Material Health Assessment Methodology

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LIST OF ACRONYMS

BAF	bioaccumulation factor
BCF	bioconcentration factor
BN	biological nutrient
BW	body weight
CASRN	Chemical Abstracts Service registry number
DOC	dissolved organic carbon
EMC	externally managed component
GHS	Globally Harmonized System
IARC	International Agency for Research on Cancer
K_{ow}	n-octanol-water partition coefficient
LC50	lethal concentration 50
LOAEL	lowest observable adverse effect level
MAK	“maximale Arbeitsplatz-Konzentration” or maximum workplace concentration
MEST	mouse ear swelling test
NOEC	no observable effect concentration
ODP	ozone depleting potential
OECD	Organisation for Economic Co-operation and Development
PET	polyethylene terephthalate
QSAR	quantitative structure-activity relationship
ThOD	theoretical oxygen demand
TLV	threshold limit value
TN	technical nutrient
US EPA	U.S. Environmental Protection Agency
VOC	volatile organic compound

REVISION HISTORY

REVISION DATE	SECTION(S)	TYPE OF CHANGE	AUTHORIZED BY
May 2017	All	This document consolidates the information in the *Cradle to Cradle Certified Material Health Assessment Methodology, Version 3.0* and its associated guidance document, *Supplemental Guidance for the Cradle to Cradle Certified Material Health Assessment Methodology, Version 3.0* into one document. These documents were merged to improve ease of use, remove redundancies, and clarify inconsistencies. Note that the section numbers between the v3.0 documents and this document do not correspond. Section numbers listed to the left within the SECTIONS column of this table are for this document.	S. Klosterhaus
May 2017	Tables 5-23	Minor edits were made within the hazard rating tables in order to highlight alignment of Cradle to Cradle Certified with the Globally Harmonized System of Classification and Labelling (GHS). This included a slight change in language within several sections, a change of several > or < signs to ⩾ or ⩽ signs in the aquatic toxicity and bioaccumulation sections and moving indication of the GHS categories to the top of all rating tables.	S. Klosterhaus
May 2017	2.2 Process	Reflects change made in December 2014 to remove the cyclability assessment from the methodology (i.e. this is one of two changes made to v3.0 in developing v3.1)	S. Klosterhaus

REVISION DATE	SECTION(S)	TYPE OF CHANGE	AUTHORIZED BY
May 2017	3.2 Information Sources	Added guidance regarding evaluation of data quality and selection of studies to assign hazard ratings using Klimisch scores. Quantitative structure-activity relationship (QSAR) modeling results and other newly developed modelling techniques may be used for additional endpoints (in addition to aquatic toxicity, bioaccumulation and persistence) upon pre-approval from C2CPII. EpiSuite and ECOSAR may not be used to model data relevant to surfactants.	S. Klosterhaus
May 2017	3.3.2 Endocrine Disruption	The YELLOW Rating Criteria have been clarified as follows: Insufficient evidence of endocrine disruption by evidence of endocrine activity without evidence of linked adverse health effects. The EU list categories were previously listed incorrectly in the GREEN and GREY rating sections. This has been corrected.	S. Klosterhaus

REVISION DATE	SECTION(S)	TYPE OF CHANGE	AUTHORIZED BY
May 2017	3.3.3 Mutagenicity	This section has been updated to list several new OECD tests that may be referred to and indicate that some older OECD tests have been archived and are no longer preferred data sources. Several examples of test result combinations that result in GREEN, YELLOW or RED hazard ratings have been added to the Rating Criteria section. The limit of 100 mg/l was removed from the Rating Criteria table. Assessors are directed to use OECD guidance to determine appropriate test ranges. The Rating Criteria have been clarified to indicate that a negative Ames AND negative Chromosome Aberration test are sufficient to assign a GREEN hazard rating to this endpoint.	S. Klosterhaus
May 2017	3.3.4 Reproductive Toxicity and Developmental Toxicity	Clarification has been added to indicate that data is required on either reproductive toxicity or developmental toxicity in order to assign a hazard rating to this endpoint. Clarification has been added to indicate that the cut-off values listed for RED, YELLOW and GREEN hazard ratings take precedence over the GHS classifications. MAK C has been moved from the GREY column of the Rating Criteria table to the YELLOW column. (It was previously mistakenly included in the GREY column.)	S. Klosterhaus

REVISION DATE	SECTION(S)	TYPE OF CHANGE	AUTHORIZED BY
May 2017	3.3.5-3.3.7 Oral, Dermal and Inhalation Toxicity	Language has been added to clarify that extrapolation to a "true" LOAEL is not allowed. Language has been added to clarify that sub-chronic or single exposure target organ toxicity studies of duration <90 days may be used only if no studies of duration >90 days are available and if criteria values have been adjusted for the study duration per point 3.9.2.9.5 of GHS Chapter 3.9.	S. Klosterhaus
May 2017	3.3.5 Oral Toxicity	Clarification has been added to indicate that in order to assign a YELLOW or GREEN rating for this endpoint, data are required on both acute and sub-chronic or chronic toxicity. Single exposure organ toxicity data are not required but must be considered when available.	S. Klosterhaus
May 2017	3.3.6 Dermal Toxicity	Clarification has been added that route to route extrapolation may be used in some cases per ECHA guidance when data are lacking. The assessor is required to document and provide all assumptions made as part of the assessment outcome. Although both acute and sub-chronic/chronic data are required for Oral Toxicity, only acute data are required for Dermal Toxicity. GHS classifications have been added to the Rating Criteria table.	S. Klosterhaus

REVISION DATE	SECTION(S)	TYPE OF CHANGE	AUTHORIZED BY
May 2017	3.3.7 Inhalation Toxicity	Clarification has been added that route to route extrapolation may be used in some cases per ECHA guidance when data are lacking. The assessor is required to document and provide all assumptions made as part of the assessment outcome. For very volatile substances (boiling point < 0°C), both acute and sub-chronic or chronic toxicity data are required in order to assign a GREEN or YELLOW rating to the Inhalation Toxicity endpoint. H335: May cause respiratory tract irritation was removed from the YELLOW column of the Rating Criteria table. It is now included as part of the YELLOW criteria for Skin, Eye and Respiratory Corrosion/Irritation.	S. Klosterhaus
May 2017	3.3.10 Sensitization of Skin and Airways	The following clarification has been added: Data on skin sensitization alone is sufficient to assign a hazard rating to this endpoint. Data on respiratory sensitization must be considered when available. Results from local lymph node assays may be used to derive a hazard rating for this endpoint. This has been clarified in the Rating Criteria table. H320 has been added to the YELLOW column of the Rating Criteria table.	S. Klosterhaus

REVISION DATE	SECTION(S)	TYPE OF CHANGE	AUTHORIZED BY
May 2017	3.3.12 Aquatic Toxicity (Fish, Daphnia & Algae Toxicity)	The following six aquatic toxicity endpoints have been combined into three endpoints: Acute Fish Toxicity, Acute Daphnia Toxicity, Acute Algae Toxicity, Chronic Fish Toxicity, Chronic Daphnia Toxicity, and Chronic Algae Toxicity. The new endpoints are: Fish Toxicity, Daphnia Toxicity and Algae Toxicity. Therefore, the total number of hazard endpoints considered is now 21 instead of 24. Generally, results from both acute and chronic studies may influence the ratings in these three aquatic toxicity endpoints. However, since chronic toxicity tests are rarely conducted, if there are no signs of toxicity in acute studies, chronic data is not required for an aquatic toxicity endpoint when acute data suggests a GREEN rating for that endpoint.	S. Klosterhaus
May 2017	3.3.14 Persistence	The following clarification was added: The half-life value chosen to determine the final rating for this hazard endpoint must reflect the dominant environmental compartment in order to be meaningful. Fugacity modeling available via the U.S. EPA's EPI Suite software may be used to estimate dominant environmental compartment of a chemical.	S. Klosterhaus
May 2017	3.3.15 Bioaccumulation	The following addition was made: QSAR Arnot/Gobas estimated BAF may be used for log K_{ow} 6-8.	S. Klosterhaus
May 2017	4.1 Exposure Assessment Methodology	The following clarification was added regarding chemicals of regulatory concern: The thresholds and use conditions as indicated by REACH apply.	S. Klosterhaus
May 2017	4.5 Combined Aquatic Toxicity Risk Flag	Clarification has been added to indicate that a RED rating is worse than a GREY rating. The matrix has been clarified and the logic behind the matrix has been described.	S. Klosterhaus
May 2017	7.3 Recycled Content Types	Added clarification that Type 4 recycled content may only be certified up through the Bronze level.	S. Klosterhaus

REVISION DATE	SECTION(S)	TYPE OF CHANGE	AUTHORIZED BY
May 2017	Terms and Definitions	The prior terms and definitions section was deleted. Refer to the relevant toxicology literature for definitions as needed.	S. Klosterhaus
March 2017	3.3.5, 3.3.6, 3.3.7	Aligned with GHS/CLP guidance for interpolation between NOAEL and LOAEL values when both are available	S. Klosterhaus
March 2018	3.3.9	Changed < and > signs to ⩽ and ⩾ for pH values corresponding with a red rating for corrosion to align with GHS	S. Klosterhaus
March 2018	3.3.14	Clarified thresholds of DOC or ThOD removal for OECD test guidelines for GREEN, YELLOW, and RED ratings.	S. Klosterhaus
September 2018	3.2 Information Sources	Clarified that the RIFM database is an acceptable source of toxicity information for fragrance molecules	S. Klosterhaus
September 2018	3.3.4 Reproductive Toxicity	Clarified that a YELLOW rating is allowed when appropriate doses have been selected, even if the highest available negative measurement is still in the RED range.	S. Klosterhaus
September 2018	3.3.4 Reproductive Toxicity	Clarified that substances on REACH Annex XVII and the Candidate List of Substances of Very High Concern due to reproductive toxicity concerns must always receive a RED hazard rating for this endpoint.	S. Klosterhaus
September 2018	3.3.14 Persistence	Clarified that when empirical evidence is insufficient, estimation of degradation by QSAR results may be used for classification.	S. Klosterhaus
September 2018	3.3.14 Persistence	Replaced two < signs with ⩽ signs in the GREEN and YELLOW rating sections so that values equal to the cut-offs were included in a hazard rating category.	S. Klosterhaus
January 2019	4.1	Updated to reference new Exposure Assessment Methodology	S. Klosterhaus
November 2021	3.3.14 Persistence	The persistence endpoint criteria for PBTs and vPvBs have been modified to align with hazard level cut-offs from ECHA/REACH	S. Klosterhaus
November 2021	3.3.15 Bioaccumulation	The bioaccumulation endpoint criteria for PBTs and vPvBs have been modified to align with hazard level cut-offs from ECHA/REACH	S. Klosterhaus

REVISION DATE	SECTION(S)	TYPE OF CHANGE	AUTHORIZED BY
November 2021	3.3.16 Combined Persistence and Bioaccumulation Hazard	Addition of a combined Persistence (P) and Bioaccumulation (B) hazard flag	S. Klosterhaus
November 2021	3.3.16 Climatic Relevance	Change from list-based approach to metrics-based approach that characterizes a molecule's climatic impacts	S. Klosterhaus
November 2021	5. Assigning Single Chemical Risk Ratings	Rules have been updated to include the new combined PB hazard flag.	S. Klosterhaus
November 2021	3.3.19 Organohalogens	Updated language to include RSL instead of Banned Chemical List	S. Klosterhaus
November 2021	3.3.20 Toxic Metals	Updated language to include RSL instead of Banned Chemical List	S. Klosterhaus
February 2022	4.5 Exposure Assessment for the Combined Persistence and Bioaccumulation Hazard Rating	Corrected exposure assumption for the Combined Persistence and Bioaccumulation Hazard Flag to include PURPLE or RED flags unless closed loop recycling is taking back 80% or more of the product.	
February 2022	3.3.2 Endocrine Disruption	Corrected language in description to match criteria in supporting table for YELLOW hazard rating. Both now consistently define YELLOW rating as having lack of adverse health effects with endocrine activity.	

1 OVERVIEW

1.1 Purpose and Content

This document describes the methodology used to assign an A, B, C, X, or GREY material assessment rating to each homogeneous material subject to review in a finished product that is applying for certification to the Cradle to Cradle Certified® Product Standard. The procedure uses toxicity data for individual chemical substances, and/or toxicity data on homogeneous mixtures where available, from peer-reviewed studies, authoritative lists, and other sources, as well as a qualitative exposure assessment that considers specific product manufacturing, use, and end-of-use scenarios to determine whether the material contains one or more substances that have the potential to adversely impact human or environmental health.

The methodology applies to all types of homogeneous materials except those for which customized methodologies have been developed:

- textile dyestuffs and pigments (see separate document, Colorants Assessment Methodology),
- biological materials (see separate document, Biological Materials Assessment Methodology),
- geological materials (see separate document, Geological Materials Assessment Methodology),
- polymeric materials (see separate document, Polymer Assessment Methodology)
- recycled content materials (see separate document, Recycled Content Assessment Methodology*)*

1.2 Supporting Documents

The following documents are to be used in conjunction with the Cradle to Cradle Certified® Material Health Assessment Methodology:

- Cradle to Cradle Certified Product Standard, Version 4.0
- Cradle to Cradle Certified Product Standard, Version 3.1
- Colorants Assessment Methodology
- Biological Materials Assessment Methodology
- Exposure Assessment Methodology
- Geological Materials Assessment Methodology
- Polymer Assessment Methodology
- Recycled Content Assessment Methodology
- Any applicable supporting documents and guidance posted on the Resources page of the C2CPII website (http://www.c2ccertified.org/resources).

2 MATERIAL HEALTH ASSESSMENT METHODOLOGY

2.1 Materials Subject to Review

Material assessments are conducted for homogeneous materials subject to review in the product being assessed for certification (Section 3.1 in the Cradle to Cradle Certified® Product Standard, Version 3.1 describes the process for identifying materials subject to review). For each certification level, material assessments are completed for a given minimum percentage of the product by weight (see Section 3.6 in the Cradle to Cradle Certified Product Standard, Version 3.1). In cases where a product is composed of only one homogeneous material, assessments are conducted for each chemical substance in the product (see Section 2.2 below).

2.2 Process Steps

An A, B, C, X, or GREY rating is assigned to a homogeneous material subject to review using the following four steps:

1. Conduct chemical hazard assessment – Using the hazard criteria provided in **Section 3**, a hazard rating of either RED, PURPLE, YELLOW, GREEN, or GREY is assigned to each of the 21 human and environmental health hazard endpoints for each chemical substance subject to review in the material (see Section 2.3 in this document which describes the process for identifying chemicals subject to review in each material). A Combined Persistence and Bioaccumulation hazard rating is also derived from the individual Persistence and Bioaccumulation ratings.

2. Conduct chemical exposure assessment – Following the exposure assessment guidelines described in **Section 4 and the Exposure Assessment Methodology document**, a risk flag of either RED, YELLOW, GREEN, or GREY is assigned to 16 of these hazard endpoints for each chemical substance using the hazard ratings and identified exposure scenarios during the final manufacture, use, and re-use of the product. A risk flag is also assigned to the Combined Persistence and Bioaccumulation hazard rating. Furthermore, the three Aquatic Toxicity endpoints are combined with the Persistence and Bioaccumulation endpoint to derive a combined Aquatic Toxicity risk flag, yielding a total of 18 risk flags.

3. Assign single chemical risk ratings – Using the rules defined in **Section 5**, a single chemical risk rating of a, b, c, x, or GREY is assigned to each chemical substance based on the chemical's risk flags.

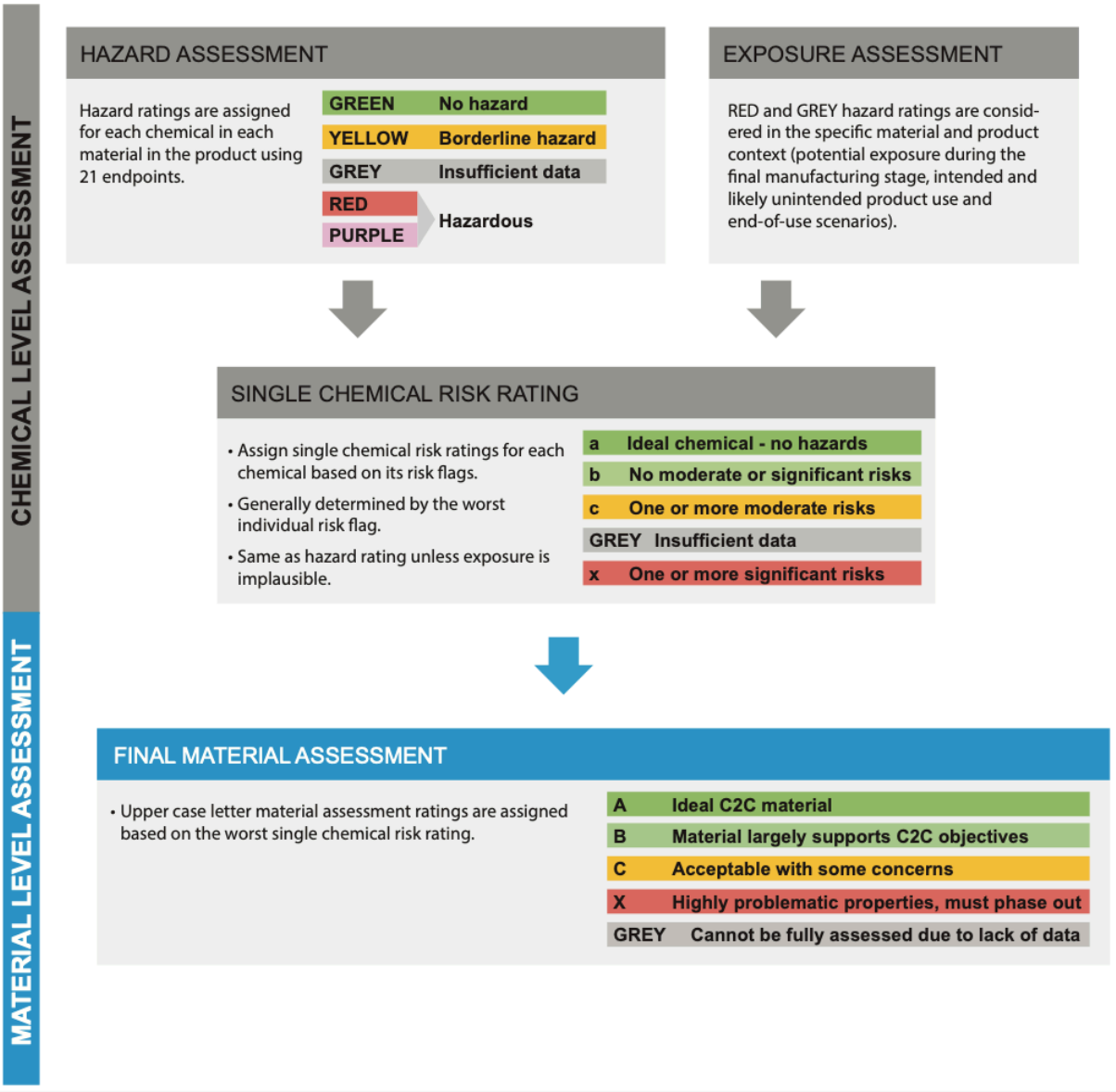
4. Assign material assessment rating – Using the rules defined in **Section 6**, a material assessment rating of A, B, C, X, or GREY is assigned to the material based on the

single chemical risk ratings. The material assessment rating is equal to the worst single chemical risk rating among all chemical substances subject to review in the material.

A summary of the material health assessment process is shown in Figure 1.

For products composed of only one homogeneous material, each chemical substance in the product receives an assessment rating following only steps 1-3 above (i.e., each chemical substance receives a single chemical risk rating but no material assessment rating is assigned to the product).

Figure 1 Cradle to Cradle Certified Material Health Assessment Methodology



2.3 Chemicals Subject to Review

The Material Health assessment is based on the chemical substances present in the finished product as it leaves the final manufacturing facility. The material assessment ratings are based on these, as well as the chemical's reaction products, during the intended and likely unintended uses of the product.

The chemicals subject to review within a homogeneous material are as specified by the Cradle to Cradle Certified Product Standard. In general, chemicals present at 100 ppm or above within a homogeneous material are subject to review unless a different limit is specified for the material type in question per one of the specialized Material Health Assessment Methodologies (e.g., Geological Materials Assessment Methodology, Biological Materials Assessment Methodology). Exceptions under Version 3.1 (as stated in Section 3.4 item 2f of the Version 3.1 standard) are: lead, mercury, hexavalent chromium, cadmium, pigments, dyes and other colorants, phthalates, halogenated organics, and scarce elements (e.g., gold, diamond) which are subject to review if present at any concentration in a material. See additional Version 3.1 exceptions below for process chemicals. Exceptions under Version 4.0 are substances with Specific Concentration Limits (SCLs) and/or Restricted Substances List (RSL) limits that are below 100 ppm, in which case the lower limit applies.

