



DfE Screen for Fragrances Human Health Criteria

1 Introduction

The DfE Screen for Fragrances was developed by the Environmental Protection Agency's Design for Environment (DfE) Program and a group of stakeholders that included the fragrance industry, cleaning product formulators, environmental non-governmental organizations, and others. This screen is designed to identify safer aroma chemicals and fragrance formulations for use in cleaning products. The contents of this screen, including definitions and toxicological preferences, were developed to facilitate use of safer chemistry under the DfE Program.

The DfE Screen for Fragrances applies to fragrances used in the following types of cleaning products: all purpose cleaners, carpet care products, machine warewash detergents, dishwash detergents, floor care products, manual dishwash detergents, hard surface cleaners, washroom cleaners, hand soaps (non-FDA regulated) and laundry detergents. Product categories that are outside the scope of this screen include air fresheners, hand soaps (those regulated by FDA), and personal care products such as lotions.

Fragrances are complex mixtures of fragrance raw materials used for the primary purpose of imparting a scent and/or masking base odor. For the purpose of this screen, a fragrance raw material is any substance, obtained by chemical synthesis or derived from a natural source.

Evaluation under the screen considers all components of a fragrance formulation. All non-aroma fragrance raw materials must meet the DfE Screen for their ingredient class (i.e. solvents must meet the DfE Screen for Safer Solvents).

More than 2,000 chemical substances with diverse chemical structures, and therefore diverse human and environmental health profiles, are used in formulation by the fragrance industry. To identify safer chemicals for this diverse set of raw materials, a range of human health endpoints serve as the basis for screening out fragrance raw materials of high concern. A fragrance must meet all the criteria for each human health endpoint in order to pass the screen.

The screening criteria for the human health endpoints in the screen apply to all chemicals present in the fragrance at or above 0.01 percent by weight. DfE's 0.01% threshold reflects a stakeholder-agreed and conservative approach to screening fragrances.

EPA may choose to perform an in-depth review of a fragrance chemical or compound under certain conditions. For example, in cases involving conflicting data, EPA would rely on GHS criteria. An example of another situation that may trigger an in-depth review includes chemicals that are detected via biomonitoring studies.

For any fragrance raw material (chemical component) that is subject to EPA or OECD formal chemical evaluation efforts and for which a screening-level hazard characterization has been developed, that hazard characterization will serve as the primary basis for evaluation under the fragrance screen. Details on how EPA develops screening-level hazard characterizations can be found at: <http://www.epa.gov/champ/>. Data not previously located for EPA or OECD formal chemical evaluation efforts may also be evaluated.

