/L *Yellow:* • Negative mutagenicity at concentration up to 100mg/L	*Green:* • Not known or suspected of being a reproductive toxin or teratogen • NOAEL>500 mg/kg bw/day (oral) • NOAEL>2.5 mg/l 6–8 hr/day (inhalative) *Yellow:* • Evidence of being a secondary non-specific reproductive toxin or teratogen	Chronic toxicity not listed as an explicit hazard in v 3.0.	*Green:* • Single Exposure Organ, Sub-Chronic, and Chronic Toxicity Endpoints for Green Rating *Yellow:* • Single Exposure Organ, Sub-Chronic, and Chronic Toxicity Endpoints for Yellow Rating	*Green:* • Not sensitizing to skin or airways via experience or test *Yellow:* • Equivocal sensitization data *Red:* • Listed as a skin or airway sensitizer or has tested positive in sensitization test	*Green:* • Single Exposure Organ, Sub-Chronic, and Chronic Toxicity Endpoints for Green Rating *Yellow:* • Single Exposure Organ, Sub-Chronic, and Chronic Toxicity Endpoints for Yellow Rating	*Green:* • Not known or suspected of being an endocrine disruptor *Yellow:* • Insufficient evidence of being an endocrine disruptor

	• LC_{50} 2500–20000 ppmV (gas) • LC_{50} 10–20 mg/m^3 (4 hr vapor) • LC_{50} 1–5 mg/m^3 (4 hr dust/mist) *Red:* • LD_{50} < 300 mg/kg (oral) • LD_{50} < 1000 mg/kg (dermal) • LC_{50} < 2500 ppmV (gas) • LC_{50} < 10 mg/m^3 (4 hr vapor) • LC_{50} < 1 mg/m^3 (4 hr dust/mist)		*Red:* • Positive mutagenicity or clastogenic invitro at concentration up to 100mg/L or GHS 1A, 1B, or 2	• NOAEL = 50–500 mg/kg bw/day (oral) • NOAEL = 0.25 mg–2.5 mg/l 6–8 hr/day (inhalative) *Red:* • Known as a reproductive toxin or teratogen as GHS 1A, 1B, or 2 • NOAEL < 50 mg/kg bw/day (oral) • NOAEL < 0.25 mg/l 6–8 hr/day (inhalative)		*Red:* • Single Exposure Organ, Sub-Chronic, and Chronic Toxicity Endpoints for Red Rating or Listed in Grandjean *et al*. text for neurotox effects		*Red:* • Single Exposure Organ, Sub-Chronic, and Chronic Toxicity Endpoints for Red Rating or Listed in Grandjean et al. text for neurotox effects	*Red:* • Listed as known or suspected endocrine disruptor supported by peer reviewed science
P2OASys (levels of concern are characterized as numerical hazard scores the smaller the number, the less hazardous)[20]	*2.00:* • LD_{50} > 5000 mg kg^{-1} (oral/dermal) • LC_{50} > 10 000 ppm (inhalation) *4.00:* • LD_{50} 500–5000 mg kg^{-1} (oral/dermal) • LC_{50} 1000–10 000 ppm (inhalation) *6.00:* • LD_{50} 50–500 mg kg^{-1} (oral/dermal) • LC_{50} 150–1000 ppm (inhalation) *8.00:* • LD_{50} 5–50 mg kg^{-1} (oral/dermal) • LC_{50} 15–150 ppm (inhalation) *10.00:* • LD_{50} < 5 mg kg^{-1} (oral/dermal) • LC_{50} < 15 ppm (inhalation)	*2.00:* • IARC/EPA Class 4,E *4.00:* • IARC/EPA Class 3,D *6.00:* • IARC/EPA Class 2B,C *8.00:* • IARC/EPA Class 2A,B *10.00:* • IARC/EPA Class 1,A	*2.00:* • L *4.00:* • L/M *6.00:* • M *8.00:* • M/H *10.00:* • H	*2.00:* • L *4.00:* • L/M *6.00:* • M *8.00:* • M/H *10.00:* • H	*2.00:* • L *4.00:* • L/M *6.00:* • M *8.00:* • M/H *10.00:* • H	For skin, eye, respiratory tract: *2.00:* • L *4.00:* • L/M *6.00:* • M *8.00:* • M/H *10.00:* • H	For respiratory sensitivity/disease: *2.00:* • L *4.00:* • L/M *6.00:* • M *8.00:* • M/H *10.00:* • H	*2.00:* • L *4.00:* • L/M *6.00:* • M *8.00:* • M/H *10.00:* • H	N/A

Table 1.2 Continued.

	Human health endpoint criteria								
Method	*Acute mammalian toxicity*	*Carcinogenicity*	*Mutagenicity/ genotoxicity*	*Reproductive/develop-mental toxicity*	*Repeat dose toxicity (also referred to as systemic/organ effects)*	*Irritation/corrosion*	*Sensitization*	*Neurotoxicity*	*Endocrine disruption*
SCRAM[a21] (levels of concern are characterized as numerical hazard scores the smaller the number, the less hazardous)	*1.0:* • E/LD_{50} >5000 mg kg^{-1} (oral/ mammal) • E/LD_{50} >100 lb $acre^{-1}$ (plant) *2.0:* • E/LD_{50} 500–5000 mg kg^{-1} (oral/ mammal) • E/LD_{50} 10–100 lb $acre^{-1}$ (plant) *3.0:* • E/LD_{50} 50–500 mg kg^{-1} (oral/ mammal) • E/LD_{50} 1–10 lb $acre^{-1}$ (plant) *4.0:* • E/LD_{50} 5–50 mg kg^{-1} (oral/ mammal) • E/LD_{50} 0.1–1 lb $acre^{-1}$ (plant) *5.0:* • E/LD_{50} ≤5 mg kg^{-1} (oral/ mammal) • E/LD_{50} ≤0.1 lb $acre^{-1}$ (plant)	*1.0:* • $1/ED_{10}$ ≤1.5[b] mg kg^{-1} d^{-1} *2.0:* • $1/ED_{10}$ 1.5–5[b] mg kg^{-1} d^{-1} *3.0:* • $1/ED_{10}$ 5–15[b] mg kg^{-1} d^{-1} *4.0:* • $1/ED_{10}$ 15–45[b] mg kg^{-1} d^{-1} *5.0:* • $1/ED_{10}$ >45[b] mg kg^{-1} d^{-1}	*1.0:* • No known mutagenic effects *2.0:* • Possible somatic line *3.0:* • Positive somatic line *4.0:* • Possible germ line *5.0:* • Positive germ line	*1.0:* • NOAEL >1000 mg kg^{-1} d^{-1} (≥ 90 d/ human) *2.0:* • NOAEL 100–1000 mg kg^{-1} d^{-1} (≥ 90 d/ human) *3.0:* • NOAEL 10–100 mg kg^{-1} d^{-1} (≥ 90 d/ human) *4.0:* • NOAEL 1–100 mg kg^{-1} d^{-1} (≥ 90 d/human) *5.0:* • NOAEL ≤1 mg kg^{-1} d^{-1} (≥ 90 d/human)	*1.0:* • NOAEL >1000 mg kg^{-1} d^{-1} (≥ 90 d/mammal) • L/NOAEL >5000 mg kg^{-1} d^{-1} (invertebrate) • L/NOAEL >100 lb $acre^{-1}$ (plant) *2.0:* • NOAEL 100–1000 mg kg^{-1} d^{-1} (≥ 90 d/mammal) • L/NOAEL 1000–5000 mg kg^{-1} d^{-1} (invertebrate) • L/NOAEL 10–100 lb $acre^{-1}$ (plant) *3.0:* • NOAEL 10–100 mg kg^{-1} d^{-1} (≥ 90 d/mammal) • L/NOAEL 100–1000 mg kg^{-1} d^{-1} (invertebrate) • L/NOAEL 1–10 lb $acre^{-1}$ (plant) *4.0:* • NOAEL 1–100 mg kg^{-1} d^{-1} (≥ 90 d/ mammal) • L/NOAEL 10–100 mg kg^{-1} d^{-1} (invertebrate) • L/NOAEL 0.1–1 lb $acre^{-1}$ (plant)	N/A	N/A	*1.0:* • NOAEL >1000 mg kg^{-1} d^{-1} (≥ 90 d/human) *2.0:* • NOAEL 100-1000 mg kg^{-1} d^{-1} (≥ 90 d/human) *3.0:* • NOAEL 10–100 mg kg^{-1} d^{-1} (≥ 90 d/human) *4.0:* • NOAEL 1–100 mg kg^{-1} d^{-1} (≥ 90 d/ human) *5.0:* • NOAEL ≤1 mg kg^{-1} d^{-1} (≥ 90 d/ human)	*1.0:* • Low potential *2.0:* Moderate potential *3.0:* High potential

