



Mixture Hazard Assessment Methodology

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REVISION HISTORY

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1 OVERVIEW

1.1 Purpose and Content

This document describes the methodology used to assign a RED, YELLOW, GREEN, or GREY hazard rating to a homogeneous mixture for a select set of toxicity endpoints based on the concentrations of individual component chemicals in the homogeneous mixture. This mixtures assessment methodology may be used as an alternative to the traditional Cradle to Cradle Certified® Material Health Assessment Methodology when assigning hazard ratings. However, instead of single chemicals receiving hazard ratings, the whole mixture will receive a hazard rating. An exposure assessment is still required after obtaining one or more hazard ratings for the mixture to complete the material health assessment.

The procedure uses toxicity data for individual chemical substances comprising the homogeneous mixture, and/or toxicity data on homogeneous mixtures where available, from peer-reviewed studies, authoritative lists, and other sources. Then, an approach based upon the European Union's Classification, Labelling and Packaging of Substances and Mixtures (CLP) Regulation (CLP Regulation) and the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) methodology pertaining to the hazard assessment of mixtures is used to assign a RED, GREY, GREEN, or YELLOW hazard rating to the entire mixture for the following set of endpoints:

- *Skin, Eye, and Respiratory irritation;*
- *Skin and Respiratory Sensitization;*
- *Aquatic Toxicity (fish, daphnia, algae), and*
- *Acute Mammalian Toxicity (oral, dermal, and inhalation)*

1.2 Recommended Use of this Document

It is recommended to use this methodology in applicable situations, since not using it may result in the consideration of specific substance hazards that are irrelevant based on the way the substance is used in the product (i.e. non-use may result in overly conservative ratings). The applicable situation for use of this methodology is when after conducting a traditional Cradle to Cradle Certified material health assessment, it is determined that a homogeneous material is X-assessed only due to a substance(s) present at a relatively low concentration (< 10%) and with a red hazard rating from one or more of the toxicity endpoints addressed in the mixtures methodology (see section 1.5 for the scope of toxicity endpoints). The following are examples of when it is appropriate to use the mixtures methodology and when it is not:

1. Material A is given an X assessment due to a substance at a concentration of 2% with a red hazard rating for carcinogenicity. The material also contains another substance at a concentration of 1% with a red hazard rating for acute oral mammalian toxicity.

Use of this methodology is not recommended because the material is X-assessed due to the presence of a substance with a red hazard rating for a toxicity endpoint not addressed in this methodology (i.e. the outcome won't change regardless of mixture rule application).

2. Material B is given a X assessment due to a substance at a concentration of 1% with a red hazard rating for fish toxicity. **Use of this methodology is recommended** because the material contains a substance at a low concentration with a red hazard rating for a toxicity endpoint addressed in this methodology (i.e. the outcome may change based on mixture rule application).
3. Material C is given an X assessment due to a substance at a concentration of 30% with a red hazard rating for skin irritation. **Use of methodology is not recommended** because this substance is at too high a concentration for this methodology to produce a different risk rating (i.e. the outcome won't change regardless of mixture rule application).

1.3 Supporting Documents

The following documents are to be used in conjunction with this mixtures methodology document:

- Cradle to Cradle Certified™ Product Standard
- Cradle to Cradle Certified™ Material Health Assessment Methodology
- Regulation (EC) No 1272/2008 Of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006.
- Globally Harmonized System of Classification and Labelling of Chemicals (GHS). Sixth revised edition (2015).

1.4 Terms and Definitions

Table 1: Terms and Definitions

Term	Definition
ATE	Acute Toxicity Estimate
CLP	Classification, Labelling, and Packaging of Substances and Mixtures (EC No. 1272/2008)
Concentration Addition	Concentration addition (CA) assumes that chemicals in a mixture act by the same mechanism/mode of action, and differ only in their potencies.
Concentration Limit	The minimum concentration for a substance to trigger the classification of a mixture for a specific hazard endpoint.
Cut-Off Value	The minimum concentration for a substance to be taken into account for GHS classification purposes (do not necessarily trigger classification).
EC	European Commission
EU	European Union
GHS	Globally Harmonized System of Classification and Labelling of Chemicals
Homogeneous Material	Material of uniform composition throughout that cannot be mechanically disjointed, in principle, into different materials.
Mixture	A homogeneous material that contains two or more chemicals that have been combined such that each chemical retains its own chemical identity.
SCL	Specific Concentration Limit
Sub-endpoint	A sub-endpoint is a toxicity endpoint that makes up a part of a Cradle to Cradle hazard endpoint.

1.5 Scope

This methodology describes the methodology for assigning a Cradle to Cradle Certified hazard rating to a mixture for the following Cradle to Cradle Certified endpoints:

- *Skin, Eye, and Respiratory Irritation;*
- *Skin and Respiratory Sensitization;*
- *Fish Toxicity (acute and chronic toxicity);*
- *Daphnia Toxicity (acute and chronic toxicity);*

- *Algae Toxicity (acute and chronic toxicity);*
- *Oral Toxicity (Acute Mammalian Toxicity only);*
- *Dermal Toxicity (Acute Mammalian Toxicity only);*
- *Inhalation Toxicity (Acute Mammalian Toxicity only);*

These endpoints are a subset of the endpoints included in the Cradle to Cradle Certified hazard assessment methodology and a subset of endpoints for which mixture hazard assessment methodology applies under the CLP/GHS systems.

Endpoints for which the mixture hazard assessment methodology applies in the CLP/GHS systems but not in the Cradle to Cradle Certified methodology include:

- *Germ Cell Mutagenicity*
- *Carcinogenicity*
- *Reproductive Toxicity*
- Specific Target Organ Toxicity & Single and Repeated Exposure

The rationale for not including these endpoints in the Cradle to Cradle Certified mixture hazard assessment methodology is that there is not a strong and consistent scientific basis for assuming that dilution of the chemical in a product results in reduced hazard for these endpoints.

2 BACKGROUND

2.1 Chemical Mixtures Toxicity Assessment

Chemical mixtures vary widely in their specific chemical contents and concentrations. Some mixtures consist of a relatively small number of chemicals (e.g., ten or fewer chemicals) and have a known composition (simple mixture). However, in many cases, mixtures comprise tens, hundreds, or thousands of chemicals and the composition is not fully known (complex mixture). The chemicals in the mixture can interact with each other, exhibiting a toxic effect either greater than (synergism) or less than (antagonism) expected, or work in a non-interactive way that does not influence each other's mode of action. Chemical interactions like antagonism or synergism occur at medium or high dose levels because at low exposure levels these interactions are not occurring or are occurring at rates that are toxicologically insignificant (EC 2014).

Two approaches have been used to assess the toxicity of mixtures: a whole-mixture approach and a component-based approach. The whole-mixture approach relies on testing of the whole product/mixture to identify the hazard of the mixture and is mainly applied to assess the effects of mixtures with (partly) unknown compositions. In this approach, the identity of the substances driving the overall response may remain unidentified (EC 2014).

A more common approach to assess the toxicity of a mixture is to consider the toxicity of its individual constituents, that is, a component-based approach. This requires more information regarding identity, concentration, and toxicity (including mode of action) of the chemicals in the mixture. When applying the component-based approach, interactions between the chemicals have to be taken into account. Two models, Concentration Addition and Independent Action, have been suggested as default models for assessing toxicological interaction and predicting mixture toxicity. Generally, models based on the Concentration Addition approach are the most frequently applied to estimate the toxicity of mixtures as they provide reliable estimates of combined effects and are considered to be more conservative than Independent Action models (EC 2014).

2.2 CLP/GHS Classification of a Mixture Based on Its Components

The consideration of mixtures toxicities for hazard endpoints is addressed within the Globally Harmonized System of Classification and Labeling of Chemicals (GHS) and the European Regulation (EC) No 1272/2008 on Classification, Labelling and Packaging (CLP) of Substances and Mixtures. The CLP came into force on 20 January 2009 in all EU Member States (EC 2008) and implements the 2nd edition of the GHS guidance into EU law. However, the original CLP legal text has been amended on a number of occasions since its original publication following updates to the GHS. The classification of mixtures under CLP/GHS basically follows the same methodology as the classification of substances and includes the same hazard classes.

It is recommended that mixture hazard classifications be derived from hazard data on the whole mixture. However, the alternative approach, which is the basis of the Cradle to Cradle Certified Mixture Hazard Assessment Methodology, is a mixture being classified based on available data on its individual component chemicals using concentration addition as the main assumption for the combined effects of multiple chemicals. Which chemicals are considered in this approach is determined by cut-off values and concentration limits that are applied accordingly.

This approach first requires gathering information on the chemical composition of the mixture, the hazards of those chemical components, and their concentrations in the mixture. Then, three different models are used to classify the hazard of the mixture under CLP/GHS. Two are additive methods and one is non-additive:

1. Additive Methods
 - a. Summation Method
 - b. Additivity Formula Method
2. Non-Additive Method

In the additive method, the concentrations of the chemicals with the same hazard are added together and if the sum of the concentrations of one or several classified substances in the mixture equals or exceeds the generic concentration limit established for that particular hazard endpoint, the mixture must then be classified for that hazard. Within this approach two models are applied: summation method and additivity formula.

In the non-additive method, the classification is based on concentration thresholds, which requires using a cut-off limit (limit of concern) and a generic concentration limit (GCL) to assign a classification. In these cases, if the mixture contains two substances each below the GCLs defined for that endpoint, even if the sum is above this limit, the mixture will not be classified (for additional details, see the CLP methodology below for these endpoints).¹

The CLP/GHS mixture hazard assessment methodology is applicable to human health and some, but not all, environmental endpoints as shown below. The hazard endpoints relevant to the Cradle to Cradle Certified Mixture Hazard Assessment Methodology are in **bold** text:

- The additive method is used for the following hazard classes:
 - **Acute Mammalian Toxicity (Oral, Dermal, Inhalation) [Additivity Formula Method]**
 - **Skin Corrosion/Irritation [Summation Method]**
 - **Serious Eye Damage/Eye Irritation [Summation Method]**
 - **Acute and Long-Term Aquatic Hazards [Summation Method]**

¹ Under CLP only, some substances may have been assigned SCLs. These could be lower or higher than GCL and are supported by data. SCLs are only available for health hazard endpoints and take precedence over any other concentration limits. SCLs are given in Annex VI of the CLP (Table 3.1), and now may also be set by REACH registrants and CLP notifiers when they submit their classifications to ECHA.

- The non-additive method is applied for the following hazard classes:
 - Germ Cell Mutagenicity
 - Carcinogenicity
 - Reproductive Toxicity
 - Specific Target Organ Toxicity & Single and Repeated Exposure
 - **Skin and Respiratory Sensitization**

In the next section, the CLP mixture hazard assessment methodology is explained in more detail for each GHS endpoint relevant to the Cradle to Cradle Certified Mixture Hazard Assessment Methodology.

2.3 CLP/GHS Endpoint Specific Mixture Hazard Classification Criteria

2.3.1 Acute Mammalian Toxicity

Mixture Hazard Assessment Method: Additivity Formula

The CLP/GHS hazard classification criteria of a mixture for the Acute Mammalian Toxicity endpoint are based on the Acute Toxicity Estimate (ATE) value of the mixture calculated from the ATE values for all relevant chemicals according to the following formula for Oral, Dermal or Inhalation Toxicity (CLP section 3.1.3.6.2, EC 2008)

$$\frac{100}{\text{ATE mixture}} = \frac{\sum_n \% \text{ chemical is in formulation}}{\text{LD}_{50} \text{ or LC}_{50} \text{ Entry}}$$

In this approach, the oral, dermal, and inhalation LD₅₀/LC₅₀ values for all the relevant mixture components are required for the calculation. The ATE value for the mixture is then compared against the GHS criteria for the Acute Mammalian Toxicity endpoint to assign a classification.