Other chemicals that are used as product inputs, but are not present in the finished product, may be assessed to provide additional information for the manufacturer and may factor into the chemical assessments required in the Water Stewardship (Version 3.1)/Water & Soil Stewardship (Version 4.0) category, but generally are not required and do not impact a product's material assessment ratings. Exceptions under Version 3.1 are **certain process chemicals that are always subject to review and must be factored into the material assessment ratings regardless of their concentration in the finished product**, even if they are not expected to be present (as stated in Section 3.4 item 2.g of the Version 3.1 standard and Section 3.4 of the Version 3.1 Guidance these are: hexavalent chromium when used as a metal plating agent, blowing agents, textile dye auxiliaries, paper and other plant-based material bleaching agents, and leather tanning agents). Separate from the material assessment ratings, all process chemicals used in the product's final manufacturing stage must be assessed to achieve the Platinum level requirement.

Materials are assessed based on the final chemical state of all substances in the material. Because of this, it is important to have an in-depth understanding of the key chemical reactions taking place and whether the chemical is still in its original form after curing or other reactions reach equilibrium. For example, UV inks contain several sensitizing and reactive chemicals in their "raw" state, but after the printing process is complete and the ink has cured, many of those substances are no longer present in their original state but rather have reacted to form a different molecular structure. Collecting chemical function data from supply chain technical staff is a good way to gain understanding of the full picture of the complex chemical mixtures present in the final material or product in order to assign the most accurate assessment rating. For example, when evaluating polyurethane foams, it is common to see polyols and isocyanates listed as separate chemicals. However, in the final foam

material they do not exist separately, but rather have reacted together to form polyurethane molecules.

3 ASSIGNING HAZARD RATINGS

3.1 Chemical Hazard Assessment Methodology

The Cradle to Cradle Certified chemical hazard assessment methodology forms the basis of each chemical's evaluation by using specified criteria to assign a hazard rating to 21 different human health, environmental health, and chemical class endpoints (Tables 1-3). The rating scheme follows a "traffic-light" hierarchy where the chemical's hazard is communicated by a GREEN, YELLOW, RED, or GREY rating for each endpoint (Table 4). Section 3.3 provides a detailed description of each endpoint and the criteria used to assign the ratings.

Table 1 Human health hazard endpoints

HUMAN HEALTH ENDPOINTS	DESCRIPTION
Carcinogenicity	Potential to cause cancer.
Endocrine Disruption	Potential to negatively affect hormone function and impact organism development.
Mutagenicity	Potential to alter DNA.
Reproductive & Developmental Toxicity	Potential to negatively impact the reproductive system as well as the potential to affect pre- and post-natal offspring development.
Oral Toxicity	Potential to cause harm via oral exposure. Both short-term (acute) and longer-term (chronic) exposures are considered.
Dermal Toxicity	Potential to cause harm via dermal exposure. Both short-term (acute) and longer-term (chronic) exposures are considered.
Inhalation Toxicity	Potential to cause harm via inhalation exposure. Both short-term (acute) and longer-term (chronic) exposures are considered.
Neurotoxicity	Potential to cause an adverse change in the structure or function of the central and/or peripheral nervous system.
Skin, Eye, and Respiratory Corrosion/Irritation	Potential to cause direct reversible or irreversible damage to the skin, eyes, or respiratory system upon short-term exposure.

Sensitization of Skin and Airways	Potential to cause an allergic reaction upon exposure to skin or via inhalation.
Other	Any additional characteristic (e.g., flammability, skin penetration potential, etc.) relevant to the overall evaluation but not included in the previous criteria.

Table 2 Environmental health endpoints

ENVIRONMENTAL HEALTH ENDPOINTS	DESCRIPTION
Fish Toxicity	Measure of toxicity to fish (both saltwater and freshwater) from single, short-term exposure, or from longer term, chronic exposure.
Daphnia Toxicity	Measure of toxicity to Daphnia (or other aquatic invertebrates) from single, short-term exposure, or from longer term, chronic exposure.
Algae Toxicity	Measure of toxicity to algae from single, short-term exposure, or from longer term, chronic exposure.
Terrestrial Toxicity	Acute toxicity to avian species and soil organisms.
Persistence	Measure of how long a substance will exist in air, soil, or water.
Bioaccumulation	Potential for a substance to accumulate in fatty tissue.
Climatic Relevance	Measure of the impact a substance has on the climate (e.g., ozone depletion, global warming).
Other	Any additional characteristic relevant to the overall evaluation but not included in the previous criteria.

Table 3 Chemical class endpoints

CHEMICAL CLASS ENDPOINTS	DESCRIPTION
Organohalogens	Presence of a carbon-halogen (i.e., fluorine, chlorine, bromine, or iodine) bond.
Toxic Metals	Presence of a toxic metal compound (antimony, arsenic, cadmium, chromium VI, cobalt, lead, mercury, nickel, thallium, tin (organotins only), radioactive elements, and vanadium are considered toxic metals).

Table 4 Rating scheme used for each of the 21 hazard endpoints

GREEN	No hazard identified for the endpoint
YELLOW	Borderline hazard identified for the endpoint
GREY	Insufficient data available to determine hazard level for the endpoint
RED	Considered hazardous for the endpoint
PURPLE	Considered hazardous for the endpoint

3.2 Information Sources

In deriving hazard ratings, assessors are to rely on the best available, most recent, and most conservative information from sources including public and private databases, QSAR modeling and other toxicological predictive software, government reports, and the scientific literature. GreenScreen® assessments conducted by a licensed GreenScreen® Profiler (i.e., Certified GreenScreen assessments) may also serve as a data source for completing the hazard assessment.

In cases where a wide variety of study results are available, the most conservative value should be used unless there is a compelling weight of evidence to do otherwise. Data quality is to be evaluated following ECHA guidelines (ECHA, 2011: Guidance on information requirements and chemical safety assessment, Chapter R.4: Evaluation of available information) and preference given to studies that have been assigned a Klimisch score of 1 (K1, "Reliable without restriction") or 2 (K2, " Reliable with restrictions"). Studies with a Klimisch score of 4 (K4, "Not assignable") may be used as supporting studies, but shall not be determinative of the hazard rating in any given endpoint unless they are used to weigh the results of two or more conflicting K1 or K2 studies.

As a first pass to screen for widely recognized and well established hazards, the use of authoritative hazard lists such as those issued by the International Agency for Research on Cancer (IARC), California's Proposition 65 List, and lists maintained by various countries

based on category criteria of the Globally Harmonized System for Classification and Labeling (GHS) will often be helpful. Some of these lists are explicitly cited in the methodology and within endpoint criteria. In instances where multiple lists cited in the methodology would lead to conflicting hazard ratings, as per the established criteria, the result from the list yielding the most conservative Cradle to Cradle Certified hazard rating (in the order RED, YELLOW, GREEN) is to be used. Alternatively, the assessor may look further into the data sources and criteria used by the list issuing agencies and evaluate it directly against the governing endpoint criteria using a weight of evidence approach. An assessment rating determined via direct evaluation of all available data meeting the quality requirements takes precedence over an assessment based solely on authoritative lists. (However, also see the note about chemicals of regulatory concern in Section 4.1.)

Quantitative structure-activity relationship *(*QSAR) modeling results and other newly developed modelling techniques may be used for the endpoints of aquatic toxicity (chronic and acute), bioaccumulation, and persistence, but only if no experimental data are available. For other endpoints, modeling results may not be used without pre-approval by C2CPII and the endpoint rating shall remain 'GREY' in the absence of experimental data (note that not all 'GREY' endpoint ratings translate to 'GREY' single chemical risk ratings, see Section 5). When using models, the assessor is responsible for determining whether or not the model is robust for the endpoint or chemical class in question. For example, at the time of writing, EpiSuite and ECOSAR are not appropriate for modeling surfactants due to limited training set data relevant to these chemicals and their unique properties.

Read-across techniques are also acceptable for filling hazard data gaps and may be used based on the best professional judgment of the assessor. For example, surrogate-based NOAELs published in the Research Institute of Fragrance Materials (RIFM) database may be used in the absence of primary data on the substance to assign a reproductive and developmental toxicity hazard rating to a fragrance molecule.

3.3 Hazard Endpoint Definitions and Rating Criteria

3.3.1 Carcinogenicity

Definition
Carcinogenicity is the measure of a chemical's potential to cause cancer or a malignant neoplasm. A malignant neoplasm is an autonomous growth of tissue that demonstrates invasive growth characteristics, capable of spreading through the organ of origin and through metastasis to other tissues while showing no physiological attributes (Klaunig et al, 2008).

Although the toxicity endpoint of carcinogenesis is definitive, often the mechanism by which neoplastic development is caused is not readily apparent given its multi-step nature. Carcinogenesis is often broken down into three stages called initiation, promotion, and progression, all of which a given chemical can influence (Boyd, 1990). Initiation is a rapid, irreversible process that results in a carcinogen-induced mutational event. Initiation alone does not result in neoplastic development as the mutated cells can have multiple outcomes

including: 1) remaining in a non-dividing state by growth control; 2) the cell may become unviable and be deleted through apoptosis; or 3) the cell may undergo division resulting in the proliferation of the initiated cells, which is also known as promotion. Progression is the final stage of carcinogenesis that results in the conversion of benign pre-neoplastic cells into neoplastic cancer. Often progression is another stage where genotoxic events take place due to the increase in DNA synthesis from the proliferation stage. Additional DNA damage including chromosomal aberration and translocations are often characteristic of progression.

Rating Criteria

The endpoint of carcinogenicity is given a GREY, RED, YELLOW, or GREEN rating based on the strength of scientific evidence available from peer-reviewed sources.

In order for a chemical to be rated RED for carcinogenicity, it is either known, presumed, or suspected to be a carcinogen based on human epidemiologic or animal studies. The YELLOW rating for carcinogenicity is reserved for chemical substances that, based on experimental evidence, cannot be classified as a carcinogen or non-carcinogen due to a lack of evidence, equivocal evidence based on experimental structure, or conflicting evidence. In order for carcinogenicity to be rated GREEN, the chemical in question is not suspected to be a human carcinogen based on evidence from long-term studies.

There are several existing classification systems that align with this rating scheme including the Threshold Limit Value (TLV), International Agency for Research on Cancer (IARC), maximum workplace concentration (MAK), and GHS. Based on these classification systems, if a chemical is listed within these publications, a hazard rating can be given for the carcinogenicity endpoint as summarized in Table 5 below.

Often chemicals are not listed by any of the classification systems adopted in this program and the assessor must determine the carcinogenicity rating of a chemical with available studies. As defined by GHS, the carcinogen classification of a chemical considers both the strength of evidence and the weight of evidence (UNECE, 2009). GHS differentiates these interrelated criteria with the following definitions:

> *Strength of evidence* – the enumeration of tumors in human and animal studies. Sufficient evidence in both human and animal studies demonstrates causality between exposure and development of cancer or an increased incidence of tumors. Limited evidence can demonstrate a positive association between exposure and incidence but cannot determine a causal relationship.
>
> *Weight of Evidence* – other factors that influence the overall likelihood that an agent may pose a carcinogenic hazard in humans. These factors include but are not limited to the following:
>
> 1. Tumor type and background incidence.
> 2. Multi-site responses.
> 3. Progression of lesions to malignancy.

4. Reduced tumor latency.
5. Whether responses are in single or both sexes.
6. Whether responses are in a single species.
7. Structural similarity or not to a chemical(s) for which there is good evidence of carcinogenicity.
8. Routes of exposure.
9. Comparison of absorption, distribution, metabolism, and excretion between test animals and humans.
10. The possibility of a confounding effect of excessive toxicity as test doses.
11. Mode of action and its relevance for humans, such as mutagenicity, cytotoxicity with growth stimulation, mitogenesis, immunosuppression (UNECE, 2009).

The strength and weight of evidence must be considered when determining whether a chemical is classifiable as a carcinogen by the definitions given above. Table 5 provides an overview of how a GREEN, YELLOW, RED, or GREY classification is reached for this endpoint:

Table 5 Rating Criteria for Carcinogenicity

Green	Yellow	Red	Grey
Not classified as GHS category 1A, 1B, or 2. Not a known, presumed or suspected carcinogen. Negative long-term cancer studies. Listed as: TLV A5, IARC 4	Not classified as GHS category 1A, 1B, or 2. Limited, marginal, equivocal or conflicting evidence of carcinogenicity. Listed as: MAK III 3A, 4, 5	Classified as GHS category 1A, 1B, or 2. Known, presumed or suspected carcinogen. Listed as: MAK III 1, 2, 3B IARC Group 1, 2A, 2B TLV A1, A2, A3 GHS Category 1A, 1B, 2 H350: May cause cancer H351: Suspected of causing cancer	No data available for classification. Listed as: IARC Group 3 TLV A4

3.3.2 Endocrine Disruption

Definition

For the purposes of this assessment methodology, it is important to recognize that endocrine disruption is considered a mode of action, not a hazard itself. Mode of action refers to the specific biochemical interaction of a drug or chemical through which a health effect is produced. A mode of action includes specific molecular targets to which a chemical will bind, in this case the endocrine system. Concurrent with this caveat the definition developed by Weybridge is adopted in this methodology:

"An endocrine disruptor is an exogenous substance that causes adverse health effects in an intact organism, or its progeny, secondary (consequent) to changes in endocrine function. A potential endocrine disruptor is a substance that possesses properties that might be expected to lead to endocrine disruption in an intact organism." (Weybridge, 1996).

The endocrine system consists of glands and hormones that guide the development, growth, reproduction, and behavior of human beings and animals.

Rating Criteria

Following the definition given by Weybridge, the evidence needed to support rating a chemical as a known or suspected endocrine disruptor is two-fold. Primarily, evidence of adverse effects to sex organs, reproductive systems, accessory tissue, and development of offspring meets one criteria of the Weybridge definition. Secondly, in vitro or in vivo data identifying chemicals that bind to endocrine receptors, alter gene transcription, affects synthesis of sex hormones, possess androgenic activity, or anti-androgenic activity (e.g., identify the ancillary operation of changes in endocrine function) are needed. Where both of these measures are met there is sufficient evidence of endocrine disruption and rating of a chemical as RED for this endpoint. Although endocrine disruption is listed under human health, evidence of this adverse health effect in animals, including avian, amphibians, and fish, will also result in a RED rating.

Tantamount to the evidence required above are definitive lists including the Colborn list and the EU list Categories 1 and 2. Appearance on these lists also results in a RED rating for a given chemical. A useful additional reference that may include both YELLOW and RED rated chemicals for this endpoint is the TEDX List of Potential Endocrine Disruptors.

Exposure concentrations have not been set for this endpoint given the complex and controversial nature of this topic. Studies have shown that endocrine disruptors can act at extremely low levels, in the parts per billion or trillion, especially at critical points in the development of a fetus (Colborn, 1996). Moreover, in some cases, high doses will actually reduce adverse health effects and disruption of the endocrine system, while low doses show greater potency. The relationship of dose to response clearly does not exist in a straightforward manner for endocrine disruption as in other endpoints, and consequently potency and exposure concentrations have not been set for this endpoint.

Table 6 lists the hazard rating criteria for endocrine disruption. In cases where there have been no adverse health effects linked to reproductive toxicity, teratogenicity, and other relevant endpoints but there is evidence for endocrine activity, a rating of YELLOW is given where there is insufficient evidence of endocrine disruption. This rating is assigned due to endocrine disruption being a mode of action. In other words, conclusive evidence of endocrine disruption cannot be determined where mechanistic studies do not link changes in endocrine function to adverse health effects.

In instances where no adverse health effects are seen in in vivo studies, absence of toxic effects can be taken as definitive evidence of no endocrine disrupting properties (ECETOC, 2009). Additionally, if no endocrine activity has been identified through appropriate studies then there is conclusive evidence that endocrine disruption is of low concern and a GREEN rating is given. Where no empirical data are available and a chemical does not appear on the aforementioned Colborn or EU list, a rating of GREY is given.

Table 6 Rating Criteria for Endocrine Disruption

Green	Yellow	Red	Grey
Not known or suspected of endocrine disruption: Adequate data indicate neither endocrine activity nor adverse health effects that are linked to endocrine activity. *or* EU list category 3A	Insufficient evidence of endocrine disruption: Data provide evidence of endocrine activity without evidence of linked adverse health effects.	Sufficient evidence of endocrine disruption: Data indicate adverse health effects that are linked to endocrine activity. *or* Chemical appears on Colborn or EU list (Cat. 1 & 2).	No data available for classification. EU list category 3B

3.3.3 Mutagenicity

Definition

This endpoint is primarily concerned with chemicals that cause mutations in both germ and somatic cells in humans and other organisms that can either be passed along to progeny or cause initiation of neoplasms. Although the latter overlaps with the endpoint of carcinogenicity (Section 3.3.1), this testing is not always available and mutagenicity testing gives insight into the potential hazard within this category.

Mutagenicity is defined as a chemical's ability to alter genetic material in cells, both germ and somatic, resulting in the transmission of changes during cell division. Genotoxicity is also commonly used in this category and is termed to agents or processes which alter the structure, information content, or segregation of DNA (UNECE, 2009). Genotoxic studies are often taken as indicators for mutagenic effects.

When multiple studies are available for the determination of a chemical's mutagenic/genotoxic character, a hierarchy of relevance is applied based on the varying characteristics of the studies available. Studies that carry the most weight in terms of supplying confidence in how a chemical will affect the health of humans are in vivo eukaryotic studies. Examples of such studies include rodent dominant lethal mutation test (OECD 478), mouse heritable translocation assay (OECD 485), mammalian bone marrow chromosome aberration test (OECD 475), mouse spot test (OECD 484), and mammalian erythrocyte micronucleus test (OECD 474) (UNECE, 2009). Such tests complement in vitro tests well since they account for whole animal processes such as absorption, tissue distribution, metabolites, and excretion of chemicals and their metabolites (Klaunig et al,

2008). When in vivo tests are not available, in vitro tests performed in eukaryotic cells are the next preferred type of study. Included within this categorization of studies is unscheduled DNA synthesis, sister chromatid exchange, chromosome aberrations, and mouse lymphoma assays. Lastly, given the rapid results and low cost, prokaryotic mutagenicity tests are considered both in Ames and E. Coli tests. For these studies to be sufficient they must include both assays where metabolic activation was used as well as those where it was not used. Since prokaryotic assays are performed in single celled organisms, do not account for whole animal processes, and have a low concordance with carcinogenic effects, these studies are given the least weight when considering the final rating for mutagenicity.

Below is a definitive list (at the time of writing) of tests developed by OECD that are applicable for this endpoint. Indicated in parenthesis is the GHS category that a positive result is typically associated with (in absence of conflicting higher weight evidence). This is provided for informational purposes and as further indication of the weight that should be applied to the different study types. Note however that Cradle to Cradle uses a more precautionary approach in applying a RED hazard rating to this endpoint than the GHS category 1 or 2 criteria.

In vivo tests in germ cells (positive result indicates or supports GHS category 1B)
OECD 478: Genetic Toxicology: Rodent Dominant Lethal Test. Tests for: Structural and numerical chromosome aberrations.
OECD 483: Mammalian Spermatogonial Chromosome Aberration Test. Tests for: Structural chromosome aberrations. Expected to be predictive of induction of heritable mutations in germ cells. Supports category 1B designation in combination with positive in vivo somatic cell test.
OECD 485: Genetic toxicology, Mouse Heritable Translocation Assay. Tests for: Structural chromosome aberrations.
OECD 488: Transgenic Rodent Somatic and Germ Cell Gene Mutation Assays. Tests for: Gene/point mutations and chromosomal rearrangements.

In vivo tests in somatic cells (positive result indicates GHS category 2 or Category 1B depending on other supporting information)
OECD 474: Mammalian Erythrocyte Micronucleus Test. Tests for: Structural and numerical chromosome aberrations.
OECD 475: Mammalian Bone Marrow Chromosome Aberration Test. Tests for: Structural chromosome aberrations.
OECD 488: Transgenic Rodent Somatic and Germ Cell Gene Mutation Assays. Tests for: Gene mutations/point mutations and chromosomal rearrangements.

In vivo genotoxicity tests in somatic cells (positive result in combination with positive *in vitro* tests indicates GHS category 2).
OECD 486: Unscheduled DNA Synthesis (UDS) Test with Mammalian Liver Cells *in vivo.* This test Identifies substances that induce DNA damage followed by DNA repair.

OECD 489: *In vivo* Mammalian Alkaline Comet Assay. This tests for DNA damage that may or may not lead to gene mutations and/or chromosome aberrations as the DNA may effectively be repaired.

