# Design for the Environment Program Alternatives Assessment Criteria for Hazard Evaluation

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To ensure that the Alternatives Assessment Criteria for Hazard Evaluation remain relevant and useful for distinguishing among chemicals, DfE may update the criteria based on experience conducting alternatives assessments and on stakeholder input. Additional developments likely to prompt criteria review, reevaluation, and possible revision include changes to the Globally Harmonized System (GHS) or EPA programmatic criteria, which are integral to the Alternatives Assessment Criteria, as well as advances in science, such as those relating to endpoint characterization or testing methodologies.

# Table of Contents

# 1. Introduction

The Design for the Environment (DfE) Program at the U.S. Environmental Protection Agency developed the Alternatives Assessment Criteria for Hazard Evaluation as a transparent tool for evaluating and differentiating among chemicals based on their human health and environmental hazards. The Criteria are applied in of DfE Alternatives Assessments (for a current list of assessments go to: http://www.epa.gov/dfe/alternative_assessments.html), and can be used by other organizations.

**What are DfE Alternatives Assessments?**
DfE Alternatives Assessments are multi-stakeholder partnerships convened to evaluate priority chemicals and functional alternatives. The goal of an alternatives assessment is to inform substitution to safer alternatives and reduce the likelihood of unintended consequences that might result if poorly understood alternatives were chosen. DfE's expertise and focus is on chemical hazard; stakeholders assist with the selection of the scope of the alternatives assessment, help EPA consider economic realities, and identify likely functional alternatives for evaluation.

**What is the basis for the Alternatives Assessment Criteria for Hazard Evaluation?**
For most endpoints, the criteria define "High," "Moderate," and "Low" concern. While many hazard classification criteria exist throughout the world, DfE has carefully chosen the criteria that form the Alternatives Assessment Criteria for Hazard Evaluation with the goal of creating a rigorous and useful system for differentiating among chemicals based on hazard. Authoritative sources – the United Nation's Globally Harmonized System (GHS) for the Classification and Labeling of Chemicals and U.S. EPA programs – are the basis for these distinctions. The criteria include endpoints used in the Screening Information Data Set (SIDS) [1], a set of endpoints internationally agreed upon for characterizing chemical hazards. In assigning a designation of Low, Moderate, or High concern for hazard, DfE uses the best information available, both experimental and modeled.

**How will the results of the DfE Alternatives Assessments be used?**
The results of the alternatives assessments provide EPA and stakeholders with a comprehensive picture of the hazards of a chemical and its alternatives. The results can be used to place chemicals on a continuum of relative hazard to inform decision-making on chemical use. To make the results accessible to a broader audience, other organizations have developed tools that supplement DfE Alternatives Assessments by weighting hazard endpoints and evaluating trade-offs. An example of such a tool is the publicly available Green Screen for Safer Chemicals [2] developed by the non-governmental organization Clean Production Action.

# 2. General Requirements

2. 1 Data for all relevant routes of exposure will be evaluated. Relevant routes can include oral, dermal, and inhalation exposures. DfE recognizes that other routes of exposure are possible, including transplacental transport, lactational transfer, and intraperitoneal or subcutaneous injection. Data from such exposure routes will be considered on a case-by-case basis.

2.2. The GHS criteria and data evaluation approach, and EPA risk assessment guidance will be applied in the review of both no observed adverse effect levels/concentrations (NOAEL/NOAEC) and lowest observed adverse effect levels/concentrations (LOAEL/LOAEC). In general, NOAEL/NOAEC and LOAEL/LOAEC values are preferred over no observed effect levels/concentrations (NOEL/NOEC) and lowest observed effect levels/concentrations (LOEL/LOEC). When available and appropriate, the results of benchmark dose modeling will also be considered [3]. In reviews that include conflicting data, a weight of evidence evaluation aimed at the protection of human health and environment will inform the hazard designation. All reviews will include an assessment of potential impacts to vulnerable populations and life stages.

2.3 Use of existing data should follow the EPA HPV Challenge Program and OECD HPV Programme data adequacy guidelines: http://www.epa.gov/HPV/pubs/general/datadfin.htm.

2.4 When gathering data for evaluation under these criteria, a review of the open literature including published peer-reviewed studies and government reports as well as any confidential business information will be conducted.

2.5 In cases where a test species or strain is known to be more or less sensitive to the test substance, this understanding will be considered in the evaluation of data against these criteria.

2.6 The degradation or metabolism of a chemical into a by-product which itself is hazardous, slow to degrade, or bioaccumulative will be considered in the hazard assessment, where relevant supporting information (such as ADME data) are available. The purpose of considering degradation products and metabolites is to gain a better understanding of the overall hazard potential of a chemical.

# 3. Terms

3.1. **Acute aquatic toxicity** means the intrinsic property of a substance to be injurious to an organism in a short-term, aquatic exposure to that substance [4].

3.2. **Acute mammalian toxicity** refers to those adverse effects occurring following oral or dermal administration of a single dose of a substance, or multiple doses given within 24 hours, or an inhalation exposure of 4 hours [5].

3.3. **ADME**: Absorption, discretion, metabolism and excretion.

3.4. **Adverse effect:** A biochemical change, functional impairment, or pathologic lesion that affects the performance of the whole organism, or reduces an organism's ability to respond to an additional environmental challenge [6].

3.5. **Attribute**: The general property of the chemical that is being evaluated (e.g. acute mammalian toxicity, persistence).

3.6. The **benchmark dose (or concentration)** is the dose (or concentration) that is associated with a specific measure or change of a biological effect. The calculation of the benchmark dose (BMD) or concentration (BMC) generally represents the central estimate of the dose or concentration associated with some level of response above background. The lower limit of an on-side 95% confidence interval is generally applied to the BMD and BMC [3].

3.7. **Bioaccumulation** is a process in which a chemical substance is absorbed in an organism by all routes of exposure as occurs in the natural environment, e.g., dietary and ambient environment sources. Bioaccumulation is the net result of competing processes of chemical uptake into the organism at the respiratory surface and from the diet and chemical elimination from the organism including respiratory exchange, fecal egestion, metabolic biotransformation of the parent compound and growth dilution [7].

3.8. **Biodegradation** is a process in which the destruction of the chemical is accomplished by the action of a living organism [8].

3.9. A chemical is termed **carcinogenic** if it is capable of increasing the incidence of malignant neoplasms, reducing their latency, or increasing their severity or multiplicity [9].

3.10. A **chemical** (or **compound**) is identified by its Chemical Abstract Service (CAS) number.

3.11. **Chronic aquatic toxicity** means the intrinsic property of a substance to cause adverse effects to aquatic organisms during aquatic exposures which are determined in relation to the life-cycle of the organism [4].

3.12. A **compound** (or **chemical**) is identified by its Chemical Abstract Service (CAS) number.

3.13. **Criteria**: Endpoints and cutoffs for attribute information. Example: oral acute mammalian toxicity LD50 must be > 50 mg/kg. Data quality requirements (including acceptable test methods and information sources) are developed for all criteria.

3.14. **Degradation product**: Compound resulting from transformation of a chemical substance through chemical, photochemical, and/or biochemical reactions [10].

3.15. **Dermal sensitizer**: A substance that will lead to an allergic response following skin contact [11].

3.16. **Developmental toxicity**: Adverse effects in the developing organism that may result from exposure prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the lifespan of the organism. The major manifestations of developmental toxicity include: (1) death of the developing organism, (2) structural abnormality, (3) altered growth, and (4) functional deficiency [12].

3.17. **EC50**: The concentration which produces effects in 50% of organisms.

3.18. **Endocrine activity** refers to a change in endocrine homeostasis caused by a chemical or other stressor from human activities (e.g., application of pesticides, the discharge of industrial chemicals to air, land, or water, or the use of synthetic chemicals in consumer products.)

3.19. An **endocrine disruptor** is an external agent that interferes in some way with the role of natural hormones in the body. An agent might disrupt the endocrine system by affecting any of the various stages of hormone production and activity, such as by preventing the synthesis of hormones, by directly binding to hormone receptors, or by interfering with the natural breakdown of hormones [13].

3.20. **Estimated concentration three (EC3)**: Estimated concentration of a test substance needed to produce a stimulation index of three in the local lymph node assay, a test used to evaluate dermal sensitization [14].

3.21. **Genotoxicity**: The more general terms genotoxic and genotoxicity apply to agents or processes which alter the structure, information content, or segregation of DNA, including those which cause DNA damage by interfering with normal replication

processes, or which in a non-physiological manner (temporarily) alter its replication. Genotoxicity test results are usually taken as indicators for mutagenic effects [15].

3.22. An **ingredient** may be one chemical or a blend of multiple chemicals that are intentionally added.

3.23. **LC50:** Median lethal concentration.

3.24. **LD50:** Median lethal dose.

3.25. **LOAEL**: Lowest Observed Adverse Effect Level

3.26. **LOAEC**: Lowest Observed Adverse Effect Concentration

3.27. **LOEC**: Lowest Observed Effect Concentration

3.28. **LOEL**: Lowest Observed Effect Level.

3.29. **Metabolite**: Any substance produced by metabolism or by a metabolic process [16].

3.30. **Mutagen**: The term mutagenic and mutagen will be used for agents which induce permanent, transmissible changes in the amount, chemical properties, or structure of the genetic material. These changes may involve a single gene or gene segment, a block of genes, parts of chromosomes, or whole chromosomes. Mutagenicity differs from genotoxicity in that the change in the former case is transmissible to subsequent cell generations.