According to CLP, in case of the total concentration of the relevant substance (s) with unknown acute toxicity being >10%, the formula presented above is corrected to adjust for the percentage of the unknown substance(s) as follows:

$$\frac{100 - (\sum_n \% \text{ chemicals unknown} > 10\%)}{\text{ATE mixture}} = \frac{\sum_n \% \text{ chemical is in formulation}}{\text{LD}_{50} \text{ or LC}_{50} \text{ Entry}}$$

2.3.2 Skin Irritation

Mixture Hazard Assessment Method: Summation Method

The GHS² hazard classification criteria of a mixture for the Skin Irritation endpoint are based on the summation method that is described in the GHS guidance (UN 2015), chapter 3.2, Table 3.2.3 (shown below in Table 2) using the relevant chemicals (i.e. present at a concentration $\geq 1\%$). A weighting factor of 10 is used for corrosive components when they are present below the generic concentration limit for a classification with Category 1 ($> 0.1\%$), but are still at a concentration that will contribute to the classification of the mixture as an irritant.

Table 2: Calculation of GHS mixture hazard classification for the Skin Irritation endpoint based on the concentration of component chemicals classified for Skin Irritation.

Sum of Chemicals Classified as:	Concentration triggering classification of a mixture as:		
	Skin Corrosive	Skin Irritant	
	Category 1	Category 2	Category 3
Skin Corrosive Categories 1A, 1B, 1C [<i>present at $\geq 1\%$</i>]	$\geq 5\%$	$\geq 1\%$ but $< 5\%$	--
Skin Irritant Category 2 [<i>present at $\geq 1\%$</i>]	--	$\geq 10\%$	$\geq 1\%$ but $< 10\%$
Skin Irritant Category 3 [<i>present at $\geq 1\%$</i>]	--	--	$\geq 10\%$
(10x Skin Corrosive Category 1A, 1B, 1C [<i>present at $\geq 0.1\%$ and $< 1\%$]</i>) + Skin Irritant Category 2 [<i>present at $\geq 1\%$</i>]	--	$\geq 10\%$	$\geq 1\%$ but $< 10\%$
(10x Skin Corrosive Category 1A, 1B, 1C [<i>present at $\geq 0.1\%$ and $< 1\%$]</i>) + Skin Irritant Category 2 [<i>present at $\geq 1\%$</i>] + Skin Irritant Category 3 [<i>present at $\geq 1\%$</i>]	--	--	$\geq 10\%$

² The GHS mixture hazard assessment methodology is used here instead of CLP as the latter did not adopt Category 3 for this endpoint (skin irritation)

Alternatively, if the product contains strong acids/bases, classification of mixture shall be based on the mixture pH as described in Table 3.2.4 of the CLP (shown in Table 3 below)³ (EC 2008). The mixture may also be classified as corrosive (GHS Category 1 skin irritant) if it has a pH ≥ 2 or a pH ≥ 11.5 per section 3.2.3.1.2 of the GHS Guidance (UN 2015).

Table 3: Calculation of GHS mixture hazard classification for the Skin Irritation endpoint based on the concentration of strong acids, bases, or corrosives in the mixture.

Chemicals	Concentration	Skin Irritation Classification for Mixture
Acid with pH ≤ 2	$\geq 1\%$	Category 1
Base with pH ≥ 11.5	$\geq 1\%$	Category 1
Other Corrosive (Categories 1A, 1B, 1C) chemicals for which additivity does not apply	$\geq 1\%$	Category 1
Other Irritant (Category 2) chemicals for which additivity does not apply, including acids and bases	$\geq 3\%$	Category 2

2.3.3 Eye Irritation

Mixture Hazard Assessment Method: Summation Method

The CLP/GHS hazard classification criteria of a mixture for the Eye Irritation endpoint are based on the summation method that is described in section 3.3.3.3 of the CLP criterion and in Table 3.3.3 (shown below in Table 4)⁴ (EC 2008) using the relevant chemicals (i.e., present in a concentration $\geq 1\%$). A weighting factor of 10 is used for corrosive components when they are present below the generic concentration limit (1%) for classification with Category 1, but are still at a concentration that will contribute to the classification of the mixture ($> 0.1\%$) as an

³ CLP Table 3.2.4 Concentration of chemicals of a mixture when the additivity approach does not apply, that would trigger classification of the mixture as hazardous to skin (EC 2008).

⁴ CLP Table 3.3.3 Generic concentration limits of chemicals of a mixture classified as Skin Corrosive Category 1 and/or Eye Irritation Category 1 or 2 for effects on the eye that trigger classification of the mixture for effects on the eye (Category 1 or 2) (EC 2008).

irritant as described in CLP section 3.3.3.3.2 (EC 2008). The calculation for this endpoint is complex, as available data on the Skin Irritation endpoint needs to be considered as well⁵.

Table 4: Calculation of GHS mixture hazard classification for the Eye Irritation endpoint based on the concentration of component chemicals classified for Eye Irritation and Skin Irritation.

Sum of Chemicals Classified as:	Concentration triggering classification of a mixture as:	
	Irreversible Eye Effects	Reversible Eye Effects
	Category 1	Category 2
Eye Effects Category 1 or Skin Corrosive Category 1A, 1B, 1C [<i>present at ≥ 1 %</i>]	≥ 3%	≥ 1% but < 3%
Eye Effects Category 2/2A [<i>present at ≥ 1 %</i>]	--	≥ 10%
(10x Eye Effects Category 1 [<i>present at ≥ 0.1 % and < 1 %</i>]) + Eye Effects Category 2/2A	--	≥ 10%
Skin Corrosive Category 1A, 1B, 1C + Eye Effects Category 1 [<i>present at ≥ 1 %</i>]	≥ 3%	≥ 1% but < 3%
10 x (Skin Corrosive Category 1A, 1B, 1C + Eye Effects Category 1 [<i>each present at ≥ 0.1 % and < 1 %</i>]) + Eye Effects Category 2A/2B [<i>present at ≥ 1 %</i>]	--	≥ 10%

Note: reproduced from EC (2008)

Alternatively, if the product contains strong acids/bases, classification of a mixture shall be based on the CLP rule described in Table 3.3.4 and shown in in Table 5 below⁶ (EC 2008).

⁵ Section 3.3.3.2 states that for this endpoint, a weighting factor needs to be applied for the chemicals that are corrosive when they are present in the mixture at a concentration of < 1% (EC 2008).

⁶ CLP Table 3.3.4 Concentration of chemicals of a mixture for which the additivity approach does not apply that trigger classification of the mixture as hazardous to the eye (EC 2008).

Table 5: Calculation of GHS mixture hazard classification for the Eye Irritation endpoint based on the concentration of strong acids, bases or corrosives in the mixture.

Chemical	Concentration	Eye Irritation Classification for Mixture
Acid with pH ≤ 2	≥ 1%	Category 1
Base with pH ≥ 11.5	≥ 1%	Category 1
Other Corrosive (Category 1) substance	≥ 1%	Category 1
Other Eye Irritant (Eye Category 2) substance	≥ 3%	Category 2

2.3.4 Respiratory Irritation

Mixture Hazard Assessment Method: Summation Method

In the CLP/GHS framework, respiratory tract irritation is considered within the specific target organ toxicity — single exposure endpoint (STOT-SE). Substances that cause mild and reversible respiratory irritation are classified to CLP/GHS Category 3 for STOT-SE. The CLP/GHS hazard classification criteria of a mixture for the respiratory irritation endpoint is based on the summation method applying a generic concentration limit of 20%, as described in section 3.8.3.4.5 of the CLP criterion (EC 2008).

2.3.5 Skin Sensitization

Mixture Hazard Assessment Method: Non-additive Method

The CLP/GHS criteria for Skin Sensitization classification of a mixture are based on the concentration threshold as described in section 3.4.3.3.1 of the CLP criterion and in Table 3.4.3 (shown below in Table 6)⁷ (EC 2008). According to this table,

⁷ CLP Table 3.4.3 Generic concentration limits of chemicals of a mixture classified as either skin sensitizers or respiratory sensitizers that trigger classification of the mixture (EC 2008).

- The mixture is classified to CLP/GHS Category 1A if it contains at least one substance that is classified to CLP/GHS Category 1A and is present at or above the threshold of 0.1%

Or

- The mixture is classified to CLP/GHS Category 1B if it contains at least one substance that is classified to CLP/GHS Category 1B and is present at or above the threshold of 1.0%.

Table 6: Calculation of GHS mixture hazard classification for the Skin Sensitization endpoint based on the concentration of component chemicals classified for Skin Sensitization.

Substance Classified as:	Concentration limits triggering classification of a mixture as:
	Skin Sensitizer
	All Physical States
Skin Sensitizer Category 1	≥ 0.1%
Skin Sensitizer Sub-category 1A	≥ 0.1%
Skin Sensitizer Sub-category 1B	≥ 1.0%

Note: Reproduced from EC (2008).

2.3.6 Respiratory Sensitization

Mixture Hazard Assessment Method: Non-additive Method

The CLP/GHS hazard classification criteria for Respiratory Sensitization of a mixture are based on the concentration threshold as described in section 3.4.3.3.1 of the CLP criterion and in Table 3.4.3 (shown below in Table 7)⁸(EC 2008). According to this table,

- The mixture is classified to CLP/GHS Category 1A if it contains at least one substance that is classified to CLP/GHS Category 1A and is present at or above the threshold of 0.1%

Or

- The mixture is classified to CLP/GHS Category 1B

⁸ CLP Table 3.4.3 Generic concentration limits of chemicals of a mixture classified as either skin sensitizers or respiratory sensitizers that trigger classification of the mixture (EC 2008).

- if it contains at least one substance (**solid/liquid**) that is classified to CLP/GHS Category 1B and is present at or above the threshold of 1.0%

Or

- The mixture is classified to CLP/GHS Category 1B if it contains at least one substance (**gas**) that is classified to CLP/GHS Category 1B and is present at or above the threshold of 0.2%

Table 7: Calculation of GHS mixture hazard classification for the Respiratory Sensitization endpoint based on the concentration of component chemicals classified for Respiratory Sensitization.

Substance Classified as:	Concentration limits triggering classification of a mixture as:	
	Respiratory Sensitizer	
	Solid/Liquid	Gas
Respiratory Sensitizer Category 1	≥ 0.1%	≥ 0.1%
Respiratory Sensitizer Sub-category 1A	≥ 0.1%	≥ 0.1%
Respiratory Sensitizer Sub-category 1B	≥ 1.0%	≥ 0.2%

Note: reproduced from EC (2008).

2.3.7 Acute and Chronic Aquatic Toxicity

Mixture Hazard Assessment Method: Summation Method

The GHS⁹ hazard classification criteria of a mixture for the Acute Aquatic Toxicity endpoint are based on the summation method that is described in the GHS guidance (UN 2015), chapter 4.1, Table 4.1.3 (shown below in Table 8)¹⁰ using the relevant chemicals (i.e., present at a concentration ≥ 0.1 %). A multiplying factor (M) is used for Acute Category 1 and Chronic Category 1 components. The multiplying factors to be applied to these components are defined using the toxicity value, as summarised in Table 4.1.5 in the GHS guidance (UN 2015) (shown below in Table 9). Therefore, in order to classify a mixture containing Acute Category 1

⁹ The GHS mixture hazard assessment methodology is used here instead of CLP as the latter did not adopt Category 2 or 3 for this endpoint (Acute Aquatic Toxicity)

¹⁰ GHS Table 4.1.3 Classification of a mixture of short-term (acute) hazards based on summation of the concentration of classified chemicals (UN 2015).

substances, the acute toxicity values for substances with a red hazard rating are required in order to determine the M-factor.

Table 8: Calculation of GHS mixture hazard classification for the Acute Aquatic Toxicity endpoint based on the concentration of component chemicals classified for Acute Aquatic Toxicity.

Sum of the Concentrations (in %) of Chemicals Classified as:	Mixture is Classified as:
Acute 1 x M ^a ≥ 25	Acute 1
(M x 10 x Acute 1) + Acute 2 ≥ 25	Acute 2
(M x 100 x Acute 1) + (10 x Acute 2) + Acute 3 ≥ 25	Acute 3

Note: reproduced from UN (2015).

Table 9: Multiplicative (M) factors corresponding to different L(E)C₅₀ or NOEC values.