In vitro tests (positive result supports a GHS category 2 indication)
OECD 471: Bacterial Reverse Mutation Test (Ames test). Tests for: point mutations.
OECD 473: *In vitro* Mammalian Chromosome Aberration Test. Tests for: Structural chromosome aberrations.
OECD 476: *In vitro* Mammalian Cell Gene Mutation Test (hprt or xprt). Tests for: Gene/point mutations
OECD 487: *In vitro* Mammalian Cell Micronucleus Test. Tests for: Structural and numerical chromosome aberrations.
OECD 490: *In vitro* Mammalian Cell Gene Mutation Tests Using the Thymidine Kinase Gene (includes methods for both the Mouse Lymphoma Assay and the TK6 assay). The MLA is more widely used and tests for point mutations and structural chromosome aberrations. Note: these tests were previously included as part of OECD 476 in an older version of the test guidelines.

Tests deleted/archived from the OECD Guidelines:
These tests may also be utilized if sufficient data based on the preferred tests listed above are not available. These tests were archived because they were rarely used for regulatory purposes, newer tests became available showing better performance for the same endpoint and/or because assays performed using mammalian cells are more relevant to humans.
OECD 477: Genetic Toxicology: Sex-Linked Recessive Lethal Test in Drosophila melanogaster. (*in vivo* heritable germ cell mutagenicity test)
OECD 479: Genetic Toxicology: In vitro Sister Chromatid Exchange Assay in Mammalian Cells. (*in vitro* genotoxicity test in somatic cells)
OECD 480: Genetic Toxicology: Saccharomyces cerevisiae, Gene Mutation Assay. (*in vitro* mutagenicity test)
OECD 481: Genetic Toxicology: Saacharomyces cerevisiae, Miotic Recombination Assay. (*in vitro* genotoxicity test in somatic cells)
OECD 482: Genetic Toxicology: DNA Damage and Repair, Unscheduled DNA Synthesis in Mammalian Cells in vitro. (*in vitro* genotoxicity test in somatic cells)
OECD 484: Genetic Toxicology: Mouse Spot Test. (*In vivo* somatic cell mutagenicity test)

Rating Criteria
Within the context of this methodology, mutagenicity is an endpoint that is solely based on empirical evidence, and neither QSAR results nor definitive global regulatory lists are relied upon for decision-making. Without any relevant studies for mutagenicity, the rating for this endpoint is GREY. Table 7 provides a summary of the rating criteria.

For the mutagenicity endpoint, a rating of GREEN is defined as a substance that has been tested and shown not to induce aberrations of chromosomes or aberrations of their segregation in *in vitro* systems. In addition, the substance has been shown not induce point mutations. For example, if only OECD 471 (Ames) and OECD 473 (chromosome aberration test) are

available, the results of both must be negative to assign a GREEN rating. A GREEN rating may also be assigned in the case that only OECD 487 (micronucleus) and OECD 473 (Ames) are available and both are negative.

A YELLOW hazard rating has been defined as a substance that has been tested and shown not to induce point mutations. For example, if OECD 471 (Ames) is negative and no other data are available, a YELLOW hazard rating is assigned. Also, for example, if one of the *in vivo* somatic cell genotoxicity tests (i.e. OECD 486 or 489) has been conducted and is positive, but there is one *in vitro* test that is negative (such as a negative OECD 490/Mouse Lymphoma Assay), then a YELLOW hazard rating is assigned.

A RED rating is assigned to this endpoint if the chemical shows statistically significant positive results in eukaryotic or prokaryotic mutagenic assays. For example, if only OECD 471 (Ames) and/or OECD 473 (chromosome aberration test) are available and one of these is positive, a RED hazard rating is assigned. In general, a positive result from a single well conducted study using one of the preferred methods in the preceding section is typically enough to give a RED rating in the absence of any additional conflicting data.

The examples above and the rating criteria in the table below represent cases of minimal data availability. In cases where additional eukaryote data are available, and the results conflict with these minimum data examples, a weight of evidence approach is taken in deriving the final hazard rating.

Assessors are to consider test ranges and/or limit values indicated for the tests under consideration in the most recent version of the OECD Guidelines for the Testing of Chemicals in evaluating the data. If a test has been performed using test substance concentrations greater than the recommended test ranges or specified limit values, the test result may be discounted at the assessor's discretion.

Table 7 Rating Criteria for Mutagenicity

Green	Yellow	Red	Grey
Not classified as GHS Category 1A, 1B, or 2. Substance does not induce aberrations of chromosomes OR substance does not induce chromosome segregation errors in *in vitro* systems. AND substance does not induce point mutations.	Not classified as GHS Category 1A, 1B, or 2. Insufficient data. Substance does not induce point mutations. Data lacking on chromosome aberration and segregation.	Classified as GHS Category 1A, 1B, or 2. or Evidence of mutagenicity supported by positive results *in vitro* or *in vivo* (see rating criteria guidance) *or* Listed as: MAK IX 1, 2, 3A, 3B, H340: May cause genetic defects H341: Suspected of causing genetic defects	No data available for classification.

3.3.4 Reproductive & Developmental Toxicity

Definition
GHS offers the following definition of reproductive toxicity:

"Reproductive toxicity includes adverse effects on sexual function and fertility in adult males and females, as well as developmental toxicity in the offspring (UNECE, 2009)*."*

Appropriate experimental design for reproductive toxicity studies includes internationally accepted test methods such as OECD Guidelines 421 – Reproduction/ Developmental Toxicity Screening Test, 422 – Combined Repeated Dose Toxicity Study with Reproduction/ Developmental Toxicity Screening Test, and methods for two-generation toxicity testing (e.g., OECD Test Guidelines 415 and 416). Studies must also use appropriate routes of administration that apply to potential human exposure. For reproductive toxicity studies, administration is often given by the oral route, which is suitable for evaluating a chemical's relevancy to human health. However, if there is evidence that this route of administration is not relevant to humans by clearly identifying mechanistic and mode of action considerations, then a positive study for reproductive toxicity should not be considered.

In principle, adverse effects on reproduction seen only at very high dose levels in animal studies (e.g. doses that induce prostration, severe inappetence, excessive mortality) would not normally lead to classification unless other information is available (e.g. toxicokinetics

information indicating that humans may be more susceptible than animals) to suggest that classification is appropriate. (UNECE, 2011)

While the GHS has included developmental toxicity under the wider category of "reproductive toxicity", there are some test methodologies that are specific to developmental toxicity and therefore it is helpful to define the term separately and provide further specific guidance here.

"Taken in its widest sense, developmental toxicity includes any effect which interferes with normal development of the conceptus, either before or after birth, and resulting from exposure of either parent prior to conception, or exposure of the developing offspring during prenatal development, or postnatally, to the time of sexual maturation. However, it is considered that classification under the heading of developmental toxicity is primarily intended to provide a hazard warning for pregnant women and men and women of reproductive capacity. Therefore, for pragmatic purposes of classification, developmental toxicity essentially means adverse effects induced during pregnancy, or as a result of parental exposure. These effects can be manifested at any point in the life span of the organisms. The major manifestations of developmental toxicity include death of the developing organism, structural abnormality, altered growth, and functional deficiency." (UNECE, 2009).

The Cradle to Cradle Certified methodology also takes a pragmatic approach to developmental toxicity where the scope of adverse effects is drawn from exposure of either parent prior to conception and prenatal exposure.

Primarily, studies that are difficult to interpret are those in which maternal toxicity that can affect the development of offspring throughout gestation and the early postnatal stage is also observed (UNECE, 2009). Generally, developmental effects seen in the presence of maternal toxicity are still rated RED unless it can be unequivocally demonstrated that the developmental effects are secondary to maternal toxicity. However, where minor developmental changes are seen (e.g., small changes in fetal/pup body weight, retardation of ossification) in association with maternal toxicity, a YELLOW rating is appropriate. Additionally, maternal mortality greater than 10% is considered excessive and the data for that dose level should not normally be considered for further consideration (UNECE, 2009).

Acceptable tests for developmental toxicity include:

- OECD Test Guideline 414, 415, and 416.
- OECD Test Guidelines 421 and 422.
- ICH Guideline S5A.
- ICH S5B.

This list is not exhaustive and studies structured similarly and within the guidelines of Good Laboratory Practices should be considered as well. The limit doses specified in the relevant OECD test, including any qualifying statements, apply.

Rating Criteria
For the purpose of rating reproductive and development toxicity, chemicals are given a GREY, RED, YELLOW, or GREEN rating based on evidence of adverse effects on sexual function, fertility, and development of offspring.

A RED rating is applied to those chemicals that have shown adverse effects to the male or female reproductive system or on the development of an embryo or fetus based on either evidence from humans or evidence from animal studies. Data from animal studies should provide clear evidence of adverse effects on human reproduction and fertility on the development of an embryo or fetus in the absence of other toxic effects. In the case of simultaneous toxic effects, the adverse effect on reproduction or development is not considered to be a secondary non-specific consequence of other toxic effects (UNECE, 2009). Collectively, this classification is for chemicals that are suspected, presumed, or known to be a reproductive or developmental toxicants. Other classifications that are harmonized with this rating include MAK Group A or B (damage to embryo or fetus in humans has been unequivocally demonstrated, or according to currently available information, damage to embryo or fetus must be expected), California's Proposition 65 list of reproductive and carcinogenic substances, and GHS's 1A, 1B, and 2 classifications.

A YELLOW rating is applied to studies that yield an equivocal result for reproductive and/or developmental toxicity. This includes where other toxic effects are present and reproductive toxicity is considered a secondary toxic effect. If a chemical is listed as a MAK Group C (there is no reason to fear damage to the embryo or fetus when MAK and BAT values are observed), this also warrants a YELLOW rating. In addition, if appropriate doses have been selected and a substance is not classified as GHS Category 1A, 1B, or 2 and exhibits no adverse effects to sexual function and fertility and/or to the development of an embryo or fetus based on human or animal studies, the substance will receive a YELLOW rating in cases where the highest dose tested was below the guidance value for a green hazard rating (in other words, in this case the highest dose tested, with a negative result, may be in the RED or YELLOW range to receive a YELLOW rating, as long as appropriate doses were selected). In general, dose levels should be spaced to produce a gradation of toxic effects. See the relevant OECD test guidelines for additional information.

A GREEN rating is applied to chemicals that have shown no adverse toxic effects to sexual function, fertility, or on the development of an embryo or fetus (i.e. data on both reproductive toxicity and developmental toxicity is not required in order to assign a GREEN rating). This evidence can be based on either human or animal studies.

Where no studies are available for the reproductive toxicity of a chemical and the chemical does not appear on either the MAK or California Proposition 65 list, a GREY rating is applied.

The hazard rating for reproductive and developmental toxicity is based on all appropriate available evidence. This includes epidemiological studies, case reports in humans, reproduction studies, and sub-chronic/chronic study results that provide relevant data to

fertility and sexual function. The impact of a study on the final rating is determined by such factors as the quality of the study, consistency of results, nature and severity of effects, level of statistical significance for intergroup differences, number of endpoint affects, relevance of route of administration to humans, and freedom from bias (UNECE, 2009). All relevant data are considered, negative and positive results alike, to reach a final rating; however, a single positive result from a study showing statistically significant results and performed with sound scientific principles affords a RED rating.

Table 8 Rating Criteria for Reproductive & Developmental Toxicity

Green	Yellow	Red	Grey
Not classified as GHS Category 1A, 1B, or 2. Exhibits no adverse effects to sexual function and fertility and/or to the development of an embryo or fetus based on human or animal studies. Oral NOAEL > 500 mg/kgBW/day. Inhalation NOAEL >2.5 mg/l 6-8 h/day.	Not classified as GHS Category 1A, 1B, or 2. Equivocal evidence of toxic effects to sexual function and fertility but considered a secondary non-specific consequence of other toxic effects present. *and/or* Equivocal evidence of adverse effects to the development of an embryo or fetus based on human or animal studies. Oral NOAEL =50-500 mg/kg BW/day. Inhalation NOAEL =0.25-2.5 mg/l 6-8 h/day. *or* Listed as: MAK C	Classified as GHS Category 1A, 1B, or 2. Known, presumed, or suspected of causing adverse effects to sexual function and fertility and/or to the development of an embryo or fetus based on human or animal studies. *and/or* Oral NOAEL < 50 mg/kg BW/day. Inhalation NOAEL <0.25 mg/l 6-8 h/day. *or* Listed as: MAK Group A or B H360: May damage fertility or the unborn child. H361: Suspected of damaging fertility or the unborn child.	No data available for classification. Listed as: MAK D

Note: The NOAEL cut-offs in the Rating Criteria for Reproductive and Developmental Toxicity table above take precedence over the GHS classifications, H-phrases and MAK groups. Exception: Substances that are on REACH Annex XVII or on the Candidate List of Substances of Very High Concern because they are toxic for reproduction must always receive a RED hazard rating for this endpoint.

3.3.5 Oral Toxicity

Definition

Oral toxicity refers to adverse effects following oral administration of a single dose (acute) or longer-term repeated exposures (sub-chronic/chronic).

The definition given by the GHS for Acute Oral Toxicity states that, "Acute toxicity refers to those adverse effects occurring following oral administration of a single dose of a substance, or multiple doses given within 24 hours." (UNECE, 2009). This definition has been adopted for this methodology.

Acute toxicity values are expressed as LD_{50} values of mg of substance per kg of organism body weight (mg/kg). LD_{50} values represent the statistically derived median dose of a substance that can be expected to cause death in 50% of the test population. However, specific

organ toxicity not resulting in death can also occur from acute exposure. This is captured here as well.

The sub-chronic (90 day - 1 year) and chronic (1-2 years) hazard endpoints are intended to capture specific target organ toxicity that may present potential adverse health effects in humans when the target organ toxicity has not been classified in other endpoints of the Cradle to Cradle Certified methodology that are subject to repeated exposure (e.g., reproductive toxicity, carcinogenicity, etc). Sub-chronic or single exposure target organ toxicity studies of duration <90 days may be used only if no studies of duration >90 days are available and if criteria values have been adjusted for the study duration per point 3.9.2.9.5 of GHS Chapter 3.9 (UN 2013). Often these types of studies do not end in mortality, thus LD_{50} values are not appropriate and the measured endpoint used for the purposes of this classification system is the lowest observable adverse effect level (LOAEL). In cases where both a measured LOAEL value (as determine by the assessor) and a NOAEL value less than the criteria value are available, refer to the CLP/GHS guidance on the application of the CLP criteria on how to interpolate between the LOAEL and NOAEL values.[1]

Rating Criteria

Chemicals are allocated to one of three toxicity categories based on acute and/or sub-chronic/chronic toxicity by the oral route of exposure, measured by the LD_{50} and LOAEL, as summarized in Table 9. In order to assign a YELLOW or GREEN rating, data are required for both acute and sub-chronic/chronic toxicity. Single exposure organ toxicity data are not required but must be considered when available. In addition, single exposure organ toxicity data may not be used in place of chronic/sub-chronic data.

[1] https://echa.europa.eu/documents/10162/23036412/clp_en.pdf/58b5dc6d-ac2a-4910-9702-e9e1f5051cc5 - p 442

Table 9 Rating Criteria for Oral Toxicity

Green	Yellow	Red	Grey
Acute: Not Classified as GHS Category 1, 2, 3, or 4. LD50 > 2000 mg/kg BW	**Acute:** Classified as GHS Category 4 *or* 300 < LD50 ≤ 2000 mg/kg BW Listed as: H302: Harmful if swallowed	**Acute:** Classified as GHS Category 1, 2, or 3 *or* LD50 ≤ 300 mg/kg BW Listed as: H300a/b: Fatal if swallowed H301 Toxic if swallowed H304: May be fatal if swallowed and enters airways	No relevant data available for classification.
Single exposure organ toxicity: Not Classified. LOAEL > 2000 mg/kg BW	**Single exposure organ toxicity:** Classified as GHS Category 2 or 3 300 < LOAEL ≤ 2000 mg/kg BW Listed as: H371: May cause damage to organs via oral exposure	**Single exposure organ toxicity:** Classified as GHS Category 1 *or* LOAEL ≤ 300 mg/kg BW Listed as: H370: Causes damage to organs via oral exposure	
Sub –Chronic/Chronic: Not Classified. LOAEL > 100 mg/kg bw/day	**Sub –Chronic/Chronic:** Classified as GHS Category 2 10 < LOAEL ≤100 mg/kg bw/day Listed as: H373: May cause damage to (organs) through prolonged or repeated dermal exposure	**Sub –Chronic/Chronic**: Classified as GHS Category 1 *or* LOAEL ≤ 10 mg/kg bw/day Listed as: H372: Causes damage to (organs) through prolonged or repeated oral exposure	

3.3.6 Dermal Toxicity

Definition

Dermal toxicity refers to adverse effects following dermal administration of a single dose (acute) or longer-term repeated exposures (sub-chronic/chronic).

The definition given by GHS for Acute Dermal Toxicity states that, “Acute toxicity refers to those adverse effects occurring following dermal administration of a single dose of a

substance, or multiple doses given within 24 hours" (UNECE, 2009). This definition has been adopted for the Cradle to Cradle Certified™ methodology.

Acute toxicity values are expressed as LD_{50} values of mg of substance per kg of organism body weight (mg/kg). LD_{50} values represent the statistically derived median dose of a substance that can be expected to cause death in 50% of the test population. However, specific organ toxicity not resulting in death can also occur from acute exposure. This is captured here as well.

The sub-chronic (90 day - 1 year) and chronic (1-2 years) hazard endpoints are intended to capture specific target organ toxicity that may present potential adverse health effects in humans when the target organ toxicity has not been classified in other criteria of the Cradle to Cradle Certified methodology that are subject to repeated exposure (e.g., reproductive toxicity, carcinogenicity, developmental toxicity). Sub-chronic or single exposure target organ toxicity studies of duration <90 days may be used only if no studies of duration >90 days are available and if criteria values have been adjusted for the study duration per point 3.9.2.9.5 of GHS Chapter 3.9 (UN 2013). Often these types of studies do not end in mortality, thus LD_{50} values are not appropriate and the measured endpoint used for the purposes of this methodology is the LOAEL. In cases where both a measured LOAEL value (as determine by the assessor) and a NOAEL value less than the criteria value are available, refer to the CLP/GHS guidance on the application of the CLP criteria on how to interpolate between the LOAEL and NOAEL values.[2]

In the case that a thorough literature search has been completed and it is determined that dermal toxicity data are not available but would be required in order to assign other than a GREY single chemical risk rating, the assessor may consider the possibility of using route to route extrapolation. The relevant ECHA guidance is to be consulted (for example, ECHA, 2012 and 2014). If extrapolation is used, then all assumptions are to be documented and provided as part of the assessment outcome.

Rating Criteria

Chemicals are allocated to one of three toxicity categories based on acute and/or sub-chronic/chronic toxicity by the dermal route of exposure as measured by the LD_{50} and LOAEL and summarized in Table 10. Single exposure and sub-chronic/chronic toxicity data must be considered when available, but are not required in order to assign a rating to the Dermal Toxicity endpoint.

[2] https://echa.europa.eu/documents/10162/23036412/clp_en.pdf/58b5dc6d-ac2a-4910-9702-e9e1f5051cc5 - p 442

Table 10 Rating Criteria for Dermal Toxicity

Green	Yellow	Red	Grey
Acute: Not Classified as GHS Category 1, 2, 3, or 4. LD50 > 2000 mg/kg BW	**Acute:** Classified as GHS Category 4 *or* 1000 < LD50 ≤ 2000 mg/kg BW Listed as: H312: Harmful in contact with skin	**Acute:** Classified as GHS Category 1, 2, or 3 or LD50 ≤ 1000 mg/kg BW Listed as: H310a/b: Fatal in contact with skin H311: Toxic in contact with skin	No relevant data available for classification.
Single exposure organ toxicity: Not Classified. LOAEL > 2000 mg/kg BW	**Single exposure organ toxicity:** Classified as GHS Category 2 or 3 *or* 1000 < LOAEL ≤ 2000 mg/kg BW Listed as: H371: May cause damage to organs via dermal exposure	**Single exposure organ toxicity:** Classified as GHS Category 1 *or* LOAEL ≤ 1000 mg/kg BW Listed as: H370: Causes damage to organs via dermal exposure	
Sub –Chronic/Chronic: Not Classified. LOAEL > 200 mg/kg bw/day	**Sub –Chronic/Chronic:** Classified as GHS Category 2 *or* 20 < LOAEL ≤ 200 mg/kg bw/day Listed as: H373: May cause damage to (organs) through prolonged or repeated dermal exposure	**Sub –Chronic/Chronic:** Classified as GHS Category 1 *or* LOAEL ≤ 20 mg/kg bw/day Listed as: H372: Causes damage to (organs) through prolonged or repeated dermal exposure	

3.3.7 Inhalation Toxicity

Definitions

Inhalation toxicity refers to adverse effects following inhalation administration of a single dose (acute) or longer-term repeated exposures (sub-chronic/chronic).

The definition given by GHS for Acute Inhalation Toxicity states that, "Acute toxicity refers to those adverse effects occurring following an inhalation exposure of 4 hours" (UNECE, 2009). This definition has been adopted for the Cradle to Cradle Certified methodology.