3.31. **Neurotoxicity**: 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 [17].

3.32. **NOAEL**: No Observed Adverse Effect Level

3.33. **NOAEC**: No Observed Adverse Effect Concentration

3.34. **NOEC**: No Observed Effect Concentration

3.35. **NOEL**: No Observed Effect Level

3.36. **Persistence**: The length of time the chemical can exist in the environment before being destroyed (i.e., transformed) by natural processes [18].

3.37. **Reproductive toxicity**: The occurrence of biologically adverse effects on the reproductive systems of females or males that may result from exposure to environmental agents. The toxicity may be expressed as alterations to the female or

male reproductive organs, the related endocrine system, or pregnancy outcomes. The manifestation of such toxicity may include, but not be limited to, adverse effects on onset of puberty, gamete production and transport, reproductive cycle normality, sexual behavior, fertility, gestation, parturition, lactation, developmental toxicity, premature reproductive senescence, or modifications in other functions that are dependent on the integrity of the reproductive systems [19].

3.38. **Respiratory sensitizer**: A substance that will lead to hypersensitivity of the airways following inhalation of the substance [11].

3.39. **Skin corrosion** is the production of irreversible damage to the skin; namely, visible necrosis through the epidermis and into the dermis, following the application of a test substance for up to 4 hours.

3.40. **Skin irritation** is the production of reversible damage to the skin following the application of a test substance for up to 4 hours [20, 21].

3.41. **Stimulation Index (SI)**: A value calculated to assess the skin sensitization potential of a test substance that is the ratio of the proliferation in treated groups to that in the concurrent vehicle control group [14].

3.42. **Suitable analog**: Suitable analogs will be based on a chemically (e.g., based on chemical structure) or biologically (e.g., based on metabolic breakdown, or likely mechanistic/mode of action considerations) similar chemical. Guidance for identifying a suitable analog can be found in OECD *Series on Testing and Assessment No. 80 Guidance on Grouping of Chemicals* [22]. The analog used must be appropriate for the attribute being evaluated.

3.43. **Weight-of-evidence**: For the purposes of this document, weight-of-evidence refers to the process of considering the strengths and weaknesses of various pieces of information in reaching and supporting a conclusion concerning a property of the substance [23].

# 4. Toxicological Criteria

Evaluation of chemicals under these criteria will be based on the best available data. In general, DfE will use data in the following order of preference: 1) measured data on the chemical being evaluated, 2) measured data from a suitable analog, and 3) estimated data from appropriate models. EPA experts will evaluate the quality and reliability of both experimental and estimated data. The majority of measured data are expected to be from laboratory experiments. However, any available human data will be considered, e.g. Human Repeat Insult Patch Tests. In many cases, the evaluation of human data will require a qualitative assessment, since the criteria are primarily based on (non-human) animal studies. Human data may require appropriate review for ethical treatment of the subjects.

In the absence of measured data on the chemical being evaluated, measured data from a suitable analog and/or estimated data from computer models will be used. In the event that there are no suitable analogs, that suitable analogs lack measured data, and the substance, or its analog cannot be modeled, the hazard endpoint cannot be evaluated and will be designated "no data."

The links and references in this document are current as of the publication date of these Criteria. In implementing these criteria, EPA will use the most recent version of each authoritative list, EPA data interpretation guidance, and test protocol when reviewing a chemical against these criteria. In the case where a GHS reference in this document is superseded by a more recent version, EPA may choose to update these criteria to incorporate that newer version. EPA will consider all sources of developing information, such as the EPA Endocrine Disruptor Screening Program [24] or enhancements to estimation models such as EPI Suite™ [25] that occur over time. For convenience, a summary of DfE's Alternatives Assessment Criteria is located in the Appendix (see Table A1 and Table A2).

## *4.1. Human Health Effects*

### 4.1.1 Acute Mammalian Toxicity

DfE's acute mammalian toxicity criteria differentiate compounds based upon a common measure of short term exposure toxicity, the median lethal dose or concentration ($LD_{50}$ or $LC_{50}$), through oral, dermal, and respiratory routes. Chemical hazard designations will be made based upon the criteria in Table 1. These values were derived from the GHS criteria [5].

**Table 1.** Acute Mammalian Toxicity Criteria for Hazard Designation

| Acute Mammalian Toxicity | Very High | High | Moderate | Low |
|---|---|---|---|---|
| **Oral LD50 (mg/kg)** | ≤ 50 | > 50 - 300 | > 300 - 2000 | > 2000 |
| **Dermal LD50 (mg/kg)** | ≤ 200 | > 200 - 1000 | > 1000 - 2000 | > 2000 |
| **Inhalation LC50 (vapor/gas) (mg/L)** | ≤ 2 | > 2 - 10 | > 10 – 20 | > 20 |
| **Inhalation LC50 (dust/mist/fume) (mg/L/day)** | ≤ 0.5 | > 0.5 - 1.0 | > 1.0 – 5 | > 5 |

### 4.1.2 Carcinogenicity

These criteria are designed to indicate whether a compound is known, presumed, or suspected to increase incidence of cancer, whether available data provide limited or marginal evidence of carcinogenicity, or whether adequate studies have been conducted to show that a chemical is not carcinogenic. Carcinogenicity designations will be made according to the criteria in Table 2. Chemicals known or presumed to be carcinogenic to humans according to the GHS criteria will be designated as Very High. Chemicals suspected to be carcinogenic to humans according to GHS criteria will be designated as High. When limited or marginal data on carcinogenicity are present, a designation of Moderate will be used. The basis for Low concern may be negative carcinogenicity studies on the chemical being evaluated or robust mechanism-based SAR analysis which may include (i) negative studies on relevant/suitable analog(s) and/or (ii) combination of lack of structural alerts and features suggestive of potential carcinogenic activity and negative supportive, short-term predictive tests.

These criteria mirror the classification approach used by the International Agency for Research on Cancer (IARC) [26], and incorporate the Globally Harmonized System (GHS) classification scheme [27]. Authoritative lists can supplement these criteria. Suggested hazard designations for chemicals classified on authoritative lists appear in Section 6.

**Table 2.** Carcinogenicity Criteria for Hazard Designation

| Carcinogenicity | Very High | High | Moderate | Low |
|---|---|---|---|---|
| **Carcinogenicity** | Known or presumed human carcinogen (equivalent to GHS Category 1A and 1B) | Suspected human carcinogen (equivalent to GHS Category 2) | Limited or marginal evidence of carcinogenicity in animals (and inadequate evidence in humans) | Negative studies or robust mechanism-based SAR (as described above) |

### 4.1.3 Mutagenicity/Genotoxicity

The Mutagenicity/Genotoxicity criteria classify chemicals based on evidence that heritable mutations are known to occur in the germ cells of humans (Very High), heritable mutations may occur in the germ cells of humans or that evidence of mutagenicity is demonstrated *in vitro* and *in vivo* (High), or evidence of mutagenicity is demonstrated *in vitro* or *in vivo* (Moderate). A Low hazard designation will be assigned for chemicals that are negative for chromosomal aberrations and gene mutations, or have no structural alerts. The criteria are taken from the GHS [15] and supplemented with considerations for mutagenicity and genotoxicity in cells other than germ cells (Table 3). As with all endpoints, a weight-of-evidence approach is applied to available data.

Authoritative lists can supplement these criteria. Suggested hazard designations for chemicals classified on authoritative lists appear in Section 6.

**Table 3.** Mutagenicity/Genotoxicity Criteria for Hazard Designations

| Mutagenicity/ Genotoxicity | Very High | High | Moderate | Low |
|---|---|---|---|---|
| **Germ cell mutagenicity** | GHS Category 1A or 1B: Substances known to induce heritable mutations or to be regarded as if they induce heritable mutations in the germ cells of humans | GHS Category 2: Substances which cause concern for humans owing to the possibility that they may induce heritable mutations in the germ cells of humans<br><br>OR | Evidence of mutagenicity supported by positive results in *in vitro* OR *in vivo* somatic cells of humans or animals | Negative for chromosomal aberrations and gene mutations, or no structural alerts. |
| **Mutagenicity and genotoxicity in somatic cells** | | Evidence of mutagenicity supported by positive results in *in vitro* AND *in vivo* somatic cells and/or germ cells of humans or animals | | |

### 4.1.4 Reproductive and Developmental Toxicity (including Developmental Neurotoxicity)

Reproductive toxicity:
DfE's reproductive toxicity criteria classify compounds based on the potential to cause adverse effects on reproductive capacity. Reproductive toxicity may be expressed as alterations to the female or male reproductive organs, the related endocrine system, or pregnancy outcomes. The manifestation of such toxicity may include, but not be limited to, adverse effects on onset of puberty, gamete production and transport, reproductive cycle normality, sexual behavior, fertility, gestation, parturition, lactation, developmental toxicity, premature reproductive senescence, or modifications in other functions that are dependent on the integrity of the reproductive systems. [19]

Developmental toxicity (including Developmental Neurotoxicity):
DfE's developmental toxicity criteria classify compounds based on the potential to cause adverse effects on development of offspring. Developmental toxicity includes adverse effects in the developing organism that may result from exposure prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the lifespan of the organism. The major manifestations of developmental toxicity include: (1) death of the developing organism, (2) structural abnormality, (3) altered growth, and (4) functional deficiency [12]. Effects associated with developmental neurotoxicity include neurobehavioral and neuropathological assessments of rat offspring following *in utero* and postnatal exposure to the test chemical.

