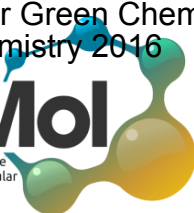




UFG
UNIVERSIDADE
FEDERAL DE GOIÁS

LabMol

Laboratório de Planejamento de
Fármacos e Modelagem Molecular



THE UNIVERSITY
of NORTH CAROLINA
at CHAPEL HILL



QSAR models of human data can enrich or replace LLNA testing for human skin sensitization

Vinicius M. Alves,^{a,b} Stephen J. Capuzzi,^a Eugene Muratov,^a Rodolpho C. Braga,^b Thomas Thornton,^a Denis Fourches,^c Judy Strickland,^d Nicole Kleinstreuer,^d Carolina H. Andrade,^b and Alexander Tropsha^{a,}*

^a University of North Carolina, Chapel Hill, USA

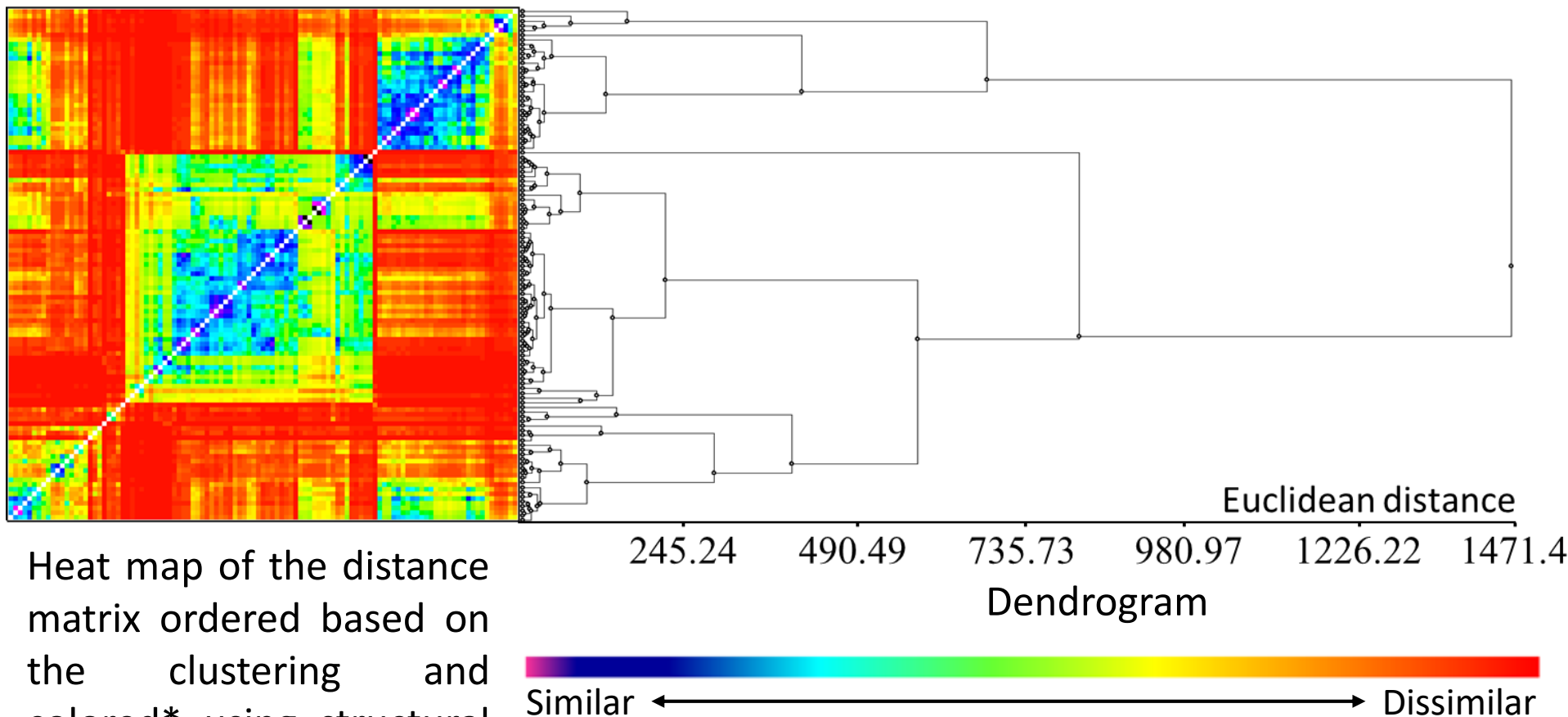
^b Federal University of Goiás, Goiás, Brazil

^c North Carolina State University, Raleigh, USA

^d ILS NIEHS, RTP, USA

**CLUSTER ANALYSIS OF
HUMAN SKIN SENSITIZATION
DATASET**

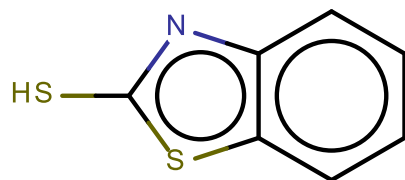
No. of compounds = 109



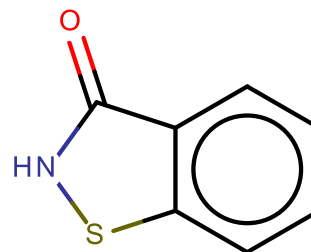
CLUSTER 1

4

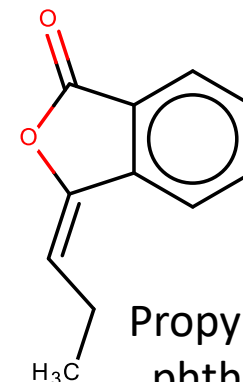
Conflicting
experimental
annotation
between
duplicates



