

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

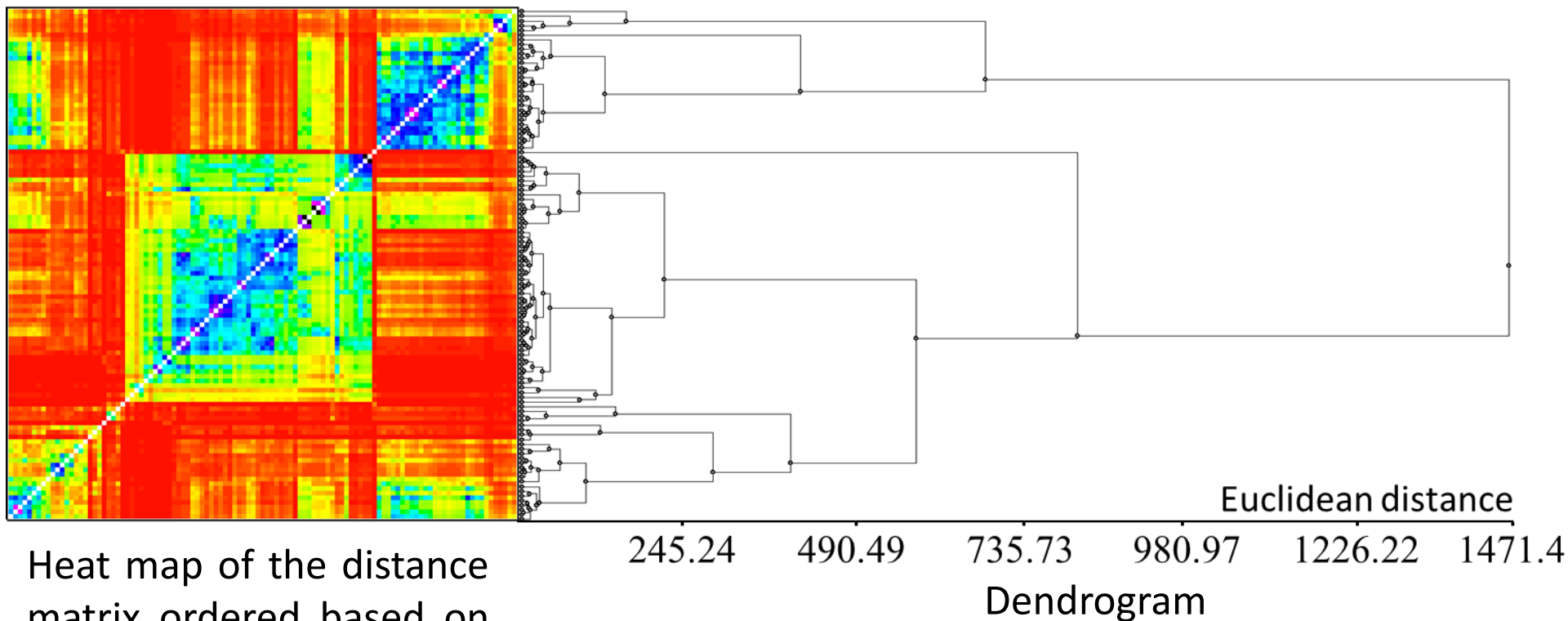
^b Federal University of Goiás, Goiás, Brazil

^c North Carolina State University, Raleigh, USA

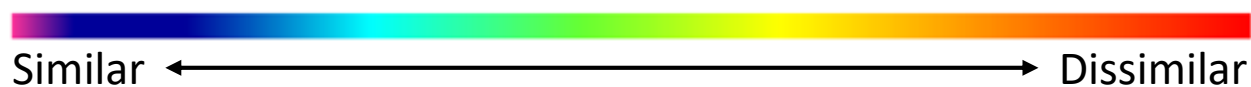
^d ILS NIEHS, RTP, USA

**CLUSTER ANALYSIS OF
HUMAN SKIN SENSITIZATION
DATASET**

No. of compounds = 109



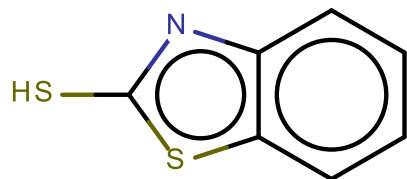
Heat map of the distance matrix ordered based on the clustering and colored* using structural similarity.



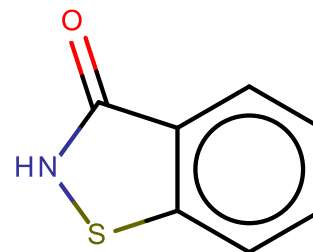
CLUSTER 1

4

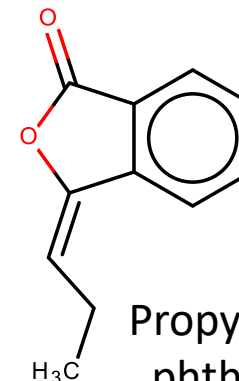
Conflicting experimental annotation between duplicates



