STUDY

Compilation of Historical Local Lymph Node Data for Evaluation of Skin Sensitization Alternative Methods

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Background: **Within the toxicology community, considerable effort is directed toward the development of alternative methods for skin sensitization testing. The availability of high-quality, relevant, and reliable in vivo data regarding skin sensitization is essential for the effective evaluation of alternative methodologies. Ideally, data derived from humans would be the most appropriate source because the test methods are attempting to predict a toxicologic effect in humans. Unfortunately, insufficient human data of the necessary quality are available, so it is necessary to rely on the best available animal data. In recent years, the local lymph node assay (LLNA) has emerged as a practical option for assessing the skin sensitization potential of chemicals. In addition to accurately identifying skin sensitizers, the LLNA can also provide a reliable measure of relative sensitization potency, information that is pivotal to the successful management of human health risks.**

Objective: **To provide a database of robust in vivo data to calibrate, evaluate, and eventually validate new approaches for skin sensitization testing.**

Methods: **LLNA data derived from previously conducted studies were compiled from the published literature and unpublished sources.**

Results: **We provide a database that comprises LLNA data on 211 individual chemicals. This extensive chemical data set encompasses both the chemical and biologic diversity of known chemical allergens. To cover the range of relative allergenic potencies, the data set includes data on 13 extreme, 21 strong, 69 moderate, and 66 weak contact allergens, classified according to each allergen's mathematically estimated concentration of chemical required to induce a threefold stimulation index. In addition, there are also 42 chemicals that are considered to be nonsensitizers. In terms of chemical diversity, the database contains data pertaining to the chemical classes represented by aldehydes, ketones, aromatic amines, quinones, and acrylates, as well as compounds that have different reactivity mechanisms. In addition to two-dimensional chemical structures, the physicochemical parameters included are log Kp, log $K_{O/W}$, and molecular weight.**

Conclusions: **The list of chemicals contained in the data set represents both the chemical and biologic diversity that is known to exist for chemical allergens and non-allergens. It is anticipated that this database will help accelerate the development, evaluation, and eventual validation of new approaches to skin sensitization assessment.**

THE EVALUATION OF THE POTENTIAL to induce allergic contact dermatitis (ACD) is an important component of the safety assessment process for a new chemical that may be encountered through the skin.[1] For many years, the guinea pig has been the species of choice for the identification of skin-sensitizing hazards. More recently, however, the local lymph node assay (LLNA) has been accepted as a valid alternative approach; its method is based on the characterization of induced proliferative responses in the draining lymph nodes after topical exposure of mice to chemicals.[2–6] The LLNA has been adopted by the Organization for Economic Cooperation and Development (OECD) as a stand-alone test for skin sensitization (OECD Test Guideline 429).[7] This adoption resulted from thorough and independent validations of the LLNA in both the United States[8] and Europe.[9] The LLNA offers clear scientific advantages as well as important animal welfare benefits (in terms of both reduction and refinement) when compared with traditional guinea pig tests. In addition to accurately identifying skin sensitization hazards, the LLNA can provide a reliable measure of relative allergenic potency,

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information that is critical to the risk assessment process. This is achieved by consideration of the vigor with which chemical allergens provoke proliferative responses in draining lymph node cells. The relative potency of a chemical sensitizer is measured by deriving what is known as the EC3 value, which indicates the test chemical concentration necessary to produce a threefold stimulation of proliferation in draining lymph nodes as compared with concurrent vehicle controls.[10] Thus, the intrinsic sensitizing potency of a chemical is defined as a function of the concentration required to elicit a threshold positive response, a stimulation index (SI) equal to 3. For this reason, the lower the EC3 value, the greater the relative skin sensitizing potency of the chemical. This approach has already been applied with some success, and the LLNA is the preferred method for estimating the potency of a contact allergen.[11,12]

Meeting the ultimate challenge of developing nonanimal predictive test methods to replace an in vivo skin sensitization test such as the LLNA requires an understanding of the biologic mechanisms involved in the development of ACD.[13,14] Specifically, the in vitro approach should be designed in such a way that the potential of a chemical to penetrate the skin, react with protein/peptide (with or without the need for biotransformation), and initiate an antigen-specific immune response are incorporated into the developed tests. Approaches could include in vitro methods, based most commonly on chemically induced responses in cell culture systems (eg, single-cell cultures or more complex models such as skin explant and skin-equivalent models), or in silico methods (eg, computer-based expert or quantitative structure activity systems).

Currently, in vitro systems for the identification of skin sensitizers are still in their infancy. One critical requirement for the development of alternative test methods will be the use of robust in vivo data to calibrate, evaluate, and eventually validate new approaches. In this article, we describe the compilation of an extensive chemical data set that embraces a range of chemicals and skin-sensitizing activity. All materials have been evaluated through LLNA; for some chemicals, it has been demonstrated that the LLNA EC3 value correlates closely with what is known of the chemical's relative ability to induce sensitization in humans.[15–17] These data provide a unique and valuable list of chemicals for which the sensitivity, selectivity, and overall accuracy of proposed alternative methods for skin sensitization can be judged. This compilation also provides an invaluable source of data with which to explore other issues, such as the relationship between chemical categorization (on the basis of mechanism of action) and potency. It could also help to define the applicability domain of the LLNA as well as that of existing alternative methodologies and those in development.

Materials and Methods

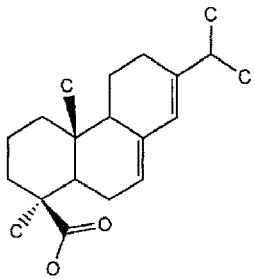
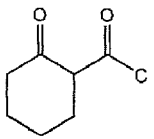
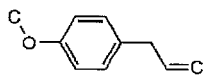
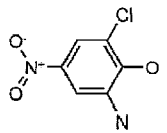
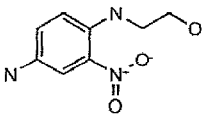
Chemicals

The chemicals identified in this article have been evaluated for skin sensitization potential with the LLNA. For each chemical listed in Table 1, the chemical abstract service (CAS) number and two-dimensional structure are specified. In addition, the molecular weight, the skin penetration coefficient (log Kp: centimeters × hours $^{-1}$, here expressed in its log scale), and the octanol-water partition coefficient (log $K_{O/W}$) values are indicated for each chemical. The structures were graphically drawn with *ChemDraw*, version 6.0 (CambridgeSoft, Cambridge, MA). The molecular weight (MW), log Kp, and log $K_{O/W}$ values were obtained by analysis of the structures with the expert system *DEREK for Windows*, version 7 (Lhasa Limited, Leeds, UK).[18] The log Kp was calculated with the equation of Potts and Guy,[19] and the log $K_{O/W}$ was calculated with Moriguchi's estimation.[20]

Local Lymph Node Assay Protocol

The LLNA was conducted as described in the literature (Fig 1).[2–6] Briefly, groups of CBA female mice (7–12 weeks of age) were exposed topically on the dorsum of both ears to 25 μL of test material or to an equal volume of the relevant vehicle alone. Treatment was performed daily for 3 consecutive days. Five days after the initiation of exposure, all mice were injected via the tail vein with 250 μL of phosphate-buffered saline containing 20 μCi of tritiated thymidine. The mice were sacrificed 5 hours later, and the draining auricular lymph nodes were excised and pooled for each experimental group or each individual animal. The incorporation of tritiated thymidine measured by beta scintillation counting was reported in disintegrations per minute. An SI was calculated for each chemical-treated group as the ratio of the disintegrations per minute in the treated group (or mean disintegrations per minute when individual animals were assessed) to the disintegrations per minute or mean disintegrations per minute of the concurrent vehicle control group. LLNA methodology assesses skin sensitization, not photosensitization. A substance was classified as a skin sensitizer if, at one or more test concentrations, it induced a threefold or greater increase in local lymph node proliferative activity when compared with concurrent vehicle-treated controls (SI, ≥ 3). The compilation of data from numerous laboratories is reported in

Table 1. Chemical Structures, Physicochemical Parameters, LLNA Data, and Potency Categorization

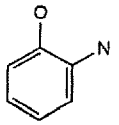
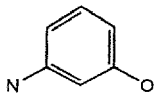
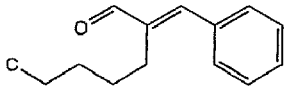
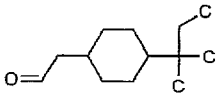
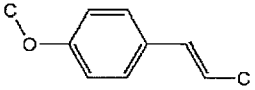
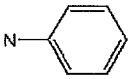
Chemical Structure	CAS No.	Log Kp	Log $K_{O/W}$	MW	Vehicle	LLNA %	LLNA %	LLNA %	LLNA %	LLNA %	LLNA %	LLNA SI	LLNA SI	LLNA SI	LLNA SI	LLNA SI	LLNA SI	LLNA EC3* (%)	Potency Category	Reference
Abietic acid 	514-10-3	−1.29	4.61	302.46	AOO	5.0	10.0	25.0	—	—	—	1.5	2	5.2	—	—	—	15	Weak	Ashby J et al.[21]
2-Acetylcyclohexanone 	874-23-7	−2.41	1.66	143.21	Acetone	10.0	20.0	40.0	—	—	—	0.8	0.7	0.8	—	—	—	NC	Nonsensitizer	P&G (unpublished)
4-Allylanisole 	140-67-0	−1.82	2.54	148.21	AOO	10.0	25.0	50.0	100.0	—	—	1.2	4.7	4.5	8	—	—	18	Weak	Unilever (unpublished)
2-Amino-6-chloro-4-nitrophenol 	6358-09-4	−3.69	0.26	188.57	AOO	0.1	0.25	0.5	1.0	2.5	—	1.7	1.4	2.1	1.5	3.4	—	2.2	Moderate	Estrada E et al.[22]
2-(4-Amino-2-nitro-phenylamino)-ethanol (HC Red No. 3) 	2871-01-41	−3.84	0.12	197.19	AOO	0.1	0.25	0.5	1.0	2.5	—	0.5	1.2	1.9	1.8	3.3	—	2.2	Moderate	Estrada E et al.[22]

AOO = acetone and olive oil (4:1); CAS = Chemical Abstract Service number; DEP = diethyl phthalate; dH2O = distilled water; DMF = dimethylformamide; DMSO = dimethyl sulfoxide; EtOH = ethanol; FEMA = Flavor and Extract Manufacturers' Association; $K_{O/W}$ = octanol-water partition coefficient (log scale); Kp = skin penetration coefficient (log scale); LLNA = local lymph node assay; MEK = methyl ethyl ketone; MW = molecular weight; NC = not calculated; P&G = Procter & Gamble Co.; RIFM = Research Institute for Fragrance Materials.

*Mathematically estimated concentration of test chemical necessary to induce a threefold stimulation index (SI).

(continued on next page)

Table 1. *Continued*

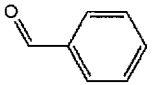
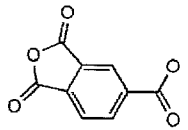
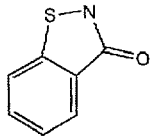
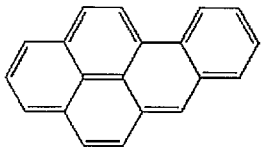
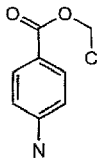
Chemical Structure	*CAS No.*	*Log Kp*	*Log $K_{O/W}$*	*MW*	*Vehicle*	*LLNA %*	*LLNA %*	*LLNA %*	*LLNA %*	*LLNA %*	*LLNA %*	*LLNA SI*	*LLNA SI*	*LLNA SI*	*LLNA SI*	*LLNA SI*	*LLNA SI*	*LLNA EC3* (%)*	*Potency Category*	*Reference*
2-Aminophenol 	95-55-6	−2.55	1.17	109.13	AOO	0.5	1.0	2.5	—	—	—	3.5	5.0	7.4	—	—	—	0.4†	Strong	Ashby J et al.[21]
3-Aminophenol 	591-27-5	−2.55	1.17	109.13	AOO	2.5	5.0	10.0	—	—	—	2.8	3.5	5.7	—	—	—	3.2	Moderate	Ashby J et al.[21]
α-Amyl cinnamic aldehyde 	122-40-7	−1.45	3.52	202.30	AOO	1.0	2.5	5.0	10.0	25.0	—	1.5	1.7	2.2	2.8	8.2	—	11	Weak	Elahi EN et al.[23]
2-(4-tert-Amylcyclohexyl)acetaldehyde (QRM 2113) 	620159-84-4	−1.59	3.28	196.33	AOO	25.0	50.0	100.0	—	—	—	2.1	4	9.1	—	—	—	37	Weak	Estrada E et al.[22]
trans-Anethol 	104-46-1	−1.82	2.54	148.21	AOO	4.5	9.0	22.6	—	—	—	13.5	24.7	37.3	—	—	—	2.3†	Moderate	Unilever (unpublished)
Aniline 	62-53-3	−2.18	1.56	93.13	AOO	5.0	10.0	25.0	50.0	100.0	—	1.1	0.9	2.0	1.9	3.3	—	89	Weak	Unilever (unpublished)

AOO = acetone and olive oil (4:1); CAS = Chemical Abstract Service number; DEP = diethyl phthalate; dH2O = distilled water; DMF = dimethylformamide; DMSO = dimethyl sulfoxide; EtOH = ethanol; FEMA = Flavor and Extract Manufacturers' Association; $K_{O/W}$ = octanol-water partition coefficient (log scale); Kp = skin penetration coefficient (log scale); LLNA = local lymph node assay; MEK = methyl ethyl ketone; MW = molecular weight; NC = not calculated; P&G = Procter & Gamble Co.; RIFM = Research Institute for Fragrance Materials.

*Mathematically estimated concentration of test chemical necessary to induce a threefold stimulation index (SI).

†Value estimated.

Table 1. *Continued*

Chemical Structure	CAS No.	Log Kp	Log $K_{O/W}$	MW	Vehicle	LLNA %	LLNA %	LLNA %	LLNA %	LLNA %	LLNA %	LLNA SI	LLNA SI	LLNA SI	LLNA SI	LLNA SI	LLNA SI	LLNA EC3* (%)	Potency Category	Reference
Benzaldehyde 	100-52-7	−2.09	1.80	106.12	AOO	1.0	2.5	5.0	10.0	25.0	—	2.1	1.7	2.2	1.8	2	—	NC	Nonsensitizer	Patlewicz G et al.[24]
1,2,4-Benzenetricarboxylic anhydride (trimellitic anhydride) 	552-30-7	−3.36	0.75	192.13	AOO	1.0	2.5	5.0	10.0	25.0	—	1.1	2	2.0	3.2	4.6	—	9.2	Moderate	Estrada E et al.[22]
1,2-Benzisothiazolin-3-one (Proxel active) 	2634-33-5	−2.64	1.42	151.18	DMF	10.0	30.0	50.0	—	—	—	3.8	4.4	4.9	—	—	—	2.3†	Moderate	Ashby J et al.[21]
Benzo[a]pyrene 	50-32-8	−0.44	5.39	252.32	AOO	0.5	1.0	2.5	—	—	—	17.6	19.2	27.0	—	—	—	0.0009†	Extreme	Ashby J et al.[21]
Benzocaine 	94-09-7	−2.65	1.52	165.19	AOO	2.5	5.0	10.0	25.0	50.0	—	2.1	1.8	2.7	1.8	1.2	—	NC	Nonsensitizer	Warbrick EV et al.[25]

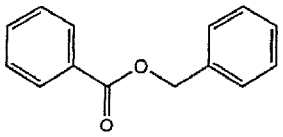
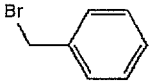
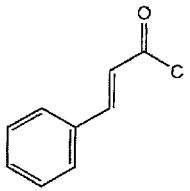
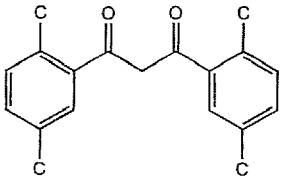
AOO = acetone and olive oil (4:1); CAS = Chemical Abstract Service number; DEP = diethyl phthalate; dH2O = distilled water; DMF = dimethylformamide; DMSO = dimethyl sulfoxide; EtOH = ethanol; FEMA = Flavor and Extract Manufacturers' Association; $K_{O/W}$ = octanol-water partition coefficient (log scale); Kp = skin penetration coefficient (log scale); LLNA = local lymph node assay; MEK = methyl ethyl ketone; MW = molecular weight; NC = not calculated; P&G = Procter & Gamble Co.; RIFM = Research Institute for Fragrance Materials.

*Mathematically estimated concentration of test chemical necessary to induce a threefold stimulation index (SI).

†Value estimated.