Acute toxicity		Chronic toxicity		
L(E)C₅₀ value (mg/L)	M factor	NOEC value (mg/L)	M factor	
			NRD^a components	RD^b components
0.1 < L(E)C ₅₀ ≤ 1	1	0.01 < NOEC ≤ 0.1	1	-
0.01 < L(E)C ₅₀ ≤ 0.1	10	0.001 < NOEC ≤ 0.01	10	1
0.001 < L(E)C ₅₀ ≤ 0.01	100	0.0001 < NOEC ≤ 0.001	100	10
0.0001 < L(E)C ₅₀ ≤ 0.001	1000	0.00001 < NOEC ≤ 0.0001	1000	100
0.00001 < L(E)C ₅₀ ≤ 0.0001	10000	0.000001 < NOEC ≤ 0.00001	10000	1000
(continue in factor 10 intervals)		(continue in factor 10 intervals)		
^a Non-rapidly degradable				
^b Rapidly degradable				

Note: reproduced from UN (2015) and EC (2008).

The CLP/GHS hazard classification criteria of a mixture for the Chronic Aquatic Toxicity endpoint are based on the theory of summation method that is described in CLP Table 4.1.2

(shown below in Table 10)¹¹ (EC 2008) using the relevant chemicals (i.e. present in a concentration $\geq 0.1\%$ for Chronic Category 1 and $\geq 1\%$ for the categories two through four)¹² and a multiplying factor (M) as described in the section above.

Table 10: Calculation of GHS mixture hazard classification for the Chronic Aquatic Toxicity endpoint based on the concentration of component chemicals classified for Acute Aquatic Toxicity.

Sum of Components Classified as:	Mixture is Classified as:
Chronic Category 1 x M ^(a) $\geq 25\%$	Chronic Category 1
(M x 10 x Chronic Category 1) + Chronic Category 2 $\geq 25\%$	Chronic Category 2
(M x 100 x Chronic Category 1) + (10 x Chronic Category 2) + Chronic Category 3 $\geq 25\%$	Chronic Category 3
Chronic Category 1 + Chronic Category 2 + Chronic Category 3 + Chronic Category 4 $\geq 25\%$	Chronic Category 4

Note: reproduced from EC (2008).

¹¹ CLP Table 4.1.2 Classification of a mixture for chronic (long term) hazards, based on summation of classified components (EC 2008).

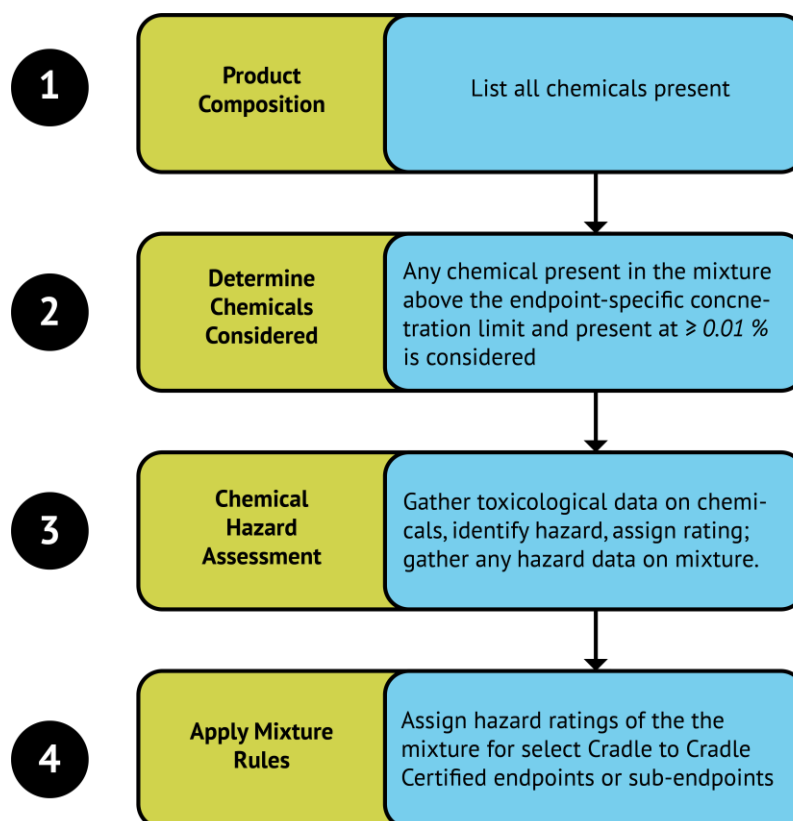
¹² According to CLP section 4.1.3.1.(EC 2008): The ‘relevant components’ of a mixture are those which are classified ‘Acute Category 1’ or ‘Chronic Category 1’ and present in a concentration of 0.1% (w/w) or greater, and those which are classified ‘Chronic Category 2’, ‘Chronic Category 3’ or ‘Chronic Category 4’ and present in a concentration of 1% (w/w) or greater, unless there is a presumption (such as in the case of highly toxic components (see 4.1.3.5.5.5) that a component present in a lower concentration can still be relevant for classifying the mixture for Aquatic Environmental hazards. Generally, for substances classified as ‘Acute Category 1’ or ‘Chronic Category 1’ the concentration is to be taken into account is (0.1 %) (see Table 1.1 in CLP (EC 2008)).

3 PROCESS FOR ASSIGNING HAZARD RATINGS TO MIXTURES

3.1 Summary of Process

Figure 1 illustrates an overview of the process to assign a Cradle to Cradle Certified hazard rating for a homogenous material (mixture) using the adapted CLP/GHS mixture hazard assessment methodology.

Figure 1: Summary of process for assigning a mixture hazard rating for a select set of Cradle to Cradle Certified endpoints or sub-endpoints.



In Step 1: the chemical composition of the homogenous material being evaluated is identified. This is accomplished by listing all chemicals present in the homogenous materials at or above 100 ppm (0.01% by weight). The chemical name and CAS number are identified for each chemical.

In Step 2: the chemicals that are included in the assessment are determined. Each chemical is screened against ECHA C&L inventory to check if any specific concentration limit (SCL) has been established for any of the relevant hazard endpoints assessed here (ECHA 2017). Then, the following steps are taken:

- Any chemical without an SCL and present at $\geq 0.01\%$ in the homogenous material is considered in the assessment.

- Any chemical with an established SCL that is present above its SCL is considered in the assessment. If an SCL exists and the substance is present below its SCL, it is not considered. Note: the SCL threshold takes precedence over the 0.01%. For example, 1,2 benzisothiazolin-3-one (CAS #2634-33-5) has an SCL of 0.05% for the Skin Sensitization endpoint (ECHA 2017; EC 2008). Therefore, if it is present in the mixture (homogenous material) below 0.05%, it is not considered in the assessment.

It is important to note that very few chemicals have an SCL established under CLP. So, in most cases, the threshold of 0.01% is applied for chemicals subject to assessment. The SCLs are given in Table 3.2, Annex VI, of the CLP Regulation (EC 2008) or alternatively they are listed in the [ECHA C&L inventory](#).

In Step 3: If available, hazard data from test data of the mixture are gathered for relevant endpoints. If test data for the mixture is not available for one or more of the endpoints, hazards associated with the individual chemicals included in **Step 2** are classified under CLP/GHS and Cradle to Cradle Certified criteria for the relevant health and environmental endpoints. For this step, toxicological data for the chemicals needs to be collected for the following endpoints, which are a subset of the full suite of 22 hazard endpoints comprising a full Cradle to Cradle Certified chemical hazard assessment:

- **Human Health Endpoints and Sub-endpoints:** Sensitization of Skin and Airways (Skin and Respiratory treated separately), Skin, Eye, and Respiratory Irritation (each treated separately) and Acute Mammalian Toxicity (comprises Oral, Dermal, and Inhalation).
- **Aquatic Toxicity Endpoints:** Aquatic Toxicity (Acute and Chronic treated separately)

Further details on the information/data sources and the methodology for Cradle to Cradle Certified chemical hazard assessment can be found in the Cradle to Cradle Certified™ Material Health Assessment Methodology document (C2CPII 2017).

In Step 4: The CLP/GHS mixture hazard assessment methodology is applied to assign hazard ratings at the material level for the hazard endpoints listed above in Step 3. The methodology for assigning mixture hazard ratings are described in Section 3.2 of this document. If the whole mixture has been tested for its hazard, then the hazard ratings derived from this take precedence over the mixture hazard ratings derived from following the Cradle to Cradle Certified hazard criteria.

3.2 Cradle to Cradle Certified Endpoint-specific Guidance on Hazard Classification for a Mixture

3.2.1 Oral, Dermal, and Inhalation Toxicity (Acute Mammalian)

Acute Mammalian Toxicity is a sub-endpoint of three separate Cradle to Cradle Certified human health endpoints (Oral Toxicity, Dermal Toxicity, and Inhalation Toxicity) which each also contain sub-endpoints for single-exposure target organ toxicity and sub-chronic/chronic.

Because the Cradle to Cradle Certified Mixture Hazard Assessment Methodology does not address single-exposure specific target organ toxicity or sub-chronic/chronic toxicity, those sub-endpoints must be assessed by the traditional material health assessment methodology. Then, the single-exposure specific target organ toxicity or sub-chronic/chronic toxicity ratings (from each individual substance) may be combined with the mixture ratings for the acute toxicity sub-endpoint from the mixture hazard assessment for each of the three exposure pathways (oral, dermal, inhalation) to obtain an overall hazard rating for the Oral, Dermal, and Inhalation Toxicity Cradle to Cradle Certified endpoints for each substance.

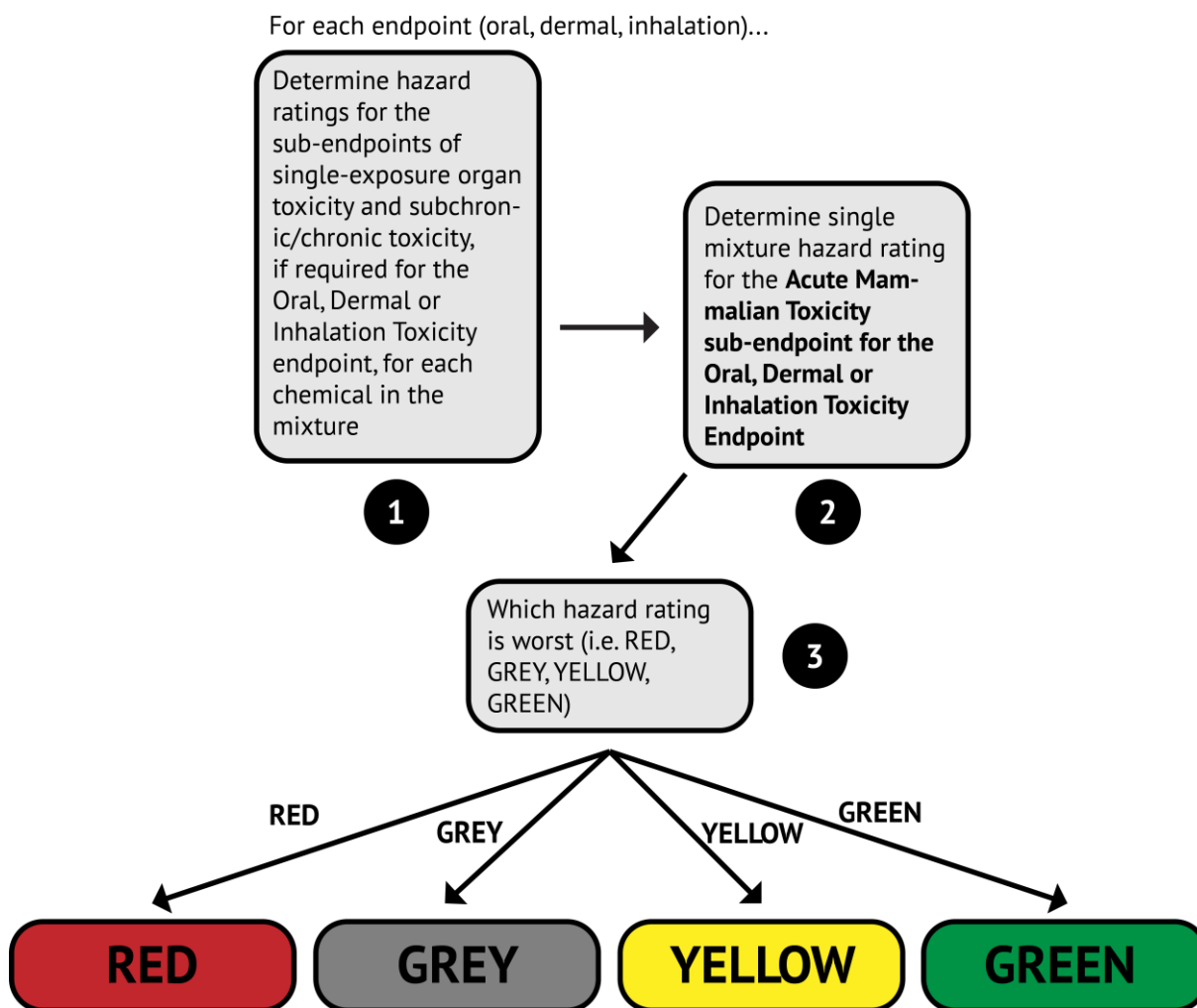


Figure 2: Summary of process for assigning a hazard score for the Cradle to Cradle Certified endpoints of oral, dermal, and inhalation toxicity that takes into account mixture hazard ratings for the Acute Mammalian Toxicity sub-endpoint for oral, dermal and inhalation toxicity endpoints.