2-Mercaptobenzothiazole



Benzisothiazolone



Propylidene
phthalate

Sensitizer

Sensitizer

Sensitizer

Sensitizer

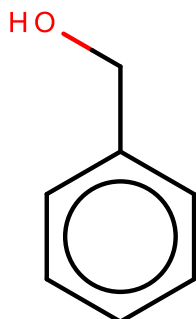
Sensitizer

Sensitizer

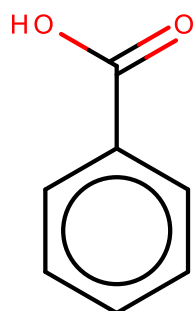
Sensitizer

Sensitizer

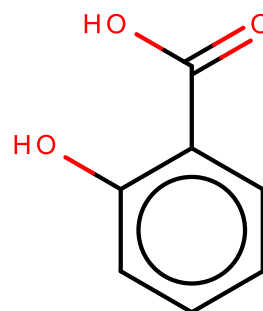
Non-sensitizer



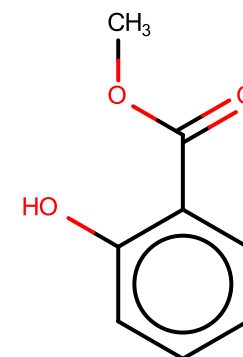
Benzyl
alcohol



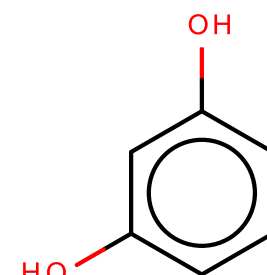
Benzoic
acid



Salicylic
acid



Methyl
salicylate



Resorcinol

Sensitizer

Non-sensitizer

Non-sensitizer

Non-sensitizer

Non-sensitizer

Non-sensitizer

Non-sensitizer

Sensitizer

Sensitizer

Sensitizer

Non-sensitizer

Non-sensitizer

Non-sensitizer

Non-sensitizer

Non-sensitizer

Human

LLNA

QSAR

Human

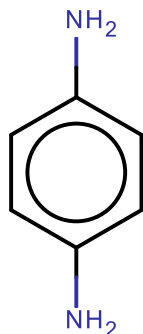
LLNA

QSAR

CLUSTER 2 - AROMATIC AMINES

5

Human
LLNA
QSAR

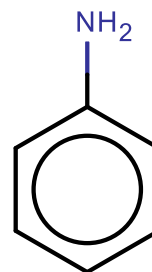


4-phenylenediamine

Sensitizer

Sensitizer

Sensitizer

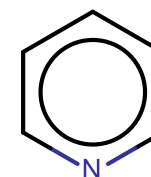


Aniline

Sensitizer

Sensitizer

Sensitizer

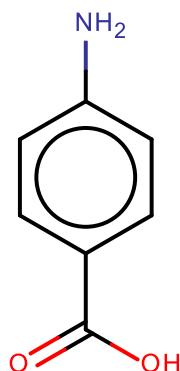


Pyridine

Sensitizer

Sensitizer

Sensitizer

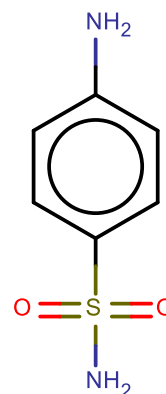


p-aminobenzoic acid

Non-sensitizer

Non-sensitizer

Sensitizer

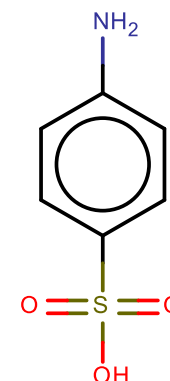


Sulfanilamide

Sensitizer

Non-sensitizer

Sensitizer



Sulfanilic acid

Non-sensitizer

Non-sensitizer

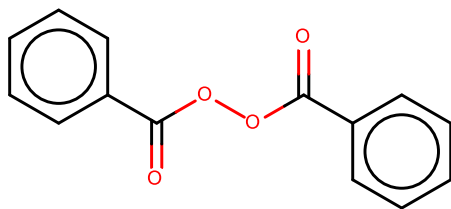
Sensitizer

Human
LLNA
QSAR

CLUSTER 3 - ESTERS OF BENZOIC ACID

6

Human
LLNA
QSAR

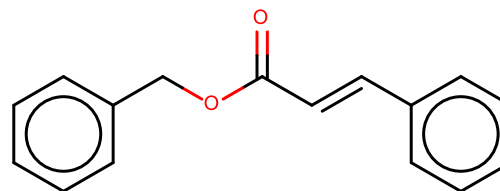


Benzoyl peroxide

Sensitizer

Sensitizer

Non-sensitizer

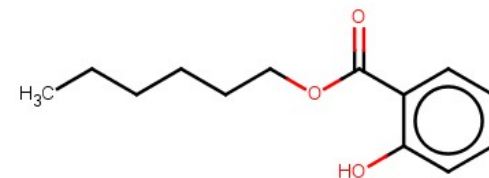


Benzyl cinnamate

Non-sensitizer

Sensitizer

Non-sensitizer

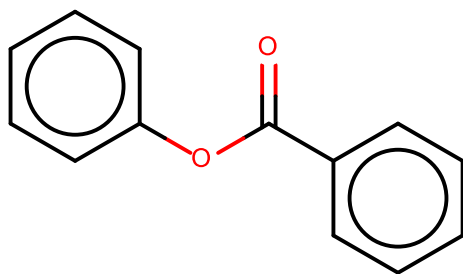


Hexyl salicylate

Non-sensitizer

Sensitizer

Non-sensitizer

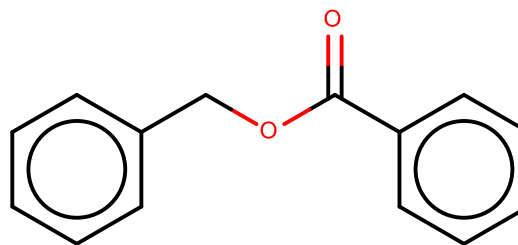


Phenyl benzoate

Sensitizer

Sensitizer

Sensitizer

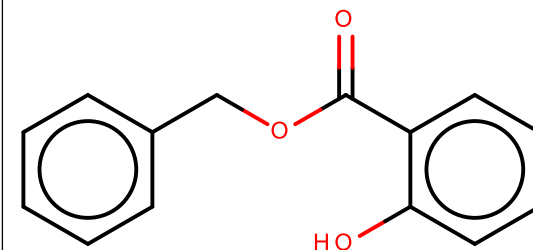


Benzyl benzoate

Non-sensitizer

Sensitizer

Non-sensitizer



Benzyl salicylate

Non-sensitizer

Sensitizer

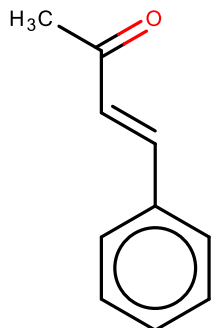
Non-sensitizer

Human
LLNA
QSAR

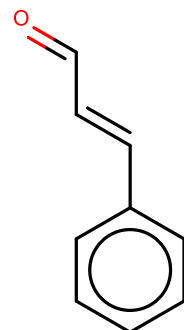
CLUSTER 4 - CINNAMYL DERIVATIVES

7

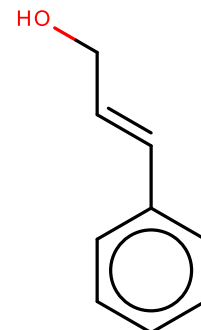
Conflicting
experimental
annotation
between
duplicates



Benzylidene acetone



Cinnamic aldehyde



Cinnamyl alcohol

Human

Sensitizer

Sensitizer

Sensitizer

LLNA

Sensitizer

Sensitizer

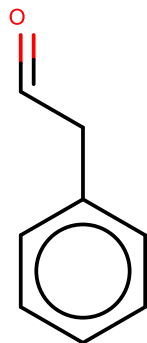
Sensitizer

QSAR

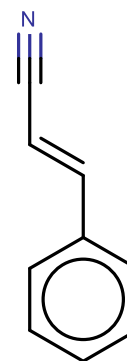
Non-sensitizer

Sensitizer

Sensitizer



Phenylacetaldehyde



Cinnamyl nitrile

Human

Sensitizer

Sensitizer

LLNA

Sensitizer

Non-sensitizer

QSAR

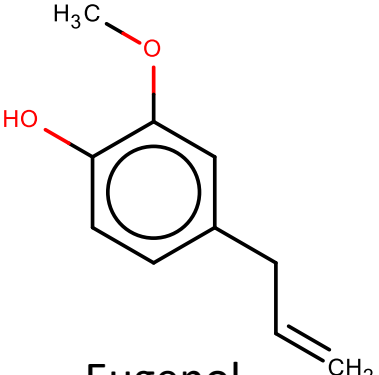
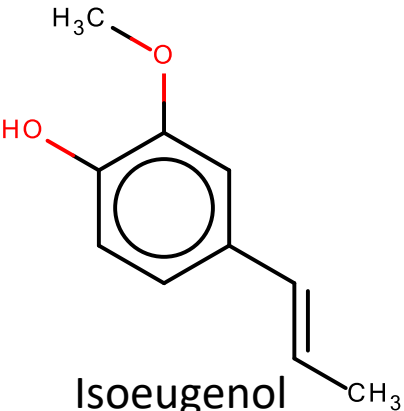
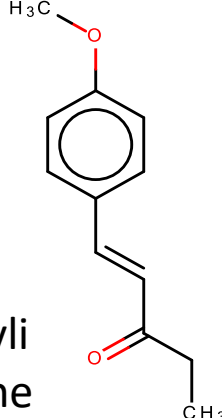
Non-sensitizer