					5.0: • NOAEL $\leq$1 mg kg^{-1} d^{-1} ($\geq$ 90 d/ mammal) • L/NOAEL $\leq$10 mg kg^{-1} d^{-1} (invertebrate) • L/NOAEL $\leq$0.1 lb $acre^{-1}$ (plant)				
CARS GreenList™	Proprietary Proprietary								
PRIO[24] (chemicals are divided into two categories: phase-out and risk-reduction substances)	*Risk-reduction:* • LD_{50} <200 mg kg^{-1} • EU R25, R26, R27, R28, R39/ 26, R39/27 and R39/28	*Phase-out:* • CMR Cat. 1 and 2 • EU R45 or R49	*Phase-out:* • CMR Cat.1 and 2 • EU R46 *Risk-reduction:* • CMR Cat. 3 • EU R68	*Phase-out:* • CMR Cat.1 and 2 • EU R60 and R61	*Phase-out:* • NOEC <30 mg kg^{-1} *Risk-reduction:* • EU R48/23, 48/24 and R48/25	N/A	*Risk-reduction:* • EU R42 and R43	N/A	There are no generally accepted criteria for endocrine-disruptive substances. An assessment is made on a case-by-case basis
Quick Scan[25] (the lower the hazard number, the higher the hazard)	*G4:* • Not classified *G3:* • Harmful or possible risk of irreversible effects through inhalation (EU R20, R68/20), in contact with skin (EU R21, R68/ 21) or if swallowed (EU R22, R68/22) • Harmful: may cause lung damage if swallowed (EU R65) *G2:* • Toxic or danger of very serious irreversible effects through inhalation (EU R23, R39/23), in contact with skin (EU R24, R39/ 24) or if swallowed (EU R25, R39/25)	*C4:* • Not classified *C2:* • Limited evidence of carcinogenicity (EU R40 CMR Cat. 3) *C1:* • May cause cancer (EU R45, R49 CMR Cat. 1 and 2)	*M4:* • Not classified *M1:* • May cause heritable genetic damage (EU R46) • Limited evidence of a carcinogenic effect (EU R40)	*R4:* • Not classified *R2:* • Possible risk of impaired fertility (EU R62) • Possible risk of harm to the unborn child (EU R63) • May cause harm to breastfed babies (EU R63) *R1:* • May impair fertility (EU R60) • May cause harm to the unborn child (EU R61)	*G4:* • Not classified • Repeat exposure may cause skin dryness or cracking (EU R66) *G3:* • Harmful: danger of serious damage to health by prolonged exposure (EU R48/20, R48/ 21, R48/22) *G1:* • Toxic: danger of serious damage to health by prolonged exposure (EU R48/23, R48/ 24, R48/25)	*G4:* • Not classified • Irritating to eyes (EU R36), respiratory system (EU R37) or skin (EU R38) *G3:* • Risk of serious damage to eyes (EU R41) *G2:* • Causes severe burns (EU R34, R35)	*G4:* • Not classified *G2:* • May cause sensitization by skin contact (EU R43) • May cause sensitization by inhalation (EU R42)	N/A	*H4:* • Not classified *H2:* • TBD

Table 1.2 Continued.

	Human health endpoint criteria								
Method	*Acute mammalian toxicity*	*Carcinogenicity*	*Mutagenicity/ genotoxicity*	*Reproductive/develop-mental toxicity*	*Repeat dose toxicity (also referred to as systemic/organ effects)*	*Irritation/corrosion*	*Sensitization*	*Neurotoxicity*	*Endocrine disruption*
	G1: • Very toxic: danger of very serious irreversible effects through inhalation (EU R26, R39/26), in contact with skin (EU R27, R39/27) or if swallowed (EU R28, R39/28)								
Column Model[26]	*Low Risk:* • Substances/preparation which may cause lung damage if swallowed (EU R65) • Vapors causing drowsiness and dizziness *Medium Risk:* • Substances/preparation harmful to health (EU R20, R21, R22) • Non-toxic gases may cause suffocation by air displacement (*e.g.* nitrogen) *High Risk:* • Toxic substances/preparations (EU R23, R24, R25) • Substances/preparation which may liberate toxic gases when in contact with water or acids (EU R29, R31)	*High Risk:* • Carcinogenic substances of category 3 (Carc. Cat. 3, K3, EU R40) • Preparations containing carcinogenic or mutagenic substances of category 3 in concentrations $\geq 1\%$ *Very High Risk:* • Carcinogenic substances of category 1 or 2 (Carc. Cat. 1, K1, Carc. Cat. 2, K2, EU R45, R49) • Preparations containing carcinogenic substances of category 1 or 2 in concentrations $\geq 0.1\%$	*High Risk:* • Mutagenic substances of category 3 (Mut. Cat. 3, M3, EU R68) • Preparations containing carcinogenic or mutagenic substances of category 3 in concentrations $\geq 1\%$ *Very High Risk:* • Mutagenic substances of category 1 or 2 (Mut. Cat.. 1, M1, Mut. Cat. 2, M2, EU R46) • Preparations containing mutagenic substances of category 1 or 2 in concentrations $\geq 0.1\%$	*Medium Risk:* • Substances which may accumulate in breast milk (EU R64) • Substances toxic to reproduction of category 3 (Repr. Cat. 3, R_E3, R_F3, EU R62, R63) • Preparations containing substances of category 3 toxic to reproduction in concentrations $\geq 5\%$ (gases $\geq 1\%$) *High Risk:* • Substances toxic to reproduction of category 1 or 2 (Repr. Cat.1, R_E1, R_F1, Repr. Cat.2, R_E2, R_F2, EU R60, R61) • Preparations containing substances toxic to reproduction of category 1 or 3 in concentrations $\geq 0.5\%$ (gases $\geq 0.2\%$)	*Low Risk:* • Otherwise chronically affecting substances (no R-phrase, but nonetheless a hazardous substance) *High Risk:* • Substances which can accumulate in the human body (EU R33)	*Low Risk:* • Irritant substances/preparations (EU R36, R37, R38) • Skin-affecting substances/preparations (EU R66) • Skin effects when working in wet environment *Medium Risk:* • Substances/preparations causing burns (corrosive) (EU R34, pH ≤ 2 or ≥ 11.5) • Substances harmful to eyesight (EU R41) *High Risk:* • Substances/preparations causing severe burns (highly corrosive) (EU R35)	*High Risk:* • Skin-sensitizing substances (EU R42, Sh) • Substances sensitizing the respiratory tract (EU R42, Sa) • Preparations containing skin or respiratory tract-sensitizing substances in a concentration $\geq 1\%$ (gases $\geq 0.2\%$)	N/A	N/A

	Very High Risk: • Very toxic substances/preparation (EU R26, R27, R28) • Substances/preparation which may liberate very toxic gases when in contact with acids (EU R32)								
GHS Column Model[27]	*Low Risk:* • Substances/preparation which may cause lung damage if aspirated (H304) • Substances/mixtures with specific target organ toxicity (single exposure), Cat. 3: drowsiness, dizziness (H336) *Medium Risk:* • Substances/mixtures, Cat. 4 (H302, H312, H332) • Non-toxic gases may cause suffocation by air displacement (*e.g.* nitrogen) *High Risk:* • Acutely toxic substances/preparations, Cat. 3 (H301, H311, H331) • Substances/mixtures that may liberate toxic gases when in contact with water or acids (EUH029, EU H031)	*High Risk:* • Carcinogenic substances of category 2 (SGS: K3, H351) *Very High Risk:* • Carcinogenic substances of categories A1.1B (AGS: K1, K2, H350, H350i) • Carcinogenic activities or processes according to TRGS 906	*High Risk:* • Substances/mixtures mutagenic to germ cells, Cat. 2 (AGS: M3, H341) *Very High Risk:* • Substances/mixtures mutagenic to germ cells, Cat 1A or 1B (AGS: M1, M2, H340)	*Medium Risk:* • Substances/mixtures that can harm babies via their mothers' milk (H362) • Substances/mixtures toxic to reproduction of category 2 (AGS: R_E3, R_F3, H361, H361f, H361d, H361fd) *High Risk:* • Substances toxic to reproduction, Cat. 1A or 1B (AGS' RE1, R_F1, R_E2, R_F2, H360, H360F, H360D, H360Fd, H360Df)	*Low Risk:* • Substances/mixtures with specific target organ toxicity (single exposure), Cat. 3: irritation of the respiratory organs (H335) • Substances chronically harmful in other ways (no H-phrase, but still a hazardous substance) *Medium Risk:* • Substances/mixtures with specific target organ toxicity (single exposure), Cat. 2: organ damage (H371) • Substances/mixtures with specific target organ toxicity (repeated exposure), Cat. 2: organ damage (H373) *High Risk:* • Substances/mixtures with specific target organ toxicity (single exposure), Cat. 1: organ damage (H370)	*Low Risk:* • Irritant substances/preparations: skin or eye (H315, H319) • Skin-affecting substances/preparations (EU R66) • Skin effects when working in wet environment • Skin-damaging substances/mixtures (EUH066) *Medium Risk:* • Substances/mixtures with corrosive effect on respiratory organs (EUH071) • Substances corrosive to the skin (H314, pH ≤ 2 or ≥ 11.5) *High Risk:* • Substances/mixtures toxic in contact with eyes (EUH070) • Eye-damaging substances/mixtures (H318)	*High Risk:* • Skin-sensitizing substances/mixtures (H317, Sh) • Substances sensitizing the respiratory tract (H334, Sa)	N/A	N/A

Table 1.2 Continued.