Acute toxicity values are expressed as LC_{50} (inhalation) values of mg of substance per volume (mg/m^3). LC_{50} values represent the statistically derived median dose of a substance that can be

expected to cause death in 50% of the test population. However, specific organ toxicity not resulting in death can also occur from acute exposure. This is captured here as well.

The sub-chronic (90 day - 1 year) and chronic (1-2 years) hazard endpoints are intended to capture specific target organ toxicity that may present potential adverse health effects in humans when the target organ toxicity has not been classified in other endpoints of the Cradle to Cradle Certified methodology that are subject to repeated exposure (e.g., reproductive toxicity, carcinogenicity, developmental toxicity). Sub-chronic or single exposure target organ toxicity studies of duration <90 days may be used only if no studies of duration >90 days are available and if criteria values have been adjusted for the study duration per point 3.9.2.9.5 of GHS Chapter 3.9 (UN 2013). Often these types of studies do not end in mortality, thus LD_{50} values are not appropriate and the measured endpoint used for the purposes of this methodology is the LOAEL. In cases where both a measured LOAEL value (as determine by the assessor) and a NOAEL value less than the criteria value are available, refer to the CLP/GHS guidance on the application of the CLP criteria on how to interpolate between the LOAEL and NOAEL values.[3]

In the case that a thorough literature search has been completed and it is determined that inhalation toxicity data are not available but would be required in order to assign other than a GREY single chemical risk rating, the assessor may consider the possibility of using route to route extrapolation. The relevant ECHA guidance is to be consulted (for example, ECHA, 2012 and 2014). If extrapolation is used, then all assumptions are to be documented and provided as part of the assessment outcome.

For inhalation toxicity, multiple forms of a substance must be considered. Inhalation of vapor/gas is considered separately from inhalation of dust/mist.

Rating Criteria

Chemicals are allocated to one of three toxicity categories based on the acute and/or sub-chronic/chronic toxicity by the inhalation route of exposure as measured by the LD_{50} and LOAEL and summarized in Table 11. For very volatile substances (boiling point < 0°C), both acute and chronic toxicity data are required in order to assign a GREEN or YELLOW rating. Single exposure organ toxicity data are to be considered if available but are not required. In addition, single exposure organ toxicity data may not be used in place of chronic/sub-chronic data.

[3] https://echa.europa.eu/documents/10162/23036412/clp_en.pdf/58b5dc6d-ac2a-4910-9702-e9e1f5051cc5 - p 442

Table 11 Rating Criteria for Inhalation Toxicity

Green	Yellow	Red	Grey
Acute: Not Classified as GHS Category 1, 2, 3, or 4. Inhalation (gas) LC50 > 20000 ppmV Inhalation (vapor) LC50 > 20 mg/l/4hr Inhalation (dust/mist) LC50 > 5 mg/l/4hr	**Acute:** Classified as GHS Category 4 *or* Inhalation (gas) 2500 < LC50 ≤ 20000 ppmV Inhalation (vapor) 10 < LC50 ≤ 20 mg/l/4hr Inhalation (dust/mist) 1.0 < LC50 ≤ 5 mg/l/4hr Listed as: H332: Harmful if inhaled	**Acute:** Classified as GHS Category 1, 2, or 3 *or* Inhalation (gas) LC50 ≤ 2500 ppmV Inhalation (vapor) LC50 ≤ 10 mg/l/4hr Inhalation (dust/mist) LC50 ≤ 1 mg/l/4hr Listed as: H330a/b: Fatal if inhaled H331: Toxic if inhaled	No relevant data available for classification.

Green	Yellow	Red	Grey
Single exposure organ toxicity: Not Classified. LOAEL (gasses) > 20000 ppmV/4hr LOAEL (vapor) > 20 mg/L/4hr LOAEL (mists/dusts) > 5.0 mg/L/4hr	**Single exposure organ toxicity:** Classified as GHS Category 2 or 3 *or* 2500 < LOAEL (gasses) ≤ 20000 ppmV/4hr 10 < LOAEL (vapor) ≤ 20 mg/L/4hr 1.0 < LOAEL (mists/dusts) ≤ 5.0 mg/L/4hr Listed as: H371: May cause damage to organs via inhalation exposure H336: May cause drowsiness or dizziness	**Single exposure organ toxicity:** Classified as GHS Category 1 *or* LOAEL (gasses) ≤ 2500 ppmV/4hr LOAEL (vapor) ≤ 10 mg/L/4hr LOAEL (mists/dusts) ≤ 1.0 mg/L/4hr Listed as: H370: Causes damage to organs via inhalation exposure	
Sub –Chronic/Chronic: Not Classified. Inhalation (Gases) LOAEL > 250 ppmV/6h/d Inhalation (Vapors) LOAEL > 1.0 mg/L/6h/d Inhalation (Dusts & Mists) LOAEL > 0.2 mg/L/6h/d	**Sub –Chronic/Chronic:** Classified as GHS Category 2 *or* Inhalation (Gases) 50 < LOAEL ≤ 250 ppmV/6h/d Inhalation (Vapors) 0.2 < LOAEL ≤ 1.0 mg/L/6h/d Inhalation (Dusts & Mists) 0.02 < LOAEL ≤ 0.2 mg/L/6h/d Listed as; H373: May cause damage to (organs) through prolonged or repeated inhalation	**Sub –Chronic/Chronic:** Classified as GHS Category 1 *or* Inhalation (Gases) LOAEL ≤ 50 ppmV/6h/d Inhalation (Vapors) LOAEL ≤ 0.2 mg/L/6h/d Inhalation (Dusts & Mists) LOAEL ≤ 0.02 mg/L/6h/d Listed as: H372: Causes damage to (organs) through prolonged or repeated inhalation	

3.3.8 Neurotoxicity

Definition

Neurotoxicity is an adverse change in the structure or function of the central and/or peripheral nervous system following exposure to a chemical, physical, or biological agent (Tilson, 1990). Structural neurotoxic effects are defined as neuroanatomical changes occurring at any level of nervous system organization. While functional neurotoxic effects include adverse changes in somatic/autonomic, sensory, motor, and/or cognitive function, structural

neurotoxic effects are defined as neuroanatomical changes occurring at any level of nervous system organization (U.S. EPA, 1998).

Neurotoxic substances can elicit cellular, anatomical, physiological, or behavioral effects. Cellular effects can include inhibition of macromolecule transmitter synthesis, alteration of ion flow, or prevention of the release of neurotransmitters. Anatomical effects include alterations of the cell body, axon, or the myelin sheath. Physiological effects may include change in neural activation or reduction of neurotransmission speed. Lastly, behavioral effects include significant changes in sensations of sight, hearing, touch, reflexes, motor functions, and cognitive functions (U.S. EPA, 1998).

For the purposes of the Cradle to Cradle Certified methodology, the alterations to the central nervous system listed above are included as evidence of neurotoxic effects. Knowledge of exact mechanisms of action for adverse effects is not necessary to conclude that a chemical is neurotoxic.

Rating Criteria

As defined above, neurotoxic effects can be seen over a number of timelines including acute/ single, sub-chronic, and chronic exposures. There are several testing methods acceptable for this endpoint, including OECD 418, 419, and 424, not all of which require specific exposure periods. Since neurotoxic effects can be seen over a range of exposure periods, the criteria for single exposure organ toxicity, sub-chronic, and chronic toxicity are applied for neurotoxicity and summarized in Table 12.

Several types of data points can be used to rate a chemical's potential for neurotoxicity based on the definitions above. Human studies can be used, including clinical evaluations, case reports, epidemiologic studies, and human laboratory exposure studies if an OAEL or NO(A)EL have been determined. Animal studies, which provide more precise exposure information and control environmental factors, can be used as well for the purposes of rating a chemical's neurotoxic effects. Within animal studies, structural, neurochemical, neurophysiological, behavioral, and neurological endpoints are considered for this endpoint. Endpoints for these types of adverse health effects are provided below and are considered in this methodology:

<u>Structural or neuropathological endpoints</u>

- Gross changes in morphology, including brain weight.
- Histologic changes in neurons or glia (neuronopathy, axonopathy, myelinopathy).

<u>Neurochemical endpoints</u>

- Alterations in synthesis, release, uptake, degradation of neurotransmitters.
- Alterations in second-messenger-associated signal transduction.
- Alterations in membrane-bound enzymes regulating neuronal activity.
- Inhibition and aging of neuropathy enzyme.
- Increases in glial fibrillary acidic protein in adults.

Neurophysiological endpoints

- Change in velocity, amplitude, or refractory period of nerve conduction.
- Change in latency or amplitude of sensory-evoked potential.
- Change in electroencephalographic pattern.

Behavioral and neurological endpoints

- Increases or decreases in motor activity.
- Changes in touch, sight, sound, taste, or smell sensations.
- Changes in motor coordination, weakness, paralysis, abnormal movement or posture, tremor, ongoing performance.
- Absence or decreased occurrence, magnitude, or latency of sensorimotor reflex.
- Altered magnitude of neurological measurement, including grip strength, hind limb splay.
- Seizures.
- Changes in rate or temporal patterning of schedule-controlled behavior.
- Changes in learning, memory, and attention.

Developmental endpoints

- Chemically induced changes in the time of appearance of behaviors during development.
- Chemically induced changes in the growth or organization of structural or neurochemical elements (USEPA, 1998).

In addition to experimental data, a survey of industrial chemicals by Grandjean et al. provides a succinct summary of chemicals that have displayed neurotoxic effects (Grandjean, 2006 and 2014). If a chemical, identified by its CAS number, appears on the Mundy list, a RED rating is given as sufficient evidence available for adverse neurotoxic effects.

Table 12 Rating Criteria for Neurotoxicity

Green	Yellow	Red	Grey
Refer to Oral, Dermal and Inhalation Toxicity Single Exposure Organ, Sub-Chronic, and Chronic Toxicity criteria within Tables 9-11 for Green Rating.	Refer to Oral, Dermal and Inhalation Toxicity Single Exposure Organ, Sub-Chronic, and Chronic Toxicity criteria within Tables 9-11 for Yellow Rating.	Refer to Oral, Dermal and Inhalation Toxicity Single Exposure Organ, Sub-Chronic, and Chronic Toxicity criteria within Tables 9-11 for Red Rating. *or* Listed in Grandjean et al. text for neurotoxic effects.	No relevant data available for classification.

3.3.9 Skin, Eye, and Respiratory Corrosion/Irritation

Definition

Corrosion is the production of irreversible damage to the skin, eyes, or respiratory system. In skin, corrosion is typified by ulcer, bleeding, bloody scabs, and, by the end of observation at 14 days, by discoloration due to blanching of the skin (UNECE, 2009). For eyes, irreversible damage is observed by grade four cornea lesions observed during the test, as well as persistent corneal opacity, adhesion, pannus, and interference with the function of the iris or other effects that impair sight (UNECE, 2009). The respiratory tract is considered to comprise the nose, nasal cavity, larynx, trachea, bronchi, and alveoli. Irreversible effects on these organs include fibrosis, dyspneoea, bronchitis, and histomorphology.

Irritation is defined as the production of reversible damage to the skin, eyes, or respiratory tract in the appropriate time frames. For skin, an application of 4 hours is expected followed by 14 days of observation while for eyes a 21-day observation period is expected for reversible effects. Reversible effects on the respiratory tract include coughing, conjunctivitis, rhinitis, and scratchy throat.

Rating Criteria

Table 13 summarizes the rating scheme for corrosion/irritation. Review of human or animal in vivo studies are the primary resources for consultation to determine the appropriate hazard rating within this endpoint. Suitable studies for skin will have application periods of up to 4 hours and observation periods of 14 days. If within this time frame, one of three animals elicits signs of corrosion as described above, a rating of RED is given. In animal studies, if a mean score between 1.5 and 4.0 is generated for two of three animals, the chemical tested may be labeled as an irritant and classified YELLOW. Inflammation that occurs throughout the observation period but no signs of corrosion are present, a YELLOW rating is also warranted. If no irritating or corrosive effects are seen on the skin in animals or from human experience, the chemical may be classified GREEN.

For damage to the eye, irreversible effects in animal studies can be defined by several endpoints. Evidence that effects on the cornea, iris, or conjunctiva have not reversed or are expected to reverse within an observation period of 21 days are classified as RED. In addition, if 2 of 3 animals have received mean scores of ≥ 3 and/or >1.5 following grading at 24, 48, and 72 hours, a RED rating is warranted. A mild to severe irritant, a YELLOW rating, can be defined by 2 of 3 test animals receiving mean scores in the following gradings:

a. corneal opacity ≥ 1.
b. iritis ≥ 1.
c. conjunctival redness ≥ 2.
d. conjunctival oedema ≥ 2.

In cases where the mean scores are less than those listed above or no effects of irritation or corrosion are seen, a GREEN classification is given.

When no human or animal studies are available, pH extremes of ≤ 2 or ≥ 11.5 are the basis for classifying a chemical as RED. Such agents are expected to cause serious damage to eyes, skin, and the respiratory tract.

Additional criteria that can be used and are often presented for regulatory purposes are European Hazard Statements (H-phrases). This convention aligns with the definitions given above for irritation and corrosion and can thus be used for hazard ratings. H-phrases of 314 and 318 are used for classifying a substance as RED, while H-phrases of 315 and 319 are used for classifying a substance as YELLOW.

Table 13 Rating Criteria for Skin, Eye, and Respiratory Corrosion/ Irritation

Green	Yellow	Red	Grey
Not Classified as GHS Category 1, 2, or 3. No irritation to skin, eyes, or respiratory tract in relevant human or animal studies	Classified as GHS Category 2 or 3 for Skin Corrosion/Irritation and/or Category 2 for Eye Damage/Irritation. Mild to severe irritation to skin, eyes, or respiratory tract in relevant human or animal studies; *or* Listed as: H315: Causes skin irritation H319: Causes serious eye irritation H320: Causes eye irritation H335: May cause respiratory tract irritation	Classified as GHS Category 1 for Skin Corrosion/Irritation or Eye Damage/Irritation. Causes burns, corrosion, or serious damage to skin, eyes, or the respiratory tract* in relevant human or animals studies; *or* pH ≤ 2 or pH ≥ 11.5 *or* Listed as: H314: Causes severe skin burns and eye damage H318: Causes serious eye damage	No relevant data available for classification.

*Note: There are no separate GHS categories for respiratory corrosion/irritation. However, per GHS version 6, if a substance is determined to be corrosive (based on data such as skin or eye data), respiratory corrosivity hazard may also be communicated by some authorities in combination with the appropriate acute toxicity symbol (e.g. "corrosive to the respiratory tract").

3.3.10 Sensitization of Skin and Airways

Definition

The clinical definition of sensitization is an eczematous skin reaction resulting from hypersensitivity upon secondary skin or inhalation contact by an allergen (Smith et al, 2001).

This adverse health effect is considered to have two phases, known as induction or sensitization and elicitation. Upon exposure to a sensitizing dose, the immune system develops a memory to the allergen and a second exposure to the same allergen elicits production of a cell-mediated or anti-body, allergic response. Accordingly, appropriate tests incorporate both of these phases in order to identify clinical responses.

For the purposes of this methodology, a skin sensitizer is a substance that will lead to an allergic response following skin contact, and a respiratory sensitizer is a substance that will lead to hypersensitivity of the airways following inhalation (UNECE, 2009).

Rating Criteria

If there is either evidence in humans or positive results from an appropriate animal test that a substance can lead to sensitization by skin contact or respiratory inhalation, then the substance will be profiled RED for this endpoint. In the case of sensitization, results from animal studies are generally more reliable than studies from human exposure. Human studies are normally not conducted in controlled experiments for the purpose of hazard classification but rather as part of risk assessment (UNECE, 2009). For skin contact sensitization, human studies can include patch testing, epidemiological studies, well-documented episodes of allergic contact dermatitis (e.g., dermatitis from epoxy resins on watch wristbands) (UNECE, 2009). In airways sensitization, human evidence can include in vivo immunological tests, in vitro immunological tests, bronchial challenge tests, or studies that indicate specific hypersensitivity reactions. It is important to note that negative human data should not normally be used to disprove positive results from animal studies (UNECE, 2009).

Animal studies can either be classified as adjuvant, where an additional agent is used to modify the effects of a substance of interest, or non-adjuvant where the substance in question is tested alone. For an adjuvant animal study to be considered positive, a response must be elicited in 30% of the population, whereas in a non-adjuvant study, 15% of the population must show sensitizing effects (UNECE, 2009). Acceptable studies include Guinea Pig Maximization, Buehler guinea pig, mouse ear swelling test (MEST), and other methods that are scientifically validated. If these tests give an elicitation between 0-15% for non-adjuvant and 0-30% for adjuvant studies, this hazard endpoint will be classified as YELLOW.

Results from local lymph node assay (LLNA) may also be used according to GHS [UN, 2015].

If the data indicates no sensitization effects were seen in any populations, then this endpoint is assigned a GREEN hazard rating. However, experimental data are not always available and in these cases MAK designations are used for reference. If a substance is not listed as a MAK sensitizer of airways (MAK Sa) or sensitizer of skin (MAK Sh), a GREY rating is given. Where a chemical is listed according to the MAK definition as a medium to strong airway or skin sensitizer, a RED profile is given. Table 14 provides a quick reference for the hazard rating criteria for sensitization.

Data on skin sensitization alone is sufficient to assign a hazard rating to this endpoint although data on respiratory sensitization must be considered when available.

Table 14 Rating Criteria for Sensitizing Effects

Green	Yellow	Red	Grey
Not classified as GHS Category 1A or 1B. Adequate data available. No evidence of sensitization in human and/ or animal studies. *or* No data from human or animal studies are available; however, the substance is not classified under GHS, not listed as H334/317 or MAK, and there is a history of safe use (10 years or more) without reported cases of sensitization, as documented by a signed statement from the substance manufacturer.	Not classified as GHS Category 1A or 1B. Non-adjuvant animal studies elicit a response 15% > population > 0%. Adjuvant animal studies elicit a response of 30% > population > 0%. *or* 1< LLNA SI < 3	Classified as GHS Category 1A or 1B for Sensitization (respiratory and skin): *or* *LLNA SI ≥ 3* *or* Listed as: GHS Category 1A or 1B for Sensitization (respiratory and/or skin) MAK skin or airways sensitizer (MAK Sa or Sh). H334: May cause allergy or asthma symptoms or breathing difficulties in inhaled. H317: May cause an allergic skin reaction.	No relevant data for classification.

3.3.11 Other (Human Health)

Definition and Rating Criteria

The Other (Human Health) endpoint is intended to cover any additional characteristic relevant to the overall evaluation of human health not covered by other endpoints.

Unlike for other endpoints, an assessor may assign a RED hazard rating based on any credible piece of information that suggests a human health hazard not addressed by other hazard endpoints. Information that is typically assessed within the scope of this endpoint includes a chemical's flammability, oxidation potential, reactivity, skin penetration potential, and volatility. Based on this information and the assessor's professional judgment, a hazard rating of either RED or GREEN is assigned. Note that YELLOW or GREY hazard ratings are not possible within this endpoint.

As for all endpoints, if different information types considered (e.g., flammability, reactivity) would lead to the assignment of different hazard ratings, a RED rating trumps all other possible assignments. For example, chemicals that could be assigned to Category 1 or 2 based

on GHS physical hazards criteria would typically receive a RED rating in this endpoint. However, other information that is too complex or too context-dependent to be amenable to the RED, YELLOW, GREEN rating scheme is also meant to be included here. For example, skin penetration potential or nanomaterial properties may or may not represent a hazard based on interactions with other hazard endpoints, material matrix composition, and the product's intended uses. In such cases, the assessor would note the relevant property and assign a RED hazard rating as a reminder to consider this additional information in the risk assessment step.

Ultimately, this endpoint also serves as a placeholder for other hazard endpoints that may be added to the standard in future revisions. As such, material assessors are expected to submit to the Institute an 'Other hazards and risks' report within two months of the Assessment Summary when a single chemical risk score of 'x' was assigned to a chemical based on a RED hazard flag in an 'Other' endpoint. The report has to provide sufficient context and documentation for an expert to understand the reasons that led to the specific chemical being considered hazardous in the situation. To protect confidential business information, generic terminology may be used to describe the material and the product in the context of the assessment that took place, but the evidence and reasoning that led to the decision must be clear. Such reports are then distributed in the Cradle to Cradle accredited Materials Assessment community and may be cited in future Assessment Summary Forms.

3.3.12 Aquatic Toxicity (Three separate endpoints: Fish, Daphnia, and Algae Toxicity)

Definition

Aquatic toxicity is the ability of a chemical to cause adverse or injurious health effects to an aquatic organism. For the purposes of the Cradle to Cradle Certified methodology, fish (vertebrate), daphnia (invertebrate), and algae are chosen since they cover a range of trophic levels and taxa in the aquatic environment and are generally representative of aquatic fauna and flora. In addition, data on these taxa are more likely to be available as they are accepted or required in many regulatory schemes. Toxicity to each of these three taxa is treated separately, as a separate endpoint, which means that they will receive three separate RED/YELLOW/GREEN/GREY hazard ratings. The discussion of the three endpoints is combined here since there are a lot of commonalities in the complicating experimental factors (such as unstable or insoluble substances), permissible modeling approaches, and in the requirements for when chronic toxicity data must be obtained in addition to acute toxicity data.