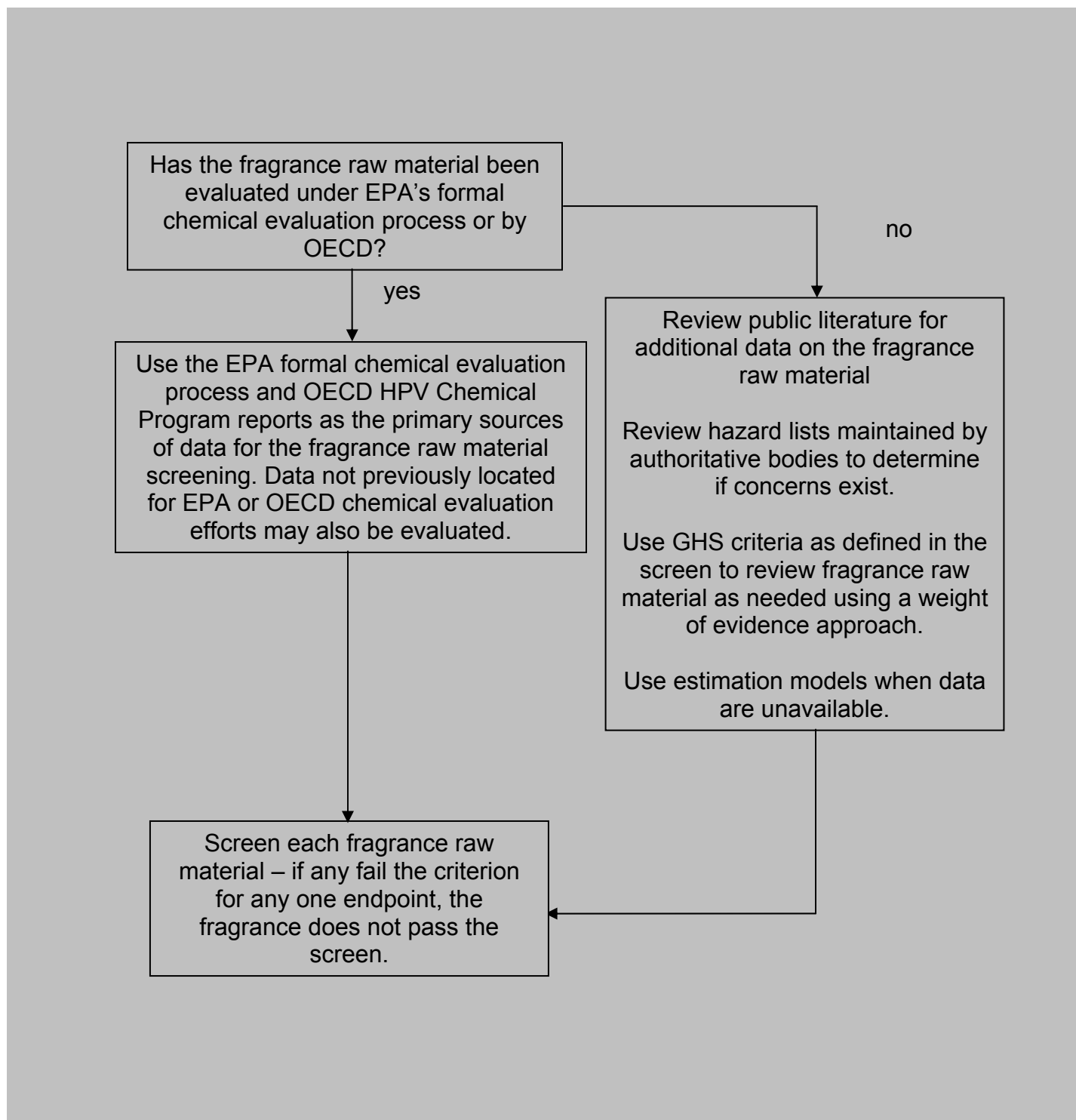
The DfE Screen for Fragrances is a pragmatic, customized approach that uses hazard-based lists, combined with literature review, modeling, and expert judgment. It is appropriately different from methods typically used by EPA to evaluate chemicals in regulatory programs conducted under the Toxic Substances Control Act (TSCA). Two factors make the DfE approach appropriate for screening fragrance materials. First, the screen will be used to evaluate fragrances that typically contain large numbers of raw materials in such small quantities that they are not reviewed under ecolabeling programs. Second, the intent in developing the fragrances screen is to provide a practical, cost-effective tool for moving the chemical components of fragrances towards safer substitutes. While the approach is streamlined, where concern exists for chemicals the intent is to understand and account for that concern. EPA will consider all sources of developing information, including enhancements to estimation models such as EPI Suite™ that occur over time, the Nanomaterials Stewardship Program, and the EPA Endocrine Disruptor Screening Program.¹

Reviews under this screen will be conducted by qualified third-parties. Reviewers will consult relevant sources and supporting documents that describe the derivation and scope of the classification criteria for the different endpoints to ensure consistent use of the information. Third-party reviewers will use credible data, and use the supporting documents referenced in the DfE Screen for Fragrances: Human Health Criteria to conduct reviews under this screen. Every subsection in Section 5 of this screen includes references for data interpretation. The third-party reviewer will proceed with the screening process as described below and as is illustrated in Diagram 1 below:

1. If the ingredient has been evaluated under EPA or OECD formal evaluation efforts, the resulting characterization(s) shall be the primary source of information for screening. Data not previously located for EPA or OECD chemical evaluation efforts may also be evaluated; and
2. If an EPA or OECD assessment is not available, the third-party reviewer will proceed with the chemical screening as described in this document.

¹ “The Agency does not consider endocrine disruption to be an adverse endpoint per se, but as a step that could lead to toxic outcomes, such as cancer or adverse reproductive effects....”[1. USEPA, *Special Report on Environmental Endocrine Disruption: An Effects Assessment and Analysis.*, in *Risk Assessment Forum*. 1997: Washington DC.

Diagram 1: Data Evaluation Process



2 General Requirements

- 2.1 The manufacturer shall fully disclose the fragrance formulation, including all raw materials (either individual chemicals or essential oils) intentionally added or present at a level of 0.01 percent by weight or higher.
- 2.2 The reviewer shall use the [European Flavour and Fragrance Association \(FFA\) Code of Practice/Labeling Manual](http://www.ffa.be/cop_2008.htm) to identify components of essential oils that are potential concerns and therefore must be screened (http://www.ffa.be/cop_2008.htm).
- 2.3 Fragrances must meet the International Fragrance Association (IFRA) Standards. The cleaning product manufacturer shall demonstrate compliance by supplying a written letter from all suppliers.