**Table 4.** Reproductive and Developmental Toxicity Criteria for Hazard Designations

| Reproductive and Developmental Toxicity | High | Moderate | Low | Very Low |
|---|---|---|---|---|
| **Oral (mg/kg/day)** | < 50 | 50 – 250 | > 250-1000 | > 1000 |
| **Dermal (mg/kg/day)** | < 100 | 100 – 500 | > 500-2000 | > 2000 |
| **Inhalation (vapor/gas) (mg/L/day)** | < 1 | 1 - 2.5 | > 2.5-20 | > 20 |
| **Inhalation (dust/mist/fume) (mg/L/day)** | < 0.1 | 0.1 - 0.5 | > 0.5-5 | > 5 |

Using all available information, two hazard designations, one for reproductive toxicity and one for developmental toxicity will be made. Parental (reproductive) and offspring (developmental) exposure to a substance through oral, dermal and respiratory routes will be evaluated using the criteria in Table 4. In general, the NOAEL and LOAEL will be considered as a basis for evaluation. The criteria were derived from the US EPA's Office of Pollution Prevention & Toxics criteria for HPV chemical categorization [28], and the EU REACH criteria for Annex IV. (Annex IV includes criteria to identify chemicals that are exempted from the registration, evaluation, and downstream user provisions of REACH because they are of minimum risk based on their intrinsic properties [29].)

Authoritative lists can supplement these criteria. Suggested hazard designations for chemicals classified on authoritative lists appear in Section 6.

### 4.1.5 Neurotoxicity

DfE's neurotoxicity criteria will classify compounds based upon observed neurotoxic effects through oral, dermal, and respiratory exposure routes. Neurotoxic effects can be observed at multiple levels of organization within the nervous system, including neurochemical, anatomical, or behavioral, and across life stages. In general, NOAEL and LOAEL values will be considered as the basis for evaluation. Chemical hazard designations will be made based on the criteria in Table 5 which were derived from GHS criteria for Specific Target Organ Toxicity Repeated Exposure [30].

The dose values in Table 5 are to be applied to 90-day repeated dose studies. Dose values are tripled for chemicals evaluated in 28-day studies and similarly modified for studies of longer durations.

**Table 5.** Neurotoxicity Criteria for Hazard Designations

| Neurotoxicity | High | Moderate | Low |
|---|---|---|---|
| **Oral (mg/kg-bw/day)** | | | |
| **90-day (13 weeks)** | <10 | 10 – 100 | >100 |
| **40-50 days** | < 20 | 20 – 200 | > 200 |
| **28-days (4 weeks)** | <30 | 30 – 300 | > 300 |
| **Dermal (mg/kg-bw/day)** | | | |
| **90-day (13 weeks)** | <20 | 20 – 200 | >200 |
| **40-50 days** | <40 | 40 – 400 | >400 |
| **28-days (4 weeks)** | <60 | 60 – 600 | >600 |
| **Inhalation(vapor/gas) (mg/L/6h/day) 90-day** | | | |
| **(13 weeks)** | <0.2 | 0.2 – 1.0 | >1.0 |
| **40-50 days** | <0.4 | 0.4 – 2.0 | >2.0 |
| **28-days (4 weeks)** | <0.6 | 0.6 – 3.0 | >3.0 |
| **Inhalation(dust/mist/fume) (mg/L/6h/day)** | | | |
| **90-day (13 weeks)** | <0.02 | 0.02 – 0.2 | >0.2 |
| **40-50 days** | <0.04 | 0.04 – 0.4 | >0.4 |
| **28-days (4 weeks)** | <0.06 | 0.06 – 0.6 | >0.6 |

### 4.1.6 Repeated Dose Toxicity

Chronic exposure will be evaluated with the results from repeated dose toxicity testing through oral, dermal, and respiratory routes. Repeated dose test methods are designed to be broadly encompassing, capturing effects on any/all major organ systems. In general, the NOAEL and LOAEL will be considered as a basis for evaluation. Chemical hazard designations will be made based upon the criteria in Table 6 which are taken from the GHS criteria for Specific Target Organ Toxicity Repeated Exposure [30], and mirror the US EPA's Office of Pollution Prevention & Toxics criteria for HPV chemical categorization [28].

The dose values in Table 6 are to be applied to 90-day repeated dose studies. Dose values are tripled for chemicals evaluated in 28-day studies and similarly modified for studies of longer durations.

Authoritative lists can supplement these criteria. Suggested hazard designations for chemicals classified on authoritative lists appear in Section 6.

**Table 6.** Repeated Dose Toxicity Criteria for Hazard Designations

| Repeated Dose Toxicity | High | Moderate | Low |
|---|---|---|---|
| **Oral (mg/kg-bw/day)** | | | |
| **90-day (13 weeks)** | <10 | 10 – 100 | >100 |
| **40-50 days** | < 20 | 20 – 200 | > 200 |
| **28-days (4 weeks)** | <30 | 30 – 300 | > 300 |
| **Dermal (mg/kg-bw/day)** | | | |
| **90-day (13 weeks)** | <20 | 20 – 200 | >200 |
| **40-50 days** | <40 | 40 – 400 | >400 |
| **28-days (4 weeks)** | <60 | 60 – 600 | >600 |
| **Inhalation(vapor/gas) (mg/L/6hrs/day) 90-day (13 weeks)** | <0.2 | 0.2 – 1.0 | >1.0 |
| **40-50 days** | <0.4 | 0.4 – 2.0 | >2.0 |
| **28-days (4 weeks)** | <0.6 | 0.6 – 3.0 | >3.0 |
| **Inhalation(dust/mist/fume) (mg/L/6hrs/day)** | | | |
| **90-day (13 weeks)** | <0.02 | 0.02 – 0.2 | >0.2 |
| **40-50 days** | <0.04 | 0.04 – 0.4 | >0.4 |
| **28-days (4 weeks)** | <0.06 | 0.06 – 0.6 | >0.6 |

### 4.1.7 Respiratory and Skin Sensitization

Evidence of whether exposure to a chemical can elicit an allergic response upon contact will be evaluated in DfE's sensitization criteria. Both dermal and respiratory sensitization will be considered. For skin sensitization and respiratory sensitization, chemical hazard designations incorporate the GHS criteria [11] as described in Table 7. Further details about the GHS criteria for categorizing chemicals as Category 1A or 1B skin sensitizers is given in Tables 8 and 9 respectively. For respiratory sensitization, a designation of no data is possible.

Authoritative lists can supplement these criteria. Suggested hazard designations for chemicals classified on authoritative lists appear in Section 6.

**Table 7.** Sensitization Criteria for Hazard Designations

| Sensitization | High | Moderate | Low |
|---|---|---|---|
| **Skin Sensitization** | High frequency of sensitization in humans and/or high potency in animals (GHS Category 1A) | Low to moderate frequency of sensitization in human and/or low to moderate potency in animals (GHS Category 1B) | Adequate data available and not GHS Category 1A or 1B |
| **Respiratory Sensitization** | Occurrence in humans or evidence of sensitization in humans based on animal or other tests (equivalent to GHS Category 1A and 1B) | Limited evidence including the presence of structural alerts | Adequate data available indicating lack of respiratory sensitization |

**Table 8.** GHS Category 1A Skin Sensitization Criteria Used for **High** Hazard Designation

| Assay | GHS Category 1A Criteria |
|---|---|
| Local lymph node assay | EC3 value ≤ 2% |
| Guinea pig maximization test | ≥ 30% responding at ≤ 0.1% intradermal induction dose or<br>≥ 60% responding at > 0.1% to ≤ 1% intradermal induction dose |
| Buehler assay | ≥ 15% responding at ≤ 0.2% topical induction dose or<br>≥ 60% responding at > 0.2% to ≤ 20% topical induction dose |

**Table 9.** GHS Category 1B Skin Sensitization Criteria Used for Moderate Hazard Designation

| Assay | GHS Category 1B Criteria |
|---|---|
| Local lymph node assay | EC3 value > 2% |
| Guinea pig maximization test | ≥ 30% to < 60% responding at > 0.1% to ≤ 1% intradermal induction dose or<br>≥ 30% responding at > 1% dermal induction dose |
| Buehler assay | ≥ 15% to < 60%responding at > 0.2% to ≤ 20% topical induction dose or<br>≥ 15% responding at > 20% topical induction dose |

### 4.1.8 Eye and Skin Irritation/Corrosivity

Data on a chemical's ability to cause eye and skin irritation/corrosivity will be reviewed under these criteria. Hazard designations will be made based upon the criteria in Table 10. These criteria were derived from the Office of Pesticide Programs Acute Toxicity Categories [31].

**Table 10.** Irritation Criteria for Hazard Designations

| Irritation/Corrosivity | Very High | High | Moderate | Low | Very Low |
|---|---|---|---|---|---|
| **Eye Irritation/Corrosivity** | Irritation persists for > 21 days or corrosive | Clearing in 8-21 days, severely irritating | Clearing in 7 days or less, moderately irritating | Clearing in less than 24 hrs, mildly irritating | Not irritating |
| **Skin Irritation/Corrosivity** | Corrosive | Severe irritation at 72 hours | Moderate irritation at 72 hours | Mild or slight irritation at 72 hours | Not irritating |

### 4.1.9 Endocrine Activity

EPA will evaluate endocrine activity rather than characterize hazard in terms of "endocrine disruption". Evidence of a chemical having endocrine activity will be summarized in a narrative.