2-Mercaptobenzothiazole



Benzisothiazolone



Propylidene phthalate

Sensitizer

Sensitizer

Sensitizer

Sensitizer

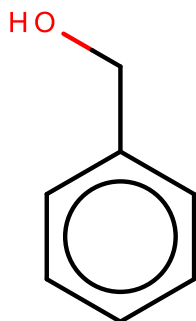
Sensitizer

Sensitizer

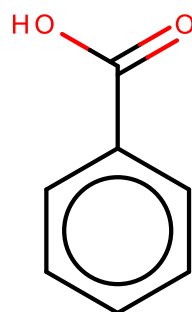
Sensitizer

Sensitizer

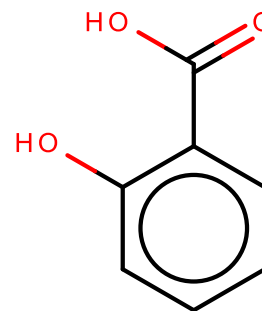
Non-sensitizer



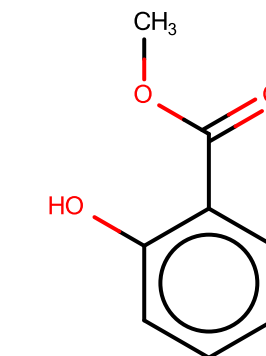
Benzyl alcohol



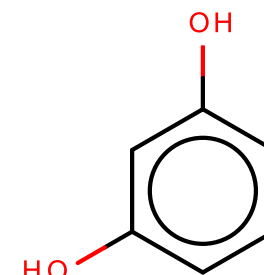
Benzoic acid



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

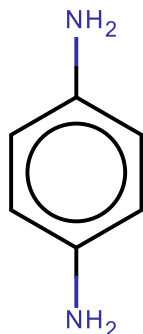
LLNA

QSAR

CLUSTER 2 - AROMATIC AMINES

5

Human
LLNA
QSAR

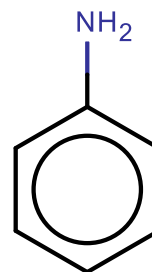


4-phenylenediamine

Sensitizer

Sensitizer

Sensitizer

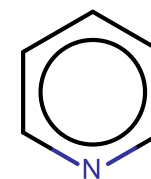


Aniline

Sensitizer

Sensitizer

Sensitizer

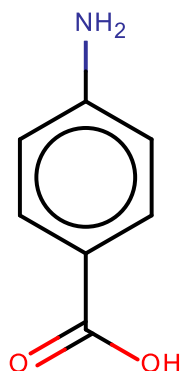


Pyridine

Sensitizer

Sensitizer

Sensitizer

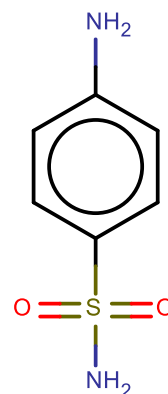


p-aminobenzoic acid

Non-sensitizer

Non-sensitizer

Sensitizer

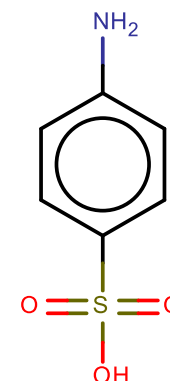


Sulfanilamide

Sensitizer

Non-sensitizer

Sensitizer



Sulfanilic acid

Non-sensitizer

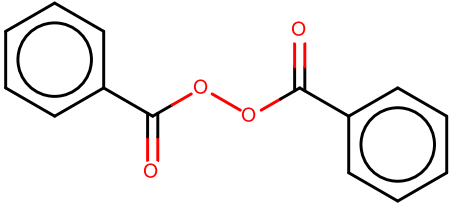
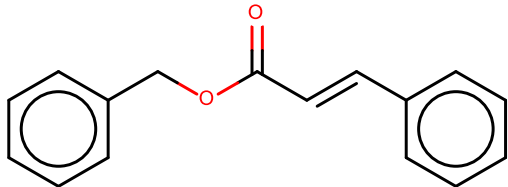
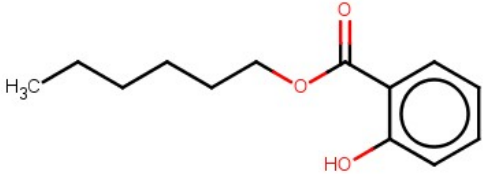
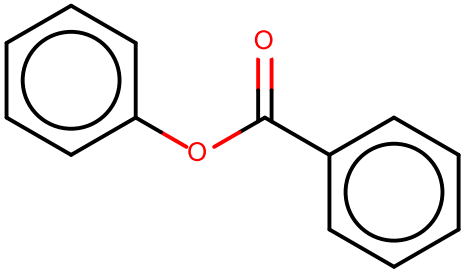
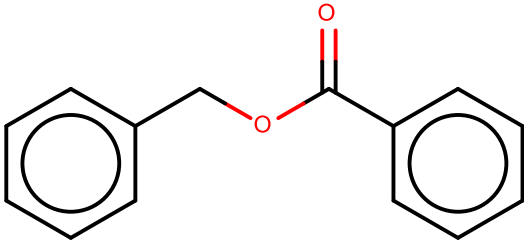
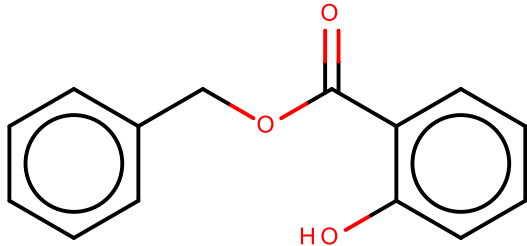
Non-sensitizer

Sensitizer

Human
LLNA
QSAR

CLUSTER 3 - ESTERS OF BENZOIC ACID

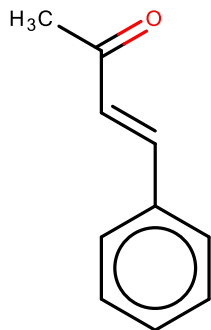
6

	 <p>Benzoyl peroxide</p>	 <p>Benzyl cinnamate</p>	 <p>Hexyl salicylate</p>
Human	Sensitizer	Non-sensitizer	Non-sensitizer
LLNA	Sensitizer	Sensitizer	Sensitizer
QSAR	Non-sensitizer	Non-sensitizer	Non-sensitizer
	 <p>Phenyl benzoate</p>	 <p>Benzyl benzoate</p>	 <p>Benzyl salicylate</p>
Human	Sensitizer	Non-sensitizer	Non-sensitizer
LLNA	Sensitizer	Sensitizer	Sensitizer
QSAR	Sensitizer	Non-sensitizer	Non-sensitizer

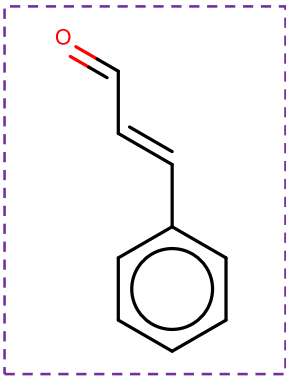
CLUSTER 4 - CINNAMYL DERIVATIVES

7

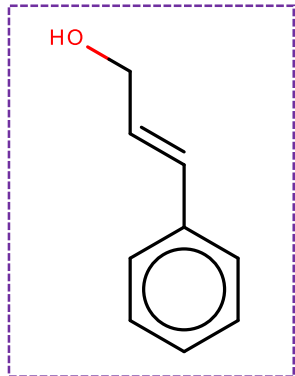
Conflicting experimental annotation between duplicates



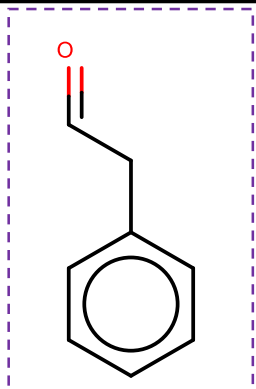
Benzylidene acetone



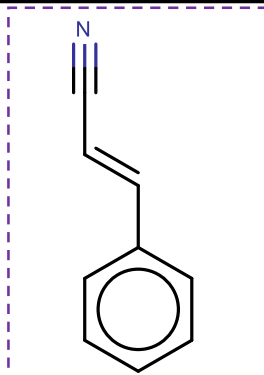
Cinnamic aldehyde



Cinnamyl alcohol



Phenylacetaldehyde



Cinnamyl nitrile

Sensitizer

Sensitizer

Sensitizer

Sensitizer

Sensitizer

Sensitizer

Non-sensitizer

Sensitizer

Sensitizer

Sensitizer

Sensitizer

Sensitizer

Non-sensitizer

Non-sensitizer

Sensitizer

Human

LLNA

QSAR

Human

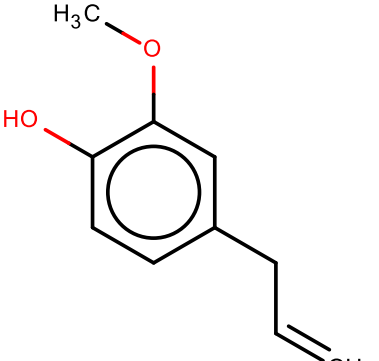
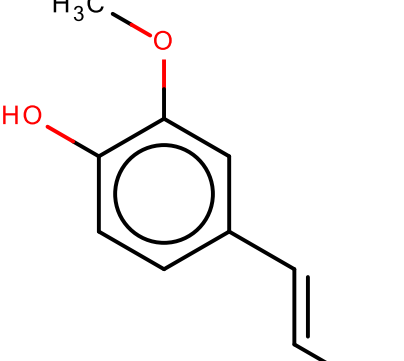
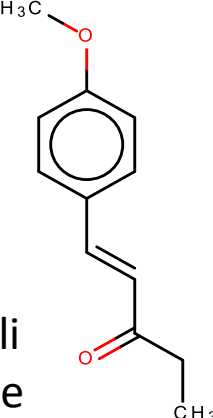
LLNA