Acute aquatic toxicity is the ability of a chemical to cause adverse or injurious health effects to an organism in a short-term aquatic exposure scenario. Chronic aquatic toxicity is the intrinsic property of a substance to cause adverse effects to aquatic organisms during aquatic exposure that is determined in relation to the life-cycle of the organism (UNECE, 2009). Similar to acute toxicity, for the purposes of the Cradle to Cradle Certified methodology, fish (vertebrate), daphnia (invertebrate), and algae are chosen since they cover a range of trophic levels and taxa in the aquatic environment and are generally representative of aquatic fauna and flora. Generally, results from both acute and chronic studies may influence the ratings in the three aquatic toxicity endpoints. However, since chronic toxicity tests are rarely

conducted, if there are no signs of toxicity in acute studies, chronic data is not required for an aquatic toxicity endpoint when acute data suggests a green rating for that endpoint (see *Availability of Acute Toxicity vs. Chronic Toxicity Data* below).

Rating Criteria

Required tests for the aquatic toxicity endpoints include 96-hour LC_{50}, 48-hour EC_{50}, and 72- to 96-hour EC_{50} for fish, daphnia, and algal toxicity respectively. Data quality and interpretation of results that are dependent on a chemical's properties are also important for these endpoints. Criteria for RED, YELLOW, and GREEN ratings are provided in Tables 15-17.

The toxicity thresholds for aquatic toxicity endpoints should preferably be drawn from data required for regulatory purposes, recognized databases, and relevant literature. As a general rule, data generated by recognized international standards (OECD guidelines EPA, ASTM, or ISO EU) or conforming with Good Laboratory Practices is preferred. In cases where this is not available, less rigorous types of data can be used, such as MSDS data, or QSAR software can be used for appropriate chemicals.

For this rating scheme, freshwater and marine species toxicity are considered equivalent. No preference is given to exposure regimes that typically are employed in four types: static, static-renewal, recirculation, and flow-through. Depending on the characteristics of a chemical, different methods are used and as long as a valid test is performed all exposure scenarios are equivalent.

Occasionally there are multiple acceptable tests for a taxonomic group. In this case, the most sensitive test (i.e., study with the lowest $L(E)C_{50}$) is used for rating purposes. This is applied on a case-by-case basis and, where large data sets are available (four or more), a mean average of the results can be used for classification (UNECE, 2009). However, this should only be applied in cases where the tests are performed on the same species.

Difficult to Test Substances – Although the criteria are intended to apply to all chemicals and substances, it is recognized that there are some substances (i.e., metals, poorly soluble chemicals, volatile chemicals) that need special consideration when interpreting test results. Testing for aquatic toxicity requires the dissolution of the substance in the test water media and continuation of a constant exposure concentration over the duration of the test period (UNECE, 2009). However, some substances make this requirement difficult and professional judgment must be applied for these chemicals that generally cause difficulties in testing.

Chemical properties that can contribute to losses of concentration in testing conditions include poorly water soluble, volatile, photo-degradable, hydrolytically unstable, oxidizable, biodegradable, adsorbing, chelating, colored, hydrophobic, ionized, or complex mixtures (UNECE, 2009). In all of these difficult testing conditions, the actual test concentration is likely to be below the nominal test concentration provided by the guideline (UNECE, 2009). If acute toxicities are reported to be <10 mg/L, the practitioner can be fairly confident in a RED rating. However, it is more difficult in cases where the $L(E)C_{50}$ is reported to be >10

mg/L, where expert judgment is needed on the validity of the study and appropriate rating for a chemical.

Unstable Substances – Unstable substances include those that are quickly hydrolyzed in water, photo-degrade, oxidize, and are volatile or biodegrade. In these cases, not only is there concentration loss in the study, but secondary degradation products arise that can have unique toxicity hazards. In cases where chemicals exhibit these properties it is essential to have data on the measured exposure concentrations at suitable time points in the study. Without this prerequisite, a study should be deemed invalid for hazard ratings. Where these data are available, the mean average of the start and end concentrations of the test can be used to calculate the $L(E)C_{50}$ (UNECE, 2009).

Where the identification of the breakdown products is known, classification of these chemicals for acute aquatic toxicity hazards should also be determined by the normal protocol. The resulting rating for acute aquatic toxicity of the breakdown products will affect the overall aquatic toxicity rating for the parent compound (i.e., a byproduct RED for acute aquatic toxicity will result in a RED rating for aquatic toxicity of the parent chemical).

Poorly Soluble Substances – Typically these chemicals are considered to be <1 mg/L, but there are additional scenarios where the guidance for these substances may be applicable. In older studies it is normal to find toxicity levels in excess of the water solubility, or where dissolved levels are below the detection limit of a method used (UNECE, 2009). Where studies of this kind are the only available data, some practical rules may be applied.

In studies that report acute toxic effects in the aquatic environment at levels in excess of the water solubility, the $L(E)C_{50}$ may be assumed to be equal to the measured water solubility. The assumption in this case is that the excess, undissolved substance did not contribute to toxicity through physical effects and should be carefully considered. Similarly, where no acute toxicity effects are seen in excess of water solubility, the $L(E)C_{50}$ may be considered to be greater than the measured water solubility (UNECE, 2009). This value still may not give clarity on the final rating a chemical should receive and it is therefore assumed that if a chemical does not show toxic effects within its range of solubility then it may be rated GREEN.

Some studies fail to report the concentration since the detection limit of the method used may not be sensitive enough and able to capture poorly soluble chemicals. In such instances, where acute toxic effects are observed, the $L(E)C_{50}$ may be considered to be less than the analytical detection limit. Where no toxicity is observed, the $L(E)C_{50}$ may be considered to be greater than the water solubility. As indicated above, in this latter case, a rating of GREEN may be given to this endpoint.

Other Factors – Several other factors can contribute to concentration loss in studies, including sedimentation, adsorption, and bioaccumulation. For sedimentation and bioaccumulation, determination of the $L(E)C_{50}$ is analogous to chemicals that exhibit instability. Adsorption tends to occur with chemicals that have high log Kow values and loss of concentration tends

to be rapid. In these instances, end of test concentrations may be used to determine exposure thresholds.

Quantitative Structure Activity Relationships (QSAR) – When no other data are available through studies, Quantitative Structure Activity Relationships (QSARs) may be used to predict the aquatic toxicity of chemicals. In particular, Ecosar v.1.11, developed by the US EPA, is used for these purposes.

No Observable Effect Concentration – Chronic effects include a range of sub-lethal endpoints and are generally expressed in terms of a No Observable Effect Concentration (NOEC). Observable endpoints from acceptable tests (OECD 210 – Fish Early Life Stage, 211 – Daphnia Reproduction, and 201 Algal Growth) include survival, growth, morphological abnormalities, and behavioral effects. Other validated and internationally accepted test methods may be used in these classification schemes that are comparable to the OECD tests listed above. The NOEC's determined in the appropriate tests are used in the Cradle to Cradle Certified methodology in order to rate a chemical for its intrinsic chronic aquatic toxicity. The criteria for each rating are provided in Tables 15-17.

Availability of Acute Toxicity vs. Chronic Toxicity Data – Typically, acute toxicity is more widely available than chronic toxicity data for aquatic species and subsequently is relied upon in many classification schemes with the appropriate combination of biodegradation and bioaccumulation data. Where both data points are available for a given aquatic toxicity endpoint, preference shall be given to chronic toxicity rather than a combination of acute toxicity with degradability and bioaccumulation data. If a substance would obtain a GREEN rating for a given toxicity endpoint based on acute toxicity data and no chronic toxicity data is available, this lack of data will not impact the hazard rating for this endpoint. However, if a substance would obtain a YELLOW rating for a given toxicity endpoint based on acute toxicity data and no chronic toxicity data is available, the rating for that endpoint shall remain GREY until chronic toxicity data can be found or estimated through modeling. This is because the unknown chronic toxic effect may be more severe than the observed acute once thus creating the risk falsely assign a YELLOW rating based solely on acute data when the actual rating would be RED due to chronic effects.

Table 15 Rating Criteria for Fish Toxicity (Vertebrate)

Green	Yellow	Red	Grey
Not Classified as GHS Category 1,2, or 3. 96 hour LC50 > 100 mg/L QSAR 96 hour LC50 > 100 mg/L	**Acute** Classified as GHS Category 3 or 10 < 96 hour LC50 ≤ 100 mg/L or 10 < QSAR 96 hour LC50 ≤ 100 mg/L AND **Chronic** 1 < NOEC ≤ 10 mg/L for chronic toxicity based on experimental or modeled results	**Acute** Classified as GHS Category 1 or 2 or 96 hour LC50 ≤ 10 mg/L or QSAR 96 hour LC50 ≤ 10 mg/L Listed as: H400: Very toxic to aquatic life OR **Chronic:** Classified as GHS Category 1,2, or 3 *or* NOEC ≤ 1 mg/L for chronic toxicity based on experimental or modeled results Listed as: H410: Very toxic to aquatic life with long lasting effects H411: Toxic to aquatic life with long lasting effects H412: Harmful to aquatic life with long lasting effects H413: may cause long lasting harmful effects to aquatic life	No relevant data for classification.

Table 16 Rating Criteria for Daphia Toxicity

Green	Yellow	Red	Grey
Not Classified as GHS Category 1,2, or 3. 48 hour L(E)C50 > 100 mg/L QSAR 48 hour L(E)C50 > 100 mg/L	**Acute** Classified as GHS Category 3 *or* 10 < 48 hour L(E)C50 10 ≤ 100 mg/L 10 < QSAR 96 hour L(E)C50 ≤ 100 mg/L AND **Chronic** 1 < NOEC ≤ 10 mg/L for chronic toxicity based on experimental or modeled results	**Acute** Classified as GHS Category 1 or 2 *or* 48 hour L(E)C50 ≤ 10 mg/L QSAR 48 hour L(E)C50 ≤ 10 mg/L OR **Chronic** Classified as GHS Category 1,2, or 3 or NOEC ≤ 1 mg/L for chronic toxicity based on experimental or modeled results Listed as: H400: Very toxic to aquatic life H410: Very toxic to aquatic life with long lasting effects H411: Toxic to aquatic life with long lasting effects H412: Harmful to aquatic life with long lasting effects H413: may cause long lasting harmful effects to aquatic life	No relevant data for classification.

Table 17 Rating Criteria for Algae Toxicity

Green	Yellow	Red	Grey
Not Classified as GHS Category 1,2, or 3. 72/ 96 hour L(E)C50 > 100 mg/L QSAR 72/ 96 hour L(E)C50 > 100 mg/L	**Acute:** Classified as GHS Category 3 *or* 10 < 72/ 96 hour L(E)C50 ≤ 100 mg/L 10 < QSAR 72/ 96 hour L(E)C50 ≤ 100 mg/L AND **Chronic:** 1 < NOEC ≤ 10 mg/L for chronic toxicity based on experimental or modeled results	**Acute:** Classified as GHS Category 1 or 2 *or* 72/ 96 hour L(E)C50 < 10 mg/L QSAR 96 hour L(E)C50 < 10 mg/L OR **Chronic;** Classified as GHS Category 1,2, or 3. NOEC ≤ 1 mg/L for chronic toxicity based on experimental or modeled results Listed as; H400: Very toxic to aquatic life H410: Very toxic to aquatic life with long lasting effects H411: Toxic to aquatic life with long lasting effects H412: Harmful to aquatic life with long lasting effects H413: may cause long lasting harmful effects to aquatic life	No relevant data for classification.

3.3.13 Terrestrial Toxicity

Definition
Terrestrial toxicity is the ability of a chemical to pose an adverse health effect to a species that lives on land. For the purposes of the Cradle to Cradle Certified methodology, toxicity to avian species and soil organisms is considered within this endpoint as they are not represented in other endpoints in this methodology. Adverse health effects can include mortality, morbidity, and/or reproduction/ developmental endpoints.

Rating Criteria
To determine the hazard rating for terrestrial toxicity, several tests may be considered for a variety of avian species and soil organisms that are considered beneficial to soil by being able to increase its productivity. Toxicity studies for birds follow the same principles described above for acute toxicity and reproductive/ developmental toxicity and are measured by LD50s and NOECs, respectively. Table 18 provides a summary of the criteria using these measures for each hazard rating used in this methodology. Acceptable experimental designs for rating include:

- OECD 205: Avian Dietary Toxicity Tests.
- OECD 206: Avian Reproduction Test.

Observable endpoints for these tests include mortality, body weights of adults and of the young at 14 days, food consumption of adults and young, gross pathological examination of adult birds, egg product, cracked eggs, egg shell thickness, viability, hatchability, and effects on young birds. If significant adverse health effects are found in these studies the appropriate rating should be applied according the criteria displayed in Table 18 (e.g., small changes in body weight would not be considered a significant adverse health effect).

The importance of soil as a key component of ecosystems is now widely recognized and understanding how organisms that contribute to soil health are affected by chemicals is important. For invertebrate species, earthworms are the most commonly tested given their predominance in soil and their importance to ecological health. There are several established tests for earthworms including:

- OECD 207: Earthworm Acute Toxicity Tests.
- OECD 220: Enchytraeid Reproduction Test.
- OECD 222: Earthworm Reproduction Test.

In addition to earthworms there are several other invertebrates and insects that are considered crucial to the health of soil, including honeybees, mites, beetles, and springtails. Several standardized tests exist for these species including:

- OECD 213: Honeybees, Acute Oral Toxicity Test.

- OECD 214: Honeybees, Acute Contact Toxicity Test.
- OECD 226: Predatory mite reproduction test in soil.
- OECD 228: Determination of Developmental Toxicity of a Test Chemical to Dipteran Dung Flies.
- OECD 232: Collembolan Reproduction Test in Soil.

All of these species are considered to be organisms important to the health of soils and are included in this endpoint for rating purposes. Table 18 summarizes the criteria for rating a chemical's effect on these species.

Table 18 Rating Criteria for Terrestrial Toxicity

	Green	Yellow	Red	Grey
Birds (Sub-acute)	Chicken LD50 > 9000 mg/kg fodder (5 days) Duck LD50 > 15000 mg/kg fodder (5 days)	Chicken LD50 900 - 9000 mg/kg fodder (5 days) Duck LD50 1500 - 15000 mg/kg fodder (5 days)	Chicken LD50 < 900 mg/kg fodder (5 days) Duck LD50 < 1500 mg/kg fodder (5 days)	No relevant data for classification.
Birds (Sub-chronic/ Chronic)	Chicken NOEC > 3000 mg/kg fodder (≥ 20 weeks) Duck NOEC > 5000 mg/kg fodder (≥ 20 weeks)	Chicken NOEC 300 - 3000 mg/kg fodder (≥ 20 weeks) Duck NOEC 500 - 5000 mg/kg fodder (≥ 20 weeks)	Chicken NOEC < 300 mg/kg fodder (≥ 20 weeks) Duck NOEC < 500 mg/kg fodder (≥ 20 weeks)	No relevant data for classification.
Toxicity for Soil Organisms (Acute)	EC50 > 1000 mg/kg dry soil	EC50 100 - 1000 mg/kg dry soil	EC50 < 100 mg/kg dry soil	No relevant data for classification.
Toxicity for Soil Organisms (Sub-chronic/ Chronic)	NOEC > 100 mg/kg dry soil	NOEC 10 - 100 mg/kg dry soil	NOEC < 10 mg/kg dry soil	No relevant data for classification.

3.3.14 Persistence

Definition

Persistence is a measure of a substance's ability to remain as a discrete chemical entity in the environment for a prolonged period of time. Biodegradation is one process by which a substance or material is broken down by microorganisms and reduced to organic and inorganic molecules, ultimately taking the form of carbon dioxide, water, and salts. It is important to note that biodegradation applies solely to organic or organometallic chemicals. The concept of biodegradability as applied to organic compounds has limited to no meaning for inorganic compounds (UNECE, 2009). Inorganic chemicals react differently in the environment through changing speciation and do not have measurable endpoints such as oxygen depletion or carbon dioxide generation as organic compounds do.

Rating Criteria

To determine the hazard rating for this endpoint, different data types may be considered with empirical data from biodegradability tests being preferred and estimation of biodegradability by QSAR results representing the least accurate. A number of OECD guidelines have been developed for biodegradation and they are used for rating purposes. Results from OECD guidelines 301: "Ready Biodegradability" may be used for GREEN, YELLOW, or RED ratings depending upon the removal of Dissolved Organic Carbon (DOC) or Theoretical Oxygen Demand (ThOD). For a GREEN classification, either 70% removal of DOC or 60% removal of ThOD must be reached in a 10-day window within the 28-day timeframe. The 10-day window begins once 10% biodegradation has been reached by DOC, ThOD, or $ThCO_2$. If the 10% biodegradation is reached but the chemical in question does not reach the required degradation within 10 days, a YELLOW rating is given. In cases where 10% biodegradation does not trigger the 10-day window, a hazard of RED is given.

Inherent biodegradability (OECD Test Guidelines 302, 304A) may be used to determine hazard ratings; however, these tests may not be used to give a GREEN rating. The optimum conditions for biodegradation set within these guidelines, primarily the adaptation of microorganisms, cannot allow a practitioner to assume ready biodegradability of inherently biodegradable substances (UNECE, 2009). Substances that have been degraded more than 70% for inherent biodegradability may be rated as YELLOW. When inherent biodegradability studies are the only available data and less than 70% removal has been observed, a rating of RED is assigned. However, if half-life or QSAR results (discussed below) conflict with this rating, reevaluation of the endpoints is considered. If inherent biodegradability tests are employed without pre-exposure and adaptation of microorganisms, these results may be used for a GREEN rating.

When empirical evidence is insufficient for ready or inherent biodegradability studies, estimation of degradation by QSAR results are used for classification. BIOWIN is the QSAR model used for this methodology, as it is publicly available and updated regularly. When identifying chemicals by their CAS number, if BIOWIN gives a result of readily biodegradable, then a rating of GREEN is given. Where BIOWIN indicates, a chemical can be degraded within weeks to months a rating of YELLOW is given. If BIOWIN labels a substance as recalcitrant, a rating of RED is given.

The half-life value chosen to determine the final rating for this hazard endpoint must reflect the dominant environmental compartment in order to be meaningful. Fugacity modeling available via the U.S. EPA's EPI Suite software offers a rapid and cost-effective way to estimate dominant environmental compartment of a chemical.

Table 19 provides a quick reference for generating hazard ratings for persistence and biodegradation.

Table 19 Persistence Hazard Rating Criteria

Green	Yellow	Red	Purple[4]	Grey
T1/2 < 16[5] days in water, soil or sediment T1/2 < 2 days in air[6] Readily biodegradable (≥70% DOC removal or ≥ 60%ThOD removal within 28 days) based on OECD guidelines (301) Predicted to be readily biodegradable by QSAR results	16 days ≤ T1/2 ≤40 days in fresh or estuarine water 16 days ≤ T1/2 ≤ 60 days in marine water 16 days ≤ T1/2 ≤ 120 days in fresh or estuarine water sediment or soil 16 days ≤ T1/2 ≤ 180 days in marine sediment 20%[7] < DOC removal < 70% based on OECD guidelines (301) 20% < ThOD removal < 60% based on OECD guidelines (301) Inherently biodegradable based on OECD guidelines (302, 304A) Predicted to be degradable within weeks to months by QSAR	40 ≤ T1/2 ≤ 60 days in fresh or estuarine water. **Note:** there is no RED value for marine water. See PURPLE value. 120 ≤ T1/2 ≤ 180 days in fresh or estuarine water sediment or soil. **Note:** there is no RED value for marine sediment. See PURPLE value. T1/2 > 2 days in air DOC and ThOD removal < 20% based on OECD guidelines Predicted to be recalcitrant by QSAR results.	T1/2 > 60 in marine, fresh or estuarine water T1/2 > 180 days in marine, fresh or estuarine water sediment or in soil	No relevant data for classification or substance is considered inorganic and not applicable to this endpoint.

[4] Note: The "Purple" category is newly introduced with Version 4.0 to align with the REACH criteria defining vPvBs.

[5] Per GHS 2015 page 460, degradation of > 70% within a 28 day period corresponds to a degradation half-life of 16 days.