*A) Data Resources*

Endocrine activity can be defined as a change in endocrine homeostasis caused by a chemical or other stressor from human activities (e.g., application of pesticides, the discharge of industrial chemicals to air, land, or water, or the use of synthetic chemicals in consumer products.). Data that will be considered include:

- In vitro data such as hormone receptor binding assays or ex vivo assays
- In vivo data from studies of intact animals or wildlife (including aquatic organisms)
- Ethically conducted human studies
- In vivo short term exposures or altered (e.g., ovariectomized) animal models
- Structural similarity to known endocrine active substances using SAR tools such as AIM, QSAR, etc.
- Additional information gleaned from studies that are indicative of a chemical's endocrine system interactions, such as changes in hormone profiles or reproductive organ weights.

*B) Criteria*

Available data for each chemical will be evaluated for evidence of the presence of endocrine activity.

- If there are no data available to evaluate this endpoint, endocrine activity is unknown, untested and would be marked with a "ND" indicating the absence of information. (No Data)
- If data show evidence of endocrine activity then the chemical will be designated as potentially endocrine active, while noting caveats and limitations.
- If data conclude no evidence of activity (no binding, perturbation, or evidence of endocrine-related adverse effects) then the chemical will be designated as having no evidence of endocrine activity, noting caveats and limitations.

In consultation with EPA toxicologists and risk assessors, DfE will provide a summary statement of the available data, including the presence of equivocal or conflicting data and any limitations to the available data. The level of confidence in the assessment will be noted.

## *4.2. Environmental Toxicity and Fate*

### 4.2.1 Aquatic Toxicity

Chemicals will be assigned hazard designations based on either the LC50 or EC50 values for acute aquatic toxicity, and the no or lowest observed effect concentration (NOEC and LOEC, respectively) for chronic aquatic toxicity. The criteria used for making chemical hazard designations are shown in Table 11. These values were derived from the GHS criteria [4], EPA Office of Pollution Prevention and Toxics' (OPPT) New Chemicals Program [32] and OPPT's criteria for HPV chemical categorization [28].

**Table 11**. Aquatic Toxicity Criteria for Hazard Designations

| Aquatic Toxicity | Very High | High | Moderate | Low |
|---|---|---|---|---|
| **Acute Aquatic Toxicity (LC50 or EC50) (mg/L)** | < 1.0 | 1 - 10 | > 10 - 100 | > 100 |
| **Chronic Aquatic Toxicity (NOEC or LOEC) (mg/L)** | < 0.1 | 0.1 - 1 | > 1 - 10 | > 10 |

### 4.2.2 Environmental Persistence

Persistence designations will be based on ultimate degradation. Degradation as the result of microbial action, hydrolysis, photolysis, and other relevant mechanisms will be considered. In the absence of data on ultimate degradation, DfE will evaluate data on primary degradation of the compound and consider the potential for persistent degradation products. Environmental monitoring data may modify how a persistence designation is determined. If Ready Biodegradability test data are available but the chemical did not pass, the chemical is evaluated based on measured data for half-life (e.g., simulation tests).

In the absence of measured data on the substance of interest, DfE will evaluate data for suitable analogs and estimated values from models such as EPI Suite or SPARC [33]. Persistence designations will be made based upon the criteria in Table 12. These values were derived from OPPT's New Chemicals Program and the DfE Master Criteria, and reflect OPPT policy on PBTs [18, 34, 35]. For persistence in air, designations of High, Moderate, and Low will not be used. Instead, a qualitative assessment of available data will be prepared.

**Table 12.** Criteria for Persistence Designations

| Environmental Persistence | Very High | High | Moderate | Low | Very Low |
|---|---|---|---|---|---|
| **Persistence in water, soil or sediment** | Half-life > 180 days or recalcitrant | Half life of 60 – 180 days | Half-life < 60 but ≥ 16 days | Half-life < 16 days OR passes Ready Biodegradability test not including the 10-day window.* | Passes Ready Biodegradability test with 10-day window.* |
| **Persistence in air** | For this endpoint, High/Moderate/Low etc. characterizations will not apply. A qualitative assessment of available data will be prepared. | | | | |

* See Ready Biodegradation test criteria [36-38].

Application of Ready Tests to Mixtures of Structurally Similar Chemicals:

According to OECD guidance, ready biodegradability tests are usually intended for pure chemicals. The ready biodegradability tests can be applied to "mixtures of structurally similar chemicals like oils and surface-active substances (surfactants)" [39]. OECD guidance states that "if a test on the mixture is performed and it is anticipated that a sequential biodegradation of the individual structures is taking place, then the 10-day window should not be applied to interpret the results of the test." EPA follows OECD recommendations on the interpretation of ready biodegradability for structurally similar mixtures.

### 4.2.3 Bioaccumulation

Data on the capacity for a compound to bioaccumulate will be evaluated. Environmental monitoring data will be considered when available. The criteria used to make bioaccumulation designations are shown in Table 13. These criteria were derived from OPPT's New Chemicals Program [34], and Arnot & Gobas 2006 [7].

**Table 13.** Criteria for Bioaccumulation Designations

| Bioaccumulation | Very High | High | Moderate | Low |
|---|---|---|---|---|
| **BAF/BCF** | > 5,000 | 5,000 – 1,000 | <1,000 – 100 | < 100 |
| **Log BAF/BCF** | >3.7 | 3.7 – 3 | <3 – 2 | < 2 |

**When experimental BAF or BCF data are available**:

1) If a measured log BAF or BCF is available and the value >2, apply the bioaccumulation criteria in Table 13.
2) If there are measured log BCF <2, consider application of the criteria on a case-by-case basis. For example, if there is a single measured log BCF <2, use the upper trophic BAF with metabolism from the BCFBAF model in EPI Suite. If there are several measured values which all support a designation of low bioaccumulation potential, then the chemical will be designated as such.
3) If there are measured log BAF < 2, then the chemical is designated as a Low for bioaccumulation.

**When experimental BAF or BCF data are not available:**

1) If there are no measured BCF or BAF values, consider the octanol-water (Kow) and octanol-air (Koa) partition coefficients. If a chemical has log Kow <2 or log Koa <5, it is given a low designation for bioaccumulation [7]; an estimated BAF or BCF is not needed. If no measured Kow and Koa values are available, they can be estimated from the EPI Suite models KOWWIN and KOAWIN or other models that may be available for these endpoints (e.g. SPARC).
2) If bioaccumulation is not Low after evaluating log Kow and log Koa as defined above, and there are no experimental bioaccumulation data, use estimated values (such as upper trophic BAF with metabolism from EPI Suite's BCFBAF model) and apply the bioaccumulation criteria in Table 13.

# 5. Additional Endpoints

The preceding section described a comprehensive set of endpoints commonly used to characterize chemical hazards. For some chemicals, additional hazard endpoints may be scientifically relevant, and could be included if data are available.

Criteria for physical hazards such as flammability and reactivity (Table 14) are taken from the GHS. Criteria for ecotoxicity in other species including bees and birds (Table 15) are taken from EPA's Office of Pesticide Programs' *Ecotoxicity Categories for Terrestrial and Aquatic Organisms* [40]. For these endpoints, DfE has included criteria it would use to characterize such hazards.

**Table 14.** Criteria for Physical Hazards

| Physical Hazards | Very High | High | Moderate | Low |
|---|---|---|---|---|
| **Explosives [40]** | GHS Unstable Explosive | GHS Explosive Division 1.1 (Mass explosion hazard), 1.2 (Severe projection hazard), or 1.3 (Fire, Blast hazard or projection hazard) | GHS Explosive Division 1.4 (Fire or projection hazard), or 1.5 (may mass explode in fire) | GHS Explosive Division 1.6 (Extremely insensitive articles with no mass explosion hazard) or not classifiable as an explosive by GHS |
| **Self-Reactive Substances [41]** | GHS Type A (Detonates/Deflagrates rapidly) or B (Liable to undergo thermal explosion) | GHS Type C (Possesses explosive properties) or D (Detonates partially when heated in confinement) | GHS Type E (Does not detonate when heated in confinement) or F (No effect when heated in confinement, not explosive) | GHS Type G (Thermally stable) or GHS not classified |
| **Substances which on contact with water emit flammable gases [42]** | GHS Category 1 | GHS Category 2 | GHS Category 3 | GHS not classified |
| **Oxidizing Gases [43]** | -- | GHS Category 1 | -- | GHS not classified |
| **Oxidizing Liquids and Solids [44, 45]** | GHS Category 1 | GHS Category 2 | GHS Category 3 | GHS not classified |

| Physical Hazards | Very High | High | Moderate | Low |
|---|---|---|---|---|
| **Organic Peroxides [46]** | GHS Type A or B | GHS Type C or D | GHS Type E or F | GHS Type G or not classified |
| **Self-heating Substances [47]** | | GHS Category 1 | GHS Category 2 | GHS not classified |
| **Substances corrosive to metal [48]** | -- | -- | GHS Category 1 | GHS not classified |

**Table 15.** Criteria for Other Forms of Ecotoxicity [49]

| Ecotoxicity | Very High | High | Moderate | Low | Very Low |
|---|---|---|---|---|---|
| **Avian (acute oral, mg/kg)** | <10 | 10-50 | 51-500 | 501-2000 | >2000 |
| **Avian (acute dietary, ppm)** | <50 | 50-500 | 501-1000 | 1001-5000 | >5000 |
| **Bees (acute, µg/bee)** | -- | <2 | 2-11 | >11 | -- |

For less commonly considered endpoints, including those that represent emerging science, such as epigenetic toxicity and loss of genetic diversity/biodiversity, criteria as well as data to characterize chemicals are limited. DfE has included them in this section as they may be relevant where data are available to differentiate among alternatives. The following list is representative of the types of endpoints that could be added if they are applicable and data are available.