QSAR

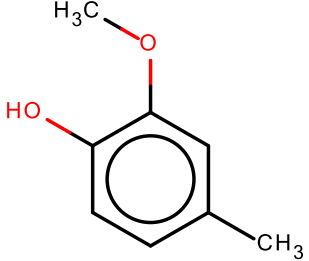
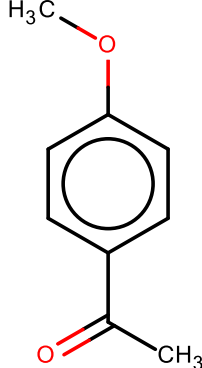
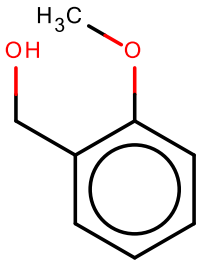
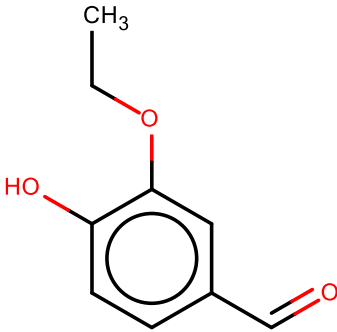
CLUSTER 5

8

Human
LLNA
QSAR

 <p>Eugenol</p>	 <p>Isoeugenol</p>	 <p>Methylanisylidene acetone</p>
<p>Sensitizer</p>	<p>Sensitizer</p>	<p>Sensitizer</p>
<p>Sensitizer</p>	<p>Sensitizer</p>	<p>Sensitizer</p>
<p>Sensitizer</p>	<p>Non-sensitizer</p>	<p>Sensitizer</p>

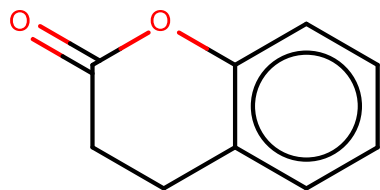
Human
LLNA
QSAR

 <p>2-Methoxy-4-methylphenol</p>	 <p>4-Methoxyacetophenone</p>	 <p>Anisyl alcohol</p>	 <p>Ethyl vanillin</p>
<p>Non-sensitizer</p>	<p>Non-sensitizer</p>	<p>Non-sensitizer</p>	<p>Non-sensitizer</p>
<p>Sensitizer</p>	<p>Non-sensitizer</p>	<p>Sensitizer</p>	<p>Non-sensitizer</p>
<p>Non-sensitizer</p>	<p>Sensitizer</p>	<p>Non-sensitizer</p>	<p>Non-sensitizer</p>

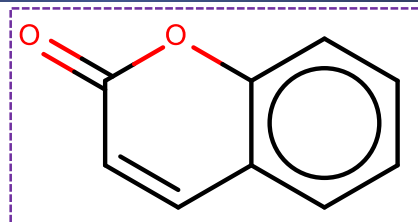
CLUSTER 6

9

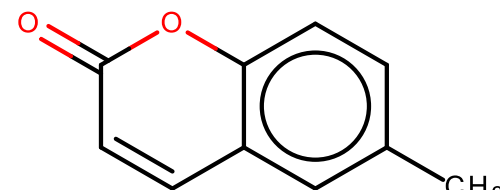
Conflicting experimental annotation between duplicates



3,4-dihydrocoumarin



Coumarin



6-methylcoumarin

Sensitizer

Sensitizer

Non-sensitizer

Sensitizer

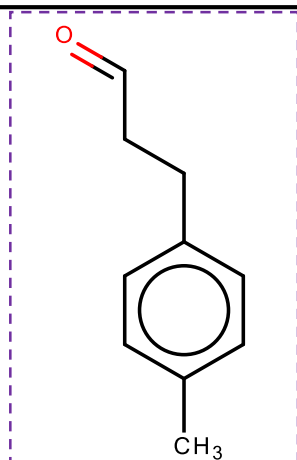
Sensitizer

Non-sensitizer

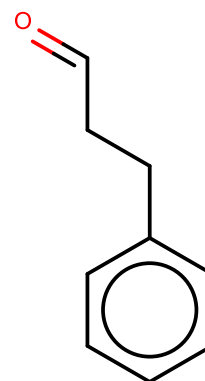
Non-sensitizer

Sensitizer

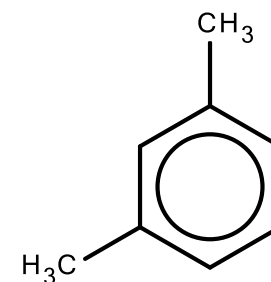
Non-sensitizer



p-methylhydrocinnamic aldehyde



Phenylpropionaldehyde



Xylene

Sensitizer

Sensitizer

Non-sensitizer

Sensitizer

Sensitizer

Sensitizer

Non-sensitizer

Non-sensitizer

Non-sensitizer

Human

LLNA

QSAR

Human

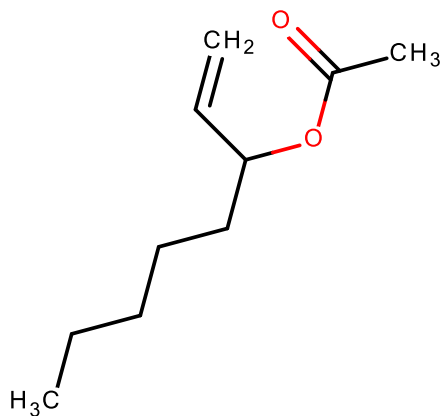
LLNA

QSAR

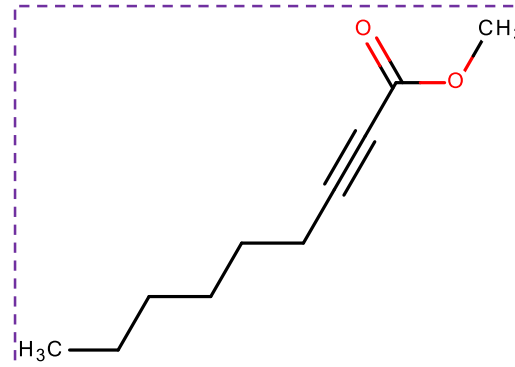
CLUSTER 7

10

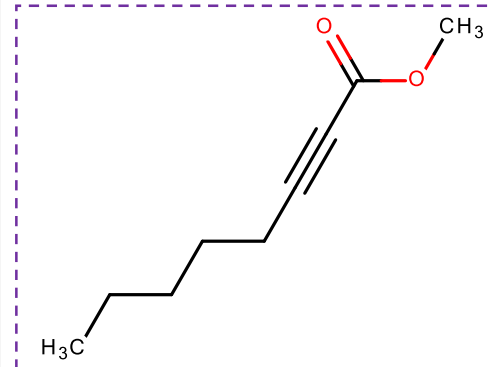
Conflicting experimental annotation between duplicates