[6] See Page 42 of this https://echa.europa.eu/documents/10162/13632/information_requirements_r11_en.pdf page 17 of US EPA P2 Framework Manual 2012 EPA-748-B12-001 https://www.epa.gov/sites/production/files/2015- 05/documents/05.pdf Also see Section 3.1 of this (older) document http://www.reach-info.de/dokumente/gutachten_gesamtpersistenz.pdf

[7] See page 38 of this ECHA/REACH document https://echa.europa.eu/documents/10162/13632/information_requirements_r11_en.pdf and OECD, 2005 see page 7, paragraph 35 http://www.oecd.org/chemicalsafety/testing/34898616.pdf

3.3.15 Bioaccumulation

Definition
Bioaccumulation is a measure of the tendency for a chemical to accumulate in an organism and is the net result of uptake, transformation, and elimination of a substance due to all routes of exposure. This is often measured by a bioaccumulation factor (BAF), which is the ratio of the concentration of a substance in a living organism (mg/kg) to the concentration of that substance in the surrounding environment (mg/L for aquatic systems). An additional endpoint that can be used to predict the bioaccumulation of a chemical in the environment is the n-octanol-water partition coefficient (K_{ow}). The K_{ow} is a measure of a chemical's lipophilicity and has been empirically shown that an increasing K_{ow} correlates with an increasing BAF. These endpoints, BAF and $K_{ow,}$ have been utilized for reference in determining the hazard rating of a chemical's potential to bioaccumulate in organisms. Note bioconcentration factors (BCF) are a type of BAF and pertain to bioaccumulation from water in laboratory tests.

Rating Criteria
Based on BCF or BAF and K_{ow} values, the rating of a chemical as GREY, PURPLE, RED, YELLOW, or GREEN for bioaccumulation potential is shown in Table 20.

Preference is given to high-quality studies that determine the BCF or BAF according to internationally accepted guidelines. The degree of bioconcentration/bioaccumulation depends on numerous intrinsic factors of the chemical but also experimental factors such as bioavailability, size of the organism, maintenance of exposure concentration, or exposure duration. GHS provides guidance on the determination of high-quality BCF studies in Annex 9 of the 3rd edition. These guidelines are used for reference in this methodology. When test data for fish species is not available, high-quality tests involving other species such as oysters, mussels, or scallops are also usable.

Experiments deriving the BCF value of low or uncertain quality can underestimate the potential for bioaccumulation. In such cases, consideration for the use of an experimentally determined K_{ow} value should be used instead. The determination of the K_{ow} value will also have to be considered as high-quality experiments or values assigned as "recommended values" are preferred. GHS provides guidelines for review of experiments in determining the K_{ow} and their overall quality in Annex 9 of the 3rd edition. These guidelines are followed for the purposes of rating a chemical for bioaccumulation.

Although the relationship between increasing K_{ow} and BCF has been empirically established, this linear relationship becomes equivocal for highly lipophilic substances ($K_{ow} > 6$). At K_{ow} values above 6, the relationship with BCF begins to decrease. This relationship has been postulated to be due to reduced membrane permeation and kinetic or reduced biotic lipid solubility for large molecules (UNECE, 2009). Based on the curvilinear relationship between K_{ow} and BCF, an upper limit of the K_{ow} is appropriate given the decreasing relationship. From the literature, the best upper limit for the K_{ow} is estimated at 8 (Bintein, 1993). When the experimental determination of K_{ow} is not always possible (e.g., very water-soluble substances, very lipophilic substances, and surfactants), a QSAR-derived K_{ow} may be used. For the

purposes of this classification, the BioWin application is used (Syracuse Research Corporation).

For some chemicals, the determination of a BCF value becomes difficult as chemical properties can limit the ability of a chemical to be soluble in lipids present in water, or available for transfer across biological membranes. These substances include poorly soluble substances and high molecular weight substances. Poorly soluble substances for which the solubility is less than the detection limit create problems in interpreting the BCF. For such substances, the bioconcentration potential should be based on the experimental determination of log K_{ow} or QSAR estimations (UNECE, 2009). For chemicals with a high molecular weight the tendency to bioaccumulate decreases. This result is possibly due to the steric hindrance of a chemical preventing passage across biological membranes. For chemicals that have a molecular weight above 1000, it has been proposed that these chemicals do not have the potential to bioaccumulate and is employed for the purposes of this rating system (CSTEE, 1999).

Cases may arise where the available bioaccumulation data give conflicting results with regard to which hazard rating should be assigned. In general, a "weight of evidence" approach should be used where the highest quality study (or studies) for BCF or BAF is used. If this approach does not give parity to the data, then the highest value should be used to determine the hazard rating.

Table 20 Rating Criteria for Bioaccumulation Potential

Green	Yellow	Red	Purple	Grey
BCF/BAF < 500 by experimental or QSAR results if log K_{ow} < 6 or log K_{ow} < 2 or Molecular weight > 1000	500 ≤ BCF/BAF ≤ 2000 by experimental or QSAR results if log K_{ow} < 6	2000 < BCF/BAF ≤ 5000 by experimental or QSAR results if log K_{ow} < 6	BCF/BAF > 5000 by experimental or QSAR results if log K_{ow} < 6.	No relevant data for classification. log K_{ow} >2 and no additional information.

*Note: QSAR estimated BCF may only be used when log K_{ow} is < 6 because the relationship is no longer linear above 6. When log K_{ow} is > 6, a measured/experimental BCF value is required. Alternatively, a QSAR estimated BAF may be used for log K_{ow} 6-8.

3.3.16 Combined Persistence and Bioaccumulation Hazard Flag

Definition

Persistence (P) and Bioaccumulation (B) receive a combined hazard flag as detailed in Table 21 below. Individual hazard ratings for Persistence and Bioaccumulation contribute to the combined flag in the following ways:

- PURPLE, RED, or GREY ratings for BOTH Persistence AND Bioaccumulation result in a combined PB Hazard Flag of PURPLE, RED, or GREY, respectively
- A PURPLE rating for Persistence OR Bioaccumulation combined with a RED rating for either results in a combined PB Hazard Flag of RED
- A GREY rating for Persistence OR Bioaccumulation combined with a RED OR PURPLE rating for either results in a combined PB Hazard Flag of RED
- ALL OTHER combinations of Persistence and Bioaccumulation hazard ratings receive a combined PB Hazard Flag of GREEN

This means that the combined Persistence and Bioaccumulation flag does not affect the overall assessment rating of a material unless it is PURPLE, RED, or GREY.

Note that the *individual* Persistence and Bioaccumulation hazard ratings are also used to derive the Combined Aquatic Toxicity risk flag as described in Section 4.6 below.

Table 211 Matrix for the Derivation of Combined Persistence and Bioaccumulation Hazard Flag

Persistence Hazard Rating	Bioaccumulation Hazard Rating	Combined PB Hazard Flag
PURPLE	**PURPLE**	**PURPLE**
PURPLE	**RED**	**RED**
RED	**PURPLE**	**RED**
RED	**RED**	**RED**
GREY	**RED or PURPLE**	**RED**
RED or PURPLE	**GREY**	**RED**
GREY	**GREY**	**GREY**
Any other combination of hazard ratings may formally be assigned a combined PB hazard flag of 'GREEN'.		

3.3.17 Climatic Relevance

Definition
The Climatic Relevance endpoint covers both a chemical's climate impacts (global warming potential) and its impacts on the ozone layer (ozone depleting potential).

The Intergovernmental Panel for Climate Change (IPCC) offers a definition of Global Warming Potential (IPCC, 1999):

> *"Global warming potential is an index that attempts to integrate the overall climate impacts of a specific action (e.g., emissions of CH4, NOx or aerosols). It relates the impact of emissions of a gas to that of emission of an equivalent mass of CO2. The duration of the perturbation is included by integrating radiative forcing over a time horizon (e.g., standard horizons for IPCC have been 20, 100, and 500 years). The time horizon thus includes the cumulative climate change and the decay of the perturbation."*

GHS offers a definition of Ozone Depleting Potential (UNECE, 2009):

> "*Ozone Depleting Potential (ODP) is an integrative quality, distinct for each halocarbon source species, that represents the extent of ozone depletion in the stratosphere expected from the halocarbon on a mass-for-mass basis relative to CFC-11. The formal definition of ODP is the ration of integrated perturbations to total ozone, for differential mass emission of a particular compound relative to an equal emission of CFC-11.*"

Rating Criteria

Hazard ratings for this endpoint are entirely list-based, as shown in Table 22. A RED rating is assigned if the chemical is included among the known greenhouse gases in Table 6.7 of the IPCC Third Assessment Report and/or is on the EPA's list of Ozone Depleting Substance substitutes with global warming potential. If a chemical is not on either of these lists, and additionally not listed as either a Class I or II Ozone Depleting Substance by the Montreal Protocol, it receives a GREEN rating for this endpoint.

Table 222 Rating Criteria for Climatic Relevance

Green	Yellow	Red	Grey
Not listed in Annexes to the Montreal Protocol, ODP = 0 and 100-yr GWP = 0 OR Insufficient data to categorize as RED, YELLOW or GREEN based on the Montreal protocol, GWP and ODP. Substance is not volatile (i.e., boiling point is > 260 °C).	Not listed in Annexes to the Montreal Protocol, ODP = 0 and 0 < 100-yr GWP[5] ≤ 10 OR Insufficient data to categorize as RED, YELLOW or GREEN based on the Montreal protocol, GWP and ODP. Substance is volatile (i.e., boiling point < 260 °C[6]) but not a volatile organohalogen. An organohalogen is any substance containing a fluorine, bromine, chlorine or iodine - carbon bond.[7]	GHS Category 1: Listed in Annexes to the Montreal Protocol. OR ODP > 0 and/or 100-yr GWP > 10	Insufficient data to categorize as RED, YELLOW or GREEN. Substance is a volatile (i.e., boiling point < 260 °C) organohalogen. **Note:** The Grey hazard rating is only relevant to volatile organohalogens that cannot be categorized as RED, YELLOW or GREEN due to lack of data.

[5] **Regarding pentane, isopentane, and cyclopentane:** Varying GWPs have been indicated from 3 to 11. These substances are Acceptable per the US EPA and the EU Commission and are to be assigned a YELLOW hazard rating for this endpoint.

[6] US EPA, Technical Overview of Volatile Organic Compounds, https://www.epa.gov/indoor-air-quality-iaq/technical-overview-volatile-organic-compounds

[7] Note: Fluorinated substances are not ozone depleting substances due to their high stability/lack of reactivity but are often potent greenhouse gases when volatile.

3.3.18 Other (Environmental Health)

Definition and Rating Criteria

Analogous to the 'Other' endpoint for Human Health hazards, this endpoint is intended to cover any additional characteristic relevant to the overall evaluation of environmental health not covered by other endpoints.

Similar to the 'Other (Human Health)' endpoint, an assessor may assign a RED hazard rating based on any credible piece of information that suggests an environmental health hazard not addressed by other hazard endpoints. Information that is typically assessed within the scope of this endpoint includes a chemical's mobility in soils, ability to mobilize heavy metals from sediment (chelating agents), and its 'Wassergefährdungsklasse' (WGK) if one has been issued by the German Federal Ministry for the Environment (Umweltbundesamt, UBA). The UBA maintains a public database of chemicals that have been assigned a WGK.

Based on this information and the assessor's professional judgment, a hazard rating of either RED or GREEN is assigned. Note that YELLOW or GREY hazard ratings are not possible within this endpoint. The expectations regarding use and reporting of this endpoint are the same as those for the 'Other (Human Health)' endpoint (Section 3.3.11).

3.3.19 Organohalogens

Definition
Organohalogens, defined as chemicals with a carbon to halogen bond (i.e., contains a carbon-to-fluorine, -chlorine, -bromine, or –iodine bond), are flagged for their tendency towards increased toxicity, bioaccumulation, and persistence as compared to non-halogenated analogs. The substances falling into this category are now ubiquitous in the environment and are being used in a variety of applications— from colorants and adhesives to plastic molding, piping, coatings, and pesticides. They are also major components of commercial formulations in furniture foam (pentaBDE), plastics for TV cabinets, consumer electronics, wire insulation, back coatings for draperies and upholstery (decaBDE), and plastics for personal computers and small appliances (octaBDE). Toxicity testing indicates that many organohalogens cause a variety of adverse effects, from liver toxicity and thyroid toxicity, to neurodevelopmental abnormalities. In addition, polytetrafluoroethylene (PTFE), a popular material for non-stick applications, is a heavily fluorinated polymer manufactured with perfluorooctanoic acid (PFOA). PFOA and the congeners of PTFE degradants have been found in polar bears, marine life, fetal umbilical cord blood, and even in human breast milk.

Dietrich Henschler, an eminent German toxicologist, studied the human health impacts and potency of organohalogens and compared them to their non-halogenated analogues (Henschler, 1994). Henschler used a large data set of organic compounds that included organochlorines - chlorinated alkanes, alkenes, butadienes, benzenes, phenols, paraffins, dioxins, furan, biphenyls, and insecticides. Four major conclusions were reached in this study:

1. The introduction of chlorine into organic compounds is almost always associated with an increase in toxic potential for a variety of toxic effects.
2. Chlorination usually produces entirely new toxic effects.
3. With introduction of chlorine most organic compounds exhibit mutagenic and carcinogenic properties not present in the non-halogenated analogue.
4. Chlorination often increases the potency of toxic effects. With little empirical data on the toxic effects of all organochlorines and the limited knowledge of chlorinated by-products in the synthesis of this chemical class, the trend identified by Henschler demonstrates that there is something inherently dangerous in chlorinating organic molecules.

Chlorination radically affects the chemical stability of organic chemicals—usually increasing it. Because many organochlorines resist natural degradation processes, even very dilute discharges tend to build up in the environment over time. Some organochlorines, such as 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), do not break down to any appreciable degree; virtually all the TCDD released into the environment will remain in one place or another

almost indefinitely. Many other organochlorines are persistent, but will degrade very slowly, with environmental half-lives in the years or decades.

Another effect of chlorination is that chlorine atoms invariably increase the ability of organic chemicals to dissolve in oils. Once oil-soluble organochlorines are released into the environment, they accumulate in the fatty tissues of living things—a process called bioaccumulation. Bioaccummulative compounds gravitate from the ambient environment into the food web, magnifying in concentration as they move upward from tiny organisms to large predators. By the time they get to the top of the food web (i.e., humans, eagles, polar bears, and other species), some organochlorines reach concentrations many millions of times greater than their levels in the ambient environment.

While not all organohalogens are toxic, they can act as precursors for dioxins and furans in fires below 450°C (Zhang et al., 2010). For example, the combustion of polyvinyl chloride (PVC) can contribute to the formation of dioxins and furans in two ways. While formation rates are minimized at high temperatures present in industrial and municipal incinerators, low temperature combustion cannot be ruled out as a likely unintended end-of-use scenario, given the prevalence of landfill fires, residential fires, and open-pit fires as a method for waste disposal in rural areas (backyard barrel burning) and developing countries (Zhang et al., 2010; US EPA, 2006). Thus, even though there may be organohalogen compounds that are safe during the use phase, there are risks during likely unintended end-of-use scenarios.

The environmental threat posed by organochlorines through their bioaccumulative and persistent nature is starting to be recognized globally as there is evidence of contamination in the upper atmosphere contributing to ozone depletion. Organochlorines such as DDT, hexachlorobenzene, chlordane, heptachlor epoxide, and lindane have been found in tree bark all over the world (IJCSAB, 1989). Dioxins have been found throughout the food chain as evidenced by EPA's estimate that 90% of the average American's dioxin exposure is from their diet (Yang, 1994). PCBs and a number of organochlorine pesticides have been identified in the bodies of seals, walruses, beluga whales, porpoises, and polar bears (Robins et al, 1982). Organochlorine pollutants even fall from the skies, having been found in falling snow throughout the arctic (Willes et al, 1993). The ubiquitous presence of organochlorine pollutants throughout the globe as well as in the fat tissue of humans, infants, and animals demonstrates an additional danger of this chemical class.

Rating Criteria

The trends discussed above are cause for concern for the organohalogen family as a whole, and subsequently any chemical with a carbon to halogen bond that is present at a concentration of 100 ppm or higher in a homogenous material receives a RED rating (the carbon-halogen bond must be present in the finished product, i.e., not hydrolyzed in the production/manufacturing process). A chemical that does not contain a carbon to halogen bond receives a GREEN rating, as shown in Table 23.

If an organohalogen (substance with a carbon-halogen bond) is present below 100 ppm in a homogenous material, it will still be subject to review (see main standard document Section

3.4, point 2f) but it will not receive a RED rating for this endpoint. This means that the risk rating for an organohalogen <100 ppm in a material will be determined by the rest of its hazard profile, while the risk rating for an organohalogen >100 ppm in a material will always be 'x'.

Note that certain halogenated materials are on the Banned List (Version 3.1) and/or Restricted Substances List (RSL) (Version 4.0) and are therefore prohibited for use in Cradle to Cradle Certified products when present above the allowable thresholds. The RSL consists of a core list, which is applicable to all material and product types, as well as additional lists that are applicable to specific material and product types. Unless noted otherwise, the lists indicate the maximum allowable concentration of each restricted substance in any homogeneous material subject to review (as defined in Section 4.3 of the Version 4.0 standard) in a certified product. See the Cradle to Cradle Certified Product Standard Version 4.0 for further information and consult the RSL for halogenated material thresholds which may be below 100 ppm for certain material and product types.

Table 233 Rating Criteria for Organohalogens

Green	Yellow	Red
Chemical does not contain a carbon to halogen (fluorine, chlorine, bromine, or iodine) bond.	Not applicable	Chemical contains a carbon to halogen (fluorine, chlorine, bromine, or iodine) bond. The carbon-halogen bond must be present in the finished product (i.e., not hydrolyzed in the production/manufacturing process). This rating applies when a substance is present at > 100 ppm within a homogeneous material. (Note: Certain halogenated materials on the Restricted Substances List are prohibited for use in a certified product when present at < 100 ppm in certain materials and product types)

3.3.20 Toxic Metals

Definition

Antimony, arsenic, cadmium, chromium VI, cobalt, lead, mercury, nickel, thallium, tin (organotins only), radioactive elements, and vanadium are considered toxic metals in the Cradle to Cradle Certified methodology. In general, these metals have shown toxic effects regardless of the speciation of the metal, even if incorporated in an organo-metal structure.

Rating Criteria

If a substance has any of the toxic metals listed above in its molecular structure and that substance is present at a concentration of 100 ppm or higher in a homogeneous material subject to review, the chemical receives a RED rating for this endpoint. If a substance does

not have any of the toxic metals listed above in its molecular structure, or the substance is present below 100ppm in the homogeneous material subject to review, the substance receives a GREEN rating for this endpoint, as shown in Table 24.

Note that certain metals are on the Banned List (Version 3.1) and/or Restricted Substances List (Version 4.0) and are therefore prohibited for use in Cradle to Cradle Certified products when present above the allowable thresholds. The RSL consists of a core list, which is applicable to all material and product types, as well as additional lists that are applicable to specific material and product types. Unless noted otherwise, the lists indicate the maximum allowable concentration of each restricted substance in any homogeneous material subject to review (as defined in Section 4.3 of the Version 4.0 standard) in a certified product. See the Cradle to Cradle Certified Product Standard Version 4.0 for further information and consult the RSL for toxic metal thresholds which may be below 100 ppm for certain material and product types.

Table 24 Rating Criteria for Toxic Metals

Green	Yellow	Red
Chemical does not contain toxic metal compound (e.g. antimony, arsenic, cadmium, chromium VI, cobalt, lead, mercury, nickel, tin (organotins only), radioactive elements, and vanadium.	Not applicable	Chemical contains toxic metal compound (e.g. antimony, arsenic, cadmium, chromium VI, cobalt, lead, mercury, nickel, thallium, tin (organotins only), radioactive elements, and vanadium. This rating applies when a substance is present at > 100 ppm within a homogeneous material. (Note: Some toxic metals on the Restricted Substances List are prohibited for use in a certified product when present at < 100 ppm in certain materials and product types)

4 EXPOSURE ASSESSMENT & ASSIGNING RISK FLAGS

4.1 Exposure Assessment Methodology

Exposure assessments must be conducted according to the methods described in the Exposure Assessment Methodology. Please refer to the most recent version of the Exposure Assessment Methodology document for further detail and instructions beyond the high-level description below.

Exposure assessments are primarily undertaken when RED or GREY hazard ratings for one or more endpoints have been assigned. (Exposure assessment is optional in the case of a YELLOW or GREEN hazard rating).

For the exposure assessment, specific studies on the substance(s) in question are researched in the context of the material matrix in which the substance(s) is/are present, the function and location of these materials in the finished product, and the product's intended and likely unintended use and end-of-use scenarios. Additionally, exposure during manufacturing is considered based on the actual manufacturing conditions as observed during the site visit. Note that the exposure assessment conducted as part of Cradle to Cradle Certified Material Health Assessments is not an exposure assessment in the traditional sense, in that no attempt is made to quantify the magnitude, frequency, or duration of any potential exposure. Instead, the goal is to assess whether or not plausible avenues of exposure exist. Based on the precautionary principle, any amount of plausible exposure is deemed to be sufficient to rate a chemical as posing a risk due to identified, suspected, or unknown health hazards.