3.2.1.1 Oral, Dermal, and Inhalation Toxicity (Acute Mammalian)

Mixture Hazard Assessment Method: Additivity Formula Method

References: For information on the Cradle to Cradle Certified hazard rating criteria please refer to sections 3.3.5, 3.3.6, and 3.3.7 and tables 9, 10, and 11 in the Cradle to Cradle Certified Material Health Assessment Methodology (C2CPII 2017). For a comparison between Cradle to Cradle Certified chemical hazard rating and GHS classification for this endpoint see section Appendix section 5.1.1 and Table 18 in this document. Differences between Cradle to Cradle Certified Mixture Hazard Assessment Methodology and CLP/GHS mixture hazard assessment methodology for this endpoint may be found in Appendix section 5.1.2.1 in this document. The ATE calculation is derived from the equations demonstrated in section 2.31.

Process for Assigning Mixture Hazard Rating

1. **Collect L(C)D₅₀ values for each exposure route for each chemical considered in the mixture.**
2. **Apply the cut-off values (Table 11) to determine which chemical components with oral, dermal, inhalation Acute Mammalian Toxicity sub-endpoint ratings are considered for the mixture hazard rating derivation in this endpoint:**

Table 11: Cut-off values by hazard rating for the Acute Mammalian Toxicity sub-endpoint.

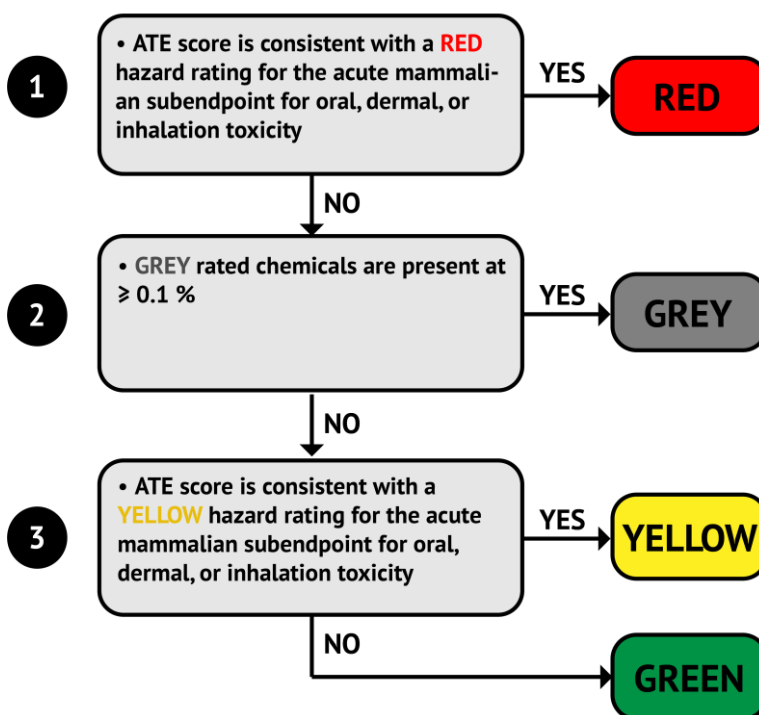
Endpoint for Chemical Component	Cut-Off Value for Consideration Toward This Mixture Hazard Rating
Acute Mammalian Toxicity (Oral, Dermal, Inhalation)	RED rated chemicals present at $\geq 0.1\%$, YELLOW rated chemicals present at $\geq 1\%$, and GREY rated chemicals $\geq 0.1\%$ ¹³

3. **Calculate the ATE value for the mixture from component chemicals' L(C)D₅₀ values (see section 2.3.1)**
4. **Assign the mixture hazard rating for the Acute Mammalian Toxicity sub-end point via the following process (also shown in Figure 3). The mixture will have a Cradle to Cradle Certified hazard rating for the Acute Mammalian Toxicity sub-endpoint of:**
 - **RED** if
 - The oral ATE for the mixture is ≤ 300 mg/kg,
 - The dermal ATE for the mixture is $\leq 1,000$ mg/kg, or
 - The inhalation ATE for the mixture is ≤ 10 mg/L (Gas or vapor) or ≤ 1 mg/L (Dust/Mist/Fumes)
 - **YELLOW** if
 - The oral ATE for the mixture is > 300 -2,000 mg/kg,
 - The dermal ATE for the mixture is $> 1,000$ -2,000 mg/kg, or
 - The inhalation ATE for the mixture is > 10 -20 mg/L (Gas or vapor) or > 1.0 -5.0

¹³ According to CLP Table 1.1: the 'relevant chemicals' of a mixture for Acute Mammalian Toxicity are those which are classified as Category 1, 2, or 3 and present at concentrations of 0.1 % or greater or are classified as Category 4 and present at concentrations of 1% or greater (w/w for solids, liquids, dusts, mists and vapors and v/v for gases) (CLP (EC 2008)).

- mg/L (Dust/Mist/Fumes)
- **GREEN** if
 - The oral ATE for the mixture is > 2,000 mg/kg,
 - The dermal ATE for the mixture is > 2,000 mg/kg, or
 - The inhalation ATE for the mixture is > 20 mg/L (Gas or vapor) or > 5.0 mg/L (Dust/Mist/Fumes)
- **GREY** if the ATE for the mixture meets YELLOW or GREEN thresholds with one or more grey substances present at or above 0.1%.

Figure 3: Mixture hazard assessment methodology flowchart for the Cradle to Cradle Certified sub-endpoint of Acute Mammalian Toxicity for Oral, Dermal, and Inhalation toxicity endpoints, respectively that results in a RED, GREY, YELLOW, or GREEN hazard rating for the mixture for those sub-endpoints.



3.2.2 Skin, Eye, and Respiratory Irritation

In the Cradle to Cradle Certified Material Health Assessment methodology *Skin, Eye, and Respiratory Irritation* comprise a single endpoint with the three exposure pathways as sub-endpoints. All three sub-endpoints are considered in combination when assessing an individual chemical. That is, only data on skin, eye, or respiratory irritation alone is required in order to rate a chemical as RED, YELLOW, or GREEN for the *Skin, Eye, and Respiratory Irritation* endpoint (though if data is available on any of the three sub-endpoints, it needs to be taken into account).

However, when assessing components of a mixture, the Skin Irritation and Eye Irritation endpoints must be considered separately since GHS/CLP mixture classifications differ for each sub-endpoint. The mixture hazard assessment methodology is not applied to the Respiratory Irritation sub-endpoint, since there is not a separate category for respiratory corrosion/irritation in GHS classification and the only hazard rating specific to Respiratory Irritation in GHS leads to a YELLOW assessment (H335). Once the mixture is classified

for the Skin Irritation and Eye Irritation sub-endpoints using the mixture hazard assessment methodology, all sub-endpoint hazard ratings will be considered jointly toward the Cradle to Cradle Certified endpoint for *Skin, Eye, and Respiratory Irritation* (**Figure 4**).

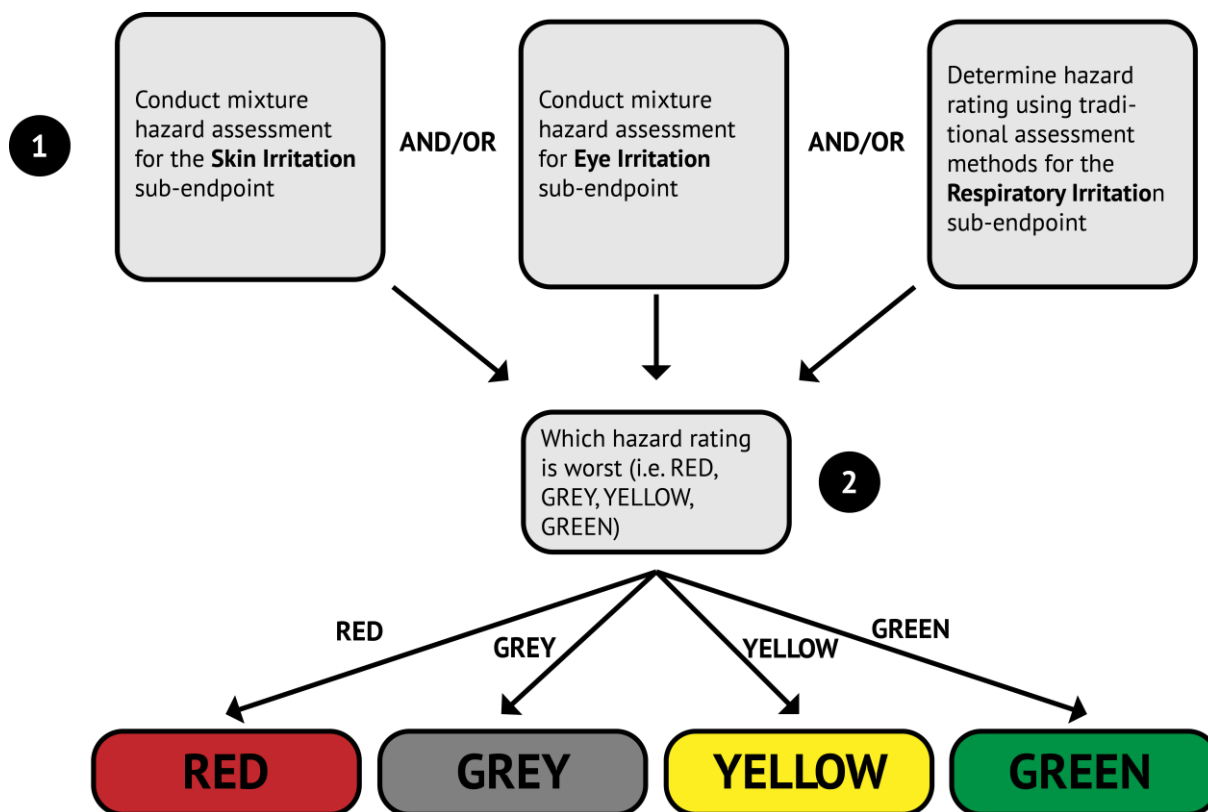


Figure 4: Summary of process for assigning a hazard rating for the Cradle to Cradle Certified endpoint of *Skin, Eye, and Respiratory Irritation* that takes into account mixture hazard ratings for the sub-endpoints of Skin Irritation and Eye Irritation.

3.4.2.1 Skin Irritation

Mixture Hazard Assessment Method: Summation Method

References: For information on the Cradle to Cradle Certified hazard rating criteria refer to sections 3.3.9 and Table 12 in the Cradle to Cradle Certified Material Health Assessment Methodology (C2CPII 2017). For a comparison between Cradle to Cradle Certified chemical hazard rating and GHS classification for this endpoint see Appendix section 5.1.1 and Table 18 in this document. Differences between the Cradle to Cradle Certified Mixture Hazard Assessment Methodology and the CLP/GHS mixture hazard assessment methodology for this endpoint may be found in Appendix section 5.1.2.2 in this document.