Method	Human health endpoint criteria								
	Acute mammalian toxicity	*Carcinogenicity*	*Mutagenicity/ genotoxicity*	*Reproductive/develop-mental toxicity*	*Repeat dose toxicity (also referred to as systemic/organ effects)*	*Irritation/corrosion*	*Sensitization*	*Neurotoxicity*	*Endocrine disruption*
	Very High Risk: • Acutely toxic substances/mixtures, Cat. 1 and 2 (H300, H310, H330) • Substances/preparations which may liberate very toxic gases when in contact with acids (EUH032)				• Substances/mixtures with specific target organ toxicity (repeated exposure), Cat. 1: organ damage (H372)				
Evaluation Matrix[28]	*Green:* • Substance is not dangerous to human health • Substance has EU R65, R67 *Yellow:* • Substance may damage health • Substance has EU R20, R22, R23, R25, R29, R31, R39/23, R39/25 *Red:* • Substance may cause severe health damage • Substance has EU R26, R28, R32, R39/26, R39/28	*Yellow:* • Substance has EU R40 *Red:* • Carcinogen Category 1 or 2 • Substance has EU R45, R49	*Red:* • Mutagen Category 1 or 2 • Substance has EU R46	*Yellow:* • Substance has EU R62, R63 *Red:* • Reproductive Toxicant Category 1, 2 or 3 • Substance has EU R60, R61, R64	*Green:* • Substance has EU R66 *Yellow:* • Substance has EU R48/20, R48/22, R68, R68/20, R68/22 *Red:* • Substance has EU R48/23, R48/25	*Green:* • Substance has only light skin effects • Substance has EU R36, R37 *Yellow:* • Substance damages skin • Substance has EU R21, R24, R34, R38, R39/24, R41, R48/21, R48/24, R68/21 *Red:* • Substance may cause health damage if taken up *via* the skin • Substance has EU R35, R24, R27, R34, R39/27	*Yellow:* • Substance has EU R42 *Red:* • Substance has EU R43	N/A	*Green:* • There is evidence/tests show that the substance is not endocrine disrupting *Yellow:* • Substance is a suspected endocrine disruptor • Test results are ambiguous *Red:* • Substance is on the list of endocrine-disrupting substances

[a]These values are multiplied by an uncertainty score before a final composite score is calculated.
[b]For carcinogenicity, multiply the $1/ED_{10}$ value by a weight of evidence factor:
- 'known human carcinogen' = 3
- 'likely human carcinogen' = 2
- 'suggestive evidence of carcinogenicity' or 'conflicting data' = 1.

Use the corrected value to score the chemical.

Table 1.3 Comparison of ecotoxicity, environmental fate and physical properties criteria among CAA methods.

	Ecotoxicity and environmental fate endpoint criteria						
Method	*Acute aquatic toxicity*	*Chronic aquatic toxicity*	*Persistence: half-life (d)*	*Bioaccumulation*	*Eutrophication*	*Explosivity*	*Flammability*
DfE Alternatives Assessment Criteria[12]	*Low:* • LC_{50}/EC_{50} >100 mg L^{-1} *Moderate:* • LC_{50}/EC_{50} 10–100 mg L^{-1} *High:* • LC_{50}/EC_{50} 1–10 mg L^{-1} *Very High:* • LC_{50}/EC_{50} <1 mg L^{-1}	*Low:* • LOEC >10 mg L^{-1} *Moderate:* • LOEC 1–10 mg L^{-1} *High:* • LOEC 0.1–1 mg L^{-1} *Very High:* • LOEC <0.1 mg L^{-1}	*Very High:* • Passes Ready Biodegradability test with 10 day window[b] *Low:* • Half-life in water, soil or sediment <16 d OR passes Ready Biodegradability test not including the 10 day window[b] *Moderate:* • Half-life in water, soil or sediment 16–60 d *High:* • Half-life in water, soil or sediment 60–180 d *Very High:* • Half-life in water, soil or sediment >180 d or recalcitrant	*Very Low:* • BCF/BAF <100 *Low:* • BCF/BAF 100–1000 *High:* • BCF/BAF 1000–100 000 *Very High:* • BCF/BAF >100 000	*Low:* • Total phosphorus in cleaning product limited to 0.5 wt% • Inorganic phosphate is not present	N/A	N/A
GreenScreen version 1.2[4]	*Low:* • $LC_{50}/EC_{50}/IC_{50}$ >100 mg L^{-1} *Moderate:* • $LC_{50}/EC_{50}/IC_{50}$ 1–100 mg L^{-1} or	*Low:* • NOEC >10 mg L^{-1} *Moderate:* • NOEC 0.1–10 mg L^{-1} or • GHS Category 2, 3 or 4	*Low:* • Half-life in soil, sediment <30 d or • Half-life in water <7 d or • Ready biodegradability	*Low:* • BCF/BAF <500 or • Absent such data, log K_{ow} <4 *Moderate:* • BCF/BAF 500 to 1000 or	N/A	*Low:* • No basis for concern identified *Moderate:* • GHS Category: Divisions 1.4, 1.5	*Low:* • No basis for concern identified *Moderate:* • GHS Category 2 – Flammable Gases or

Table 1.3 Continued.

	Ecotoxicity and environmental fate endpoint criteria						
Method	*Acute aquatic toxicity*	*Chronic aquatic toxicity*	*Persistence: half-life (d)*	*Bioaccumulation*	*Eutrophication*	*Explosivity*	*Flammability*
	• GHS Category 2 or 3 *High:* • $LC_{50}/EC_{50}/IC_{50}$ <1 mg L^{-1} or • GHS Category 1	*High:* • NOEC <0.1 mg L^{-1} or • GHS Category 1	*Moderate:* • Half-life in soil, sediment 30–60 d or • Half-life in water 7–40 d *High:* • Half-life in soil, sediment >60–180 d or • Half-life in water >40–60 d or • Potential for long-range environmental transport *Very High:* • Half-life in soil or sediment >180 d or • Half-life in water >60 d	• Absent such data, log K_{ow} >4–4.5 or • Suggestive evidence of bioaccumulation in humans or wildlife *High:* • BCF/BAF >1000–5000 or • Absent such data, log K_{ow} >4.5–5 or • Weight of evidence demonstrates bioaccumulation in humans or wildlife *Very High:* • BCF/BAF >5000 or • Absent such data, log K_{ow} >5		*High:* • GHS Category: Unstable Explosives or Division 1.1, 1.2 or 1.3	• GHS Category 2 – Flammable Aerosols or • GHS Category 3 or 4 – Flammable Liquids *High:* • GHS Category 1 – Flammable Gases or • GHS Category 1 – Flammable Aerosols or • GHS Category1 or 2 – Flammable Liquids
C2C version 3.0[19] (Includes only Ingredient Characterization Criteria)	*Green:* • LC_{50} >100 mg/L (96 hr) (fish) • $L(E)C_{50}$ >100 mg/L (48 hr) (daphnia) • $L(E)C_{50}$ >100 mg/L (72/96 hr) (algae) *Yellow:* • LC_{50} = 10–100 mg/L (96 hr) (fish) • $L(E)C_{50}$ = 10–100 mg/L (48 hr) (daphnia) • $L(E)C_{50}$ = 10–100 mg/L (72/96 hr) (algae) *Red:* • LC_{50} <10 mg/L (96 hr) (fish)	*Green:* • NOEC >10 mg/L *Yellow:* • NOEC = 1–10 mg/L *Red:* • NOEC <1 mg/L	*Green:* • Half-life in water, soil, sediment <30/90 days; • Readily biodegradable (based on OECD tests) *Yellow:* • Half-life in air, soil, sediment = 30/90–60/180 days; • Ultimately biodegradable *Red:* • Half-life in water, soil >60/180 days; • Not readily biodegradable	*Green:* • BCF <100 *Yellow:* • BCF = 100–500 *Red:* • BCF >500	N/A	N/A	N/A