Sensitizer

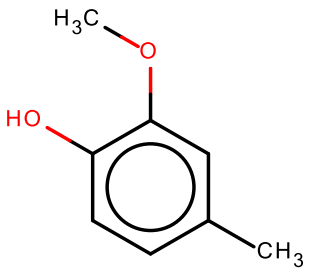
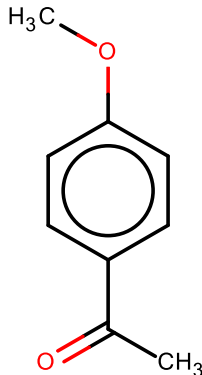
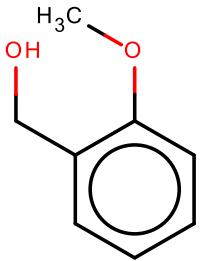
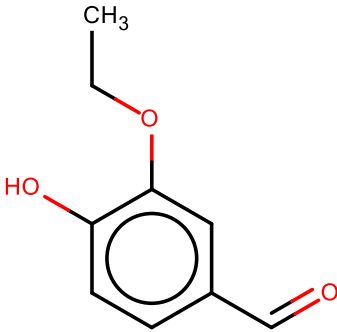
CLUSTER 5

8

Human
LLNA
QSAR

		
Eugenol	Isoeugenol	Methylchavicol acetone
Sensitizer	Sensitizer	Sensitizer
Sensitizer	Sensitizer	Sensitizer
Sensitizer	Non-sensitizer	Sensitizer

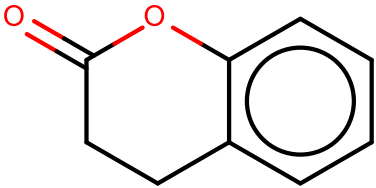
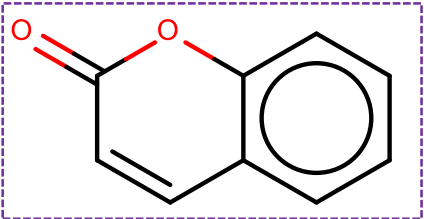
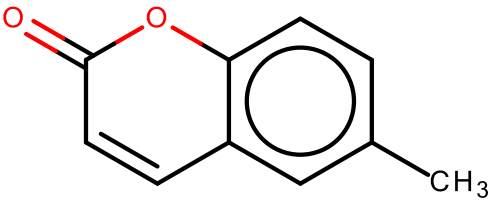
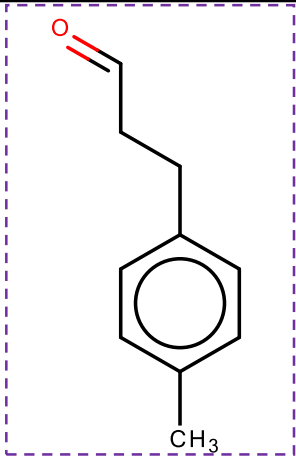
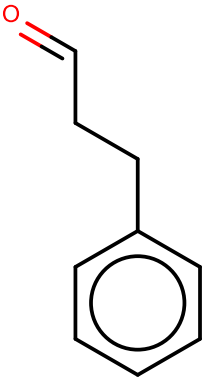
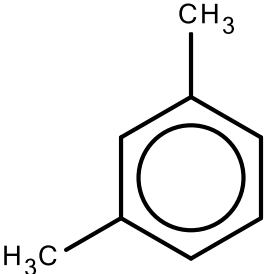
Human
LLNA
QSAR

			
2-Methoxy-4-methylphenol	4-Methoxyacetophenone	Anisyl alcohol	Ethyl vanillin
Non-sensitizer	Non-sensitizer	Non-sensitizer	Non-sensitizer
Sensitizer	Non-sensitizer	Sensitizer	Non-sensitizer
Non-sensitizer	Sensitizer	Non-sensitizer	Non-sensitizer

CLUSTER 6

9

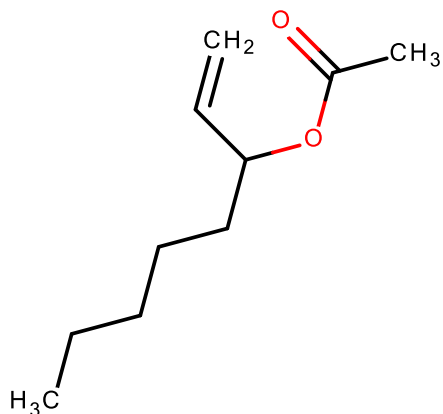
Conflicting
experimental
annotation
between
duplicates

			
	3,4-dihydrocoumarin	Coumarin	6-methylcoumarin
Human	Sensitizer	Sensitizer	Non-sensitizer
LLNA	Sensitizer	Sensitizer	Non-sensitizer
QSAR	Non-sensitizer	Sensitizer	Non-sensitizer
			
	<i>p</i> -methylhydrocinnamic aldehyde	Phenylpropionaldehyde	Xylene
Human	Sensitizer	Sensitizer	Non-sensitizer
LLNA	Sensitizer	Sensitizer	Sensitizer
QSAR	Non-sensitizer	Non-sensitizer	Non-sensitizer

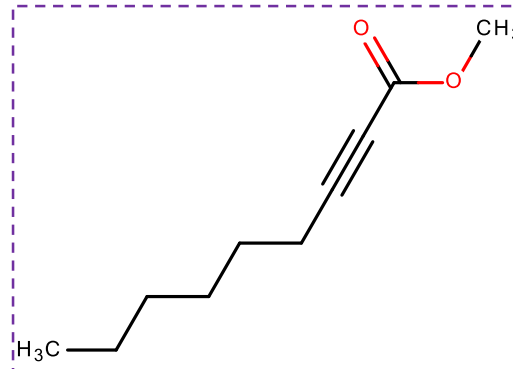
CLUSTER 7

10

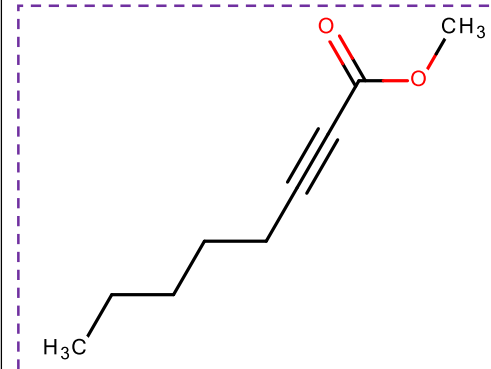
Conflicting
experimental
annotation
between
duplicates