Process for Assigning Mixture Hazard Rating

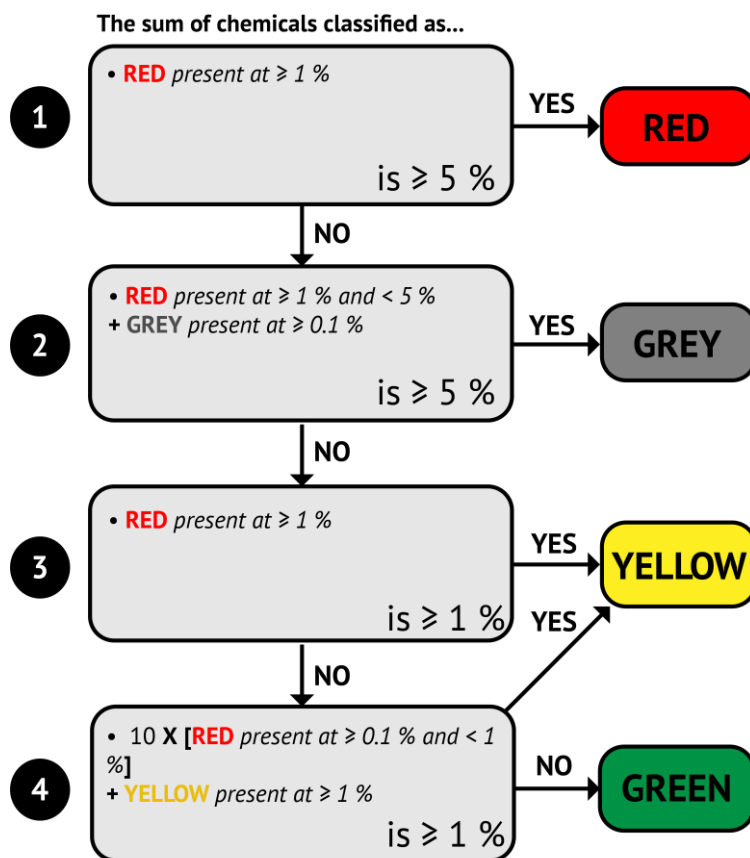
1. **Apply the cut-off values (Table 12)** to determine which chemical components with Skin Irritation hazard are considered when deriving the mixture hazard rating for this sub-endpoint:

Table 12: Cut-off value by hazard rating for the Skin Irritation sub-endpoint.

Endpoint for Chemical Component of Mixture	Cut-off Value for Consideration Toward This Mixture Hazard Rating		
	RED	YELLOW	GREY
Skin Irritation	≥ 1 % for RED rated	≥ 0.1 % for RED rated and ≥ 1% for YELLOW rated	≥ 1% for RED rated, ≥ 0.1 % for GREY rated

2. **Assign the mixture hazard rating** for the Skin Irritation sub-end point via the following process (also illustrated in **Figure 5**). The mixture will have a Cradle to Cradle Certified hazard rating for the Skin Irritation sub-endpoint of:
 - **RED** if
 - The sum of chemicals classified as RED (present in concentrations ≥ 1 %) makes up ≥ 5 % of the mixture.
 - **GREY** if the conditions for a RED rating are not fulfilled **AND**:
 - The sum of chemicals classified as RED (present in concentrations ≥ 1 %) makes up < 5 % of the mixture; **AND**
 - The sum of chemicals classified as RED (present in concentrations ≥ 1 %) and GREY (present in concentrations ≥ 0.1 %) makes up ≥ 5 % of the mixture.
 - **YELLOW** if the conditions for a RED or GREY rating are not fulfilled **AND**:
 - The sum of chemicals classified as RED (present in concentrations ≥ 1 %) make up ≥ 1 % but < 5 % of the mixture; **OR**
 - [10 X the sum of chemicals classified as RED (present in concentrations ≥ 0.1 % but < 1 %) + the sum of chemicals classified as YELLOW (present in concentrations ≥ 1 %)] makes up ≥ 1 % of the mixture.
 - **GREEN** if
 - The conditions for neither a RED, nor a YELLOW, nor a GREY hazard mixture rating are met.

Figure 5: Mixture hazard assessment methodology flowchart for the Cradle to Cradle Certified Skin Irritation sub-endpoint that results in a RED, GREY, YELLOW, or GREEN hazard rating for the mixture for that sub-endpoint.



3.2.2.2 Eye Irritation

Mixture Hazard Assessment Method: Summation Method

References: For information on the Cradle to Cradle Certified hazard rating criteria refer to sections 3.3.9 and Table 12 in the Cradle to Cradle Certified Material Health Assessment Methodology (C2CPII 2017). For a comparison between Cradle to Cradle Certified chemical hazard rating and GHS classification for this endpoint see Appendix section 5.1.1 and Table 18 in this document. Differences between Cradle to Cradle Certified Mixture Hazard Assessment Methodology and the CLP/GHS mixture hazard assessment methodology for this endpoint may be found in Appendix section 5.1.2.3 in this document.

Process for Assigning Mixture Hazard Rating

1. **Apply the cut-off values (Table 13)** to determine which chemical components with Eye Irritation or Skin Irritation* sub-endpoint chemical hazard ratings are considered when deriving the mixture hazard rating for the Eye Irritation sub-endpoint

Table 13: Cut-off values by hazard rating for the Eye Irritation sub-endpoint.

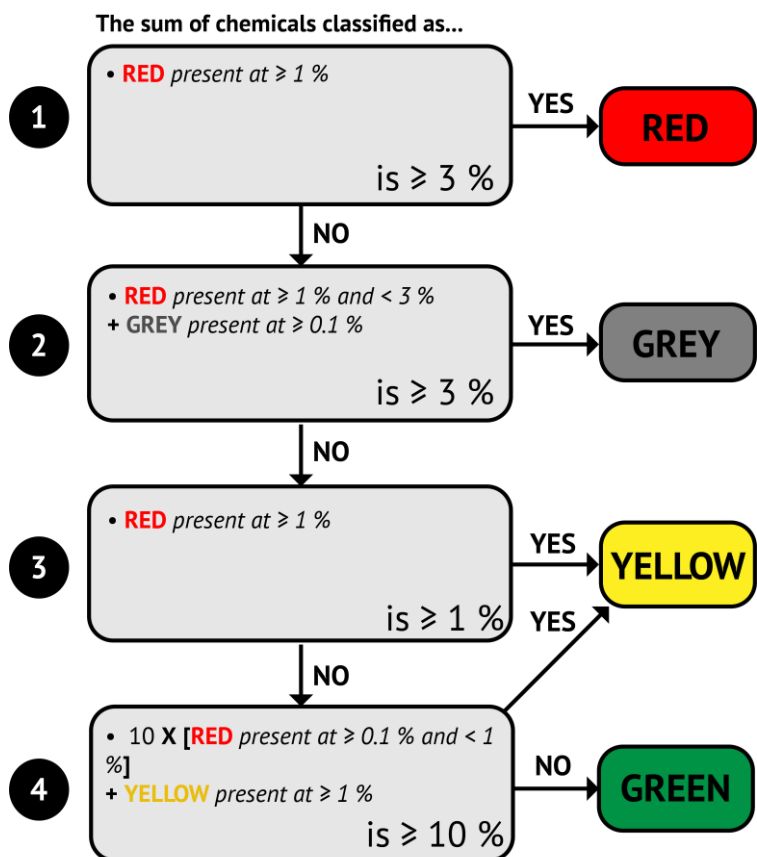
Endpoint for Chemical Components	Cut-off Value for Consideration Toward This Mixture Hazard Rating		
	RED	YELLOW	GREY
Eye Irritation	≥ 1 % for RED rated	≥ 1 % for RED rated, OR between 0.1 % and 1 % for RED rated + ≥ 1% for YELLOW rated	≥ 1% and < 3 % for RED rated, ≥ 0.1 % for GREY rated
Skin Irritation*	≥ 1 % for RED rated	Not considered	Not considered

*Skin Irritation endpoints for chemical components are only considered in combination with Eye Irritation endpoints.

2. **Assign the mixture hazard rating** for the Eye Irritation sub-end point via the following process (also illustrated in **Figure 6**). The mixture will have a Cradle to Cradle Certified hazard rating for the Skin Irritation sub-endpoint of:

- **RED** if
 - The sum of chemicals classified as RED (present in concentrations ≥ 1 %) makes up ≥ 3 % of the mixture.
- **GREY** if the conditions for a RED rating are not fulfilled **AND**:
 - The sum of chemicals classified as RED (present in concentrations ≥ 1 %) makes up < 3 % of the mixture; **AND**
 - The sum of chemicals classified as RED (present in concentrations ≥ 1 %) and GREY (present in concentrations ≥ 0.1 %) makes up ≥ 3 % of the mixture.
- **YELLOW** if the conditions for a GREY rating are not fulfilled **AND**:
 - The sum of chemicals classified as RED (present in concentrations ≥ 1 %) make up ≥ 1 % but < 3 % of the mixture; **OR**
 - [10 X the sum of chemicals classified as RED (present in concentrations ≥ 0.1 % but < 1 %) + the sum of chemicals classified as YELLOW (present in concentrations ≥ 1 %)] makes up ≥ 10 % of the mixture
- **GREEN** if
 - The conditions for neither a RED, nor a YELLOW, nor a GREY hazard mixture ratings are met.

Figure 6: Mixture hazard assessment methodology flowchart for the Cradle to Cradle Certified sub-endpoint of Eye Irritation that results in a RED, GREY, YELLOW, or GREEN hazard rating for the mixture for that sub-endpoint.



3.2.3 Skin and Respiratory Sensitization

In the Cradle to Cradle Certified Material Health Assessment Methodology, *Skin and Respiratory Sensitization* is assessed as one endpoint (C2CPII 2017). However, when assessing components of a mixture, the Skin Sensitization sub-endpoint is considered separately from the Respiratory Sensitization sub-endpoint toward the mixture hazard classification. Only once the mixture itself is classified can both sub-endpoint categories for *Skin and Respiratory Sensitization* be considered jointly.

Both Skin Sensitization and Respiratory Sensitization data must be assessed if data are available. However, only data on one of the sub-endpoints is necessary to obtain a non-GREY rating. Then, the mixture hazard rating for this Cradle to Cradle Certified endpoint is determined by the worst hazard rating of Skin and Respiratory Sensitization (RED, GREY, YELLOW, GREEN in that order). This process is summarized in Figure 7.

The process for assigning a mixture hazard rating for Skin Sensitization or Respiratory Sensitization is identical to the standard Cradle to Cradle Material Health Assessment Methodology with regard to GHS Category 1 and 1A skin sensitizers. With regard to mixtures containing Category 1B skin or respiratory sensitizers – the mixture will be classified as RED if it contains at least one substance that is classified as a CLP/GHS Category 1B skin or respiratory sensitizer and is present at or above the threshold of 1.0 %

Another difference with the Cradle to Cradle Material Health Assessment Methodology that may occur is when an SCL exists for a chemical for either sensitization sub-endpoint that is above or below the standard 0.01 % threshold. In either of these cases, the SCL will take precedence over the 0.01 % threshold.¹⁴ And, if that chemical is present above that SCL threshold for either sub-endpoint, the mixture will receive a RED hazard rating.