(*continued on next page*)

Table 1. *Continued*

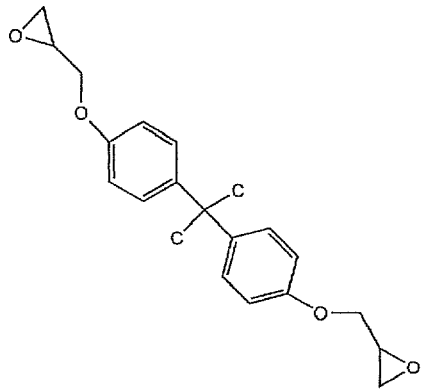
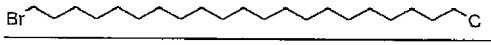
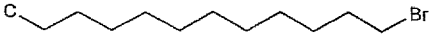
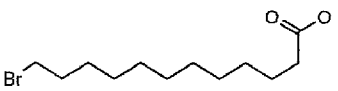
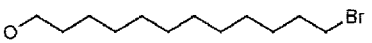
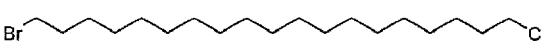
Chemical Structure	*CAS No.*	*Log Kp*	*Log $K_{O/W}$*	*MW*	*Vehicle*	*LLNA %*	*LLNA %*	*LLNA %*	*LLNA %*	*LLNA %*	*LLNA %*	*LLNA SI*	*LLNA SI*	*LLNA SI*	*LLNA SI*	*LLNA SI*	*LLNA SI*	*LLNA EC3* (%)*	*Potency Category*	*Reference*
p-Benzoquinone 	106-51-4	−2.55	1.17	108.10	AOO	0.5	1.0	2.5	—	—	—	36.4	42.3	52.3	—	—	—	0.0099[†]	Extreme	Basketter DA, Scholes EW.[26]
Benzyl benzoate 	120-51-4	−1.79	3.14	212.25	AOO	5.0	25.0	—	—	—	—	2.3	3.5	—	—	—	—	17	Weak	Smith CK, Hotchkiss SA.[27]
Benzyl bromide 	100-39-0	−1.95	2.56	171.04	AOO	0.25	0.5	1.0	2.5	5.0	—	3.5	11.5	16.1	16.4	25.1	—	0.2[†]	Strong	Unilever (unpublished)
Benzylidene acetone (4-phenyl-3-buten-2-one) 	122-57-6	−1.81	2.54	146.19	AOO	10.0	25.0	50.0	—	—	—	8.5	13.6	12.8	—	—	—	3.7[†]	Moderate	Ryan CA et al.[28]
Bis-1,3-(2,5-dimethylphenyl)-propane-1,3-dione 		−1.34	4.37	282.38	Acetone	10.0	20.0	40.0	—	—	—	1.8	1.6	2.1	—	—	—	NC	Nonsensitizer	P&G (unpublished)

AOO = acetone and olive oil (4:1); CAS = Chemical Abstract Service number; DEP = diethyl phthalate; dH2O = distilled water; DMF = dimethylformamide; DMSO = dimethyl sulfoxide; EtOH = ethanol; FEMA = Flavor and Extract Manufacturers' Association; $K_{O/W}$ = octanol-water partition coefficient (log scale); Kp = skin penetration coefficient (log scale); LLNA = local lymph node assay; MEK = methyl ethyl ketone; MW = molecular weight; NC = not calculated; P&G = Procter & Gamble Co.; RIFM = Research Institute for Fragrance Materials.

*Mathematically estimated concentration of test chemical necessary to induce a threefold stimulation index (SI).

[†]Value estimated.

Table 1. *Continued*

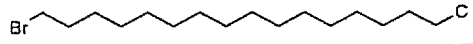
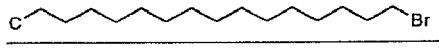
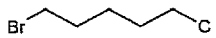
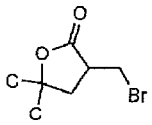
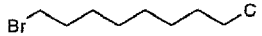
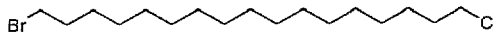
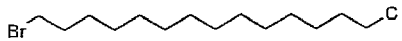
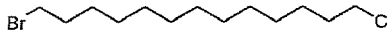
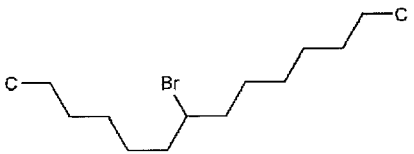
Chemical Structure	CAS No.	Log Kp	Log $K_{O/W}$	MW	Vehicle	LLNA %	LLNA %	LLNA %	LLNA %	LLNA %	LLNA %	LLNA SI	LLNA SI	LLNA SI	LLNA SI	LLNA SI	LLNA SI	LLNA EC3* (%)	Potency Category	Reference
Bisphenol A-diglycidyl ether 	1675-54-3	−1.89	4.09	340.42	AOO	1.0	3.0	10.0	—	—	—	2.0	6.0	17.4	—	—	—	1.5	Moderate	Warbrick EV et al.[29]
1-Bromobutane 	109-65-9	−2.26	1.82	137.02	AOO	5.0	10.0	25.0	—	—	—	1.1	1.2	1.0	—	—	—	NC	Nonsensitizer	Ashby J et al.[21]
1-Bromodocosane 	6938-66-5	−0.66	6.25	389.51	AOO	2.5	5.0	10.0	—	—	—	1.2	1.6	3.7	—	—	—	8.3	Moderate	Estrada E et al.[22]
1-Bromododecane 	143-15-7	−1.55	3.79	249.24	AOO	5.0	10.0	25.0	—	—	—	1.1	1.4	4.5	—	—	—	18	Weak	Basketter DA et al.[30]
12-Bromododecanoic acid 	73367-80-3	−2.28	3.02	279.22	AOO	5.0	10.0	25.0	—	—	—	1.3	2	3.9	—	—	—	18	Weak	Unilever (unpublished)
12-Bromo-1-dodecanol 	3344-77-2	−1.92	3.40	265.24	AOO	5.0	10.0	25.0	—	—	—	2.2	4.3	9.8	—	—	—	6.9	Moderate	Estrada E et al.[22]
1-Bromoeicosane 	4276-49-7	−0.84	5.76	361.45	AOO	5.0	10.0	25.0	—	—	—	2.1	6.2	8.4	—	—	—	6.1	Moderate	Estrada E et al.[22]

AOO = acetone and olive oil (4:1); CAS = Chemical Abstract Service number; DEP = diethyl phthalate; dH2O = distilled water; DMF = dimethylformamide; DMSO = dimethyl sulfoxide; EtOH = ethanol; FEMA = Flavor and Extract Manufacturers' Association; $K_{O/W}$ = octanol-water partition coefficient (log scale); Kp = skin penetration coefficient (log scale); LLNA = local lymph node assay; MEK = methyl ethyl ketone; MW = molecular weight; NC = not calculated; P&G = Procter & Gamble Co.; RIFM = Research Institute for Fragrance Materials.

*Mathematically estimated concentration of test chemical necessary to induce a threefold stimulation index (SI).

(*continued on next page*)

Table 1. *Continued*

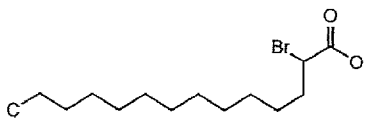
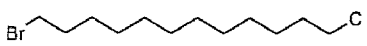
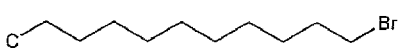
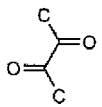
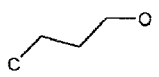
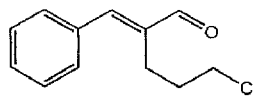
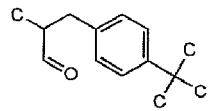
Chemical Structure	CAS No.	Log Kp	Log $K_{O/W}$	MW	Vehicle	LLNA %	LLNA %	LLNA %	LLNA %	LLNA %	LLNA %	LLNA SI	LLNA SI	LLNA SI	LLNA SI	LLNA SI	LLNA SI	LLNA EC3* (%)	Potency Category	Reference
1-Bromoheptadecane 	3508-00-7	−1.11	5.02	319.37	AOO	5.0	10.0	25.0	—	—	—	3.2	6	9.6	—	—	—	4.8†	Moderate	Basketter DA et al.[30]
1-Bromohexadecane 	112-82-3	−1.20	4.77	305.34	AOO	1.0	2.5	5.0	10.0	25.0	50.0	1.1	3.3	7.9	11.1	13.5	16.8	2.3	Moderate	Basketter DA et al.[30]
1-Bromohexane 	111-25-1	−2.09	2.31	165.07	AOO	1.0	10.0	50.0	—	—	—	1.7	2.9	18.6	—	—	—	10	Weak	Estrada E et al.[22]
3-Bromomethyl-5,5-dimethyl-dihydro-2(3H)-furanone 	154750-20-6	−2.72	1.79	207.07	AOO	3.19	6.37	12.74	—	—	—	2.7	5.1	7.1	—	—	—	3.6	Moderate	Estrada E et al.[22]
1-Bromononane 	693-58-3	−1.82	3.05	207.16	AOO	5.0	10.0	25.0	—	—	—	1.2	1.4	2.8	—	—	—	NC	Nonsensitizer	Basketter DA et al.[30]
1-Bromooctadecane 	112-89-0	−1.02	5.26	333.40	AOO	5.0	10.0	25.0	—	—	—	1.8	2.2	4.5	—	—	—	15	Weak	Basketter DA et al.[30]
1-Bromopentadecane 	629-72-1	−1.28	4.53	291.32	AOO	5.0	10.0	25.0	—	—	—	2.9	7.8	19.6	—	—	—	5.1	Moderate	Ashby J et al.[21]
1-Bromotetradecane 	112-71-0	−1.37	4.28	277.29	AOO	5.0	10.0	25.0	—	—	—	1.5	3.3	11.3	—	—	—	9.2	Moderate	Basketter DA et al.[30]
7-Bromotetradecane 	74036-97-8	−1.37	4.28	277.29	AOO	5.0	10.0	25.0	—	—	—	0.9	1.2	3.6	—	—	—	21	Weak	Estrada E et al.[22]

AOO = acetone and olive oil (4:1); CAS = Chemical Abstract Service number; DEP = diethyl phthalate; dH2O = distilled water; DMF = dimethylformamide; DMSO = dimethyl sulfoxide; EtOH = ethanol; FEMA = Flavor and Extract Manufacturers' Association; $K_{O/W}$ = octanol-water partition coefficient (log scale); Kp = skin penetration coefficient (log scale); LLNA = local lymph node assay; MEK = methyl ethyl ketone; MW = molecular weight; NC = not calculated; P&G = Procter & Gamble Co.; RIFM = Research Institute for Fragrance Materials.

*Mathematically estimated concentration of test chemical necessary to induce a threefold stimulation index (SI).

†Value estimated.

Table 1. *Continued*

Chemical Structure	CAS No.	Log Kp	Log Kow	MW	Vehicle	LLNA %	LLNA %	LLNA %	LLNA %	LLNA %	LLNA %	LLNA SI	LLNA SI	LLNA SI	LLNA SI	LLNA SI	LLNA SI	LLNA EC3* (%)	Potency Category	Reference
2- Bromotetradecanoic acid 	10520-81-7	−2.10	3.51	307.27	AOO	5.0	10.0	25.0	—	—	—	4.7	7.7	10.1	—	—	—	3.4†	Moderate	Unilever (unpublished)
1-Bromotridecane 	765-09-3	−1.46	4.03	263.26	AOO	5.0	10.0	25.0	—	—	—	1.6	2.9	10.4	—	—	—	10	Weak	Basketter DA et al.[30]
1-Bromoundecane 	693-67-4	−1.64	3.54	235.21	AOO	5.0	10.0	25.0	—	—	—	1.3	1.4	3.9	—	—	—	20	Weak	Basketter DA et al.[30]
2,3-Butanedione 	431-03-8	−2.76	0.68	86.09	AOO	5.0	10.0	25.0	—	—	—	1.4	2.8	5.2	—	—	—	11	Weak	Roberts DW et al.[31]
1-Butanol 	71-36-3	−2.42	1.06	74.12	dH2O	5.0	10.0	20.0	—	—	—	1.6	1.2	1.4	—	—	—	NC	Nonsensitizer	Ryan CA et al.[28]
α-Butyl cinnamic aldehyde 	7492-44-6	−1.54	3.28	188.27	AOO	1.0	2.5	5.0	10.0	25.0	—	1.4	1.7	1.7	2.1	13	—	11	Weak	Elahi EN et al.[25]
p-tert-Butyl-a-ethyl hydrocinnamal (Lilial) 	80-54-6	−1.46	3.52	204.31	AOO	1.0	2.5	10.0	25.0	50.0	—	1.3	2.5	2.0	3.7	9.3	—	19	Weak	Basketter DA et al.[16]

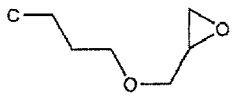
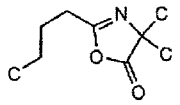
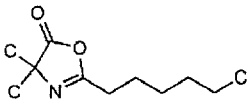
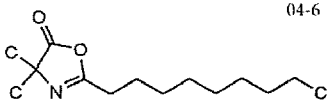
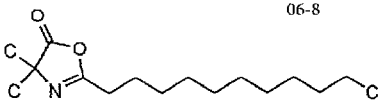
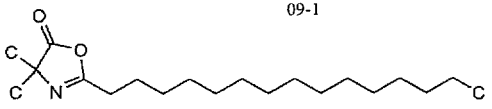
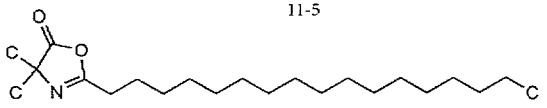
AOO = acetone and olive oil (4:1); CAS = Chemical Abstract Service number; DEP = diethyl phthalate; dH2O = distilled water; DMF = dimethylformamide; DMSO = dimethyl sulfoxide; EtOH = ethanol; FEMA = Flavor and Extract Manufacturers' Association; $K_{O/W}$ = octanol-water partition coefficient (log scale); Kp = skin penetration coefficient (log scale); LLNA = local lymph node assay; MEK = methyl ethyl ketone; MW = molecular weight; NC = not calculated; P&G = Procter & Gamble Co.; RIFM = Research Institute for Fragrance Materials.

*Mathematically estimated concentration of test chemical necessary to induce a threefold stimulation index (SI).

†Value estimated.

(*continued on next page*)

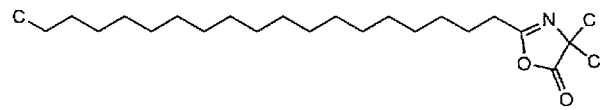
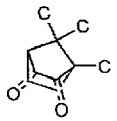
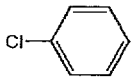
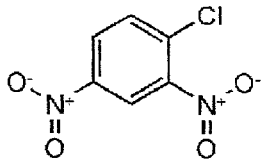
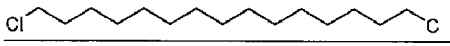
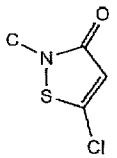
Table 1. *Continued*

Chemical Structure	*CAS No.*	*Log Kp*	*Log $K_{O/W}$*	*MW*	*Vehicle*	*LLNA %*	*LLNA %*	*LLNA %*	*LLNA %*	*LLNA %*	*LLNA %*	*LLNA SI*	*LLNA SI*	*LLNA SI*	*LLNA SI*	*LLNA SI*	*LLNA SI*	*LLNA EC3* (%)*	*Potency Category*	*Reference*
Butyl glycidyl ether 	2426-08-6	−2.51	1.42	130.19	AOO	10.0	25.0	50.0	—	—	—	1.4	2.2	5.6	—	—	—	31	Weak	Basketter DA et al.[32]
C4 Azlactone 	176664-99-6	−2.67	1.52	169.22	AOO	0.52	1.31	2.62	5.23	—	—	1.1	2.3	4.1	11.7	—	—	1.8	Moderate	Estrada E et al.[22]
C6 Azlactone 	176665-02-4	−2.49	2.01	197.28	AOO	0.61	1.52	3.05	—	—		1.2	3.5	7.6	—	—	—	1.3	Moderate	Estrada E et al.[22]
C9 Azlactone 	176665-04-6	−2.23	2.75	239.36	AOO	1.85	3.7	7.4	—	—	—	1.4	4.6	10.1	—	—	—	2.8	Moderate	Estrada E et al.[22]
C11 Azlactone 	176665-06-8	−2.05	3.24	267.41	AOO	8.3	20.7	41.3	—	—	—	1.3	4	8.5	—	—	—	16	Weak	Estrada E et al.[22]
C15 Azlactone 	176665-09-1	−1.69	4.23	323.52	AOO	10.0	25.0	50.0	—	—	—	1.8	4.1	7.5	—	—	—	18	Weak	Estrada E et al.[22]
C17 Azlactone 	176665-11-5	−1.51	4.72	351.58	AOO	10.87	27.17	54.33	—	—	—	1.7	4.3	4.6	—	—	—	19	Weak	Estrada E et al.[22]

AOO = acetone and olive oil (4:1); CAS = Chemical Abstract Service number; DEP = diethyl phthalate; dH2O = distilled water; DMF = dimethylformamide; DMSO = dimethyl sulfoxide; EtOH = ethanol; FEMA = Flavor and Extract Manufacturers' Association; $K_{O/W}$ = octanol-water partition coefficient (log scale); Kp = skin penetration coefficient (log scale); LLNA = local lymph node assay; MEK = methyl ethyl ketone; MW = molecular weight; NC = not calculated; P&G = Procter & Gamble Co.; RIFM = Research Institute for Fragrance Materials.

*Mathematically estimated concentration of test chemical necessary to induce a threefold stimulation index (SI).