1-Octen-3-yl acetate



Methyl 2-nonynoate



Methyl 2-octynoate

Sensitizer

Sensitizer

Sensitizer

Non-sensitizer

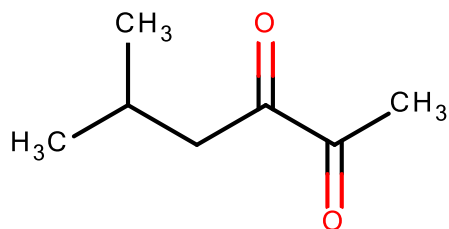
Sensitizer

Sensitizer

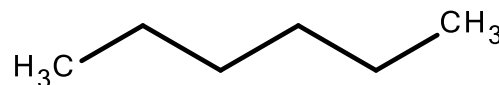
Non-sensitizer

Sensitizer

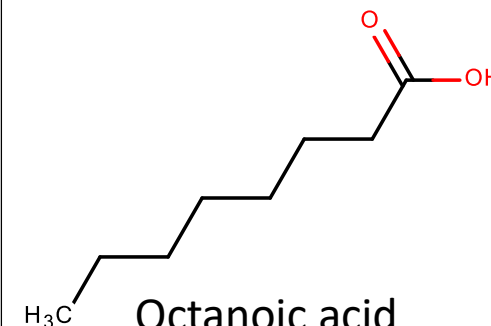
Sensitizer



Methylhexanedione



Hexane



Octanoic acid

Sensitizer

Non-sensitizer

Non-sensitizer

Sensitizer

Non-sensitizer

Non-sensitizer

Non-sensitizer

Non-sensitizer

Non-sensitizer

Human

LLNA

QSAR

Human

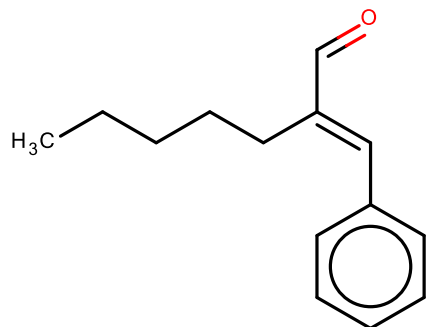
LLNA

QSAR

CLUSTER 8 - CINNAMYL DERIVATIVES

11

Human
LLNA
QSAR

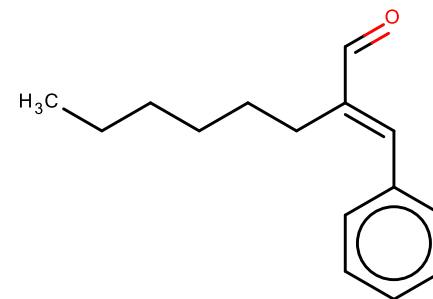


α -amylcinnamic aldehyde

Non-sensitizer

Sensitizer

Non-sensitizer

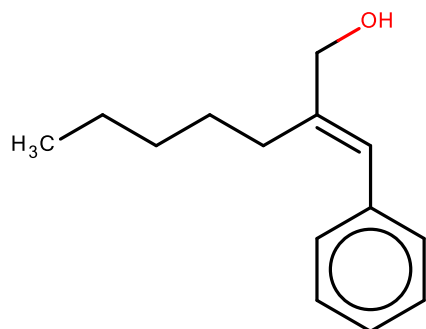


Hexyl cinnamic aldehyde

Non-sensitizer

Sensitizer

Non-sensitizer

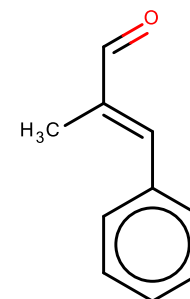


α -amylcinnamyl alcohol

Sensitizer

Non-sensitizer

Non-sensitizer



α -methyl cinnamic aldehyde

Non-sensitizer

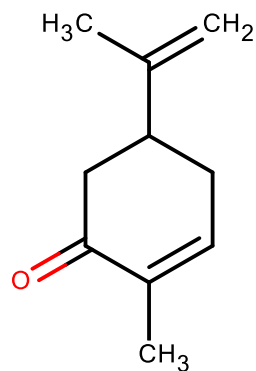
Sensitizer

Non-sensitizer

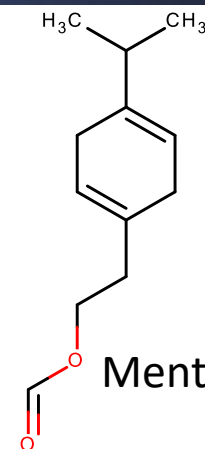
Human
LLNA
QSAR

CLUSTER 9 - TERPENES

12



Carvone



Menthadiene-7-methyl formate

Sensitizer

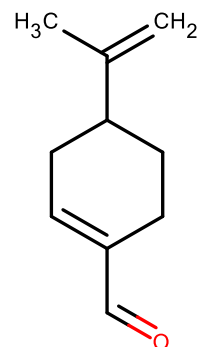
Sensitizer

Sensitizer

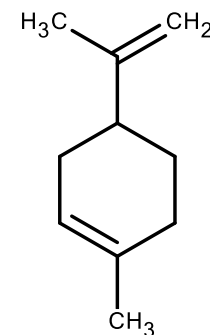
Non-sensitizer

Non-sensitizer

Non-sensitizer



Perillaldehyde



d-Limonene

Sensitizer

Non-sensitizer

Sensitizer

Sensitizer

Sensitizer

Sensitizer

Human

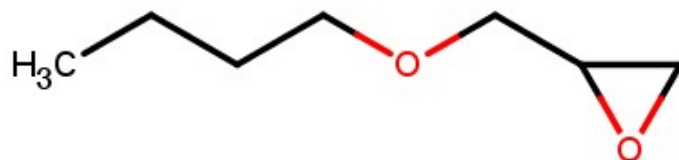
LLNA

QSAR

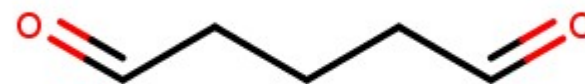