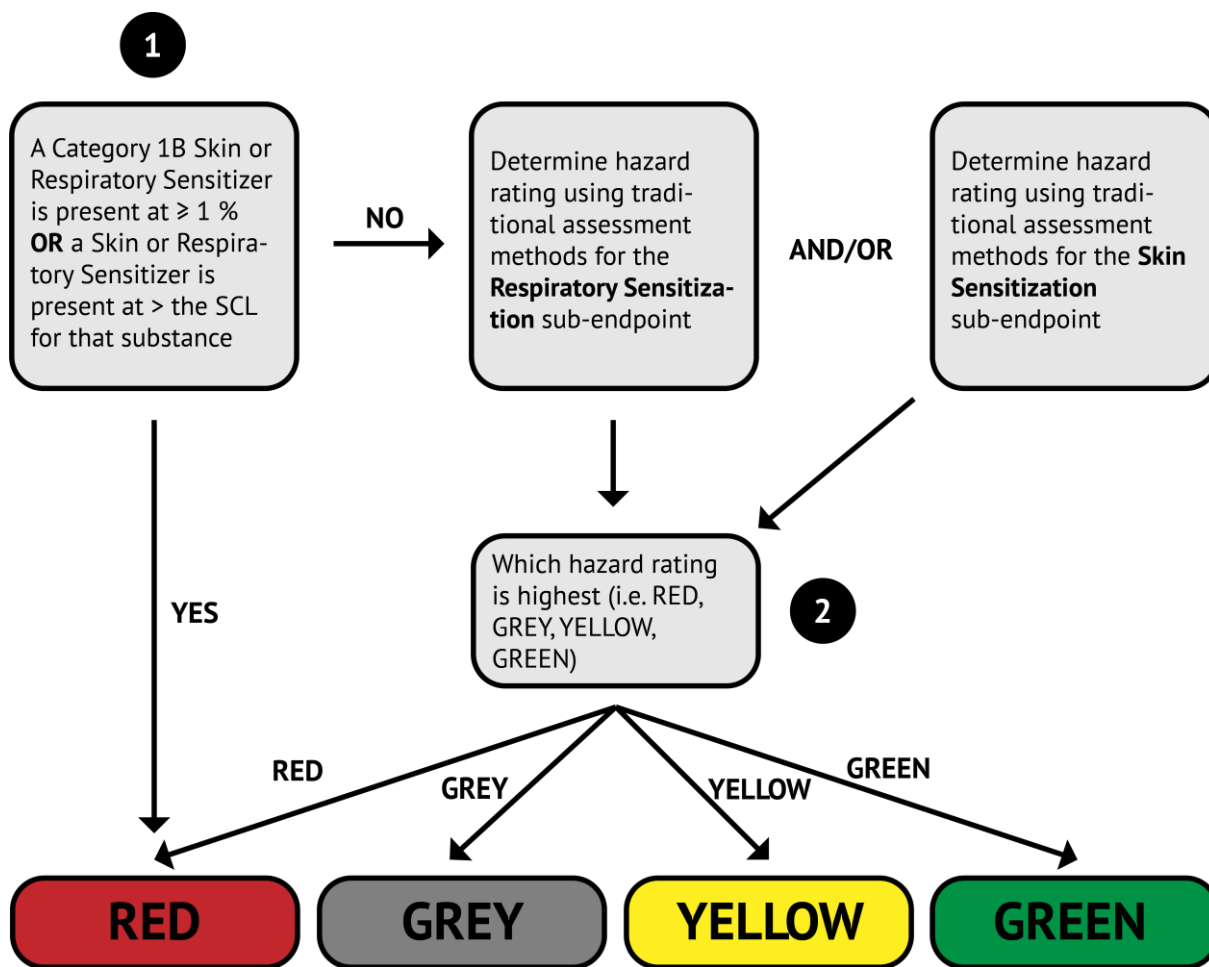


Figure 7: Summary of process for assigning a hazard rating of a mixture for the Cradle to Cradle Certified endpoint of *Skin and Respiratory Sensitization*.

3.2.4 Acute and Chronic Aquatic Toxicity

In the Cradle to Cradle Certified Material Health Assessment Methodology, the Acute and Chronic Aquatic Toxicity endpoints comprise of three toxicity endpoints for the different aquatic taxa (*Fish Toxicity* [acute and chronic toxicity]; *Daphnia Toxicity* [acute and chronic toxicity];

¹⁴ SCL's must be considered for formulated consumer products – pending acceptance by CSB for version 4.

Algae Toxicity [acute and chronic toxicity]). However, when assessing the hazard of a mixture, the Acute Aquatic Toxicity sub-endpoint is considered separately from the Chronic Aquatic Toxicity sub-endpoint in the mixture hazard classification for Acute Aquatic Toxicity. Then, once the mixture itself is classified, the two sub-endpoint categories for each taxon (i.e. acute and chronic) are considered jointly. This process is summarized in Figure 8. The mixture assessment for Chronic Aquatic Toxicity (see section 3.4.7.2) is only required when the Acute Aquatic Toxicity mixture hazard assessment results in a YELLOW rating. However, if Chronic Aquatic Toxicity data is available it should be considered.

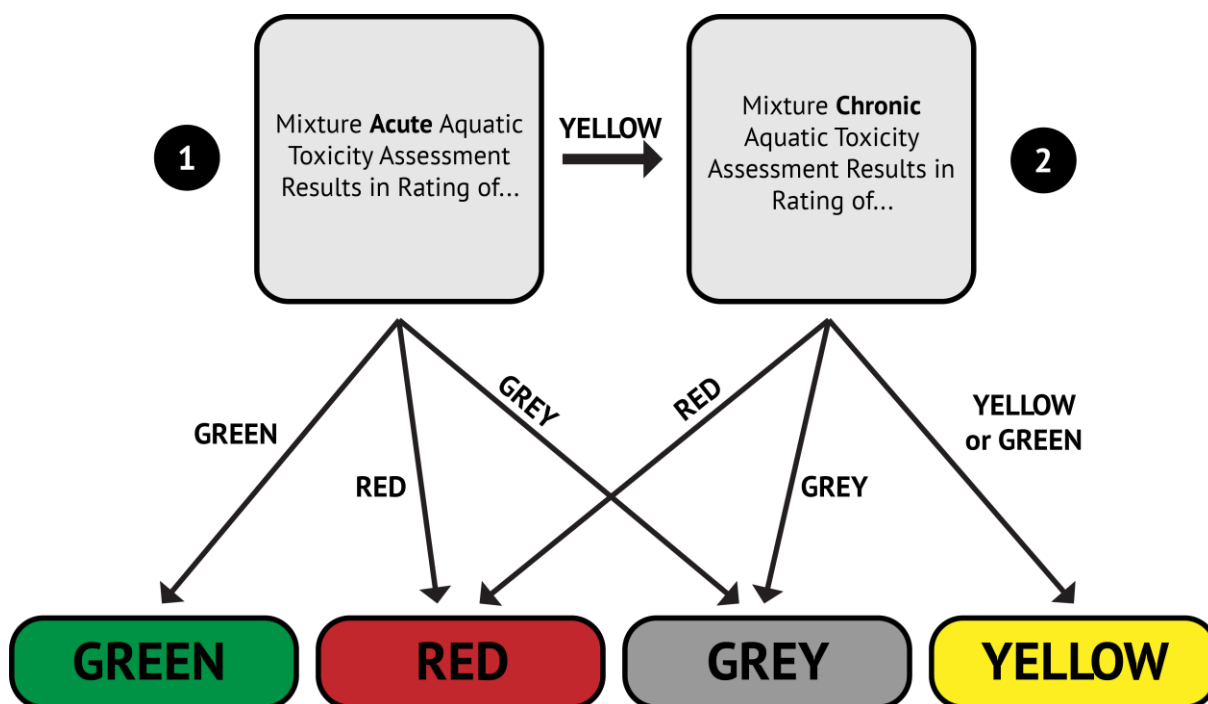


Figure 8: Summary of process for assigning a hazard rating for each of the three Cradle to Cradle Certified endpoints for Acute and Chronic Aquatic Toxicity (Fish, Daphnia, Algae) that takes into account mixture hazard ratings for the sub-endpoints of Acute Aquatic Toxicity and Chronic Aquatic Toxicity.

3.2.4.1 Fish, Daphnia and Algae Toxicity (Acute Toxicity)

Mixture Hazard Assessment Method: Summation Method

References: For information on the Cradle to Cradle Certified hazard rating criteria refer to sections 3.3.12 and Tables 16, 17, and 17 in the Cradle to Cradle Certified Material Health Assessment Methodology (C2CPII 2017). For a comparison between Cradle to Cradle

Certified chemical hazard rating and GHS classification for this endpoint see Appendix section 5.1.1 and Table 18 in this document. Differences between the Cradle to Cradle Certified Mixture Hazard Assessment Methodology and the CLP/GHS mixture hazard assessment methodology for this endpoint may be found in Appendix section 5.1.2.6 in this document.

Process for Assigning Mixture Hazard Rating

- Determine Cradle to Cradle Certified chemical hazard rating and M factor from GHS classification and/or L(E)C₅₀ values (Table 14).** Cradle to Cradle Certified chemical hazard ratings for Acute Aquatic Toxicity are designated as Acute 1, Acute 2, YELLOW, GREEN, or GREY. If classified as Acute 1, determine what M factor applies. If only GHS classification or H-statements are available, and no toxicity data is available, the M-factor may be assumed to equal one.

Table 14: M Factors by L(E)C₅₀ values (mg/l) and GHS Chronic Aquatic Toxicity Classification or designated Cradle to Cradle Certified hazard ratings for the Chronic Toxicity sub-endpoint (fish, daphnia, or algae).

L(E)C ₅₀ value (mg/l) or GHS Acute Aquatic Toxicity Classification for Fish, Daphnia, or Algae	Designated Hazard Classification	Designated M factor
No data available	GREY	N/A
> 100 or GHS Not Classified	GREEN ^a	N/A
100 ≥ L(E)C ₅₀ > 10; GHS Acute Category 3: H402	YELLOW	N/A
10 ≥ L(E)C ₅₀ > 1; GHS Acute Category 2; H401	Acute 2	N/A
1 ≥ L(E)C ₅₀ > 0.1; GHS Acute Category 1; H400	Acute 1	1
0.1 ≥ L(E)C ₅₀ > 0.01		10
0.01 ≥ L(E)C ₅₀ > 0.001		100
0.001 ≥ L(E)C ₅₀ > 0.0001		1000
(continue in factor 10 intervals)		10 X previous entry

- Apply the cut-off values (Table 15)** to determine which chemical components with Acute Aquatic Toxicity sub-endpoint hazard ratings are considered when deriving each mixture hazard rating for the Acute Aquatic Toxicity sub-endpoint.

Table 15: Cut-off values by chemical hazard rating for the Acute Aquatic Toxicity (daphnia, fish, algae) sub-endpoints.

