

Design for the Environment Program Alternatives Assessment Criteria for Hazard Evaluation

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The criteria within this document will be applied during upcoming DfE Alternatives Assessments. Lessons learned from the application of the criteria during those assessments will be incorporated into a finalized version.

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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 concern for human health and environmental hazard. The Criteria will be applied in upcoming DfE Alternatives Assessments (for a current list of assessments to go: http://www.epa.gov/dfe/alternative_assessments.html). The Criteria could form the basis for decision-making by other organizations such as manufacturers, retailers, other government agencies, and non-governmental organizations.

DfE Alternatives Assessments are multi-stakeholder partnerships that evaluate a chemical of concern and its likely alternatives with the goal of "informing substitution" to safer alternatives. The assessments are intended to reduce the likelihood of the unintended consequences that might result if poorly understood alternatives were chosen. The Alternatives Assessment Criteria can be used to place chemicals on a continuum of relative hazard to inform decision making.

The criteria are robust and comprehensive, including consideration for human health and environmental hazards. For most endpoints, the criteria define "High," "Moderate," and "Low" concern. Authoritative sources – the United Nation's Globally Harmonized System (GHS) for the Classification and Labeling of Hazard Substances and U.S. EPA programs – are the basis for these distinctions. In assigning a designation of Low, Moderate, or High concern for hazard, DfE uses the best information available, both experimental and modeled.

2. General Requirements

- 2.1 Data for all relevant routes of exposure will be evaluated.
- 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 [1]. In reviews that include conflicting data, a weight of evidence evaluation will inform the hazard designation with a conservative approach aimed at the protection of human health and the environment. 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 Any known sensitivity of the test species or strain will be considered in the evaluation of data against these criteria.

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 [2].
- 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 [3].
- 3.3. **Attribute:** The general property of the chemical that is being evaluated (e.g. acute mammalian toxicity, persistence).
- 3.4. 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 [1].
- 3.5. **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 [4].
- 3.6. **Biodegradation** is a process in which the destruction of the chemical is accomplished by the action of a living organism [5].
- 3.7. **Carcinogen** denotes a chemical substance or mixture of chemical substances which induces cancer or increases its incidence [6].
- 3.8. A **chemical** is identified by its Chemical Abstract Service (CAS) number.
- 3.9. **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 [2].
- 3.10. **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.
- 3.11. **Dermal sensitizer:** A substance that will lead an allergic response following skin contact [7].

- 3.12. **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 [8].
- 3.13. **EC50:** Half maximal effective concentration.
- 3.14. **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.)
- 3.15. 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 [9].
- 3.16. **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. [10]
- 3.17. **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 [11].
- 3.18. An **ingredient** may be one chemical or a blend of multiple chemicals that are intentionally added.
- 3.19. **LC50:** Median lethal concentration.
- 3.20. **LD50:** Median lethal dose.
- 3.21. **LOAEL:** Lowest Observed Adverse Effect Level
- 3.22. **LOAEC:** Lowest Observed Adverse Effect Concentration
- 3.23. **LOEC:** Lowest Observed Effect Concentration

- 3.24. **LOEL:** Lowest Observed Effect Level.
- 3.25. **Mutagen:** The term mutagenic and mutagen will be used for agents giving rise to an increased occurrence of mutations in populations of cells and/or organisms [11].
- 3.26. **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 [12].
- 3.27. **NOAEL:** No Observed Adverse Effect Level
- 3.28. **NOAEC:** No Observed Adverse Effect Concentration
- 3.29. **NOEC:** No Observed Effect Concentration
- 3.30. **NOEL:** No Observed Effect Level
- 3.31. **Persistence:** The length of time the chemical can exist in the environment before being destroyed (i.e., transformed) by natural processes [13].
- 3.32. **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 [14].
- 3.33. **Respiratory sensitizer:** A substance that will lead to hypersensitivity of the airways following inhalation of the substance [7].
- 3.34. **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 [15].
- 3.35. **Skin irritation** is the production of reversible damage to the skin following the application of a test substance for up to 4 hours [15].
- 3.36. **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. [10]
- 3.37. **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* [16]. The analog used must be appropriate for the attribute being evaluated.