1-Octen-3-yl acetate



Methyl 2-nonynoate



Methyl 2-octynoate

Human

Sensitizer

Sensitizer

Sensitizer

LLNA

Non-sensitizer

Sensitizer

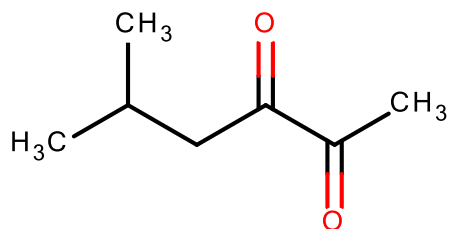
Sensitizer

QSAR

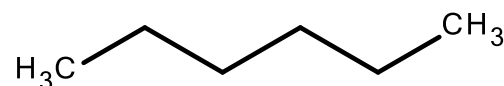
Non-sensitizer

Sensitizer

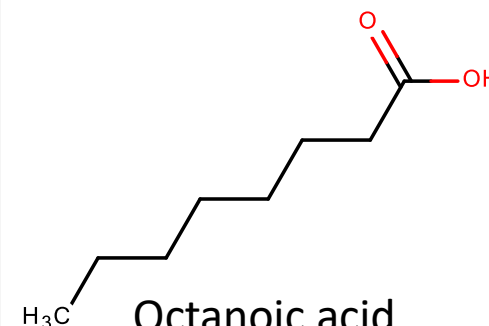
Sensitizer



Methylhexanedione



Hexane



Octanoic acid

Human

Sensitizer

Non-sensitizer

Non-sensitizer

LLNA

Sensitizer

Non-sensitizer

Non-sensitizer

QSAR

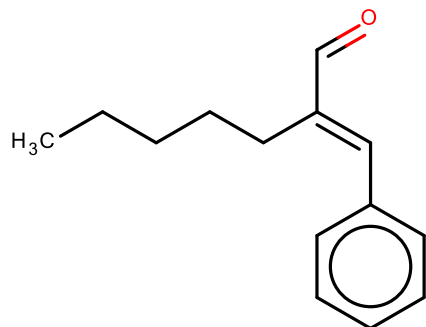
Non-sensitizer

Non-sensitizer

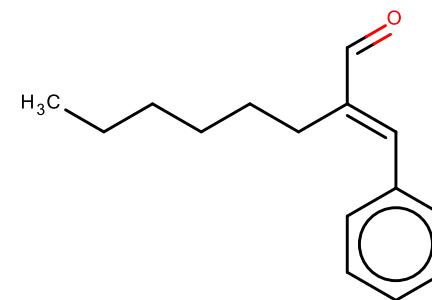
Non-sensitizer

CLUSTER 8 - CINNAMYL DERIVATIVES

11



α -amylcinnamic aldehyde



Hexyl cinnamic aldehyde

Non-sensitizer

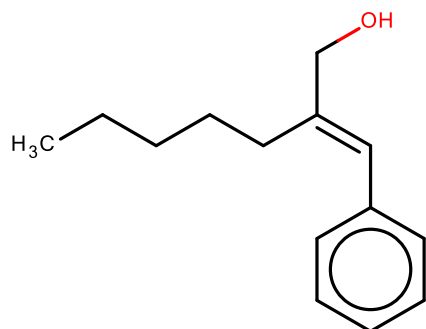
Non-sensitizer

Sensitizer

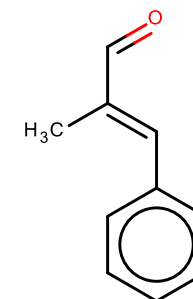
Sensitizer

Non-sensitizer

Non-sensitizer



α -amylcinnamyl alcohol



α -methyl cinnamic aldehyde

Sensitizer

Non-sensitizer

Non-sensitizer

Sensitizer

Non-sensitizer

Non-sensitizer

Human

LLNA

QSAR

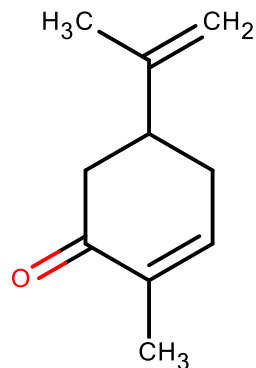
Human

LLNA

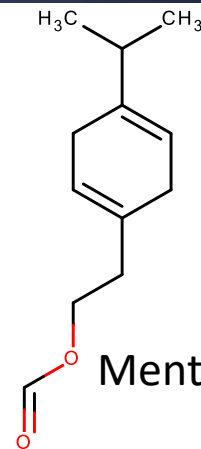
QSAR

CLUSTER 9 - TERPENES

12



Carvone



Menthadiene-7-methyl formate

Human

Sensitizer

Sensitizer

LLNA

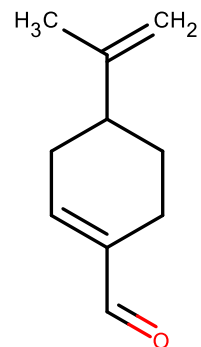
Sensitizer

Non-sensitizer

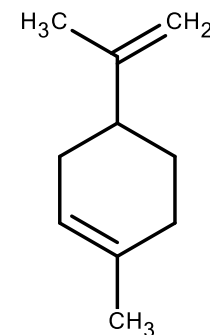
QSAR

Non-sensitizer

Non-sensitizer



Perillaldehyde



d-Limonene

Human

Sensitizer

Non-sensitizer

LLNA

Sensitizer

Sensitizer

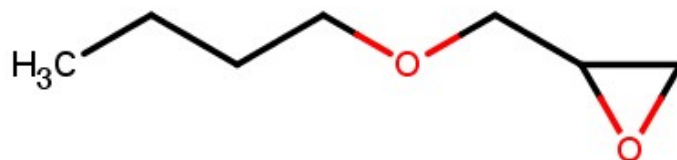
QSAR

Sensitizer

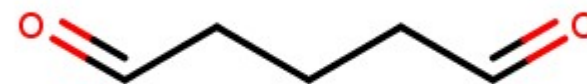
