ACADEMIC PRESS

Available online at www.sciencedirect.com

SCIENCE DIRECT®

Regulatory Toxicology and Pharmacology 37 (2003) 218–273

Regulatory Toxicology and Pharmacology

www.elsevier.com/locate/yrtph

The safety assessment of fragrance materials

David R. Bickers,[a,*] Peter Calow,[b] Helmut A. Greim,[c] Jon M. Hanifin,[d] Adrianne E. Rogers,[e] Jean-Hilaire Saurat,[f] I. Glenn Sipes,[g] Robert L. Smith,[h] and Hachiro Tagami[i]

[a] *Columbia University, New York, NY, USA*
[b] *The University of Sheffield, Sheffield, England, UK*
[c] *Technical University, Munich, Germany*
[d] *Oregon Health Sciences University, Portland, OR, USA*
[e] *Boston University, Boston, MA, USA*
[f] *University of Geneva, Geneva, Switzerland*
[g] *University of Arizona, Tucson, AZ USA*
[h] *Imperial College, London, UK*
[i] *Tohoku University, Sendai, Japan*

Received 20 May 2002

Abstract

Safety evaluation of the large number of diverse chemicals used as fragrance ingredients follows a systematic prioritization of data generation and analysis, consideration of exposure and critical analysis of the quality of the available information. In prior publications the research priorities used by the Research Institute for Fragrance Materials (RIFM), and the methods of exposure estimation used by industry have been summarized. This paper provides details of the approach used by the RIFM Expert Panel (REXPAN), to examine the dermal effects, systemic toxicity and environmental consequences of the use of and exposure to fragrance materials, which allow a reliable determination of safe use under intended conditions. The key to the usefulness of this analysis is the grouping of more than 2600 discrete ingredients into classes, based on chemical structures. Research sponsored by RIFM, data supplied by member companies, and relevant published reports from many sources are all considered during hazard characterization. A discussion is provided of REXPAN's decision tree approach to assessing the dermal, systemic and environmental endpoints and the types and quality of data included. This overall process results in well-documented conclusions which are provided to the International Fragrance Association (IFRA) as the basis for consideration of a new or existing Fragrance Material Standard and to industry for appropriate product risk management actions.

1. Introduction

Fragrance materials are used in a wide variety of consumer products ranging from perfumes to skin products such as creams, lotions, detergents, and various other personal and household products. The potential for exposure to these materials in our society is, therefore, very high, particularly for those products that come into direct contact with the skin. It is essential to minimize the number of potential skin disorders linked to the use of fragrances including irritant dermatitis, dyschromia, allergic contact dermatitis, and photosensitivity (phototoxicity and photoallergy) associated with fragrances. A given fragrance product may contain 50–300 different ingredients, any one of which may give the product a certain esthetic and commercial "edge" that a given manufacturer will be anxious to protect. Since the details of ingredients and formulations are carefully guarded by each proprietary organization, the fragrance industry is often perceived as rather less than forthcoming by consumers and their physicians. The widespread use of fragrances in perfumery (Fenn, 1989) and the development of perfumes (Schreiber, 1996) have been described in detail.

* Corresponding author. Address: Research Institute for Fragrance Materials, Inc. (RIFM), 50 Tice Boulevard, Woodcliff Lake, NJ 07677, USA. Fax: 1-201-689-8088.

0273-2300/03/$ - see front matter © 2003 Elsevier Science (USA). All rights reserved.
doi:10.1016/S0273-2300(03)00003-5

In general, three areas are of concern: harmful effects of fragrance chemicals on the skin including irritant dermatitis, allergic contact dermatitis, phototoxicity, and photoallergy; toxic effects that might arise through transdermal absorption of the fragrance chemical; environmental consequences of fragrance chemicals in sewage and waste water from sewage treatment plants. In order to address these concerns in a systematic and responsible manner, the international fragrance industry established, in 1966, the science-based, not-for-profit Research Institute for Fragrance Materials (RIFM). The mission of the organization is to:

1. Engage in research and evaluation of fragrance materials through an independent Expert Panel.
2. Determine safety in use.
3. Gather, analyze, and publish scientific information.
4. Distribute scientific data and safety assessment judgments to RIFM members, industry associations and other interested parties.
5. Maintain an active dialogue with official international agencies.

At the time RIFM was established, its leadership elected to create an Expert Advisory Panel (hereafter referred to as the Panel) of scientists and physicians to guide and advise the Institute. Accordingly, the first meeting of the Panel took place at the Chemist's Club, New York City on July 7th 1967, chaired by a toxicologist, Dr. Bernard Oser. Since that time, the Panel, drawn from the United States, Europe and Asia, has continued to meet regularly three times per year. Two of the original Panel members, both dermatologists, Drs. Raymond R. Suskind and Donald J. Birmingham, served for 30 years, and they and their colleagues established the Panel's standards for independence and scientific validation of its decisions. Requirements for appointment to Panel membership include expertise in the fields of dermatology, toxicology, pathology, and/or environmental science; independence from the fragrance industry; and a research-based scientific background. The Panel periodically reviews its composition and identifies and elects new members and its chair. RIFM provides administrative support and sponsorship and day-to-day oversight of studies that have been requested by the Panel. See Opdyke (1984) for a historical perspective.

Recently, some changes in the data review and evaluation process have been made. These relate to the manner in which the Panel pursues its activities and provides results to industry for proper stewardship of its products. The entire process is summarized schematically in Fig. 1.

Outside experts and RIFM staff scientists provide consultation as needed. All information derived from the studies is maintained by RIFM in a database that currently includes 2665 fragrance materials, both natural and synthetic. This database contains relevant reports from RIFM and the fragrance industry, as well as

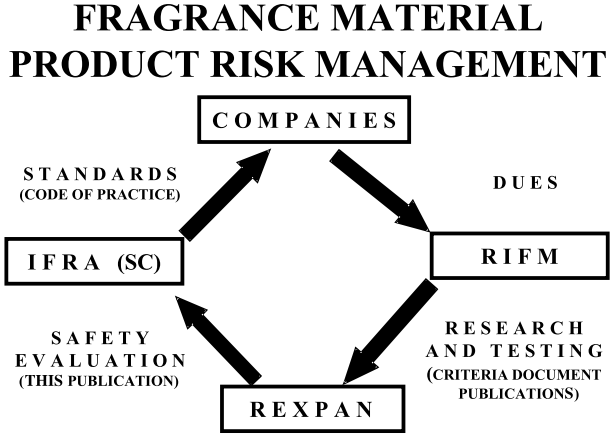


Fig. 1.

data from all pertinent published medical, toxicological and environmental literature (more than 39,000 references).

In its early years, the Panel gave priority to dermal safety issues and accordingly the majority of experts were dermatologists and/or scientists with expertise in skin toxicology. More recently, with the growing awareness of the potential for transdermal absorption and inhalation and ingestion of fragrance materials leading to systemic exposure and toxicity, it has become necessary to expand the Panel's focus. At present the Panel is multidisciplinary in nature with members having expertise in dermatology, pharmacokinetics, toxicokinetics, toxicology, pathology, and environmental science.

The purpose of this paper is to outline the principles and procedures used by the Panel to assess the safety of both existing and newly developed fragrance materials. The overall approach is described in four documents. The first is the method by which RIFM selects its human health research priorities, through a consideration of volume of use, structure activity and known toxic effects (Ford et al., 2000). A similar system is used to select environmental priorities through the use of predicted effect and no-effect concentrations (Salvito et al., 2002). Risk also is addressed by means of estimating exposure from the use of fragrance ingredients in cosmetic products (Cadby et al., 2002). This paper describes the process employed by the Panel to assess hazard and exposure, using chemical structure groupings to predict and evaluate effects, a decision tree approach to determining the adequacy of data for review, and a determination of safety under intended conditions of use.

2. Principles

RIFM's scientific process for data collection and evaluation is described in Fig. 2. Key to the initiation of any work is an exhaustive survey of the published and

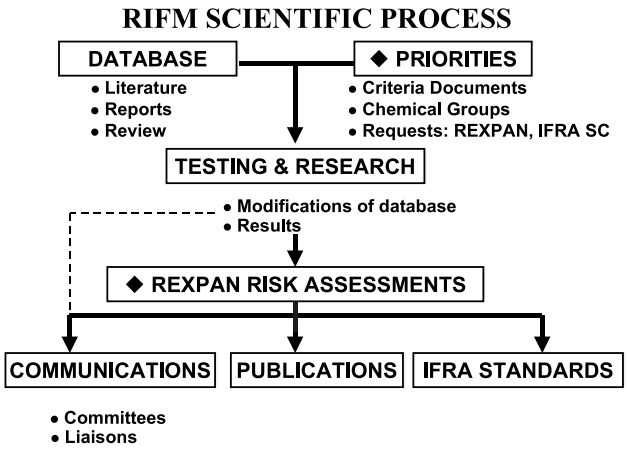


Fig. 2.

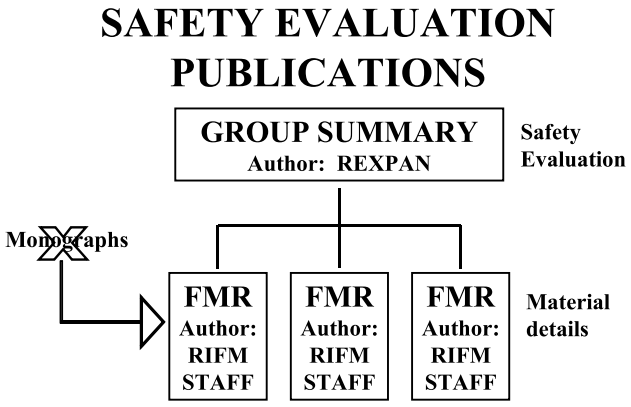


Fig. 3.

proprietary literature to determine what is known about an individual fragrance ingredient. Concurrently, the criteria documents are used to select priorities for data generation. A preliminary assessment is then prepared for critical evaluation.

It is necessary to have a systematic process and criteria for prioritization for subsequent review of structurally related groups of materials. This takes into account the major factors of volume of use, which determines potential exposure, and the presence of structural alerts, which may be a cause for concern. In addition, new safety information concerning a particular material may trigger a review of the chemical group and may require additional testing to address concerns.

The Panel considers its responsibility to plan for sufficient testing to assure safe use of fragrance materials and also to avoid redundant testing if safety can be assured from evaluation of metabolism and structure–activity relationships that permit meaningful metabolic and toxicological predictions. Upon completion of its review, the Panel reaches a conclusion, which is transferred to industry for any necessary risk management actions, and is published in peer-reviewed scientific literature. In the past, these largely were monographs, published in the journal, *Food and Chemical Toxicology*. Recently, more comprehensive safety evaluation publications have been prepared for linalool and related esters (Fig. 3). The rationale is described later in this section. The group summary section of the paper considers the available data regarding the members of a chemical structure class. Companion Fragrance Material Reviews are included to supplement the group summary thereby providing a more complete monograph than the older reports.

2.1. Chemical features of fragrance materials

To perform an adequate safety assessment of fragrance materials requires that their basic chemical characteristics be defined. Chemical structure helps to predict transdermal absorption, metabolism and disposition and functional groups that can influence toxicity. Despite encompassing more than 2600 discrete chemicals, fragrance materials can be classified into some 23 basic structural groups (see Table 1 and Appendix A).

In a joint exercise of the Expert Panel, RIFM staff scientists and industry scientists, discrete organic chemicals were divided into structural groups (structures are identified in Appendix B). Materials were classified based on the structural moiety most likely to be of significance toxicologically and rendering the groups as similar as possible between molecules by structural type.

Table 1
Classification of fragrance ingredients based on chemical structure[a]

Structural group	No. of chemicals
Esters	707
Alcohols	302
Ketones	259
Aldehydes	207
Ethers	100
Hydrocarbons	82
Acetals	63
Lactones	61
Carboxylic acids	42
Phenols	40
Nitriles	39
Dioxanes	31
Pyrans	27
Miscellaneous	27
Schiff's bases	26
Heterocyclics	25
Epoxides	25
Sulfur containing	24
Pyrazines	22
Amines/amides	18
Quinolines	14
Musks	10
Coumarins	4
Total	2155

[a] For a more detailed classification based on structure and structural sub-types with examples see Appendix A

Subsequent subdivisions of major groups were established using the same principles and in an effort to create structure–activity groups of reasonable and workable size, typically no more than 25 materials.

Using this analytical approach permits some generalizations. Of the 2127 fragrance materials listed, 88% are structurally simple, low molecular weight, predominately semi-volatile substances consisting of carbon, hydrogen, and oxygen. By contrast, nitrogen-containing chemicals account for only 6.7% of the total materials, and there are only five halogen-containing materials in the inventory. Note that in Appendices A and B, a halogenated group of materials is listed. This is for completeness; however, the materials have a zero volume of use and are in the process of being considered by the International Fragrance Association (IFRA) for a ban. The majority of fragrance materials can be assigned to several homologous groups of structurally related materials in which one might reasonably predict some degree of consistency of metabolism and toxicity. For example, the structure is reviewed for the presence or absence of "structural alerts" normally associated with toxicity, such as α,β-unsaturated ketones, arylamines, epoxides, and aromatic nitro compounds, and for functional groups that might be metabolized to a toxic alert function (e.g., the epoxidation of an unsaturated double bond).

Structural alerts for potential toxicity of fragrance ingredients are those already defined by Ford et al. (2000) combined with expert judgment. The choice of which member of a structural group should be submitted to fuller testing is made on a case-by-case basis. Thus, in the case of linalool, quite besides this terpene alcohol, some seventeen simple esters of this compound are used as fragrance ingredients. Review of these structures leads to the conclusion that the likely molecule of concern is linalool itself, particularly as there is good evidence of the rapid hydrolysis of such esters to the parent alcohol and respective carboxylic acids. For this reason, linalool itself was selected for extensive toxicological testing in order to provide data to support the class as a whole and to avoid redundant testing. In some cases, the judgment is more difficult. One example of this is with the group of fragrance materials classified as nitriles (organocyanides). A critical question with these substances is whether or not they can release toxic inorganic cyanide. Review of the structures of the organonitriles, of which there are currently 39 in use as fragrance ingredients, showed that there were some structural subtypes and it was necessary, therefore, to test at least one structure from each subtype with respect to cyanide release. Subsequent in vivo studies showed that only one out of the five representatives tested released cyanide and this was an example of the arylalkylcyanide group, benzyl cyanide. The results suggest that other types of organocyanides used as fragrance ingredients are not significant sources of cyanide release (Potter et al., 2001a; Potter et al., 2001b).

These structural homologies allow safety issues to be considered within the context of the information that exists for the structural group as a whole. For example, in the assessment of the safety of an aldehyde from a particular group, reference can be made to the safety data that exist with the compound itself and for the structural class as a whole. In the case of esters, of which there are many in the database, safety can be assessed both with respect to the ester structural analogues and with respect to the individual carboxylic acids and alcohols, the constitutive components (possible metabolites) of the esters. In many cases existing information for a structural group may obviate the need to submit a particular individual substance to full toxicological testing. In other cases it may be necessary to test one or more particular members of a structural class to obtain more robust data to solidify assessment of the class as a whole.

2.2. Safety assessment of a fragrance material

2.2.1. Assessment of exposure

Assessment of exposure to a fragrance ingredient is an essential part of the safety evaluation process. IFRA is responsible for providing such information on a regular basis by conducting periodic volume of use surveys of the fragrances supplied by industry. Such information is essential for indicating use levels and also for defining priorities for safety review and major changes in use patterns. In general, high volume use materials are given highest priority for safety assessment. About 60% of the use of fragrance materials is in soaps, fabric softeners, cleaners and detergents and the remaining 40% in cosmetics, toiletry, and perfumery products. Human exposure to fragrance ingredients is greatest in the latter categories.

Accurate estimation of potential exposure requires consideration of: concentration of fragrance ingredients in the consumer product(s); total amount of consumer product(s) applied or used; and "wash-off" or "skin retention" characteristics of the chemical, including evaporative loss.

The concentrations of specific fragrance materials in a fragrance mixture are supplied by IFRA. Estimates of use patterns of fragrance materials in cosmetic products, on a product-by-product basis, are obtained from the cosmetic and fragrance industries. Such data provide the basis for developing conservative estimates of total exposure from different consumer products as shown in Table 2 (Ford et al., 2000). These estimates of dermal exposure are crucial since they indicate the extent of possible skin and also systemic exposure. The Panel has chosen to assume complete transdermal penetration unless specific absorption data are available. The estimates

Table 2
Calculation of dermal exposure (potential systemic exposure) of a 60 kg person to a specific fragrance ingredient in a cosmetic product

Type of cosmetic product	Grams applied	Applications per day	Retention factor	Fragrance mixture/ product	Fragrance ingredient/ mixture	Ingredient/ product	Ingredient (mg/day)	Ingredient (mg/kg/day)
Body lotion	8.00	0.71	1.00	0.004	x	0.004x	22.7x	0.38x
Face cream	0.80	2.00	1.00	0.003	x	0.003x	4.8x	0.08x
Eau de toilette	0.75	1.00	1.00	0.08	x	0.08x	60.0x	1.0x
Fragrance cream	5.00	0.029	1.00	0.04	x	0.04x	58.0x	0.97x
Anti-perspirant	0.50	1.00	1.00	0.01	x	0.01x	5.0x	0.083x
Shampoo	8.00	1.00	0.01	0.005	x	0.005x	0.04x	0.007x
Bath products	17.00	0.29	0.001	0.02	x	0.02x	0.01x	0.0016x
Shower gel	5.00	1.00	0.01	0.012	x	0.012x	0.64x	0.011x
Toilet soap	0.80	6.00	0.01	0.015	x	0.015x	0.72x	0.012x
Hair spray	5.00	2.00	0.01	0.005	x	0.005x	0.5x	0.0083x
Total = 2.55x								

Note: x is the fractional amount of fragrance ingredient/fragrance mixture.

are used in making decisions concerning safety and requirements for further information or testing.

Three procedures currently are used to estimate skin deposition as the major route of fragrance ingredient exposure following cosmetic use. Acute exposure is determined from average maximum concentrations of formulas used in hydroalcoholic products. For chronic exposure, conservative assumptions are made using the upper 97.5th percentile concentration of fragrance ingredients. A third indication comes from volume of use surveys, which measure the quantities of different ingredients used annually by industry. This exposure information is used in conjunction with the results of descriptive toxicity and disposition studies to arrive at a safety evaluation for fragrance ingredients. Additional documentation of the process for deriving exposure estimates has been published by Cadby et al. (2002).

Total systemic exposure (assuming 100% transdermal penetration) to a specific fragrance ingredient is estimated by summing the values for the different product types and expressed as mg/kg/body weight/day, based on a 60 kg adult. With the acquisition of experimental data on skin penetration the data are reevaluated.

2.2.2. Dermatological considerations

A reasonable estimate of total exposure of human skin for purposes of determining potential systemic exposure is provided in Table 2. However, for purposes of assessing potential local skin reactions, the Panel requests that IFRA also supply an estimate for maximum concentrations of specific fragrance ingredients in products. These products are typically alcohol-based and are applied to relatively small areas of skin. These concentrations of a fragrance ingredient are then evaluated for irritant dermatitis, allergic contact dermatitis, phototoxicity, and photoallergy. It is essential that these evaluations be made in humans. There is, as yet, no animal model that can be relied upon to predict human responses in a precise manner. However, for safety purposes and to minimize unnecessary sensitization of human volunteers, animal studies may be useful as a first step to screen for the skin reactivity of fragrance ingredients.

The development of irritant and allergic reactions to fragrance materials applied to the skin is an extremely complex process that must take into consideration transdermal penetration, interactions of the compound with proteins and other substances in the skin, and immunogenicity of the compound. The skin exposure in terms of dose per unit area may be highly important (Kimber et al., 1999; Robinson et al., 2000; Gerberick et al., 2001). The threshold above which the chemical causes adverse reactions is likewise crucial for determining whether it can be incorporated safely into commercial products. Current methods, using animal and human skin for testing, require subjective readings and the reactions often are difficult to interpret. This is true of many bioassays. Development of new techniques is a high priority and basic research in this area has been initiated by the Panel and presented at research meetings such as the Experimental Contact Dermatitis Research Group (Api and Ford, 1999; Hanifin and Bickers, 1999).