- 3.38. **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 [17].

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. 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 [18] or enhancements to estimation models such as EPI Suite™ [19] that occur over time. For convenience, a summary of DfE’s Alternatives Assessment Criteria is located in the Appendix (see Table A1).

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 (LD₅₀ or LC₅₀), 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 [20].

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 determine whether a compound is known, presumed, or suspected to increase incidence of cancer, whether current data on carcinogenicity is equivocal, or whether adequate studies have been conducted to show no increase in cancer incidents. Carcinogenicity designations will be made according to the criteria in Table 2. Chemicals known, presumed, or suspected to be carcinogenic to humans according to the authoritative lists in Table 3 will be designated as High. When equivocal data or only positive structural alerts are present, a designation of Moderate will be used. The basis for Low concern may include negative carcinogenicity studies on the chemical being evaluated or negative studies on an analog and lack of structural alerts, in addition to mechanistic considerations.

Table 2. Carcinogenicity Criteria for Hazard Designation

Carcinogenicity	High	Moderate	Low
Carcinogenicity	Positive results	Equivocal results	Negative studies and no structural alerts

Table 3. Criteria and Authoritative Lists Used to Designate **High** Hazard for Carcinogenicity

Authoritative Body	Classifications for High Hazard Designation
Globally Harmonized System (GHS) [6]	Category 1A – Known to have carcinogenic potential for humans Category 1B – Presumed to have carcinogenic potential for humans Category 2 – Suspected human carcinogens
National Toxicology Program (NTP)	Known to be Human Carcinogen Reasonably Anticipated to be Human Carcinogen
U.S. Environmental Protection Agency (EPA)	(2005/1999) Carcinogenic to humans, Likely to be carcinogenic to humans, or Suggestive evidence of carcinogenic potential (1996) Known/Likely (1986) Group A – Human Carcinogen, Group B – Probable human carcinogen, or Group C – Possible human carcinogen
International Agency for Research on Cancer (IARC)	Group 1 – carcinogenic to humans Group 2A – probably carcinogenic to humans Group 2B – possibly carcinogenic to humans
EU CMR List [21]	Category 1 – Known to be carcinogenic to humans Category 2 – Should be regarded as if carcinogenic to humans Category 3 – Cause for concern for humans owing to possible carcinogenic effects
EU Risk Phrases [21]	R45: May cause cancer R49: May cause cancer by inhalation R40: Limited evidence of a carcinogenic effect <i>And all combination risk phrases containing one or more of the above.</i>

4.1.3. Mutagenicity/Genotoxicity

The Mutagenicity/Genotoxicity criteria classify compounds based upon capacity to cause gene mutations and/or chromosomal aberrations, whether current data are equivocal, or whether adequate studies have been conducted that show lack of mutagenic potential. Mutagenic/Genotoxic designations will be made according the criteria in Table 4. Those compounds showing positive results and/or categorized by one of the authoritative bodies in Table 5 will receive a High designation. When equivocal data or only positive structural data are present, a designation of Moderate will be used. A Low hazard designation will be assigned for chemicals with negative test data and no structural alerts.

Table 4. Mutagenicity/Genotoxicity Criteria for Hazard Designations

Mutagenicity/Genotoxicity	High	Moderate	Low
Mutagenicity/Genotoxicity	Positive results	Equivocal results	Negative for chromosomal aberrations and gene mutations, and no structural alerts.

Table 5. Criteria and Authoritative Lists Used to Designate **High** Hazard for Mutagenicity/Genotoxicity

Authoritative Body	Classifications for High Hazard Designation
Globally Harmonized System (GHS) [11]	Category 1A – Chemicals known to induce heritable mutations in germ cells of humans Category 1B – Chemicals which should be regarded as if they induce heritable mutations in the germ cells of humans Category 2 – Chemicals which cause concern for humans owing to the possibility that they may induce heritable mutations in the germ cells of humans
EU CMR List [21]	Category 1 – Substances known to be mutagenic to humans Category 2 – Substances which should be regarded as if they are mutagenic to humans Category 3 – Substances which cause concern for human owing to possible mutagenic effects
EU Risk Phrases [21]	R46: May cause heritable genetic damage R68: Possible risk of irreversible effects <i>And all combination risk phrases containing one or more of the above</i>

4.1.4. Reproductive and Developmental Toxicity

DfE’s reproductive and developmental criteria classify compounds based upon the potential to cause adverse effects on reproductive capacity and/or subsequent development of the offspring through oral, dermal and respiratory exposure routes. 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. These values were derived from the US EPA’s Office of Pollution Prevention & Toxics criteria for HPV chemical categorization [22].