3 Terms

- 3.1 **Acute aquatic toxicity** is the intrinsic property of a substance to be injurious to an organism in a short-term exposure to that substance. (GHS)
- 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. (GHS)
- 3.3 **Attribute:** The general property of the fragrance or raw material that is being evaluated (i.e. acute mammalian toxicity, biodegradability).
- 3.4 **Auxiliary fragrance raw material:** Any ingredient in the fragrance whose primary function is something other than to impart a scent. For the purposes of this screen, this may include solvents, surfactants, chelating agents, and anti-oxidants.
- 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, i.e., 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. [2]
- 3.6 **Biodegradation** is a process in which the destruction of the chemical is accomplished by the action of a living organism. (Handbook of Property Estimation Methods for Chemicals, 2000)
- 3.7 **Carcinogen** denotes a chemical substance or mixture of chemical substances which induces cancer or increases its incidence. (GHS)
- 3.8 **Chronic aquatic toxicity** is the potential or actual properties of a substance to cause adverse effects to aquatic organisms during exposures which are determined in relation to the life cycle of the organism. (GHS)
- 3.9 A **component of an essential oil** is defined as a chemical constituent of the essential oil present in the fragrance at greater than 0.01 weight %.
- 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 Degradation products of concern** are chemicals formed from degradation of fragrance chemicals with high acute aquatic toxicity ($L/E/IC_{50} \leq 10\text{ppm}$) and which mineralize $<60\%$ in 28 days.
- 3.12 Dermal sensitizer:** A substance that will induce an allergic response following skin contact (GHS)
- 3.13 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. (EPA Risk Assessment Guidelines)
- 3.14 Fragrance (or fragrance finished product):** A complex mixture of fragrance raw materials for use in a cleaning product for the primary purpose of imparting a scent and/or masking base odor.
- 3.15 Fragrance compound:** A blend of fragrance ingredients, representing a specific fragrance formula. (IFRA Code of Practice)
- 3.16 Fragrance raw material:** Any substance, obtained by chemical synthesis or derived from a natural source, intentionally added or present in a fragrance at greater than 0.01 percent by weight whose primary purpose is to impart scent. In the context of this screen, fragrance raw materials include aroma chemicals, fragrant extracts (essential oils), and components of essential oils.
- 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. (GHS)
- 3.18 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. (GHS)
- 3.19 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. (US EPA Risk Assessment Guidelines)
- 3.20 Persistence:** A chemical's persistence refers to the length of time the chemical can exist in the environment before being destroyed (i.e., transformed) by natural processes. (EPA PBT Final Rule)
- 3.21 Photo sensitizer:** A substance that will lead to an allergic response following skin contact under the influence of light exposure.
- 3.22 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. (US EPA Risk Assessment Guidelines)

- 3.23 Respiratory sensitizer:** A substance that will induce hypersensitivity of the airways following inhalation of the substance. (GHS)
- 3.24 System toxicity/organ effects repeated exposure:** Substances that produce specific target organ/systemic toxicity arising from a repeated exposure. All significant health effects that can impair function, both reversible and irreversible, immediate and/or delayed are included. (GHS)

4 Preferences

- 4.1** When data are developed specifically for review under this screen, data collected from dermal and inhalation exposure routes are preferred over oral exposure data because the former are more likely routes of exposure for cleaning products. When data are developed for repeated dose toxicity, EPA requests that a functional observational battery be added to the test method to provide neurotoxicity information.
- 4.2** The GHS criteria and data evaluation approach and EPA risk assessment guidance will inform professional judgment in the review of both NOAEL and LOAEL values. NOAEL and LOAEL values are preferred to no observed effect levels and lowest observed effect levels. In reviews that include conflicting data, a weight of evidence approach will determine a pass or fail.
- 4.3** Measured data and analogs will be preferred over estimation models. Acceptable 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. Estimation models may supplement data evaluation as part of weight of evidence.
- 4.4** 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>.
- 4.5** The links and references in this document are current as of the publication date of this screen. The reviewer must use the most recent version of each authoritative list, all data interpretation guidance, and each test protocol when reviewing fragrances against this screen. In the case where a link or reference in this document is superseded by a more recent version, the more recent version must be used.

5 Attributes of Concern for all Fragrances

All fragrance raw materials present at 100 ppm (or 0.01 percent by weight) or greater in the fragrance will be screened using the criteria described below.