	• $L(E)C_{50} < 10$ mg/L (48 hr) (daphnia) • $L(E)C_{50} < 10$ mg/L (72/96 hr) (algae)						
P2OASys[20] (levels of concern are characterized as numerical hazard scores; the smaller the number, the less hazardous)	*2.00:* • $LC_{50} > 1000$ mg L^{-1} (aquatic) • $EC_{50} > 100$ mg L^{-1} (plant) *4.00:* • LC_{50} 50–1000 mg L^{-1} (aquatic) • EC_{50} 10–100 mg L^{-1} (plant) *6.00:* • LC_{50} 1–50 mg L^{-1} (aquatic) • EC_{50} 1–10 mg L^{-1} (plant) *8.00:* • LC_{50} 0.1–1 mg L^{-1} (aquatic) • EC_{50} 0.1–1 mg L^{-1} (plant) *10.00:* • $LC_{50} < 0.1$ mg L^{-1} (aquatic) • $EC_{50} < 0.1$ mg L^{-1} (plant)	*2.00:* • NOAEC > 0.2 mg L^{-1} (fish) *4.00:* • NOAEC 0.02 mg L^{-1} (fish) *6.00:* • NOAEC 0.002 mg L^{-1} (fish) *8.00:* • NOAEC 0.0002 mg L^{-1} (fish) *10.00:* • NOAEC < 0.00002 mg L^{-1} (fish)	*2.00:* • L • BOD/hydrolysis half-life 4 d *4.00:* • L/M • BOD/hydrolysis half-life 10 d *6.00:* • M • BOD/hydrolysis half-life 100 d *8.00:* • M/H • BOD/hydrolysis half-life 500 d *10.00:* • H • BOD/hydrolysis half-life > 500 d	*2.00:* • BCF < 10 • Log $K_{ow} < 1$ *4.00:* • BCF 100 • Log K_{ow} 2 *6.00:* • BCF 200 • Log K_{ow} 4 *8.00:* • BCF 1000 • Log K_{ow} 6 *10.00:* • BCF > 1000 • Log $K_{ow} > 6$	N/A	*2.00:* • 0.0 *4.00:* • 1.0 *6.00:* • 2.0 *8.00:* • 3.0 *10.00:* • 4.0	*2.00:* • 0.0 *4.00:* • 1.0 *6.00:* • 2.0 *8.00:* • 3.0 *10.00:* • 4.0
SCRAM[a21] (levels of concern are characterized as numerical hazard scores; the smaller the number, the less hazardous)	*1.0:* • $E/LC_{50} > 1000$ mg L^{-1} (aquatic animals) • $E/LC_{50} > 1000$ mg L^{-1} (plant) *2.0:* • E/LC_{50} 100–1000 mg L^{-1} (aquatic animals)	*1.0:* • NOEC > 100 mg L^{-1} (fish/amph.) • NOEC > 5000 mg L^{-1} (invertebrate) • NOEC > 100 mg L^{-1} (plant) *2.0:* • NOEC 10–100 mg L^{-1} (fish/amph.)	*1.0:* • Half-life < 4 d (biota, air, water, soil, sediment) *2.0:* • Half-life 4–20 d (biota, air, water, soil, sediment)	*1.0:* • BCF/BAF ≤ 100 *2.0:* • BCF/BAF 100–1000 *3.0:* • BCF/BAF 1000–10 000	N/A	N/A	N/A

Table 1.3 Continued.

Method	*Ecotoxicity and environmental fate endpoint criteria*						
	Acute aquatic toxicity	*Chronic aquatic toxicity*	*Persistence: half-life (d)*	*Bioaccumulation*	*Eutrophication*	*Explosivity*	*Flammability*
	• E/LC_{50} 100–1000 mg L^{-1} (plant) *3.0:* • E/LC_{50} 10–100 mg L^{-1} (aquatic animals) • E/LC_{50} 10–100 mg L^{-1} (plant) *4.0:* • E/LC_{50} 1–10 mg L^{-1} (aquatic animals) • E/LC_{50} 1–10 mg L^{-1} (plant) *5.0:* • $E/LC_{50} \leq 1$ mg L^{-1} (aquatic animals) • $E/LC_{50} \leq 1$ mg L^{-1} (plant)	• NOEC 1000–5000 mg L^{-1} (invertebrate) • NOEC 10–100 mg L^{-1} (plant) *3.0:* • NOEC 1–10 mg L^{-1} (fish/amph.) • NOEC 100–1000 mg L^{-1} (invertebrate) • NOEC 1–10 mg L^{-1} (plant) *4.0:* • NOEC 0.1–1 mg L^{-1} (fish/amph.) • NOEC 10–100 mg L^{-1} (invertebrate) • NOEC 0.1–1 mg L^{-1} (plant) *5.0:* • NOEC ≤ 0.1 mg L^{-1} (fish/amph.) • NOEC ≤ 10 mg L^{-1} (invertebrate) • NOEC ≤ 0.1 mg L^{-1} (plant)	*3.0:* • Half-life 20–50 d (biota, air, water, soil, sediment) *4.0:* • Half-life 50–100 d (biota, air, water, soil, sediment) *5.0:* • Half-life >100 d (biota, air, water, soil, sediment)	*4.0:* • BCF/BAF 10 000–100 00 *5.0:* • BCF/BAF $>100\,000$			
CARS GreenList™	Proprietary Proprietary						
PRIO (chemicals are divided into two categories: phase-out and risk-reduction substances)[24]	*Risk-reduction:* • $E/LC_{50} < 0.1$ mg L^{-1}	*Phase-out:* • NOEC < 0.01 mg L^{-1}	*Phase-out:* • Half-life in seawater >60 d • Half-life in freshwater >40 d • Half-life in marine sediment >180 d	*Phase-out:* • BCF >2000 *Risk-reduction:* • Log $K_{ow} \geq 4.5$	N/A	N/A	N/A

			• Half-life in freshwater sediment >120d • Half-life in soil >120 d *Risk-reduction:* • Substances that are not readily or inherently biodegradable				
Quick Scan[25] (the lower the hazard number, the higher the hazard)	*T4:* • LC_{50} >10 mg L^{-1} *T3:* • LC_{50} ≤10 mg L^{-1} *T2:* • LC_{50} ≤1 mg L^{-1} *T1:* • LC_{50} ≤0.1 mg L^{-1}	*T4:* • NOEC >1 mg L^{-1} *T3:* • NOEC ≤1 mg L^{-1} *T2:* • NOEC ≤0.1 mg L^{-1} *T1:* • NOEC 0.01 mg L^{-1}	*P4:* • Readily biodegradable *P3:* • Inherently biodegradable; adaptive or incomplete *P2:* • Inherently biodegradable; slow *P1:* • Not inherently biodegradable; no fast abiotic degradation	*B4:* • BCF <100 *B3:* • BCF ≥100 *B2:* • BCF ≥500 B1b: • BCF ≥2000 B1a: • BCF ≥5000	N/A	N/A	N/A
Column Model[26]	*Low Risk:* • Not water-polluting substances/preparations (NWG, formerly WGK 0) *Moderate Risk:* • Substances/preparations of the German water pollution class WGK 1	*Low Risk:* • Not water-polluting substances/preparations (NWG, formerly WGK 0) *Moderate Risk:* • Substances/preparations of the German water pollution class WGK 1	N/A	N/A	N/A	*Very High Risk:* • Explosive substances/preparations (EU R2, R3) • Oxidizing substances/preparations (EU R7, R8, R9) • Substances/preparations with specific properties (EU R1, R4, R5, R6, R7, R14, R16, R18, R19, R30, R44)	*Low Risk:* • Inflammable or hardly flammable substances/preparations (for liquids flashpoint >100 °C) *Moderate Risk:* • Hardly flammable substance/preparations (flashpoint 55–100 °C)

Table 1.3 Continued.