Sensitizer

CLUSTER 10

13



Butyl glycidyl ether



Glutaraldehyde

Human

Sensitizer

Sensitizer

LLNA

Sensitizer

Sensitizer

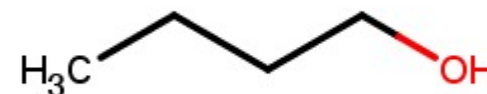
QSAR

Non-sensitizer

Sensitizer



t-2-hexenal



Butanol

Human

Sensitizer

Non-sensitizer

LLNA

Sensitizer

Non-sensitizer

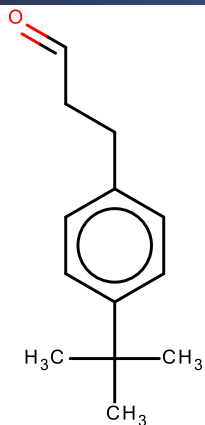
QSAR

Sensitizer

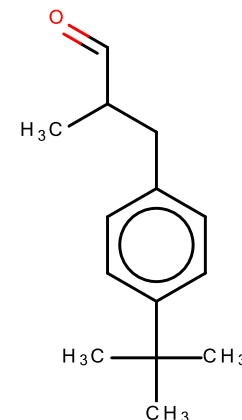
Non-sensitizer

CLUSTER 11

14



Bourgeonal



Lilial

Sensitizer

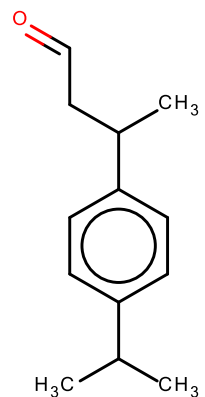
Sensitizer

Sensitizer

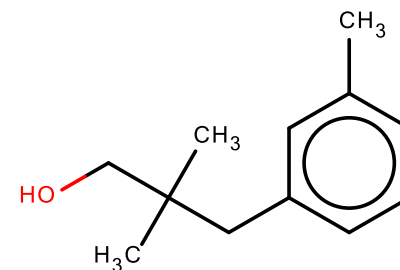
Sensitizer

Sensitizer

Sensitizer



Cyclamen
aldehyde



Majantal

Non-sensitizer

Non-sensitizer

Sensitizer

Non-sensitizer

Sensitizer

Sensitizer

Human

LLNA

QSAR

Human

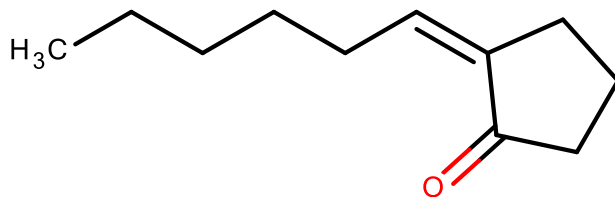
LLNA

QSAR

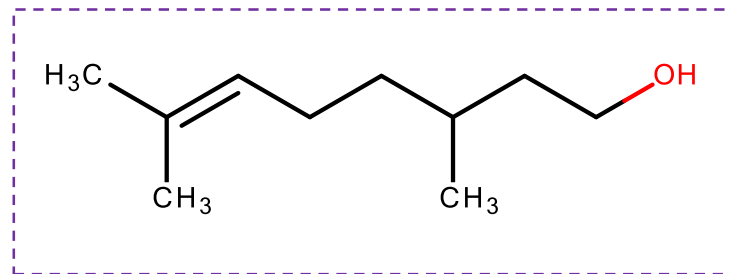
CLUSTER 12

15

Conflicting experimental annotation between duplicates



2-Hexylidene cyclopentanone



dl-Citronellol

Sensitizer

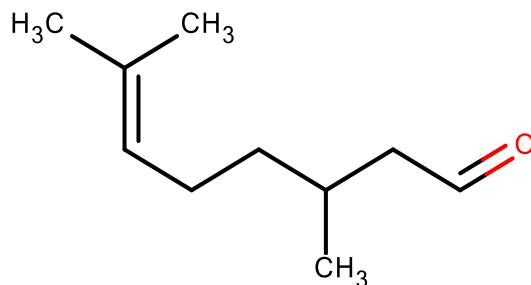
Sensitizer

Sensitizer

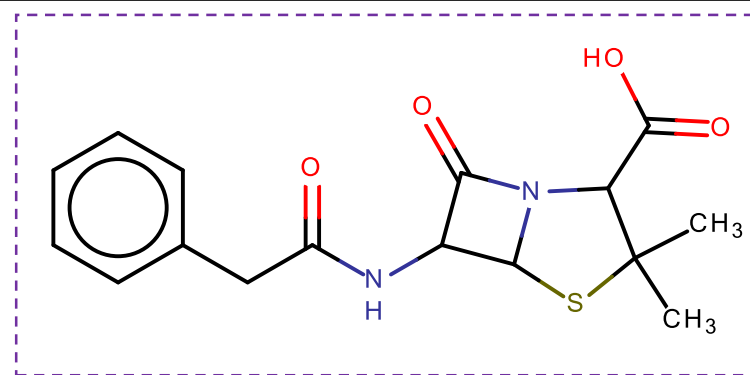
Sensitizer

Non-sensitizer

Non-sensitizer



Citronella oil



Penicillin G

Non-sensitizer

Sensitizer

Non-sensitizer

Sensitizer

Non-sensitizer

Sensitizer

Human

LLNA

QSAR

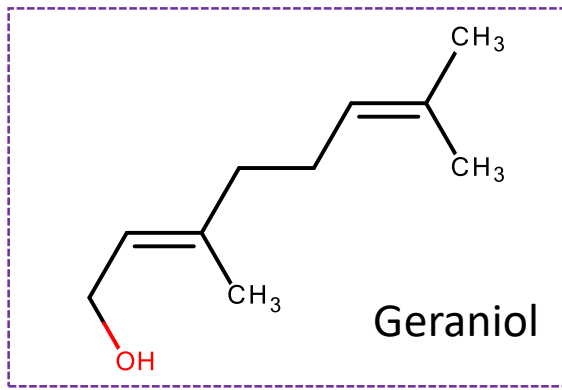
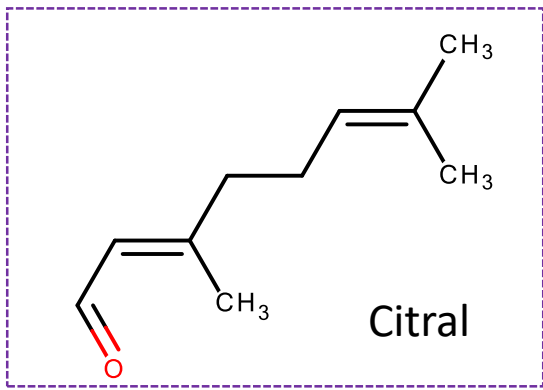
Human

LLNA

QSAR

CLUSTER 13 - OTHER TERPENOIDS

Conflicting experimental annotation between duplicates



Human
LLNA
QSAR

Sensitizer

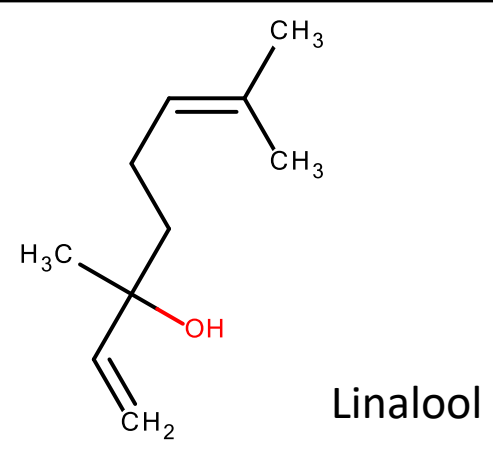
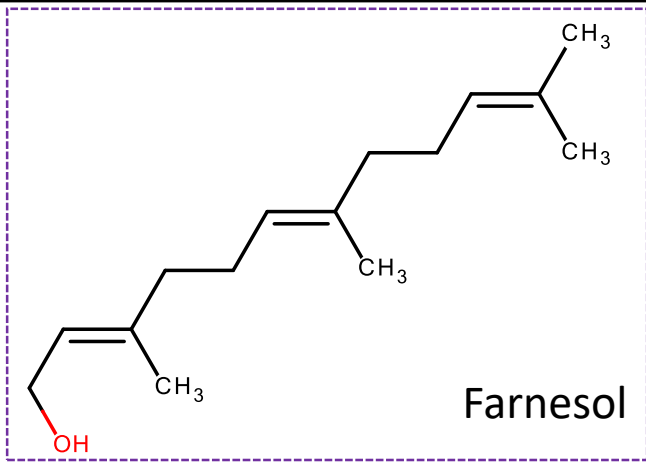
Sensitizer