- Domestic animal toxicity
- Epigenetic toxicity
- Eutrophication
- Global warming potential
- Lactational or transplacental transfer
- Loss of genetic diversity/biodiversity
- Non-target phytotoxicity
- Specific target organ toxicity – single exposure
- Mobility in the environmental media
- Ozone formation
- Wildlife developmental impairment
- Wildlife growth impairment
- Wildlife survival impairment
- Wildlife reproductive impairment
- Immunotoxicity

# 6. Designating Hazard Using Authoritative Lists

Authoritative lists can expedite the evaluation of chemicals in a hazard assessment. In many cases, classifications under authoritative lists are used directly in the hazard criteria in this document. For purposes of transparency and guidance to others who may use these criteria, DfE suggests below the way in which many authoritative lists could be used to classify chemicals in the DfE Alternatives Assessment Criteria. In its own Alternatives Assessments, DfE will evaluate the basis of the classification of a chemical to verify that it is relevant to the alternatives assessment criteria.

## *6.1 Acute Mammalian Toxicity*

**Table 16**. Classifications from Authoritative Lists that May Be Used to Designate **Very High** Hazard for Acute Mammalian Toxicity

| Authoritative Body | Classifications for Very High Hazard Designation |
|---|---|
| EU Risk Phrases [50] | R26: Very toxic by inhalation<br>R27: Very toxic in contact with skin<br>R28: Very toxic if swallowed |
| EU Classification, Labeling, and Packaging (CLP) [51] | H300: Fatal if swallowed<br>H310: Fatal in contact with skin<br>H330: Fatal if inhaled |

**Table 17**. Classifications from Authoritative Lists that May Be Used to Designate **High** Hazard for Acute Mammalian Toxicity

| Authoritative Body | Classifications for High Hazard Designation |
|---|---|
| EU Classification, Labeling, and Packaging (CLP) [51] | H301: Toxic if swallowed<br>H311: Toxic in contact with skin<br>H331: Toxic if inhaled |

**Table 18**. Classifications from Authoritative Lists that May Be Used to Designate **Moderate** Hazard for Acute Mammalian Toxicity

| Authoritative Body | Classifications for Moderate Hazard Designation |
|---|---|
| EU Classification, Labeling, and Packaging (CLP) [51] | H302: Harmful if swallowed<br>H312: Harmful in contact with skin<br>H332: Harmful if inhaled |

**Table 19**. Classifications from Authoritative Lists that May Be Used to Designate **Very High** or **High** Hazard for Acute Mammalian Toxicity

| Authoritative Body | Classifications for Very High or High Hazard Designation |
|---|---|
| EU Risk Phrases [50] | R23: Toxic by inhalation<br>R24: Toxic in contact with skin<br>R25: Toxic if swallowed |

**Table 20**. Classifications from Authoritative Lists that May Be Used to Designate **High** or **Moderate** Hazard for Acute Mammalian Toxicity

| Authoritative Body | Classifications for High or Moderate Hazard Designation |
|---|---|
| EU Risk Phrases [50] | R20: Harmful by inhalation<br>R21: Harmful in contact with skin<br>R22: Harmful if swallowed |

## *6.2 Carcinogenicity*

**Table 21.** Classifications from Authoritative Lists that May Be Used to Designate **Very High** Hazard for Carcinogenicity

| Authoritative Body | Classifications for Very High Hazard Designation |
|---|---|
| National Toxicology Program (NTP) | Known to be Human Carcinogen<br>Reasonably Anticipated to be Human Carcinogen |
| U.S. Environmental Protection Agency (EPA) | (2005/1999) Carcinogenic to humans, Likely to be carcinogenic to humans, (1996) Known/Likely<br>(1986) Group A – Human Carcinogen, Group B – Probable human carcinogen |
| International Agency for Research on Cancer (IARC) | Group 1 – carcinogenic to humans<br>Group 2A – probably carcinogenic to humans |
| EU CMR List [50] | Category 1 – Known to be carcinogenic to humans<br>Category 2 – Should be regarded as if carcinogenic to humans |
| EU Risk Phrases [50] | R45: May cause cancer<br>R49: May cause cancer by inhalation<br>*And all combination risk phrases containing R45 or R49*. |
| EU Classification, Labeling, and Packaging (CLP) [50] | H350: May cause cancer<br>H350i: May cause cancer by inhalation |

**Table 22.** Classifications from Authoritative Lists that May Be Used to Designate **High** Hazard for Carcinogenicity

| Authoritative Body | Classifications for High Hazard Designation |
|---|---|
| U.S. Environmental Protection Agency (EPA) | Suggestive evidence of carcinogenic potential<br>(1986) Group C – Possible human carcinogen |
| International Agency for Research on Cancer (IARC) | Group 2B – Possibly carcinogenic to humans |
| EU CMR List [50] | Category 3 – Cause for concern for humans owing to possible carcinogenic effects |
| EU Risk Phrases [50] | R40: Limited evidence of a carcinogenic effect<br>*And all combination risk phrases containing R40.* |
| EU Classification, Labeling, and Packaging (CLP) [51] | H351: Suspected of causing cancer |

**Table 23.** Classifications from Authoritative Lists that May Be Used to Designate **Very High** or **High** Hazard for Carcinogenicity

| Authoritative Body | Classifications for Very High or High Hazard Designation |
|---|---|
| NIOSH Occupational Carcinogen List | http://www.cdc.gov/niosh/topics/cancer/npotocca.html |
| Cal Prop 65 | Chemicals Known to the State to Cause Cancer<br>http://oehha.ca.gov/prop65/prop65_list/Newlist.html |

## *6.3 Mutagenicity/Genotoxicity*

**Table 24.** Classifications from Authoritative Lists that May Be Used to Designate **Very High** Hazard for Mutagenicity/Genotoxicity

| Authoritative Body | Classifications for Very High Hazard Designation |
|---|---|
| EU CMR List [50] | Category 1: Substances known to be mutagenic to man<br>Category 2: Substances which should be regarded as if they are mutagenic to man |
| EU Risk Phrases [50] | R46: May cause heritable genetic damage<br>*And all combination risk phrases containing R46.* |
| EU Classification, Labeling, and Packaging (CLP) [51] | H340: May cause genetic defects |

**Table 25.** Criteria and Authoritative Lists Used to Designate **High** Hazard for Mutagenicity/Genotoxicity

| Authoritative Body | Classifications for High Hazard Designation |
|---|---|
| EU CMR List [50] | Category 3 – Substances which cause concern for man owing to possible mutagenic effects |
| EU Risk Phrases [50] | R68: Possible risk of irreversible effects<br>*And all combination risk phrases containing R68.* |
| EU Classification, Labeling, and Packaging (CLP) [51] | H341: Suspected of causing genetic defects |

## *6.4 Reproductive and Developmental Toxicity*

**Table 26.** Classifications from Authoritative Lists that May Be Used to Designate **High** Hazard for Reproductive or Developmental Toxicity

| Authoritative Body | Classifications for High Hazard Designation |
|---|---|
| EU Classification, Labeling, and Packaging (CLP) [51] | H362: May cause harm to breast-fed children |

**Table 27.** Classifications from Authoritative Lists that May Be Used to Designate **High** or **Moderate** Hazard for Reproductive or Developmental Toxicity

| Authoritative Body | Classifications for High or Moderate Hazard Designation |
|---|---|
| Cal Prop 65 | Chemicals Known to the State to Cause Reproductive Toxicity<br>http://oehha.ca.gov/prop65/prop65_list/Newlist.html |

**Table 28.** Authoritative Lists or Reports That Do Not Include Threshold Levels and Therefore Do Not Correlate with DfE's Hazard and Potency-Based Criteria*

| Authoritative Body | Explanation |
|---|---|
| National Toxicology Program Office of Health Assessment and Translation [52] | Designations of "clear", "some", or "limited" evidence of adverse effects to human reproduction are risk-based determinations. Therefore, they do not directly translate to DfE's hazard-based criteria. |
| EU CMR List [50] | Category 1: Substances known to impair fertility in humans or cause developmental toxicity in humans<br>Category 2: Substances which should be regarded as if they impair fertility in humans or cause developmental toxicity to humans<br>Category 3: Cause concern for human fertility or possible developmental toxic effects |
| EU Risk Phrases [50] | R60: May impair fertility<br>R61: May cause harm to the unborn child<br>R62: Possible risk of impaired fertility<br>R63: Possible risk of harm to the unborn child<br>R64: May cause harm to breast-fed babies<br>*And all combination risk phrases containing R60-64.* |
| EU Classification, Labeling, and Packaging (CLP) [51] | H360: May damage fertility or the unborn child<br>H361: Suspected of damaging fertility or the unborn child |

*Although these lists and reports do not directly correlate with DfE criteria, a review of the basis for designation can support DfE hazard evaluations.