5.1 ACUTE MAMMALIAN TOXICITY

5.1.1 Criteria and Data Evaluation

To be acceptable under the screen, fragrance raw materials must have a median lethal dose or concentration greater than those values listed in Table 1. Fragrance raw materials shall be evaluated for acute mammalian toxicity based on test data or weight of evidence from literature review, analogs, models and professional judgment. Acute mammalian toxicity will be evaluated for all routes of exposure where data are available. Data must be available on at least one route of exposure for each fragrance raw material. Failure to pass this endpoint by any route of exposure results in failure to pass the screen.

Table 1 – Acute Mammalian Toxicity

| Route of Exposure | Median Lethal Dose/Concentration |
|---|---|
| Oral LD50 (mg/kg bw) | >50 |
| Dermal LD50 (mg/kg bw) | >200 |
| Inhalation, gas LC50 (ppmV) | >500 |
| Inhalation, vapor LC50 (mg/L) | >2.0 |
| Inhalation, dust/mist/fumes LC50 (mg/L) | >0.5 |

5.1.2 Supporting Information

The following EU Risk Phrases [3] can be used to streamline the evaluation of fragrance raw materials for acute mammalian toxicity:

- R20 “Harmful by inhalation”;
- R21 “Harmful in contact with skin”;
- R22 “Harmful if swallowed”;
- R23 “Toxic by inhalation”;
- R24 “Toxic in contact with skin”;
- R25 “Toxic if swallowed”;
- R26 “Very toxic by inhalation”;
- R27 “Very toxic in contact with skin”;
- R28 “Very toxic if swallowed”; and
- All combinations of risk phrases containing one or more of the above.

5.1.3 Test Methods for GHS Review

- OPPTS Harmonized Guideline 870.1100: Acute oral toxicity [4];
- OPPTS Harmonized Guideline 870.1200: Acute dermal toxicity [5];
- OPPTS Harmonized Guideline 870.1300: Acute inhalation toxicity [6];
- OECD Test Guideline 420: Acute Oral Toxicity-Fixed Dose Method [7];
- OECD Test Guideline 423: Acute Oral Toxicity – Acute Toxic Class Method [8];
- OECD Test Guideline 425: Acute Oral Toxicity – Up-and-Down Procedure [9];
- OECD Test Guideline 402: Acute Dermal Toxicity [10]; and
- OECD Test Guideline 403: Acute Inhalation Toxicity [11].

5.1.4 Data Interpretation

For additional information, see GHS Ch 3.1 Acute Toxicity [12].

5.2 CARCINOGENICITY

5.2.1 Criteria and Data Evaluation

Fragrance raw materials considered carcinogens by one of the authoritative bodies in Table 2 do not pass the screen.

Table 2 – Carcinogens

| Authoritative Body | Criteria that will not pass the DfE Screen |
|---|--|
| 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 [3] | Category 1 – Known Category 2 – Should be considered carcinogenic to humans Category 3 – Possible carcinogenic effects |
| EU Risk Phrases ^a [3] | R45: “May cause cancer” R49: “May cause cancer by inhalation” R40: “Limited evidence of a carcinogenic effect” |
| ^a Any combination containing one or more of the risk phrases above shall also not pass the screen. | |

5.2.2 Supplemental Criteria: GHS Review

In the case where carcinogenicity data have not been reviewed by IARC, NTP, EPA, or by the EU in the context of the CMR list and R-phrases, a supplemental assessment may be performed. When a supplemental assessment is performed, GHS criteria will be used to review all available data. Additionally, if a fragrance raw material appears on the list of substances prioritized for testing for endocrine disruption by the European Commission [13, 14], the raw material will be screened against GHS criteria using test data or weight of evidence. Components not on the established lists in Table 2, but that are considered known or presumed human carcinogens (Category 1), or suspected human carcinogens (Category 2) under GHS [15], will not pass the screen.

5.2.3 Test Methods for GHS Review

- OECD Test Guideline 451: Carcinogenicity Studies [16];
- OECD Test Guideline 453: Combined Chronic Toxicity/Carcinogenicity Studies [17];
- OPPTS Harmonized Guidelines 870.4200: Carcinogenicity [18];
- OPPTS Harmonized Guidelines 870.4300: Combined chronic toxicity/carcinogenicity [19] and
- 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” [20].