As with testing of cosmetics and skin care products, there is no ideal in vivo animal surrogate for detecting irritant dermatitis, allergic contact dermatitis, phototoxicity and photoallergy. There is a great need for laboratory indicators of skin effects ex vivo. Techniques must be developed for experimental contact allergen surrogates in vitro and in vivo which correlate with skin reaction types. Additionally, there is a need to identify surrogate biomarkers for effects of fragrance materials, for example, using immunohistochemistry of skin biopsies to assess effects on cytokines, growth factors and inflammatory mediators. It is conceivable that direct analysis of tissue fluid samples for mediators and cytokines could be useful in determining effects as well.

2.2.3. Transdermal penetration and cutaneous metabolism

Fragrance materials may undergo significant percutaneous absorption into the systemic circulation (Hotchkiss, 1998). For some fragrance materials, such as the nitromusks, dermal absorption is a complex process involving, among other things, the functional concept of a "reservoir" skin compartment, from which the agent can be released over time. The degree of dermal absorption of some fragrance materials, such as phenylethyl alcohol (Hotchkiss, 1998; Ford et al., 1987) and coumarin (Hotchkiss, 1998; Ford et al., 2001) is quite significant; whereas, for others such as the nitromusks, (Hawkins and Ford, 1999; Hawkins et al., 2002) it is minimal. There is evidence indicating that percutaneous absorption through human skin is higher for chemicals having an octanol–water partition coefficient within the range 1.3–2.0.

Information on the extent of dermal absorption in human volunteers can be used in the determination of "safety factors" for establishing safe levels of human exposure based on animal data using exposure routes other than skin. With 100% dermal absorption no adjustment is needed in extrapolating toxicity from parenteral exposure; whereas, if dermal absorption is 1%, a factor of 100 can be used.

Some fragrance materials are metabolized in the skin, examples being the hydrolysis of esters such as benzyl acetate (Hotchkiss et al., 1992) and diethylphthalate and the oxidative metabolism of coumarin (Ford et al., 2001). Such metabolism may alter the biological activity of absorbed chemicals particularly when compared to other routes of administration and, thus, may have local effects as well as systemic effects. Thus, the dermal allergic responses linked to some fragrance materials, may be related to their cutaneous transformation to bioreactive metabolites capable of forming adducts with skin proteins able to function as allergens.

2.2.4. Toxicological data

The safety evaluation of a fragrance material includes a broad range of toxicological information, both for the compound itself and for structurally related chemicals belonging to the same chemical group. Such information includes data on acute, sub-chronic and chronic toxicity, mutagenicity, dermal irritation, skin sensitization photoirritation, photoallergy, developmental and reproductive toxicity, and carcinogenicity.

For some fragrance materials with high volume of use, a comprehensive program of toxicological investigation is undertaken by RIFM. This comprehensive approach for individual fragrance chemicals may be modified when dealing with structurally related compounds. The data needed for each compound are determined individually, to permit an assessment on the basis of data, scientific experience and the exercise of judgment. For example, in some cases it may be better to expend resources on further toxicological study of a key member of a structural group than to repeat studies in other group members. This helps to provide additional scientific underpinning of the structure–activity relationships that are being used to evaluate the group as a whole.

2.2.5. Metabolism and toxicokinetics

Knowledge of drug metabolism permits prediction of the likely metabolic fate of a chemical on the basis of its structure. This can be done by identifying the functional groups present in the molecule and the metabolic options that these can present. Factors such as species, dose and route of administration must also be taken into account. For the majority of fragrance materials, such as the esters, aldehydes, alcohols, carboxylic acids, and simple non-nitrogenous compounds, it is possible to make reasonable predictions of their metabolic fate and detoxication processes.

For the largest single group of fragrance materials, the esters, it can be predicted that they will undergo metabolic hydrolysis to their respective alcohol and carboxylic acid components, which will, in turn, be metabolized along well-established pathways. An abundance of data supports this contention. Safety evaluation of an ester can be greatly facilitated by toxicity and metabolic data for the component alcohol and carboxylic acid. If there is no adequate database to permit prediction of metabolic fate, it may be necessary to undertake metabolic studies on the compound per se or on a pivotal member of its structural group.

Toxicokinetic data are used in safety evaluation to provide information on the pattern of clearance of a fragrance chemical from the systemic circulation and evaluate the possibility of accumulation in peripheral tissues such as adipose tissue.

2.2.6. Environmental consequences

Since 60% of the use of fragrance materials is in soaps, fabric softeners, cleaners and detergents, the materials may enter the general environment by release into the water sewage system. Indeed such occurrences have been well-studied for some fragrance materials (Balk and Ford, 1999a,b; Tas et al., 1997). There are two aspects of environmental concern that are addressed by the Panel. One is potential ecological damage with concerns for organisms in the static water column and sediments, soil organisms, fish-eating predators and worm-eating predators, including emphasis on bioconcentration and/or biodegradation. The other concern is for the unintended exposures of humans to fragrance materials from potential environmental contact. Modern analytical methodologies can assist in the identification of fragrance materials in environmental

media and it is important to determine whether there is any risk to human health from such exposure.

3. Safety evaluation procedures

The methods and criteria for determining priority of review and for establishing an adequate database for safety evaluation of fragrance ingredients have been presented by Ford et al. (2000). Some background on the approach to the toxicology and safety of fragrances also is available (Ford, 1991). The Panel utilizes a stepwise decision tree type of approach (Cramer and Ford, 1978) for the evaluation of fragrance chemicals for systemic effects (Fig. 4) dermatological effects (Fig. 5) and environmental fate and effects (Fig. 6). These flow charts employ a diamond box to indicate a decision and a square or rectangular box to indicate information. As shown, certain data are considered to be fundamental, while others are ancillary. Also, some paths reach an end, where either a decision is made or no other data are needed. It should be emphasized, however, that the decision tree approach is used only as a set of guidelines and each chemical is considered on a case-by-case basis in the context of its structural class. The following sections are meant to supplement the steps involved and the types of data evaluated as shown in the decision trees.

If an OECD Guideline for toxicity testing exists, those protocols are followed. Additional parameters may be added; however, the study will comply with OECD Guidelines (OECD, 1998).

3.1. Acute toxicity

Fragrance chemicals are derived from classes of chemicals generally characterized by low toxicity. The determination of acute toxicity parameters such as the LD50 is unnecessary if such information is available from other types of studies such as dose-setting investigations required before undertaking a 90-day study. There is an extensive historic database on the acute toxicity of most of the major structural classes of fragrance materials; this is used when appropriate. However, the nature and use level of the great majority of fragrance ingredients are such that acute toxicity is rarely, if ever, an issue.

3.2. Irritant dermatitis

Studies of dermal irritation are conducted in laboratory animals and/or humans prior to testing for sensitization. Such studies are normally conducted by using a single occluded patch under the same conditions as used in the skin sensitization test (Draize et al., 1944; Kligman, 1966; Kligman and Epstein, 1975).

3.3. Allergic contact dermatitis

RIFM has approached sensitization studies with fragrance materials as primary prevention of sensitization in the healthy, normal population. The current method is a 3-phase sensitization safety evaluation. It involves a hazard assessment using an animal model,

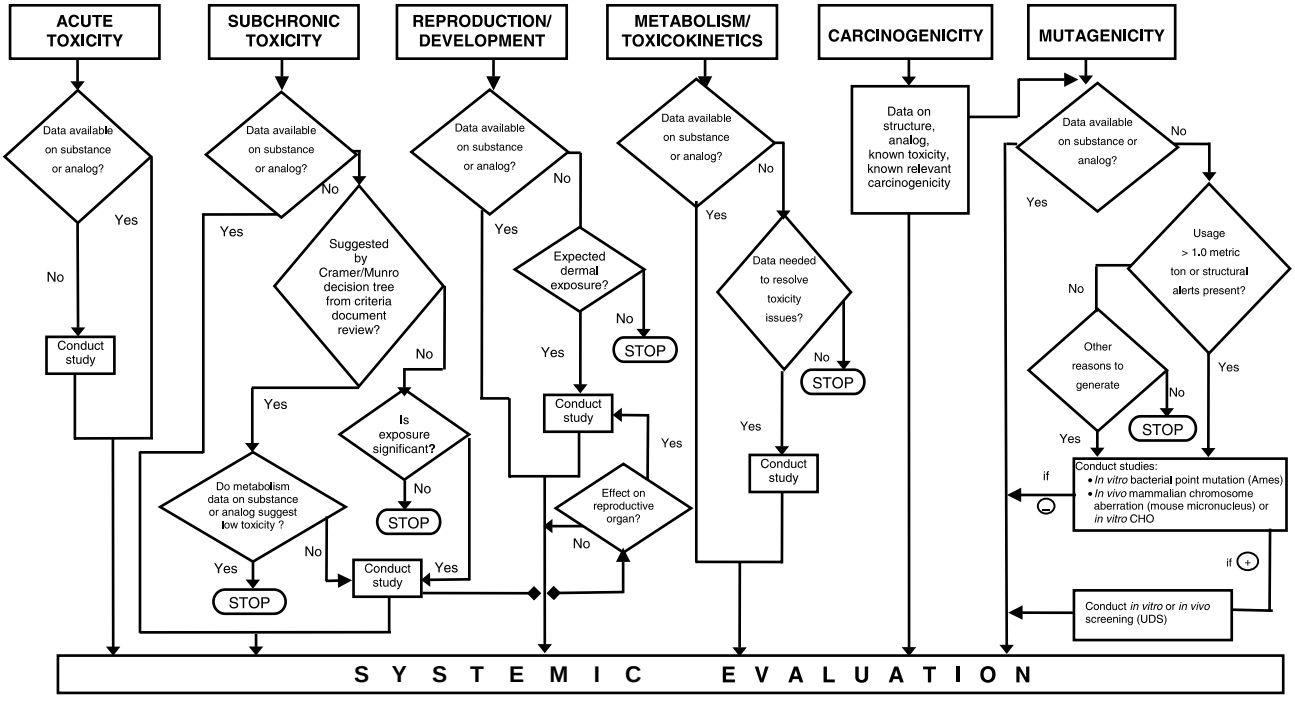


Fig. 4.

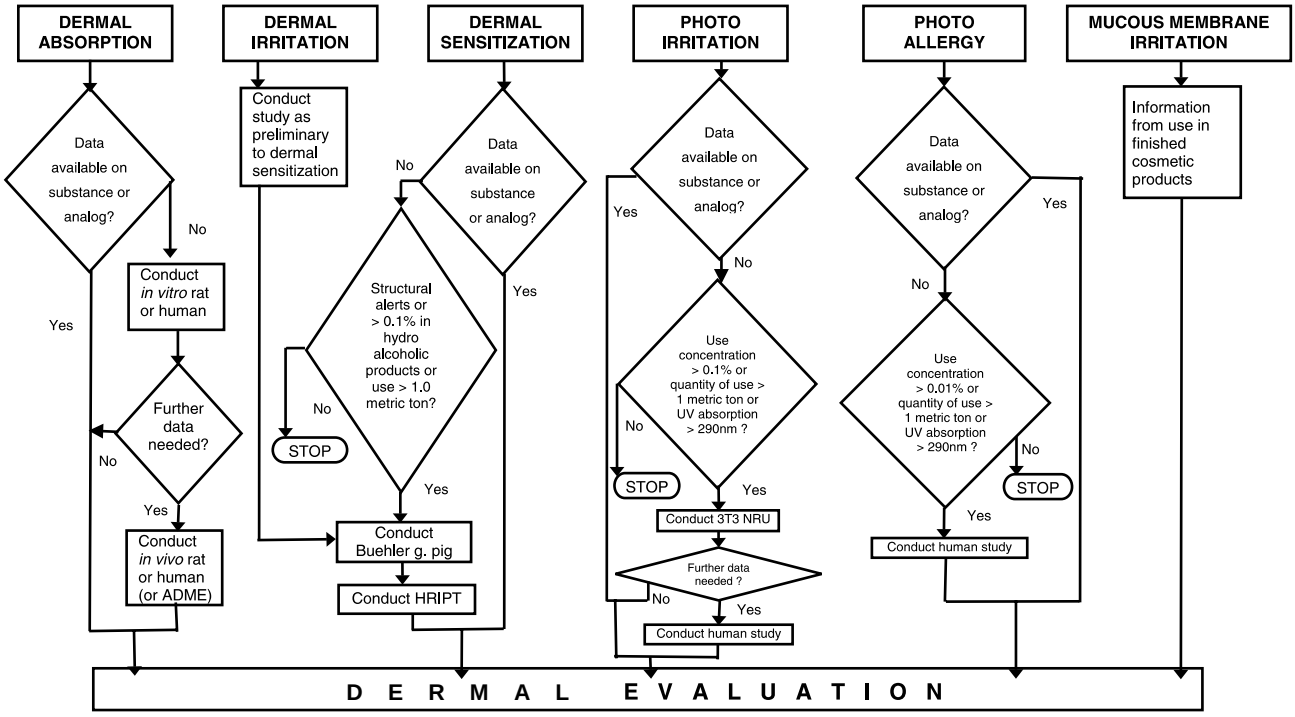


Fig. 5.

followed by an exposure assessment using declared levels of use, and finally, a safety assessment in a human repeated insult patch test (HRIPT). The animal test method is used to identify the sensitization potential and a no observed effect level (NOEL). Following a review of the NOEL and the maximum skin level, a safety assessment in humans can be conducted (Api, 2002).

3.4. Phototoxicity

Fragrance ingredients with significant absorption in the ultraviolet range (290–400 nm) can cause phototoxic and photoallergic reactions. Testing is usually based on a review of the absorption spectrum for the fragrance ingredient, as well as from closely related materials. The test methodology is essentially the same as for irritation except that a duplicate patch site is irradiated either immediately after application of the fragrance ingredient or after patch removal (Morikawa et al., 1974; Sams and Epstein, 1967). Testing may not be necessary if lack of phototoxicity has been demonstrated with appropriately validated in vitro tests, such as the 3T3 Neutral Red Uptake (Spielmann et al., 1998).

3.5. Photoallergy

Human photopatch testing is considered to be the definitive test. While true photoallergy is rare, it must be assessed. Patches containing the material for testing are applied in duplicate and immediately covered with light-opaque material. Twenty-four hours later one set of patches is exposed to 5 J/cm^2 of UVA and evaluated after 48 h (Kaidbey and Kligman, 1980).

3.6. Sub-chronic toxicity

The need for studies of sub-chronic toxicity (normally a 28- or 90-day repeated dose study in rats) depends upon the evaluation of all the available information, including data for structural analogues, exposure and metabolism. Such studies may include the dermal or oral route of administration; the choice is made on a case-by-case basis. The dermal route more closely reflects the manner of use but is unlikely to provide information regarding potential systemic toxicity if transdermal penetration is low or if the compound is an irritant. If the objective is to characterize systemic toxicity, oral or parenteral administration is preferred. Chronic dermal application may cause chronic irritation and inflammation, which may confound the interpretation of the findings. The endpoint of a sub-chronic study, after dermal or oral administration, is to establish a no observed adverse effect level (NOAEL), which can be used in the safety evaluation process and the setting of "safety factors." To identify systemic or dermal toxic potentials, the highest dose tested should be effective in eliciting one or more endpoints.

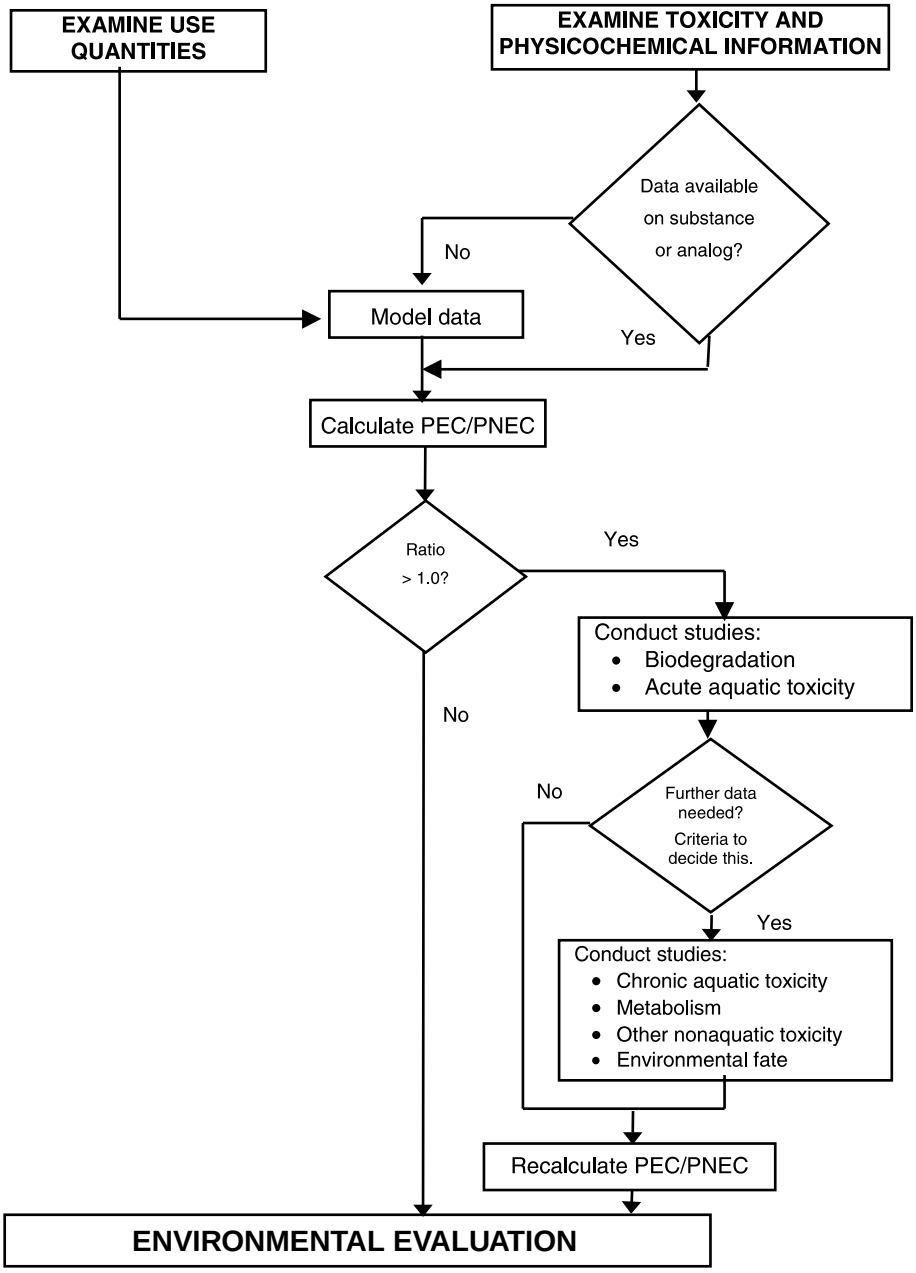


Fig. 6.

3.7. Reproductive and developmental studies

Reproductive and developmental studies may be necessary. Sub-chronic studies may reveal hormone-related changes and effects upon the reproductive organs. Structurally related compounds should be reviewed for effects on reproduction and development.

It is not feasible to test every fragrance chemical for potential effects on reproduction and development, but it is the policy of the Panel to ensure that one or more members of a structural group have been so evaluated. In addition, use level and human dermal absorption are considered. Reproductive and developmental effects typically are assessed in standard rat or rabbit bioassays.