Human

LLNA

QSAR



Butyl glycidyl ether



Glutaraldehyde

Human

Sensitizer

Sensitizer

LLNA

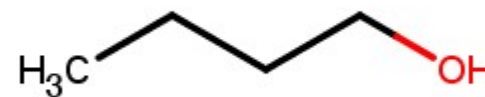
Sensitizer

Sensitizer

QSAR

Non-sensitizer

Sensitizer

*t*-2-hexenal

Butanol

Human

Sensitizer

Non-sensitizer

LLNA

Sensitizer

Non-sensitizer

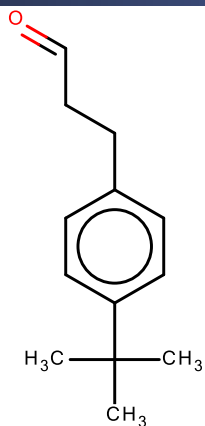
QSAR

Sensitizer

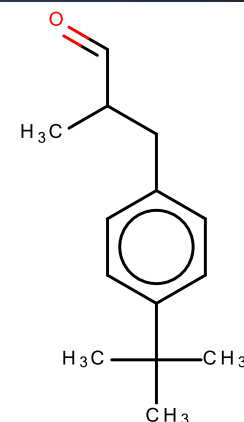
Non-sensitizer

CLUSTER 11

14



Bourgeonal



Lilial

Sensitizer

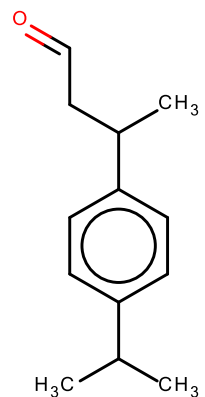
Sensitizer

Sensitizer

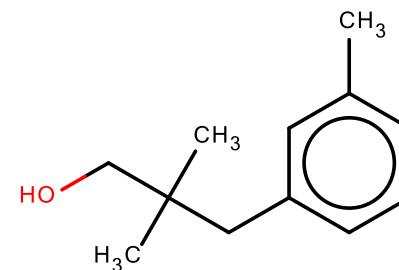
Sensitizer

Sensitizer

Sensitizer



Cyclamen
aldehyde



Majantal

Non-sensitizer

Non-sensitizer

Sensitizer

Non-sensitizer

Sensitizer

Sensitizer

Human

LLNA

QSAR

Human

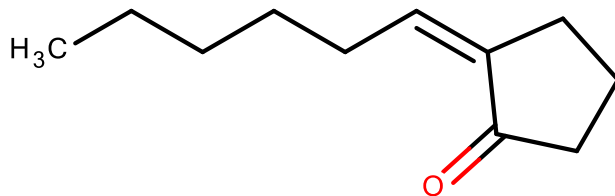
LLNA

QSAR

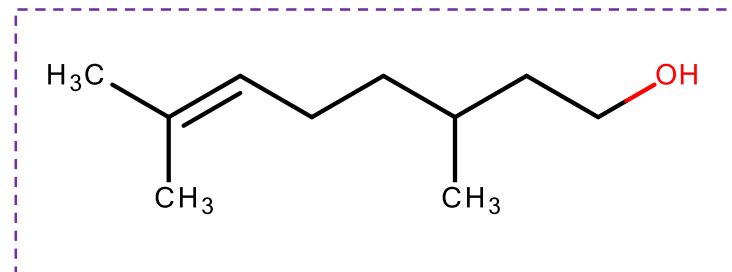
CLUSTER 12

15

Conflicting
experimental
annotation
between
duplicates



2-Hexylidene cyclopentanone



dl-Citronellol

Sensitizer

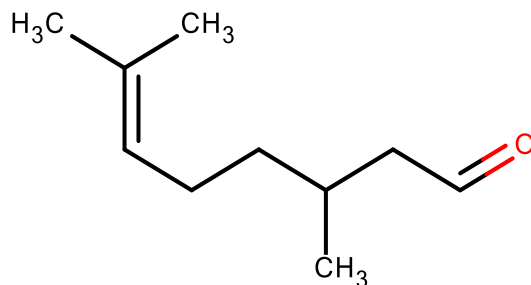
Sensitizer

Sensitizer

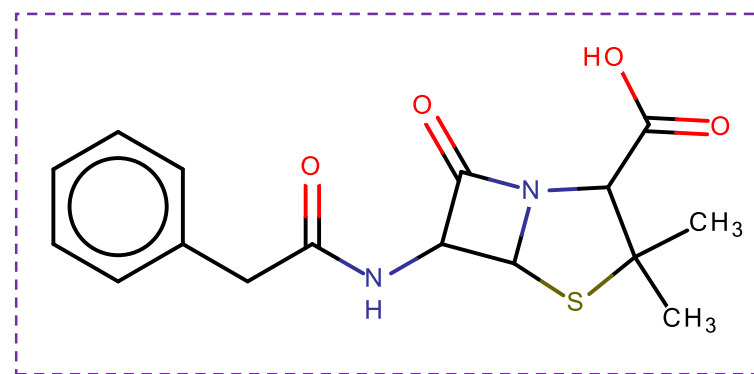
Sensitizer

Non-sensitizer

Non-sensitizer



Citronella oil



Penicillin G

Non-sensitizer

Sensitizer

Non-sensitizer

Sensitizer

Non-sensitizer

Sensitizer

Human

LLNA

QSAR

Human

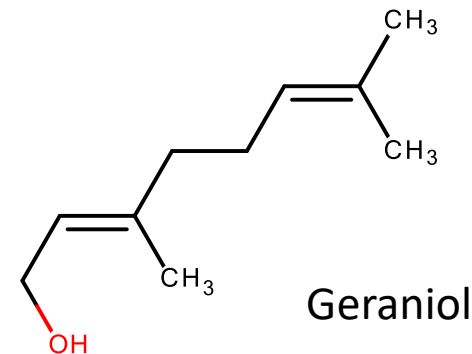
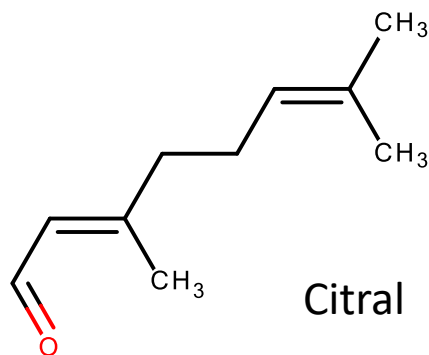
LLNA

QSAR

CLUSTER 13 - OTHER TERPENOIDS

16

Conflicting
experimental
annotation
between
duplicates



Sensitizer

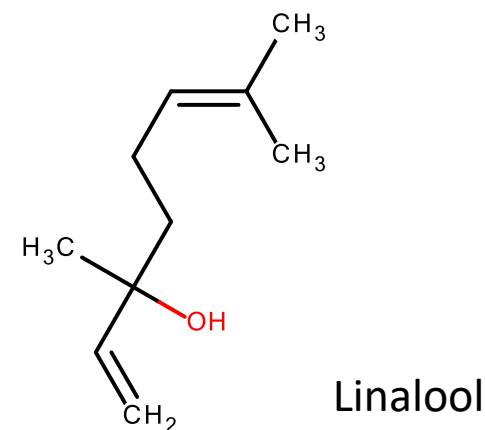
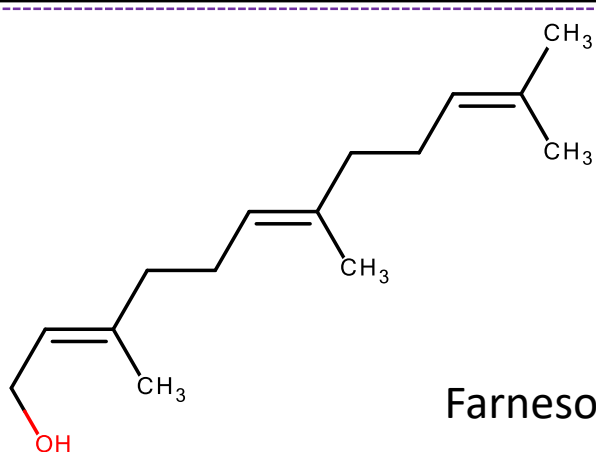
Sensitizer