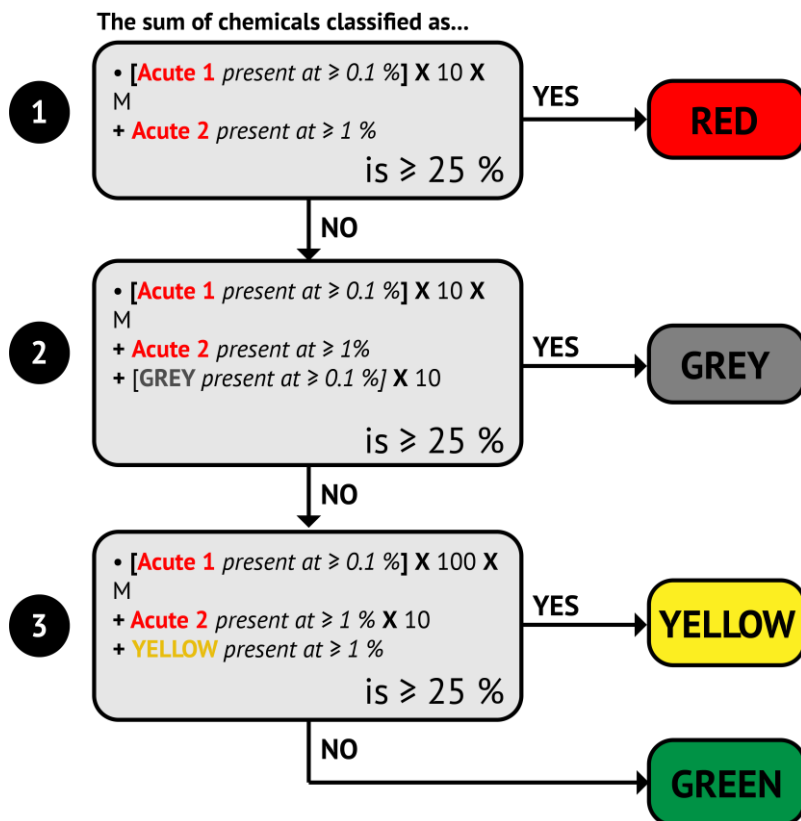
Sub-endpoint for Chemical Component	Cut-off Values for Consideration Toward This Mixture Hazard Rating		
	RED	YELLOW	GREY

Acute Aquatic Toxicity	≥ 0.1 % for Acute 1 rated chemicals, ≥ 1 % for Acute 2, chemicals	≥ 0.1 % for Acute 1 rated chemicals, ≥ 1 % for Acute 2 rated chemicals, ≥ 1 % for YELLOW rated chemicals	≥ 0.1 % for Acute 1 rated chemicals, ≥ 1 % for Acute 2, and ≥ 0.1 % for GREY rated
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3. **Assign the mixture hazard rating** for the Acute Aquatic Toxicity sub-end point via the following process (also illustrated in **Figure 9**). The mixture will have a Cradle to Cradle Certified hazard rating for the Acute Aquatic Toxicity sub-endpoint of:

- **RED** if
 - [10 X the sum of chemicals classified as Acute 1 (present in concentrations ≥ 0.1 %) X M + the sum of chemicals classified as Acute 2 (present in concentrations ≥ 1 %)] is ≥ 25 %.
- **GREY** if the conditions for assigning a RED hazard mixture rating are not met **AND**:
 - [10 X the sum of chemicals classified as Acute 1 (present in concentrations ≥ 0.1 %) X M + the sum of chemicals classified as Acute 2 (present in concentrations ≥ 1 %) + 10 X the sum of chemicals classified as GREY (present in concentrations ≥ 0.1 %)] is ≥ 25 %
- **YELLOW** if conditions for assigning a RED or GREY hazard mixture rating are not met **AND**:
 - [100 X the sum of chemicals classified as Acute 1 (present in concentrations ≥ 0.1 %) X M + 10 X the sum of chemicals classified as Acute 2 (present in concentrations ≥ 1 %) + the sum of chemicals classified as YELLOW (present in concentrations ≥ 1 %)] is ≥ 25 %.
- **GREEN** if
 - If the conditions for assigning a RED, YELLOW, and GREY rating are not met.

Figure 9: Mixture hazard assessment methodology flowchart for the Cradle to Cradle Certified sub-endpoint of Acute Aquatic Toxicity (for Fish, Daphnia, and Algae) that results in a RED, GREY, YELLOW, or GREEN hazard rating for the mixture for that sub-endpoint.



3.2.4.2 Fish, Daphnia, and Algae Toxicity (Chronic Toxicity)

Mixture Hazard Assessment Method: Summation Method

References: For information on the Cradle to Cradle Certified hazard rating criteria refer to sections 3.3.12 and Tables 15, 16, and 17 in the Cradle to Cradle Certified Material Health Assessment Methodology (C2CPII 2017). For a comparison between Cradle to Cradle Certified chemical hazard rating and GHS classification for this endpoint see Appendix section 5.1.1 and Table 18 in this document. Differences between the Cradle to Cradle Certified Mixture Hazard Assessment Methodology and the CLP/GHS mixture hazard assessment methodology for this endpoint may be found in Appendix section 5.1.2.7 in this document.

Process for Assigning Mixture Hazard Rating

- 1. Determine Cradle to Cradle Certified chemical hazard rating and M factor from GHS classification and/or L(E)C₅₀ values (Table 16).** Cradle to Cradle Certified chemical hazard ratings for Chronic Aquatic Toxicity are designated as Chronic 1, Chronic 2, Chronic 3, Chronic 4, YELLOW, GREEN, or GREY. If classified as Chronic 1, determine what M factor applies. If only GHS classification or H-statements are available, and no toxicity data is available, the M-factor may be assumed to equal one.

Table 16: M Factors by NOEC values (mg/l) and GHS Chronic Aquatic Toxicity Classification or Cradle to Cradle Certified hazard rating for The Chronic Toxicity sub-endpoint (fish, daphnia, or algae).

NOEC value (mg/l) or GHS Chronic Aquatic Toxicity Classification for Fish, Daphnia, or Algae	Designated Hazard Classification	Designated M factor
No data available	GREY	N/A
NOEC > 10	GREEN	N/A
10 ≥ NOEC > 1	YELLOW	N/A
GHS Category Chronic 4; H413	Chronic 4	N/A
GHS Category Chronic 3; H412	Chronic 3	N/A
1 ≥ NOEC > 0.1 or GHS Category Chronic 2; H411	Chronic 2	N/A
0.1 ≥ NOEC > 0.01; GHS Category Chronic 2; H410	Chronic 1	1
0.01 ≥ NOEC > 0.001		10
0.001 ≥ NOEC > 0.0001		100
0.0001 ≥ NOEC > 0.00001		1000
continue in factor 10 intervals)		10 X previous entry

2. **Apply the cut-off values (Table 17)** to determine which chemical components with Chronic Aquatic Toxicity must be considered when deriving each hazard mixture rating for the Chronic Toxicity sub-endpoint.

Table 17: Cut-off values by chemical hazard rating for the Chronic Aquatic Toxicity (daphnia, fish, algae) sub-endpoints.

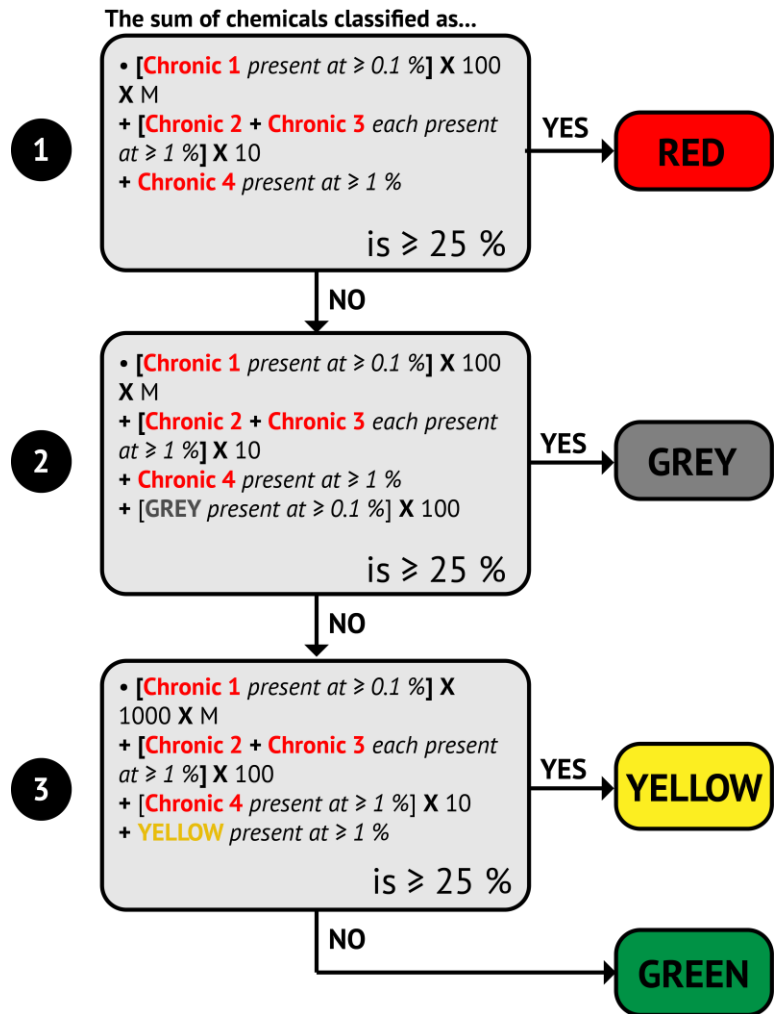
Endpoint for Chemical Component	Cut-off Values for Consideration Toward This Mixture Hazard Rating		
	RED	YELLOW	GREY
Chronic Aquatic Toxicity	<p>≥ 0.1 % for Chronic 1¹⁵ rated chemicals),</p> <p>≥ 1 % for Chronic 2, 3, and 4 rated chemicals</p>	<p>≥ 1 % for YELLOW rated chemicals</p>	<p>≥ 0.1 % for GREY rated</p>

3. Assign the mixture hazard rating for the Chronic Aquatic Toxicity sub-end point via the following process (also demonstrated in **Figure 10**). The mixture will have a Cradle to Cradle Certified hazard rating for the Acute Aquatic Toxicity sub-endpoint of:

- **RED** if
 - [100 X the sum of chemicals classified as Chronic 1 (present in concentrations ≥ 0.1) X M + 10 X the sum of chemicals classified as Chronic 2 and Chronic 3 (each present in concentrations ≥ 1 %) + the sum of chemicals classified as Chronic 4 (present in concentrations ≥ 1 %)] is ≥ 25 %.
- **GREY** if the conditions for assigning a RED hazard mixture rating are not met **AND**:
 - [100 X the sum of chemicals classified as Chronic 1 (present in concentrations ≥ 0.1) X M + 10 X the sum of chemicals classified as Chronic 2 and Chronic 3 (each present in concentrations ≥ 1 %) + the sum of chemicals classified as Chronic 4 (present in concentrations ≥ 1 %) + 100 X the sum of chemicals classified as GREY] is ≥ 25 %.
- **YELLOW** if the conditions for assigning a RED or GREY hazard mixture rating are not met **AND**:
 - [1000 X the sum of chemicals classified as Chronic 1 (present in concentrations ≥ 0.1) X M + 100 X the sum of chemicals classified as Chronic 2 and Chronic 3 (each present in concentrations ≥ 1 %) + 10 X the sum of chemicals classified as Chronic 4 (present in concentrations ≥ 1 %) + the sum of chemicals classified as YELLOW (present in concentrations ≥ 1 %)] is ≥ 25 % of the mixture
- **GREEN** if
 - If the conditions for assigning a RED, YELLOW, and GREY hazard mixture rating are not met.

¹⁵ If the Chronic 1 chemical is highly toxic (NOEC ≤ 0.01 mg/ml), this chemical will also be considered if at a concentration < 0.1 %.

Figure 10: Process to assign mixture hazard ratings for the Cradle to Cradle Certified Chronic Aquatic Toxicity sub-endpoint (for Fish, Daphnia, and Algae).



4 GENERAL DATA AND INFORMATION SOURCES

1. Cradle to Cradle Products Innovation Institute (C2CPII). 2017. Cradle to Cradle Certified™ Products Standard Version 3.1. Material Health Assessment Methodology. Available: http://s3.amazonaws.com/c2c-website/resources/certification/standard/MTD_Material_Health_Assessment_FINAL_052617.pdf
2. European Commission (EC). 2008. Regulation (EC) No 1272/2008 Of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006. Available: <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2008:353:0001:1355:EN:PDF>
3. European Commission (EC). 2014. Assessment of Mixtures - Review of Regulatory Requirements and Guidance. Available: <https://ecvam.jrc.ec.europa.eu/news/assessment-mixures-report>
4. United Nations (UN). 2015. Globally Harmonized System of Classification and Labelling of Chemicals (GHS). Sixth revised edition. Available: http://www.unece.org/trans/danger/publi/ghs/ghs_rev06/06files_e.html

5 APPENDIX

5.1 CLP/GHS Criteria and Mixture Hazard Assessment Methodology in the Context of Cradle to Cradle Certified Material Health Assessment

5.1.1 Mapping CLP/GHS Hazard Ratings to Cradle to Cradle Certified Hazard Ratings

In order to perform a Cradle to Cradle Certified Mixture Hazard Assessment based on the GHS/CLP mixture hazard assessment methodology, it is helpful to have an understanding of how the RED, YELLOW, GREEN, and GREY chemical hazard ratings correspond to GHS/CLP chemical hazard classification. Table 11 details how Cradle to Cradle Certified chemical hazard ratings compare to GHS/CLP chemical hazard classifications.

Table 18: How Cradle to Cradle Certified Hazard Ratings correspond with CLP/GHS Classifications and H-statements.