3.8. Metabolism and toxicokinetics

Metabolic and toxicokinetic data are essential for safety evaluation. For fragrance materials with little if any transdermal penetration, the issues of metabolism and kinetics are not essential. However, for those materials that are absorbed, it is important to

Table 3
Summary matrix of safety data for linalool and its esters

	Acute oral LD50	Acute dermal LD50	Subchronic oral	Subchronic dermal	Genotoxicity bacterial/ mammalian	Metabolism
Linalool	*rats* 2790 mg/kg (95% C.I. 2440–3180 mg/kg) *mice* 2200 mg/kg 3500 mg/kg 3920 mg/kg ± 300 mg/kg	*rabbits* 5610 mg/kg (95% C.I. 3580–8370 mg/kg)	NOAEL 90 day study in rats 50 mg/kg/day (food intake and weight gain significantly depressed in males but this was attributed to poor palatability)	NOAEL 13 week study in rats 250 mg/kg/day (transient erythema and depressed activity) 1000 mg/kg/day (decreased weight gain, decreased activity and erythema)	NOE[a] Ames assay with *S. typhimurium* and *E. coli* Rec-assay with *B. subtilis* (3 studies) NOE at 17 μg/disk questionable effects at 630–10,000 μg/disk positive at 10,000 μg/disk NOE Micronucleus test (mice) Chromosome aberration assay (CHO or Chinese hamster fibroblast cells) UDS assay (rat hepatocytes) Mouse lymphoma assay (when osmolarity and pH were controlled)	Primarily through conjugation with glucuronic acid; majority excreted in the urine, feces and expired air
Linalyl acetate	*rats* 10,000 mg/kg 14,550 mg/kg (C.I. 12,300–17,170 mg/kg) *mice* 13,360 mg/kg (95% C.I. 11,920–15,000 mg/kg) 13, 540 mg/kg ± 900 mg/kg	*rabbits* > 5000 mg/kg	NOAEL 90 day study in rats 24.2 mg/kg/day (food intake and weight gain slightly depressed in females)	NA[b]	NOE Ames assay with *S. typhimurium* Rec-assay with *B. subtilis* NOE Chromosome aberration assay (human lymphocytes) UDS assay (rat hepatocytes)	Hydrolyzed to corresponding alcohol and carboxylic acid; carboxylic acid formed by hydrolysis is easily and rapidly metabolized, normally as a fatty acid that undergoes β-oxidation

Table 3 (*continued*)

	Acute oral LD50	Acute dermal LD50	Subchronic oral	Subchronic dermal	Genotoxicity bacterial/ mammalian	Metabolism
Linalyl benzoate	*rats* > 5000 mg/kg *mice* 9400 mg/kg $\pm$ 390 mg/kg	*rabbits* > 5000 mg/kg	NA	NA	NA	Hydrolyzed to corresponding alcohol and carboxylic acid; carboxylic acid is conjugated and excreted
Linalyl butyrate	*rats* > 5000 mg/kg *mice* > 8900 mg/kg	*rabbits* > 5000 mg/kg	NA	NA	NA	Hydrolyzed to corresponding alcohol and carboxylic acid; carboxylic acid formed by hydrolysis is easily and rapidly metabolized, normally as a fatty acid that undergoes β-oxidation
Linalyl cinnmate	*rats* 9960 mg/kg (C.I. 8230–12,050 mg/kg) *mice* $> 39,040$ mg/kg	*rabbits* > 5000 mg/kg	NOEL 17 week study in rats 500 mg/kg/day	NA	NA	Hydrolyzed to corresponding alcohol and carboxylic acid; cinnamic acid is conjugated and excreted or metabolized to benzoic acid
Linalyl formate	*rats* > 5000 mg/kg *mice* 5490 mg/kg $\pm$ 730 mg/kg	*rabbits* > 5000 mg/kg	NA	NA	NA	Hydrolyzed to corresponding alcohol and carboxylic acid; carboxylic acid formed by hydrolysis is easily and rapidly metabolized, normally as a fatty acid that undergoes β-oxidation
Linalyl hexanoate	*mice* $37,870$ mg/ kg $\pm$ 1940 mg/kg	NA	NA	NA	NA	Hydrolyzed to corresponding alcohol and carboxylic acid; carboxylic acid formed by hydrolysis is easily and rapidly metabolized, normally as a fatty acid that undergoes β-oxidation

Linalyl isobutyrate	*rats* $> 36,300$ mg/kg *mice* 15,100 mg/kg (95% C.I. 12,330–18,500 mg/kg) $> 17,698$ mg/kg	*rabbits* > 5000 mg/kg	NOEL 18 week study in rats 500 mg/kg/day	NA	NA	Hydrolyzed to corresponding alcohol and carboxylic acid; carboxylic acid formed by hydrolysis is easily and rapidly metabolized, normally as a fatty acid that undergoes β-oxidation
Linalyl isovalerate	*rats* > 5000 mg/kg *mice* $25,170$ mg/kg $\pm$ 2650 mg/kg	*rabbits* > 5000 mg/kg	NA	NA	NA	Hydrolyzed to corresponding alcohol and carboxylic acid; carboxylic acid formed by hydrolysis is easily and rapidly metabolized, normally as a fatty acid that undergoes β-oxidation
Linalyl phenylacetate	*rats* > 5000 mg/kg *mice* $15,480$ mg/kg $\pm$ 1930 mg/kg	*rabbits* > 5000 mg/kg	NA	NA	NA	Hydrolyzed to corresponding alcohol and carboxylic acid; carboxylic acid is conjugated and excreted
Linalyl propionate	*rats* > 5000 mg/kg *mice* $13,870$ mg/kg $\pm$ 1790 mg/kg	*rabbits* > 5000 mg/kg	NA	NA	NA	Hydrolyzed to corresponding alcohol and carboxylic acid; carboxylic acid formed by hydrolysis is easily and rapidly metabolized, normally as a fatty acid that undergoes β-oxidation

[a] No effects.
[b] None available.

Table 4
Summary matrix of dermatological safety studies

	Skin irritation (human)	Skin irritation (animals)	Skin sensitization (human) maximization test	Skin sensitization (animals)
Linalool[c]	NOE[a] 20% in petrolatum	NOE (guinea pigs) 10% (vehicle not specified) NOE (rabbits) 3% in peanut oil	NOE 20% in petrolatum	Open epicutaneous test in guinea pigs 20%—NOE Maximization test in guinea pigs 10%—NOE Modified draize in guinea pigs 10%—NOE
Linalyl acetate	NOE 32% in acetone	NOE (miniature swine) 100% 100% moderate irritation in guinea pigs 5% in diethyl phthalate slight irritation in rabbits	20% in petrolatum (0/25 reactions) 12% (vehicle not reported) 0/25 reactions 10% in petrolatum Five test panels (2/22, 0/26, 0/27, 1/26, 0/30 reactions)	Maximization test in guinea pigs 5%—NOE
Linalyl benzoate	NOE 8% in petrolatum	5% in diethyl phthalate very slight irritation in rabbits	NOE 8% in petrolatum	NA[b]
Linalyl butyrate	NOE 8% in petrolatum	5% in diethyl phthalate very slight irritation in rabbits	NOE 8% in petrolatum	NA
Linalyl cinnamate	NOE 8% in petrolatum	5% in diethyl phthalate very slight irritation in rabbits	NOE 8% in petrolatum	NA
Linalyl formate	NOE 10% in petrolatum	5% in diethyl phthalate very slight irritation in rabbits	NOE 10% in petrolatum	NA
Inalyl isobutyrate	NOE 8% in petrolatum	5% in diethyl phthalate very slight irritation in rabbits	NOE 8% in petrolatum	Open epicutaneous test in guinea pigs 8%—NOE
Linalyl isovalerate	NOE 20% in petrolatum	5% in diethyl phthalate very slight irritation in rabbits	NOE 20% in petrolatum	NA
Linalyl phenylacetate	NOE 4% in petrolatum	NOE (rabbits) 5% in diethyl phthalate	NOE 4% in petrolatum	NA
Linalyl propionate	NOE 8% in petrolatum	5% in diethyl phthalate very slight irritation in rabbits	NOE 8% in petrolatum	Open epicutaneous test in guinea pigs 8%—NOE

[a] No effects.
[b] None available.
[c] $C(CH_3)_2{=}CH{-}[CH_2]_2{-}C(CH_3)(OH){-}CH{=}CH_2$.

know the metabolic profile, how rapidly the compound and its metabolic products are eliminated and whether they can accumulate in tissues. For the major classes of fragrance materials there exists a sufficient metabolism database, which allows reasonable predictions concerning the likely fate of a compound. If no such data are available, it may be necessary to perform metabolic studies in a test species, usually the rat, and sometimes in human volunteers. Comparative studies in rodents and human volunteers using classical toxicokinetic models, permit comparative exposures to be evaluated and allow a more satisfactory evaluation of the results of animal sub-chronic studies and the derivation of "safety factors."

3.9. Mutagenicity (genotoxicity)

Mutagenicity data are available for the main structural classes of fragrance materials. Currently, mutagenicity is a systemic consideration, as it relates to genetic effects and also to carcinogenicity. Potential site of

contact genotoxicity or photogenotoxicity effects are an area for future development.

Testing for mutagenicity is required if there are no adequate data for structural analogues, if structural alerts for genotoxicity are present or if the annual usage levels exceed 0.1 metric ton per year. Normally, an in vitro point mutation assay (Ames test) and an in vitro mammalian cell chromosomal aberration study (e.g., mouse micronucleus test) are used in the first instance. If the results of these studies are positive, in vivo studies such as the unscheduled DNA synthesis (UDS) or an in vivo mammalian cytogenetics study are performed. The Panel considers the advantages and disadvantages of the different test systems when interpreting the results from genotoxicity testing.

3.10. Carcinogenicity

For such a complex endpoint it is necessary to take into account a wide variety of data. Data on chemical structure and structural analogues, the presence or absence of alert structures and information on the carcinogenic properties of related chemical structures are used. Other information includes the metabolic profile, metabolic activation and mutagenicity data for the compound and structural analogues. The history of human use of the chemical as a fragrance ingredient or in other forms such as food is useful.

3.11. Assessment of environmental risks

The assessment of risks to wildlife from fragrance materials follows an iterative approach that starts with a prioritization based upon worst-case assumptions (Salvito et al., 2002). Each step employs a risk-quotient (RQ) approach, similar to that used in European Union (EU) chemicals legislation (European Commission, 1996). This compares a predicted environmental concentration (PEC) of the substance with a threshold concentration below which adverse effects for ecological systems are unlikely, the so-called predicted no-effect concentration (PNEC). The RQ is then calculated as PEC/PNEC. If the RQ is less than one it indicates an acceptable situation; if it is above one, additional data and refinement of data are needed and may indicate a need to control the substance under consideration.

Within the risk assessment framework adopted by RIFM, the initial prioritization involves some extreme presumptions in predicting exposures (PECs) for the aquatic environment: that all material used by consumers goes down the drain (nothing lost to atmosphere); that in sewage treatment there may be partitioning between liquid and sediment phases but there is no degradation; that there is minimal dilution in receiving waters. Similarly, the PNECs are estimated from structure activity relationships, the outputs of which are as EC50s; these are divided by an uncertainty factor of one million to give the PNEC. The assumptions made at this stage in the risk assessment are much more stringent than those used in other regulatory procedures (e.g., European Commission, 1996). The Panel believes that substances with RQs less than one give little cause for concern, provided usage levels are sound and do not change.

Substances that have RQs greater than one need further attention. For example, refinements of the PEC focus on more realistic estimates of losses to atmosphere by volatilization, on biodegradation in sewage treatment works (STWs) and on dilution in receiving waters. Similarly, refinements in the PNECs use more sophisticated structure–activity models to predict endpoints and may incorporate values derived from ecotoxicological tests. With the support of the Panel, RIFM is sponsoring research programs that are addressing biodegradation of fragrance materials in STWs under realistic scenarios (Federle et al., 2000; Langworthy et al., 2000).

All these risk assessments, at every stage in the iterative process, depend on realistic estimates of usage, which drive exposure and, hence, the PECs. The Panel fully supports RIFM initiatives to obtain usage data and measurements of environmental concentrations (MECs) for key substances. In this way we can compare MECs with PECs to assess their usefulness and use MECs as more relevant elements in the refined risk assessments.

3.12. Reaching a conclusion

Following a full review of all relevant data for any material (X) and its structural analogues, the Panel may conclude any of the following:

- The Panel has determined that there are no safety concerns for Compound X under the present declared levels of use and calculated exposures.
- Compound X has been placed ''On Hold'' pending the outcome of further studies and evaluation.
- The Panel has determined that because of safety considerations for Compound X, it should not be used as a fragrance ingredient at a concentration greater than Y%.

3.13. The structural group approach: a case example: linalool and its esters

In order to illustrate the ''Structural Group Approach'' in the safety assessment of fragrance materials, it may be useful to consider this process in the evaluation of one particular structurally related group of substances, namely, linalool and its esters. Besides linalool itself, some nine simple ester derivatives are also used as fragrance ingredients. These esters are either esters of linalool with simple aliphatic carboxylic acids or with

aromatic or arylacetic acids. The a priori assumption in the "Structural Group Approach" is that one would anticipate that among a group of structurally related materials a reasonable homology in terms of toxicity profile and metabolic fate. The corollary of this approach is that if adequate toxicity, metabolic and dermal safety data is available for certain pivotal compounds in the group, then comprehensive studies, for all substances in the group, become unnecessary. The pivotal compound in this group is clearly linalool itself. The ester derivatives of linalool would be expected to undergo metabolic hydrolysis in vivo to this terpene derivative as well as the associated carboxylic acid. Indeed experimental data exists which shows that one of the linalool esters (linalyl acetate) could undergo hydrolysis in vivo (JECFA, 1999) and it is reasonable to project that other simple ester derivatives would undergo a parallel fate.

A "Summary Matrix of Safety Data" for Linalool and its esters and a "Safety Matrix of Dermatological Safety Studies" are shown in the two accompanying Tables 3 and 4. These tables are of necessity a succint compilation of the available safety data for linalool and its esters and are intended to show at a glance the matrix of safety information that is available for these substances. For more information on this basic data the interested reader is referred to the detailed publication for these compounds (Bickers et al., 2003). Perusal of these tables shows that a comprehensive safety database exists for both the pivotal compound, linalool, as well as its simple acetate ester. The data is incomplete for several of the other esters. Further perusal of Tables 3 and 4 show that linalool and its esters have a low acute toxicity in rodents irrespective of whether administered orally or dermally. Subchronic oral studies indicate NOAEL values for linalool and its acetate ester of 50 and 24.2 mg/kg/day respectively without evidence of target organ damage. Genotoxicity studies (bacterial and mammalian) are uniformly negative with respect to both linalool and its acetate ester. The metabolic fate of linalool is relatively well defined as it undergoes metabolic conjugation with glucuronic acid (Parke et al., 1974) and to a lesser extent oxidation to hydroxylated metabolites (Chadha and Madyastha, 1984). These are pathways that raise no obvious questions in terms of safety concerns. With respect to the esters of linalool one would predict with confidence that they would undergo hydrolysis in vivo to linalool and the corresponding carboxylic acid. Indeed, linalyl acetate, as representative of the ester series, is known to undergo hydrolysis in various model situations including rat intestinal mucosa, liver and blood as well as simulated gastric and intestinal juices (JECFA, 1999). Furthermore, it is a well recognized general fact that simple esters undergo metabolic hydrolysis in vivo to their corresponding alcohol and acid components, a reaction mediated by tissue carboxylesterases and, in particular, the β-esterases (Heymann, 1980; Anders, 1989). The carboxylic acids released from the hydrolysis of the linalyl esters themselves raise no safety concerns; their toxicology is well understood as is their metabolic detoxication which is known to be by conjugation and in the case of the aliphatic carboxylic acids by β-oxidation.

Table 4 shows the "Summary Matrix of Dermatological Safety Studies" for linalool and its esters. Numerous animal and human skin irritation and skin sensitization studies have been carried out on these compounds; the database is comprehensive and raises no obvious questions of dermal safety.

The UV absorption profiles of linalool and nine of the linalyl esters indicate that they do not absorb UV light at wavelengths in the range of 290–400 nm and, therefore, would have no potential to elicit photoirritation or photoallergy under the current conditions of use as fragrance ingredients. While linalyl cinnamate does absorb UV light, peaking at 275 nm and returning to baseline at 316 nm, the potential human exposure to linalyl cinnamate is low since the volume of use is less than one metric ton and the maximum skin level is 0.4%. In addition, cinnamic acid, a metabolite of linalyl cinnamate, did not exhibit phototoxic effects (Pathak and Fitzpatrick, 1959; RIFM, 2002) or photoallergic effects when tested in guinea pigs (RIFM, 2002).

On the basis of structural relationship, the availability of a comprehensive toxicology and metabolic data base for linalool itself as well as the simple acetate ester, the dermal safety studies and the data available for individual compounds in the series, it can be concluded that the use of these materials as fragrance ingredients, under declared conditions of use, raise no safety concerns.

4. Summary

The Panel has been directly involved in the publication of monographs evaluating approximately 1100 fragrance ingredients and in the decision by IFRA to prohibit or restrict the use of about 10% of those. For example, the Panel evaluated the data on Fig Leaf Absolute in February, 1980. Based on sensitization reactions at 5% and strong phototoxic reactions, the Panel concluded that the material should be banned. A RIFM Advisory Letter (RIFM, 1980) was issued to all members stating the potential for induction of skin and phototoxic reactions. As a result, an IFRA Guideline (now renamed a Standard) was issued in October, 1980 (IFRA, 1980), which stated, "Fig Leaf Absolute should not be used as a fragrance ingredient based on test results of RIFM showing sensitizing and extreme phototoxic potential for this material." A RIFM monograph then was published in November, 1982 (Opdyke and Letizia, 1982).

The most recent compilation of monographs in Special Issue IX, addressed some of the lesser-known and lower volume ingredients (Letizia et al., 2000). Its Foreword also described the changes to the publication process, which will replace monographs that presented only experimental data with documents that provide an overall safety assessment of a specific fragrance ingredient or a group of related fragrance ingredients. These Group Summaries and Fragrance Material Reviews, when published, may use a format similar to that used by the Cosmetic Ingredient Review, published as Safety Assessments (Andersen, 2001) or the Flavor and Extract Manufacturers Association Expert Panel (Adams et al., 1996).

There is no doubt that the fragrance industry faces great challenges in the years ahead. Consumers' expectations require increased transparency of safety evaluation without sacrificing proprietary knowledge. There is a need for greater experimental and epidemiological research to determine adverse health effects, and particularly, to determine the frequency of allergic contact sensitization to fragrance chemicals in order to set safe limits. Evaluation of natural mixtures containing aroma chemicals may require different approaches than evaluation of discrete aroma chemicals; for example, structure–activity predictions and metabolic forecasts may not always be feasible.

There is a need for the fragrance industry to provide standardized, pure patch test allergens for use by dermatologists to provide more specificity in diagnosis of fragrance allergy and in epidemiological studies. There also is a great need to better understand the concordance of patch test elicitation data, with those developed through the use of induction testing, as described above. REXPAN recognizes the utility of patch test data and has begun efforts to incorporate this information into safety evaluations. Naldi (2002) has described important population parameters, which REXPAN has used to plan an elicitation threshold study, developed in conjunction with international dermatologists, following the basic method described by Andersen et al. (2001).

In environmental risk assessments the RIFM framework concentrates on impacts to freshwater ecosystems, as do most such assessments. However, there can be soil contamination from fragrance materials due to the spreading of sewage sludge on land. The likely fate of fragrance materials through this route is being considered in another RIFM-sponsored research project. Finally, there is a need for an increased rate of publication of results to provide more rapid information transfer for dermatologists, other medical practitioners, regulators, toxicologists, environmentalists and, of course, industry. There is considerable basis for agreement by both industry and scientific institutions about what is needed.

The estimation of risk associated with the use of fragrance materials in humans must address systemic effects, dermatological effects and environmental effects. The role of REXPAN in this process involves developing a detailed description of the chemical groupings used and the application of decision tree algorithms to assess biological and environmental effects. This procedure is necessarily iterative and requires regular review of new compounds as well as reassessment of existing compounds based upon new knowledge. The goal is to apply the most current scientific information to the analytical process to minimize human risk associated with the use of fragrance materials.