Sensitizer

Sensitizer

Non-sensitizer

Sensitizer



Sensitizer

Non-sensitizer

Sensitizer

Non-sensitizer

Sensitizer

Non-sensitizer

Human

LLNA

QSAR

Human

LLNA

QSAR

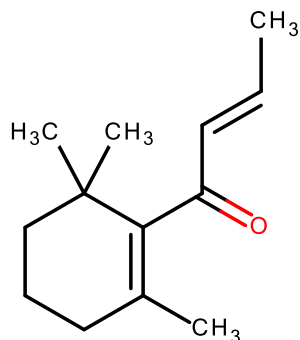
CLUSTER 14 - DAMASCONES

17

Human

LLNA

QSAR

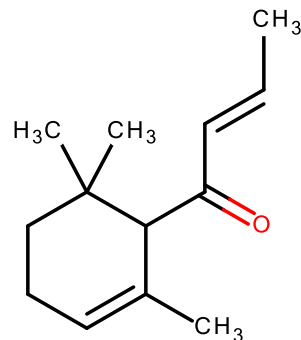


Damascone

Non-sensitizer

Sensitizer

Non-sensitizer

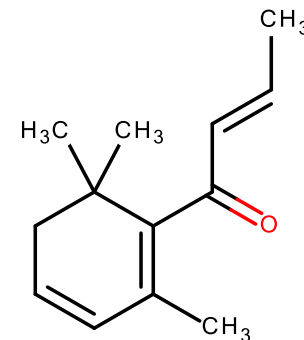


α Damascone

Non-sensitizer

Sensitizer

Non-sensitizer

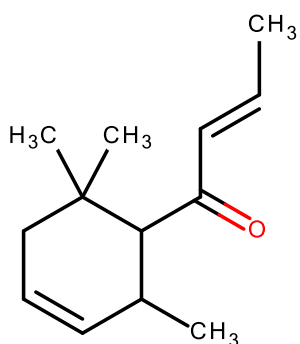


β Damascone

Non-sensitizer

Sensitizer

Non-sensitizer

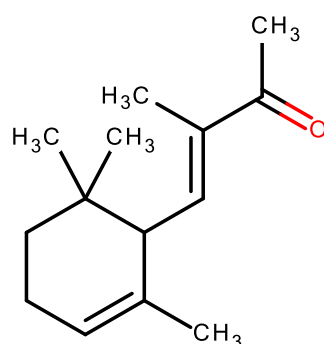


δ Damascone

Sensitizer

Sensitizer

Non-sensitizer

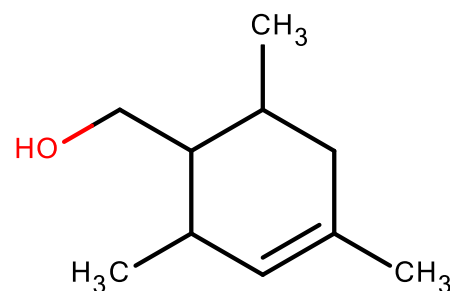


Isomethyl- α -ionone

Non-sensitizer

Sensitizer

Non-sensitizer

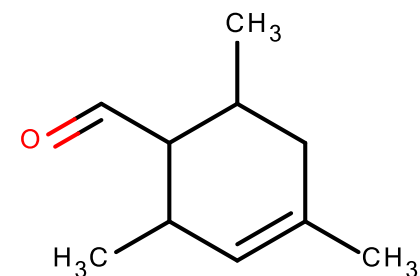


Isocyclogeraniol

Sensitizer

Non-sensitizer

Non-sensitizer



Isocyclocitral

Non-sensitizer

Sensitizer

Non-sensitizer

Human

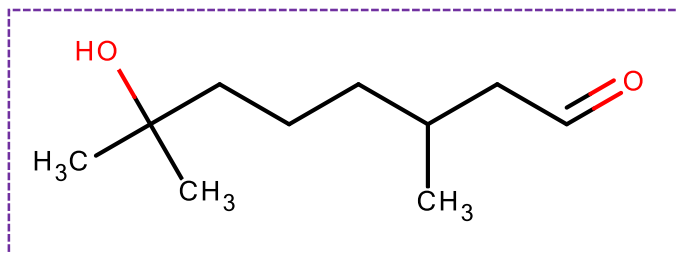
LLNA

QSAR

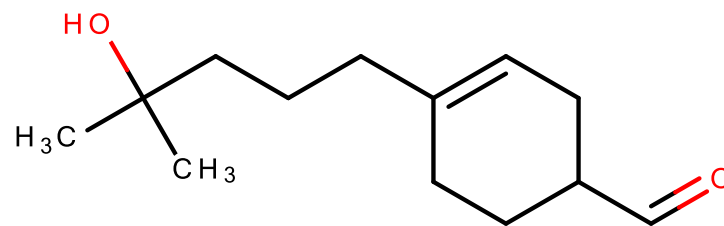
CLUSTER 15

18

Conflicting
experimental
annotation
between
duplicates



Hydroxycitronellal



Lyrar

Human

Sensitizer

Non-sensitizer

LLNA

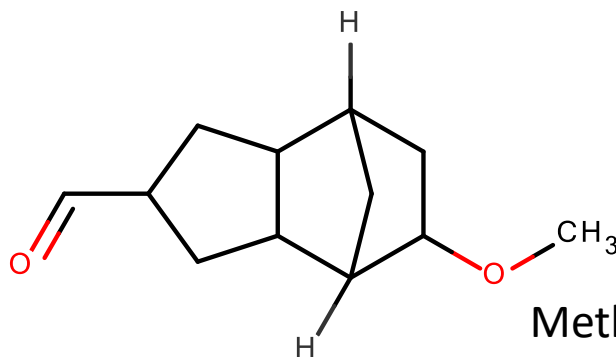
Sensitizer

Sensitizer

QSAR

Non-sensitizer

Non-sensitizer



Methoxy dicyclopentadiene