Sensitizer

Sensitizer

Non-sensitizer

Sensitizer



Human
LLNA
QSAR

Sensitizer

Non-sensitizer

Sensitizer

Non-sensitizer

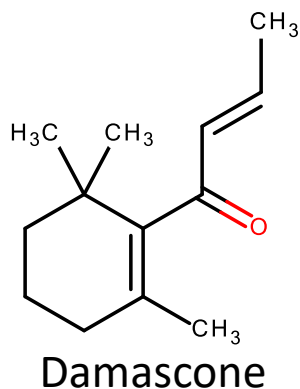
Sensitizer

Non-sensitizer

CLUSTER 14 - DAMASCONES

17

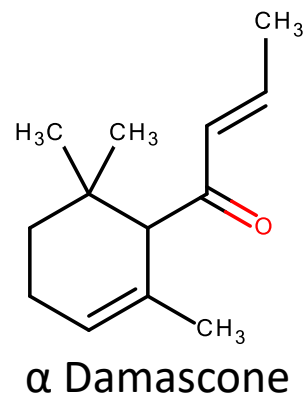
Human
LLNA
QSAR



Non-sensitizer

Sensitizer

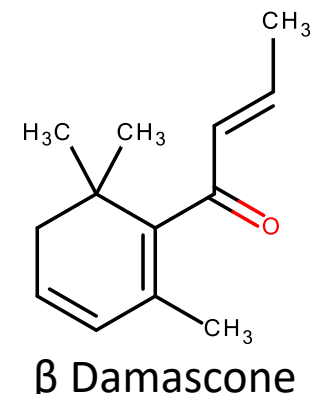
Non-sensitizer



Non-sensitizer

Sensitizer

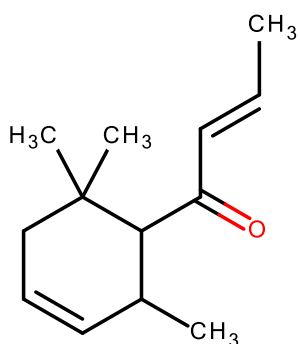
Non-sensitizer



Non-sensitizer

Sensitizer

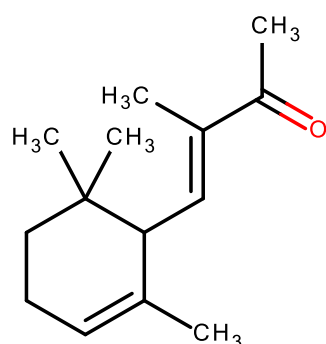
Non-sensitizer



Sensitizer

Sensitizer

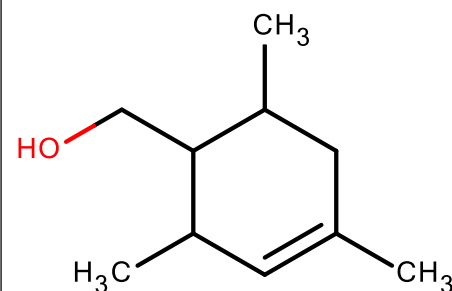
Non-sensitizer



Non-sensitizer

Sensitizer

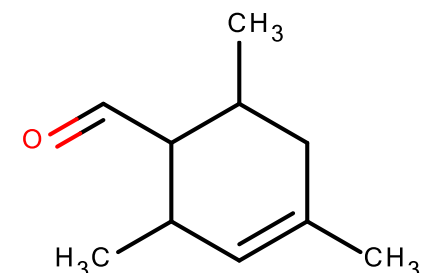
Non-sensitizer



Sensitizer

Non-sensitizer

Non-sensitizer



Non-sensitizer

Sensitizer

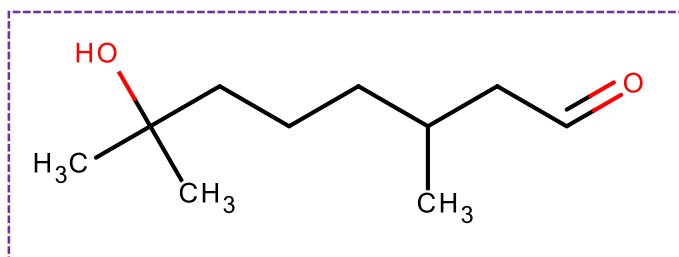
Non-sensitizer

Human
LLNA
QSAR

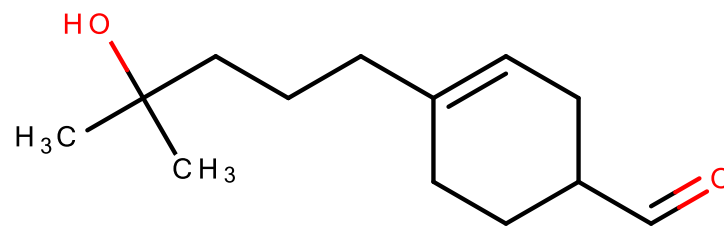
CLUSTER 15

18

Conflicting experimental annotation between duplicates



Hydroxycitronellal



Lyral

Human

Sensitizer

Non-sensitizer

LLNA

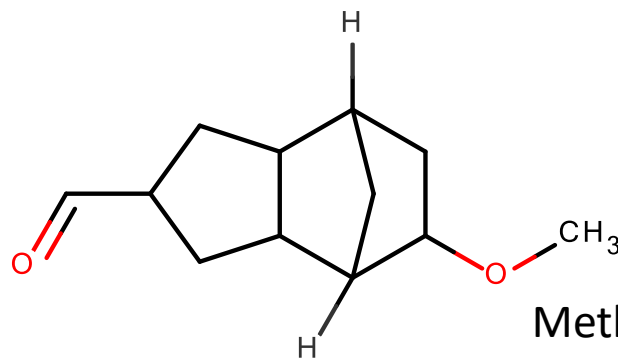
Sensitizer

Sensitizer

QSAR

Non-sensitizer

Non-sensitizer



Methoxy dicyclopentadiene
carboxaldehyde

Human