Acknowledgments

The authors wish to acknowledge Steve Meekins, Peter Cadby, Dave Carroll and Mark Sprecker for their help in classifying the materials into groups, and thank the RIFM staff for its assistance in manuscript preparation.

Appendix A. Detailed chemical classification of fragrance chemicals

Sub group	Number of materials	Example 1 CAS #	Example 2 CAS #	Example 3 CAS #
Acetals				
Aliphatic aldehyde/aliphatic alcohol	32	Acetaldehyde ethyl *trans*-3-hexenyl acetal 60763-40-8	Citral diethyl acetal 7492-66-2	Isocycloeugenol 72066-75-2
Aliphatic aldehyde/aromatic alcohol and aromatic aldehyde/ aliphatic alcohol	28	Propyl phenethyl acetal 7493-57-4	α-Amylcinnamaldehyde dimethyl acetal 91-87-2	Cyclamen aldehyde ethylene glycol acetal 72845-85-3
Ketals	3	Ethylacetoacetate ethylene glycol ketal 6413-10-1	Cyclohexanone diethyl ketal 1670-47-9	Cyclohexanone 1,3-butylene glycol ketal 6413-26-9

Appendix A (*continued*)

Sub group	Number of materials	Example 1 CAS #	Example 2 CAS #	Example 3 CAS #
Alcohols				
Straight chain saturated	22	1-Decanol 112-30-1	Lauryl alcohol 112-53-8	Amyl alcohol 71-41-0
Straight chain unsaturated	20	9-Decen-1-ol 13019-22-2	*cis*-3-hexenol 928-96-1	Dodec-2-en-1-ol 22104-81-0
Branched chain saturated	23	Isobutyl alcohol 78-83-1	3-Methyloctan-3-ol 5340-36-3	Isoamyl alcohol 123-51-3
Branched chain unsaturated	32	3-Methyl-1-octyn-3-ol 23580-51-0	Phytol 150-86-7	Dimyrcetol 18479-58-8
Miscellaneous	3	Ethylcellulose 9004-57-3	Cytenol No. CAS #	Orrivenol No. CAS #
Alkyl cyclic main group	33	Arbanol 7070-15-7	2-Cyclohexylethyl alcohol 4442-79-9	Dihydro-β-ionol 3293-47-8
Alkyl cyclic ionols	8	α-Ionol 25312-34-9	α-Methylionol 70172-00-8	Tetrahydroionol 4361-23-3
Terpene cyclic	46	Cedrol 77-53-2	Terpineol 8000-41-7	l-Menthol 2216-51-5
Terpene chain	34	Geraniol 106-24-1	Linalool 78-70-6	Dihydromyrcenol 53219-21-9
Cyclic	42	Cyclohexanol 108-93-0	β-Ambrinol 670-24-6	Dihydrocarveol (R, R, R) 38049-26-2
Aryl alkyl	39	Cinnamyl alcohol 104-54-1	Phenethyl alcohol 60-12-8	*p*-Isopropylbenzyl alcohol 536-60-7
Aldehydes				
Aryl	21	Diisopropylbenzaldehyde 68459-95-0	Vanillin 121-33-5	Benzaldehyde 100-52-7
Aryl alkyl phenyl alky	4	3-Phenylbutanal 16251-77-7	5-Methyl-2-phenyl-2-hexenal 21834-92-4	2-(ar-Ethylphenyl) butyraldehyde 68228-11-5
Aryl alkyl aryl acetaldehydes	7	Phenylacetaldehyde 122-78-1	*p*-Tolylacetaldehyde 104-09-6	Cuminacetaldehyde 1335-44-0
Aryl alkyl cinnamic and propionaldehydes	21	2-Phenylpropionaldehyde 93-53-8	*p*-Methoxyhydratropaldehyde 5462-06-6	*p*-Methylhydrocinnamic aldehyde 5406-12-2
Alkyl cyclic	13	4-(2,6,6-Trimethyl-2-cyclohexen)-2-methylbutanal 65405-84-7	2,6,6-Trimethyl-2-cyclohexene-1-acetaldehyde 472-64-0	2-Methyl-4-(2,6,6-trimethyl cyclohex-1-en-1-yl)-2-butenal 3155-71-3
Cinnamic	8	α-Amylcinnamaldehyde 122-40-7	α-Hexylcinnamaldehyde 101-86-0	Cinnamaldehyde 104-55-2
Cyclic	35	Isocyclocitral 1335-66-6	Formylethyltetramethyl tetralin 58243-85-9	Cedr-8-en-15-al 28387-62-4
Saturated	30	Isobutyraldehyde 78-84-2	Hydroxycitronellal 107-75-5	Valeraldehyde 110-62-3
Straight chain unsaturated	38	*cis*-6-Nonenal 2277-19-2	10-Undecenal 112-45-8	Hexen-2-al 6728-26-3
Branched chain unsaturated	30	Citral 5392-40-5	Geranial 141-27-5	Geranyl oxyacetaldehyde 65405-73-4
Amines/amides				
Main group	14	Diphenylamine 122-39-4	*p*-Methyltetrahydroquinoline 91-61-2	Acetanilide 103-84-4

Appendix A (*continued*)

Sub group	Number of materials	Example 1 CAS #	Example 2 CAS #	Example 3 CAS #
Oximes	4	5-Methyl-3-heptanone oxime 22457-23-4	Phenylacetaldehyde oxime 7028-48-0	1-Bicyclo[2.2.1]hept-5-en-2-ylethan-1-one-oxime 65416-21-9
Carboxylic acids				
Straight chain saturated	14	Decanoic acid 334-48-5	Butyric acid 107-92-6	Stearic acid 57-11-4
Straight chain unsaturated	3	10-Undecenoic acid 112-38-9	Oleic acid 112-80-1	Linolenic acid 463-40-1
Cyclic and aromatic	10	Cinnamic acid 621-82-9	Phenoxyacetic acid 122-59-8	Benzoic acid 65-85-0
Branched chain saturated	7	Isovaleric acid 503-74-2	Citric acid 77-92-9	2-Methylvaleric acid 97-61-0
Branched chain unsaturated	8	3,7-Dimethyl-6-octenoic acid 502-47-6	Geranic acid 459-80-3	2-Methyl-*trans*-2-butenoic acid 80-59-1
Coumarins				
Coumarins	4	Coumarin 91-64-5	Dihydrocoumarin 119-84-6	4,6-Dimethyl-8-*tert*-butylcoumarin 17874-34-9
Dioxanes				
Dioxanes	31	2-Butyl-4,4,6-trimethyl-1,3-dioxane 54546-26-8	Ethyl dioxa spiro undecene 64165-57-7	2-(3-Heptyl)-1,3-dioxolane 4359-47-1
Epoxides				
Epoxides	25	*cis*-Carvone oxide 33204-74-9	Caryophyllene oxide 1139-30-6	*cis*-Linalool 3,6-oxide 5989-33-3
Esters				
Formates—Phenyl	6	Anisyl formate 122-91-8	Eugenyl formate 10031-96-6	Benzyl formate 104-57-4
Formates—Aliphatic saturated straight chain	5	Heptyl formate 112-23-2	Ethyl formate 109-94-4	Octyl formate 112-32-3
Formates—Aliphatic branched chain saturated	3	Isoamyl formate 110-45-2	Isobutyl formate 542-55-2	3,5,5-Trimethylhexyl formate 67355-38-8
Formates—Aliphatic straight chain unsaturated	1	*cis*-3-Hexenyl formate 33467-73-1		
Formates—Aliphatic unsaturated branched	1	2,6-Dimethyloct-7-en-2-yl formate 25279-09-8		
Formates—Terpene acyclic	6	Neryl formate 2142-94-1	Citronellyl formate 105-85-1	Geranyl formate 105-86-2
Formates—Terpene cyclic	10	Cedryl formate 39900-38-4	Isobornyl formate 1200-67-5	Terpinyl formate 2153-26-6
Formates—Aryl alkyl	4	Phenethyl formate 104-62-1	α, α-Dimethyl henethyl formate 10058-43-2	Cinnamyl formate 104-65-4
Formates—Cyclic	5	Cyclododecyl formate 59052-82-3	4,4,8-Trimethyl tricyclo[6.3.1.02,5] dodecan-1-yl formate 58096-46-1	Octahydro-4,7-methano-1H-indene-2-methyl formate 64644-32-2

Appendix A (*continued*)

Sub group	Number of materials	Example 1 CAS #	Example 2 CAS #	Example 3 CAS #
Acetates—Phenyl	9	*p*-Tolyl acetate 140-39-6	Isoeugenyl acetate 93-29-8	m-Tolyl acetate 122-46-3
Acetates—Aliphatic saturated straight chain	31	Propyl acetate 109-60-4	Nonyl acetate 143-13-5	Ethyl acetate 141-78-6
Acetates—Aliphatic branched chain saturated	18	Methyl isobutyl carbinyl acetate 108-84-9	3,6-Dimethyl-3-octanyl acetate 60763-42-0	Isoamyl acetate 123-92-2
Acetates—Aliphatic straight chain unsaturated	13	10-Undecen-1-yl acetate 112-19-6	*cis*-3-Hexen-1-yl acetate 3681-71-8	1-Octen-3-yl acetate 2442-10-6
Acetates—Aliphatic unsaturated branched	13	3-Methyl-1-octen-3-yl acetate 66008-66-0	2-Isopropyl-5-methyl-2-hexene-1-yl acetate 40853-56-3	2,7-Dimethyl-5-octen-4-yl acetate 102-58-9
Acetates—Terpene acyclic	14	Dihydromyrcenyl acetate 53767-93-4	Geranyl acetate 105-87-3	Linalyl acetate 115-95-7
Acetates—Terpene cyclic	31	Cedryl acetate 77-54-3	Isobornyl acetate 125-12-2	Dihydroterpinyl acetate 80-25-1
Acetates—Aryl alkyl	22	*p*-Isopropylbenzyl acetate 59230-57-8	Benzyl acetate 140-11-4	Phenethyl acetate 103-45-7
Allyl	18	Allyl butyrate 2051-78-7	Allyl heptanoate 142-19-8	Allyl phenylacetate 1797-74-6
Acetates—Cyclic	30	Cyclododecyl acetate 6221-92-7	4-*tert*-Butylcyclohexyl acetate 32210-23-4	Amylcyclohexyl acetate (mixed isomers) 67874-72-0
Phthalates	6	Dimethyl phthalate 131-11-3	Di(2-ethylhexyl) phthalate 117-81-7	Dibutyl phthalate 84-74-2
Salicylates	18	*trans*-2-Hexenyl salicylate 68133-77-7	3-Methyl-2-butenyl salicylate 68555-58-8	Isoamyl salicylate 87-20-7
Anthranilates	11	*cis*-3-Hexenyl anthranilate 65405-76-7	Methyl anthranilate 134-20-3	Linalyl anthranilate 7149-26-0
Acetoacetate—Aliphatic saturated straight chain	2	Ethyl acetoacetate 141-97-9	Methyl acetoacetate 105-45-3	
Acetoacetate—Terpene acyclic	1	Geranyl acetoacetate 10032-00-5		
Acetoacetate—Terpene cyclic	1	Menthyl acetoacetate 59557-05-0		
Acetoacetate—Aryl alkyl	1	Benzyl acetoacetate 5396-89-4		
Butyrate—Phenyl	1	Anisyl butyrate 6963-56-0		
Butyrate—Aliphatic saturated straight chain	7	Ethyl butyrate 105-54-4	Butyl butyrate 109-21-7	Hexyl butyrate 2639-63-6
Butyrate—Aliphatic branched chain saturated	5	Isobutyl butyrate 539-90-2	Isoamyl butyrate 106-27-4	3,7-Dimethyl-1-octanyl butyrate
Butyrate—Aliphatic straight chain unsaturated	3	*cis*-3-Hexenyl butyrate 16491-36-4	*trans*-2-Hexenyl butyrate 53398-83-7	2-Methyl-5-(2-methyl-3-methylenebicyclo[2.2.1]hept-2-yl)-pent-2-enyl butyrate 67633-98-1
Butyrate—Aliphatic unsaturated branched	1	5-(2,3-Dimethyl tricyclo[2.2.1.02,6]hept-3-yl)-2-methylpent-2-enyl butyrate	67633-99-2	

Appendix A (*continued*)

Sub group	Number of materials	Example 1 CAS #	Example 2 CAS #	Example 3 CAS #
Butyrate—Terpene acyclic	5	Citronellyl butyrate 141-16-2	Geranyl butyrate 106-29-6	Linalyl butyrate 78-36-4
Butyrate—Terpene cyclic	2	α, α-Dimethyl phenethyl butyrate 10094-34-5	Terpinyl butyrate 2153-28-8	
Butyrate—Aryl alkyl	4	Benzyl butyrate 103-37-7	Cinnamyl butyrate 103-61-7	Phenethyl butyrate 103-52-6
Butyrate—Cyclic	2	Cyclohexyl butyrate 1551-44-6	1-Cyclohexylethyl butyrate 63449-88-7	
Octanoates—Phenyl	1	*p*-Tolyl octanoate 59558-23-5		
Octanoates—Aliphatic saturated straight chain	7	Decanoic acid, ester with 1,2,3-propanetriol octanoate 65381-09-1	Methyl octanoate 111-11-5	Amyl octanoate 638-25-5
Octanoates—Aliphatic branched chain saturated	2	Isopropyl octanoate 5458-59-3	Isoamyl octanoate 2035-99-6	
Octanoates—Aliphatic straight chain unsaturated	1	*trans*-2-Hexenyl octanoate 53398-86-0		
Octanoates—Aryl alkyl	1	Benzyl octanoate 10276-85-4		
Isobutyrates —Phenyl	2	*p*-Tolyl isobutyrate 103-93-5	Vanillin isobutyrate 20665-85-4	
Isobutyrates—Aliphatic saturated straight chain	5	Butyl isobutyrate 97-87-0	Octyl isobutyrate 109-15-9	Ethyl isobutyrate 97-62-1
Isobutyrates—Aliphatic branched chain saturated	3	Methyl pentyl isobutyrate No. CAS #	2-Ethylhexyl isobutyrate 35061-61-1	Isobutyl isobutyrate 97-85-8
Isobutyrates—Aliphatic straight chain unsaturated	2	*cis*-3-Hexenyl isobutyrate 41519-23-7	(E)-Hex-3-enyl isobutyrate 84682-20-2	
Isobutyrates—Aliphatic unsaturated branched	1	1,3-Dimethylbut-3-enyl isobutyrate 80118-06-5		
Isobutyrates—Terpene acyclic	5	Citronellyl isobutyrate 97-89-2	Geranyl isobutyrate 2345-26-8	Linalyl isobutyrate 78-35-3
Isobutyrates—Terpene cyclic	1	Terpinyl isobutyrate 7774-65-4		
Isobutyrates—Aryl alkyl	8	Benzyl isobutyrate 103-28-6	Phenethyl isobutyrate 103-48-0	2-Phenoxyethyl isobutyrate 103-60-6
Isobutyrates—Cyclic	4	Maltyl isobutyrate 65416-14-0	3a,4,5,6,7,7a-Hexahydro-4,7-methano-1H-inden-5-yl isobutyrate 67634-20-2	Decahydro-2-naphthyl isobutyrate 67874-78-6
Fatty acids—Aliphatic saturated straight chain	19	Butyl lactate 138-22-7	Isopropyl palmitate 142-91-6	Methyl linoleate 112-63-0
Fatty acids—Aliphatic branched chain saturated	4	Isopropyl myristate 110-27-0	2-Ethylhexyl palmitate 29806-73-3	
Fatty acids—Aliphatic straight chain unsaturated	1	*cis*-3-Hexenyl lactate 61931-81-5		
Fatty acids—Terpene cyclic	1	l-Menthyl lactate 59259-38-0		
Fatty acids—Aryl alkyl	1	Benzyl laurate 140-25-0		

Appendix A (*continued*)

Sub group	Number of materials	Example 1 CAS #	Example 2 CAS #	Example 3 CAS #
Phenylacetates—Phenyl	5	*p*-Tolyl phenylacetate 101-94-0	Eugenyl phenylacetate 10402-33-2	Anisyl phenylacetate 102-17-0
Phenylacetates—Aliphatic saturated straight chain	5	Ethyl phenylacetate 101-97-3	Methyl phenylacetate 101-41-7	Butyl phenylacetate 122-43-0
Phenylacetates—Aliphatic branched chain saturated	3	Isobutyl phenylacetate 102-13-6	Isoamyl phenylacetate 102-19-2	Isopropyl phenylacetate 4861-85-2
Phenylacetates—Aliphatic straight chain unsaturated	2	*trans*-2-Hexenyl phenylacetate 68133-78-8	3-Hexenyl phenylacetate 42436-07-7	
Phenylacetates—Terpene acyclic	4	Geranyl phenylacetate 102-22-7	Linalyl phenylacetate 7143-69-3	Citronellyl phenylacetate 139-70-8
Phenylacetates—Terpene cyclic	2	l-Menthyl phenylacetate 26171-78-8	Guaiacyl phenylacetate 4112-89-4	
Phenylacetates—Aryl alkyl	3	Phenethyl phenylacetate 102-20-5	Benzyl phenylacetate 102-16-9	Cinnamyl phenylacetate 7492-65-1
Phenylacetates—cyclic	1	Cyclohexyl phenylacetate 42288-75-5		
Acetylinic	4	Methyl 2-octynoate 111-12-6	Ethyl 2-nonynoate 10031-92-2	Methyl 2-nonynoate 111-80-8
Benzoates—Phenyl	4	Phenyl benzoate 93-99-2	Isoeugenol benzoate 4194-00-7	*p*-Cresyl benzoate 614-34-6
Benzoates—Aliphatic saturated straight chain	6	Methyl benzoate 93-58-3	Ethyl benzoate 93-89-0	Hexyl benzoate 6789-88-4
Benzoates—Aliphatic saturated branched	3	Isopropyl benzoate 939-48-0	Isoamyl benzoate 94-46-2	Isobutyl benzoate 120-50-3
Benzoates—Aliphatic straight chain unsaturated	1	*cis*-3-Hexenyl benzoate 25152-85-6		
Benzoates—Aliphatic branched chain unsaturated	1	3-Methyl-2-butenyl benzoate 5205-11-8		
Benzoates—Terpene acyclic	3	Geranyl benzoate 94-48-4	Linalyl benzoate 126-64-7	Citronellyl benzoate 10482-77-6
Benzoates—Aryl alkyl	9	Phenethyl benzoate 94-47-3	Methyl *p*-methylbenzoate 99-75-2	Propyl *p*-hydroxybenzoate 94-13-3
Cinnamates—Phenyl	1	Benzyl cinnamate 103-41-3		
Cinnamates—Aliphatic saturated straight chain	4	Ethyl cinnamate 103-36-6	Methyl cinnamate 103-26-4	Butyl cinnamate 538-65-8
Cinnamates—Aliphatic branched chain saturated	3	Isoamyl cinnamate 7779-65-9	Isobutyl cinnamate 122-67-8	Isopropyl cinnamate 7780-06-5
Cinnamates—Aliphatic straight chain unsaturated	1	(*Z*)-3-Hexenyl cinnamate 68133-75-5		
Cinnamates—Terpene acyclic	1	Linalyl cinnamate 78-37-5		
Cinnamates—Aryl alkyl	3	Cinnamyl cinnamate 122-69-0	Phenethyl cinnamate 103-53-7	3-Phenylpropyl cinnamate 122-68-9
Miscellaneous —Phenyl	4	Ethyl 3-hydroxy-3-phenylpropionate 5764-85-2	*p*-Tolyl 3-methylcrotonate 24700-20-7	4-Methyl-2-phenyl-2-pentenal 26643-91-4
Miscellaneous—Aliphatic saturated straight chain	49	Hexyl 2,2-dimethylpropanoate 5434-57-1	Octyl crotonate 22874-79-9	Methyl abietate 68186-14-1
Miscellaneous—Aliphatic branched chain saturated	15	Isopropyl tiglate 6284-46-4	Ethyl levulinate 539-88-8	2-Methylpropyl 3-methylbutyrate 589-59-3