Table 6. Reproductive and Developmental Toxicity Criteria for Hazard Designations

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

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 7 which were derived from GHS criteria for Specific Target Organ Toxicity Repeated Exposure [23].

The dose values in Table 7 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 7. Neurotoxicity Criteria for Hazard Designations

Neurotoxicity	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

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. 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 8 which were derived from the US EPA's Office of Pollution Prevention & Toxics criteria for HPV chemical categorization [22].

The dose values in Table 8 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 8. Repeated Dose Toxicity Criteria for Hazard Designations

Repeated Dose Toxicity	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

4.1.7. Respiratory and Skin Sensitization

Evidence of whether repeated exposure to a chemical can induce an allergic response upon contact will be evaluated in DfE's sensitization criteria. Both dermal and respiratory sensitization will be considered. Chemical hazard designations will be made based upon the criteria in Table 9 which were derived from the GHS guidance values [7]. The GHS criteria for categorizing chemicals as Category 1A or 1B is given in Tables 10 and 11 respectively. For Respiratory Sensitization, designations of High, Moderate, and Low will not be used. Instead, a qualitative assessment of the available data will be prepared.

Table 9. Sensitization Criteria for Hazard Designations

Sensitization	High	Moderate	Low
Skin Sensitization	High frequency of sensitization in humans and/or high potency in animals (GHS Cat. 1A)	Low to moderate frequency of sensitization in human and/or low to moderate potency in animals (GHS Cat. 1B)	Adequate data available and not GHS Cat. 1A or 1B
Respiratory Sensitization	For this endpoint, High/Moderate/Low etc. characterizations will not apply. A qualitative assessment of the available data will be prepared.		

Table 10. GHS Sensitization Criteria for **High** Hazard Designation

Assay	GHS Category 1A Criteria
Local lymph node assay	EC3 value \leq 2%
Guinea pig maximization test	\geq 30% responding at \leq 0.1% intradermal induction dose <u>or</u> \geq 60% responding at $>$ 0.1% to \leq 1% intradermal induction dose
Buehler assay	\geq 15% responding at \leq 0.2% topical induction dose <u>or</u> \geq 60% responding at $>$ 0.2% to \leq 20% topical induction dose

Table 11. GHS Sensitization Criteria for **Moderate** Hazard Designation

Assay	GHS Category 1B Criteria
Local lymph node assay	EC3 value $>$ 2%
Guinea pig maximization test	\geq 30% to $<$ 60% responding at $>$ 0.1% to \leq 1% intradermal induction dose <u>or</u> \geq 30% responding at $>$ 1% dermal induction dose
Buehler assay	\geq 15% to $<$ 60% responding at $>$ 0.2% to \leq 20% topical induction dose <u>or</u> \geq 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 12. These criteria were derived from the OPP Acute Toxicity Categories [24].

Table 12. 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 lowest observed effect concentration (LOEC) for chronic aquatic toxicity. The criteria used for making chemical hazard designations are shown in Table 13. These values were derived from the EPA Office of Pollution Prevention and Toxics’ (OPPT’s) New Chemicals Program [25] and OPPT’s criteria for HPV chemical categorization [22].

Table 13. 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 (LOEC) (mg/L)	< 0.1	0.1 - 1	> 1 - 10	> 10

4.2.2. Environmental Persistence

Persistence designations will be based on ultimate degradation. In the absence of data on ultimate degradation, DfE will evaluate data on primary degradation of the compound and consider the potential for degradation products of concern. 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.