Table 1. *Continued*

Chemical Structure	CAS No.	Log Kp	Log $K_{O/W}$	MW	Vehicle	LLNA %	LLNA %	LLNA %	LLNA %	LLNA %	LLNA %	LLNA SI	LLNA SI	LLNA SI	LLNA SI	LLNA SI	LLNA SI	LLNA EC3* (%)	Potency Category	Reference
C19 Azlactone 		−1.34	5.21	379.63	AOO	11.73	29.33	58.67	—	—	—	2.5	3.1	2.5	—	—	—	26	Weak	Estrada E et al.[22]
Camphorquinone 	465-29-2	−2.20	2.15	166.22	AOO	5.0	10.0	25.0	—	—	—	2.8	3.0	1.7	—	—	—	10	Weak	Roberts DW et al.[31]
Chlorobenzene 	108-90-7	−1.85	2.19	112.56	AOO	5.0	10.0	25.0	—	—	—	1.1	1.7	1.6	—	—	—	NC	Nonsensitizer	Ashby J et al.[21]
1-Chloro-2,4-dinitrobenzene 	97-00-7	−4.05	−0.13	202.55	AOO	0.01	0.025	0.05	0.1	0.25	—	1.5	1.8	2.4	8.9	38.0	—	0.05	Extreme	Loveless SE et al.[33]
1-Chlorohexadecane 	4860-03-1	−1.01	4.65	260.89	AOO	5.0	10.0	25.0	—	—	—	1.6	3.3	5.7	—	—	—	9.1	Moderate	Unilever (unpublished)
5-Chloro-2-methyl-4-isothiazolin-3-one 	26172-55-4	−2.98	0.92	149.60	DMF	0.01	0.03	0.10	—	—	—	3.5	12.3	27.7	—	—	—	0.009†	Extreme	Ashby J et al.[21]

AOO = acetone and olive oil (4:1); CAS = Chemical Abstract Service number; DEP = diethyl phthalate; dH2O = distilled water; DMF = dimethylformamide; DMSO = dimethyl sulfoxide; EtOH = ethanol; FEMA = Flavor and Extract Manufacturers' Association; $K_{O/W}$ = octanol-water partition coefficient (log scale); Kp = skin penetration coefficient (log scale); LLNA = local lymph node assay; MEK = methyl ethyl ketone; MW = molecular weight; NC = not calculated; P&G = Procter & Gamble Co.; RIFM = Research Institute for Fragrance Materials.

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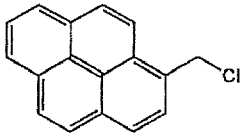
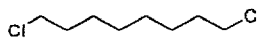
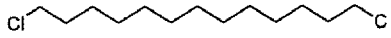
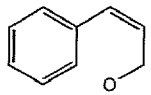
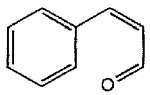
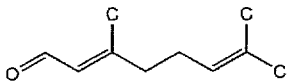
†Value estimated.

(*continued on next page*)

Table 1. *Continued*

Chemical Structure	*CAS No.*	*Log Kp*	*Log $K_{O/W}$*	*MW*	*Vehicle*	*LLNA %*	*LLNA %*	*LLNA %*	*LLNA %*	*LLNA %*	*LLNA %*	*LLNA SI*	*LLNA SI*	*LLNA SI*	*LLNA SI*	*LLNA SI*	*LLNA SI*	*LLNA EC3* (%)*	*Potency Category*	*Reference*
1-Chloromethylpyrene 	1086-00-6	−0.77	4.89	250.73	AOO	0.025	0.05	0.1	—	—	—	11.6	15.4	18.6	—	—	—	0.005†	Extreme	Ashby J et al.[21]
1-Chlorononane 	2473-01-0	−1.64	2.93	162.70	AOO	10.0	25.0	50.0	—	—	—	1	1.6	2.3	—	—	—	NC	Nonsensitizer	Unilever (unpublished)
1-Chlorooctadecane 	3386-33-2	−0.83	5.14	288.95	AOO	10.0	25.0	50.0	—	—	—	1.7	4.8	7.3	—	—	—	16	Weak	Estrada E et al.[22]
1-Chlorotetradecane 	2425-54-9	−1.19	4.16	232.84	AOO	10.0	25.0	50.0	—	—	—	1.1	3.9	6.3	—	—	—	20	Weak	Estrada E et al.[22]
Cinnamic alcohol 	104-54-1	−1.91	2.29	134.18	AOO	10.0	25.0	50.0	90.0	—		1.8	3.5	3.9	5.7	—	—	21	Weak	Estrada E et al.[22]
Cinnamic aldehyde 	104-55-2	−1.90	2.29	132.16	AOO	0.5	1.0	2.5	5.0	10.0	—	1.4	0.9	1.9	7.1	15.8	—	3.0	Moderate	Basketter DA et al.[16]
Citral 	5392-40-5	−1.85	2.54	152.24	AOO	5.0	10.0	25.0	—	—	—	1.2	2.1	6.3	—	—	—	13	Weak	Patlewicz G et al.[34]

AOO = acetone and olive oil (4:1); CAS = Chemical Abstract Service number; DEP = diethyl phthalate; dH2O = distilled water; DMF = dimethylformamide; DMSO = dimethyl sulfoxide; EtOH = ethanol; FEMA = Flavor and Extract Manufacturers' Association; $K_{O/W}$ = octanol-water partition coefficient (log scale); Kp = skin penetration coefficient (log scale); LLNA = local lymph node assay; MEK = methyl ethyl ketone; MW = molecular weight; NC = not calculated; P&G = Procter & Gamble Co.; RIFM = Research Institute for Fragrance Materials.

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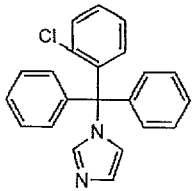
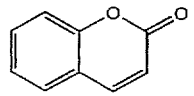
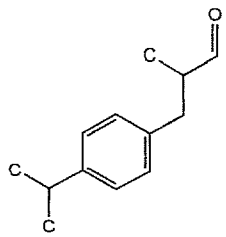
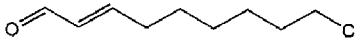
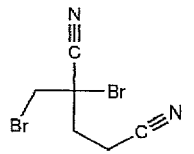
†Value estimated.

Table 1. *Continued*

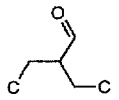
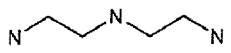
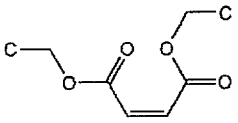
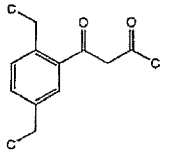
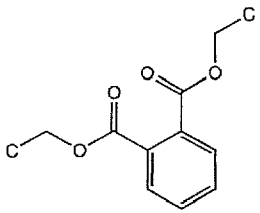
Chemical Structure	*CAS No.*	*Log Kp*	*Log $K_{O/W}$*	*MW*	*Vehicle*	*LLNA %*	*LLNA %*	*LLNA %*	*LLNA %*	*LLNA %*	*LLNA %*	*LLNA SI*	*LLNA SI*	*LLNA SI*	*LLNA SI*	*LLNA SI*	*LLNA SI*	*LLNA EC3* (%)*	*Potency Category*	*Reference*
Clotrimazole 	23593-75-1	−1.02	5.35	344.85	AOO	2.5	5.0	10.0	—	—	—	1.6	3.1	3.0	—	—	—	4.8	Moderate	Estrada E et al.[22]
Coumarin 	91-64-5	−2.26	1.91	146.15	AOO	5.0	10.0	25.0	—	—	—	2.7	2.9	2.3	—	—	—	NC	Nonsensitizer	RIFM/FEMA database
Cyclamen aldehyde 	103-95-7	−1.55	3.28	190.29	AOO	1.0	2.5	10.0	25.0	50.0	—	1.4	1.3	1.8	3.3	5.2	—	22	Weak	Basketter DA et al.[16]
trans-2-Decenal 	3913-71-1	−1.86	2.54	154.25	AOO	0.5	1.0	2.5	5.0	10.0	—	1.3	1.1	3	6	9.5	—	2.5	Moderate	Patlewicz G et al.[34]
1,2-Dibromo-2,4-dicyanobutane 	35691-65-7	−2.99	1.91	265.94	AOO	0.5	1.0	2.5	5.0	—	—	1.4	3.4	3.5	5.4	—	—	0.9	Strong	Unilever (unpublished)

AOO = acetone and olive oil (4:1); CAS = Chemical Abstract Service number; DEP = diethyl phthalate; dH2O = distilled water; DMF = dimethylformamide; DMSO = dimethyl sulfoxide; EtOH = ethanol; FEMA = Flavor and Extract Manufacturers' Association; $K_{O/W}$ = octanol-water partition coefficient (log scale); Kp = skin penetration coefficient (log scale); LLNA = local lymph node assay; MEK = methyl ethyl ketone; MW = molecular weight; NC = not calculated; P&G = Procter & Gamble Co.; RIFM = Research Institute for Fragrance Materials.

*Mathematically estimated concentration of test chemical necessary to induce a threefold stimulation index (SI).

(*continued on next page*)

Table 1. *Continued*

Chemical Structure	*CAS No.*	*Log Kp*	*Log $K_{O/W}$*	*MW*	*Vehicle*	*LLNA %*	*LLNA %*	*LLNA %*	*LLNA %*	*LLNA %*	*LLNA %*	*LLNA SI*	*LLNA SI*	*LLNA SI*	*LLNA SI*	*LLNA SI*	*LLNA SI*	*LLNA EC3* (%)*	*Potency Category*	*Reference*
Diethyl acetaldehyde 	97-96-1	−2.23	1.56	100.16	AOO	25.0	50.0	75.0	100.0	—	—	1.2	0.8	2.4	16.3	—	—	76	Weak	Patlewicz G et al.[34]
Diethylenetriamine 	111-40-0	−3.14	0.29	103.17	AOO	10.0	25.0	—	—	—	—	6.4	12.1	—	—	—	—	5.8	Moderate	Basketter DA et al.[32]
Diethyl maleate 	141-05-9	−3.14	0.89	172.18	AOO	25.0	50.0	100.0	—	—	—	16.3	22.6	13.1	—	—	—	5.8†	Moderate	Ryan CA et al.[28]
1-(2,5-Diethylphenyl)butane-1,3-dione 	167998-76-7	−1.84	3.14	221.32	Acetone	10.0	20.0	40.0	—	—	—	3.9	19.2	18.7	—	—	—	9.6†	Moderate	P&G (unpublished)
Diethylphthalate 	84-66-2	−2.75	1.87	222.24	AOO	25.0	50.0	100.0	—	—	—	1.0	1.3	1.5	—	—	—	NC	Nonsensitizer	Ryan CA et al.[28]

AOO = acetone and olive oil (4:1); CAS = Chemical Abstract Service number; DEP = diethyl phthalate; dH2O = distilled water; DMF = dimethylformamide; DMSO = dimethyl sulfoxide; EtOH = ethanol; FEMA = Flavor and Extract Manufacturers' Association; $K_{O/W}$ = octanol-water partition coefficient (log scale); Kp = skin penetration coefficient (log scale); LLNA = local lymph node assay; MEK = methyl ethyl ketone; MW = molecular weight; NC = not calculated; P&G = Procter & Gamble Co.; RIFM = Research Institute for Fragrance Materials.

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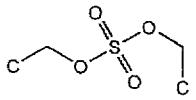
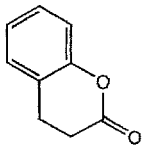
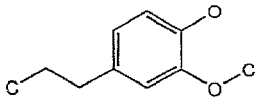
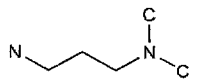
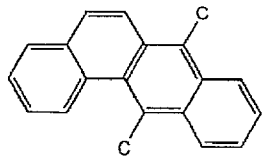
Chemical Structure	*CAS No.*	*Log Kp*	*Log $K_{O/W}$*	*MW*	*Vehicle*	*LLNA %*	*LLNA %*	*LLNA %*	*LLNA %*	*LLNA %*	*LLNA %*	*LLNA SI*	*LLNA SI*	*LLNA SI*	*LLNA SI*	*LLNA SI*	*LLNA SI*	*LLNA EC3* (%)*	*Potency Category*	*Reference*
Diethyl sulfate 	64-67-5	−3.73	−0.09	154.18	AOO	1.0	2.5	10.0	—	—	—	0.8	1.9	12.0	—	—	—	3.3	Moderate	Ashby J et al.[21]
3,4-Dihydrocoumarin 	119-84-6	−2.27	1.91	148.16	AOO	2.5	5.0	10.0	—	—	—	1.6	2.5	6.6	—	—	—	5.6	Moderate	Ashby J et al.[21]
Dihydroeugenol 	2785-87-7	−2.20	2.15	166.22	AOO	5.1	10.1	25.3	—	—	—	2.7	3.6	7.8	—	—	—	6.8	Moderate	Smith CK, Hotchkiss SA.[27]
1,4-Dihydroquinone 	123-31-9	−2.56	1.17	110.11	AOO	0.1	0.25	0.5	1.0	2.5	—	2.8	5.8	13.7	15.2	13.1	—	0.11	Strong	Kimber I et al.[35]
3-Dimethylaminopropylamine 	109-55-7	−2.69	0.92	102.18	AOO	0.5	1.0	2.5	5.0	10.0	—	1.3	1.1	3.5	7.0	13.9	—	2.2	Moderate	Wright ZM et al.[36]
7,12-Dimethylbenz[α]anthracene 	57-97-6	−0.46	5.39	256.35	DMF	0.025	0.5	1.0	—	—	—	7.6	17.7	15.6	—	—	—	0.006†	Extreme	Ashby J et al.[21]

AOO = acetone and olive oil (4:1); CAS = Chemical Abstract Service number; DEP = diethyl phthalate; dH2O = distilled water; DMF = dimethylformamide; DMSO = dimethyl sulfoxide; EtOH = ethanol; FEMA = Flavor and Extract Manufacturers' Association; $K_{O/W}$ = octanol-water partition coefficient (log scale); Kp = skin penetration coefficient (log scale); LLNA = local lymph node assay; MEK = methyl ethyl ketone; MW = molecular weight; NC = not calculated; P&G = Procter & Gamble Co.; RIFM = Research Institute for Fragrance Materials.

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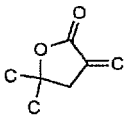
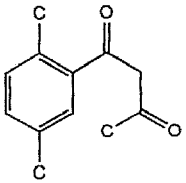
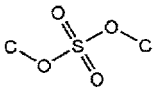
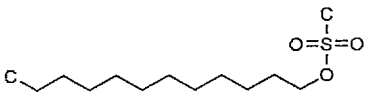
(*continued on next page*)

Table 1. *Continued*

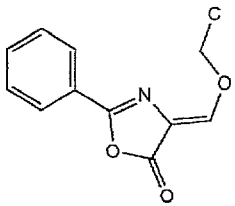
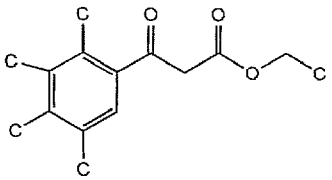
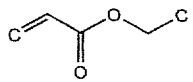
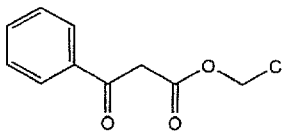
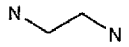
Chemical Structure	CAS No.	Log Kp	Log $K_{O/W}$	MW	Vehicle	LLNA %	LLNA %	LLNA %	LLNA %	LLNA %	LLNA %	LLNA SI	LLNA SI	LLNA SI	LLNA SI	LLNA SI	LLNA SI	LLNA EC3* (%)	Potency Category	Reference
5,5-Dimethyl-3-methylene-dihydro-2(3H)-furanone 	29043-97-8	−2.48	1.42	126.16	AOO	2.0	4.0	8.0	—	—	—	3	7.4	9.2	—	—	—	1.8†	Moderate	Ashby J et al.[21]
1-(2,5-Dimethylphenyl)butane-1,3-dione 	56290-55-2	−2.02	2.65	193.27	Acetone	10.0	20.0	40.0	—	—	—	2.3	5.1	9.5	—	—	—	13	Weak	P&G (unpublished)
Dimethyl sulfate 	77-78-1	−3.91	−0.59	126.13	AOO	0.25	0.5	1.0	—	—	—	3.8	6.0	5.7	—	—	—	0.19†	Strong	Ashby J et al.[21]
Dimethylsulfoxide 	67-68-5	−2.79	0.57	78.13	AOO	25.0	50.0	100.0	—	—	—	2.7	2.3	3.9	—	—	—	72	Weak	Estrada E et al.[22]
Dodecyl methane sulfonate 	51323-71-8	−2.55	2.51	264.42	AOO	5.0	10.0	25.0	—	—	—	2.1	3.3	9	—	—	—	8.8	Moderate	Ashby J et al.[21]

AOO = acetone and olive oil (4:1); CAS = Chemical Abstract Service number; DEP = diethyl phthalate; dH2O = distilled water; DMF = dimethylformamide; DMSO = dimethyl sulfoxide; EtOH = ethanol; FEMA = Flavor and Extract Manufacturers' Association; $K_{O/W}$ = octanol-water partition coefficient (log scale); Kp = skin penetration coefficient (log scale); LLNA = local lymph node assay; MEK = methyl ethyl ketone; MW = molecular weight; NC = not calculated; P&G = Procter & Gamble Co.; RIFM = Research Institute for Fragrance Materials.

*Mathematically estimated concentration of test chemical necessary to induce a threefold stimulation index (SI).

†Value estimated.