Appendix A (*continued*)

Sub group	Number of materials	Example 1 CAS #	Example 2 CAS #	Example 3 CAS #
Miscellaneous—Aliphatic straight chain unsaturated	26	*trans*-2-Hexenyl pentanoate 56922-74-8	*cis*-3-Hexenyl tiglate 67883-79-8	3-Hexenyl 2-methyl-butanoate 10094-41-4
Miscellaneous—Aliphatic unsaturated branched	6	2-Butenoic acid, 2-methyl-, 2-methyl-2-butenyl ester, (*E*, *E*)-72845-40-0	1,3-Dimethylbutyl 2-butenoate 35206-51-0	*n*-Hexyl 2-butenoate 19089-92-0
Miscellaneous —Terpene acyclic	6	Citronellyl tiglate 24717-85-9	Geranyl tiglate 7785-33-3	Geranyl crotonate 56172-46-4
Miscellaneous—Terpene cyclic	1	8-(Acetoxymethyl) isolongifolene 61826-56-0		
Miscellaneous—Aryl alkyl	12	Phenylethyl methacrylate 3683-12-3	Benzyl *trans*-2-methyl-2-butenoate 37526-88-8	Phenethyl tiglate 55719-85-2
Miscellaneous—Cyclic	9	Ethylene dodecanedioate 54982-83-1	Ethylene brassylate 105-95-3	1-Acetoxy-1-ethynyl-2-sec-butylcyclohexane 37172-05-7
Propionates—Phenyl	2	Anisyl propionate 7549-33-9	*p*-Tolyl propionate 7495-84-3	
Propionates—Aliphatic saturated straight chain	7	Ethyl propionate 105-37-3	Propyl propionate 106-36-5	Methyl propionate 554-12-1
Propionates—Aliphatic branched chain saturated	5	Isobornyl propionate 2756-56-1	Isoamyl propionate 105-68-0	Isononyl propionate 65155-45-5
Propionates—Aliphatic straight chain unsaturated	3	*cis*-3-Hexenyl propionate 33467-74-2	*trans*-2-Hexenyl propionate 53398-80-4	9-Decenyl propionate 68480-06-8
Propionates—Terpene acyclic	5	Citronellyl propionate 141-14-0	Geranyl propionate 105-90-8	Linalyl propionate 144-39-8
Propionates—Terpene cyclic	4	Terpinyl propionate 80-27-3	laevo-Carvyl propionate 97-45-0	2-Bornyl propionate 20279-25-8
Propionates—Aryl alkyl	7	Benzyl propionate 122-63-4	α-Methylbenzyl propionate 120-45-6	Phenethyl propionate 122-70-3
Propionates—Cyclic	6	Tricyclodecenyl propionate 17511-60-3	2-*tert*-Butylcyclohexyl propionate 40702-13-4	4-(Isopropyl) cyclohexyl propionate 63449-95-6
Dioic–Trioic	32	Triethyl orthoformate 122-51-0	Dimethyl succinate 106-65-0	Citronellyl ethyl oxalate 60788-25-2
Carboxylates—Aliphatic saturated straight chain	4	Ethyl (3a.α,4.β,7.β,7a.α)-octahydro-4,7-methano-3aH-indene-3a-carboxylate 80623-07-0	Ethyl (3a.α,4.α,7.α.,7a.α)-octahydro-4,7-methano-3aH-indene-3a-carboxylate 80657-64-3	Methyl 3,3-dimethyl bicyclo [2.2.1] heptane-2-carboxylate 52557-97-8
Carboxylates—Aliphatic straight chain unsaturated	11	Ethyl cyclohex-3-ene-1-carboxylate 15111-56-5	Ethyl 2-ethyl-3,6, 6-trimethyl cyclohexenecarboxylate 94333-50-3	Methyl 2,6,6-trimethyl cyclohex-2-ene-1-carboxylate 28043-10-9
Carboxylates—Cyclic	3	Methyl 1-methylcyclohex-3-enecarboxylate 6493-80-7	Ethyl tricyclo [3.3.1.13,7]decane-1-carboxylate 2094-73-7	Methyl cyclooctanecarboxylate 3724-54-7

Appendix A (*continued*)

Sub group	Number of materials	Example 1 CAS #	Example 2 CAS #	Example 3 CAS #
Carboxylates—Miscellaneous	1	Ethyl nicotinate 614-18-6		
Hexanoates—Aliphatic saturated straight chain	5	Ethyl hexanoate 123-66-0	Hexyl hexanoate 6378-65-0	Methyl hexanoate 106-70-7
Hexanoates—Aliphatic branched chain saturated	3	Isobutyl hexanoate 105-79-3	Isoamyl hexanoate 2198-61-0	Isopropyl hexanoate 2311-46-8
Hexanoates—Aliphatic straight chain unsaturated	1	*cis*-3-Hexenyl hexanoate 31501-11-8		
Hexanoates—Terpene acyclic	2	Geranyl hexanoate 10032-02-7	Linalyl hexanoate 7779-23-9	
Valerates—Aliphatic saturated straight chain	4	Propyl valerate 141-06-0	Methyl valerate 624-24-8	Amyl valerate 2173-56-0
Valerates—Aliphatic branched chain saturated	1	3-Methylbutyl valerate 2050-09-1		
Valerates—Aliphatic straight chain unsaturated	1	*cis*-3-Hexenyl valerate 35852-46-1		
Valerates—Aryl alkyl	1	Benzyl valerate 10361-39-4		
Isovalerates—Aliphatic saturated straight chain	6	Hexyl isovalerate 10032-13-0	Ethyl isovalerate 108-64-5	Butyl isovalerate 109-19-3
Isovalerates—Aliphatic branched chain saturated	2	Isoamyl isovalerate 659-70-1	Isopropyl isovalerate 32665-23-9	
Isovalerates —Aliphatic straight chain unsaturated	2	*trans*-2-Hexenyl isovalerate 68698-59-9	*cis*-3-Hexenyl isovalerate 35154-45-1	
Isovalerates —Aliphatic unsaturated branched	1	3-Methylbut-3-enyl isovalerate 54410-94-5		
Isovalerates—Terpene acyclic	5	Citronellyl isovalerate 68922-10-1	Linalyl isovalerate 1118-27-0	Geranyl isovalerate 109-20-6
Isovalerates—Terpene cyclic	4	Bornyl isovalerate (endo-)76-50-6	Menthyl isovalerate 16409-46-4	Isobornyl isovalerate 7779-73-9
Isovalerates—Aryl alkyl	3	Cinnamyl isovalerate 140-27-2	Benzyl isovalerate 103-38-8	Phenethyl isovalerate 140-26-1
Ethers				
Aliphatic saturated	20	Eucalyptol(1,8-cineole) 470-82-6	Decyl methyl ether 7289-52-3	1,4-Cineole 470-67-7
Aliphatic unsaturated	13	(*Z*)-1-(1-Methoxypropoxy) hex-3-ene 97358-55-9	(4-Methoxybutylidene) cyclohexane 93777-41-4	1-Methoxytridec-5-ene 93981-59-0
Aromatic	51	*trans*-Anethole 4180-23-8	Isosafrole 120-58-1	Eugenyl methyl ether 93-15-2
Terpene	16	Isobornyl methyl ether 5331-32-8	Linalyl methyl ether 60763-44-2	Cedrol methyl ether 19870-74-7
Heterocyclics				
Furans	17	Furfural 98-01-1	5-Methylfurfural 620-02-0	Furfuryl alcohol 98-00-0
Miscellaneous	8	2-Acetylthiazole 24295-03-2	2-Methylbenzoxazole 95-21-6	4-Butyl-5-methylthiazole 57246-60-3
Hydrocarbons				
Acyclic terpenes	5	Myrcene 123-35-3	3,7-Dimethyl-1,3,6-octatriene 13877-91-3	Dihydromyrcene 2436-90-0

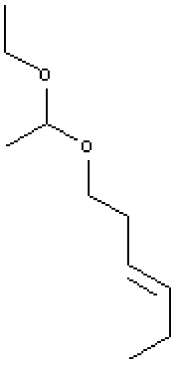
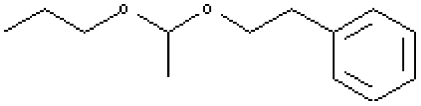
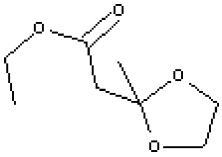
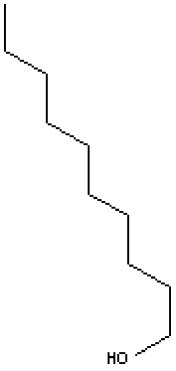
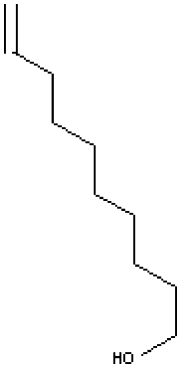
Appendix A (*continued*)

Sub group	Number of materials	Example 1 CAS #	Example 2 CAS #	Example 3 CAS #
Cyclic terpenes	26	D-Limonene 5989-27-5	*p*-Cymene 99-87-6	β-Pinene 127-91-3
Sesquiterpenes	11	β-Caryophyllene 87-44-5	α-Cedrene 469-61-4	β-Patchouline 514-51-2
Aliphatic	25	Dimyrcene 20016-72-2	Decane 124-18-5	Isoprene 78-79-5
Aromatic	15	Ethylbenzene 100-41-4	1,1,3-Trimethyl-3-phenylindane 3910-35-8	*p*,α-Dimethylstyrene 1195-32-0
Ketones				
Cyclopentanones	26	Dihydroisojasmone 95-41-0	2-Hexylcyclopentanone 13074-65-2	Methyl jasmonate 1211-29-6
Cyclohexanones	17	4-t-Amylcyclohexanone 16587-71-6	2-Cyclohexylcyclohexa none 90-42-6	3-Methyl-5-propyl-2-cyclohexen-1-one 3720-16-9
Diones	11	2,3-Hexanedione 3848-24-6	Diacetyl 431-03-8	5-Methyl-2,3-hexanedione 13706-86-0
Aromatic	40	Methyl β-naphthyl ketone 93-08-3	Cinnamylidene acetone 4173-44-8	*p*-Methoxypropiophenone 121-97-1
Alicyclic	41	Acetyl cedrene 32388-55-9	Cyclopentadecanone 502-72-7	1-(2,6,6-Trimethyl-2-cyclohexen-1-yl)pent-1-en-3-one 7779-30-8
Aliphatic unsaturated	32	6-Methyl-5-hepten-2-one 110-93-0	3,4,5,6-Tetrahydropseudoionone 4433-36-7	5-Hexen-2-one 109-49-9
Aliphatic saturated	32	2-Octanone 111-13-7	1-(*p*-Methoxyphenyl)-2-propanone 122-84-9	Cyclohexyl methyl pentanone 4927-39-3
Terpene	28	D-Carvone 2244-16-8	Fenchone 1195-79-5	Isolongifolanone 14727-47-0
Cyclohexyl	32	Allyl α-ionone 79-78-7	Isodamascone 39872-57-6	β-Ionone 14901-07-6
Lactones				
Lactones	49	γ-Valerolactone 108-29-2	ω-Pentadecalactone 106-02-5	Hydroxynonanoic acid, δ-lactone 3301-94-8
Furanones	4	5-(*cis*-3-Hexenyl) dihydro-5-methyl-2(3H)furanone 70851-61-5	1,5,5,9-Tetramethyl-13-oxatricyclo (8.3.0.0(4,9)) tridecane 3738-00-9	2-Ethyl-4-hydroxy-5-methyl-3(2H)-furanone 27538-09-6
Phthalate/phthalide	3	3-Propylidenephthalide 17369-59-4	3-*n*-Butylphthalide 6066-49-5	3-Butylidenephthalide 551-08-6
Pyranones	5	5-Butyl-5-ethylytetrahydro-2H-pyran-2-one 67770-79-0	4,6-Dimethyl-2H-pyran-2-one 675-09-2	Tetrahydro-6-(2-pentenyl)-2H-pyran-2-one 34686-71-0
Miscellaneous				
Polyols and their ethers	21	Diethylene glycol 111-46-6	Glycerol 56-81-5	Dipropylene glycol monoethyl ether 15764-24-6
Halogens	5	Trichloromethyl phenyl carbinyl acetate 90-17-5	Bromstyrol 103-64-0	

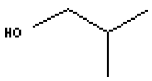
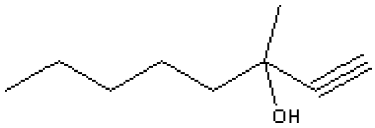
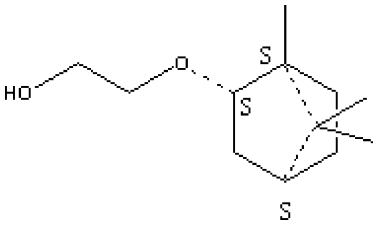
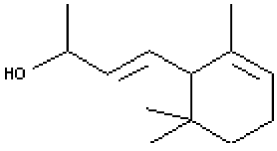
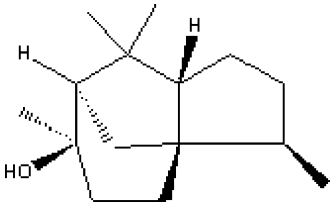
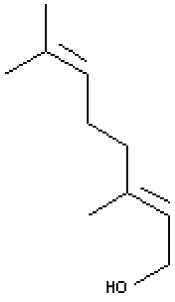
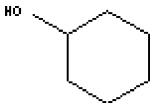
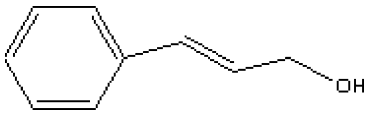
Appendix A (*continued*)

Sub group	Number of materials	Example 1 CAS #	Example 2 CAS #	Example 3 CAS #
Miscellaneous	1	1,6-Octadiene, 7-methyl-3-methylene-, acid-hydrated, hydrocarbon fractions, washed 90480-40-3		
Musks				
Nitromusks	5	Musk ketone 81-14-1	Musk xylol 81-15-2	Moskene 116-66-5
Polycyclic musks	5	AHTN 21145-77-7	HHCB 1222-05-5	AHMI 15323-35-0
Nitriles				
Nitriles	39	Cinnamyl nitrile 1885-38-7	Cuminyl nitrile 13816-33-6	Dodecanenitrile 2437-25-4
Phenols				
Phenols	40	Isoeugenol 97-54-1	Thymol 89-83-8	Methyl atrarate 4707-47-5
Pyrans				
Pyrans	27	4-Acetoxy-3-pentyltetrahydropyran 18871-14-2	Nerol oxide 1786-08-9	(+)-*cis*-Rose oxide 4610-11-1
Pyrazines				
Pyrazines	22	2-Methoxy-3(5 and 6)-isopropylpyrazine 25773-40-4	2-Ethyl-3-methylpyrazine 15707-23-0	3-Ethylpyridine 536-78-7
Quinolines				
Quinolines	14	6-Isopropylquinoline 135-79-5	Isopropylquinoleine 1333-53-5	1,2,3,4-Tetrahydro-4-methylquinoleine 19343-78-3
Schiff's bases				
Schiff's bases	26	Cinnamic aldehyde-methyl anthranilate (Schiff base) 94386-48-8	Lilial-methyl anthranilate (Schiff base) 91-51-0	Hydroxycitronellal-Indole (Schiff base) 68527-79-7
Sulfur containing				
Sulfur containing	24	Allyl sulfide 592-88-1	4-Methoxy-2-methyl-2-butanethiol 94087-83-9	Phenethyl isothiocyanate 2257-09-2

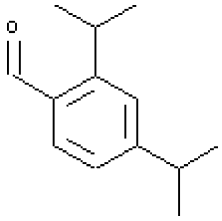
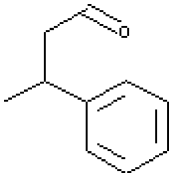
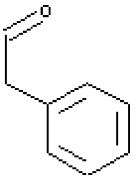
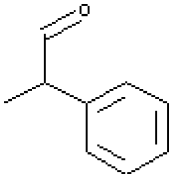
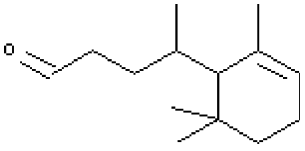
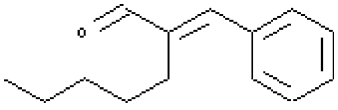
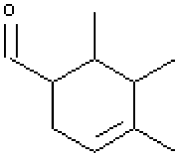
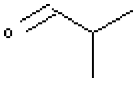
Appendix B. Structures for example chemicals from classification of fragrance chemicals

Sub group	Sample compund CAS #	Structure
Acetals		
Aliphatic aldehyde/aliphatic alcohol	Acetaldehyde ethyl *trans*-3-hexenyl acetal 60763-40-8	
Aliphatic aldehyde/aromatic alcohol and aromatic aldehyde/aliphatic alcohol	Propyl phenethyl acetal 7493-57-4	
Ketals	Ethylacetoacetate ethylene glycol ketal 6413-10-1	
Alcohols		
Straight chain saturated	1-Decanol 112-30-1	
Straight chain unsaturated	9-Decen-1-ol 13019-22-2	

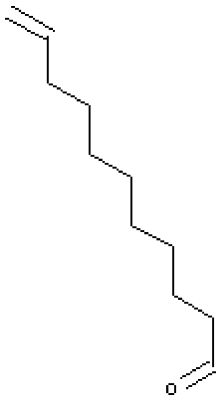
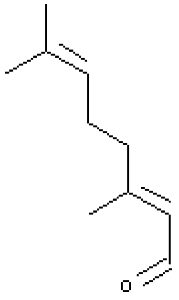
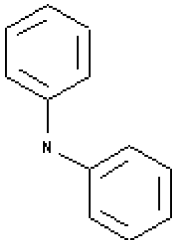
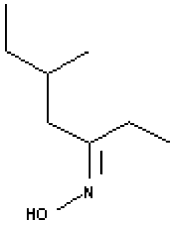
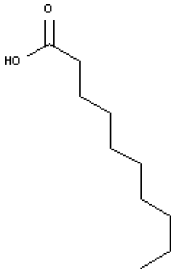
Appendix B (*continued*)

Sub group	Sample compund CAS #	Structure
Branched chain saturated	Isobutyl alcohol 78-83-1	
Branched chain unsaturated	3-Methyl-1-octyn-3-ol 23580-51-0	
Miscellaneous	Ethylcellulose 9004-57-3	Structures unavailable for this subgroup
Alkyl cyclic main group	Arbanol 7070-15-7	
Alkyl cyclic ionols	α-Ionol 25312-34-9	
Terpene cyclic	Cedrol 77-53-2	
Terpene chain	Geraniol 106-24-1	
Cyclic	Cyclohexanol 108-93-0	
Aryl alkyl	Cinnamyl alcohol 104-54-1	

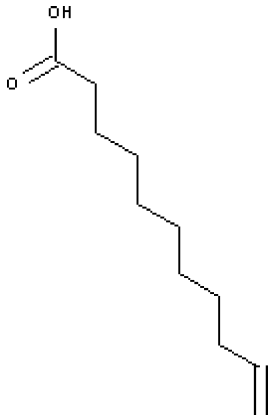
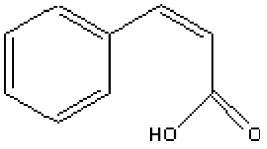
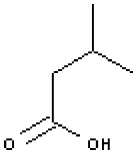
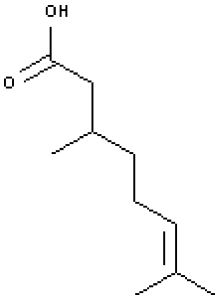
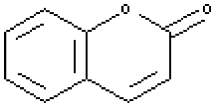
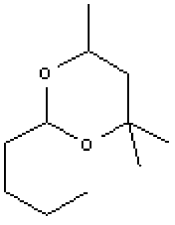
Appendix B (*continued*)