5.2.4 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”. [21];
- EU Dangerous Preparations Directive Article 6 and Annex II (1999/45/EC and subsequent updates/amendments) [22-24];
- GHS Ch 3.6 Carcinogenicity [15];

- Section 2, Hazard Assessment in Guidelines for Carcinogen Risk Assessment (Risk Assessment Forum) (EPA 2005), http://oaspub.epa.gov/eims/eimscomm.getfile?p_download_id=439797 [25] and
- The following link can be used to identify substances prioritized for testing for endocrine disruption by the European Commission: http://ec.europa.eu/environment/endocrine/strategy/substances_en.htm#priority_list. To download the list of substances, see the zipped file under the heading “Priority List” [13].
- The following report describes the process used to develop the endocrine disrupters priority list: http://ec.europa.eu/environment/endocrine/documents/final_report_2007.pdf [14].

5.3 **GENETIC TOXICITY**

5.3.1 **Criteria and Data Evaluation**

Fragrance raw materials considered mutagens or genetic toxicants by authoritative bodies in Table 4 do not pass the screen. Additional requirements may also apply, based on test data and weight of evidence.

Table 3 – Mutagenicity and Genetic Toxicity

| Authoritative Body | Criteria that will not pass the DfE Screen |
|---|---|
| EU CMR List [3] | Category 1 – “Substances known to be mutagenic to man” Category 2 – “Substances which should be regarded as if they are mutagenic to man” Category 3 – “Substances which cause concern for man owing to possible mutagenic effects” |
| EU Risk Phrases [3] | R46: “May cause heritable genetic damage” ^a R68: “Possible risk of irreversible effects” |
| ^a Any combination containing R46 shall also not pass the screen. | |

5.3.2 **Supplemental Criteria: GHS Review**

In the case where mutagenicity or genetic toxicity data have not been reviewed by the EU in the context of the CMR list or R-phrases, a supplemental assessment may be performed. When a supplemental assessment is performed, GHS criteria will be used to review all available data. Components not on the established lists in Table 3, but that are known to induce heritable mutations in germ cells (Category 1A), or should be regarded as if they induce heritable mutations in germ cells (Category 1B) or may induce heritable mutations in germ cells (Category 2) under GHS [15], will not pass the screen.

5.3.3 **Test Methods for GHS Review**

- OECD Test Guideline 478: Genetic Toxicology: Rodent Dominant Lethal Test [26];
- OECD Test Guideline 485: Genetic Toxicology, Mouse Heritable Translocation Assay [27];
- OECD Test Guideline 475: Mammalian Bone Marrow Chromosome Aberration Test [28];
- OECD Test Guideline 484: Genetic Toxicology: Mouse Spot Test [29];
- OECD Test Guideline 474: Mammalian Erythrocyte Micronucleus Test [30];
- OECD Test Guideline 483: Mammalian Spermatogonial Chromosome Aberration Test [31];
- OECD Test Guideline 486: Unscheduled DNA Synthesis (UDS) Test with Mammalian Liver Cells *in vivo* [32];
- OECD Test Guideline 473: *In vitro* Mammalian Chromosome Aberration Test [33];
- OECD Test Guideline 476: *In vitro* Mammalian Cell Gene Mutation Test [34]; and
- OECD Test Guideline 471: Bacterial Reverse Mutation Test [35].
- OECD Test Guideline 479: Genetic Toxicology: *In Vitro* Sister Chromatid Exchange Assay in Mammalian Cells [36]

- OPPTS Harmonized Guideline 870.5100: Bacterial reverse mutation test [37]
- OPPTS Harmonized Guideline 870.5375: In vitro mammalian chromosome aberration test [38]
- OPPTS Harmonized Guideline 870.5300: In vitro mammalian cell gene mutation test [39]
- OPPTS Harmonized Guideline 870.5395: Mammalian erythrocyte micronucleus test [40]
- OPPTS Harmonized Guideline 870.5385: Mammalian bone marrow chromosomal aberration test [41]
- OPPTS Harmonized Guideline 870.5380: Mammalian spermatogonial chromosomal aberration test [42]

5.3.4. Data Interpretation

The following sources should be consulted for additional information:

- 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”. [21]
- EU Dangerous Preparations Directive Article 6 and Annex II (1999/45/EC and subsequent updates/amendments) [22-24]; and
- GHS Ch 3.5 Germ Cell Mutagenicity [43].

5.4 REPEATED DOSE AND NEUROTOXICITY

5.4.1 Criteria

If a fragrance contains one or more fragrance raw materials that are considered systemic or neurotoxicants per GHS, then the compound must be evaluated using the GHS criteria for mixtures [44, 45]. To pass the screen, the fragrance must not be considered a specific target organ toxicant by any route of exposure (i.e., no GHS Category 1 or Category 2 fragrances).