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 [26]. Persistence designations will be made based upon the criteria in Table 14. These values were derived from OPPT’s New Chemicals Program and the DfE Master Criteria, and reflect OPPT policy on PBTs [27-29]. 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 14. 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.* No degradation products of concern.	Passes Ready Biodegradability test with 10-day window.* No degradation products of concern.
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 [30-32].

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 15. These criteria were derived from OPPT’s New Chemicals Program [27], and Arnot & Gobas 2006 [4].

Table 15. Criteria for Bioaccumulation Designations

Bioaccumulation	Very High	High	Moderate	Low
Bioaccumulation (BAF / BCF)	> 100,000	100,000 – 1,000	1,000 – 100	< 100

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 15.
- 2) If there are measured log BCF or log BAF values <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. If there are several measured values which all support a designation of low bioaccumulation potential, then the chemical will be designated as such.

When experimental BAF or BCF data are not available:

- 1) If there are no measured BCF or BAF values, consider the octanol-water (K_{ow}) and octanol-air (K_{oa}) partition coefficients. If a chemical has $\log K_{ow} <2$ and $\log K_{oa} <5$, it is given a low designation for bioaccumulation [ref Gobas 2006]; an estimated BAF or BCF is not needed. If no measured K_{ow} and K_{oa} 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 $\log K_{ow}$ and $\log K_{oa}$ 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 15.

5. 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.

5.1. Acute Mammalian Toxicity – Test Methods

- OPPTS Harmonized Guideline 870.1100: Acute oral toxicity [33]
- OPPTS Harmonized Guideline 870.1200: Acute dermal toxicity [34]
- OPPTS Harmonized Guideline 870.1300: Acute inhalation toxicity [35]
- OECD Test Guideline 420: Acute Oral Toxicity-Fixed Dose Method [36]
- OECD Test Guideline 423: Acute Oral Toxicity – Acute Toxic Class Method [37]
- OECD Test Guideline 425: Acute Oral Toxicity – Up-and-Down Procedure [38]
- OECD Test Guideline 402: Acute Dermal Toxicity [39]
- OECD Test Guideline 403: Acute Inhalation Toxicity [40]

5.1.1. Sources for Data Interpretation

- GHS Ch 3.1 Acute Toxicity [3]
- EU Dangerous Substances Directive, <http://ecb.jrc.ec.europa.eu/documentation/>. To access the list of substances carrying Risk Phrases, click on “CLASSIFICATION-LABELLING”, then “DIRECTIVE 67-548-EEC”, then “ANNEX I OF DIRECTIVE 67-548-EEC”, and then either of the files listed as: “Annex I of Directive 67548EEC” [41]

5.2. Carcinogenicity – Test Methods

- OECD Test Guideline 451: Carcinogenicity Studies [42]
- OECD Test Guideline 453: Combined Chronic Toxicity/Carcinogenicity Studies [43]
- OPPTS Harmonized Guidelines 870.4200: Carcinogenicity [44]
- OPPTS Harmonized Guidelines 870.4300: Combined chronic toxicity/carcinogenicity [45]
- 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” [46]

Alternative Test Methods for Carcinogenicity

- Modeled data from sources such as OncoLogic™ [47] are acceptable when data are unavailable.

5.2.1. Sources for Data Interpretation

- EU Dangerous Preparations Directive Article 6 and Annex II (1999/45/EC and subsequent updates/amendments) [48-50]
- EU Dangerous Substances Directive, <http://ecb.jrc.ec.europa.eu/documentation/>. To access the list of substances carrying Risk Phrases, click on “CLASSIFICATION-LABELLING”, then “DIRECTIVE 67-548-EEC”, then “ANNEX I OF DIRECTIVE 67-548-EEC”, and then either of the files listed as: “Annex I of Directive 67548EEC” [41]
- GHS Ch 3.6 Carcinogenicity [6]
- Section 2, Hazard Assessment in Guidelines for Carcinogen Risk Assessment http://oaspub.epa.gov/eims/eimscomm.getfile?p_download_id=439797 [51]
- Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens, available at: <http://cfpub.epa.gov/ncea/CFM/recordisplay.cfm?deid=160003> [52]

5.3. Genetic Toxicity – Test Methods

Per GHS [11], results from multiple, acceptable test methods must be used in conjunction for evaluation of genetic toxicity.