Method	*Ecotoxicity and environmental fate endpoint criteria*						
	Acute aquatic toxicity	*Chronic aquatic toxicity*	*Persistence: half-life (d)*	*Bioaccumulation*	*Eutrophication*	*Explosivity*	*Flammability*
	High Risk: • Substances/preparations without warning symbols N, but with hazards indications EU R52, R3 • Substances/preparations of the German water pollution class WGK 2 *Very High Risk:* • Substances/preparations with the warning symbol N and hazards indications EU R50, R51, R53, R54, R55, R56, R57, R58, R59 • Substances/preparations of the German water pollution class WGK 3	*High Risk:* • Substances/preparations without warning symbols N, but with hazards indications EU R52, R3 • Substances/preparations of the German water pollution class WGK 2 *Very High Risk:* • Substances/preparations with the warning symbol N and hazards indications EU R50, R51, R53, R54, R55, R56, R57, R58, R59 • Substances/preparations of the German water pollution class WGK 3					*High Risk:* • Flammable substances/preparations (EU R10) *Very High Risk:* • Extremely flammable gases and liquids (EU R12) • Spontaneously flammable substances/preparations (EU R17) • Highly flammable substances/preparations (EU R11) Substances/preparations liberating extremely flammable gases when in contact with water (EU R15)
GHS Column Model[27]	*Low Risk:* • Substances/mixtures of the German water pollution class WGK 1 • Substances/mixtures chronically hazardous to the aquatic environment, Cat. 4 (H413)	*Low Risk:* • Substances/mixtures of the German water pollution class WGK 1 • Substances/mixtures chronically hazardous to the aquatic environment, Cat. 4 (H413)	N/A	N/A	N/A	*Low Risk:* • Self-reactive substances/mixtures, Type G (no H-phrase) • Organic peroxides, Type G (no H-phrase) *Moderate Risk:* • Self-reactive substances/mixtures,	*Low Risk:* • Not readily flammable substances/mixtures(flashpoint >60–$100\ ^{\circ}C$, no H-phrase) *Moderate Risk:* • Flammable aerosols, Cat. 2 (H223) • Flammable liquids, Cat. 3 (H226)

Moderate Risk:
- Substances/preparations of the German water pollution class WGK 2
- Substances/mixtures chronically hazardous to the aquatic environment, Cat. 3 (H412)

High Risk:
- Substances/mixtures chronically hazardous to the aquatic environment, Cat. 1 (H410) and Cat. 2 (H411)
- Substances hazardous to the ozone layer (H420)

Very High Risk:
- Substances/mixtures acutely hazardous to the aquatic environment, Cat. 1 (H400)
- Substances/preparations of the German water pollution class WGK 3

Moderate Risk:
- Substances/preparations of the German water pollution class WGK 2
- Substances/mixtures chronically hazardous to the aquatic environment, Cat. 3 (H412)

High Risk:
- Substances/mixtures chronically hazardous to the aquatic environment, Cat. 1 (H410) and Cat. 2 (H411)

Very High Risk:
- Substances/mixtures acutely hazardous to the aquatic environment, Cat. 1 (H400)
- Substances/preparations of the German water pollution class WGK 3

Types E and F (H242)
- Organic peroxides, Types E and F (H242)
- Self-heating substances/mixtures, Cat. 2 (H252)
- Oxidizing liquids or solids, Cat. 3 (H272)
- Gases under pressure (H280, H281)
- Substances/mixtures corrosive to metals (H290)

High Risk:
- Self-reactive substances/mixtures, Types C and D (H242)
- Organic peroxides Types C and D (H242)
- Self-heating substances/mixtures Cat. 1 (H251)
- Oxidizing gases, Cat. 1 (H270)
- Oxidizing liquids or solids, Cat. 2 (H272)
- Substances/mixtures with certain properties (EUH001, EUH006, EUH014, EUH018, EUH019, EUH044)

Very High Risk:
- Unstable explosive substances/mixtures (H200)
- Explosive substances/mixtures/products, divisions 1.1 (H201), 1.2 (H202), 1.3
- Flammable solids, Cat. 2 (H228) Substances/mixtures which in contact with water emit flammable gases, Cat. 3 (H261)

High Risk:
- Flammable aerosols, Cat. 1 (H222)
- Flammable liquids, Cat. 2 (H225)
- Flammable solids, Cat. 1 (H228)
- Substances/mixtures which in contact with water emit flammable gases, Cat. 2 (H261)

Very High Risk:
- Flammable gases, Cat. 1 (H220) and Cat. 2 (H221)
- Flammable liquids, Cat. 1 (H224)
- Substances/mixtures which in contact with water emit flammable gases, Cat. 1 (H260)

Table 1.3 Continued.

	Ecotoxicity and environmental fate endpoint criteria						
Method	*Acute aquatic toxicity*	*Chronic aquatic toxicity*	*Persistence: half-life (d)*	*Bioaccumulation*	*Eutrophication*	*Explosivity*	*Flammability*
						(H203), 1.4 (H204), 1.5 (H205) and 1.6 (without H-phrase) • Self-reactive substances/mixtures, Types A (H240) and B (H241) • Organic peroxides, Types A (H240) and B (H241) • Pyrophoric liquids or solids, Cat. 1 (H250) • Oxidizing liquids or solids, Cat. 1 (H271)	
Evaluation Matrix[28]	*Green:* • Low aquatic toxicity *Yellow:* • LC_{50} <0.1 mg L^{-1} • Substance has EU R50, R51, R52	*Green:* • Low aquatic toxicity *Yellow:* • Substance has EU R50, R51, R52 *Red:* • NOEC <0.01 mg L^{-1}	*Green:* • There is evidence that the substance is not a PBT or vPvB • Substance is not classified as dangerous to the environment *Yellow:* • Based on available information, it cannot be excluded that the substance is a PBT/vPvB	*Green:* • There is evidence that the substance is not a PBT or vPvB • Substance is not classified as dangerous to the environment *Yellow:* • Based on available information, it cannot be excluded that the substance is a PBT/vPvB	N/A	*Green:* • Substance has no EU R-phrase *Red:* • Substance is explosive, oxidizing	*Green:* • Substance has no EU R-phrase *Yellow:* • Substance has EU R10, R11, R15 *Red:* • Substance is very flammable or pyrophoric • Substance has EU R7, R8, R9

	Red: • Substance fulfills the REACH PBT criteria: half-life in seawater >40 d half-life in freshwater >40 d half-life in marine sediment >180 d half-life in freshwater sediment >120 d half-life in soil >120 d • Substance fulfills the REACH vPvB criteria: half-life in seawater >60 d half-life in freshwater >60 d half-life in marine sediment >180 d half-life in freshwater sediment >180 d half-life in soil >180 d	*Red:* • Substance fulfills the REACH PBT criteria: BCF >2000 • Substance fulfills the REACH vPvB criteria: BCF >5000

[a]These values are multiplied by an uncertainty score before a final composite score is calculated.
[b]No degradation products of concern.

CAA paradigm evaluates human health and environmental hazard criteria, and it is important to remember that these criteria are dynamic and change over time.

1.4.1 US EPA's Design for the Environment (DfE)

The US EPA's DfE program works with industry, environmental groups and academia to reduce risk to human health and the environment.[6] The US EPA DfE Alternative Assessments program employs a variety of design approaches to reduce the overall human health and environmental impact of a product or process. DfE's Alternatives Assessment framework is a hazard-based assessment tool for evaluating and differentiating among chemicals based on their concern for human health and environmental hazard, in the process promoting informed substitution.[10,11] DfE's Alternatives Assessments follow six broad steps, as illustrated in Figure 1.3.[10]

As part of a DfE Alternatives Assessment, chemicals are evaluated for numerous health effect and environmental endpoints, including carcinogenicity, mutagenicity, reproductive and developmental toxicity, acute and repeat dose toxicity, toxicity to aquatic organisms and environmental fate.[11] For most hazard endpoints, DfE criteria define 'High,' 'Moderate,' and 'Low' concern. Authoritative sources [the United Nation's Globally Harmonized System (GHS) for the Classification and Labeling of Hazard Substances and US EPA programs] are the basis for these distinctions. Both experimental and modeled data are used in assigning a hazard designation of High, Moderate or Low. In the absence of experimental data, measured data from a suitable analog are preferred over estimated data. Approved modeling tools include EPI Suite, ECOSAR, OncoLogic and the Endocrine Disruptor Screening Program to predict possible hazards.