5.4.2 Data Evaluation: Review of Fragrance Raw Materials

Each fragrance raw material that is evaluated using GHS must be screened for general systemic toxicity/organ effects and neurotoxicity effects. If a fragrance raw material meets any of the conditions below, it must be reviewed based on GHS criteria, using test data or weight of evidence:

- Requiring at least one of the specified EU Risk Phrases [3]
 - R33 “Danger of cumulative effects” (repeated exposure)
 - R39 “Danger of very serious irreversible effects” (single exposure)
 - R48 “Danger of serious damage to health by prolonged exposure” (repeated exposure)
 - R68 “Possible risk of irreversible effects” (single exposure), or
- Having new data not yet incorporated into the EU Risk Phrases, or
- Appears on the list of substances prioritized for testing for endocrine disruption by the European Commission. [13, 14].

Table 5a – GHS Category 1 – Specific Target Organ Toxicity – Repeated Exposure

| Route of Exposure | Guidance values ¹ |
|---|------------------------------|
| Oral (mg/kg-bw/day) | < 10 |
| Dermal (mg/kg-bw/day) | < 20 |
| Inhalation (gas) (ppm/6h/day) | < 50 |
| Inhalation (vapor) (mg/L/6h/day) | < 0.2 |
| Inhalation (dust/mist/fume) (mg/L/6h/day) | < 0.02 |
| ¹ The doses provided are for 90-day studies. Guidance values are tripled for chemicals evaluated in 28-day studies and similarly modified for studies of longer durations. | |

Table 5b – GHS Category 2 – Specific Target Organ Toxicity – Repeated Exposure

| Route of Exposure | Guidance values ¹ |
|---|------------------------------|
| Oral (mg/kg-bw/day) | 10 -100 |
| Dermal (mg/kg-bw/day) | 20 - 200 |
| Inhalation (gas) (ppm/6h/day) | 50 - 250 |
| Inhalation (vapor) (mg/L/6h/day) | 0.2 - 1.0 |
| Inhalation (dust/mist/fume) (mg/L/6h/day) | 0.02 - 0.2 |
| ¹ The doses provided are for 90-day studies. Guidance values are tripled for chemicals evaluated in 28-day studies and similarly modified for studies of longer durations. | |

If one or more fragrance raw materials meet GHS criteria for Category 1 or Category 2 Specific Target Organ Toxicity – Repeated Exposure, then the fragrance must be evaluated per GHS mixture rules (see section 5.4.3).

5.4.3 Data Evaluation: Review of Fragrances

Fragrance raw materials that meet GHS criteria for Category 1 or Category 2 Specific Target Organ Toxicity – Repeated Exposure will be limited based on percentage as described by the GHS mixture rules. The GHS mixture rules (GHS section 3.9.3.4 – *Classification of mixtures when data are available for all components or only for some components of the mixture [45]*) will be applied. To pass the screen, the fragrance must not be considered a specific target organ toxicant by any route of exposure (i.e., no GHS Category 1 or Category 2 fragrances).

5.4.4 Test Methods for GHS Review, Preferred

- OECD Test Guideline 408: Repeated Dose 90-Day Oral Toxicity Study in Rodents [46];
- OECD Test Guideline 409: Repeated Dose 90-Day Oral Toxicity Study in Non-Rodents [47];
- OECD Test Guideline 411: Subchronic Dermal Toxicity: 90-day Study [48];
- OECD Test Guideline 413: Subchronic Inhalation Toxicity: 90-day Study [49];
- OPPTS Harmonized Guideline 870.3100: 90-Day oral toxicity in rodents [50];
- OPPTS Harmonized Guideline 870.3150: 90-Day oral toxicity in nonrodents [51];
- OPPTS Harmonized Guideline 870.3250: 90-Day dermal toxicity [52]; and
- OPPTS Harmonized Guideline 870.3465: 90-Day inhalation toxicity [53].

5.4.5 Test Methods for GHS Review, Acceptable

- OECD Test Guideline 412: Repeated Dose Inhalation Toxicity: 28-day [54];
- OECD Test Guideline 410: Repeated Dose Dermal Toxicity: 28-day Study [55];
- OECD Test Guideline 407: Repeated Dose 28-day Oral Toxicity Study in Rodents [56];

- OECD Test Guideline 422: Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test [57];
- OPPTS Harmonized Guideline 870.3050: Repeated dose 28-day oral toxicity study in rodents [58]; and
- OPPTS Harmonized Guideline 870.3200: 28-Day dermal toxicity [59];

5.4.6 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”. [21]
- EU Dangerous Preparations Directive Article 6 and Annex II (1999/45/EC and subsequent updates/amendments) [22-24]
- GHS Ch 3.9 Specific Target Organ Toxicity Repeated Exposure [45],
- The following link can be used to identify substances prioritized for testing for endocrine disruption by the European Commission:
http://ec.europa.eu/environment/endocrine/strategy/substances_en.htm#priority_list. To download the list of substances, see the zipped file under the heading “Priority List”. [13] [13]
- The following report describes the process used to develop the endocrine disrupters priority list: http://ec.europa.eu/environment/endocrine/documents/final_report_2007.pdf[14].