Sub group	Sample compund CAS #	Structure
Aldehydes		
Aryl	Diisopropylbenzaldehyde 68459-95-0	
Aryl alkyl phenyl alky	3-Phenylbutanal 16251-77-7	
Aryl alkyl aryl acetaldehydes	Phenylacetaldehyde 122-78-1	
Aryl alkyl cinnamic and propionaldehydes	2-Phenylpropionaldehyde 93-53-8	
Alkyl cyclic	4-(2,6,6-Trimethyl-2-cyclohexen)-2-methylbutanal 65405-84-7	
Cinnamic	α-Amylcinnamaldehyde 122-40-7	
Cyclic	Isocyclocitral 1335-66-6	
Saturated	Isobutyraldehyde 78-84-2	

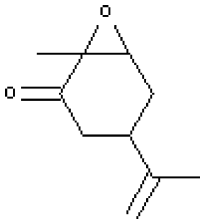
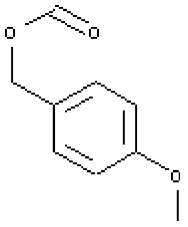
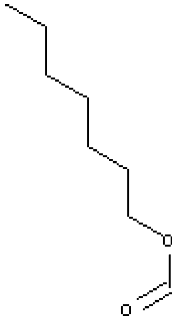
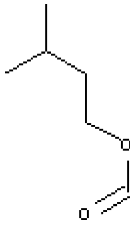
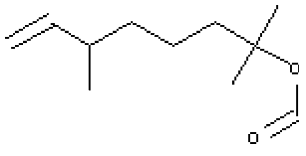
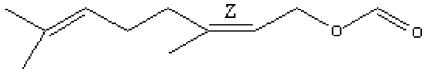
Appendix B (*continued*)

Sub group	Sample compund CAS #	Structure
Straight chain unsaturated	10-Undecenal 112-45-8	
Branched chain unsaturated	Citral 5392-40-5	
Amines/amides Main group	Diphenylamine 122-39-4	
Oximes	5-Methyl-3-heptanone oxime 22457-23-4	
Carboxylic acids Straight chain saturated	Decanoic acid 334-48-5	

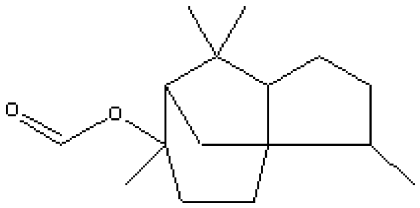
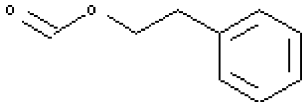
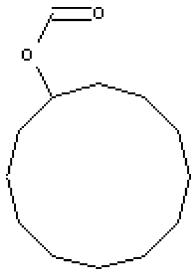
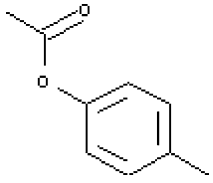
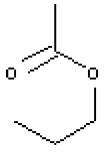
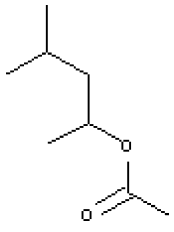
Appendix B (*continued*)

Sub group	Sample compund CAS #	Structure
Straight chain unsaturated	10-Undecenoic acid 112-38-9	
Cyclic and aromatic	Cinnamic acid 621-82-9	
Branched chain saturated	Isovaleric acid 503-74-2	
Branched chain unsaturated	3,7-Dimethyl-6-octenoic acid 502-47-6	
Coumarins		
Coumarins	Coumarin 91-64-5	
Dioxanes	2-Butyl-4,4,6-trimethyl-1,3-dioxane 54546-26-8	

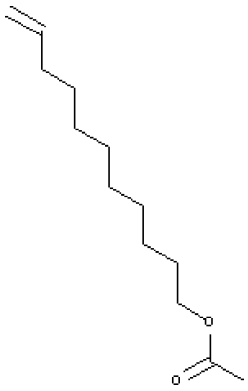
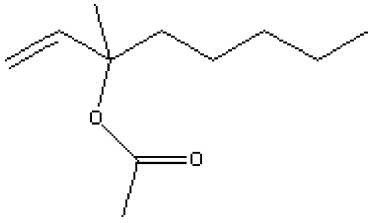
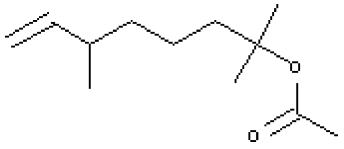
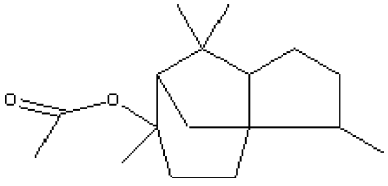
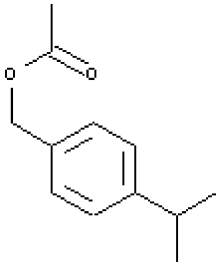
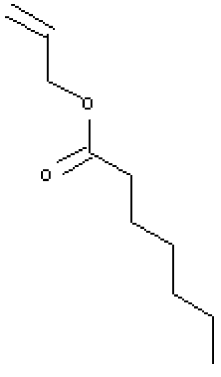
Appendix B (*continued*)

Sub group	Sample compund CAS #	Structure
Epoxides		
Epoxides	*cis*-Carvone oxide 33204-74-9	
Esters		
Formates—Phenyl	Anisyl formate 122-91-8	
Formates—Aliphatic saturated straight chain	Heptyl formate 112-23-2	
Formates—Aliphatic branched chain saturated	Isoamyl formate 110-45-2	
Formates—Aliphatic straight chain unsaturated	*cis*-3-Hexenyl formate 33467-73-1	
Formates—Aliphatic unsaturated branched	2,6-Dimethyloct-7-en-2-yl formate 25279-09-8	
Formates—Terpene acyclic	Neryl formate 2142-94-1	

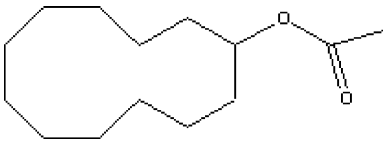
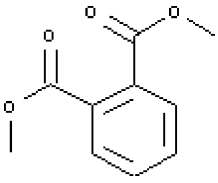
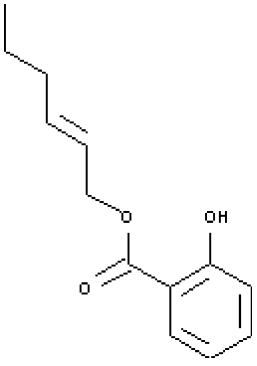
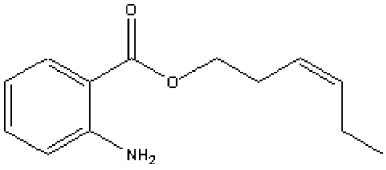
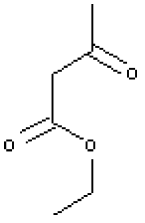
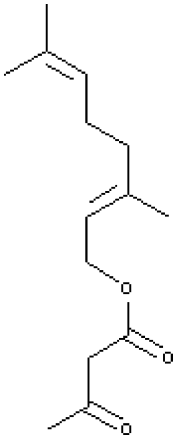
Appendix B (*continued*)

Sub group	Sample compund CAS #	Structure
Formates—Terpene cyclic	Cedryl formate 39900-38-4	
Formates—Aryl alkyl	Phenethyl formate 104-62-1	
Formates—Cyclic	Cyclododecyl formate 59052-82-3	
Acetates—Phenyl	*p*-Tolyl acetate 140-39-6	
Acetates—Aliphatic saturated straight chain	Propyl acetate 109-60-4	
Acetates—Aliphatic branched chain saturated	Methyl isobutyl carbinyl acetate 108-84-9	

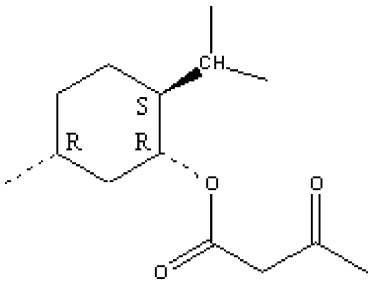
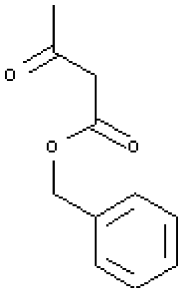
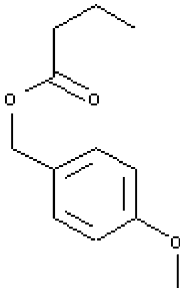
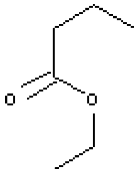
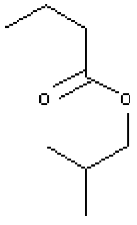
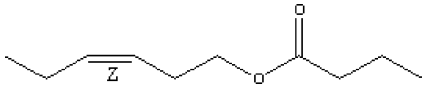
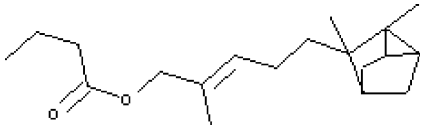
Appendix B (*continued*)

Sub group	Sample compund CAS #	Structure
Acetates—Aliphatic straight chain unsaturated	10-Undecen-1-yl acetate 112-19-6	
Acetates—Aliphatic unsaturated branched	3-Methyl-1-octen-3-yl acetate 66008-66-0	
Acetates—Terpene acyclic	Dihydromyrcenyl acetate 53767-93-4	
Acetates—Terpene cyclic	Cedryl acetate 77-54-3	
Acetates—Aryl alkyl	*p*-Isopropylbenzyl acetate 59230-57-8	
Allyl	Allyl heptanoate 142-19-8	

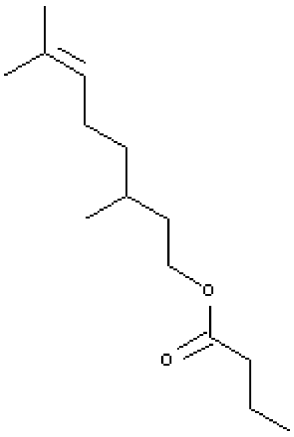
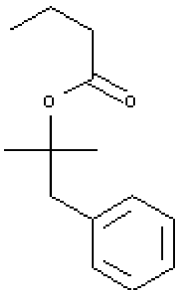
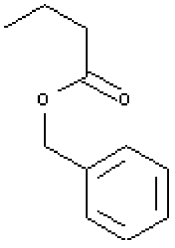
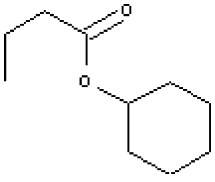
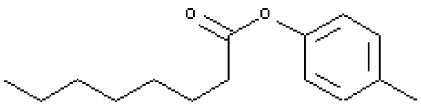
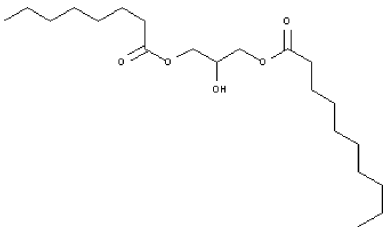
Appendix B (*continued*)

Sub group	Sample compund CAS #	Structure
Acetates—Cyclic	Cyclododecyl acetate 6221-92-7	
Phthalates	Dimethyl phthalate 131-11-3	
Salicylates	*trans*-2-Hexenyl salicylate 68133-77-7	
Anthranilates	*cis*-3-Hexenyl anthranilate 65405-76-7	
Acetoacetate—Aliphatic saturated straight chain	Ethyl acetoacetate 141-97-9	
Acetoacetate—Terpene acyclic	Geranyl acetoacetate 10032-00-5	

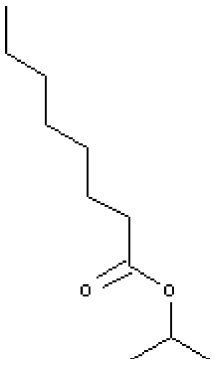
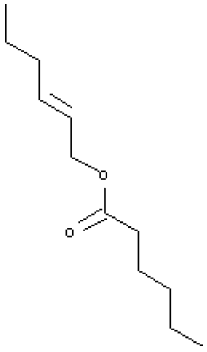
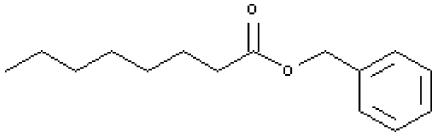
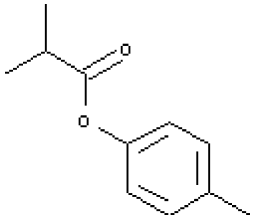
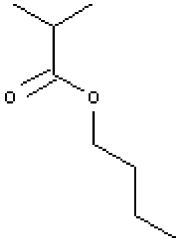
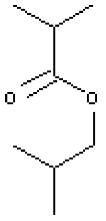
Appendix B (*continued*)

Sub group	Sample compund CAS #	Structure
Acetoacetate—Terpene cyclic	Menthyl acetoacetate 59557-05-0	
Acetoacetate—Aryl alkyl	Benzyl acetoacetate 5396-89-4	
Butyrate—Phenyl	Anisyl butyrate 6963-56-0	
Butyrate—Aliphatic saturated straight chain	Ethyl butyrate 105-54-4	
Butyrate—Aliphatic branched chain saturated	Isobutyl butyrate 539-90-2	
Butyrate—Aliphatic straight chain unsaturated	*cis*-3-Hexenyl butyrate 16491-36-4	
Butyrate—Aliphatic unsaturated branched	5-(2,3-Dimethyl tricyclo [2.2.1.02,6]hept-3-yl)-2-methylpent-2-enyl butyrate 67633-99-2	

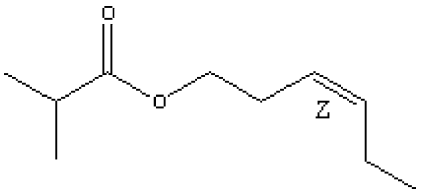
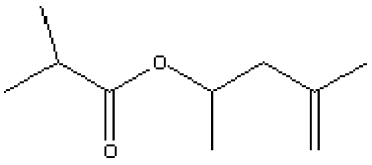
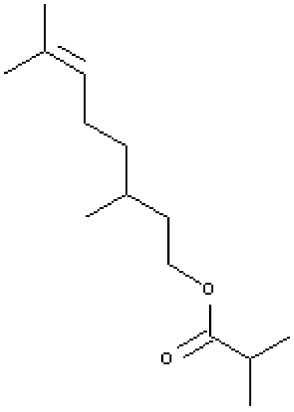
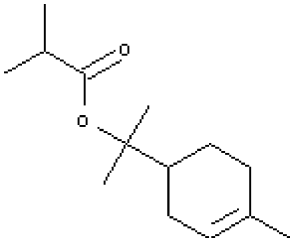
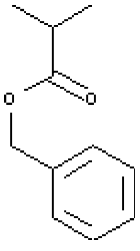
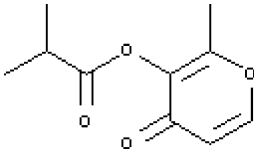
Appendix B (*continued*)

Sub group	Sample compund CAS #	Structure
Butyrate—Terpene acyclic	Citronellyl butyrate 141-16-2	
Butyrate—Terpene cyclic	α, α-Dimethyl phenethyl butyrate 10094-34-5	
Butyrate—Aryl alkyl	Benzyl butyrate 103-37-7	
Butyrate—Cyclic	Cyclohexyl butyrate 1551-44-6	
Octanoates—Phenyl	*p*-Tolyl octanoate 59558-23-5	
Octanoates—Aliphatic saturated straight chain	Decanoic acid, ester with 1,2,3-propanetriol octanoate 65381-09-1	

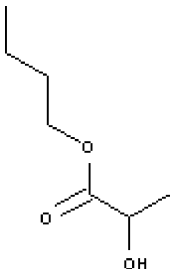
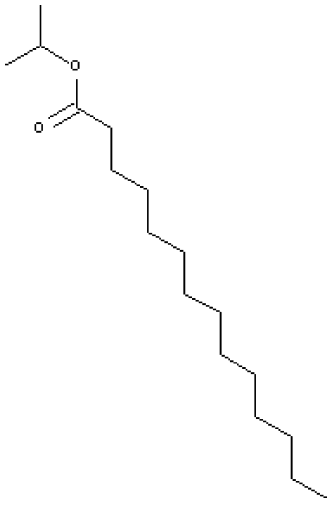
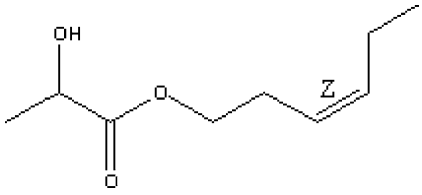
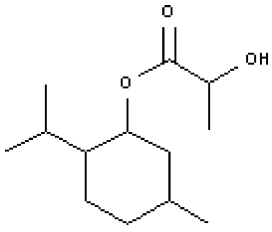
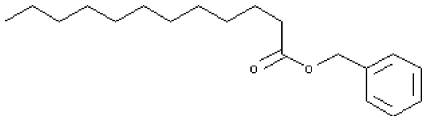
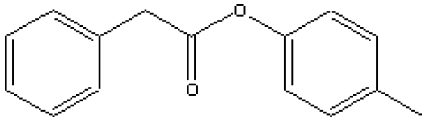
Appendix B (*continued*)

Sub group	Sample compund CAS #	Structure
Octanoates—Aliphatic branched chain saturated	Isopropyl octanoate 5458-59-3	
Octanoates—Aliphatic straight chain unsaturated	*trans*-2-Hexenyl octanoate 53398-86-0	
Octanoates—Aryl alkyl	Benzyl octanoate 10276-85-4	
Isobutyrates —Phenyl	*p*-Tolyl isobutyrate 103-93-5	
Isobutyrates—Aliphatic saturated straight chain	Butyl isobutyrate 97-87-0	
Isobutyrates—Aliphatic branched chain saturated	Isobutyl isobutyrate 97-85-8	

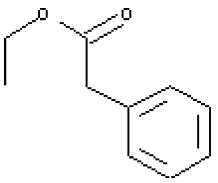
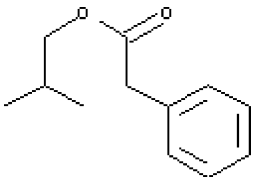
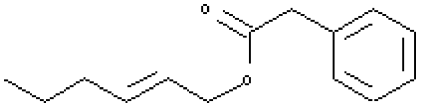
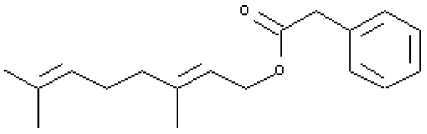
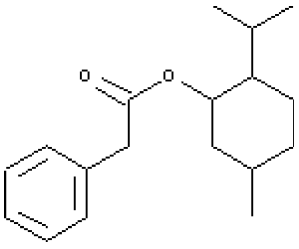
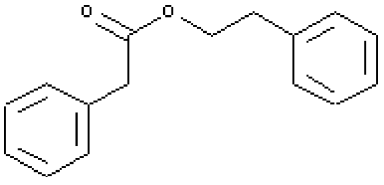
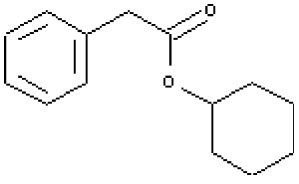
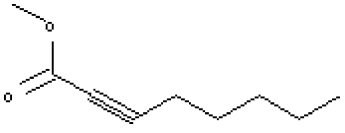
Appendix B (*continued*)