## *6.5 Repeated Dose Toxicity*

**Table 29**. Classifications from Authoritative Lists that May Be Used to Designate **High** Hazard for Repeated Dose Toxicity

| Authoritative Body | Classifications for High Hazard Designation |
|---|---|
| EU Risk Phrases [50] | R48(23/24/25): Danger of serious damage to health by prolonged exposure (repeated exposure) |
| EU Classification, Labeling, and Packaging (CLP) [51] | H372: Causes damage to organs |

**Table 30**. Classifications from Authoritative Lists that May Be Used to Designate Moderate Hazard for Repeated Dose Toxicity

| Authoritative Body | Classifications for Moderate Hazard Designation |
|---|---|
| EU Classification, Labeling, and Packaging (CLP) [51] | H373: May cause damage to organs |

**Table 31**. Classifications from Authoritative Lists that May Be Used to Designate High or Moderate Hazard for Repeated Dose Toxicity

| Authoritative Body | Classifications for High or Moderate Hazard Designation |
|---|---|
| EU Risk Phrases [50] | R48(20/21/22): Danger of serious damage to health by prolonged exposure |

## *6.6 Respiratory and Skin Sensitization*

**Table 32.** Classifications from Authoritative Lists that May Be Used to Designate High Hazard for Respiratory Sensitization

| Authoritative Body | Classifications for High Hazard Designation |
|---|---|
| EU Risk Phrases [50] | R42: May cause sensitization by inhalation |
| EU Classification, Labeling, and Packaging (CLP) [51] | H334: May cause allergy or asthma symptoms or breathing difficulties if inhaled |

**Table 33**. Classifications from Authoritative Lists that May Be Used to Designate High or Moderate Hazard for Skin Sensitization

| Authoritative Body | Classifications for High or Moderate Hazard Designation |
|---|---|
| EU Risk Phrases [50] | R43: May cause sensitization by skin contact |
| EU Classification, Labeling, and Packaging (CLP) [51] | H317: May cause an allergic skin reaction |

**Table 34**. Classifications from Authoritative Lists that May Be Used to Designate High or Moderate Hazard for Respiratory Sensitization

| Authoritative Body | Classifications for High or Moderate Hazard Designation |
|---|---|
| Association of Occupational and Environmental Clinics (AOEC) Exposure Code List [53] | G (generally accepted)<br>Rs (sensitizer-induced asthma)<br>Rr (reactive airway dysfunction syndrome or RADS)<br>Rrs (both Rs and Rr) |

## *6.7 Aquatic Toxicity*

**Table 35**. Classifications from Authoritative Lists that May Be Used to Designate **Very High** Hazard for Acute Aquatic Toxicity

| Authoritative Body | Classifications for Very High Hazard Designation |
|---|---|
| EU Risk Phrases [50] | R50: Very toxic to aquatic organisms |
| EU Classification, Labeling, and Packaging (CLP) [51] | H400: Very toxic to aquatic life |

# 7. Test Methods and Data Interpretation

This section lists examples of test methods used to develop data from which hazard designations based upon the criteria in Section 4 will be made. In developing hazard designations we will consider both peer-reviewed, published studies as well as unpublished data. Published, peer-reviewed and guideline studies will be given the greatest weight.

## *7.1 Acute Mammalian Toxicity – Test Methods*

- OPPTS Harmonized Guideline 870.1100: Acute oral toxicity [54]
- OPPTS Harmonized Guideline 870.1200: Acute dermal toxicity [55]
- OPPTS Harmonized Guideline 870.1300: Acute inhalation toxicity [56]
- OECD Test Guideline 420: Acute Oral Toxicity-Fixed Dose Method [57]
- OECD Test Guideline 423: Acute Oral Toxicity – Acute Toxic Class Method [58]
- OECD Test Guideline 425: Acute Oral Toxicity – Up-and-Down Procedure [59]
- OECD Test Guideline 402: Acute Dermal Toxicity [60]
- OECD Test Guideline 403: Acute Inhalation Toxicity [61]

### 7.1.1 Sources for Data Interpretation

- GHS Chapter 3.1 Acute Toxicity [5]
- To access the list of substances carrying EU Risk Phrases and Hazard Statements, go to: http://esis.jrc.ec.europa.eu/, and click on the CLP/GHS tab. One can search for a specific chemical or download the entire list of classified substances (Annex VI). Table 3.1 lists substances along with their EU Hazard Statements, and Table 3.2 lists substances along with their Risk Phrases.

## *7.2 Carcinogenicity – Test Methods*

- OECD Test Guideline 451: Carcinogenicity Studies [62]
- OECD Test Guideline 453: Combined Chronic Toxicity/Carcinogenicity Studies [63]
- OPPTS Harmonized Guidelines 870.4200: Carcinogenicity [64]
- OPPTS Harmonized Guidelines 870.4300: Combined chronic toxicity/carcinogenicity [65]
- NTP 2 Year Study Protocol: "Specifications for the conduct of studies to evaluate the toxic and carcinogenic potential of chemical, biological and physical agents in laboratory animals for the National Toxicology Program" [66]

### 7.2.1 Sources for Data Interpretation

- To access the list of substances carrying EU Risk Phrases and Hazard Statements, go to: http://esis.jrc.ec.europa.eu/, and click on the CLP/GHS tab. One can search for a specific chemical or download the entire list of classified substances (Annex

VI). Table 3.1 lists substances along with their EU Hazard Statements, and Table 3.2 lists substances along with their Risk Phrases.
- Section 2, Hazard Assessment in Guidelines for Carcinogen Risk Assessment http://oaspub.epa.gov/eims/eimscomm.getfile?p_download_id=439797 [67]
- Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens, available at: http://www.epa.gov/ttn/atw/childrens_supplement_final.pdf [68]

## *7.3 Mutagenicity/Genotoxicity – Test Methods*

- OECD Test Guideline 471 (OPPTS 870.5100): Bacterial Reverse Mutation Test [69, 70]
- OECD Test Guideline 473 (OPPTS 870.5375): *In vitro* Mammalian Chromosome Aberration Test [71, 72]
- OECD Test Guideline 474 (OPPTS 870.5395): Mammalian Erythrocyte Micronucleus Test [73, 74]
- OECD Test Guideline 475 (OPPTS 870.5385): Mammalian Bone Marrow Chromosome Aberration Test [75, 76]
- OECD Test Guideline 476 (OPPTS 870.5300): *In vitro* Mammalian Cell Gene Mutation Test [77, 78]
- OECD Test Guideline 483 (OPPTS 870.5380): Mammalian Spermatogonial Chromosome Aberration Test [79, 80]
- OECD Test Guideline 486: Unscheduled DNA Synthesis (UDS) Test with Mammalian Liver Cells *in vivo* [81]. This guideline does **NOT** substitute in the necessary minimum set for either the gene mutation or the chromosome aberration test.

### 7.3.1 Sources for Data Interpretation

- To access the list of substances carrying EU Risk Phrases and Hazard Statements, go to: http://esis.jrc.ec.europa.eu/, and click on the CLP/GHS tab. One can search for a specific chemical or download the entire list of classified substances (Annex VI). Table 3.1 lists substances along with their EU Hazard Statements, and Table 3.2 lists substances along with their Risk Phrases.
- GHS Chapter 3.5 Germ Cell Mutagenicity [15]

## *7.4 Reproductive and Developmental Toxicity – Test Methods*

**Fertility Test Methods**

- OECD Test Guideline 415: One-Generation Reproduction Toxicity Study [82]
- OECD Test Guideline 416: Two-Generation Reproduction Toxicity Study [83]
- OPPTS Harmonized Guideline 870.3800: Reproduction and fertility effects [84]
- OECD Test Guideline 421: Reproduction/Developmental Toxicity Screening Test [85]

- OECD Test Guideline 422: Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test [86]
- OPPTS Harmonized Guideline 870.3550: Reproduction/developmental toxicity screening test [87]
- OPPTS Harmonized Guideline 870.3650: Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test [88]

**Developmental Toxicity Test Methods**

- OECD Test Guideline 414: Prenatal Developmental Toxicity Study [89]
- OECD Test Guideline 421: Reproduction/Developmental Toxicity Screening Test [85]
- OECD Test Guideline 422: Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test [86]
- OECD Test Guideline 426: Developmental Neurotoxicity Study [90]
- OPPTS Harmonized Guideline 870.3800: Reproduction and fertility effects [84]
- OPPTS Harmonized Guideline 870.3550: Reproduction/developmental toxicity screening test [87]
- OPPTS Harmonized Guideline 870.3650: Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test [88]
- OPPTS Harmonized Guideline: 870.6300 Developmental neurotoxicity study [91]

### 7.4.1 Sources for Data Interpretation

- To access the list of substances carrying EU Risk Phrases and Hazard Statements, go to: http://esis.jrc.ec.europa.eu/, and click on the CLP/GHS tab. One can search for a specific chemical or download the entire list of classified substances (Annex VI). Table 3.1 lists substances along with their EU Hazard Statements, and Table 3.2 lists substances along with their Risk Phrases.
- GHS Chapter 3.7 Reproductive Toxicity [92]
- Part A, Section 3, Hazard Characterization in *Guidelines for Reproductive Toxicity Risk Assessmen*t, http://www.epa.gov/raf/publications/pdfs/REPRO51.PDF[19]
- Part A, Section 3, Hazard Characterization in *Guidelines for Developmental Toxicity Risk Assessmen*t, http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=23162 [12]