Cradle to Cradle Certified Endpoint	Sub-Endpoint for Mixture Classification Purposes	CLP/GHS Chemical Hazard Classification or Data Corresponding to Cradle to Cradle Certified Chemical Hazard Ratings			
		RED	YELLOW	GREEN	GREY
Acute Toxicity (Oral, Dermal, or Inhalation)	Acute Mammalian Toxicity (Oral, Dermal, or Inhalation)	CLP/GHS Category 1, 2 or 3 (H300, H301, 3311, H330, H331)	CLP/GHS Category 4 (H302, H312, H332)	Not classified per CLP/GHS.	No data identified.
Skin, Eye, and Respiratory Irritation	Skin Irritation	CLP/GHS Cat. 1A, B, or C for Skin Irritation (H314)	GHS Cat. 2 (H315) or Cat 3 (H316) for Skin Irritation	No evidence of Skin Irritation in human or animal studies.	No data identified.
	Eye Irritation	CLP/GHS Cat. 1 for Eye Irritation (H318)	CLP/GHS Cat 2A (H319), or GHS Cat. 2B (H320) for Eye Irritation	No evidence of Eye Irritation in human and/or animal studies	No data identified.

	Respiratory Irritation	Respiratory Irritation endpoint not considered for chemical substances for the Cradle to Cradle Certified Mixture Hazard Assessment Methodology.			
Skin and Respiratory Sensitization	Skin Sensitization	GHS Cat. 1 for Skin Sensitization	Triggers positive responses in animal testing, but not enough to trigger GHS classification	No evidence of Skin Sensitization in human or animal studies	No data identified
	Respiratory Sensitization	GHS Cat. 1 for Respiratory Sensitization	Triggers positive responses in animal testing, but not enough to trigger GHS classification	No evidence of Skin Sensitization in human or animal studies	No data identified
Acute Aquatic Toxicity		GHS Cat. 1 (H400), GHS Category 2 (H401). <i>L(E)C₅₀ is ≤ 10 mg/L.</i>	GHS Cat. 3 (H402). <i>10 < L(E)C₅₀ ≤ 100 mg/ml or 1 < NOEC ≤ 10 mg/ml.</i>	Not Classified for Acute or Chronic. <i>L(E)C₅₀ ≥ 100 mg/L in any of three trophic levels or NOEC > 10 mg/ml.</i>	No data identified for acute toxicity.
Chronic Aquatic Toxicity		GHS Category 1 (H410), 2 (H411), 3 (H412), or 4 (H413). <i>NOEC is < 1 mg/ml.</i>	<i>1 < NOEC ≤ 10 mg/ml</i>	GHS Not Classified. <i>NOEC > 10 mg/ml.</i>	No data identified for chronic toxicity.

5.1.2 Differences Between the GHS/CLP Mixture Hazard Assessment Methodology and the Cradle to Cradle Certified Mixture Hazard Assessment Methodology.

5.1.2.1 Oral, Dermal, and Inhalation Toxicity (Acute Mammalian)

The Cradle to Cradle Certified criteria for assessing the hazard of a mixture for this endpoint are very similar to the CLP/GHS criteria. The main difference is in how a GREY rating for a mixture is derived. CLP/GHS has no guidance as to rating a mixture as GREY. In the case of Cradle to Cradle Certified criteria, a GREY rating is derived if only GREY rated chemicals (present at $\geq 0.1\%$) are present in the mixture and no RED rated chemicals (present at $\geq 0.1\%$) are present in the mixture.

5.1.2.2 Skin Irritation

Because a GHS Category 2 (H315: Causes Skin Irritation) and a GHS Category 3 (H316: Causes mild Skin Irritation) both correspond to Cradle to Cradle Certified YELLOW hazard rating for Skin Irritation, the methodology is significantly simplified. As a result, the Cradle to Cradle Certified Mixture Hazard Assessment Methodology is also more conservative than the GHS methodology since GHS Category 3 are grouped with GHS Category 2 chemicals. This means that if GHS Category 3 chemicals are present at concentrations $> 1\%$, as opposed to 10% as indicated by the CLP/GHS criteria, the mixture is rated overall as YELLOW.

Weighting factors and concentration limits in the CLP/GHS methodology are applied similarly in Cradle to the Cradle Certified Mixture Hazard Assessment Methodology.

5.1.2.3 Eye Irritation

The CLP/GHS mixture hazard assessment methodology also takes into account chemical components' Skin Irritation hazard ratings toward the Eye Irritation mixture hazard classification. However, Skin Irritation is only taken into account if it would contribute to a GHS Category 1 hazard mixture rating (or a Cradle to Cradle Certified RED mixture hazard rating) for Eye Irritation. The Cradle to Cradle Certified Mixture Hazard Assessment Methodology similarly combine Skin Irritation and Eye Irritation hazard ratings for chemical components toward an overall mixture hazard assessment.

Weighting factors and concentration limits in the CLP/GHS mixture hazard assessment methodology is applied similarly in the Cradle to Cradle Certified Mixture Hazard Assessment Methodology.

5.1.2.4 Skin Sensitization

The main difference between the GHS/CLP mixture hazard assessment methodology and the Cradle to Cradle Certified Mixture Hazard Assessment Methodology for this sub-endpoint is that a chemical that produces mild Skin Sensitization is assigned a YELLOW hazard rating for Skin Sensitization in the Cradle to Cradle Certified Mixture Hazard Assessment Methodology, but is not classifiable per CLP/GHS.

5.1.2.5 Respiratory Sensitization

The main difference between GHS/CLP and Cradle to Cradle Certified mixture hazard assessment methodology for this sub-endpoint is that a chemical that produces a positive response in animal studies is assigned a YELLOW hazard rating in the Cradle to Cradle Certified Mixture Hazard Assessment Methodology, but is not classifiable per CLP/GHS.

5.1.2.6 Fish, Daphnia, and Algae Toxicity (Acute Toxicity)

The Cradle to Cradle Certified chemical hazard rating criteria for Acute Aquatic Toxicity are not directly correlated to GHS hazard classification criteria for this endpoint: a chemical with a Cradle to Cradle Certified hazard rating of RED corresponds either to GHS Category 1 ($LC_{50}/EC_{50} \leq 1$ mg/L; H400) or GHS Category 2 ($LC_{50}/EC_{50} > 1$ but ≤ 10 mg/L; H401). However, the YELLOW hazard rating corresponds to a GHS Category 3 ($LC_{50}/EC_{50} > 10$ but ≤ 100 mg/L; H402). Therefore, in order to create the Cradle to Cradle Certified Mixture Hazard Assessment Methodology that apply GHS mixture hazard assessment criteria, chemicals that are assigned a Cradle to Cradle Certified hazard rating of RED need to be split into two categories based on their LC_{50}/EC_{50} values. These include chemicals with $LC_{50}/EC_{50} \leq 1$ mg/L (Acute 1) and chemicals with $LC_{50}/EC_{50} > 1$ but ≤ 10 mg/L (Acute 2). These two terminologies are used below in the process for assigning the mixture hazard rating.

The concentration limits in the GHS mixture hazard assessment methodology applies similarly in the Cradle to Cradle Certified Mixture Hazard Assessment Methodology. According to the GHS mixture hazard assessment methodology, a classification is relevant only when chemicals classified as Acute Aquatic Toxicity Category 1 (RED rated and Acute 1 under Cradle to Cradle Certified) are present at $\geq 0.1\%$, while the chemicals classified as Acute Aquatic Toxicity Category 2 (RED rated and Acute 2 under Cradle to Cradle Certified) or 3 (YELLOW rated under Cradle to Cradle Certified) is present at $\geq 1\%$ ¹⁶.

5.1.2.7 Fish, Daphnia, and Algae Toxicity (Chronic Toxicity)

The Cradle to Cradle Certified chemical hazard rating criteria for Chronic Aquatic Toxicity are not directly correlated with CLP/GHS hazard classification criteria for this endpoint. Mainly, a chemical with a GHS Category Chronic 1 (H410), GHS Category Chronic 2 (H411), GHS Category Chronic 3 (H412), and GHS Category 4 (H413) corresponds to a Cradle to Cradle Certified hazard rating of RED. However, there is no corresponding CLP/GHS classification for

¹⁶ According to CLP section 4.1.3.1 and the GHS guidance (UN 2015) section 4.1.3.1: The 'relevant components' of a mixture are those which are classified as 'Acute Category 1' or 'Chronic Category 1' and present in a concentration of 0.1% (w/w) or greater, and those which are classified as 'Acute/Chronic Category 2', 'Acute/Chronic Category 3' or 'Chronic Category 4' and are present at a concentration of 1% (w/w) or greater, unless there is a presumption (such as in the case of highly toxic components (see 4.1.3.5.5.5) that a component present in a lower concentration can still be relevant for classifying the mixture for Aquatic Environmental hazards. Generally, for substances classified as 'Acute Category 1' or 'Chronic Category 1' the concentration to be taken into account is (0.1 %) (see Table 1.1 in CLP (EC 2008)).

the YELLOW hazard rating. These differences in hazard criteria result in the following differences in the mixture hazard assessment methodology criteria:

- Chemicals that are assigned a Cradle to Cradle Certified hazard rating of RED need to be split into four categories based on their CLP/GHS classification. These include **Chronic 1** (H410), **Chronic 2** (H411), **Chronic 3** (H412) and **Chronic 4** (H413). These terminologies are used below for the process for assigning the mixture hazard rating for this endpoint.
- Because a Cradle to Cradle Certified YELLOW hazard rating criteria for a Chronic Aquatic Toxicity corresponds to a chemical not being classified per CLP/GHS (not associated with H statement), the CLP/GHS mixture assessment principles described in the process for assigning a mixture hazard rating for Categories 2, 3, and 4 are applied here to determine the Cradle to Cradle Certified hazard rating of YELLOW for the mixture.
- CLP/GHS criteria take into account the biodegradability and persistence of the component chemical when classifying the GHS Category and M-factor for Chronic Aquatic Toxicity. However, because persistence and bioaccumulation is evaluated separately under the Cradle to Cradle Certified hazard assessment methodology, only the NOEC values are considered toward Chronic 1 categorization, unless GHS classification or H-statements are available for that chemical component.
- CLP/GHS criteria take into account Acute Aquatic Toxicity with persistence/bioaccumulation data to fill in data gaps in Chronic Aquatic Toxicity data. However, because Acute Aquatic Toxicity is considered in combination with Chronic Aquatic Toxicity when evaluating the overall mixture, only NOEC values are considered here, unless GHS classification or H-statements are available for that chemical component.

The concentration limits in the GHS mixture hazard assessment methodology applies similarly in Cradle to Cradle Certified Mixture Hazard Assessment Methodology. According to the GHS mixture hazard assessment methodology, a classification is relevant only when the substance classified as Chronic Aquatic Toxicity Category 1 (RED rated and Chronic 1 under Cradle to Cradle Certified) is present at $\geq 0.1\%$, while chemicals classified as Chronic Aquatic Toxicity Categories 2, 3, or 4 (RED rated and Chronic 2, 3, or 4 under Cradle to Cradle Certified) are present at $\geq 1\%$.¹⁷ This is applied to Cradle to Cradle Certified Mixture Hazard Assessment Methodology.

¹⁷ According to CLP section 4.1.3.1 and the GHS guidance (UN 2015) section 4.1.3.1: The ‘relevant components’ of a mixture are those which are classified as ‘Acute Category 1’ or ‘Chronic Category 1’ and present in a concentration of 0.1% (w/w) or greater, and those which are classified as ‘Acute/Chronic Category 2’, ‘Acute/Chronic Category 3’ or ‘Chronic Category 4’ and are present at a concentration of 1% (w/w) or greater, unless there is a presumption (such as in the case of highly toxic components (see 4.1.3.5.5.5) that a component present in a lower concentration can still be relevant for classifying the mixture for Aquatic Environmental hazards. Generally, for substances classified as ‘Acute Category 1’

or 'Chronic Category 1' the concentration to be taken into account is (0.1 %) (see Table 1.1 in CLP (EC 2008)).