- OECD Test Guideline 471 (OPPTS 870.5100): Bacterial Reverse Mutation Test [53, 54]
- OECD Test Guideline 473 (OPPTS 870.5375): *In vitro* Mammalian Chromosome Aberration Test [55, 56]
- OECD Test Guideline 474 (OPPTS 870.5395): Mammalian Erythrocyte Micronucleus Test [57, 58]
- OECD Test Guideline 475 (OPPTS 870.5385): Mammalian Bone Marrow Chromosome Aberration Test [59, 60]
- OECD Test Guideline 476 (OPPTS 870.5300): *In vitro* Mammalian Cell Gene Mutation Test [61, 62]
- OECD Test Guideline 483 (OPPTS 870.5380): Mammalian Spermatogonial Chromosome Aberration Test [63, 64]
- OECD Test Guideline 486: Unscheduled DNA Synthesis (UDS) Test with Mammalian Liver Cells *in vivo* [65]. This guideline does **NOT** substitute in the necessary minimum set for either the gene mutation or the chromosome aberration test.

5.3.1. Sources for Data Interpretation

- EU Dangerous Substances Directive, <http://ecb.jrc.ec.europa.eu/documentation/>. To access the list of substances carrying Risk Phrases, click on “CLASSIFICATION-LABELLING”, then “DIRECTIVE 67-548-EEC”, then “ANNEX I OF DIRECTIVE 67-548-EEC”, and then either of the files listed as: “Annex I of Directive 67548EEC” [41]

- EU Dangerous Preparations Directive Article 6 and Annex II (1999/45/EC and subsequent updates/amendments) [48-50]
- GHS Ch 3.5 Germ Cell Mutagenicity [11]

5.4. Neurotoxicity – Test Methods

- OECD Test Guideline 424: Neurotoxicity Study in Rodents [66]
- OPPTS Harmonized Guideline 870.6200: Neurotoxicity screening battery [67]
- OECD Test Guideline 426: Developmental Neurotoxicity Study [68]
- OPPTS Harmonized Guideline: 870.6300 Developmental neurotoxicity study [69]

5.4.1. Sources for Data Interpretation

- Section 3, Hazard Characterization in *Guidelines for Neurotoxicity Risk Assessment* [12]
- GHS Ch. 3.9 Specific Target Organ Toxicity Repeated Exposure [23]

5.5. Repeated Dose Toxicity – Test Methods

- OECD Test Guideline 408: Repeated Dose 90-Day Oral Toxicity Study in Rodents [70]
- OECD Test Guideline 409: Repeated Dose 90-Day Oral Toxicity Study in Non-Rodents [71]
- OECD Test Guideline 411: Subchronic Dermal Toxicity: 90-day Study [72]
- OECD Test Guideline 413: Subchronic Inhalation Toxicity: 90-day Study [73]
- OPPTS Harmonized Guideline 870.3100: 90-Day oral toxicity in rodents [74]
- OPPTS Harmonized Guideline 870.3150: 90-Day oral toxicity in nonrodents [75]
- OPPTS Harmonized Guideline 870.3250: 90-Day dermal toxicity [76]
- OPPTS Harmonized Guideline 870.3465: 90-Day inhalation toxicity [77]
- OECD Test Guideline 407: Repeated Dose 28-day Oral Toxicity Study in Rodents [78]
- OECD Test Guideline 410: Repeated Dose Dermal Toxicity: 28-day Study [79]
- OECD Test Guideline 412: Repeated Dose Inhalation Toxicity: 28-day Study [80]
- OECD Test Guideline 422: Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test [81]
- OPPTS Harmonized Guideline 870.3050: Repeated dose 28-day oral toxicity study in rodents [82]
- OPPTS Harmonized Guideline 870.3200: 28-Day dermal toxicity [83]

5.5.1. Sources for Data Interpretation

- GHS Ch 3.9 Specific Target Organ Toxicity Repeated Exposure [23]