For each chemical that has been flagged with a RED or GREY hazard rating for one or more hazard endpoints, an exposure assessment is conducted. The high-level steps for completing an exposure assessment are described below. Please refer to the Exposure Assessment Methodology for full instructions.

1. The product's intended and likely unintended use and end–of-use scenarios are defined (see Section 4.2 for the definition of intended and likely unintended use and end-of-use scenarios). Furthermore, the manufacturing scenario is observed during the site visit and included in the set of scenarios to be evaluated for step 2.
2. The potential for exposure to the chemical (as present in the material) via all pathways relevant to any of the flagged hazard endpoints is assessed. If exposure is not plausible at any level, in any of the defined scenarios, via any exposure pathway relevant to a specific endpoint with a RED or GREY hazard rating, the risk flag for that endpoint will be YELLOW.
3. The environmental fate of the chemical is assessed along with its potential for migrating out of the material(s) in which it is present.

- For this chemical within the specific material matrix, have credible studies been conducted on:
    i. leaching potential?
    ii. offgassing?
    iii. physical migration?
- If yes, are these studies relevant to and do they cover all conditions for the scenarios identified in step 1?
- If yes, is there a preponderance of evidence suggesting that the chemical will remain bound within its material matrix, precluding plausible exposure via any pathway to humans or the environment for all scenarios identified in step 1?

  For example, certain plastic additives are considered reactive, i.e., they react with the other monomer(s) and become part of the polymer backbone and therefore are not free to migrate out of the finished resin. Much the same way, it has been shown that lead in cast aluminum is bound in the metal matrix and poses little to no risk.

- If yes, for any endpoints with a RED or GREY hazard rating, the risk flag for that endpoint will be YELLOW.

After the exposure assessment has been completed for each chemical that had one or more RED or GREY hazard ratings, any endpoint that has not been assigned a YELLOW risk flag based on the exposure considerations above, is assigned a risk flag equal to it's hazard rating. This means that endpoints with a YELLOW hazard rating will generally receive a YELLOW risk flag (unless they can form hazardous reaction products, see Section 4.3, or an optional exposure assessment is conducted, see Section 4.4) and endpoints with a GREEN hazard rating will receive a GREEN risk flag (unless they can form hazardous reaction products, see Section 4.3). Endpoints with a RED hazard rating may receive a RED or YELLOW risk flag depending on the exposure assessment (as described above). Similarly, endpoints with a GREY hazard rating may receive a GREY or YELLOW risk flag depending on the exposure assessment.

Note that if a chemical is of regulatory concern, the assessment may not be altered regardless of the exposure assessment, and the chemical will always have a risk flag equal to its hazard rating. For this purpose a chemical of regulatory concern is defined as any chemical currently restricted under REACH (Annex XVII), on the REACH candidate list for Substances of Very High Concern (SVHC), or on the POPs list of the Stockholm Convention. The regulatory thresholds and use conditions as indicated by REACH apply. An exposure assessment may be completed when these substances are used in non-regulated applications or below the indicated threshold. This set of lists is subject to change. The most current version of the lists or regulations referenced here is to be used at the time of the Material Health assessment is being conducted. The Exposure Assessment Methodology also notes several additional cases in which exposure assessments are either not necessary or are not allowed.

4.2 Intended and Likely Unintended Use and End-of-Use Scenarios

The intended and likely unintended end-of-use scenarios must cover the end-of-use fate of 80% or more of the products sold by the applicant. For example, if the assessor deems that incineration is not a likely unintended use scenario because the applicant has a well developed take-back program or only sells the product in regions with the appropriate recycling infrastructure in place, then it must be demonstrated that 80% or more of the products sold during the certification period can reasonably be assumed to arrive in one of the other end-of-use scenarios that are considered likely. Alternatively, all common end-of-use scenarios: recycling, composting, landfill, incineration, and uncontrolled burning (including backyard burning) must be considered likely end-of-use scenarios for the purpose of the exposure assessment, in which case the percentage of fates covered by the assessment does not need to be quantified.

To identify the intended and likely unintended use scenarios, the material health assessor must consult with the applicant to understand the full extent of a product's intended and likely unintended uses. For each chemical that has been flagged with a RED or GREY hazard rating for one or more hazard endpoints, the assessor must apply their professional judgment to establish whether, given the product scenarios and material context, exposure is plausible to humans via oral, dermal, or inhalation pathways or to the environment via volatile emissions, water, or other pathways. The scenarios must include all aspects of a product's reasonably foreseeable use and maintenance. The following additional guidelines apply to specific product groups and specific materials within products:

- For fabrics or parts of products composed thereof (e.g., upholstered furniture, rugs, apparel), washing in a machine or by hand across a range of temperatures must be considered.
- For solid, non-granular, non-powder homogenous materials that are not readily abraded during their intended use (i.e. not tires, or brake-pads, etc.), inhalation exposure to substances contained in the material may be deemed as non-plausible
- For any parts that can be disassembled with common household tools, disassembly and dermal contact to any materials thus accessible must be considered.
- For any kitchen ware or containers intended for use with food or beverages, exposure and possible leaching under a variety of solvents (water, vegetable oil, alcohol, etc.) and pH ranges (pH 3-10) must be considered, as must heating in the presence of liquids such as might occur on a stove, in an oven, dishwasher, microwave, or closed car, etc. where applicable.
- For products marketed towards infants, the possibility of oral exposure must be considered as a likely unintended use scenario in all cases.
- If hexavalent chromium is used in any plating processes, exposure is always assumed and the plated material will be X.
- For blowing agents used in the manufacture of foam, environmental and human exposure is also always assumed.

- For other blowing agents and chemicals subject to review regardless of the concentration in the finished product, if a chemical is known to volatize completely during manufacture, it is assumed to be present at less than 100 ppm in the final material or product.

4.3 Reaction Products

As part of the exposure assessment, it should be noted if peer-reviewed studies exist suggesting that reaction products of concern to human or environmental health can be produced from a chemical in any assessed material during any of the scenarios defined in step 1. Noted potential reaction products are then individually assessed as if they were part of the homogeneous material being assessed. The reaction product then receives a risk flag for each hazard endpoint and these risk flags are combined with those of the parent chemical. In combining the risk flags of a parent chemical with those of its reaction product(s), the most conservative risk flag (in the order RED, GREY, YELLOW, GREEN) among them is used for each endpoint. For example, a chemical may receive a RED risk flag for carcinogenicity if it is deemed to have the potential for carcinogenic reaction products in the product scenarios considered, even if the chemical itself is not carcinogenic and received a GREEN hazard rating for the endpoint (e.g., a non-hazardous azo-dye with the potential for forming aromatic amines, which are carcinogenic).

4.4 Optional Exposure Assessment for Endpoints with Yellow Hazard Ratings

An exposure assessment as described above may also be conducted for chemicals that do not have RED or GREY hazard ratings, but do have one or more YELLOW hazard ratings. To this end, the same three steps would be followed as described above for the chemicals with RED or GREY hazard ratings; however, if no plausible routes for exposure exist, the resulting risk flag would be GREEN rather than YELLOW. As described in Section 4, such an assessment helps to differentiate between a chemical that would merit a ‘b’ single chemical risk rating due to lack of exposure potential, but would otherwise receive a ‘c’ single chemical risk rating based on its hazard only.

This step is optional since there are no criteria in the standard that would differentiate between materials containing ‘b’ versus ‘c’ chemicals. However, certain manufacturers are striving to increase the number of ‘b’ chemicals in their products regardless of the requirements posed for certification. Additionally, when substituting for an ‘x’ chemical, a manufacturer may prefer a ‘b’ chemical over a ‘c’ chemical.

4.5 Exposure Assessment for the Combined Persistence and Bioaccumulation Hazard Rating

If the combined Persistence and Bioaccumulation hazard flag is PURPLE or RED, exposure must be assumed unless a closed loop recycling system is taking back 80% or more of the product and exposure is not likely during the manufacturing and use phases. If the combined PB hazard flag is GREY, the usual steps in the Exposure Assessment Methodology apply. In

cases where exposure is assumed, the combined PB risk flag is the same as the combined PB hazard flag.

Note that the *individual* Persistence and Bioaccumulation hazard ratings are also used to derive the Combined Aquatic Toxicity risk flag as described in Section 4.6 below.

4.6 Combined Aquatic Toxicity Risk Flags

A 'combined Aquatic Toxicity risk flag' is derived for each chemical based on the worst of its three Aquatic Toxicity risk flags (for Fish Toxicity, Daphnia Toxicity, and Algae Toxicity), as well as its Persistence and Bioaccumulation hazard ratings. Table 25 illustrates how the worst Aquatic Toxicity risk flag (among all six flags in the order RED, GREY, YELLOW, GREEN with RED being worse than GREY), the Persistence hazard rating, and the Bioaccumulation hazard rating work together to generate a single combined Aquatic Toxicity risk flag. A chemical's combined Aquatic Toxicity risk flag corresponds to the bold value in the fourth column of the table within the row that contains the chemical's unique combination of ratings for worst Aquatic Toxicity risk flag (column 1), Persistence hazard rating (column 2), and Bioaccumulation hazard rating (column 3). Note that the Aquatic Toxicity risk ratings along with the hazard ratings for Bioaccumulation and Persistence factor into a chemical's single chemical risk rating through the combined Aquatic Toxicity risk flag, thus reducing the number of discrete endpoints used in deriving the single chemical risk rating from 21 to 18.

The rules that define the combined Aquatic Toxicity risk flag are as follows. Table 25 shows all possible combinations and the resulting combined Aquatic Toxicity risk flags based on these rules:

1. If the worst Aquatic Toxicity risk flag is RED, then the combined Aquatic Toxicity risk flag is RED with the following exception:
    a. If Persistence and Bioaccumulation (P&B) are both GREEN, then the combined flag is YELLOW
2. If the worst Aquatic Toxicity risk flag is GREY, then the combined Aquatic Toxicity risk flag is GREY with the following exceptions:
    a. If P&B are both either RED or PURPLE, then the combined flag is RED
    b. If P&B are both GREEN, then the combined flag is YELLOW
3. If the worst Aquatic Toxicity risk flag is YELLOW, then the combined Aquatic Toxicity risk flag is YELLOW with the following exceptions:
    a. If P&B are both either RED or PURPLE, then the combined flag is RED
    b. If P&B are both GREY, or if one is RED or PURPLE and the other is GREY, then the combined flag is GREY
    c. If P&B are both GREEN, then the combined flag is GREEN
4. If the worst Aquatic Toxicity risk flag is GREEN, then the combined Aquatic Toxicity risk flag is GREEN with the following exception:
    a. If P&B are both RED or PURPLE or GREY, then the combined flag is YELLOW

Table 25 Matrix for the Derivation of Combined Aquatic Toxicity Risk Flags

WORST AQUATIC TOXICITY RISK FLAG	PERSISTENCE HAZARD RATING	BIOACCUMULATION HAZARD RATING	**COMBINED AQUATIC TOXICITY RISK FLAG**
RED	NOT GREEN*	ANY	**RED**
RED	GREEN	NOT GREEN*	**RED**
GREY OR YELLOW	RED OR PURPLE	RED OR PURPLE	**RED**
GREY	RED OR PURPLE	NOT RED OR PURPLE**	**GREY**
GREY	NOT RED OR PURPLE**	RED OR PURPLE	**GREY**
GREY	GREY OR YELLOW	ANY	**GREY**
GREY	ANY	GREY OR YELLOW	**GREY**
RED OR GREY	GREEN	GREEN	**YELLOW**
YELLOW	GREY	GREY OR RED OR PURPLE	**GREY**
YELLOW	GREY OR RED OR PURPLE	GREY	**GREY**
YELLOW	NOT GREEN*	GREEN OR YELLOW	**YELLOW**
YELLOW	GREY OR YELLOW	NOT GREEN*	**YELLOW**
YELLOW	GREEN	GREEN	**GREEN**
GREEN	RED OR PURPLE OR GREY	RED OR PURPLE OR GREY	**YELLOW**
GREEN	GREEN OR YELLOW	ANY	**GREEN**

GREEN	ANY	GREEN OR YELLOW	**GREEN**

*not GREEN = Endpoint may be assigned any hazard rating other than GREEN.
**not RED OR PURPLE = Endpoint may be assigned any hazard rating other than RED or PURPLE.

5 ASSIGNING SINGLE CHEMICAL RISK RATINGS

A single chemical risk rating of a, b, c, x, or GREY is assigned to each chemical substance subject to review in a homogeneous material based on the chemical's risk flags. The single chemical risk assessment rating system is shown in Table 26.

Table 26 Single Chemical Risk Assessment Rating System

a	No moderate or significant hazards identified for the chemical. This chemical is ideal from a human and environmental health perspective.
b	No moderate or significant risks identified for the chemical
c	One or more moderate risks identified for the chemical
x	One or more significant risks identified for the chemical
GREY	Insufficient data

Single chemical risk ratings are assigned using the following hierarchy of rules:

1. If the chemical has received a combined PB risk flag of PURPLE (see Section 2.3 above regarding the combined PB risk flag), the single chemical risk rating is 'x' and steps 2-6 below do not apply.
2. If the chemical has received a RED risk flag in any of the 17 endpoints resulting from the risk assessment (see Section 4 regarding the combined Aquatic Toxicity risk flag), the single chemical risk rating is 'x' and steps 3-6 below do not apply.
3. Otherwise, if the chemical has received a GREY risk flag for any endpoint other than Carcinogenicity, Endocrine Disruption, Neurotoxicity, Climatic Relevance, or Terrestrial Toxicity, the single chemical risk rating is 'GREY' and steps 4-6 below do not apply.
4. Otherwise, if the chemical has received any YELLOW risk flags or any GREY risk flags for Carcinogenicity, Endocrine Disruption, Neurotoxicity, Climatic Relevance, or Terrestrial Toxicity, the single chemical risk rating is 'c' and step 5 and 6 below do not apply.
5. Otherwise, if the chemical has received any YELLOW hazard ratings, the single chemical risk rating is 'b' and step 6 below does not apply (the chemical has received only 'GREEN' risk flags, but one or more YELLOW hazard rating).
6. Otherwise, the single chemical risk rating is 'a' (the chemical has received only 'GREEN' hazard ratings).

While single chemical risk ratings are assigned to individual chemicals, these ratings apply only in the context of the material and product for which they were assigned (see Section 4). They are not transferable to other materials or products.

6 ASSIGNING MATERIAL ASSESSMENT RATINGS

The material assessment rating for a homogeneous material equals the "worst" single chemical risk rating among the chemical substances subject to review within the material. The rules are as follows:

1. If any substances subject to review within the material have received a single chemical risk rating of 'x', the assessment rating for the material is 'X' and steps 2-4 do not apply.
2. Otherwise, if any substances subject to review within the material have received a single chemical risk rating of GREY, the assessment rating for the material is GREY and steps 3 and 4 do not apply.
3. Otherwise, if any substances subject to review within the material have received a single chemical risk rating of 'c', the assessment rating for the material is 'C' and step 4 and 5 do not apply.
4. Otherwise, if any substances subject to review within the material have received a single chemical risk rating of 'b', the assessment rating for the material is 'B' and step 5 does not apply.
5. Otherwise, the material assessment rating is 'A' (the material contains only substances without known, suspected, or undefined hazards in any of the evaluated endpoints).

Table 27 Material Assessment Ratings

A	No moderate or significant hazards identified for the material. The material is ideal from a human and environmental health perspective.
B	No moderate or significant risks identified for the material.
C	One or more moderate risks identified for the material. The material is still acceptable for use.
X	One or more significant risks identified for the material. The optimization of the product requires phasing out this substance or material.
GREY	This material cannot be fully assessed due to either lack of full material disclosure or lack of toxicity information for one or more substances.

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8 HAZARD DATA RESOURCES

8.1 Resources Referenced in Chemical Hazard Criteria Tables

The following resources are specifically referenced within the chemical hazard criteria tables:

1. International Agency for the Research on Cancer (IARC) – provides a list of classifications by CAS Registry Number order http://monographs.iarc.fr/ENG/Classification/index.php.
2. United Nations Globally Harmonized System of Classification and Labeling of Chemicals (GHS) Revision 4, 2011 http://www.unece.org/trans/danger/publi/ghs/ghs_rev04/04files_e.html. Hazard categories and statements that have been developed based on the GHS are available on some MSDS and through other sources listed below.
3. United Nations Globally Harmonized System of Classification and Labeling of Chemicals (GHS) Revision 6, 2015. United Nations Globally Harmonized System of Classification and Labeling of Chemicals (GHS)
4. Maximum Workplace Concentrations (MAK) -- available for purchase from Wiley-VCH.
5. American Conference of Governmental & Industrial Hygienists (ACGIH) -- Total Limit Values (TLVs) for carcinogenicity may be available though the Hazardous Substances Databank http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB or for purchase from ACGIH.
6. Colborn List (of endocrine disruptors): http://www.ourstolenfuture.com/Basics/chemlist.htm.
7. EU Priority list of endocrine disruptors (download available here): http://ec.europa.eu/environment/endocrine/strategy/substances_en.htm#priority_list
8. California Proposition 65 List, Chemicals Known to the State to Cause Cancer or Reproductive Toxicity: http://oehha.ca.gov/prop65/prop65_list/newlist.html.
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http://www.unece.org/fileadmin/DAM/trans/danger/publi/ghs/ghs_rev05/English/03e_part3.pdf

14. BIOWIN™ (and other QSAR models): available through the U.S. Environmental Protection Agency, Estimation Program Interface (EPI) Suite, http://www.epa.gov/oppt/exposure/pubs/episuite.htm.
15. Montreal Protocol, Ozone Depleting Substances; available through U.S. EPA http://www.epa.gov/ozone/science/ods/index.html.

8.2 Additional Chemical Hazard Profiling Resources

Additional useful chemical hazard profiling references for finding TLVs, LD50s, LC50s, LOAELs, NOAELs, half-lives, ready and inherent biodegradability test results, BCF and K_{ow} values, and other relevant data and information include:

1. European Chemical Substances Information System (ESIS) http://ecb.jrc.ec.europa.eu/esis/.
2. Australian Inventory of Chemical Substances (AICS): http://www.nicnas.gov.au/Industry/AICS/Search.asp.
3. National Toxicology Program (NTP) http://ntp-apps.niehs.nih.gov/ntp_tox/index.cfm.
4. U.S. Environmental Protection Agency (EPA), Ecotox (aquatic and terrestrial toxicity) http://cfpub.epa.gov/ecotox/.
5. U.S. Environmental Protection Agency, EPI Suite – Estimation Program Interface. https://www.epa.gov/tsca-screening-tools/download-epi-suitetm-estimation-program-interface-v411
6. U.S. Environmental Protection Agency, High Production Volume Information System (HPVIS) http://www.epa.gov/hpvis/.
7. U.S. Environmental Protection Agency, ACToR: http://actor.epa.gov/actor/faces/ACToRHome.jsp
8. Safe Work Australia, Hazardous Substance Information System http://hsis.ascc.gov.au/SearchHS.aspx.
9. Human and Environmental Risk Assessment on ingredients of household cleaning products (HERA project) http://www.heraproject.com/RiskAssessment.cfm.
10. International Programme on Chemical Safety (INCHEM) http://www.inchem.org/
11. MSDS online: http://www.msdsonline.com/ (available through purchase)
12. United Nations Globally Harmonized System of Classification and Labeling of Chemicals (GHS) Revision 3, 2009 http://www.unece.org/trans/danger/publi/ghs/ghs_rev03/03files_e.html.

8.3 Resources for Probable Routes of Human and Occupational Exposure

Information regarding probable routes of human exposure and occupational exposure concerns may be found in several of the resources listed above in the chemical hazard profiling section. The following will also be useful:

1. Hazardous Substances Data Bank: http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB.
2. NIOSH Pocket Guide to Occupational Hazards: http://www.cdc.gov/niosh/npg/.

9 APPENDIX - HAZARD ENDPOINT CRITERIA SUMMARY TABLE

Table 28 below lists the criteria for all human and environmental health hazard endpoints used for evaluation in the Cradle to Cradle Certified Product Standard.