Table 1. *Continued*

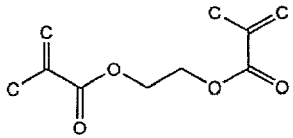
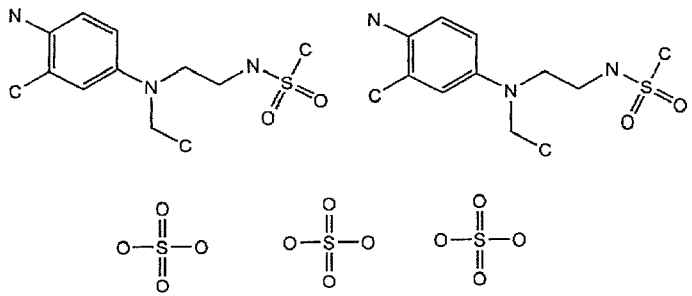
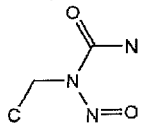
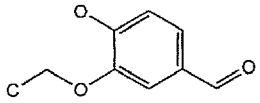
Chemical Structure	*CAS No.*	*Log Kp*	*Log $K_{O/W}$*	*MW*	*Vehicle*	*LLNA %*	*LLNA %*	*LLNA %*	*LLNA %*	*LLNA %*	*LLNA %*	*LLNA SI*	*LLNA SI*	*LLNA SI*	*LLNA SI*	*LLNA SI*	*LLNA SI*	*LLNA EC3* (%)*	*Potency Category*	*Reference*
4-Ethoxymethylene-2-phenyl-2-oxazolin-5-one (oxazolone) 	15646-46-5	−2.71	1.87	217.22	AOO	0.0025	0.005	0.01	0.025	0.05	—	2.9	4.9	12.0	22.0	33.0	—	0.003	Extreme	Loveless SE et al.[33]
3-Ethoxy-1-(2',3',4',5'-tetramethylphenyl)propane-1,3-dione 	170928-69-5	−2.11	3.00	248.32	Acetone	10.0	20.0	40.0	—	—	—	1.1	1.7	3.7	—	—	—	33	Weak	P&G (unpublished)
Ethyl acrylate 	140-88-5	−2.67	0.92	100.12	AOO	10.0	25.0	50.0	—	—	—	1.2	2.7	5	—	—	—	28	Weak	Warbrick EV et al.[29]
Ethyl benzoylacetate 	94-02-0	−2.46	2.01	192.21	Acetone	10.0	20.0	40.0	—	—	—	0.9	0.9	1.2	—	—	—	NC	Nonsensitizer	P&G (unpublished)
Ethylenediamine free base 	107-15-3	−2.95	0.19	60.10	AOO	0.1	0.25	0.5	1.0	2.5	5.0	1.1	1.2	1.6	1.9	3.3	6.1	2.2	Moderate	Kimber I et al.[35]

AOO = acetone and olive oil (4:1); CAS = Chemical Abstract Service number; DEP = diethyl phthalate; dH2O = distilled water; DMF = dimethylformamide; DMSO = dimethyl sulfoxide; EtOH = ethanol; FEMA = Flavor and Extract Manufacturers' Association; $K_{O/W}$ = octanol-water partition coefficient (log scale); Kp = skin penetration coefficient (log scale); LLNA = local lymph node assay; MEK = methyl ethyl ketone; MW = molecular weight; NC = not calculated; P&G = Procter & Gamble Co.; RIFM = Research Institute for Fragrance Materials.

*Mathematically estimated concentration of test chemical necessary to induce a threefold stimulation index (SI).

(*continued on next page*)

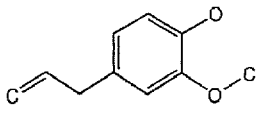
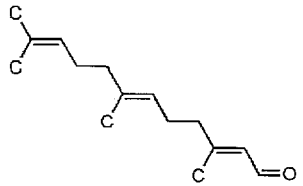
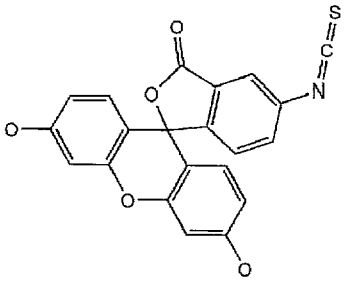
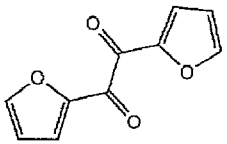
Table 1. *Continued*

Chemical Structure	*CAS No.*	*Log Kp*	*Log $K_{O/W}$*	*MW*	*Vehicle*	*LLNA %*	*LLNA %*	*LLNA %*	*LLNA %*	*LLNA %*	*LLNA %*	*LLNA SI*	*LLNA SI*	*LLNA SI*	*LLNA SI*	*LLNA SI*	*LLNA SI*	*LLNA EC3* (%)*	*Potency Category*	*Reference*
Ethylene glycol dimethacrylate 	97-90-5	−2.95	1.38	198.22	MEK	10.0	25.0	50.0	—	—	—	1.2	2.4	7	—	—	—	28	Weak	Unilever (unpublished)
4-(N-Ethyl-N-2-methan-sulphonamido-ethyl)-2-methyl-1,4-phenylenediamine (CD3) 	25646-71-3	−9.33	−2.12	836.97	DMSO	0.1	1.0	5.0	10.0	—	—	1.2	4.5	5.9	6.3	—	—	0.6	Strong	Ryan CA et al.[28]
N-Ethyl-*N*-nitrosourea 	759-73-9	−3.95	−0.73	117.11	AOO	0.25	1.0	10.0	—	—	—	1.0	2.7	22.3	—	—	—	1.1	Moderate	Ashby J et al.[21]
Ethyl vanillin 	121-32-4	−2.65	1.52	166.18	AOO	2.5	5.0	10.0	25.0	50.0	—	0.65	1.05	0.74	0.36	0.29	—	NC	Nonsensitizer	Basketter DA et al.[16]

AOO = acetone and olive oil (4:1); CAS = Chemical Abstract Service number; DEP = diethyl phthalate; dH2O = distilled water; DMF = dimethylformamide; DMSO = dimethyl sulfoxide; EtOH = ethanol; FEMA = Flavor and Extract Manufacturers' Association; $K_{O/W}$ = octanol-water partition coefficient (log scale); Kp = skin penetration coefficient (log scale); LLNA = local lymph node assay; MEK = methyl ethyl ketone; MW = molecular weight; NC = not calculated; P&G = Procter & Gamble Co.; RIFM = Research Institute for Fragrance Materials.

*Mathematically estimated concentration of test chemical necessary to induce a threefold stimulation index (SI).

Table 1. *Continued*

Chemical Structure	CAS No.	Log Kp	Log $K_{O/W}$	MW	Vehicle	LLNA %	LLNA %	LLNA %	LLNA %	LLNA %	LLNA %	LLNA SI	LLNA SI	LLNA SI	LLNA SI	LLNA SI	LLNA SI	LLNA EC3* (%)	Potency Category	Reference
Eugenol 	97-53-0	−2.19	2.15	164.20	AOO	2.5	5.0	10.0	25.0	—	—	1.6	1.5	2.4	5.5	—	—	13	Weak	Loveless SE et al.[33]
Farnesal 	502-67-0	−1.39	3.77	220.36	AOO	1.0	2.5	5.0	10.0	25.0	—	0.6	1.1	1.7	2.5	7	—	12	Weak	Patlewicz G et al.[34]
Fluorescein-5-isothiocyanate 	3326-32-7	−2.74	3.32	389.38	Acetone/ dibutyl phthalate, 50/50	0.5	1.0	2.5	—	—	—	8.6	11.7	16.6	—	—	—	0.14[†]	Strong	Ashby J et al.[21]
Formaldehyde[‡] C=O	50-00-0	−2.67	0.33	30.03	Acetone	0.093	0.185	0.37	0.925	1.85	—	1.1	2.3	2.3	3.9	4.0	—	0.61	Strong	Hilton J et al.[37]
Furil 	492-94-4	−2.90	1.38	190.15	AOO	5.0	10.0	25.0	—	—	—	1.2	1.7	2.2	—	—	—	NC	Nonsensitizer	Roberts DW et al.[31]

AOO = acetone and olive oil (4:1); CAS = Chemical Abstract Service number; DEP = diethyl phthalate; dH2O = distilled water; DMF = dimethylformamide; DMSO = dimethyl sulfoxide; EtOH = ethanol; FEMA = Flavor and Extract Manufacturers' Association; $K_{O/W}$ = octanol-water partition coefficient (log scale); Kp = skin penetration coefficient (log scale); LLNA = local lymph node assay; MEK = methyl ethyl ketone; MW = molecular weight; NC = not calculated; P&G = Procter & Gamble Co.; RIFM = Research Institute for Fragrance Materials.

*Mathematically estimated concentration of test chemical necessary to induce a threefold stimulation index (SI).

[†]Value estimated.

[‡]Concentration shown as actual concentration of formaldehyde. Material tested was formalin (37% formaldehyde).

(*continued on next page*)

Table 1. *Continued*

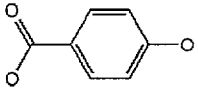
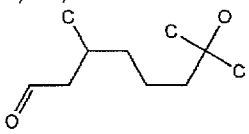
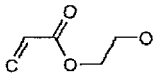
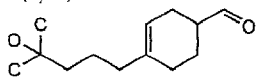
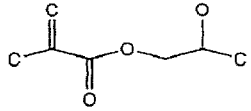
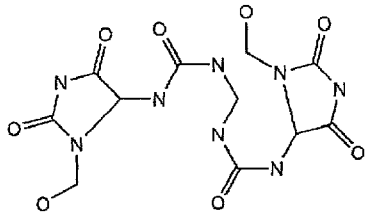
Chemical Structure	*CAS No.*	*Log Kp*	*Log $K_{O/W}$*	*MW*	*Vehicle*	*LLNA %*	*LLNA %*	*LLNA %*	*LLNA %*	*LLNA %*	*LLNA %*	*LLNA SI*	*LLNA SI*	*LLNA SI*	*LLNA SI*	*LLNA SI*	*LLNA SI*	*LLNA EC3* (%)*	*Potency Category*	*Reference*
Geraniol	106-24-1	−1.86	2.54	154.25	75% EtOH/ 25% DEP	1.0	3.0	10.0	30.0	50.0	—	1.0	1.0	1.3	3.4	3.9	—	26	Weak	Lalko J et al.[38]
Glutaraldehyde[§]	111-30-8	−2.67	0.92	100.12	Acetone	0.05	0.125	0.25	0.5	1.25	2.5	1.3	4.3	7.6	11.6	17.7	18.0	0.1	Strong	Hilton J et al.[37]
Glycerol	56-81-5	−3.25	0.05	92.09	DMF	25.0	50.0	100.0	—	—	—	1.1	0.7	0.5	—	—	—	NC	Nonsensitizer	Ryan CA et al.[28]
Glyoxal	107-22-2	−2.94	0.19	58.04	AOO	1.0	2.5	5.0	10.0	25.0	—	2.5	4.2	5.2	10.3	15.8	—	1.4	Moderate	Patlewicz G et al.[34]
2,4-Heptadienal	5910-85-0	−2.11	1.80	110.16	AOO	0.5	1.0	2.5	5.0	10.0	—	1.1	1.4	1.9	3.7	8.1	—	4.0	Moderate	Estrada E et al.[22]
Hexane	110-54-3	−1.87	1.94	86.18	AOO	25.0	50.0	100.0	—	—	—	0.8	0.8	2.2	—	—	—	NC	Nonsensitizer	Basketter DA et al.[39]
trans-2-Hexenal	6728-26-3	−2.21	1.56	98.15	AOO	0.5	1.0	2.5	5.0	10.0	—	1.2	1.2	2.3	2.6	6.4	—	5.5	Moderate	Estrada E et al.[22]
Hexyl cinnamic aldehyde	101-86-0	−1.36	3.77	216.32	AOO	2.5	5.0	10.0	25.0	50.0	—	1.3	1.1	2.5	10.0	17.0	—	11	Weak	Loveless SE et al.[33]

AOO = acetone and olive oil (4:1); CAS = Chemical Abstract Service number; DEP = diethyl phthalate; dH2O = distilled water; DMF = dimethylformamide; DMSO = dimethyl sulfoxide; EtOH = ethanol; FEMA = Flavor and Extract Manufacturers' Association; $K_{O/W}$ = octanol-water partition coefficient (log scale); Kp = skin penetration coefficient (log scale); LLNA = local lymph node assay; MEK = methyl ethyl ketone; MW = molecular weight; NC = not calculated; P&G = Procter & Gamble Co.; RIFM = Research Institute for Fragrance Materials.

*Mathematically estimated concentration of test chemical necessary to induce a threefold stimulation index (SI).

[§]Concentration shown as actual concentration of glutaraldehyde. Material tested was 50% glutaraldehyde solution.

Table 1. *Continued*

Chemical Structure	*CAS No.*	*Log Kp*	*Log $K_{O/W}$*	*MW*	*Vehicle*	*LLNA %*	*LLNA %*	*LLNA %*	*LLNA %*	*LLNA %*	*LLNA %*	*LLNA SI*	*LLNA SI*	*LLNA SI*	*LLNA SI*	*LLNA SI*	*LLNA SI*	*LLNA EC3* (%)*	*Potency Category*	*Reference*
4-Hydrobenzoic acid 	99-96-7	−2.83	1.03	138.12	DMSO	5.0	10.0	25.0	—	—	—	1.4	1.5	1.3	—	—	—	NC	Nonsensitizer	Ashby J et al.[21]
Hydroxycitronellal 	107-75-5	−2.24	2.15	172.27	AOO	2.5	5.0	10.0	25.0	50.0	—	2.2	1	0.8	1.1	7.1	—	33	Weak	Basketter DA et al.[16]
2-Hydroxyethyl acrylate 	818-61-1	−3.05	0.54	116.12	AOO	5.0	10.0	25.0	—	—	—	10.7	14.8	18.1	—	—	—	1.4†	Moderate	Scholes EW et al.[40]
3 and 4-(4-Hydroxy-4-methylpentyl)-3-cyclohexene-1-carboxaldehyde (Lyral) 	31906-04-4	−1.95	2.89	210.32	AOO	1.0	2.5	5.0	10.0	25.0	—	0.6	0.7	0.6	1.3	4.9	—	17	Weak	Patlewicz G et al.[34]
2-Hydroxypropyl methacrylate 	923-26-2	−2.87	1.03	144.17	AOO	10.0	25.0	50.0	—	—	—	1.1	1.2	1.3	—	—	—	NC	Nonsensitizer	Basketter DA, Scholes EW.[26]
Imidazolidinylurea 	39236-46-9	−7.22	−3.00	388.30	DMF	10.0	25.0	50.0	—	—	—	1.7	3.1	5.5	—	—	—	24	Weak	Basketter DA, Scholes EW.[26]

AOO = acetone and olive oil (4:1); CAS = Chemical Abstract Service number; DEP = diethyl phthalate; dH2O = distilled water; DMF = dimethylformamide; DMSO = dimethyl sulfoxide; EtOH = ethanol; FEMA = Flavor and Extract Manufacturers' Association; $K_{O/W}$ = octanol-water partition coefficient (log scale); Kp = skin penetration coefficient (log scale); LLNA = local lymph node assay; MEK = methyl ethyl ketone; MW = molecular weight; NC = not calculated; P&G = Procter & Gamble Co.; RIFM = Research Institute for Fragrance Materials.

*Mathematically estimated concentration of test chemical necessary to induce a threefold stimulation index (SI).

†Value estimated.

(*continued on next page*)

Table 1. *Continued*

Chemical structure	CAS No	$\log K_{ow}$	$\log K_p$	MW	Vehicle	LLNA %	LLNA %	LLNA %	LLNA %	LLNA %	LLNA %	LLNA SI	LLNA SI	LLNA SI	LLNA SI	LLNA SI	LLNA SI	LLNA EC3* (μ_M)	Potency Category	Reference
1-Iododecane	4292-19-7	−1.75	3.91	296.24	AOO	5.0	10.0	25.0	—	—	—	1.7	2.3	5.7	—	—	—	13	Weak	Estrada E et al.[22]
1-Iodohexadecane	544-77-4	−1.39	4.89	352.35	AOO	10.0	25.0	50.0	—	—	—	1.6	3.9	6.4	—	—	—	19	Weak	Estrada E et al.[22]
1-Iodohexane	638-45-9	−2.29	2.43	212.08	AOO	10.0	25.0	50.0	—	—	—	0.9	1.2	2.5	—	—	—	NC	Nonsensitizer	Unilever (unpublished)
1-Iodononane	4282-42-2	−2.02	3.17	254.16	AOO	10.0	25.0	50.0	—	—	—	1.3	3.1	4.6	—	—	—	24	Weak	Estrada E et al.[22]
1-Iodooctadecane	629-93-6	−1.22	5.39	380.40	AOO	5.0	10.0	25.0	—	—	—	1	1.4	1.9	—	—	—	NC	Nonsensitizer	Unilever (unpublished)
1-Iodotetradecane	19218-94-1	−1.57	4.40	324.29	AOO	10.0	25.0	50.0	—	—	—	1.7	6.9	9.7	—	—	—	14	Weak	Ashby J et al.[21]
Isoeugenol	97-54-1	−2.19	2.15	164.20	AOO	0.50	1.0	5.0	—	—	—	1	1.1	12.4	—	—	—	1.2	Moderate	Basketter DA, Cadby P.[41]
Isononanoyl chloride	57077-36-8	−1.99	2.54	176.69	AOO	5.0	10.0	25.0	—	—	—	6.6	10.6	12.6	—	—	—	2.7†	Moderate	Unilever (unpublished)
Isopropanol	67-63-0	−2.51	0.82	60.10	AOO	10.0	25.0	50.0	—	—	—	1.7	1.1	1.0	—	—	—	NC	Nonsensitizer	Basketter DA et al.[39]

AOO = acetone and olive oil (4:1); CAS = Chemical Abstract Service number; DEP = diethyl phthalate; dH2O = distilled water; DMF = dimethylformamide; DMSO = dimethyl sulfoxide; EtOH = ethanol; FEMA = Flavor and Extract Manufacturers' Association; $K_{O/W}$ = octanol-water partition coefficient (log scale); Kp = skin penetration coefficient (log scale); LLNA = local lymph node assay; MEK = methyl ethyl ketone; MW = molecular weight; NC = not calculated; P&G = Procter & Gamble Co.; RIFM = Research Institute for Fragrance Materials.