carboxaldehyde

Human

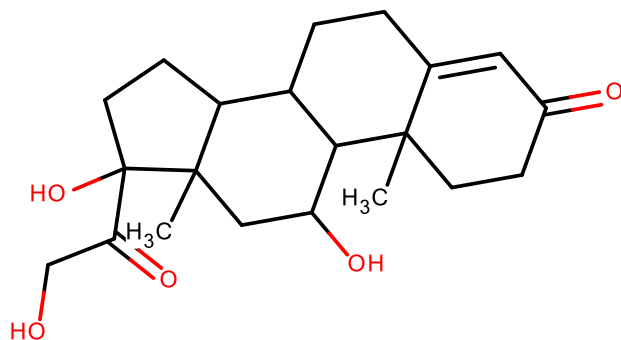
Non-sensitizer

LLNA

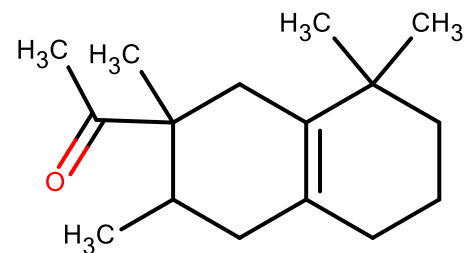
Non-sensitizer

QSAR

Sensitizer



Hydrocortisone



Isocyclemone E

Human
LLNA
QSAR

Non-sensitizer

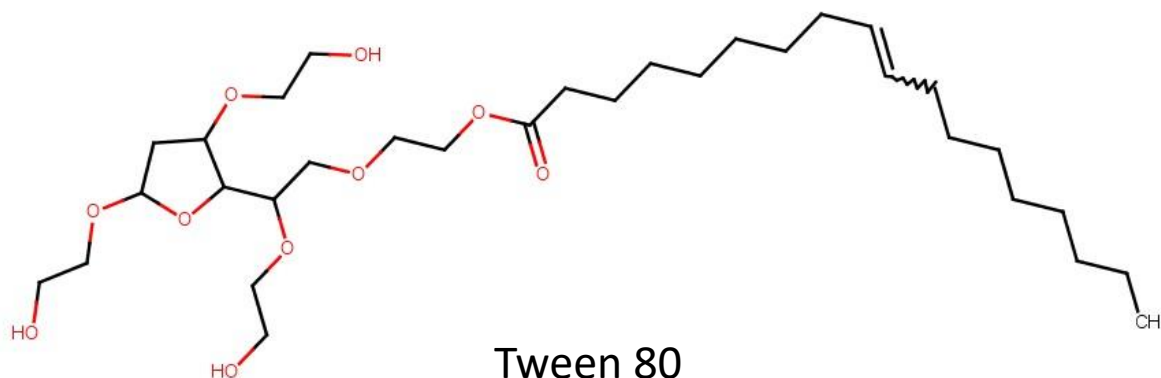
Non-sensitizer

Non-sensitizer

Sensitizer

Non-sensitizer

Sensitizer



Tween 80

Human
LLNA
QSAR

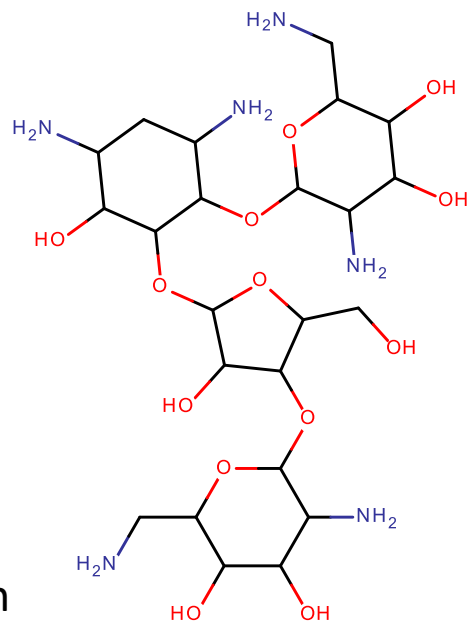
Non-sensitizer

Non-sensitizer

Sensitizer

CLUSTER 17 - AMINOGLYCOSIDES

20

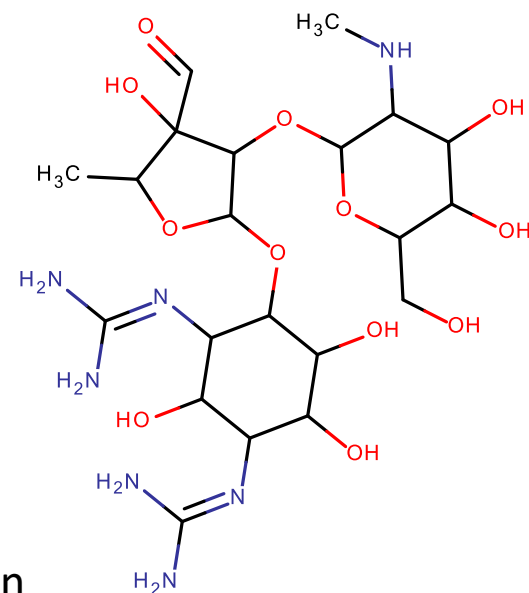


Neomycin

Sensitizer

Non-sensitizer

Sensitizer



Streptomycin

Sensitizer

Non-sensitizer

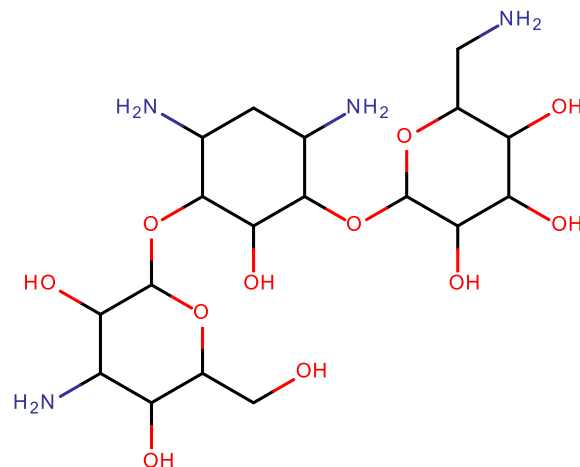
Sensitizer

Kanamycin

Sensitizer

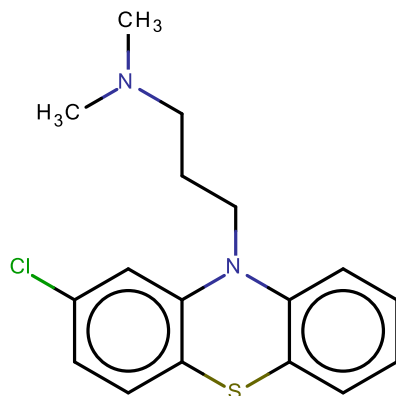
Non-sensitizer

Sensitizer

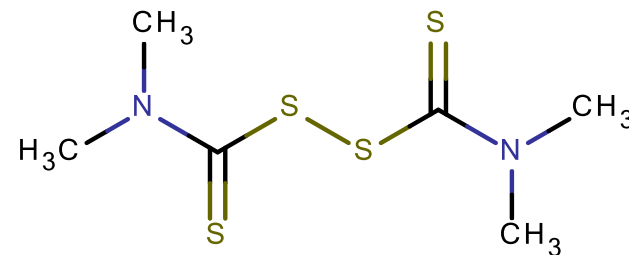


Human
LLNA
QSAR

Human
LLNA
QSAR



Chlorpromazine



Tetramethylthiuram-disulfide

Human

Sensitizer

Sensitizer

LLNA

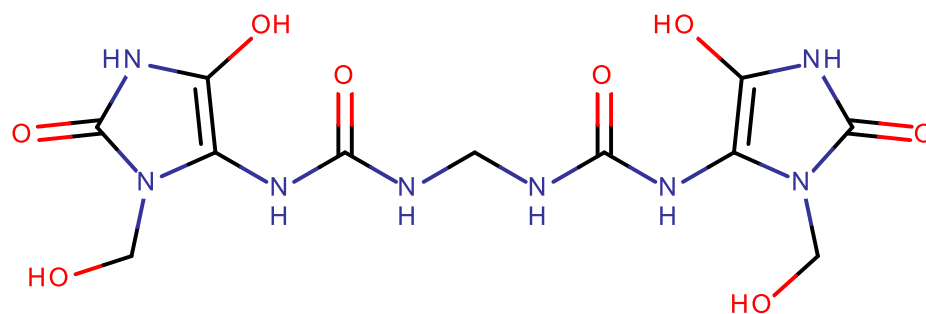
Sensitizer

Sensitizer

QSAR

Sensitizer

Sensitizer



Imidazolidinyl urea

Human

Sensitizer

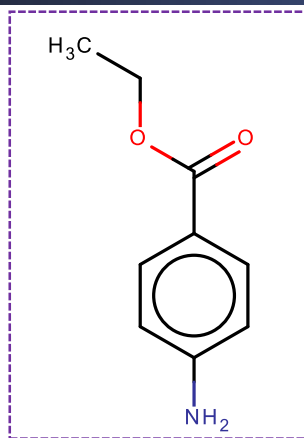
LLNA

Sensitizer

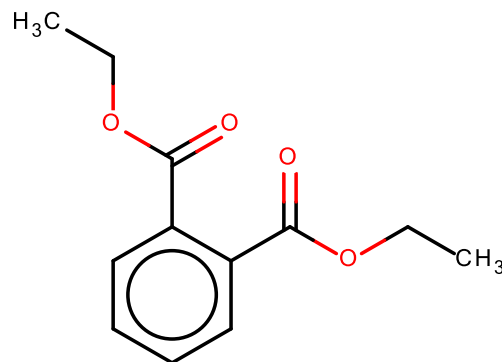
QSAR

Sensitizer

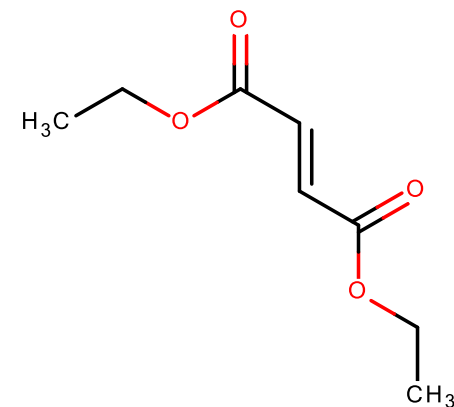
Conflicting
experimental
annotation
between
duplicates