Non-sensitizer

LLNA

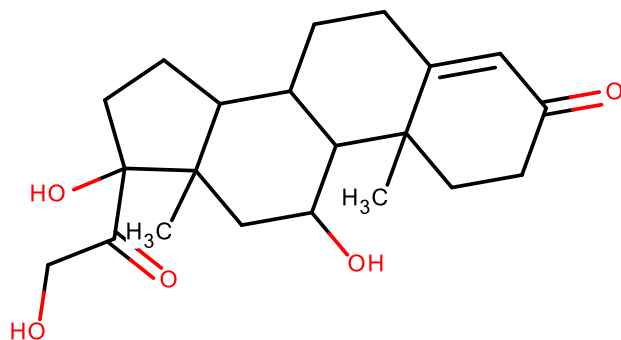
Non-sensitizer

QSAR

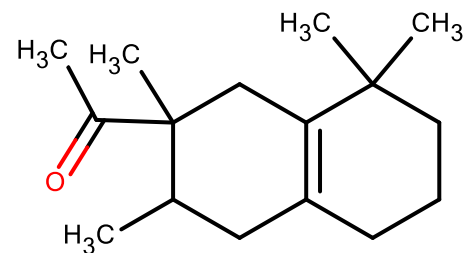
Sensitizer

CLUSTER 16

19



Hydrocortisone



Isocyclemone E

Human

Non-sensitizer

Non-sensitizer

LLNA

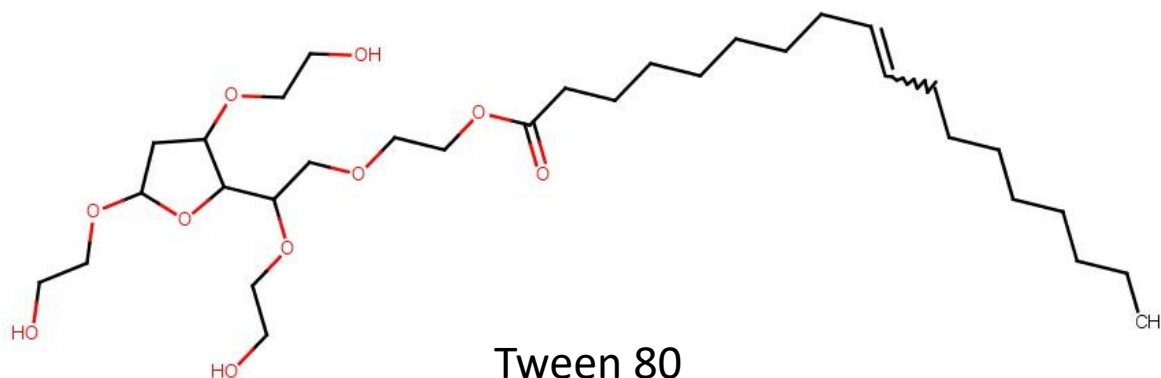
Non-sensitizer

Sensitizer

QSAR

Non-sensitizer

Sensitizer



Tween 80

Human

Non-sensitizer

LLNA

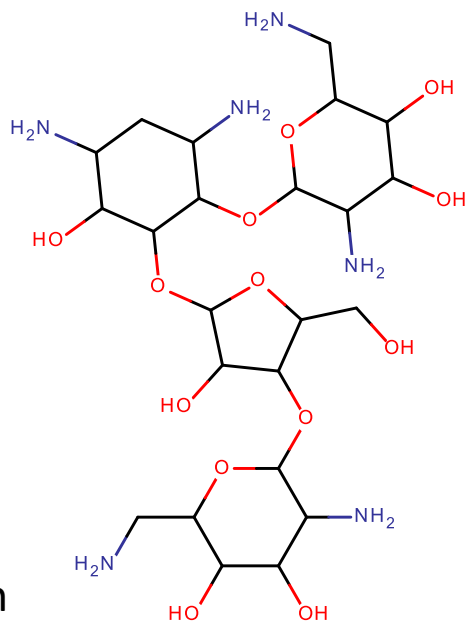
Non-sensitizer

QSAR

Sensitizer

CLUSTER 17 - AMINOGLYCOSIDES

20

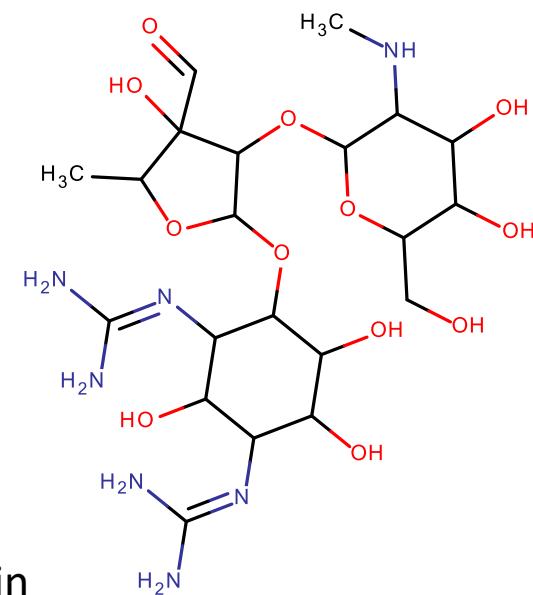


Neomycin

Sensitizer

Non-sensitizer

Sensitizer



Streptomycin

Sensitizer

Non-sensitizer

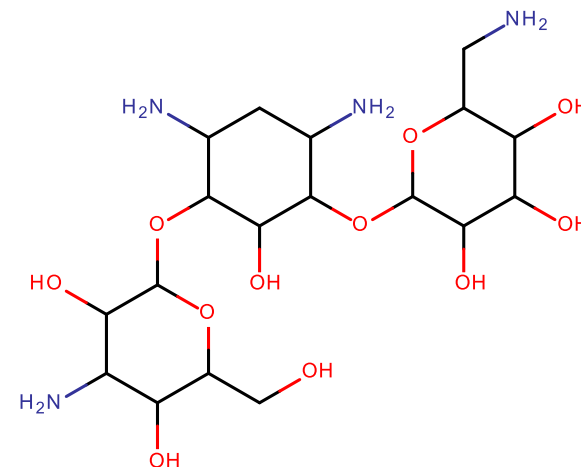
Sensitizer

Kanamycin

Sensitizer

Non-sensitizer

Sensitizer



Human

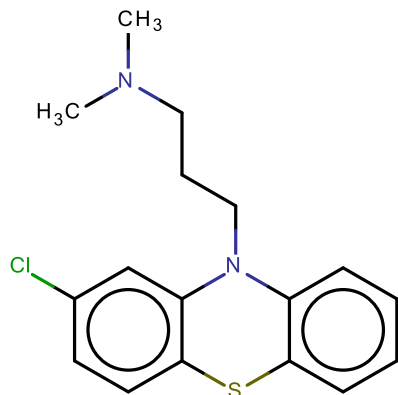
LLNA

QSAR

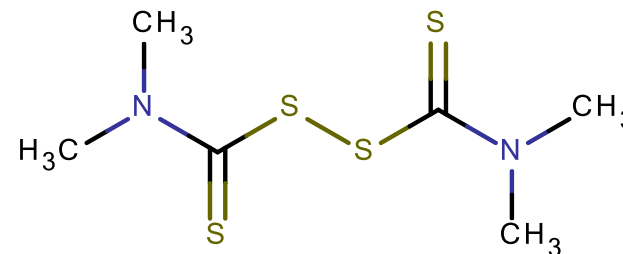
Human

LLNA

QSAR



Chlorpromazine



Tetramethylthiuram-disulfide

Human

Sensitizer

Sensitizer

LLNA

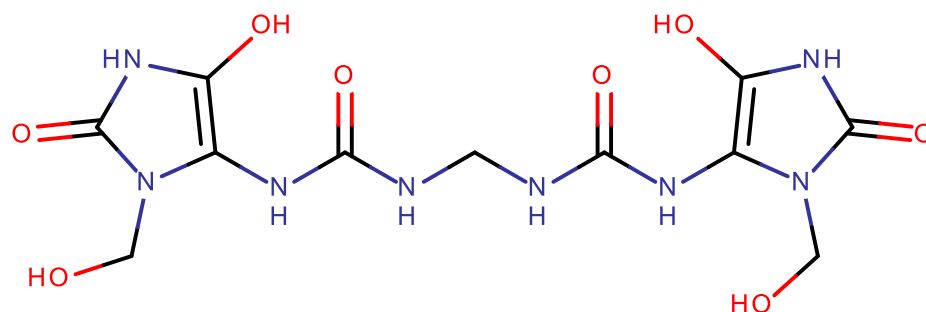
Sensitizer

Sensitizer

QSAR

Sensitizer

Sensitizer



Imidazolidinyl urea

Human

Sensitizer

LLNA

Sensitizer

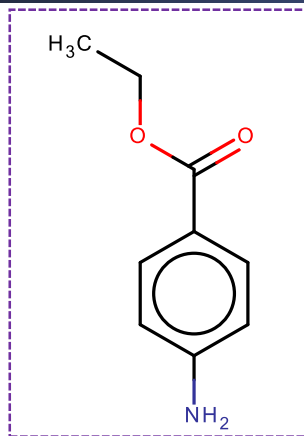
QSAR

Sensitizer

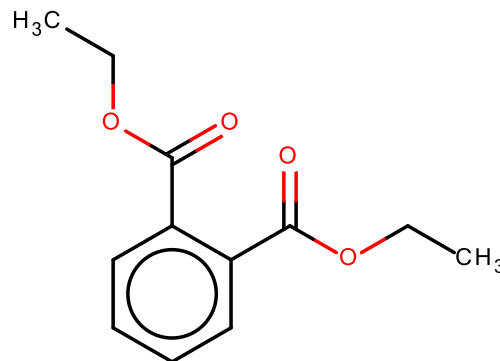
CLUSTER 19

22