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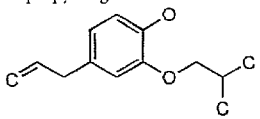
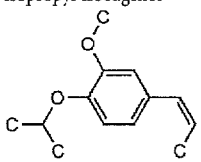
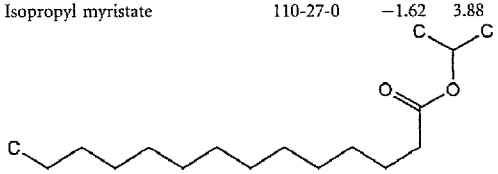
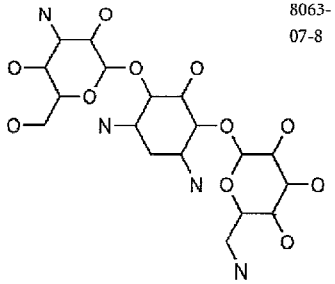
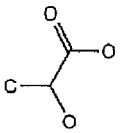
†Value estimated.

Table 1. *Continued*

Chemical Structure	CAS No.	Log Kp	Log $K_{O/W}$	MW	Vehicle	LLNA %	LLNA %	LLNA %	LLNA %	LLNA %	LLNA %	LLNA SI	LLNA SI	LLNA SI	LLNA SI	LLNA SI	LLNA SI	LLNA EC3* (%)	Potency Category	Reference
Isopropyl eugenol 	51474-90-9	−1.93	2.89	206.29	AOO	12.0	29.0	59.0	—	—	—	1.8	1.8	2.2	—	—	—	NC	Nonsensitizer	Bertrand F et al.[42]
Isopropyl isoeugenol 	2953-00-7	−1.93	2.89	206.29	AOO	0.6	1.2	3.0	—	—	—	3	5.7	10.7	—	—	—	0.6†	Strong	Bertrand F et al.[42]
Isopropyl myristate 	110-27-0	−1.62	3.88	270.46	AOO	25.0	50.0	100.0	—	—	—	2.1	3.3	3.4	—	—	—	44	Weak (false positive)	Ryan CA et al.[28]
Kanamycin 	59-01-8; 8063-07-8	−6.31	−0.90	484.50	AOO	5.0	10.0	25.0	—	—	—	2.2	0.8	1	—	—	—	NC	Nonsensitizer	Basketter DA et al.[43]
Lactic acid 	50-21-5	−3.24	0.05	90.08	DMSO	5.0	10.0	25.0	—	—	—	1.0	1.4	2.2	—	—	—	NC	Nonsensitizer	Basketter DA et al.[34]

AOO = acetone and olive oil (4:1); CAS = Chemical Abstract Service number; DEP = diethyl phthalate; dH2O = distilled water; DMF = dimethylformamide; DMSO = dimethyl sulfoxide; EtOH = ethanol; FEMA = Flavor and Extract Manufacturers' Association; $K_{O/W}$ = octanol-water partition coefficient (log scale); Kp = skin penetration coefficient (log scale); LLNA = local lymph node assay; MEK = methyl ethyl ketone; MW = molecular weight; NC = not calculated; P&G = Procter & Gamble Co.; RIFM = Research Institute for Fragrance Materials.

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(*continued on next page*)

Table 1. *Continued*

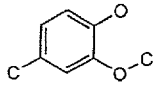
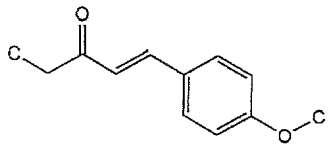
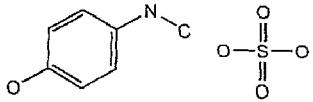
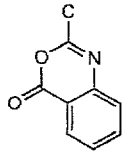
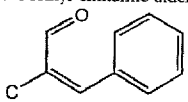
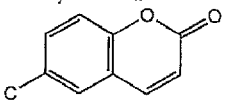
Chemical Structure	CAS No.	Log Kp	Log $K_{O/W}$	MW	Vehicle	LLNA %	LLNA %	LLNA %	LLNA %	LLNA %	LLNA %	LLNA SI	LLNA SI	LLNA SI	LLNA SI	LLNA SI	LLNA SI	LLNA EC3* (%)	Potency Category	Reference
Lauryl gallate (dodecyl gallate)	1166-52-5	−2.51	3.21	338.44	DMSO	1.0	10.0	25.0	50.0	—	—	12.1	29.7	29.3	36.0	—	—	0.3[†]	Strong	P&G (unpublished)
R(+)- Limonene	5989-27-5	−1.47	2.93	136.24	AOO	25.0	50.0	100.0	—	—	—	1.8	2.4	4.0	—	—	—	69	Weak	Warbrick EV et al.[29]
Linalool	78-70-6	−1.86	2.54	154.25	AOO	25.0	50.0	100.0	—	—	—	2.5	4.8	8.3	—	—	—	30	Weak	Ryan CA et al.[28]
2-Mercaptobenzothiazole	149-30-4	−2.46	1.80	167.24	DMF	1.0	3.0	10.0	—	—	—	2.3	4.4	8.6	—	—	—	1.7	Moderate	Basketter DA et al.[44]
4′Methoxyacetophenone	100-06-1	−2.28	1.91	150.18	AOO	10.0	25.0	50.0	—	—	—	1.3	1.0	1.0	—	—	—	NC	Nonsensitizer	Ryan CA et al.[28]

AOO = acetone and olive oil (4:1); CAS = Chemical Abstract Service number; DEP = diethyl phthalate; dH2O = distilled water; DMF = dimethylformamide; DMSO = dimethyl sulfoxide; EtOH = ethanol; FEMA = Flavor and Extract Manufacturers' Association; $K_{O/W}$ = octanol-water partition coefficient (log scale); Kp = skin penetration coefficient (log scale); LLNA = local lymph node assay; MEK = methyl ethyl ketone; MW = molecular weight; NC = not calculated; P&G = Procter & Gamble Co.; RIFM = Research Institute for Fragrance Materials.

*Mathematically estimated concentration of test chemical necessary to induce a threefold stimulation index (SI).

[†]Value estimated.

Table 1. *Continued*

Chemical Structure	CAS No.	Log Kp	Log $K_{O/W}$	MW	Vehicle	LLNA %	LLNA %	LLNA %	LLNA %	LLNA %	LLNA %	LLNA SI	LLNA SI	LLNA SI	LLNA SI	LLNA SI	LLNA SI	LLNA EC3* (%)	Potency Category	Reference
2-Methoxy-4-methyl-phenol 	93-51-6	−2.38	1.66	138.17	AOO	4.2	8.4	21.0	—	—	—	1.8	5	8.5	—	—	—	5.8	Moderate	Estrada E et al.[22]
1-(p-Methoxyphenyl)-1-penten-3-one 	104-27-8	−2.00	2.65	190.24	AOO	10.0	25.0	50.0	—	—	—	3.5	10.0	26.1	—	—	—	9.3†	Moderate	Ryan CA et al.[28]
4-(Methylamino)phenol sulfate (Metol) 	55-55-0	−4.16	−0.13	221.23	DMF	0.5	1.0	2.5	—	—	—	2.5	3.4	6.7	—	—	—	0.8	Strong	Basketter DA, Scholes EW.[29]
2-Methyl-4H,3,1-benzoxazin-4-one (Product 2040) 	525-76-8	−2.62	1.52	161.16	DMSO	5.0	10.0	25.0	—	—	—	7.6	9.2	10.8	—	—	—	0.7†	Strong	Unilever (unpublished)
α-Methyl cinnamic aldehyde 	101-39-3	−1.81	2.54	146.19	AOO	1.0	2.5	5.0	10.0	25.0	—	1.8	1.5	3.4	3.3	15.3	—	4.5	Moderate	Elahi EN et al.[23]
6-Methylcoumarin 	92-48-8	−2.17	2.15	160.17	Acetone	5.0	10.0	25.0	—	—	—	1.0	1.0	1.1	—	—	—	NC	Nonsensitizer	Ashby J et al.[21]

AOO = acetone and olive oil (4:1); CAS = Chemical Abstract Service number; DEP = diethyl phthalate; dH2O = distilled water; DMF = dimethylformamide; DMSO = dimethyl sulfoxide; EtOH = ethanol; FEMA = Flavor and Extract Manufacturers' Association; $K_{O/W}$ = octanol-water partition coefficient (log scale); Kp = skin penetration coefficient (log scale); LLNA = local lymph node assay; MEK = methyl ethyl ketone; MW = molecular weight; NC = not calculated; P&G = Procter & Gamble Co.; RIFM = Research Institute for Fragrance Materials.

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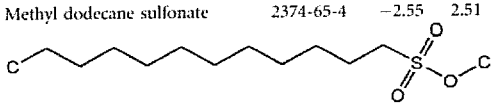
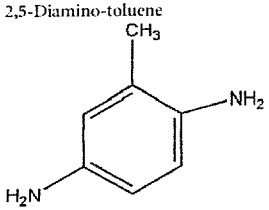
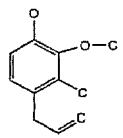
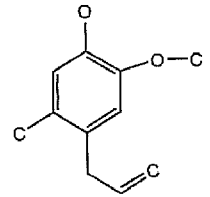
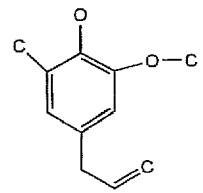
†Value estimated.

(*continued on next page*)

Table 1. *Continued*

Chemical Structure	CAS No.	Log Kp	Log $K_{O/W}$	MW	Vehicle	LLNA %	LLNA %	LLNA %	LLNA %	LLNA %	LLNA %	LLNA SI	LLNA SI	LLNA SI	LLNA SI	LLNA SI	LLNA SI	LLNA EC3* (%)	Potency Category	Reference
Methyl dodecane sulfonate 	2374-65-4	−2.55	2.51	264.42	AOO	1.0	2.5	5.0	—	—	—	21.6	39.9	48.6	—	—	—	0.39†	Strong	Basketter DA, Scholes EW.[26]
2,5-Diamino-toluene 	95-70-5	−2.46	1.416	122.08	DMSO	0.125	0.25	0.5	1.0	—	—	2.6	3.5	4.1	5.5	—	—	0.2	Strong	P&G (internal)
3-Methyleugenol 	186743-26-0	−2.10	2.40	178.23	AOO	11.0	27.0	54.0	—	—	—	1.5	2.3	6.4	—	—	—	32	Weak	Bertrand F et al.[42]
5-Methyleugenol 	186743-25-9	−2.10	2.40	178.23	AOO	11.0	27.0	54.0	—	—	—	2.7	4.9	4.3	—	—	—	13	Weak	Bertrand F et al.[42]
6-Methyleugenol 	186743-24-8	−2.10	2.40	178.23	AOO	11.0	27.0	54.0	—	—	—	1.9	4.9	8.3	—	—	—	17	Weak	Bertrand F et al.[42]

AOO = acetone and olive oil (4:1); CAS = Chemical Abstract Service number; DEP = diethyl phthalate; dH2O = distilled water; DMF = dimethylformamide; DMSO = dimethyl sulfoxide; EtOH = ethanol; FEMA = Flavor and Extract Manufacturers' Association; $K_{O/W}$ = octanol-water partition coefficient (log scale); Kp = skin penetration coefficient (log scale); LLNA = local lymph node assay; MEK = methyl ethyl ketone; MW = molecular weight; NC = not calculated; P&G = Procter & Gamble Co.; RIFM = Research Institute for Fragrance Materials.

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†Value estimated.

Table I. *Continued*

Chemical Structure	CAS No.	Log Kp	Log $K_{O/W}$	MW	Vehicle	LLNA %	LLNA %	LLNA %	LLNA %	LLNA %	LLNA %	LLNA SI	LLNA SI	LLNA SI	LLNA SI	LLNA SI	LLNA SI	LLNA EC3* (%)	Potency Category	Reference
Methyl hexadecene sulfonate	26452-48-2	−2.19	3.49	318.52	AOO	5.0	10.0	25.0	—	—	—	26.7	35.4	32.9	—	—	—	0.8†	Strong	Ashby J et al.[21]
Methyl hexadecyl sulfonate	4230-15-3	−2.20	3.49	320.53	AOO	5.0	10.0	25.0	—	—	—	1	1.3	1.5	—	—	—	NC	Nonsensitizer	Unilever (unpublished)
5-Methyl-2,3-hexanedione	13706-86-0	−2.50	1.42	128.17	AOO	25.0	50.0	100.0	—	—	—	2.9	6.0	14.3	—	—	—	26	Weak	Ryan CA et al.[28]
p-Methylhydrocinnamic aldehyde	5406-12-2	−1.82	2.54	148.21	AOO	2.5	5.0	10.0	25.0	50.0	—	1.2	1.4	2.6	4.2	10.7	—	14	Weak	Basketter DA et al.[16]
Methyl 4-hydroxybenzoate (methylparaben)	99-76-3	−2.74	1.28	152.15	DMF	10.0	25.0	50.0	—	—	—	0.8	0.9	0.8	—	—	—	NC	Nonsensitizer	Ryan CA et al.[28]
2-Methyl-5-hydroxyethylaminophenol	55302-96-0	−2.66	1.52	167.21	AOO	0.1	0.25	0.5	1.0	2.5	—	1.2	0.8	3.6	2.6	7.4	—	0.4	Strong	Estrada E et al.[22]

AOO = acetone and olive oil (4:1); CAS = Chemical Abstract Service number; DEP = diethyl phthalate; dH2O = distilled water; DMF = dimethylformamide; DMSO = dimethyl sulfoxide; EtOH = ethanol; FEMA = Flavor and Extract Manufacturers' Association; $K_{O/W}$ = octanol-water partition coefficient (log scale); Kp = skin penetration coefficient (log scale); LLNA = local lymph node assay; MEK = methyl ethyl ketone; MW = molecular weight; NC = not calculated; P&G = Procter & Gamble Co.; RIFM = Research Institute for Fragrance Materials.

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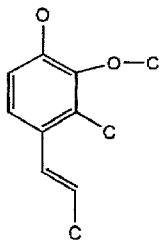
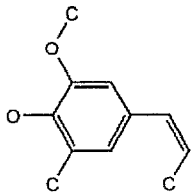
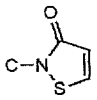
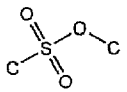
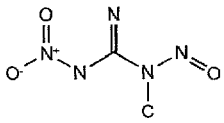
(*continued on next page*)

Table 1. *Continued*

Chemical Structure	*CAS No.*	*Log Kp*	*Log $K_{O/W}$*	*MW*	*Vehicle*	*LLNA %*	*LLNA %*	*LLNA %*	*LLNA %*	*LLNA %*	*LLNA %*	*LLNA SI*	*LLNA SI*	*LLNA SI*	*LLNA SI*	*LLNA SI*	*LLNA SI*	*LLNA EC3* (%)*	*Patency Category*	*Reference*
3-Methylisoeugenol 	186743-29-3	−2.10	2.40	178.23	AOO	2.5	5.5	11.0	—	—	—	2.2	4.3	6.0	—	—	—	3.6	Moderate	Bertrand F et al.[42]
6-Methylisoeugenol 	13041-12-8	−2.10	2.40	178.23	AOO	2.5	5.5	11.0	—	—	—	5.9	11.1	15.7	—	—	—	1.6[†]	Moderate	Bertrand F et al.[42]
2-Methyl-2H-isothiazol-3-one 	2682-20-4	−2.94	0.68	115.15	AOO	0.25	0.5	1.0	2.5	5.0	—	1.5	1.5	1.8	3.8	2.5	—	1.9	Moderate	Estrada E et al.[22]
Methyl methanesulfonate 	66-27-3	−3.53	−0.20	110.13	AOO	0.25	1.0	10.0	—	—	—	0.7	0.7	3.6	—	—	—	8.1	Moderate	Ashby J et al.[21]
1-Methyl-3-nitro-1-nitrosoguanidine 	70-25-7	−5.13	−2.13	147.09	AOO	0.05	0.1	0.25	—	—	—	27.5	60.4	78.3	—	—	—	0.03[†]	Extreme	Ashby J et al.[21]

AOO = acetone and olive oil (4:1); CAS = Chemical Abstract Service number; DEP = diethyl phthalate; dH2O = distilled water; DMF = dimethylformamide; DMSO = dimethyl sulfoxide; EtOH = ethanol; FEMA = Flavor and Extract Manufacturers' Association; $K_{O/W}$ = octanol-water partition coefficient (log scale); Kp = skin penetration coefficient (log scale); LLNA = local lymph node assay; MEK = methyl ethyl ketone; MW = molecular weight; NC = not calculated; P&G = Procter & Gamble Co.; RIFM = Research Institute for Fragrance Materials.