5.5 REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

5.5.1 Criteria and Data Evaluation

Fragrance raw materials considered reproductive or developmental toxicants by one of the authoritative bodies in Table 6a do not pass the screen.

Table 6a – Reproductive/Developmental Toxicity

| Authoritative Body | Criteria that will not pass the DfE Screen |
|---|--|
| EU CMR List [3] | Category 1: “known” to impair fertility in humans or cause developmental toxicity in humans” Category 2: “should be regarded as if” they impair fertility to humans or cause developmental toxicity to humans” Category 3 “cause concern for human fertility or to possible developmental toxic effects” |
| EU Risk Phrases ^a [3] | R60: “May impair fertility” R61: “May cause harm to the unborn child” R62: “Possible risk of impaired fertility” R63: “Possible risk of harm to the unborn child” R64: “May cause harm to breastfed babies” |
| ^a Any combination containing one or more of the risk phrases above shall also not pass the screen. | |

5.5.2 Supplemental Criteria: GHS Review

In the case where reproductive or developmental toxicity data have not been reviewed by the EU in the context of the CMR list or R-phrases, a supplemental assessment may be performed. When a supplemental assessment is performed, GHS criteria and the guidance values in Table 6b will be used to review all available data. Additionally, if a fragrance raw material appears on the list of substances

prioritized for testing for endocrine disruption by the European Commission [13, 14], the raw material will be screened against GHS criteria using test data or weight of evidence.

Table 6b – Reproductive/Developmental Toxicity

| Route of Exposure | Guidance Values |
|---|------------------------|
| Oral (mg/kg-bw/day) | >250 |
| Dermal (mg/kg-bw/day) | >200 |
| Inhalation (gas) (ppm/6h/day) | >250 |
| Inhalation (vapor) (mg/L/6h/day) | >1.0 |
| Inhalation (dust/mist) (mg/L/6h/day) | >0.2 |

5.5.3 Test Methods for GHS Review

5.5.3.1 Fertility test methods, preferred

- OECD Test Guideline 415: One-Generation Reproduction Toxicity Study [60] and
- OECD Test Guideline 416: Two-Generation Reproduction Toxicity Study [61].

5.5.3.2 Fertility test methods, acceptable

The following test methods may be used to identify reproductive toxicity, per GHS [62]:

- OPPTS Harmonized Guideline 870.3800: Reproduction and fertility effects [63];
- OECD Test Guideline 421: Reproduction/Developmental Toxicity Screening Test [64];
- OECD Test Guideline 422: Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test [57];
- OPPTS Harmonized Guideline 870.3550: Reproduction/developmental toxicity screening test [65]
- OPPTS Harmonized Guideline 870.3650: Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test [66].

5.5.3.3 Developmental toxicity test methods, preferred

- OECD Test Guideline 414: Prenatal Developmental Toxicity Study [67]

5.5.3.4 Developmental toxicity test methods, acceptable

The following test methods may be used to identify developmental toxicity, per GHS [62]:

- OPPTS Harmonized Guideline 870.3800: Reproduction and fertility effects [63];
- OECD Test Guideline 421: Reproduction/Developmental Toxicity Screening Test [64];
- OECD Test Guideline 422: Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test [57];
- OPPTS Harmonized Guideline 870.3550: Reproduction/developmental toxicity screening test [65]; and
- OPPTS Harmonized Guideline 870.3650: Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test [66].

5.5.4 Data Interpretation

The following sources should be consulted for additional information:

- 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”. [21];
- EU Dangerous Preparations Directive Article 6 and Annex II (1999/45/EC and subsequent updates/amendments) [22-24];
- GHS Ch 3.7 Reproductive Toxicity [62]
- Part A, Section 3, Hazard Characterization in *Guidelines for Reproductive Toxicity Risk Assessment* (EPA 1998), <http://www.epa.gov/ncea/raf/pdfs/repro51.pdf> [68].
- Part A, Section 3, Hazard Characterization in *Guidelines for Developmental Toxicity Risk Assessment* (EPA 1991), <http://www.epa.gov/NCEA/raf/pdfs/devtox.pdf> [69].
- The following link can be used to identify substances prioritized for testing for endocrine disruption by the European Commission:
http://ec.europa.eu/environment/endocrine/strategy/substances_en.htm#priority_list. To download the list of substances, see the zipped file under the heading “Priority List”. [13]
- The following report describes the process used to develop the endocrine disrupters priority list: http://ec.europa.eu/environment/endocrine/documents/final_report_2007.pdf [14].