Benzocaine



Diethyl phthalate



Diethylmaleate

Sensitizer

Non-sensitizer

Sensitizer

Sensitizer

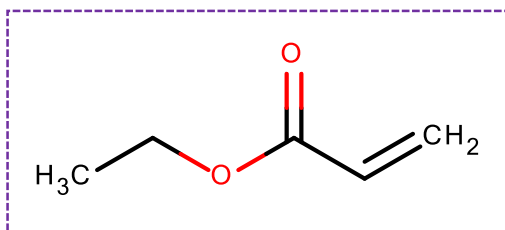
Non-sensitizer

Sensitizer

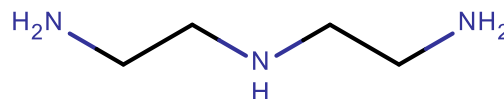
Sensitizer

Sensitizer

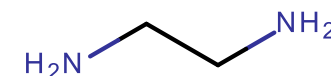
Sensitizer



Ethyl acrylate



Diethylenetriamine



Ethylenediamine

Sensitizer

Sensitizer

Sensitizer

Sensitizer

Sensitizer

Sensitizer

Sensitizer

Sensitizer

Sensitizer

Human

LLNA

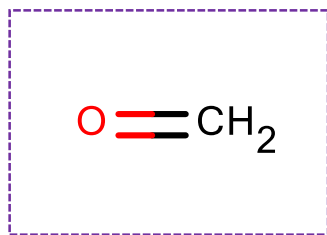
QSAR

Human

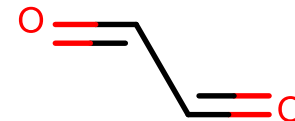
LLNA

QSAR

Conflicting
experimental
annotation
between
duplicates



Formaldehyde



Glyoxal

Sensitizer

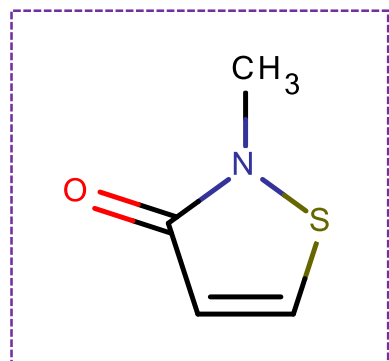
Sensitizer

Sensitizer

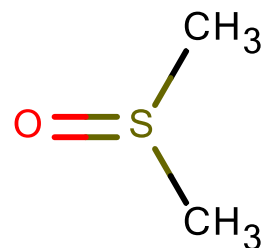
Sensitizer

Sensitizer

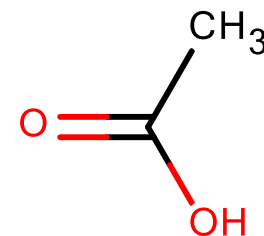
Sensitizer



Methylisothiazolinone



Dimethyl sulfoxide



Lead acetate

Sensitizer

Non-sensitizer

Non-sensitizer

Sensitizer

Sensitizer

Non-sensitizer

Sensitizer

Sensitizer

Non-sensitizer

Human

LLNA

QSAR

Human

LLNA

QSAR

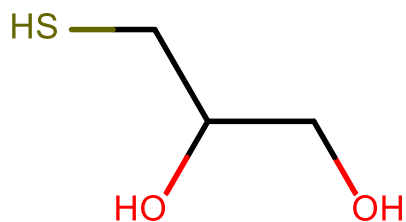
CLUSTER 21

24

Human

LLNA

QSAR

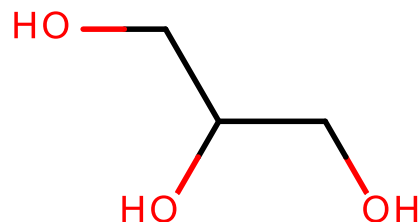


Thioglycerol

Sensitizer

Sensitizer

Non-sensitizer

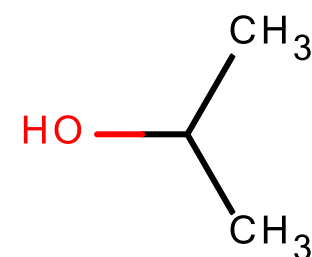


Glycerol

Non-sensitizer

Non-sensitizer

Non-sensitizer

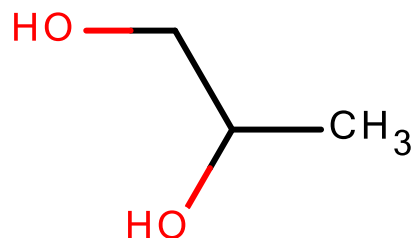


Isopropanol

Non-sensitizer

Non-sensitizer

Non-sensitizer

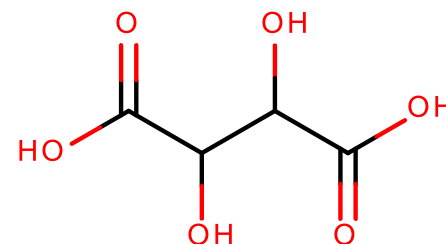


Propylene glycol

Non-sensitizer

Non-sensitizer

Non-sensitizer



Tartaric acid

Non-sensitizer

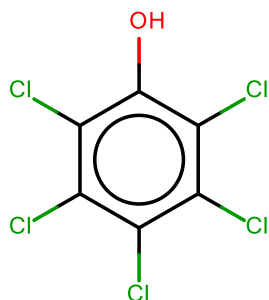
Non-sensitizer

Non-sensitizer

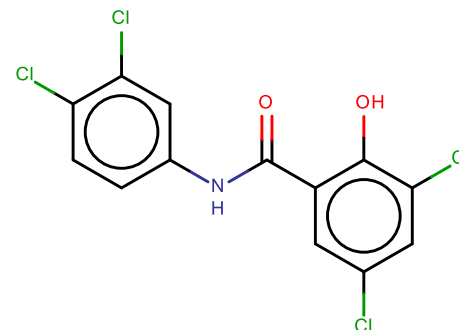
Human

LLNA

QSAR



Pentachlorophenol



3,3',4',5-Tetrachlorosalicylanilide

Sensitizer

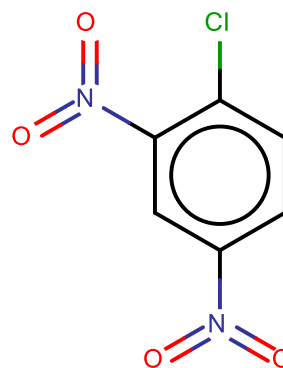
Sensitizer

Sensitizer

Sensitizer

Sensitizer

Sensitizer



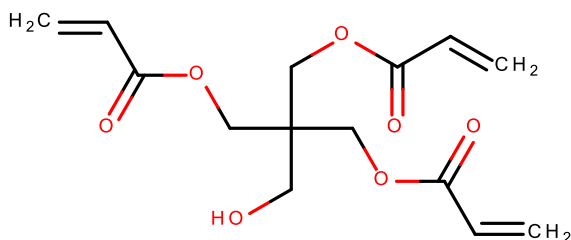
2,4-Dinitrochlorobenzene

Sensitizer

Sensitizer

Sensitizer

Conflicting
experimental
annotation
between
duplicates

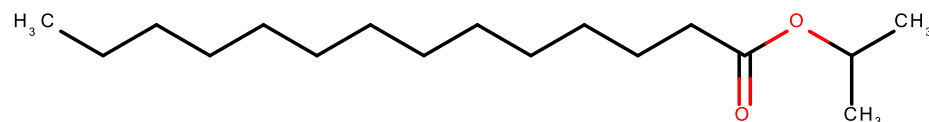


Pentaerythritol
triacylate

Sensitizer

Non-sensitizer

Sensitizer

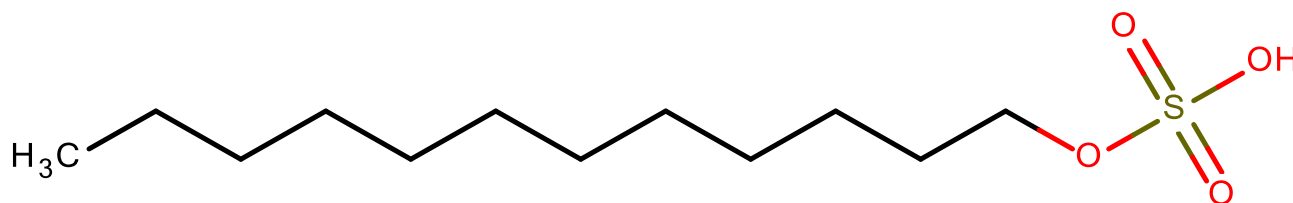


Isopropyl myristate

Non-sensitizer

Sensitizer

Non-sensitizer



Sodium lauryl sulfate

Non-sensitizer

Sensitizer

Non-sensitizer

Human

LLNA

QSAR

Human

LLNA

QSAR