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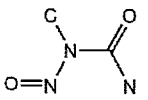
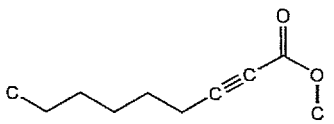
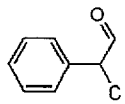
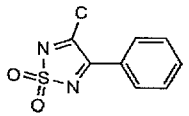
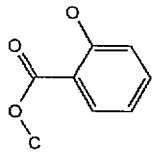
Table 1. *Continued*

Chemical Structure	*CAS No.*	*Log Kp*	*Log $K_{O/W}$*	*MW*	*Vehicle*	*LLNA %*	*LLNA %*	*LLNA %*	*LLNA %*	*LLNA %*	*LLNA %*	*LLNA SI*	*LLNA SI*	*LLNA SI*	*LLNA SI*	*LLNA SI*	*LLNA SI*	*LLNA EC3* (%)*	*Potency Category*	*Reference*
N-Methyl-*N*-nitrosourea 	684-93-5	−4.04	−0.97	103.08	AOO	0.05	0.1	0.25	—	—	—	2.7	7.1	15.4	—	—	—	0.05	Extreme	Ashby J et al.[21]
Methyl 2-nonynoate 	111-80-8	−2.22	2.15	168.24	80% EtOH	5.0	10.0	20.0	—	—	—	10.4	17.7	24.4	—	—	—	2.5†	Moderate	Ryan CA et al.[28]
α-Methylphenylacetaldehyde 	93-53-8	−1.91	2.29	134.18	AOO	0.5	1.0	2.5	5.0	10.0	—	2	2.2	1	2.2	5.2	—	6.3	Moderate	Patlewicz G et al.[34]
3-Methyl-4-phenyl-1,2,5-thiadiazole-1,1-dioxide (MPT) 	3775-21-1	−3.18	1.14	208.24	AOO	0.1	0.25	0.5	1.0	2.5	—	1.3	1.1	2.1	1.9	5.6	—	1.4	Moderate	Estrada E et al.[22]
Methyl salicylate 	119-36-8	−2.74	1.28	152.15	AOO	1.0	2.5	5.0	10.0	20.0	—	1.0	1.1	1.6	1.4	0.9	—	NC	Nonsensitizer	Kimber I et al.[35]

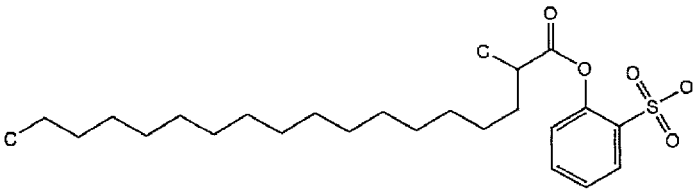
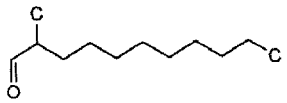
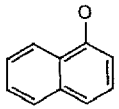
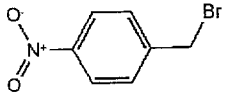
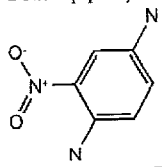
AOO = acetone and olive oil (4:1); CAS = Chemical Abstract Service number; DEP = diethyl phthalate; dH2O = distilled water; DMF = dimethylformamide; DMSO = dimethyl sulfoxide; EtOH = ethanol; FEMA = Flavor and Extract Manufacturers' Association; $K_{O/W}$ = octanol-water partition coefficient (log scale); Kp = skin penetration coefficient (log scale); LLNA = local lymph node assay; MEK = methyl ethyl ketone; MW = molecular weight; NC = not calculated; P&G = Procter & Gamble Co.; RIFM = Research Institute for Fragrance Materials.

*Mathematically estimated concentration of test chemical necessary to induce a threefold stimulation index (SI).

†Value estimated.

(*continued on next page*)

Table 1. *Continued*

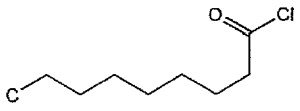
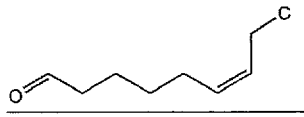
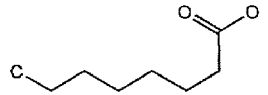
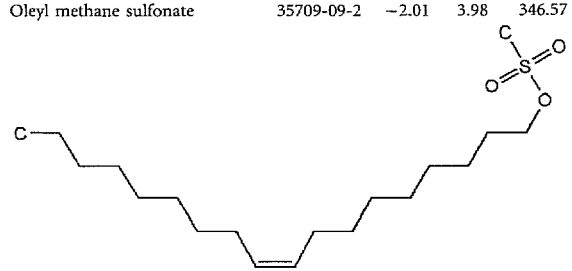
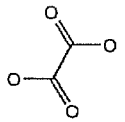
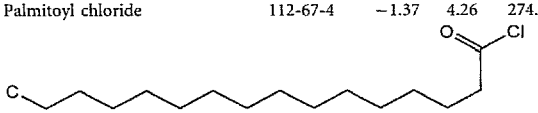
Chemical Structure	CAS No.	Log Kp	Log $K_{O/W}$	MW	Vehicle	LLNA %	LLNA %	LLNA %	LLNA %	LLNA %	LLNA %	LLNA SI	LLNA SI	LLNA SI	LLNA SI	LLNA SI	LLNA SI	LLNA EC3* (%)	Potency Category	Reference
Methyl 2-sulphophenyl octadecanoate 	—	−2.17	4.69	454.67	AOO	2.5	5.0	10.0	—	—	—	5.1	11.6	25.6	—	—	—	2.0[†]	Moderate	Unilever (unpublished)
2-Methylundecanal 	110-41-8	−1.69	3.03	184.32	AOO	0.5	1.0	2.5	5.0	10.0	—	1.4	1.3	1.3	2.4	3	—	10	Weak	Patlewicz G et al.[34]
1-Naphthol 	90-15-3	−1.80	2.54	144.17	AOO	0.1	0.25	0.5	1.0	2.5	—	1.4	1	1.2	1.5	8.5	—	1.3	Moderate	Estrada E et al.[22]
4-Nitrobenzyl bromide 	100-11-8	−3.04	1.40	216.03	AOO	0.01	0.03	0.05	0.1	—	—	0.9	1.3	3.5	11.5	—	—	0.05	Extreme	Unilever (unpublished)
2-Nitro-p-phenylenediamine 	5307-14-2	−3.65	0.01	153.14	AOO	0.1	0.25	0.5	1.0	2.5	—	1.8	2.2	3.3	7.9	11.9	—	0.4	Strong	Estrada E et al.[22]

AOO = acetone and olive oil (4:1); CAS = Chemical Abstract Service number; DEP = diethyl phthalate; dH2O = distilled water; DMF = dimethylformamide; DMSO = dimethyl sulfoxide; EtOH = ethanol; FEMA = Flavor and Extract Manufacturers' Association; $K_{O/W}$ = octanol-water partition coefficient (log scale); Kp = skin penetration coefficient (log scale); LLNA = local lymph node assay; MEK = methyl ethyl ketone; MW = molecular weight; NC = not calculated; P&G = Procter & Gamble Co.; RIFM = Research Institute for Fragrance Materials.

*Mathematically estimated concentration of test chemical necessary to induce a threefold stimulation index (SI).

[†]Value estimated.

Table 1. *Continued*

Chemical Structure	CAS No.	Log Kp	Log $K_{O/W}$	MW	Vehicle	LLNA %	LLNA %	LLNA %	LLNA %	LLNA %	LLNA %	LLNA SI	LLNA SI	LLNA SI	LLNA SI	LLNA SI	LLNA SI	LLNA EC3* (%)	Potency Category	Reference
Nonanoyl chloride 	764-85-2	−1.99	2.54	176.69	AOO	5.0	10.0	25.0	—	—	—	12.7	19.4	20.9	—	—	—	1.8†	Moderate	Ashby J et al.[21]
cis-6-Nonenal 	2277-19-2	−1.95	2.29	140.23	AOO	10.0	25.0	50.0	100.0	—	—	1.6	3.2	4.5	13.7	—	—	23	Weak	Patlewicz G et al.[34]
Octanoic acid 	124-07-2	−2.42	1.66	144.21	AOO	10.0	25.0	50.0	—	—	—	0.7	1.0	1.6	—	—	—	NC	Nonsensitizer	Basketter DA et al.[39]
Oleyl methane sulfonate 	35709-09-2	−2.01	3.98	346.57	AOO	5.0	10.0	25.0	—	—	—	1	1.3	3	—	—	—	25	Weak	Roberts DW, Basketter DA.[45]
Oxalic acid 	144-62-7	−3.69	−0.59	90.03	DMF	5.0	10.0	25.0	—	—	—	2.4	2.8	3.4	—	—	—	15	Weak	Unilever (unpublished)
Palmitoyl chloride 	112-67-4	−1.37	4.26	274.88	AOO	5.0	10.0	25.0	—	—	—	2.1	3.3	4.5	—	—	—	8.8	Moderate	Ashby J et al.[21]

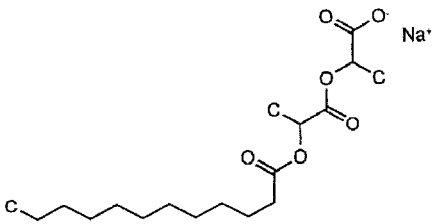
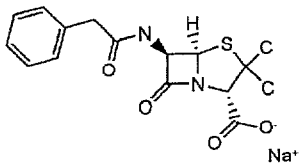
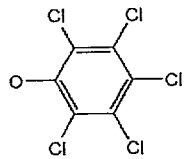
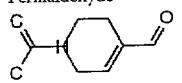
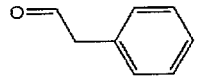
AOO = acetone and olive oil (4:1); CAS = Chemical Abstract Service number; DEP = diethyl phthalate; dH2O = distilled water; DMF = dimethylformamide; DMSO = dimethyl sulfoxide; EtOH = ethanol; FEMA = Flavor and Extract Manufacturers' Association; $K_{O/W}$ = octanol-water partition coefficient (log scale); Kp = skin penetration coefficient (log scale); LLNA = local lymph node assay; MEK = methyl ethyl ketone; MW = molecular weight; NC = not calculated; P&G = Procter & Gamble Co.; RIFM = Research Institute for Fragrance Materials.

*Mathematically estimated concentration of test chemical necessary to induce a threefold stimulation index (SI).

†Value estimated.

(*continued on next page*)

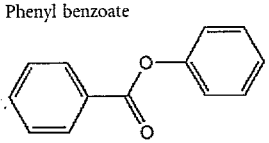
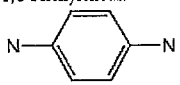
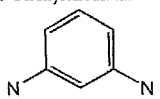
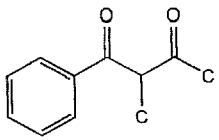
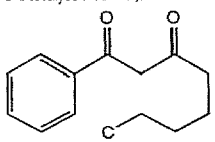
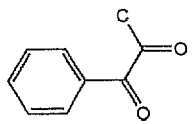
Table 1. *Continued*

Chemical Structure	CAS No.	Log Kp	Log $K_{O/W}$	MW	Vehicle	LLNA %	LLNA %	LLNA %	LLNA %	LLNA %	LLNA %	LLNA SI	LLNA SI	LLNA SI	LLNA SI	LLNA SI	LLNA SI	LLNA EC3* (%)	Potency Category	Reference
Pationic 138C (sodium lauroyl lactylate) 	13557-75-0	−3.12	2.58	366.43	AOO	5.0	10.0	25.0	—	—	—	1.4	2.5	3.9	—	—	—	15	Weak	Unilever (unpublished)
Penicillin G 	61-33-6	−3.41	2.09	356.37	DMSO	2.5	5.0	10.0	25.0	50.0	—	1.0	1.0	1.4	2.1	6.6	—	30	Weak	Kimber I et al.[35]
Pentachlorophenol 	87-86-5	−2.37	2.79	266.34	DMSO	10.0	25.0	50.0	—	—	—	2.1	3.5	5.4	—	—	—	20	Weak	Basketter DA et al.[43]
Perillaldehyde 	2111-75-3	−1.83	2.54	150.22	AOO	0.5	1.0	2.5	5.0	10.0	—	1.2	1.1	0.9	4.3	—	—	8.1	Moderate	Patlewicz G et al.[34]
Phenylacetaldehyde 	122-78-1	−2.00	2.05	120.15	AOO	1.0	2.5	5.0	10.0	25.0	—	0.7	1.8	7.8	8.8	19.0	—	3	Moderate	Basketter DA et al.[16]

AOO = acetone and olive oil (4:1); CAS = Chemical Abstract Service number; DEP = diethyl phthalate; dH2O = distilled water; DMF = dimethylformamide; DMSO = dimethyl sulfoxide; EtOH = ethanol; FEMA = Flavor and Extract Manufacturers' Association; $K_{O/W}$ = octanol-water partition coefficient (log scale); Kp = skin penetration coefficient (log scale); LLNA = local lymph node assay; MEK = methyl ethyl ketone; MW = molecular weight; NC = not calculated; P&G = Procter & Gamble Co.; RIFM = Research Institute for Fragrance Materials.

*Mathematically estimated concentration of test chemical necessary to induce a threefold stimulation index (SI).

Table 1. *Continued*

Chemical Structure	*CAS No.*	*Log Kp*	*Log $K_{O/W}$*	*MW*	*Vehicle*	*LLNA %*	*LLNA %*	*LLNA %*	*LLNA %*	*LLNA %*	*LLNA %*	*LLNA SI*	*LLNA SI*	*LLNA SI*	*LLNA SI*	*LLNA SI*	*LLNA SI*	*LLNA EC3* (%)*	*Potency Category*	*Reference*
Phenyl benzoate 	93-99-2	−1.88	2.89	198.22	AOO	5.0	10.0	25.0	—	—	—	2.3	2.1	3.5	—	—	—	20	Weak	Unilever (unpublished)
1,4-Phenylenediamine 	106-50-3	−2.55	1.17	108.14	AOO	0.05	0.1	0.25	0.5	1.0	—	1.9	2.3	4.0	5.7	6.6	—	0.16	Strong	Warbrick EV et al.[46]
3-Phenylenediamine 	108-45-2	−2.55	1.17	108.14	AOO	2.5	5.0	10.0	—	—	—	11.7	15.4	19.2	—	—	—	0.49†	Strong	Ashby J et al.[21]
1-Phenyl-2-methylbutane-1,3-dione 	6668-24-2	−2.11	2.40	179.24	Acetone	10.0	20.0	40.0	—	—	—	1.7	2.0	4.2	—	—	—	29	Weak	P&G (unpublished)
1-Phenyloctane-1,3-dione 	55846-68-1	−1.84	3.14	221.32	Acetone	10.0	20.0	40.0	—	—	—	2.8	6.6	8.7	—	—	—	11	Weak	P&G (unpublished)
1-Phenyl-1,2-propanedione 	579-07-7	−2.27	1.91	148.16	AOO	5.0	10.0	25.0	—	—	—	12.8	17.7	20.1	—	—	—	1.3†	Moderate	Roberts DW et al.[31]

AOO = acetone and olive oil (4:1); CAS = Chemical Abstract Service number; DEP = diethyl phthalate; dH2O = distilled water; DMF = dimethylformamide; DMSO = dimethyl sulfoxide; EtOH = ethanol; FEMA = Flavor and Extract Manufacturers' Association; $K_{O/W}$ = octanol-water partition coefficient (log scale); Kp = skin penetration coefficient (log scale); LLNA = local lymph node assay; MEK = methyl ethyl ketone; MW = molecular weight; NC = not calculated; P&G = Procter & Gamble Co.; RIFM = Research Institute for Fragrance Materials.

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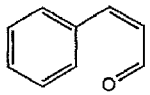
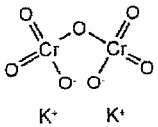
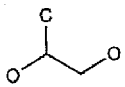
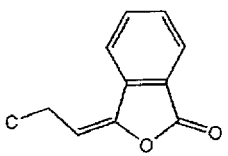
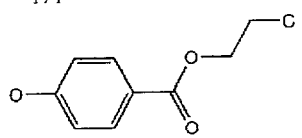
(*continued on next page*)

Table 1. *Continued*

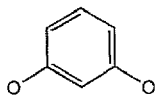
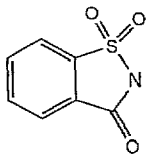
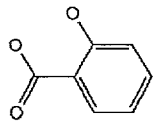
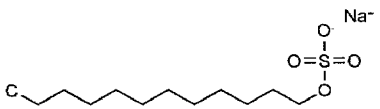
Chemical Structure	*CAS No.*	*Log Kp*	*Log $K_{O/W}$*	*MW*	*Vehicle*	*LLNA %*	*LLNA %*	*LLNA %*	*LLNA %*	*LLNA %*	*LLNA %*	*LLNA SI*	*LLNA SI*	*LLNA SI*	*LLNA SI*	*LLNA SI*	*LLNA SI*	*LLNA EC3* (%)*	*Potency Category*	*Reference*
3-Phenyl propenal 	14371-10-9	−1.90	2.29	132.16	AOO	1.0	2.5	5.0	10.0	25.0	—	2.4	4.7	8.8	10.2	13.1	—	1.4	Moderate	Patlewicz G et al.[34]
Potassium dichromate 	7778-50-9	−6.10	−2.24	294.18	DMSO	0.025	0.05	0.1	0.25	0.5	—	1.6	1.4	3.8	5.3	16.1	—	0.08	Extreme	Kimber I et al.[47]
β-Propriolactone 	57-57-8	−2.85	0.43	72.06	AOO	0.025	1.0	2.5	—	—	—	1.5	13.0	19.9	—	—	—	0.15	Strong	Ashby J et al.[21]
Propylene glycol 	57-55-6	−2.88	0.43	76.10	dH2O	50.0	100.0	—	—	—	—	1.2	1.6	—	—	—	—	NC	Nonsensitizer	Basketter DA et al.[39]
3-Propylidenephthalide 	17369-59-4	−2.08	2.40	174.20	AOO	5.0	10.0	20.0	—	—	—	4.9	9.1	15.1	—	—	—	3.7†	Moderate	Ryan CA et al.[28]
Propylparaben 	94-13-3	−2.56	1.77	180.20	AOO	5.0	10.0	25.0	—	—	—	1.4	1.0	1.3	—	—	—	NC	Nonsensitizer	Ashby J et al.[21]

AOO = acetone and olive oil (4:1); CAS = Chemical Abstract Service number; DEP = diethyl phthalate; dH2O = distilled water; DMF = dimethylformamide; DMSO = dimethyl sulfoxide; EtOH = ethanol; FEMA = Flavor and Extract Manufacturers' Association; $K_{O/W}$ = octanol-water partition coefficient (log scale); Kp = skin penetration coefficient (log scale); LLNA = local lymph node assay; MEK = methyl ethyl ketone; MW = molecular weight; NC = not calculated; P&G = Procter & Gamble Co.; RIFM = Research Institute for Fragrance Materials.