## *7.5 Neurotoxicity – Test Methods*

- OECD Test Guideline 424: Neurotoxicity Study in Rodents [93]
- OPPTS Harmonized Guideline 870.6200: Neurotoxicity screening battery [94]

### 7.5.1 Sources for Data Interpretation

- Section 3, Hazard Characterization in *Guidelines for Neurotoxicity Risk Assessmen*t [17]

- GHS Chapter 3.9 Specific Target Organ Toxicity Repeated Exposure [30]

## *7.6 Repeated Dose Toxicity – Test Methods*

- OECD Test Guideline 408: Repeated Dose 90-Day Oral Toxicity Study in Rodents [95]
- OECD Test Guideline 409: Repeated Dose 90-Day Oral Toxicity Study in Non-Rodents [96]
- OECD Test Guideline 411: Subchronic Dermal Toxicity: 90-day Study [97]
- OECD Test Guideline 413: Subchronic Inhalation Toxicity: 90-day Study [98]
- OPPTS Harmonized Guideline 870.3100: 90-Day oral toxicity in rodents [99]
- OPPTS Harmonized Guideline 870.3150: 90-Day oral toxicity in nonrodents [100]
- OPPTS Harmonized Guideline 870.3250: 90-Day dermal toxicity [101]
- OPPTS Harmonized Guideline 870.3465: 90-Day inhalation toxicity [102]
- OECD Test Guideline 407: Repeated Dose 28-day Oral Toxicity Study in Rodents [103]
- OECD Test Guideline 410: Repeated Dose Dermal Toxicity: 28-day Study [104]
- OECD Test Guideline 412: Repeated Dose Inhalation Toxicity: 28-day Study [105]
- OECD Test Guideline 422: Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test [86]
- OPPTS Harmonized Guideline 870.3050: Repeated dose 28-day oral toxicity study in rodents [106]
- OPPTS Harmonized Guideline 870.3200: 28-Day dermal toxicity [107]

### 7.6.1 Sources for Data Interpretation

- GHS Chapter 3.9 Specific Target Organ Toxicity Repeated Exposure [30]
- To access the list of substances carrying EU Risk Phrases and Hazard Statements, go to: http://esis.jrc.ec.europa.eu/, and click on the CLP/GHS tab. One can search for a specific chemical or download the entire list of classified substances (Annex VI). Table 3.1 lists substances along with their EU Hazard Statements, and Table 3.2 lists substances along with their Risk Phrases.

## *7.7 Skin Sensitization – Test Methods*

- OECD Test Guideline 406: Skin Sensitization [108]
- OECD Test Guideline 429: Skin Sensitization: Local Lymph Node Assay [14]
- OPPTS Harmonized Guideline 870.2600: Skin Sensitization [109]

### 7.7.1 Sources for Data Interpretation

- To access the list of substances carrying EU Risk Phrases and Hazard Statements, go to: http://esis.jrc.ec.europa.eu/, and click on the CLP/GHS tab. One can search for a specific chemical or download the entire list of classified substances (Annex

VI). Table 3.1 lists substances along with their EU Hazard Statements, and Table 3.2 lists substances along with their Risk Phrases.
- GHS Chapter 3.4 Respiratory and Skin Sensitization [11]

## *7.8 Endocrine Activity – Test Methods*

Test methods to support the evaluation of endocrine activity include those developed by the EPA's Endocrine Disruptor Screening Program (EDSP). More information about currently available screening assays can be found on the EDSP website: http://www.epa.gov/endo/.

## *7.9 Aquatic Toxicity – Test Methods*

**Acute Toxicity Test Methods for Fish**
- OECD Test Guideline 203: Fish, Acute Toxicity Test [110]
- OPPTS Harmonized Guideline 850.1075: Fish acute toxicity test, freshwater and marine [111]

NOTE – EPA may request that the test be carried out using semi-static renewal or a flow-through system with mean measured concentration. Any new testing should be done in consultation with EPA.

**Acute Toxicity Test Methods for Aquatic Invertebrates**
- OECD Test Guideline 202, Part 1, Daphnia sp., Acute Immobilisation Test [112]
- OPPTS Harmonized Guideline 850.1010: Aquatic invertebrate acute toxicity test, freshwater daphnids [113]
- OPPTS Harmonized Guideline 850.1035: Mysid acute toxicity test [114]

NOTE – EPA may request that the test be carried out using semi-static renewal or a flow-through system with mean measured concentration. Any new testing should be done in consultation with EPA. A 96-hour Mysid shrimp acute toxicity test can be used in place of a daphnid acute toxicity test when the latter is not available.

**Acute Toxicity Test Methods for Algae**
- OECD Test Guideline 201, Alga, Growth Inhibition Test (and biomass) [115]
- OPPTS Harmonized Guideline 850.5400: Algal toxicity, Tiers I and II (including growth inhibition and biomass) [116]

**Alternative Test Methods, Acute Aquatic Toxicity**

The following test methods may be considered, when relevant:
- OPPTS Harmonized Guideline 850.1085: Fish acute toxicity mitigated by humic acid [117]
- OPPTS Harmonized Guideline 850.1025: Oyster acute toxicity test (shell deposition)

[118]
- OPPTS Harmonized Guideline 850.1045: Penaeid acute toxicity test [119]
- OPPTS Harmonized Guideline 850.1055: Bivalve acute toxicity test (embryo larval) [120]
- OPPTS Harmonized Guideline 850.4400: Aquatic plant toxicity test using *Lemna spp.* Tiers I and II [121]
- OPPTS Harmonized Guideline 850.1735: Whole Sediment Acute Toxicity Invertebrates, Freshwater [122]
- OPPTS Harmonized Guideline 850.1740: Whole Sediment Acute Toxicity Invertebrates, Marine [123]
- In the absence of data on the chemical, modeled data from sources such as ECOSAR [124] are acceptable when the chemical can be reasonably included in an ECOSAR class or modeled data can be supported by experimental data from a suitable analog.

**Chronic Toxicity Test Methods for Fish**
- OECD Test Guideline 204: Fish, Prolonged Toxicity Test: 14-Day Study [125]
- OECD Test Guideline 210: Fish, Early-Life Stage Toxicity Test [126]
- OECD Test Guideline 212: Fish, Short-term Toxicity Test on Embryo and Sac-Fry Stages [127]
- OECD Test Guideline 215: Fish, Juvenile Growth Test [128]
- OECD Test Guideline 229: Fish Short Term Reproduction Assay [129]
- OECD Test Guideline 230: 21-day Fish Assay: A Short-Term Screening for Oestrogenic and Androgenic Activity, and Aromatase Inhibition [130]
- OPPTS Harmonized Guideline 850.1400: Fish Early-Life Stage Toxicity Test [131]
- OPPTS Harmonized Guideline 850.1500: Fish Life Cycle Toxicity [132]

**Chronic Toxicity Test Methods for Aquatic Invertebrates**
- OECD Test Guideline 211: Daphnia magna Reproduction Test [133]
- OPPTS Harmonized Guideline 850.1300: Daphnid Chronic Toxicity Test [134]
- OPPTS Harmonized Guideline 850.1350: Mysid Chronic Toxicity Test [135]

**Chronic Toxicity Test Methods for Plants and Algae**
- OECD Test Guideline 221: Lemna sp. Growth Inhibition Test [136]
- OPPTS Harmonized Guideline 850.4450: Aquatic Plants Field Study, Tier III [137]

**Alternative Test Methods, Chronic Aquatic Toxicity**
- In the absence of data on the chemical, modeled data from sources such as ECOSAR [124] are acceptable when the chemical can be reasonably included in an ECOSAR class or modeled data can be supported by experimental data from a suitable analog.

### 7.9.1 Sources for Data Interpretation

- U.S. EPA Design for the Environment Program Master Criteria for Safer Ingredients [35]
- U.S. EPA ECOSAR [124]

- To access the list of substances carrying EU Risk Phrases and Hazard Statements, go to: http://esis.jrc.ec.europa.eu/, and click on the CLP/GHS tab. One can search for a specific chemical or download the entire list of classified substances (Annex VI). Table 3.1 lists substances along with their EU Hazard Statements, and Table 3.2 lists substances along with their Risk Phrases.

## *7.10 Environmental Persistence – Test Methods*

Data from experimental methods are generally preferred over estimations of persistence. It is noted that simulation tests are likely to better describe the biodegradability of a chemical in specific environmental conditions and may also contribute useful information to the review. Environmental monitoring data may modify how a persistence designation is determined.