DfE CAAs do not specify a favored alternative, but do promote informed substitution when combined with cost, performance and national and international regulatory initiatives and requirements. DfE's Alternatives Assessments are used by the Office of Pollution Prevention and Toxics (OPPT) in EPA's Office of Chemical Safety and Pollution Prevention (OCSPP) to seek safer alternatives. Currently, Chemical Action Plans are the primary source for identifying chemical candidates for risk management and specifying actions. EPA proposes to further evaluate the chemicals and address risks. DfE has applied their alternatives assessment paradigm to flame retardants in furniture and printed circuit boards, along with identifying alternatives to chemicals for which there are Agency Action Plans, including nonylphenol ethoxylate surfactants, bisphenol A alternatives in thermal and paper and alternatives to the flame retardants decabromodiphenyl ether (decaBDE) and hexabromocyclododecane.[12]

1.4.2 CPA's GreenScreen™

The GreenScreen™ for Safer Chemicals (version 1.2) is a quantitative chemical screening method designed to help manufacturers identify chemicals of

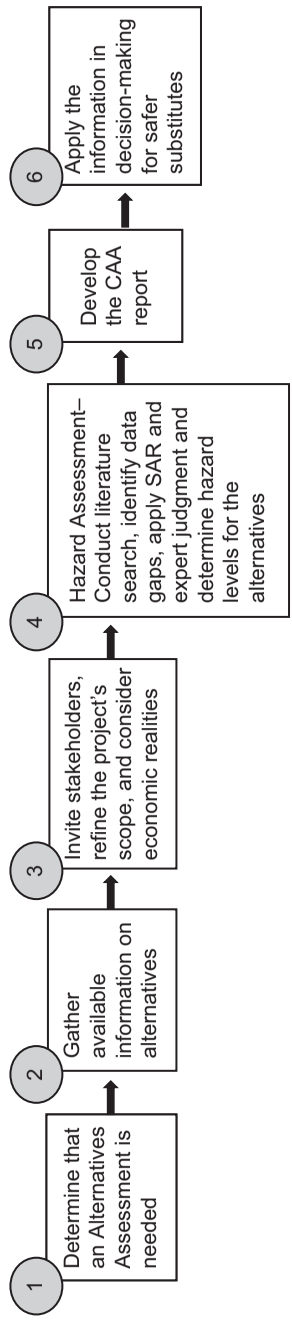

Figure 1.3 US EPA's six broad steps in conducting a DfE alternatives assessment.[10]

concern and inherently less hazardous alternatives to benefit humans and the environment.[13] The structure of the GreenScreen™ method builds from the alternatives assessment approach developed by the US EPA's DfE CAA program.[11] Similarly to a DfE CAA, the GreenScreen™ was developed as a comparative hazard assessment method that assists in selecting chemicals that are inherently safer for humans and the environment. Both GreenScreen™ DfEs are based on the principles of Green Chemistry[14] and focus on managing chemical risk by reducing hazard rather than controlling exposure to potentially toxic chemicals. As part of a GreenScreen™ evaluation process, each ingredient or chemical is assigned a hazard concern level. Individual hazards are evaluated for 18 hazard endpoints (such as carcinogenicity, reproductive toxicity, neurotoxicity aquatic toxicity, persistence and bioaccumulation) and then a level of concern of High, Moderate or Low is assigned for each endpoint for each chemical. Two hazards, persistence and bioaccumulation, have an additional level of concern of Very High to reflect the growing international consensus in defining very persistent and very bioaccumulative (vPvB) chemicals. The threshold values for each hazard endpoint are based on those established by the EPA's DfE program and also the GHS where available. After a chemical has been evaluated against criteria for each hazard endpoint, the results are collectively scored to one of the following GreenScreen™ Benchmark scores:[16,17]

- Benchmark 1: Avoid (Chemical of High Concern).
- Benchmark 2: Use (But Search for Safer Substitutes).
- Benchmark 3: Use (But Still Opportunity for Improvement).
- Benchmark 4: Prefer (Safer Chemical).
- Benchmark 'U': Undetermined (Insufficient Data).

To progress from a lower GreenScreen™ Benchmark score (more hazardous) to a higher (less hazardous) GreenScreen™ Benchmark score, a chemical and its feasible and relevant transformation products must pass all criteria specified under the lower Benchmark. The criteria become increasingly more stringent for environmental and human health and safety and also for data completeness for each Benchmark. Depending on the type and number of data gaps, a chemical may either receive either a downgraded Benchmark score or be assigned Benchmark 'U' to indicate insufficient data. The criteria for Benchmark One align with those that governments in Europe, Canada and the USA use to characterize substances of very high concern.

Figure 1.2 identifies the hazard-based scores for the plasticizer di(2-ethylhexyl) terephthalate (DEHT), which result in a GreenScreen™ Benchmark score of 3: 'Use (But Still Opportunity for Improvement).'

CPA's GreenScreen™ (version 1.0) was initially developed to assess only organic chemicals.[18] Because some inorganic chemicals are recalcitrant and others are persistent as stable moieties, hazard criteria for persistence are not always relevant to inorganics. Persistence alone does not indicate that a

chemical is hazardous. Chemicals that are persistent as well as bioaccumulative and toxic are of high concern, as their concentration in the environment increases over time, allowing for more opportunity to exert a toxic effect on human health or aquatic or terrestrial organisms. In 2011, GreenScreen™ (version 1.2) was expanded to address hazards from inorganics such as mineral oxides to allow for comparison of inorganic chemicals used as flame retardants.[17] Under GreenScreen™ version 1.2 criteria, a persistent inorganic chemical with a Low hazard rating for human- and eco-toxicity across all hazard endpoints and a Low hazard rating for bioaccumulation will not be considered problematic. Inorganic chemicals that are only persistent may reach Benchmark 4 [the best score: Prefer (Safer Chemical)]. The GreenScreen™ is not intended to address all critical elements of sustainability. It does not consider social equity or important life-cycle impacts such as energy quantity and quality like other alternatives assessments. A GreenScreen™ assessment does not necessarily include reagents used to synthesize a chemical. Rather, the GreenScreen™ focuses on hazard assessment of chemicals from their point of generation. The GreenScreen™ is a CHA that can be used in a modular way with any other desired components of a full CAA.

1.4.3 Cradle to Cradle® (C2C)

The Cradle to Cradle® method (C2C) began as a proprietary product certification program that incorporates CHA and can be used for CAA. It is currently being maintained and administered by the Cradle to Cradle Products Innovation Institute (C2CPII)[19] and is moving toward greater transparency. C2C uses the metabolism of Nature as a model for human industry – products or materials that cannot be metabolized by the natural world should never enter it. Rather, they should be considered as 'technical nutrients' and designed to flow in technical cycles. Evaluation criteria are grouped into the following categories: 'Material Health,' 'Material Reutilization,' 'Renewable Energy and Carbon Management,' 'Water' and 'Social Fairness.' Materials and products are certified as Basic, Bronze, Silver, Gold or Platinum, based on how the criteria are met. For the Material Health evaluation, all ingredients are 'scored' based on their impact on human and environmental health. Ingredients are evaluated against all common endpoints mentioned above and scored as Green (Little to No Risk), Yellow (Low to Moderate Risk), Red (High Risk) or Grey (Incomplete Data). The C2C paradigm goes further to evaluate a product based on Material Reutilization. The percentage of the product that is considered 'Recyclable or Compostable' is combined with the percentage of the product that is manufactured from 'Recycled or Renewable Content' to calculate a Nutrient Reutilization Score.

In addition to the materials used, the amount of energy and water (both quantity and quality) required for product manufacture and assembly is

evaluated for certification. The ultimate goal of C2C design is to have all energy inputs come from 'current solar income' (*i.e.* geothermal, wind, biomass, hydro and photovoltaic energy sources). For Gold certification, at least 50% of purchased electricity is renewably sourced or offset with renewable energy projects, and 50% of direct onsite emissions are offset. For Silver, Gold and Platinum certification levels, the applicant must create or adopt a set of principles or guidelines to illustrate the manufacturing facility's strategies for protecting and preserving the quality and supply of water resources. An audit of the facility is required for Bronze and higher certification. For Gold certification, the applicant must demonstrate that the facility has optimized all product-related process chemicals in effluent. Finally, the organization must adopt and make public one or more statements regarding their social and ethical performance goals such as fair labor practices, corporate and personal ethics, customer service and local community outreach. As detailed in the Cradle to Cradle Certified^{CM} Products Standard, requirements for the Social Fairness category increase relative to the specific certification level.[19]

1.4.4 TURI's Pollution Prevention Options Analysis System (P2OASys)

In 1997, the Toxics Use Reduction Institute (TURI) at the University of Massachusetts developed the Pollution Prevention Options Assessment System (P2OASys) tool to help companies determine the potential environmental, worker and public health impacts of alternative technologies aimed at reducing toxics use. The P2OASys tool is a downloadable software package that assists industry in two ways: it systematically examines the potential environmental and worker impacts of toxic use reduction options in a comprehensive manner, examining the total impacts of process changes, rather than simply those of chemical change, and compares toxic use reduction options with the company's current process based on quantitative and qualitative factors.[20] The user inputs both quantitative and qualitative data on a chemical's toxicity, ecological effects and physical properties. Data needed for P2OASys are available through vendors, existing databases or the Toxics Use Reduction Institute. In addition, data for up to three alternatives can be entered as a comparison with the original material. Embedded formulae in the P2OASys program can provide a numerical hazard score for each endpoint for the ingredient(s) in question. For example, if a chemical has an oral LD_{50} of 5000 mg kg^{-1}, it may be assigned a standardized hazard score of 2; the higher the score, the greater is the hazard. Endpoints include human effects, aquatic hazards, persistence/bioaccumulation, atmospheric hazard, disposal hazard, energy/resource use and exposure potential.