5.6 PHOTO SENSITIZATION

No fragrance raw material considered a photo sensitizer according to the International Flavor & Fragrance Association Standards and Code of Practice (IFRA CoP, current amendment) [70] will pass the screen.

5.7 RESPIRATORY SENSITIZATION

5.7.1 Criteria and Data Evaluation

Although recognized animal models for the testing of respiratory hypersensitivity are not available at present, the following will be applied when models are available. Fragrance raw materials that carry the EU Risk Phrase R42: “May cause sensitization by inhalation” [3] do not pass the screen.

5.7.2 Supplemental Criteria: GHS Review

In the case where respiratory sensitization data have not been reviewed by the EU in the context of R-phrases, a supplemental assessment may be performed. When a supplemental assessment is performed, GHS criteria will be used to review all available data. Materials considered Category 1: “Respiratory Sensitizer” under GHS [71] do not pass the screen.

5.7.3 Data Interpretation

The following sources should be consulted for additional information:

- 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”. [21];
- EU Dangerous Preparations Directive Article 6 and Annex II (1999/45/EC and subsequent updates/amendments) [22-24]; and

- GHS Ch 3.4 Respiratory and Skin Sensitization [71].

5.8 **SKIN SENSITIZATION**

5.8.1 **Criteria**

Each fragrance raw material that is considered a dermal sensitizer under GHS may be present in the cleaning product formulation at a level no greater than 0.01 percent by weight. A fragrance raw material shall be considered a dermal sensitizer if it falls in one of the categories below. (When evaluating dermal sensitization, percutaneous dermal absorption is assumed to be 100%.)

- EU Risk Phrase R43: “May cause sensitization by skin contact” [3];
- EU 26 Allergens List, found at http://ec.europa.eu/enterprise/chemicals/legislation/detergents/legislation/allergenic_subst.pdf;
- International Flavor & Fragrance Association Standards and Code of Practice (IFRA CoP) [70]: Fragrance raw material is listed as a dermal sensitizer; or
- GHS Category 1: “Dermal Sensitizer” [71].

5.8.1.1 **Supplemental Criteria – Quantitative Risk Assessment (QRA) Thresholds**

From the Research Institute of Fragrance Materials Standards and Code of Practice, “no fragrance raw materials shall be present in the cleaning product above the QRA threshold specified for the fragrance raw material for the intended category of use [70].”

5.8.1.2 **Supplemental Criteria – *d*-Limonene**

When *d*-Limonene is used at a level above the threshold for sensitizers (0.01 percent by weight), it may be present because of its solvent properties. Where this is the case, the DfE screening approach treats *d*-Limonene as a solvent, and no longer considers this chemical under the DfE Screen for Fragrances.

The oxidation products of *d*-Limonene have tested positive for dermal sensitization but may be used in a DfE-recognized product in concentrations at which the potential oxidation products may be present at 20 millimoles per liter (mmol/L) or less (corresponding to a *d*-Limonene concentration of 1.36 % or less, as a percent by weight) in an overall formulation. Because of their high potential toxicity to aquatic organisms, *d*-Limonene should not be used in products that will be directly released to the environment. Also, products that contain *d*-Limonene should not also contain oxidizers, like hydrogen peroxide, which may accelerate the formation of *d*-Limonene oxidation products and harm product integrity.

5.8.2 **Test Methods for GHS Review**

- OPPTS Harmonized Guideline 870.2600: Skin Sensitization [72];
- OECD Test Guideline 406: Skin Sensitisation [73]; and
- OECD Test Guideline 429: Skin Sensitisation: Local Lymph Node Assay [74].

5.8.3 **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”. [21];
- EU Dangerous Preparations Directive Article 6 and Annex II (1999/45/EC and subsequent updates/amendments) [22-24];
- GHS Ch 3.4 Respiratory or Skin Sensitization [71];

- EU Cosmetics Directive 7th Amendment (76/768/EEC and subsequent updates/amendments) [75]; and
- International Flavor and Fragrance Association Standards and Code of Practice (43rd amendment) [70].

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