**Test Methods for Persistence**

- OECD Test Guideline 301: Ready Biodegradability (sections A-F) [36]
- OECD Test Guideline 310: Ready Biodegradability – CO2 in sealed vessels [37]
- OPPTS Harmonized Guideline 835.3110: Ready biodegradability [38]
- If the compound degrades by more than 40% in 28 days during one of the Ready Biodegradability tests specified above or by more than 60% in one of the Inherent Biodegradability tests detailed in OECD Test Guidelines 302 (A-C) [138-140], then the half-life of a chemical is likely to be less than 60 days [141].
- OECD Test Guideline 303A (OPPTS 835.3240): Aerobic Sewage Treatment: Activated Sludge Units [142, 143]
- OECD Test Guideline 309 (OPPTS Harmonized Guideline 835.3190): Aerobic Mineralization in Surface Water - Simulation Biodegradation Test [144, 145]
- OECD Test Guideline 314: Simulation Tests to Assess the Biodegradability of Chemicals Discharged in Wastewater (Note: TG 314 uses elements of OECD TG 301, 303A, 309, 310, and 311) [146]
- OPPTS Harmonized Guideline 835.3280–Simulation Tests to Assess the Primary and Ultimate Biodegradability of Chemicals Discharged to Wastewater [147]
- OPPTS Harmonized Guideline 835.3170 - Shake Flask Die-Away Test [148]
- OPPTS Harmonized Guideline 835.3180 - Sediment/Water Microcosm Biodegradation Test [149]

**Other Methods of Degradation**

On a case-by-case basis, DfE will consider other routes of degradation in the environment, such as hydrolysis or photolysis, and degradation in other relevant media, for example, soil or sediment. In evaluating such degradation studies, DfE will consider the relevance of that degradation pathway to the chemical in question as well as the significance of the degradation.

### 7.10.1 Sources for Data Interpretation

- U.S. EPA Design for the Environment Program Master Criteria for Safer Ingredients [35]
- U.S. EPA EPI Suite™ [25]
- SPARC [33]
- Revised Introduction to the OECD Guidelines for Testing of Chemicals, Section 3 [39]
- OPPTS 835.0001 Principles and Strategies Related to Biodegradation Testing of Organic Chemicals under the Toxic Substances Control Act (TSCA) [150]

## *7.11 Bioaccumulation – Test Methods*

A field-measured BAF (located in the literature) is the most preferred data for indicating bioaccumulation. Environmental monitoring data will be considered when available.

**Alternative Test Methods for Bioaccumulation**

When a field-measured BAF is not available, the following test methods may be used:

- OECD Test Guideline 305: Bioconcentration: Flow-through Fish Test [151]
- OPPTS Harmonized Guideline 850.1710: Oyster BCF [152]
- OPPTS Harmonized Guideline 850.1730: Fish BCF [153]
- Modeled data from sources such as EPI Suite™ [25] are acceptable when data are unavailable.

### 7.11.1 Sources for Data Interpretation

- U.S. EPA Design for the Environment Program Master Criteria for Safer Ingredients [35]
- U.S. EPA EPI Suite™ [25]
- SPARC [33]

# 8. Appendix – Alternatives Assessment Criteria Quick Reference

**Table A1.** Human Health Effects

| Human Health Effects | | | | | |
|---|---|---|---|---|---|
| **Acute Mammalian Toxicity** | **Very High** | **High** | **Moderate** | **Low** | |
| Oral LD50 (mg/kg) | ≤ 50 | > 50 - 300 | > 300 - 2000 | > 2000 | |
| Dermal LD50 (mg/kg) | ≤ 200 | > 200 - 1000 | > 1000 - 2000 | > 2000 | |
| Inhalation LC50 (vapor/gas) (mg/L) | ≤ 2 | > 2 -10 | > 10 - 20 | > 20 | |
| Inhalation LC50 (dust/mist/fume) (mg/L) | ≤ 0.5 | > 0.5 - 1.0 | > 1.0 - 5 | > 5 | |
| **Carcinogenicity** | **Very High** | **High** | **Moderate** | **Low** | |
| | Known or presumed human carcinogen (GHS Category 1A and 1B) | Suspected human carcinogen (GHS Category 2) | Limited or marginal evidence of carcinogenicity in animals (and inadequate evidence in humans) | Negative studies or robust mechanism-based SAR | |
| **Mutagenicity/Genotoxicity** | **Very High** | **High** | **Moderate** | **Low** | |
| Germ cell mutagenicity | GHS Category 1A or 1B: Substances known to induce heritable mutations or to be regarded as if they induce heritable mutations in the germ cells of humans | GHS Category 2: Substances which cause concern for humans owing to the possibility that they may induce heritable mutations in the germ cells of humans | Evidence of mutagenicity supported by positive results in *in vitro* OR *in vivo* somatic cells of humans or animals | Negative for chromosomal aberrations and gene mutations, or no structural alerts. | |
| Mutagenicity and Genotoxicity in Somatic Cells | | OR<br>Evidence of mutagenicity supported by positive results in *in vitro* AND *in vivo* somatic cells and/or germ cells of humans or animals | | | |
| **Reproductive Toxicity** | | **High** | **Moderate** | **Low** | **Very Low** |
| Oral (mg/kg/day) | | < 50 | 50 - 250 | > 250 - 1000 | > 1000 |
| Dermal (mg/kg/day) | | < 100 | 100 - 500 | > 500 - 2000 | > 2000 |
| Inhalation (vapor, gas, mg/L/day) | | < 1 | 1 - 2.5 | > 2.5 - 20 | > 20 |
| Inhalation (dust/mist/fume, mg/L/day) | | < 0.1 | 0.1 - 0.5 | > 0.5 - 5 | > 5 |
| **Developmental Toxicity** | | **High** | **Moderate** | **Low** | **Very Low** |
| Oral (mg/kg/day) | | < 50 | 50 - 250 | > 250 | > 1000 |
| Dermal (mg/kg/day) | | < 100 | 100 - 500 | > 500 | > 2000 |
| Inhalation (vapor, gas, mg/L/day) | | < 1 | 1 - 2.5 | > 2.5 | > 20 |
| Inhalation (dust/mist/fume, mg/L/day) | | < 0.1 | 0.1 - 0.5 | > 0.5 | > 5 |
| **Neurotoxicity (90-day study)** | | **High** | **Moderate** | **Low** | |
| Oral (mg/kg-bw/day) | | < 10 | 10 - 100 | > 100 | |
| Dermal (mg/kg-bw/day) | | < 20 | 20 - 200 | > 200 | |
| Inhalation (vapor/gas) (mg/L/6h/day) | | < 0.2 | 0.2 - 1.0 | > 1.0 | |
| Inhalation (dust/mist/fume) (mg/L/6h/day) | | < 0.02 | 0.02 - 0.2 | > 0.2 | |
| **Repeated Dose Toxicity (90-day study)** | | **High** | **Moderate** | **Low** | |
| Oral (mg/kg-bw/day) | | < 10 | 10 - 100 | > 100 | |
| Dermal (mg/kg-bw/day) | | < 20 | 20 - 200 | > 200 | |
| Inhalation (vapor/gas) (mg/L/6h/day) | | < 0.2 | 0.2 - 1.0 | > 1.0 | |
| Inhalation (dust/mist/fume) (mg/L/6h/day) | | < 0.02 | 0.02 - 0.2 | > 0.2 | |
| **Sensitization** | | **High** | **Moderate** | **Low** | |
| Skin sensitization | | High frequency of sensitization in humans and/or high potency in animals (GHS Category 1A) | Low to moderate frequency of sensitization in human and/or low to moderate potency in animals (GHS Category 1B) | Adequate data available and not GHS Category 1A or 1B | |
| Respiratory Sensitization | | Occurrence in humans or evidence of sensitization in humans based on animal or other tests (equivalent to GHS Category 1A and 1B) | Limited evidence including the presence of structural alerts | Adequate data available indicating lack of respiratory sensitization | |
| **Irritation/Corrosivity** | **Very High** | **High** | **Moderate** | **Low** | **Very Low** |
| Eye Irritation/Corrosivity | Irritation persists for > 21 days or corrosive | Clearing in 8-21 days, severely irritating | Clearing in 7 days or less, moderately irritating | Clearing in less than 24 hrs, mildly irritating | Not irritating |
| Skin Irritation/Corrosivity | Corrosive | Severe irritation at 72 hours | Moderate irritation at 72 hours | Mild or slight irritation at 72 hours | Not irritating |
| **Endocrine Activity** | For this endpoint, High/Moderate/Low etc. characterizations will not apply. Evidence will be summarized in a narrative. | | | | |

**Table A2.** Environmental Toxicity and Fate

| Environmental Toxicity and Fate | | | | | |
|---|---|---|---|---|---|
| **Aquatic Toxicity** | **Very High** | **High** | **Moderate** | **Low** | |
| Acute Aquatic Toxicity (LC50 or EC50) (mg/L) | < 1.0 | 1 - 10 | > 10 - 100 | > 100 | |
| Chronic Aquatic Toxicity (LOEC) (mg/L) | < 0.1 | 0.1 - 1 | > 1 - 10 | > 10 | |
| **Environmental Persistence** | **Very High** | **High** | **Moderate** | **Low** | **Very Low** |
| Persistence in water, soil or sediment | Half-life > 180 days or recalcitrant | Half life of 60 – 180 days | Half-life < 60 but ≥ 16 days | Half-life < 16 days OR passes Ready Biodegradability test not including the 10-day window. | Passes Ready Biodegradability test with 10-day window. |
| Persistence in air (half-life days) | For this endpoint, High/Moderate/Low etc. characterizations will not apply. A qualitative assessment of available data will be prepared. | | | | |
| **Bioaccumulation (BAF / BCF)** | **Very High** | **High** | **Moderate** | **Low** | |
| BCF/BAF | > 5,000 | 5,000 – 1,000 | <1,000 – 100 | < 100 | |
| Log BCF/BAF | >3.7 | 3.7-3 | <3-2 | <2 | |

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