1.4.5 The Chemical Scoring and Ranking Assessment Model (SCRAM)

The Chemical Scoring and Ranking Assessment Model (SCRAM) was developed to rank or score chemicals based on persistence, bioaccumulation and toxicity.[21] The program was initially developed for use in the Great Lakes area but is not site specific. This program consists of a simple spreadsheet system that allows the assessor to calculate an index (scores range from 1 to 5) based on the potential exposure and toxicity of chemicals. In addition, unlike other assessment tools, SCRAM addresses the uncertainty of these rankings due to a lack of data. Instead of ignoring a chemical with a large data gap, SCRAM will assign an uncertainty score that, along with its persistence, bioaccumulation and toxicity scores, is used to rank the chemical relative to others in question. In-house libraries and on-line databases are searched for data describing persistence, bioaccumulation and toxicity of a chemical in question. A minimum of one data point is required for bioaccumulation and is scored on the basis of bioaccumulation factors (BAF), bioconcentration factors (BCF) or the octanol/water partition coefficients (K_{ow}). A minimum of one data point is required for scoring a chemical in the persistence category. Persistence is scored based on half-lives in five environmental compartments: biota, air, soil, sediment and water. Measured data take priority over estimated data; however, multi-media models such as the US EPA's EpiSuite and ECOSAR are acceptable when measured data are not available. Uncertainty points are assigned based on the source of the data, whether they are measured or estimated or surrogate data. The final bioaccumulation chemical score is multiplied by the final persistence score and the result is then multiplied by a weighing factor of 1.4. The environmental fate of a chemical is emphasized in SCRAM because of the potential for a chemical deemed not toxic during laboratory studies later potentially to be found to cause toxicity through other mechanisms. A minimum of one data point in at least one toxicity category is required. Acute toxicity scores are composed of two components, acute aquatic and acute terrestrial toxicity, and are based on E/LC_{50} values for aquatic organisms and E/LD_{50} values for terrestrial organisms. Subchronic/chronic scores are based on LO(A)ELs and NO(A)ELs for aquatic and terrestrial organisms in addition to human toxicity values. The subchronic/chronic scores represent repeat dose toxicity, general organ toxicity and also carcinogenicity, mutagenicity, neurotoxicity, immunotoxicity, reproductive and developmental toxicity and endocrine disruption. The most conservative (or lowest) acute and subchronic/chronic data are used when scoring for toxicity. Both the acute toxicity score and the subchronic/chronic toxicity scores are added to uncertainty scores before being summed with the bioaccumulation and persistence scores for a final chemical score. The final chemical score is summed together with a final uncertainty score to give a final composite score that can be compared with

those of other chemicals. The relative rankings of chemicals can aid scientists in determining which chemicals need more regulation and/or additional research.

1.4.6 Chemicals Assessment and Ranking System (CARS)

The Chemicals Assessment and Ranking System (CARS) is a decision support tool developed by the Zero Waste Alliance (ZWA) that provides a process for inventorying, assessing and ranking chemicals.[22] Similarly to the SCRAM paradigm, chemicals are ranked according to their potential impacts on human health and safety, ecological health and ecosystem-wide impacts. CARS has been used in support of environmental management systems such as those defined by ISO 14000. The first step is an inventory of chemicals used within an organization based on Material Safety Data Sheets (MSDS). The next step is to screen those chemicals against the CARS database to identify any suspected or potential carcinogens, teratogens, persistence bioaccumulative toxins, global warming gases, ozone-depleting chemicals and more. The CARS database utilizes hazard lists from sources such as the US EPA, the American Conference of Governmental Industrial Hygienists (ACGIH), the National Toxicology Program (NTP) and the International Agency for Research on Cancer (IARC). A Prioritization Criteria Worksheet summarizes the results of the screen and provides a summary of chemicals of concern and the products that contain them. Products are then ranked based on their frequency of use, potential human health and safety impacts, ecological and global impacts and life-cycle costs associated with storage, disposal, training and management. CARS is used to prioritize chemical products for replacement. Specific methods and criteria used in CARS to rank chemicals are not publicly accessible.

1.4.7 SC Johnson & Son's Greenlist™

In 2001, the US company SC Johnson & Son (SCJ) developed a system known as Greenlist™ to classify ingredients found in SCJ products based on each chemical's impact on the environment and human health.[23] So far, SCJ has used Greenlist™ to rate over 95% of their products, and although the Greenlist™ criteria can be obtained from SCJ, the list of chemicals evaluated under Greenlist™ is not made public. The Greenlist™ process has been validated by the UK's Forum for the Future and the US EPA. Each potential ingredient receives a rating from 0 (Restricted Use) to 3 (Best). The company strives to continually improve its overall Greenlist™ ratings. According to SCJ, 27% of ingredients used in its products are classified as 'best' ingredients.[23] Greenlist™ chemical ratings are confidential, so individual chemical and product scores are not available. SCJ licenses the overall GreenList™ process to other companies free of charge,[23] but the total number of

companies who have adopted GreenList™ and tailored this process to their own needs is unknown.

1.4.8 PRIO

PRIO is an automated, web-based tool intended to reduce the risks to human health and the environment from chemicals.[24] Developed by the Swedish Chemicals Agency, this model recommends phasing out high-priority chemicals to achieve a non-toxic environment. The tool is not intended to rate or score chemicals based on their human health and environmental hazards, rather it is used to identify the hazardous properties of a chemical. PRIO applies only to chemicals of high concern and categorizes them into two groups: phase-out substances and priority risk-reduction substances. Phase-out substances are those that are of such high concern that they should not be used, such as PBT (Persistent, Bioaccumulative and Toxic) chemicals. Priority risk-reduction substances are those to which special attention should be paid. The criteria used by PRIO have been based on REACH legislation and EU risk phrases. The only criteria against which phase-out substances are evaluated are carcinogenicity, mutagenicity, reproductive toxicity and endocrine disruption. In addition to these, compounds are also assessed as to whether or not they contain any hazardous metals (mercury, cadmium and lead). Priority risk-reduction substances are evaluated for acute and chronic toxicity, sensitization and mutagenicity. Both categories are evaluated for their environmental hazards: persistence and bioaccumulation. Phase-out substances are also assessed for their ozone depletion properties.

1.4.9 The Quick Scan

The Quick Scan method was developed by the Dutch Ministry of Housing, Spatial Planning and the Environment to implement a chemicals substitution policy for chemicals with high hazards.[25] The Quick Scan attempts to develop chemical profiles based on hazard data, classify chemicals into categories of concern and assist industry in taking action for chemicals of high concern. The endpoints assessed during a Quick Scan include persistence (P), bioaccumulation (B), (eco)toxicity (T), health damage in humans (He), carcinogenicity (C), mutagenicity (M), reprotoxicity (R) and hormone disruptive effects (Ho). Hazard data on the chemical in question are gathered and then assessed in order to assign the chemical the appropriate hazard level. Chemicals are also categorized based on the level of concern: 'Very High Concern,' 'High Concern,' 'Concern,' 'Low Concern,' 'No Data, Very High Concern.' Concern categories are adjusted based on the likelihood of exposure. For example, the Quick Scan has four categories of exposure potential based on chemical use: intermediates, industrial applications, professional use and consumer use. Chemicals of Very High Concern are not to be used whereas substances of High Concern are not permitted for use in consumer products or in open profession use. Substances of Concern are permitted with

limitations. The Quick Scan does not lead the user to a final selection, but only screens chemicals into broad categories based on a level of concern.

1.4.10 The Column Model and GHS Column Model

The Column Model was developed by the German Institute for Occupational Safety to comply with the German Hazardous Substances Ordinance that requires companies to replace hazardous substances with substances with a lower health risk. Since being introduced in 2001, the Column Model[26] has been updated to reflect GHS hazard classifications.[27] Similarly to the Dutch Quick Scan, chemical hazard data are presented in tabular form including six endpoints: acute health hazards, chronic health hazards, environmental hazards, fire and explosion hazards, exposure potential and hazards caused by procedures. Each chemical or ingredient is evaluated against each endpoint and assigned one of five hazard levels: very high, high, medium, low and negligible. Unlike the Quick Scan, the Column Method does not categorize chemicals based on levels of concern. The criteria used to assign a hazard level are determined primarily by risk phrases (R-phrases) (for the original Column Model) or hazard phrases (H-phrases) (for the newer GHS Column Model). Assessors are responsible for identifying and analyzing data. The Column Model and GHS Column Model are not comparative methods; however, the models can be used in two different ways: dominance analysis and positional analysis. In dominance analysis, two alternatives are compared and if one is 'dominated' by the other (*i.e.* poses a greater risk), the dominated alternative is discarded and another selected for comparison until one, non-dominated alternative exceeds all those analyzed. In positional analysis, the decision is made based on the criteria considered most important to the user.