*Mathematically estimated concentration of test chemical necessary to induce a threefold stimulation index (SI).

†Value estimated.

Table 1. *Continued*

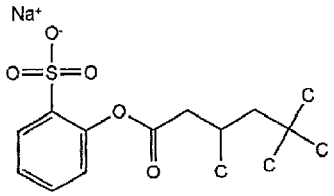
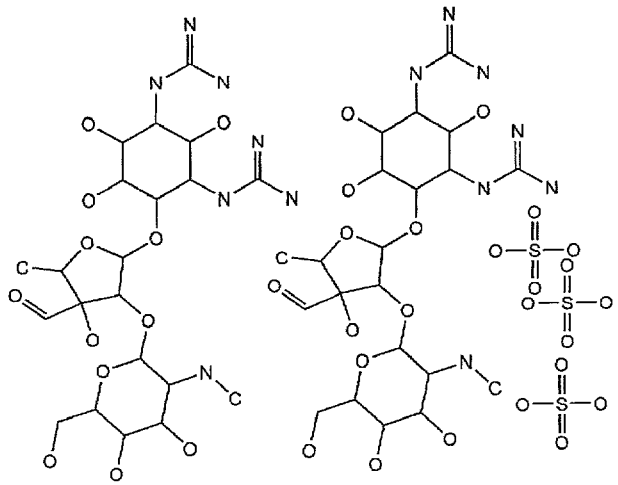
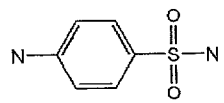
Chemical Structure	*CAS No.*	*Log Kp*	*Log $K_{O/W}$*	*MW*	*Vehicle*	*LLNA %*	*LLNA %*	*LLNA %*	*LLNA %*	*LLNA %*	*LLNA %*	*LLNA SI*	*LLNA SI*	*LLNA SI*	*LLNA SI*	*LLNA SI*	*LLNA SI*	*LLNA EC3* (%)*	*Potency Category*	*Reference*
Pyridine 	110-86-1	−2.27	1.31	79.10	AOO	25.0	50.0	100.0	—	—	—	1.1	2.3	3.9	—	—	—	72	Weak	Basketter DA et al.[43]
Resorcinol 	108-46-3	−2.56	1.17	110.11	DMF	5.0	10.0	25.0	—	—	—	2.2	2.2	2.7	—	—	—	NC	Nonsensitizer	Basketter DA et al.[32]
Saccharin 	81-07-2	−3.38	0.64	183.18	DMSO	25.0	50.0	75.0	—	—	—	1.3	1.5	1.5	—	—	—	NC	Nonsensitizer	Warbrick EV et al.[29]
Salicylic acid 	69-72-7	−2.83	1.03	138.12	AOO	5.0	10.0	25.0	—	—	—	0.8	1.5	2.5	—	—	—	NC	Nonsensitizer	Basketter DA et al.[39]
Sodium lauryl sulfate 	151-21-3	−3.15	1.87	288.38	DMF	1.0	2.5	5.0	10.0	20.0	—	0.9	1.1	1.7	2.6	3.5	—	14.0	Weak (false positive)	Loveless SE et al.[33]

AOO = acetone and olive oil (4:1); CAS = Chemical Abstract Service number; DEP = diethyl phthalate; dH2O = distilled water; DMF = dimethylformamide; DMSO = dimethyl sulfoxide; EtOH = ethanol; FEMA = Flavor and Extract Manufacturers' Association; $K_{O/W}$ = octanol-water partition coefficient (log scale); Kp = skin penetration coefficient (log scale); LLNA = local lymph node assay; MEK = methyl ethyl ketone; MW = molecular weight; NC = not calculated; P&G = Procter & Gamble Co.; RIFM = Research Institute for Fragrance Materials.

*Mathematically estimated concentration of test chemical necessary to induce a threefold stimulation index (SI).

(*continued on next page*)

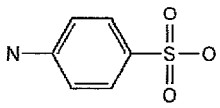
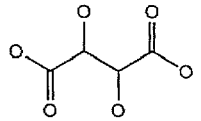
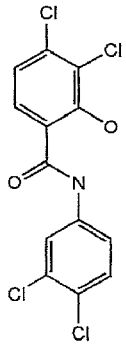
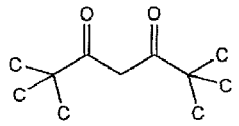
Table 1. *Continued*

Chemical Structure	CAS No.	Log Kp	Log $K_{O/W}$	MW	Vehicle	LLNA %	LLNA %	LLNA %	LLNA %	LLNA %	LLNA %	LLNA SI	LLNA SI	LLNA SI	LLNA SI	LLNA SI	LLNA SI	LLNA EC3* (%)	Potency Category	Reference
Sodium 3,5,5-trimethylhexanoyloxy benzenesulfonate 	94612-91-6	−3.19	2.23	336.38	DMSO	5.0	10.0	25.0	—	—	—	2.3	4.8	7.8	—	—	—	6.4	Moderate	Ashby J et al.[21]
Streptomycin sulfate 	3810-74-0	−17.65	−8.50	1457.38	DMF	2.5	5.0	10.0	25.0	50.0	—	1.2	1.4	1.3	2.0	1.9	—	NC	Nonsensitizer	Kimber I et al.[35]
Sulfanilamide 	63-74-1	−3.49	0.40	172.20	DMF	10.0	25.0	50.0	—	—	—	1	1	0.9	—	—	—	NC	Nonsensitizer	Basketter DA et al.[32]

AOO = acetone and olive oil (4:1); CAS = Chemical Abstract Service number; DEP = diethyl phthalate; dH2O = distilled water; DMF = dimethylformamide; DMSO = dimethyl sulfoxide; EtOH = ethanol; FEMA = Flavor and Extract Manufacturers' Association; $K_{O/W}$ = octanol-water partition coefficient (log scale); Kp = skin penetration coefficient (log scale); LLNA = local lymph node assay; MEK = methyl ethyl ketone; MW = molecular weight; NC = not calculated; P&G = Procter & Gamble Co.; RIFM = Research Institute for Fragrance Materials.

*Mathematically estimated concentration of test chemical necessary to induce a threefold stimulation index (SI).

Table 1. *Continued*

Chemical Structure	*CAS No.*	*Log Kp*	*Log $K_{O/W}$*	*MW*	*Vehicle*	*LLNA %*	*LLNA %*	*LLNA %*	*LLNA %*	*LLNA %*	*LLNA %*	*LLNA SI*	*LLNA SI*	*LLNA SI*	*LLNA SI*	*LLNA SI*	*LLNA SI*	*LLNA EC3* (%)*	*Potency Category*	*Reference*
Sulfanilic acid 	121-57-3	−3.49	0.40	173.19	DMF	5.0	10.0	25.0	—	—	—	1.5	1.9	2.2	—	—	—	NC	Nonsensitizer	Basketter DA et al.[48]
Tartaric acid 	87-69-4	−4.25	−0.87	150.09	DMF	5.0	10.0	25.0	—	—	—	1.6	3.5	6.7	—	—	—	8.7	Moderate	Unilever (unpublished)
Tetrachlorosalicylanilide 	1154-59-2	−2.38	3.49	351.02	Acetone	0.25	0.5	1.0	—	—	—	11.2	14.4	18.0	—	—	—	0.04†	Extreme	Basketter DA et al.[32]
2,2,6,6-Tetramethyl-heptane-3,5-dione 	1118-71-4	−2.15	2.40	186.30	Acetone	10.0	20.0	40.0	—	—	—	2.1	2.8	3.4	—	—	—	27	Weak	P&G (unpublished)

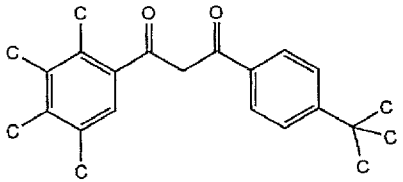
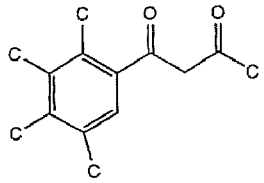
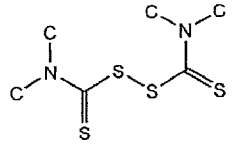
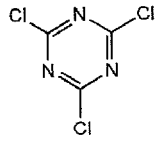
AOO = acetone and olive oil (4:1); CAS = Chemical Abstract Service number; DEP = diethyl phthalate; dH2O = distilled water; DMF = dimethylformamide; DMSO = dimethyl sulfoxide; EtOH = ethanol; FEMA = Flavor and Extract Manufacturers' Association; $K_{O/W}$ = octanol-water partition coefficient (log scale); Kp = skin penetration coefficient (log scale); LLNA = local lymph node assay; MEK = methyl ethyl ketone; MW = molecular weight; NC = not calculated; P&G = Procter & Gamble Co.; RIFM = Research Institute for Fragrance Materials.

*Mathematically estimated concentration of test chemical necessary to induce a threefold stimulation index (SI).

†Value estimated.

(*continued on next page*)

Table 1. *Continued*

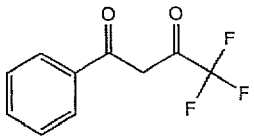
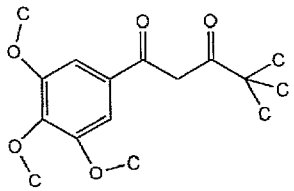
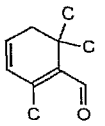
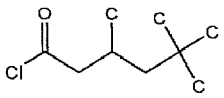
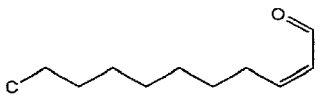
Chemical Structure	CAS No.	Log Kp	Log $K_{O/W}$	MW	Vehicle	LLNA %	LLNA %	LLNA %	LLNA %	LLNA %	LLNA %	LLNA SI	LLNA SI	LLNA SI	LLNA SI	LLNA SI	LLNA SI	LLNA EC3* (%)	Potency Category	Reference
1-(2',3',4'5'-Tetramethylphenyl)-3-(4'-tertbutylphenyl) propane-1,3-dione 	55846-68-9	−0.97	5.35	336.47	Acetone	10.0	20.0	40.0	—	—	—	1.6	1.2	1.6	—	—	—	NC	Nonsensitizer	P&G (unpublished)
1-(2',3'4'5'-Tetramethylphenyl)butane-1,3-dione 	167998-73-4	−1.84	3.14	221.32	Acetone	10.0	20.0	40.0	—	—	—	7.0	22.1	22.4	—	—	—	8.3†	Moderate	P&G (unpublished)
Tetramethylthiuram disulfide 	137-26-8	−3.36	1.17	240.42	AOO	2.5	5.0	10.0	—	—	—	2.4	2.9	5.1	—	—	—	5.2	Moderate	Basketter DA et al.[43]
2,4,6-Trichloro-1,3,5-triazine (cyanuric chloride) 	108-77-0	−3.29	0.78	184.41	AOO	1.0	2.5	5.0	—	—	—	21.8	28.9	34.0	—	—	—	0.09†	Extreme	Ashby J et al.[21]

AOO = acetone and olive oil (4:1); CAS = Chemical Abstract Service number; DEP = diethyl phthalate; dH2O = distilled water; DMF = dimethylformamide; DMSO = dimethyl sulfoxide; EtOH = ethanol; FEMA = Flavor and Extract Manufacturers' Association; $K_{O/W}$ = octanol-water partition coefficient (log scale); Kp = skin penetration coefficient (log scale); LLNA = local lymph node assay; MEK = methyl ethyl ketone; MW = molecular weight; NC = not calculated; P&G = Procter & Gamble Co.; RIFM = Research Institute for Fragrance Materials.

*Mathematically estimated concentration of test chemical necessary to induce a threefold stimulation index (SI).

†Value estimated.

Table 1. *Continued*

Chemical Structure	CAS No.	Log Kp	Log $K_{O/W}$	MW	Vehicle	LLNA %	LLNA %	LLNA %	LLNA %	LLNA %	LLNA %	LLNA SI	LLNA SI	LLNA SI	LLNA SI	LLNA SI	LLNA SI	LLNA EC3* (%)	Potency Category	Reference
4,4,4-Trifluro-1-phenylbutane-1,3-dione 	326-06-7	−2.27	2.52	219.18	Acetone	10.0	20.0	40.0	—	—	—	2.1	3.0	4.6	—	—	—	20	Weak	P&G (unpublished)
1-(3′,4′,5′-Trimethoxyphenyl)-4-dimethylpentane-1,3,-dione 	135099-98-8	−2.78	2.47	297.37	Acetone	10.0	20.0	40.0	—	—	—	2.8	1.1	0.7	—	—	—	NC	Nonsensitizer	P&G (unpublished)
1,1,3-Trimethyl-2-formylcyclohexa-2,4-diene (Safranal) 	116-26-7	−1.83	2.54	150.22	AOO	0.5	1.0	2.5	5.0	10.0	—	0.7	1.1	1.1	2.7	3.3	—	7.5	Moderate	Patlewicz G et al.[34]
3,5,5-Trimethylhexanoyl chloride 	36727-29-4	−1.99	2.54	176.69	AOO	5.0	10.0	25.0	—	—	—	7.2	12.0	19.0	—	—	—	2.7†	Moderate	Ashby J et al.[21]
Undec-10-enal 	112-45-8	−1.77	2.79	168.28	AOO	5.0	10.0	25.0	50.0	75.0	—	1.7	5.3	7.5	8.7	8.8	—	6.8	Moderate	Patlewicz G et al.[34]

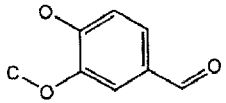
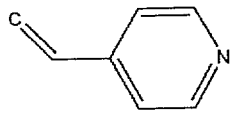
AOO = acetone and olive oil (4:1); CAS = Chemical Abstract Service number; DEP = diethyl phthalate; dH2O = distilled water; DMF = dimethylformamide; DMSO = dimethyl sulfoxide; EtOH = ethanol; FEMA = Flavor and Extract Manufacturers' Association; $K_{O/W}$ = octanol-water partition coefficient (log scale); Kp = skin penetration coefficient (log scale); LLNA = local lymph node assay; MEK = methyl ethyl ketone; MW = molecular weight; NC = not calculated; P&G = Procter & Gamble Co.; RIFM = Research Institute for Fragrance Materials.

*Mathematically estimated concentration of test chemical necessary to induce a threefold stimulation index (SI).

†Value estimated.

(*continued on next page*)

Table 1. *Continued*

Chemical Structure	*CAS No.*	*Log Kp*	*Log $K_{O/W}$*	*MW*	*Vehicle*	*LLNA %*	*LLNA %*	*LLNA %*	*LLNA %*	*LLNA %*	*LLNA %*	*LLNA SI*	*LLNA SI*	*LLNA SI*	*LLNA SI*	*LLNA SI*	*LLNA SI*	*LLNA EC3* (%)*	*Potency Category*	*Reference*
Vanillin 	121-33-5	−2.74	1.28	152.15	AOO	2.5	5.0	10.0	25.0	50.0	—	0.9	1.4	1.5	1.2	1.4	—	NC	Nonsensitizer	Basketter DA et al.[16]
Vinylidene dichloride 	75-35-4	−2.28	1.45	96.94	AOO	10.0	25.0	50.0	—	—	—	0.8	0.8	0.9	—	—	—	NC	Nonsensitizer	Warbrick EV et al.[29]
Vinyl pyridine 	1337-81-1	−2.08	1.80	105.14	AOO	2.5	5.0	10.0	—	—	—	7.4	14.2	14.8	—	—	—	1.6†	Moderate	Ashby J et al.[21]

AOO = acetone and olive oil (4:1); CAS = Chemical Abstract Service number; DEP = diethyl phthalate; dH2O = distilled water; DMF = dimethylformamide; DMSO = dimethyl sulfoxide; EtOH = ethanol; FEMA = Flavor and Extract Manufacturers' Association; $K_{O/W}$ = octanol-water partition coefficient (log scale); Kp = skin penetration coefficient (log scale); LLNA = local lymph node assay; MEK = methyl ethyl ketone; MW = molecular weight; NC = not calculated; P&G = Procter & Gamble Co.; RIFM = Research Institute for Fragrance Materials.

*Mathematically estimated concentration of test chemical necessary to induce a threefold stimulation index (SI).

†Value estimated.