5.6. Reproductive and Developmental Toxicity – Test Methods

Fertility Test Methods

- OECD Test Guideline 415: One-Generation Reproduction Toxicity Study [84]
- OECD Test Guideline 416: Two-Generation Reproduction Toxicity Study [85]
- OPPTS Harmonized Guideline 870.3800: Reproduction and fertility effects [86]
- OECD Test Guideline 421: Reproduction/Developmental Toxicity Screening Test [87]
- OECD Test Guideline 422: Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test [81]
- OPPTS Harmonized Guideline 870.3550: Reproduction/developmental toxicity screening test [88]
- OPPTS Harmonized Guideline 870.3650: Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test [89]

Developmental Toxicity Test Methods

- OECD Test Guideline 414: Prenatal Developmental Toxicity Study [90]
- OPPTS Harmonized Guideline 870.3800: Reproduction and fertility effects [86]
- OECD Test Guideline 421: Reproduction/Developmental Toxicity Screening Test [87]
- OECD Test Guideline 422: Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test [81]
- OPPTS Harmonized Guideline 870.3550: Reproduction/developmental toxicity screening test [88]
- OPPTS Harmonized Guideline 870.3650: Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test [89]

5.6.1. Sources for Data Interpretation

- EU Dangerous Substances Directive, <http://ecb.jrc.ec.europa.eu/documentation/>. To access the list of substances carrying Risk Phrases, click on “CLASSIFICATION-LABELLING”, then “DIRECTIVE 67-548-EEC”, then “ANNEX I OF DIRECTIVE 67-548-EEC”, and then either of the files listed as: “Annex I of Directive 67548EEC” [41]
- EU Dangerous Preparations Directive Article 6 and Annex II (1999/45/EC and subsequent updates/amendments) [48-50]
- GHS Ch 3.7 Reproductive Toxicity [91]
- Part A, Section 3, Hazard Characterization in *Guidelines for Reproductive Toxicity Risk Assessment*, <http://www.epa.gov/ncea/raf/pdfs/repro51.pdf> [14]
- Part A, Section 3, Hazard Characterization in *Guidelines for Developmental Toxicity Risk Assessment*, <http://www.epa.gov/NCEA/raf/pdfs/devtox.pdf> [8]

5.7. Skin Sensitization – Test Methods

- OECD Test Guideline 406: Skin Sensitization [92]
- OECD Test Guideline 429: Skin Sensitization: Local Lymph Node Assay [10]
- OPPTS Harmonized Guideline 870.2600: Skin Sensitization [93]

5.7.1. Sources for Data Interpretation

- EU Dangerous Substances Directive, <http://ecb.jrc.ec.europa.eu/documentation/>. To access the list of substances carrying Risk Phrases, click on “CLASSIFICATION-LABELLING”, then “DIRECTIVE 67-548-EEC”, then “ANNEX I OF DIRECTIVE 67-548-EEC”, and then either of the files listed as: “Annex I of Directive 67548EEC” [41]
- EU Dangerous Preparations Directive Article 6 and Annex II (1999/45/EC and subsequent updates/amendments) [48-50]
- GHS Ch 3.4 Respiratory and Skin Sensitization [7]

5.8. Acute Aquatic Toxicity

Test Methods for Fish

- OECD Test Guideline 203: Fish, Acute Toxicity Test [94]
- OPPTS Harmonized Guideline 850.1075: Fish acute toxicity test, freshwater and marine [95]

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.

Test Methods for Aquatic Invertebrates

- OECD Test Guideline 202, Part 1, Daphnia sp., Acute Immobilisation Test [96]
- OPPTS Harmonized Guideline 850.1010: Aquatic invertebrate acute toxicity test, freshwater daphnids [97]
- OPPTS Harmonized Guideline 850.1035: Mysid acute toxicity test[98]

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.