1.4.11 Evaluation Matrix

Developed for the German Federal Environmental Agency, the Evaluation Matrix is an aggregated data method, similar to the Column Method, which defines risk levels for specific endpoints and uses.[28] The Evaluation Matrix is a template that allows the assessor to perform an evaluation based on sustainability using substance-specific criteria. Chemicals are evaluated using tables with specific indicators and the colors green, yellow, red and white are used to indicate the result. Eight substance-specific criteria are evaluated and involve checking to see if that chemical is present on several lists of problematic substances, the possible dangerous physico-chemical properties of the substance, human toxicity, problematic properties related to the environment, mobility within the environment, the origin of the raw materials used, emission of greenhouse gases and resource consumption. Information on the substance's mobility can be found in its MSDS such as EU risk phrases or in other publicly available resources. The criterion used when evaluating whether or not a substance is a PVT or vPvB chemical

is that of REACH Annex XIII (see Tables 1.2 and 1.3). Following the evaluation against these endpoints, substances are placed into one of four categories: Green (No action is needed, because available information indicates that the chemical is not problematic), Yellow (No action is needed, because the available information indicates problematic substance properties), Red (There is a high priority to act, because the available information indicates very problematic substance properties), White (There is a need to gather further information, because no or few data are available). A risk index can be created by weighting the endpoints and then summing up the weighted values.

1.5 Challenges Facing Chemicals Alternatives Assessment Methods

Several drawbacks exist when conducting a CAA. The primary challenge is associated with the correct management of hazard and other trade-offs. Switching from a chemical that poses a moderate human health risk to an alternative whose degradation products are aquatically toxic would not be a desirable substitution. This is one example how using CHA and life-cycle thinking would be beneficial when conducting a CAA. It is important to note that although several of the above-mentioned CAA methods use criteria that are more in-depth, not all CAA methods take into account parameters such as resource consumption, energy usage or recyclability. Another primary challenge is complete characterization of the hazard profile for a chemical that has an incomplete data set for human health effects or environmental fate and toxicity.

1.5.1 Chemicals Alternatives Assessments and Data Gaps

In instances where data gaps exist for a chemical (either for a health effects or environmental effects endpoint), it is sometimes possible to characterize the potential hazard of that chemical by evaluating data on chemical surrogates or using software to predict the chemical's potential hazard.

1.5.1.1 Selection of Chemical Surrogates. Hazard characterization data gaps can often be addressed by evaluating hazard data pertaining to one or more structurally similar surrogates. This approach is based on the assumption that a chemical's structure imparts properties that relate to biological activity and that a group of chemicals that produce the same activity have something similar about their chemistry and/or structure. According to the OECD guidelines, an analog selected to fill a data gap must be data rich and share similar physical and chemical properties, including behavior in physical or biological process, with the original compound.[29] Chemicals produced by similar methods by the same company and used for similar purposes make good potential analogs. In addition, degradation products of the parent compound can be used as surrogates,

especially if the parent compound is expected to break down readily in the environment.

The US EPA (2010)[30] and OECD (2007)[29] have defined guidelines for identifying similar substances to use analogs based on the following commonalities:

- A common functional group or substance (*e.g.* phenols, aldehydes).
- A common precursor or breakdown product may result in structurally similar chemicals, which can be used to examine related chemicals such as acids/esters/salts (*e.g.* short-chain alkyl methacrylate esters which are metabolized to methacrylic acid).
- An incremental or constant change (*e.g.* increased carbon chain length; typically used for physico-chemical properties such as boiling point).
- Common constituents or chemical class, similar carbon range numbers – used with substances of unknown or variable composition, complex reaction products or biological material.

At all times, the practitioner must include the rationale for his or her choice of analog(s) in the CAA.

1.5.1.2 Software Modeling to Address Data Gaps. If a structurally similar analog is not available, a modeling software program may be suitable to satisfy any data gaps. These computerized systems predict toxicity using structure–activity relationships. Examples of software programs used in CAAs include (but are not limited to) the following:

- OncoLogic (carcinogenicity): http://www.epa.gov/oppt/sf/pubs/oncologic.htm
- Toxicity Estimation Software Tool (TEST): http://www.epa.gov/nrmrl/std/qsar/qsar.html#TEST
- Estimation Program Interface (EPI) Suite (environmental fate): http://www.epa.gov/oppt/exposure/pubs/episuite.htm
- Ecological Structure–Activity Relationships (ECOSAR) (aquatic toxicity): http://www.epa.gov/oppt/newchems/tools/21ecosar.htm
- ToxTree (toxic hazard estimation): http://toxtree.sourceforge.net/
- OECD QSAR Toolbox (www.qsartoolbox.org)
- VEGA (Virtual Models for Evaluating the Properties of Chemicals within a Global Architecture) (www.vega-qsar.eu/download.html).

All output/estimates generated from modeling programs should be appended to a CAA to promote transparency, accuracy and accountability. In some cases, data gaps cannot be filled because viable analogs are not available and the models may not be appropriate. In such situations, data gaps must be clearly presented and weighted in the assessment.

1.6 Conclusion

Finding safer alternatives to problematic chemicals is a growing global concern. The development of frameworks, tools and paradigms has been fueled by

regulatory and non-regulatory initiatives at all levels, such as REACH in the European Union and the widespread adoption of the United Nation's GHS around the world. Ideally, a CAA supports the intelligent creation, use and substitution of chemicals to benefit humankind in manners that will not harm the environment or organisms inhabiting the environment.

A number of the CAA methods described in this chapter have advantages over others. Some CAA paradigms place an emphasis on human health hazards, whereas others only address environmental hazards. None of the CAA methods in this chapter are yet automated and require 30–60 h of highly technical work per chemical to characterize its potential hazard. CAA methods require the evaluator to be skilled in toxicology, chemistry, ecotoxicology and environmental science, in addition to having a working knowledge of LCA methods and concepts. Not all CAA paradigms consider LCA attributes. As the complexities of the substance being evaluated (chemical, material, product) increase, so do the complexities of the CAA evaluation. The best CAA paradigms are those that are flexible, adhere strictly to transparency and can be modified in order to meet the specific goals of the evaluator.

Improvement in CAA requires greater transparency in the actual methods employed as part of a CAA. Of the CCA methods discussed in this chapter, only the US EPA's DfE Alternatives Assessment, CPA's GreenScreen™ and Cradle to Cradle® have publicly available criteria and background materials. Most of the CAA methodologies were developed a decade ago, so it is likely that hundreds if not thousands of CAAs have been performed using one of the CAA methods described in this chapter. Despite this, there is no central database that can be accessed to search for completed CAAs. An online database that could index completed CAAs using different CAA paradigms would save time and resources by minimizing duplication of effort among CAA assessors who currently end up performing CAAs that other organizations have likely assessed under one or more of the prevailing CAA methods.

To date, a chemical's human health or environmental footprint has taken a backseat to attributes such as a chemical's impact on a product's performance, reliability or price in the marketplace. This way of thinking is not sustainable or preferable, as only a portion of a chemical's true cost and impact are considered—or paid for—in the marketplace. Similarly, banning or restricting chemicals on an *ad hoc* basis is not a solution to our current system, nor is a system of positive lists allowing the use of only certain chemicals, as that stifles innovation and continuous improvement. Early measures such as the Montreal Protocol and the Basel Convention, and more recently REACH and GHS, demonstrate that faults in the current system are recognized; however, these initiatives do not instill a fundamental change in our way of thinking. CAAs provide a powerful means to improve upon the *status quo* by establishing methods to inform chemical substitution in a scientifically rigorous and defensible manner. Obviously, there is great room for refinement and improvement in CAA methods, as this is a relatively young discipline. It is not the nature of humans—or any living entity—to start out by giving up.[15]

Recognizing the value of CAA and fostering greater adoption of CAA methods provide stakeholders with much-needed tools to address a serious deficiency in the way in which chemicals are used in society, as maintaining the *status quo* is analogous to admitting defeat. As humankind's understanding of the full costs and benefits of chemicals matures, it is critical that we cease using those chemicals that can permanently impair human health or the environment.

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