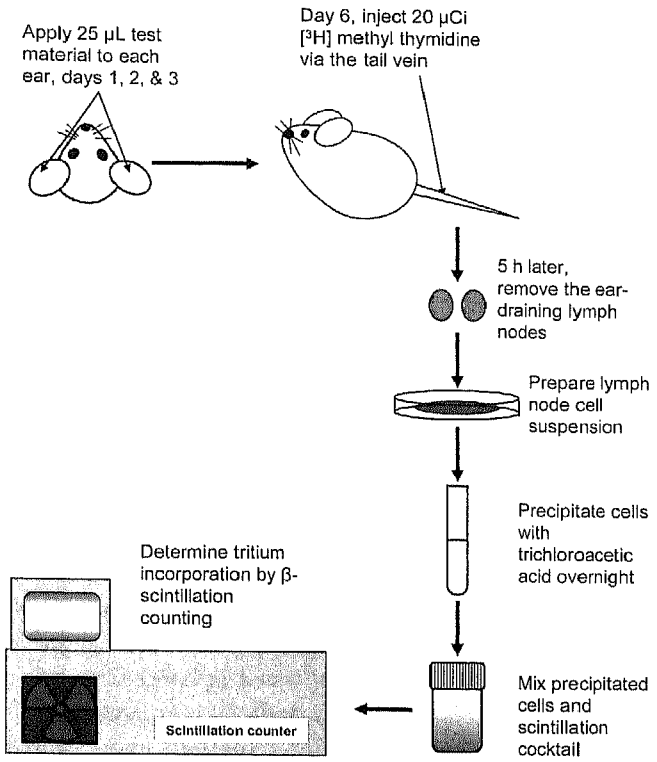


Figure 1. Schematic of local lymph node assay.

this article and in Table 1. The data are derived from previous studies that used LLNA methodology as described in the OECD guideline.[7] References for the sources of LLNA data for each of the chemicals are listed in Table 1.[16,21–48]

Potency Estimation in the Local Lymph Node Assay

The approach to the estimation of the relative skin sensitization potency of chemicals in the LLNA has been previously described in detail.[10] It is based on the mathematical estimation of the concentration of chemical necessary to obtain a threshold positive response (SI = 3); this is termed the EC3 value. When the LLNA dose-response curve included concentrations that induced at least one SI greater than 3 and one SI less than 3, EC3 values were calculated by linear interpolation. For chemicals that induced an SI greater than or equal to 3 at all concentrations tested, an EC3 value was extrapolated from the two lowest doses used.[49] For conducting this extrapolation method, a dose response should be evident. The relative sensitizing potencies of the chemical allergens were categorized with a recently proposed arbitrary classification scheme.[11] The system, shown in Table 2, is composed of four sensitization potency categories based on EC3 values. Compounds that did not induce a threefold increase at any concentration tested (generally > 20%) are categorized as nonsensitizing.

Results

Skin Sensitization Data Set: Chemical Information

Table 1 lists 211 chemical compounds along with their respective CAS numbers and two-dimensional chemical structures. It is clear from review of the structures themselves that the data set embraces the wide chemical diversity known to exist among skin allergens. For example, aldehydes, ketones, aromatic amines, quinones, and acrylates are represented in the data set. It is also known that the chemical data set lists compounds that demonstrate different protein reactivity mechanisms (eg, Schiff base, Michael addition). The physicochemical diversity of the allergens is reflected also by the log $K_{O/W}$ values, which range from less than −3 to greater than 5 (Table 3 and Fig 2). The majority of the allergens (92.3%), however, have log $K_{O/W}$ values in the ranges of −1 to 3 and 3 to 5. This is not surprising because chemicals with these ranges are known to be very good and good skin permeants, respectively.[19,50–53] The potency of an allergen does not seem to be associated with any one log $K_{O/W}$ range (eg, extreme allergens are represented in four of the five log $K_{O/W}$ categories). The nonallergens represented in the database have a log $K_{O/W}$ distribution similar to that of the allergens. Similar ranges of log Kp values are evident for both the allergens and nonallergens (data not shown).

Not surprisingly, all of the allergens listed in Table 1 have an MW of less than 500 D, which is consistent with what has been published previously.[54] The MW distribution of the allergens shows that the majority are in the ranges of 100 to 200 D (52.7%) and 200 to 300 D (26.6%) (Table 4 and Fig 3). It is generally believed that chemical allergens have low MWs (< 500 D) and log $K_{O/W}$ values of greater than 1, which are thought to favor the penetration of the chemical across the lipid-rich stratum corneum.[55] For the most part, all potency categories are associated with the MW cutoff ranges depicted in Table 4. The distribution of the nonallergens in the database is similar to that of the allergens.

Table 2. Classification of Relative Skin Sensitization Potency by Local Lymph Node Assay EC3 Values

EC3 Value (%)	*Potency Classification*
≥ 10 to ≤ 100	Weak
≥ 1 to < 10	Moderate
≥ 0.1 to < 1	Strong
< 0.1	Extreme

Table 3. Log $K_{O/W}$ (Log P) Distribution of Allergens by Potency Classification

Log $K_{O/W}$ Range	*Skin Penetration*	*Allergen Potency* Distribution*
< -3	Very poor skin permeant, very hydrophobic	0
≥ -3 to -1	Poor skin permeant, hydrophilic	4 (2E, 1S, 0M, 1W)
≥ -1 to 3	Very good skin permeant, amphiphilic	113 (7E, 17S, 54M, 35W)
≥ 3 to 5	Good skin permeant, slightly lipophilic	43 (2E, 3S, 11M, 27W)
≥ 5	Moderate skin permeant but decreasing with increasing log $K_{O/W}$	9 (2E, 0S, 4M, 3W)

*Designated as E (extreme), S (strong), M (moderate), and W (weak).

Skin Sensitization Data Set: Biologic Data

The LLNA data for each of the 211 chemicals are displayed in Table 1. The data set includes weak, moderate, strong, and extreme skin sensitizers, as well as nonsensitizers. The LLNA data in this database were from studies that used the standard LLNA protocol as described in OECD Test Guideline 429.[7] For some chemicals (such as those that formed the basis of the various interlaboratory trials), several different EC3 values were available albeit within a narrow range. In each of these cases, the data shown in Table 1 derive from one representative experiment that we feel reflects accurately the results obtained with the chemical. For all of the studies represented in Table 1, a common vehicle as described in OECD Test Guideline 429 was used (eg, acetone and olive oil 4:1 [AOO], and dimethyl sulfoxide). In instances in which the chemical was tested in more than one vehicle, the data set for AOO was selected.

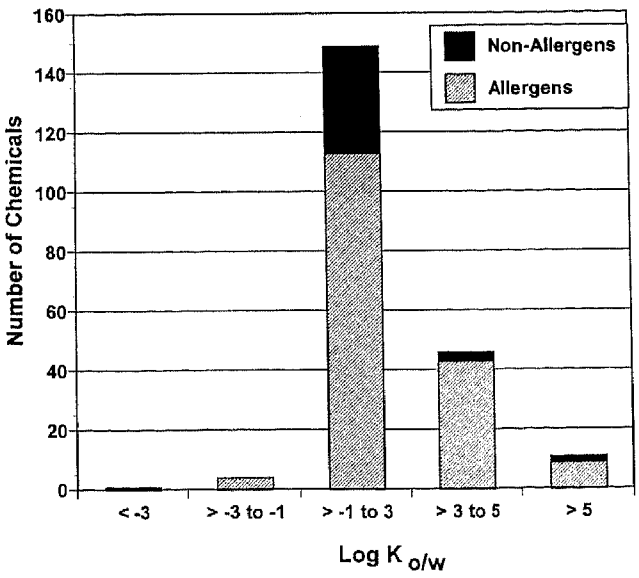


Figure 2. Distribution of log $K_{O/W}$ values of allergens and nonallergens.

The specific reference for the source of the LLNA data for each chemical is indicated in Table 1. The data set includes 42 nonsensitizers, 66 weak sensitizers, 69 moderate sensitizers, 21 strong sensitizers, and 13 extreme sensitizers, for a total of 211 compounds (Fig 4). For the nonsensitizers, materials that did not give a positive response in the LLNA up to the highest dose tested were included (data for nonsensitizers were most often tested at concentrations of > 20%). For positive chemicals in the LLNA database, EC3 values (calculated from linear interpolation) range from as low as 0.003% (for the sensitizer oxazolone) to as high as 89% (for aniline). In Table 1, we have also included EC3 values estimated by the extrapolation method; these are indicated by a footnote marker. Of course, caution should be used in interpreting and using extrapolated EC3 values that have been estimated from less-than-perfect dose-response data. However, it is our opinion that these data can still provide important benchmark information to investigators who are developing alternative skin sensitization testing methods.

Discussion

One major focus area for scientists from academia and industry over the past decade has been to develop alternative nonanimal test methods for skin sensitization testing.

Table 4. Molecular Weight Distribution of Allergen Potency

MW Range	*Allergen Potency* Distribution*
< 100	10 (0E, 2S, 3M, 5W)
≥ 100 to 200	89 (5E, 11S, 45M, 28W)
≥ 200 to 300	45 (7E, 4S, 12M, 22W)
≥ 300 to 400	23 (1E, 3S, 8M, 11W)
≥ 400	2 (0E, 1S, 1M, 0W)

MW = molecular weight.
*Designated as E (extreme), S (strong), M (moderate), and W (weak).

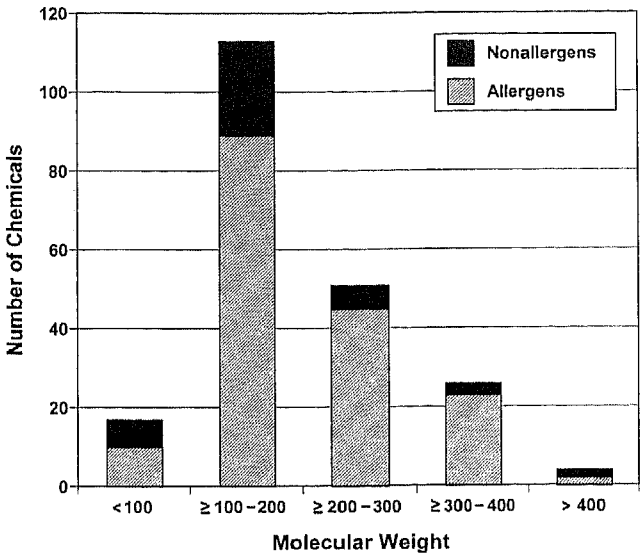


Figure 3. Distribution of molecular weights of allergens and nonallergens.

It is an enormous challenge to reproduce accurately in vitro the complex immunobiologic mechanisms that act in concert to permit skin sensitization. For example, numerous cell types (eg, T lymphocytes, Langerhans cells, keratinocytes) and a plethora of immune and inflammatory mediators (including cytokines and chemokines) are involved in the initiation and expression of an ACD response. The key to success will be the development of a test method or methods that incorporate all aspects of our understanding of the chemistry and biology of contact allergy.

Whatever new methods are developed, whether they are in silico quantitative structure activity system models or in vitro cell-based methods, they will be required to have their performance characteristics assessed, particularly their sensitivity, selectivity, and overall accuracy. This in turn requires the selection of a robust chemical data set to interrogate and calibrate the method.[49,56] One essential criterion is that the activity of each of the chemicals used must be supported by relevant and reliable in vivo data of high quality. In addition, it is important to select chemicals that display a wide range of potencies and that represent the relevant classes of chemicals and physical properties of the materials known to cause the specific endpoint. To this end, we compiled a data set of chemicals to be used for evaluating alternative approaches to skin sensitization testing that meet these criteria and that encompass the chemical and biologic diversity of chemicals known to cause skin sensitization in animals and/or in humans.

The chemicals listed in Table 1 have clearly different protein reaction mechanisms (eg, Schiff base formation, Michael addition) and include representatives from various chemical classes of materials, including aldehydes, ketones, diketones, acrylates, and aromatic amines. The two-dimensional structure and CAS number of each compound is provided to aid investigators in obtaining the correct materials. It is well known that skin allergens must have a relatively low MW ($\leq$ 500 D)[54] and appropriate physicochemical properties (eg, lipophilicity).[27,57] The chemicals compiled in this data set demonstrate a distribution of log $K_{O/W}$ values and MWs that are consistent with chemicals known to be good to very good skin penetrants (see Tables 3 and 4 and Figs 2 and 3). It is known also that chemicals of equal molecular weight can have very different skin penetration potentials, depending on their lipophilicity. For example, most skin permeants are amphiphilic (or amphipathic) chemicals with a trend toward slight lipophilicity. It is also interesting that the allergenic potency of the chemicals compiled in the database are not associated with any one particular log $K_{O/W}$ or MW category (see Tables 3 and 4). The nonallergens in the database show similar distributions for the log $K_{O/W}$ and MW categories.

In addition to chemical diversity, it is particularly important that the enormous range of potencies known for skin allergens be encompassed. It is believed that differences between contact allergens with respect to their relative skin sensitizing potencies can span four or more orders of magnitude.[11,15,58] The chemicals compiled in this LLNA database display a range of potencies, which is referred to as the EC3 value.[10] The preferred method for deriving EC3 values is linear interpolation using the data points (concentration and SI) immediately above and below the SI value of 3 on the LLNA dose-response curve. In addition, we employed a method for estimating EC3 values that can be applied in instances in which none of the

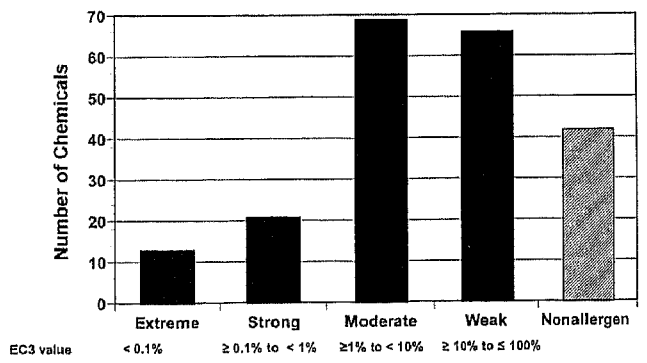


Figure 4. European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC) potency category distribution for allergens.

tested concentrations results in an SI of less than 3 and in which there is clear evidence of a dose response.[49] Although caution needs to be taken when employing this extrapolation method to obtain an EC3 value estimate, the method can provide information regarding likely threshold values and may obviate the need for repeat animal testing. It is also important to note that the data sets provided in this article are representative of the types of dose responses observed in the assay. For some chemicals (eg, camphorquinone), a decrease in SI values at the highest concentration tested may be indicative of local or systemic toxicity. Additional information such as body weight data can provide guidance in interpreting these types of responses.

The LLNA EC3 values listed in Table 1 show an enormous range of potency, covering four orders of magnitude, from weak allergens to extreme allergens. Each of the ECETOC potency categories established by the European Centre for Ecotoxicology and Toxicology of Chemicals[11,12] is well represented among the 211 chemicals in the data set (ie, 42 nonsensitizers, 66 weak sensitizers, 69 moderate sensitizers, 21 strong sensitizers, and 13 extreme sensitizers) (see Fig 4). Our experience is that the allergenic potency for mice as determined with the LLNA is similar to that known for humans.[16,17,59]

In terms of hazard identification (to the standards required globally for regulatory classification), the LLNA demonstrates the same accuracy as the Buehler and guinea pig maximization tests for predicting the human response.[8] Thus, there are a few compounds that demonstrate discordance between the LLNA results and human experience. For completeness, we chose to include those chemicals as well in this data set. For example, benzocaine, methyl 4-hydroxybenzoate (methylparaben), streptomycin sulfate, and vanillin are chemicals that are not detected as skin sensitizers in the LLNA but that have been reported as human allergens.[16,17,25,28,35] It is important to note that none of these chemicals that escaped detection in the LLNA are considered significant human contact allergens, nor do they typically give positive results in guinea pig tests. In addition, there are chemicals that give positive responses in the LLNA but are not considered skin allergens in humans. For example, isopropyl myristate and sodium lauryl sulfate yielded positive LLNA responses (albeit weak) whereas human experience suggests that these compounds are nonallergens.[28,33]

It is well known that some chemical allergens require biotransformation to be capable of initiating a skin sensitization response in vivo.[27] Thus, chemicals that are known to undergo activation or metabolism in the skin to acquire reactivity are represented in this data set. (Such chemicals are called prohaptens; for example, eugenol and isoeugenol are considered to be prohaptens.)[27,42] Because it is known that some chemical allergens must undergo biotransformation prior to reacting with proteins/peptides, it will be critical to incorporate a metabolism component into alternative assays in order to address these types of molecules.

An important measure of any new in vitro test method will be the extent of its usefulness in the skin sensitization risk assessment process. Although it would be of value to have in vitro methods available to assess the skin sensitization hazard of novel chemicals, it would be more valuable to have available methods that can extrapolate that hazard as risk to humans.[1] In addition to determining skin sensitization potential (hazard), the LLNA yields important information for assessing sensitization risk, the relative allergenic potency of a chemical.[15,17,28] Therefore, it will be useful to compare any new in vitro skin sensitization test method to the murine LLNA for its ability to determine allergenic potency. On the other hand, in vitro methods that can be used only for hazard identification would still be valuable because they can be used for screening purposes and will help to reduce the need for animal testing.

The list of chemicals contained in the data set represents both the chemical and biologic diversity known to exist for chemical allergens and nonallergens. It is our hope that publishing this LLNA data set will provide investigators with key information needed to accelerate the development and subsequent evaluation of alternative test methods and ultimately reduce the reliance on animals for assessing the skin sensitization potential of new chemicals.

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