Sub group	Sample compund CAS #	Structure
Isobutyrates—Aliphatic straight chain unsaturated	*cis*-3-Hexenyl isobutyrate 41519-23-7	
Isobutyrates—Aliphatic unsaturated branched	1,3-Dimethylbut-3-enyl isobutyrate 80118-06-5	
Isobutyrates—Terpene acyclic	Citronellyl isobutyrate 97-89-2	
Isobutyrates—Terpene cyclic	Terpinyl isobutyrate 7774-65-4	
Isobutyrates—Aryl alkyl	Benzyl isobutyrate 103-28-6	
Isobutyrates—Cyclic	Maltyl isobutyrate 65416-14-0	

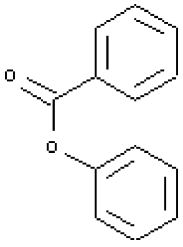
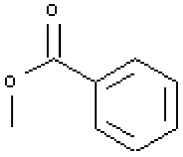
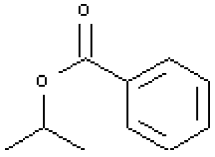
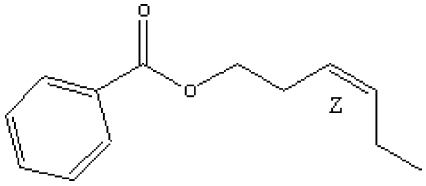
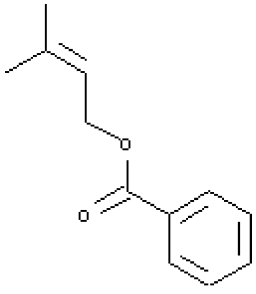
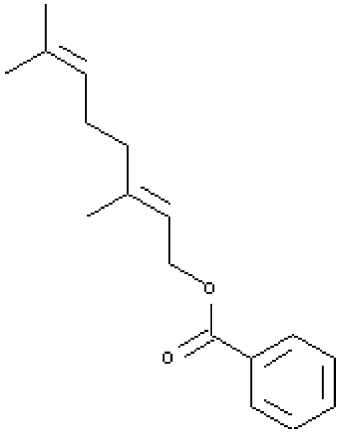
Appendix B (*continued*)

Sub group	Sample compund CAS #	Structure
Fatty acids—Aliphatic saturated straight chain	Butyl lactate 138-22-7	
Fatty acids—Aliphatic branched chain saturated	Isopropyl myristate 110-27-0	
Fatty acids—Aliphatic straight chain unsaturated	*cis*-3-Hexenyl lactate 61931-81-5	
Fatty acids—Terpene cyclic	l-Menthyl lactate 59259-38-0	
Fatty acids—Aryl alkyl	Benzyl laurate 140-25-0	
Phenylacetates—Phenyl	*p*-Tolyl phenylacetate 101-94-0	

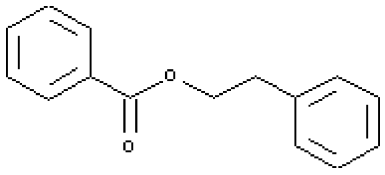
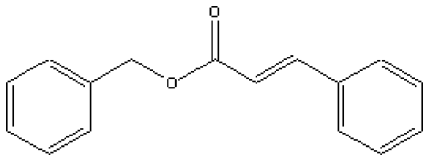
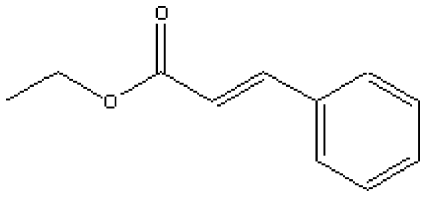
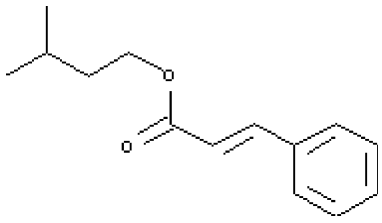
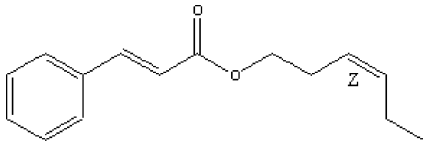
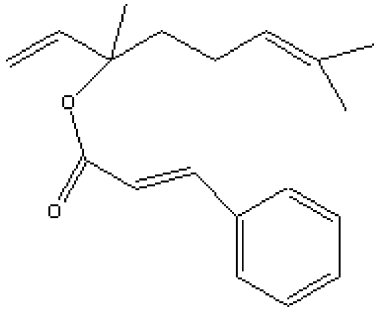
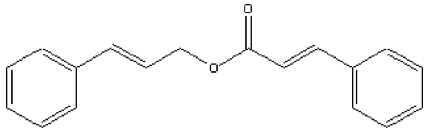
Appendix B (*continued*)

Sub group	Sample compund CAS #	Structure
Phenylacetates—Aliphatic saturated straight chain	Ethyl phenylacetate 101-97-3	
Phenylacetates—Aliphatic branched chain saturated	Isobutyl phenylacetate 102-13-6	
Phenylacetates—Aliphatic straight chain unsaturated	*trans*-2-Hexenyl phenylacetate 68133-78-8	
Phenylacetates—Terpene acyclic	Geranyl phenylacetate 102-22-7	
Phenylacetates—Terpene cyclic	l-Menthyl phenylacetate 26171-78-8	
Phenylacetates—Aryl alkyl	Phenethyl phenylacetate 102-20-5	
Phenylacetates—Cyclic	Cyclohexyl phenylacetate 42288-75-5	
Acetylinic	Methyl 2-octynoate 111-12-6	

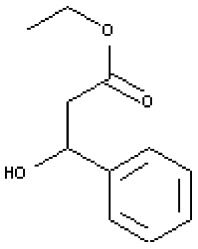
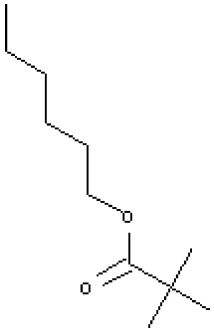
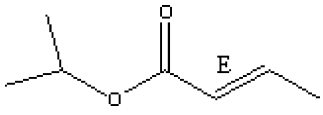
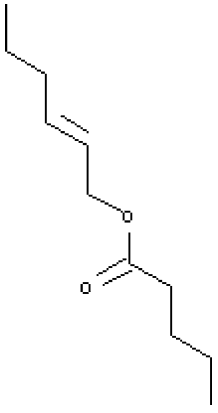
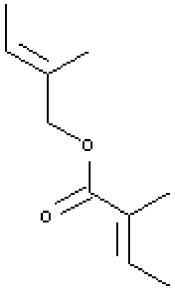
Appendix B (*continued*)

Sub group	Sample compund CAS #	Structure
Benzoates—Phenyl	Phenyl benzoate 93-99-2	
Benzoates—Aliphatic saturated straight chain	Methyl benzoate 93-58-3	
Benzoates—Aliphatic saturated branched	Isopropyl benzoate 939-48-0	
Benzoates—Aliphatic straight chain unsaturated	*cis*-3-Hexenyl benzoate 25152-85-6	
Benzoates—Aliphatic branched chain unsaturated	3-Methyl-2-butenyl benzoate 5205-11-8	
Benzoates—Terpene acyclic	Geranyl benzoate 94-48-4	

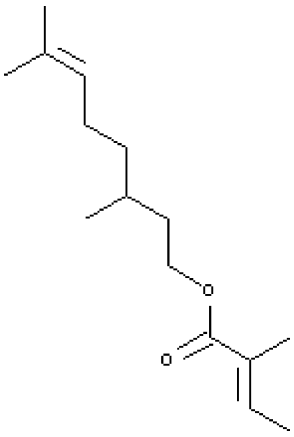
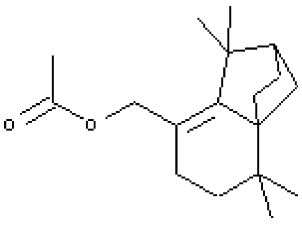
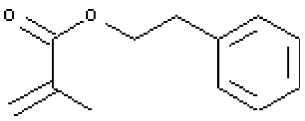
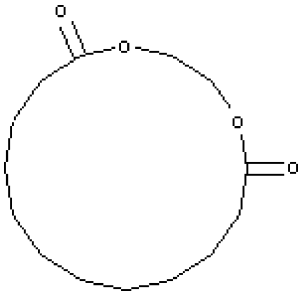
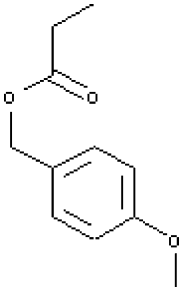
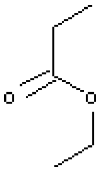
Appendix B (*continued*)

Sub group	Sample compund CAS #	Structure
Benzoates—Aryl alkyl	Phenethyl benzoate 94-47-3	
Cinnamates—Phenyl	Benzyl cinnamate 103-41-3	
Cinnamates—Aliphatic saturated straight chain	Ethyl cinnamate 103-36-6	
Cinnamates—Aliphatic branched chain saturated	Isoamyl cinnamate 7779-65-9	
Cinnamates—Aliphatic straight chain unsaturated	(*Z*)-3-Hexenyl cinnamate 68133-75-5	
Cinnamates—Terpene acyclic	Linalyl cinnamate 78-37-5	
Cinnamates—Aryl alkyl	Cinnamyl cinnamate 122-69-0	

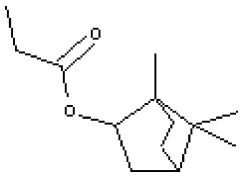
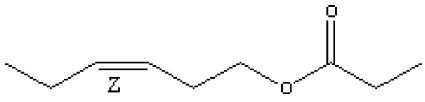
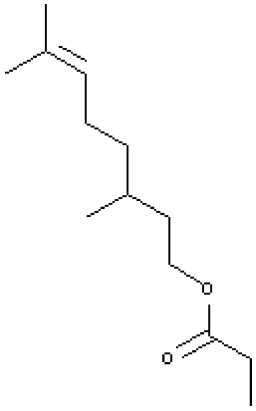
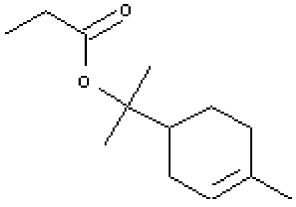
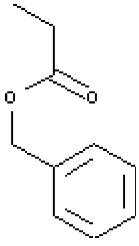
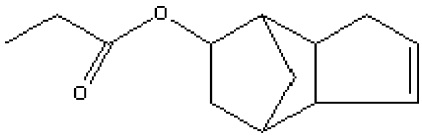
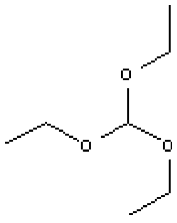
Appendix B (*continued*)

Sub group	Sample compund CAS #	Structure
Miscellaneous—Phenyl	Ethyl 3-hydroxy-3-phenylpropionate 5764-85-2	
Miscellaneous—Aliphatic saturated straight chain	Hexyl 2,2-dimethylpropanoate 5434-57-1	
Miscellaneous—Aliphatic branched chain saturated	Isopropyl tiglate 6284-46-4	
Miscellaneous—Aliphatic straight chain unsaturated	*trans*-2-Hexenyl pentanoate 56922-74-8	
Miscellaneous—Aliphatic unsaturated branched	2-Butenoic acid, 2-methyl-, 2-methyl-2-butenyl ester,(*E*,*E*)-72845-40-0	

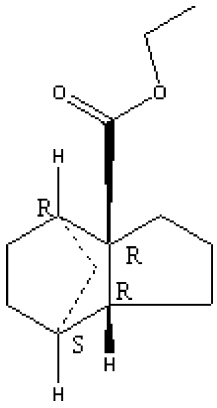
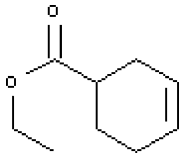
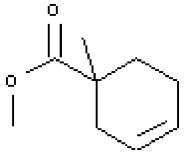
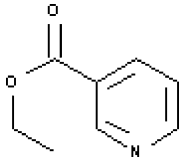
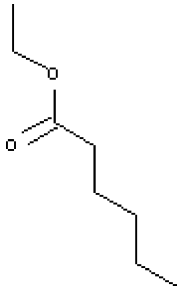
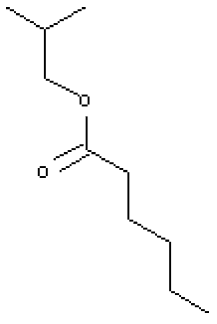
Appendix B (*continued*)

Sub group	Sample compund CAS #	Structure
Miscellaneous—Terpene acyclic	Citronellyl tiglate 24717-85-9	
Miscellaneous—Terpene cyclic	8-(Acetoxymethyl) isolongifolene 61826-56-0	
Miscellaneous—Aryl alkyl	Phenylethyl methacrylate 3683-12-3	
Miscellaneous—Cyclic	Ethylene dodecanedioate 54982-83-1	
Propionates—Phenyl	Anisyl propionate 7549-33-9	
Propionates—Aliphatic saturated straight chain	Ethyl propionate 105-37-3	

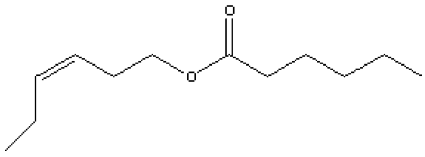
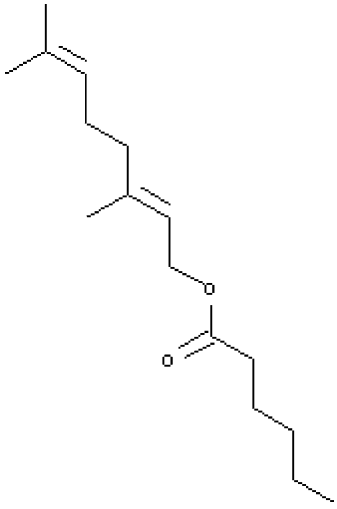
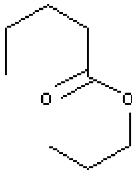
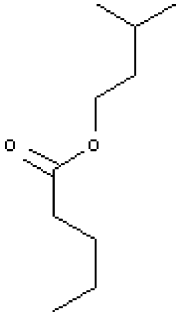
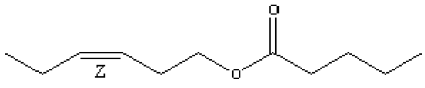
Appendix B (*continued*)

Sub group	Sample compund CAS #	Structure
Propionates—Aliphatic branched chain saturated	Isobornyl propionate 2756-56-1	
Propionates—Aliphatic straight chain unsaturated	*cis*-3-Hexenyl propionate 33467-74-2	
Propionates—Terpene acyclic	Citronellyl propionate 141-14-0	
Propionates—Terpene cyclic	Terpinyl propionate 80-27-3	
Propionates—Aryl alkyl	Benzyl propionate 122-63-4	
Propionates—Cyclic	Tricyclodecenyl propionate 17511-60-3	
Dioic–Trioic	Triethyl orthoformate 122-51-0	

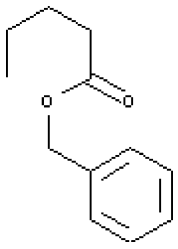
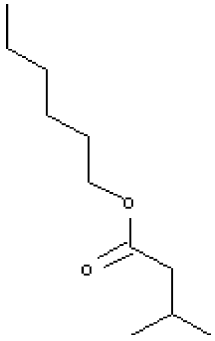
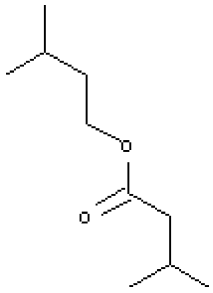
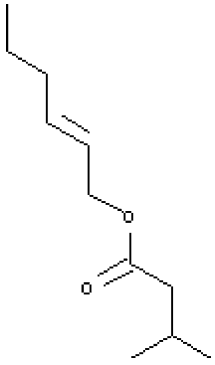
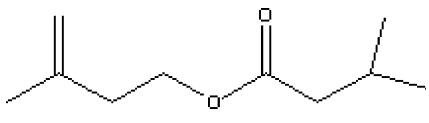
Appendix B (*continued*)

Sub group	Sample compund CAS #	Structure
Carboxylates—Aliphatic saturated straight chain	Ethyl (3a.α,4.β,7.β,7a.α)-octahydro-4,7-methano-3aH-indene-3a-carboxylate 80623-07-0	
Carboxylates—Aliphatic straight chain unsaturated	Ethyl cyclohex-3-ene-1-carboxylate 15111-56-5	
Carboxylates—Cyclic	Methyl 1-methylcyclohex-3-enecarboxylate 6493-80-7	
Carboxylates—Miscellaneous	Ethyl nicotinate 614-18-6	
Hexanoates—Aliphatic saturated straight chain	Ethyl hexanoate 123-66-0	
Hexanoates—Aliphatic branched chain saturated	Isobutyl hexanoate 105-79-3	

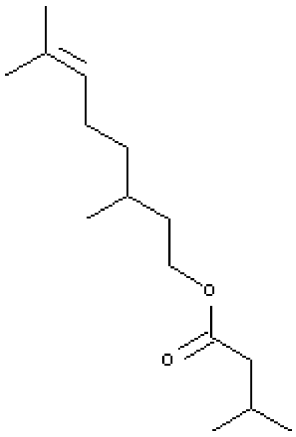
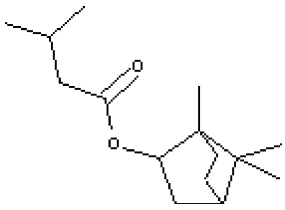
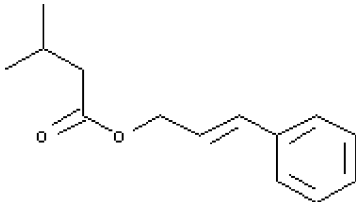
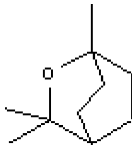
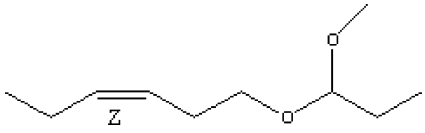
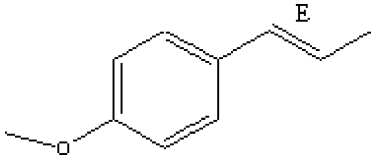
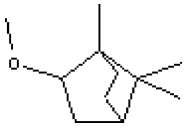
Appendix B (*continued*)

Sub group	Sample compund CAS #	Structure
Hexanoates—Aliphatic straight chain unsaturated	*cis*-3-Hexenyl hexanoate 31501-11-8	13 
Hexanoates—Terpene acyclic	Geranyl hexanoate 10032-02-7	
Valerates—Aliphatic saturated straight chain	Propyl valerate 141-06-0	
Valerates—Aliphatic branched chain saturated	3-Methylbutyl valerate 2050-09-1	
Valerates—Aliphatic straight chain unsaturated	*cis*-3-Hexenyl valerate 35852-46-1	18 

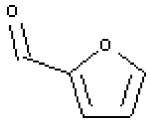
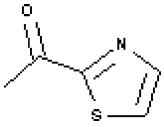
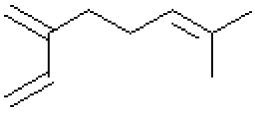
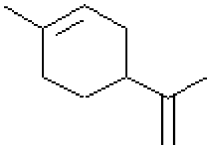
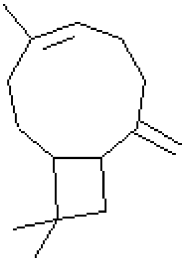
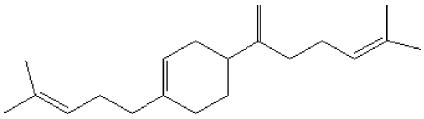
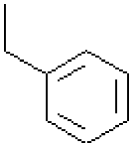
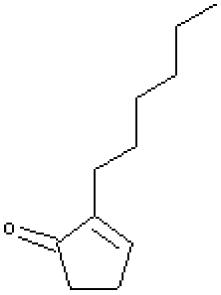
Appendix B (*continued*)