Table 288 Summary of Hazard Criteria

ENDPOINT	Green	Yellow	Red	Grey
Carcinogenicity	Not classified as GHS category 1A, 1B, or 2. Not a known, presumed or suspected carcinogen. Negative long-term cancer studies. Listed as: TLV A5, IARC 4	Not classified as GHS category 1A, 1B, or 2. Limited, marginal, equivocal or conflicting evidence of carcinogenicity. Listed as: MAK III 3A, 4, 5	Classified as GHS category 1A, 1B, or 2. Known, presumed or suspected carcinogen. Listed as: MAK III 1, 2, 3B IARC Group 1, 2A, 2B TLV A1, A2, A3 GHS Category 1A, 1B, 2 H350: May cause cancer H351: Suspected of causing cancer	No data available for classification. Listed as: IARC Group 3 TLV A4

ENDPOINT	Green	Yellow	Red	Grey
Endocrine Disruption	Not known or suspected of endocrine disruption: Adequate data indicate neither endocrine activity nor adverse health effects that are linked to endocrine activity. *or* EU list category 3A	Insufficient evidence of endocrine disruption: Data provide evidence of endocrine activity without evidence of linked adverse health effects.	Sufficient evidence of endocrine disruption: Data indicate adverse health effects that are linked to endocrine activity. *or* Chemical appears on Colborn or EU list (Cat. 1 & 2).	No data available for classification. EU list category 3B
Mutagenicity	Not classified as GHS Category 1A, 1B, or 2. Substance does not induce aberrations of chromosomes OR substance does not induce chromosome segregation errors in *in vitro* systems. AND substance does not induce point mutations.	Not classified as GHS Category 1A, 1B, or 2. Insufficient data. Substance does not induce point mutations. Data lacking on chromosome aberration and segregation.	Classified as GHS Category 1A, 1B, or 2. or Evidence of mutagenicity supported by positive results *in vitro* or *in vivo* (see rating criteria guidance) *or* Listed as: MAK IX 1, 2, 3A, 3B, H340: May cause genetic defects H341: Suspected of causing genetic defects	No data available for classification.

ENDPOINT	Green	Yellow	Red	Grey
Reproductive & Developmental Toxicity	Not classified as GHS Category 1A, 1B, or 2. Exhibits no adverse effects to sexual function and fertility and/or to the development of an embryo or fetus based on human or animal studies. Oral NOAEL > 500 mg/kgBW/day. Inhalation NOAEL >2.5 mg/l 6-8 h/day.	Not classified as GHS Category 1A, 1B, or 2. Equivocal evidence of toxic effects to sexual function and fertility but considered a secondary non-specific consequence of other toxic effects present. *and/or* Equivocal evidence of adverse effects to the development of an embryo or fetus based on human or animal studies. Oral NOAEL =50-500 mg/kg BW/day. Inhalation NOAEL =0.25-2.5 mg/l 6-8 h/day. *or* Listed as: MAK C	Classified as GHS Category 1A, 1B, or 2. Known, presumed, or suspected of causing adverse effects to sexual function and fertility and/or to the development of an embryo or fetus based on human or animal studies. *and/or* Oral NOAEL < 50 mg/kg BW/day. Inhalation NOAEL <0.25 mg/l 6-8 h/day. *or* Listed as: MAK Group A or B H360: May damage fertility or the unborn child. H361: Suspected of damaging fertility or the unborn child.	No data available for classification. Listed as: MAK D

ENDPOINT	Green	Yellow	Red	Grey
Oral Toxicity	**Acute:** Not Classified as GHS Category 1, 2, 3 or 4. LD50 > 2000 mg/kg BW	**Acute:** Classified as GHS Category 4 *or* 300 < LD50 ≤ 2000 mg/kg BW Listed as: H302: Harmful if swallowed	**Acute:** Classified as GHS Category 1,2, or 3 *or* LD50 ≤ 300 mg/kg BW Listed as: H300a/b: Fatal if swallowed H301 Toxic if swallowed H304: May be fatal if swallowed and enters airways	No relevant data available for classification.
	Single exposure organ toxicity: Not Classified. LOAEL > 2000 mg/kg BW	**Single exposure organ toxicity:** Classified as GHS Category 2 or 3 300 < LOAEL ≤ 2000 mg/kg BW Listed as: H371: May cause damage to organs via oral exposure	**Single exposure organ toxicity:** Classified as GHS Category 1 *or* LOAEL ≤ 300 mg/kg BW Listed as: H370: Causes damage to organs via oral exposure	
	Sub – Chronic/Chronic: Not Classified. LOAEL > 100 mg/kg bw/day	**Sub – Chronic/Chronic:** Classified as GHS Category 2 10 < LOAEL ≤100 mg/kg bw/day Listed as: H373: May cause damage to (organs) through prolonged or repeated dermal exposure	**Sub – Chronic/Chronic**: Classified as GHS Category 1 *or* LOAEL ≤ 10 mg/kg bw/day Listed as: H372: Causes damage to (organs) through prolonged or repeated oral exposure	

ENDPOINT	Green	Yellow	Red	Grey
Dermal Toxicity	**Acute:** Not Classified as GHS Category 1, 2, 3, or 4. LD50 > 2000 mg/kg BW **Single exposure organ toxicity:** Not Classified. LOAEL > 2000 mg/kg BW **Sub – Chronic/Chronic:** Not Classified. LOAEL > 200 mg/kg bw/day	**Acute:** Classified as GHS Category 4 *or* 1000 < LD50 ≤ 2000 mg/kg BW Listed as: H312: Harmful in contact with skin **Single exposure organ toxicity:** Classified as GHS Category 2 or 3 *or* 1000 < LOAEL ≤ 2000 mg/kg BW Listed as: H371: May cause damage to organs via dermal exposure **Sub – Chronic/Chronic:** Classified as GHS Category 2 *or* 20 < LOAEL ≤ 200 mg/kg bw/day Listed as: H373: May cause damage to (organs) through prolonged or repeated dermal exposure	**Acute:** Classified as GHS Category 1,2, or 3 or LD50 ≤ 1000 mg/kg BW Listed as: H310a/b: Fatal in contact with skin H311: Toxic in contact with skin **Single exposure organ toxicity:** Classified as GHS Category 1 *or* LOAEL ≤ 1000 mg/kg BW Listed as: H370: Causes damage to organs via dermal exposure **Sub – Chronic/Chronic:** Classified as GHS Category 1 *or* LOAEL ≤ 20 mg/kg bw/day Listed as: H372: Causes damage to (organs) through prolonged or repeated dermal exposure	No relevant data available for classification.

ENDPOINT	Green	Yellow	Red	Grey
Inhalation Toxicity	**Acute:** Not Classified as GHS Category 1,2,3 or 4. Inhalation (gas) LC50 > 20000 ppmV Inhalation (vapor) LC50 > 20 mg/l/4hr Inhalation (dust/mist) LC50 > 5 mg/l/4hr **Single exposure organ toxicity:** Not Classified. LOAEL (gasses) > 20000 ppmV/4hr LOAEL (vapor) > 20 mg/L/4hr LOAEL (mists/dusts) > 5.0 mg/L/4hr	**Acute:** Classified as GHS Category 4 *or* Inhalation (gas) 2500 < LC50 ≤ 20000 ppmV Inhalation (vapor) 10 < LC50 ≤ 20 mg/l/4hr Inhalation (dust/mist) 1.0 < LC50 ≤ 5 mg/l/4hr Listed as: H332: Harmful if inhaled **Single exposure organ toxicity:** Classified as GHS Category 2 or 3 *or* 2500 < LOAEL (gasses) ≤ 20000 ppmV/4hr 10 < LOAEL (vapor) ≤ 20 mg/L/4hr 1.0 < LOAEL (mists/dusts) ≤ 5.0 mg/L/4hr Listed as: H371: May cause damage to organs via inhalation exposure H336: May cause drowsiness or dizziness	**Acute:** Classified as GHS Category 1,2 or 3 *or* Inhalation (gas) LC50 ≤ 2500 ppmV Inhalation (vapor) LC50 ≤ 10 mg/l/4hr Inhalation (dust/mist) LC50 ≤ 1 mg/l/4hr Listed as: H330a/b: Fatal if inhaled H331: Toxic if inhaled **Single exposure organ toxicity:** Classified as GHS Category 1 *or* LOAEL (gasses) ≤ 2500 ppmV/4hr LOAEL (vapor) ≤ 10 mg/L/4hr LOAEL (mists/dusts) ≤ 1.0 mg/L/4hr Listed as: H370: Causes damage to organs via inhalation exposure	No relevant data available for classification.

ENDPOINT	Green	Yellow	Red	Grey
Inhalation Toxicity (cont.)	**Sub – Chronic/Chronic:** Not Classified. Inhalation (Gases) LOAEL > 250 ppmV/6h/d Inhalation (Vapors) LOAEL > 1.0 mg/L/6h/d Inhalation (Dusts & Mists) LOAEL > 0.2 mg/L/6h/d	**Sub – Chronic/Chronic:** Classified as GHS Category 2 *or* Inhalation (Gases) 50 < LOAEL ≤ 250 ppmV/6h/d Inhalation (Vapors) 0.2 < LOAEL ≤ 1.0 mg/L/6h/d Inhalation (Dusts & Mists) 0.02 < LOAEL ≤ 0.2 mg/L/6h/d Listed as; H373: May cause damage to (organs) through prolonged or repeated inhalation	**Sub – Chronic/Chronic:** Classified as GHS Category 1 *or* Inhalation (Gases) LOAEL ≤ 50 ppmV/6h/d Inhalation (Vapors) LOAEL ≤ 0.2 mg/L/6h/d Inhalation (Dusts & Mists) LOAEL ≤ 0.02 mg/L/6h/d Listed as: H372: Causes damage to (organs) through prolonged or repeated inhalation	
Neurotoxicity	Refer to Oral, Dermal and Inhalation Toxicity Single Exposure Organ, Sub-Chronic, and Chronic Toxicity criteria for Green Rating.	Refer to Oral, Dermal and Inhalation Toxicity Single Exposure Organ, Sub-Chronic, and Chronic Toxicity criteria for Yellow Rating.	Refer to Oral, Dermal and Inhalation Single Exposure Organ, Sub-Chronic, and Chronic Toxicity criteria for Red Rating. *or* Listed in Grandjean et al. text for neurotoxic effects.	No relevant data available for classification.

ENDPOINT	Green	Yellow	Red	Grey
Skin, Eye, and Respiratory Corrosion/ Irritation	Not Classified as GHS Category 1, 2, or 3. No irritation to skin, eyes, or respiratory tract in relevant human or animal studies.	Classified as GHS Category 2 or 3 for Skin Corrosion/Irritation and/or Category 2 for Eye Damage/Irritation. Mild to severe irritation to skin, eyes, or respiratory tract in relevant human or animal studies; *or* Listed as: H315: Causes skin irritation H319: Causes serious eye irritation H320: Causes eye irritation H335: May cause respiratory tract irritation	Classified as GHS Category 1 for Skin Corrosion/Irritation or Eye Damage/Irritation. Causes burns, corrosion, or serious damage to skin, eyes, or the respiratory tract* in relevant human or animals studies; *or* pH ≤ 2 or pH ≥ 11.5 *or* Listed as: H314: Causes severe skin burns and eye damage H318: Causes serious eye damage	No relevant data available for classification.

ENDPOINT	Green	Yellow	Red	Grey
Sensitization of Skin and Airways	Not classified as GHS Category 1A or 1B. Adequate data available. No evidence of sensitization in human and/ or animal studies. *or* No data from human or animal studies are available; however, the substance is not classified under GHS, not listed as H334/317 or MAK, and there is a history of safe use (10 years or more) without reported cases of sensitization, as documented by a signed statement from the substance manufacturer.	Not classified as GHS Category 1A or 1B. Non-adjuvant animal studies elicit a response 15% > population > 0%. Adjuvant animal studies elicit a response of 30% > population > 0%. *or* 1< LLNA SI < 3	Classified as GHS Category 1A or 1B for Sensitization (respiratory and skin): *or* *LLNA SI >=3* *or* Listed as: GHS Category 1A or 1B for Sensitization (respiratory and/or skin) MAK skin or airways sensitizer (MAK Sa or Sh). H334: May cause allergy or asthma symptoms or breathing difficulties in inhaled. H317: May cause an allergic skin reaction.	No relevant data for classification.

ENDPOINT	Green	Yellow	Red	Grey
Fish Toxicity	Not Classified as GHS Category 1, 2, or 3. 96 hour LC50 > 100 mg/L QSAR 96 hour LC50 > 100 mg/L	**Acute** Classified as GHS Category 3 or 10 < 96 hour LC50 ≤ 100 mg/L or 10 < QSAR 96 hour LC50 ≤ 100 mg/L AND **Chronic** 1 < NOEC ≤ 10 mg/L for chronic toxicity based on experimental or modeled results	**Acute** Classified as GHS Category 1 or 2 or 96 hour LC50 ≤ 10 mg/L or QSAR 96 hour LC50 ≤ 10 mg/L Listed as: H400: Very toxic to aquatic life OR **Chronic:** Classified as GHS Category 1,2, or 3 *or* NOEC ≤ 1 mg/L for chronic toxicity based on experimental or modeled results Listed as: H410: Very toxic to aquatic life with long lasting effects H411: Toxic to aquatic life with long lasting effects H412: Harmful to aquatic life with long lasting effects H413: may cause long lasting harmful effects to aquatic life	No relevant data for classification.

ENDPOINT	Green	Yellow	Red	Grey
Daphnia Toxicity	Not Classified as GHS Category 1, 2, or 3. 48 hour L(E)C50 > 100 mg/L QSAR 48 hour L(E)C50 > 100 mg/L	**Acute** Classified as GHS Category 3 *or* 10 < 48 hour L(E)C50 10 ≤ 100 mg/L 10 < QSAR 96 hour L(E)C50 ≤ 100 mg/L AND **Chronic** 1 < NOEC ≤ 10 mg/L for chronic toxicity based on experimental or modeled results	**Acute** Classified as GHS Category 1 or 2 *or* 48 hour L(E)C50 ≤ 10 mg/L QSAR 48 hour L(E)C50 ≤ 10 mg/L OR **Chronic** Classified as GHS Category 1,2 or 3 or NOEC ≤ 1 mg/L for chronic toxicity based on experimental or modeled results Listed as: H400: Very toxic to aquatic life H410: Very toxic to aquatic life with long lasting effects H411: Toxic to aquatic life with long lasting effects H412: Harmful to aquatic life with long lasting effects H413: may cause long lasting harmful effects to aquatic life	No relevant data for classification.

ENDPOINT	Green	Yellow	Red	Grey
Algae Toxicity	Not Classified as GHS Category 1, 2, or 3. 72/ 96 hour L(E)C50 > 100 mg/L QSAR 72/ 96 hour L(E)C50 > 100 mg/L	**Acute:** Classified as GHS Category 3 *or* 10 < 72/ 96 hour L(E)C50 ≤ 100 mg/L 10 < QSAR 72/ 96 hour L(E)C50 ≤ 100 mg/L AND **Chronic:** 1 < NOEC ≤ 10 mg/L for chronic toxicity based on experimental or modeled results	**Acute:** Classified as GHS Category 1 or 2 *or* 72/ 96 hour L(E)C50 < 10 mg/L QSAR 96 hour L(E)C50 < 10 mg/L OR **Chronic;** Classified as GHS Category 1,2, or 3. NOEC ≤ 1 mg/L for chronic toxicity based on experimental or modeled results Listed as; H400: Very toxic to aquatic life H410: Very toxic to aquatic life with long lasting effects H411: Toxic to aquatic life with long lasting effects H412: Harmful to aquatic life with long lasting effects H413: may cause long lasting harmful effects to aquatic life	No relevant data for classification.
Terrestrial Toxicity: Birds (Sub-acute)	Chicken LD50 > 9000 mg/kg fodder (5 days) Duck LD50 > 15000 mg/kg fodder (5 days)	Chicken LD50 900 - 9000 mg/kg fodder (5 days) Duck LD50 1500 - 15000 mg/kg fodder (5 days)	Chicken LD50 < 900 mg/kg fodder (5 days) Duck LD50 < 1500 mg/kg fodder (5 days)	No relevant data for classification.

ENDPOINT	Green	Yellow	Red	Grey
Terrestrial Toxicity: Birds (Sub-chronic/ Chronic)	Chicken NOEC > 3000 mg/kg fodder (≥ 20 weeks) Duck NOEC > 5000 mg/kg fodder (≥ 20 weeks)	Chicken NOEC 300 - 3000 mg/kg fodder (≥ 20 weeks) Duck NOEC 500 - 5000 mg/kg fodder (≥ 20 weeks)	Chicken NOEC < 300 mg/kg fodder (≥ 20 weeks) Duck NOEC < 500 mg/kg fodder (≥ 20 weeks)	No relevant data for classification.
Terrestrial Toxicity: Toxicity for Soil Organisms (Acute)	EC50 > 1000 mg/kg dry soil	EC50 100 - 1000 mg/kg dry soil	EC50 < 100 mg/kg dry soil	No relevant data for classification.
Terrestrial Toxicity: Toxicity for Soil Organisms (Sub-chronic/ Chronic)	NOEC > 100 mg/kg dry soil	NOEC 10 - 100 mg/kg dry soil	NOEC < 10 mg/kg dry soil	No relevant data for classification.

ENDPOINT	Green	Yellow	Red	Purple	Grey
Persistence and Biodegradation	T1/2 < 16[2] days in water, soil or sediment T1/2 < 2 days in air[3] Readily biodegradable (≥70% DOC removal or ≥ 60%ThOD removal within 28 days) based on OECD guidelines (301) Predicted to be readily biodegradable by QSAR results	16 days ≤ T1/2 ≤40 days in fresh or estuarine water 16 days ≤ T1/2 ≤ 60 days in marine water 16 days ≤ T1/2 ≤ 120 days in fresh or estuarine water sediment or soil 16 days ≤ T1/2 ≤ 180 days in marine sediment 20%[4] < DOC removal < 70% based on OECD guidelines (301) 20% < ThOD removal < 60% based on OECD guidelines (301) Inherently biodegradable based on OECD guidelines (302, 304A) Predicted to be degradable within weeks to months by QSAR	40 ≤ T1/2 ≤ 60 days in fresh or estuarine water. **Note:** there is no RED value for marine water. See PURPLE value. 120 ≤ T1/2 ≤ 180 days in fresh or estuarine water sediment or soil. **Note:** there is no RED value for marine sediment. See PURPLE value. T1/2 > 2 days in air DOC and ThOD removal < 20% based on OECD guidelines Predicted to be recalcitrant by QSAR results.	T1/2 > 60 in marine, fresh or estuarine water T1/2 > 180 days in marine, fresh or estuarine water sediment or in soil	No relevant data for classification *or* substance is considered inorganic and not applicable to this endpoint.
Bioaccumulation	BCF/BAF < 500 by experimental or QSAR results if log K_{ow} < 6 or log K_{ow} < 2 or Molecular weight > 1000	500 ≤ BCF/BAF ≤ 2000 by experimental or QSAR results if log K_{ow} < 6	2000 < BCF/BAF ≤ 5000 by experimental or QSAR results if log K_{ow} < 6	BCF/BAF > 5000 by experimental or QSAR results if log K_{ow} < 6.	No relevant data for classification. log K_{ow} >2 and no additional information.

ENDPOINT	Green	Yellow	Red	Grey
Climatic Relevance	Not listed in Annexes to the Montreal Protocol, ODP = 0 and 100-yr GWP = 0 OR Insufficient data to categorize as RED, YELLOW or GREEN based on the Montreal protocol, GWP and ODP. Substance is not volatile (i.e., boiling point is > 260 °C).	Not listed in Annexes to the Montreal Protocol, ODP = 0 and 0 < 100-yr GWP ≤ 10 OR Insufficient data to categorize as RED, YELLOW or GREEN based on the Montreal protocol, GWP and ODP. Substance is volatile (i.e., boiling point < 260 °C) but not a volatile organohalogen. An organohalogen is any substance containing a fluorine, bromine, chlorine or iodine - carbon bond.	GHS Category 1: Listed in Annexes to the Montreal Protocol. OR ODP > 0 and/or 100-yr GWP > 10	Insufficient data to categorize as RED, YELLOW or GREEN. Substance is a volatile (i.e., boiling point < 260 °C) organohalogen. **Note:** The Grey hazard rating is only relevant to volatile organohalogens that cannot be categorized as RED, YELLOW or GREEN due to lack of data.
Organohalogens	Chemical does not contain a carbon to halogen (fluorine, chlorine, bromine, or iodine) bond. This rating applies when a substance is present at ≥ 100 ppm within a homogeneous material.	Not applicable (i.e. substance is present at <100 ppm within a homogeneous material).	Chemical contains a carbon to halogen (fluorine, chlorine, bromine, or iodine) bond. The carbon-halogen bond must be present in the finished product (i.e., not hydrolyzed in the production/manufacturing process). This rating applies when a substance is present at ≥ 100 ppm within a homogeneous material.	Not applicable.

ENDPOINT	Green	Yellow	Red	Grey
Toxic Metals	Chemical does not contain toxic metal compound (e.g. antimony, arsenic, cadmium, chromium VI, cobalt, lead, mercury, nickel, tin (organotins only), radioactive elements, and vanadium. This rating applies when a substance is present at ≥ 100 ppm within a homogeneous material.	Not applicable (i.e. substance is present at <100 ppm within a homogeneous material).	Chemical contains toxic metal compound (e.g. antimony, arsenic, cadmium, chromium VI, cobalt, lead, mercury, nickel, thallium, tin (organotins only), radioactive elements, and vanadium. This rating applies when a substance is present at > 100 ppm within a homogeneous material. (Note: Some toxic metals on the Restricted Substances List are prohibited for use in a certified product when present at < 100 ppm in certain materials and product types).	Not applicable.