Test Methods for Algae

- OECD Test Guideline 201, Alga, Growth Inhibition Test (and biomass) [99]
- OPPTS Harmonized Guideline 850.5400: Algal toxicity, Tiers I and II (including growth inhibition and biomass) [100]

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 [101]
- OPPTS Harmonized Guideline 850.1025: Oyster acute toxicity test (shell deposition) [102]
- OPPTS Harmonized Guideline 850.1045: Penaeid acute toxicity test [103]
- OPPTS Harmonized Guideline 850.1055: Bivalve acute toxicity test (embryo larval) [104]
- OPPTS Harmonized Guideline 850.4400: Aquatic plant toxicity test using *Lemna spp.* Tiers I and II [105]
- Modeled data from sources such as EPI Suite™ [19] are acceptable when data are unavailable.

5.8.1. Sources for Data Interpretation

- U.S. EPA Design for the Environment Program Master Criteria for Safer Ingredients [28]
- U.S. EPA EPI Suite™ [19]

5.9. Persistence

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) [30]
- OECD Test Guideline 310: Ready Biodegradability – CO₂ in sealed vessels [31]
- OPPTS Harmonized Guideline 835.3110: Ready biodegradability [106]
- 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) [107-109], then the half-life of a chemical is likely to be less than 60 days [110].
- OECD Test Guideline 303A (OPPTS 835.3240): Aerobic Sewage Treatment: Activated Sludge Units [111, 112]
- OECD Test Guideline 309 (OPPTS Harmonized Guideline 835.3190): Aerobic Mineralization in Surface Water - Simulation Biodegradation Test [113, 114]
- 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) [115]

- OPPTS Harmonized Guideline 835.3280–Simulation Tests to Assess the Primary and Ultimate Biodegradability of Chemicals Discharged to Wastewater [116]
- OPPTS Harmonized Guideline 835.3170 - Shake Flask Die-Away Test [117]
- OPPTS Harmonized Guideline 835.3180 - Sediment/Water Microcosm Biodegradation Test [118]

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.

5.9.1. Sources for Data Interpretation

- U.S. EPA Design for the Environment Program Master Criteria for Safer Ingredients [28]
- U.S. EPA EPI Suite™ [19]
- SPARC [26]
- Revised Introduction to the OECD Guidelines for Testing of Chemicals, Section 3 [119]
- OPPTS 835.0001 Principles and Strategies Related to Biodegradation Testing of Organic Chemicals under the Toxic Substances Control Act (TSCA) [120]

5.10. Bioaccumulation

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 [121]
- OPPTS Harmonized Guideline 850.1710: Oyster BCF [122]
- OPPTS Harmonized Guideline 850.1730: Fish BCF [123]
- Modeled data from sources such as EPI Suite™ [19] are acceptable when data are unavailable.

5.10.1. Sources for Data Interpretation

- U.S. EPA Design for the Environment Program Master Criteria for Safer Ingredients [28]
- U.S. EPA EPI Suite™ [19]
- SPARC [26]

6. Appendix

Table A1. Alternatives Assessment Criteria Quick Reference

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		High	Moderate	Low	
		Positive results	Equivocal results	Negative studies and no structural alerts	
Mutagenicity/Genotoxicity		High	Moderate	Low	
		Positive results	Equivocal results	Negative for chromosomal aberrations and gene mutations, and no structural alerts. Adequate data available.	
Reproductive and Developmental Toxicity		High	Moderate	Low	
Oral (mg/kg/day)		< 50	50 - 250	> 250	
Dermal (mg/kg/day)		< 100	100 - 500	> 500	
Inhalation (vapor, gas, mg/L/day)		< 1	1 - 2.5	> 2.5	
Inhalation (dust/mist/fume, mg/L/day)		< 0.1	0.1 - 0.5	> 0.5	
Neurotoxicity		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		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 Cat. 1A)	Low to moderate frequency of sensitization in human and/or low to moderate potency in animals (GHS Cat. 1B)	Adequate data available and not GHS Cat. 1A or 1B	
Respiratory Sensitization	For this endpoint, High/Moderate/Low etc. characterizations will not apply. A qualitative assessment of available data will be prepared.				
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. A qualitative assessment of available data will be prepared.				
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. No degradation products of concern.	Passes Ready Biodegradability test with 10-day window. No degradation products of concern.
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	
	> 100,000	100,000 – 1,000	1,000 – 100	< 100	

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