Sub group	Sample compund CAS #	Structure
Valerates—Aryl alkyl	Benzyl valerate 10361-39-4	
Isovalerates—Aliphatic saturated straight chain	Hexyl isovalerate 10032-13-0	
Isovalerates—Aliphatic branched chain saturated	Isoamyl isovalerate 659-70-1	
Isovalerates—Aliphatic straight chain unsaturated	*trans*-2-Hexenyl isovalerate 68698-59-9	
Isovalerates—Aliphatic unsaturated branched	3-Methylbut-3-enyl isovalerate 54410-94-5	

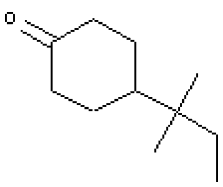
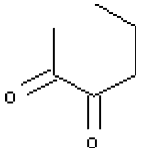
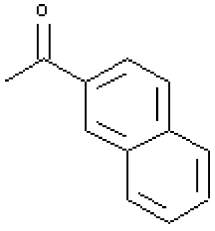
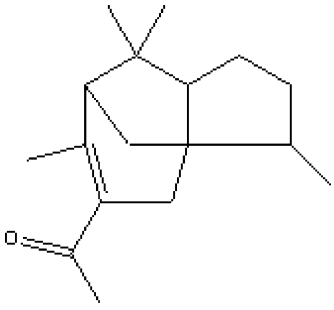
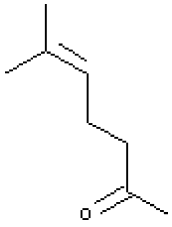
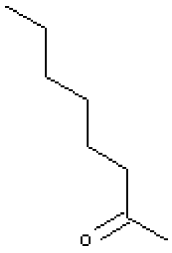
Appendix B (*continued*)

Sub group	Sample compund CAS #	Structure
Isovalerates—Terpene acyclic	Citronellyl isovalerate 68922-10-1	
Isovalerates—Terpene cyclic	Bornyl isovalerate (endo-)76-50-6	
Isovalerates—Aryl alkyl	Cinnamyl isovalerate 140-27-2	
Ethers		
Aliphatic saturated	Eucalyptol(1,8-cineole) 470-82-6	
Aliphatic unsaturated	(*Z*)-1-(1-Methoxypropoxy) hex-3-ene 97358-55-9	
Aromatic	*trans*-Anethole 4180-23-8	
Terpene	Isobornyl methyl ether 5331-32-8	

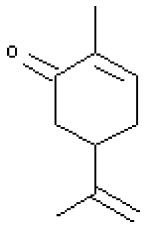
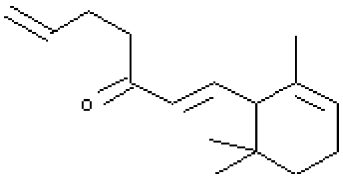
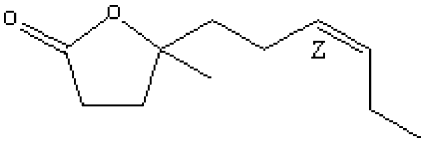
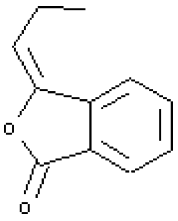
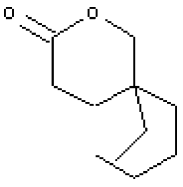
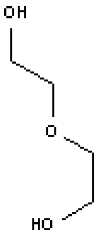
Appendix B (*continued*)

Sub group	Sample compund CAS #	Structure
Heterocyclics		
Furans	Furfural 98-01-1	
Miscellaneous	2-Acetylthiazole 24295-03-2	
Hydrocarbons		
Acyclic terpenes	Myrcene 123-35-3	
Cyclic terpenes	D-Limonene 5989-27-5	
Sesquiterpenes	β-Caryophyllene 87-44-5	
Aliphatic	Dimyrcene 20016-72-2	
Aromatic	Ethylbenzene 100-41-4	
Ketones		
Cyclopentanones	Dihydroisojasmone 95-41-0	

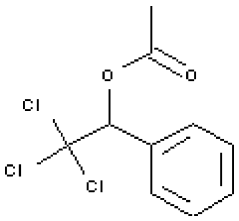
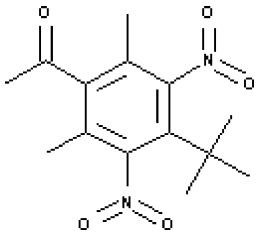
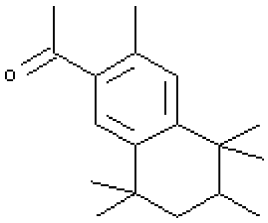
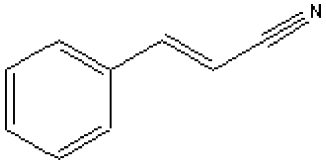
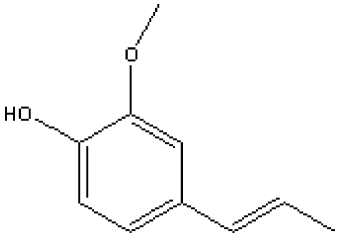
Appendix B (*continued*)

Sub group	Sample compund CAS #	Structure
Cyclohexanones	4-t-Amylcyclohexanone 16587-71-6	
Diones	2,3-Hexanedione 3848-24-6	
Aromatic	Methyl β-naphthyl ketone 93-08-3	
Alicyclic	Acetyl cedrene 32388-55-9	
Aliphatic unsaturated	6-Methyl-5-hepten-2-one 110-93-0	
Aliphatic saturated	2-Octanone 111-13-7	

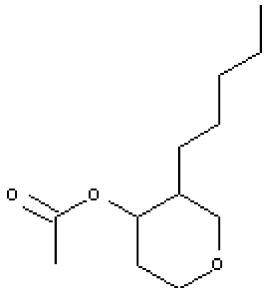
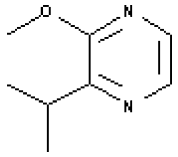
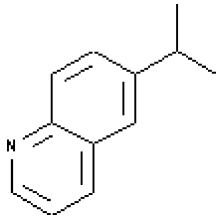
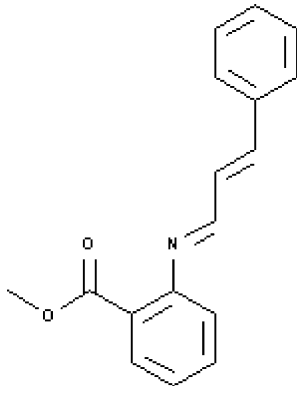
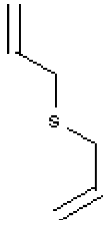
Appendix B (*continued*)

Sub group	Sample compund CAS #	Structure
Terpene	D-Carvone 2244-16-8	
Cyclohexyl	Allyl α-ionone 79-78-7	
Lactones		
Lactones	γ-Valerolactone 108-29-2	
Furanones	5-(*cis*-3-Hexenyl)dihydro-5-methyl-2(3H)furanone 70851-61-5	
Phthalate/phthalide	3-Propylidenephthalide 17369-59-4	
Pyranones	5-butyl-5-ethylytetrahydro-2H-pyran-2-one 67770-79-0	
Miscellaneous		
Polyols and their ethers	Diethylene glycol 111-46-6	

Appendix B (*continued*)

Sub group	Sample compund CAS #	Structure
Halogens	Trichloromethyl phenyl carbinyl acetate 90-17-5	
Miscellaneous	1,6-Octadiene,7-methyl-3-methylene, acid-hydrated, hydrocarbon fractions, washed 90480-40-3	No structure available for this compound
Musks		
Nitromusks	Musk ketone 81-14-1	
Polycyclic Musks	AHTN 21145-77-7	
Nitriles		
Nitriles	Cinnamyl nitrile 1885-38-7	
Phenols		
Phenols	Isoeugenol 97-54-1	

Appendix B (*continued*)

Sub group	Sample compund CAS #	Structure
Pyrans		
Pyrans	4-Acetoxy-3-pentyltetrahydropyran 18871-14-2	
Pyrazines		
Pyrazines	2-Methoxy-3(5 and 6)-isopropylpyrazine 25773-40-4	
Quinolines		
Quinolines	6-Isopropylquinoline 135-79-5	
Schiff's bases		
Schiff's bases	Cinnamic aldehyde-methyl anthranilate (Schiff base) 94386-48-8	
Sulfur containing		
Sulfur containing	Allyl sulfide 592-88-1	

References

Adams, T.B., Hallagan, J.B., Putnam, J.M., Gierte, T.L., Doull, J., Munro, I.C., Newberne, P.S., Portoghese, P.S., Smith, R.L., Wagner, B.M., Weil, C.S., Woods, L.A., Ford, R.A., 1996. The FEMA GRAS assessment of alicyclic substances used as flavor ingredients. Food and Chemical Toxicology 34, 763–828.

Anders, M.W., 1989. Biotransformation and bioactivation of xenobiotics by the kidney. In: Hutson, D.H., Caldwell, J., Paulson, G.D. (Eds.), Intermediary Xenobiotic Metabolism in Animals. Taylor and Francis, New York, pp. 81–97.

Andersen, F.A. (Ed.), 2001. Safety assessment of cosmetic ingredients: forty-third report of the cosmetic ingredient review expert panel; Bergfeld, W.F., Belsito, D.V., Snyder, P.W., Klaassen, C.D., Schroeter, A.L., Shank, R.C., Slaga, T.J. International Journal of Toxicology 20(Suppl. 2), iii-85.

Andersen, K.E., Johansen, J.D., Bruze, M., Frosch, P.J., Goossens, A., Lepoittevin, J.-P., Rastogi, S., White, I., Menne, T., 2001. The time–dose–response relationship for elicitation of contact dermatitis in isoeugenol allergic individuals. Toxicology and Applied Pharmacology 170, 166–171.

Api, A.M., 2002. Sensitization methodology and primary prevention of the Research Institute for Fragrance Materials, Inc. Dermatology 205, 84–87.

Api, A.M., Ford, R.A., 1999. Photoallergenicity studies in humans with AHTN and HHCB. First Meeting of the Experimental Contact Dermatitis Research Group, Cincinnati, OH, May 20–22.

Balk, F., Ford, R.A., 1999a. Environmental risk assessment for the polycyclic musks AHTN and HHCB in the EU.I. Fate and exposure assessment. Toxicology Letters 111, 57–79.

Balk, F., Ford, R.A., 1999b. Environmental risk assessment for the polycyclic musks, AHTN and HHCB. II. Effect assessment and risk characterization. Toxicology Letters 111, 81–94.

Bickers, D., Greim, H., Hanifin, J.H., Rogers, A.E., Saurat, J.H., Sipes, I.G., Smith, R.L., Tagami, H., 2003. A toxicologic and dermatologic assessment of linalool and related esters when used as fragrance ingredients. Food and Chemical Toxicology, in press.

Cadby, P.A., Troy, W.R., Vey, M.G.H., 2002. Consumer exposure to fragrance ingredients: providing estimates for safety evaluation. Regulatory Toxicology and Pharmacology 36, 246–252.

Chadha, A., Madyastha, K.M., 1984. Metabolism of geraniol and linalool in the rat and effects on liver and lung microsomal enzymes. Xenobiotica 14, 365–374.

Cramer, G.M., Ford, R.A., 1978. Estimation of toxic hazard—a decision tree approach. Food and Cosmetics Toxicology 16, 255–276.

Draize, J.H., Woodard, G., Calvery, H.O., 1944. Methods for the study of irritation and toxicity of substance applied topically to the skin and mucous membranes. Journal of Pharmacology and Experimental Therapeutics 82 (2), 377–390.

European Commission, 1996. Technical Guidance Document in support of Directive 96/67/EEC on risk assessment of new notified substances and Regulation (EC) No. 1488/94 on risk assessment of existing substances (Parts I, II, III, and IV). EC catalogue numbers CR 48-96-001, 002, 003, 004-EN-C.

Federle, T.W., Langworthy, D.E., Itrich, N.R., Simonich, S.L., 2000. Biotransformation of the polycyclic musk, HHCB, in activated sludge and river water. Third SETAC World Congress, 10th Annual SETAC Europe, Brighton, United Kingdom, May 21–25.

Fenn, R.S., 1989. Aroma chemical usage trends in modern perfumery. Perfumer and Flavorist 14, 3–10.

Ford, R.A., Api, A.M., Hawkins, D.R., 1987. Absorption, distribution and excretion of topical doses of 14C-phenylethyl alcohol (PEA). The Toxicologist 7 (1), 237.

Ford, R.A., 1991. The Toxicology and Safety of Fragrances. In: Muller, P.M. (Ed.), Perfumes: Art, Science and Technology. Elsevier, Amsterdam, pp. 441–463.

Ford, R.A., Domeyer, B., Easterday, O., Maier, K., Middleton, J., 2000. Criteria for development of a database for safety evaluation of fragrance ingredients. Regulatory Toxicology and Pharmacology 31, 155–181.

Ford, R.A., Hawkins, D.R., Mayo, B.C., Api, A.M., 2001. The in vivo dermal absorption and metabolism of [4-^{14}C]coumarin by rats and by human volunteers under simulated conditions of use in fragrances. Food and Chemical Toxicology 39, 153–162.

Gerberick, G.F., Robinson, M.K., Felter, S.P., White, I.R., Basketter, D.A., 2001. Understanding fragrance allergy using an exposure-based risk assessment approach. Contact Dermatitis 45 (6), 333–340.

Hanifin, J.M., Bickers, D.R., 1999. Considerations for testing irritancy, allergy and photoreactivity in fragrance safety evaluations, First Meeting of the Experimental Contact Dermatitis Research Group, Cincinnati, OH, May 20–22.

Hawkins, D.R., Ford, R.A., 1999. Dermal absorption and distribution of musk ambrette, musk ketone and musk xylene in rats. Toxicology Letters 111, 95–103.

Hawkins, D.R., Elsom, L.F., Kirkpatrick, D., Ford, R.A., Api, A.M., 2002. Dermal absorption and distribution of musk ambrette, musk ketone and musk xylene in human subjects. Toxicology Letters 131, 147–151.

Heymann, E., 1980. Carboxylesterases and amidases. In: Jakoby, W.B. (Ed.), Enzymatic Basis of Detoxication. Academic Press, New York, pp. 291–323.

Hotchkiss, S.A.M., 1998. Absorption of fragrance ingredients using in vitro models with human skin. In: Fragrances: Beneficial and Adverse Effects, 125–135.

Hotchkiss, S.A.M., Miller, J.M., Caldwell, J., 1992. Percutaneous absorption of benzyl acetate through rat skin in vitro 2. Effect of vehicle and occlusion. Food and Chemical Toxicology 30, 145–153.

IFRA, 1980. Code of Practice, International Fragrance Association, Geneva, October. (Current versions are available at http://www.ifraorg.org).

Joint Expert Committee on Food Additives, 1999. Safety evaluation of certain food additives. Who Food Additives Series: 42. Prepared by the Fifty-first meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA). World Health Organization, Geneva 1999.

Kaidbey, K.H., Kligman, A.M., 1980. Photomaximization test for identifying photoallergen contact sensitizers. Contact Dermatitis 6, 161–169.

Kimber, I., Gerberick, G.F., Basketter, D.A., 1999. Thresholds in contact sensitization: theoretical and practical considerations. Food and Chemical Toxicology 37, 553–560.

Kligman, A.M., 1966. The identification of contact allergens by human assay. III. The maximization test: a procedure for screening and rating sensitizers. Journal of Investigative Dermatology 47 (5), 393–409.

Kligman, A.M., Epstein, W., 1975. Updating the maximization test for identifying contact allergens. Contact Dermatitis 1, 231–239.

Langworthy, D.E., Itrich, N.R., Federle, T.W., 2000. Biotransformation of mineralisation of acetyl cedrene in activated sludge and river water. Third SETAC World Congress, 10th Annual SETAC Europe, Brighton, United Kingdom, May 21–25.

Letizia, C.S., Cocchiara, J., Wellington, G.A., Funk, C., Api, A.M., 2000. Special issue IX: monographs on fragrance raw materials. Food and Chemical Toxicology 38 (Suppl.), 236.

Morikawa, F., Nakayama, Y., Fukuda, M., Hamano, M., Yokoyama, Y., Nagura, T., Ishihara, M., Toda, K., 1974. Techniques for evaluation of phototoxicity and photoallergy in laboratory animals and man. In: Fitzpatrick, T.B., Pathak, M.A., Harber, L.C., Seiji, M., Kukita, A. (Eds.), Sunlight and Man: Normal and Abnormal Photobiologic Responses. University Tokyo Press, Tokyo, pp. 529–557.

Naldi, L., 2002. The epidemiology of fragrance allergy: questions and needs. Dermatology 205, 89–97.

Opdyke, D.L.J., Letizia, C.S., 1982. Monographs on fragrance raw materials, fig leaf absolute. Food and Chemical Toxicology 20 (Suppl.), 691–692.

Opdyke, D.L., 1984. The RIFM Story. In: The Cosmetic Industry, 231–243 (Chapter 14).

Organisation for Economic Co-operation and Development, 1998. OECD Guidelines for the Testing of Chemicals. 2, rue Andre-Pascal, 75775 Paris, Cedex 16, France.

Parke, D.V., Rahman, K.H.M.Q., Walker, R., 1974. Effect of linalool on hepatic drug-metabolizing enzymes in the rat. Biochemical Society Transactions 2, 615–618.

Pathak, M.A., Fitzpatrick, T.B., 1959. Relationship of molecular configuration to the activity of furocoumarins which increase the cutaneous responses following long wave ultraviolet radiation. Journal of Investigative Dermatology 32 (Part 2), 255–262.

Potter, J., Smith, R.L., Api, A.M., 2001a. Urinary thiocyanate levels as a biomarker for the generation of inorganic cyanide from benzyl cyanide in the rat. Food and Chemical Toxicology 39 (2), 141–146.

Potter, J., Smith, R.L., Api, A.M., 2001b. An assessment of the release of inorganic cyanide form the fragrance materials benzyl cyanide geranyl nitrile and citronellyl nitrile applied dermally to the rat. Food and Chemical Toxicology 39 (2), 147–151.

Research Institute for Fragrance Materials, Inc., 2002. Topical photoallergy screening test of cinnamaldehyde and cinnamic acid in male albino hairless guinea pigs, including primary irritation, phototoxicity and contact hypersensitivity evaluations. RIFM Audited Draft Final Report, 20 June.

RIFM, 1980. Advisory Letter to Membership, Number 29, February 11.

Robinson, M.K., Gerberick, G.F., Ryan, C.A., McNamee, P., White, I.R., Basketter, D.A., 2000. The importance of exposure estimation in the assessment of skin sensitization risk. Contact Dermatitis 42, 251–259.

Salvito, D.T., Senna, R.J., Federle, T.W., 2002. A framework for prioritizing fragrance materials for aquatic risk assessment. Environmental Toxicology and Chemistry 21, 1301–1308.

Sams Jr., N.M., Epstein, J.H., 1967. Experimental production of drug phototoxicity in guinea pigs, using sunlight. Journal of Investigative Dermatology 48, 89–94.

Schreiber, W.L., 1996. Perfumes, Kirk–Othmer Encyclopedia of Chemical Technology, fourth ed., vol. 18, pp. 172–201.

Spielmann, H., Balls, M., Dupuis, J., Pape, W.J., Pechovity, G., DeSilva, O., Holzhutter, H.G., Clothier, R., Desolle, P., Gerberick, F., Lovell, W.W., Maurer, T., Pfannenbecker, U., Potthast, J.M., Csato, M., Sladowski, D., Steiling, W., Brantom, P., 1998. The international EU/COLIPA invitro phototoxicity validation study: results of phase II (Blind Trial). Part 1. The 3T3 phototoxicity test. Toxicology In Vitro 12 (3), 305–327.

Tas, J.W., Balk, F., Ford, R.A., van de Plassche, E.J., 1997. Environmental risk assessment of musk ketone and musk xylene in the Netherlands in accordance with the EU-TGD. Chemosphere 35, 29783–30002.