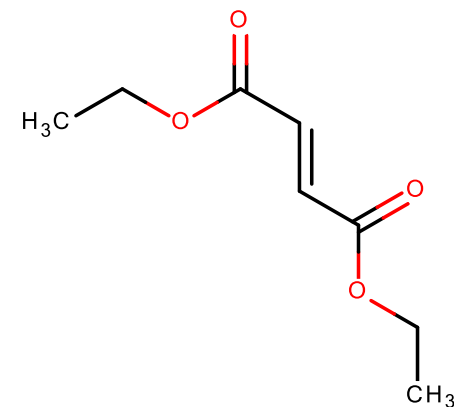
Conflicting experimental annotation between duplicates



Benzocaine



Diethyl phthalate



Diethylmaleate

Human

Sensitizer

Non-sensitizer

Sensitizer

LLNA

Sensitizer

Non-sensitizer

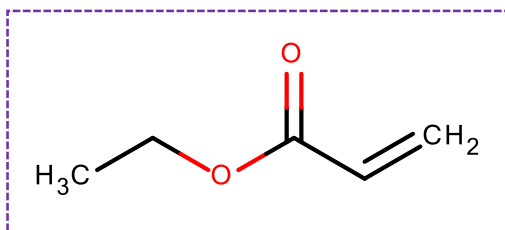
Sensitizer

QSAR

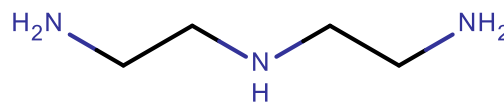
Sensitizer

Sensitizer

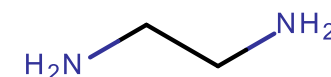
Sensitizer



Ethyl acrylate



Diethylenetriamine



Ethylenediamine

Human

Sensitizer

Sensitizer

Sensitizer

LLNA

Sensitizer

Sensitizer

Sensitizer

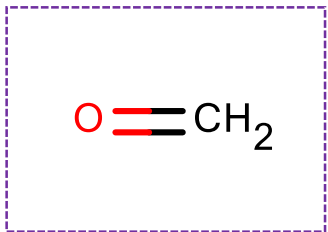
QSAR

Sensitizer

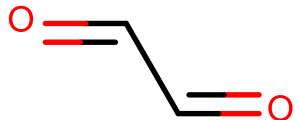
Sensitizer

Sensitizer

Conflicting experimental annotation between duplicates



Formaldehyde

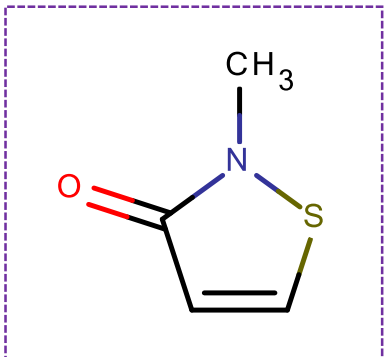


Glyoxal

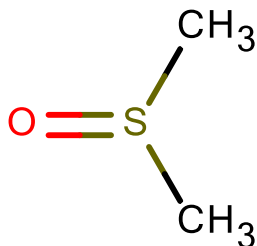
Human
LLNA
QSAR

Sensitizer
Sensitizer
Sensitizer

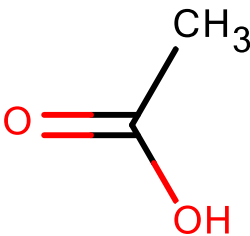
Sensitizer
Sensitizer
Sensitizer



Methylisothiazolinone



Dimethyl sulfoxide



Lead acetate

Human
LLNA
QSAR

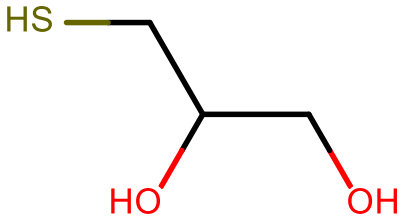
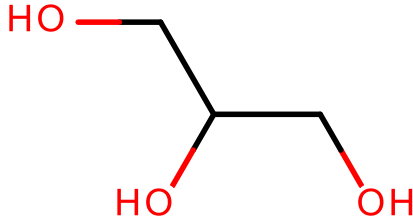
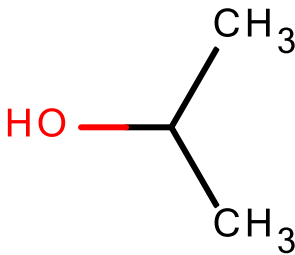
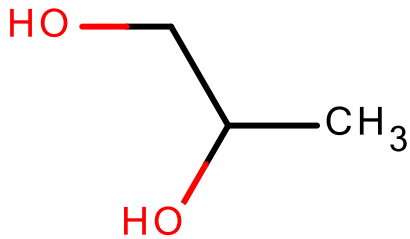
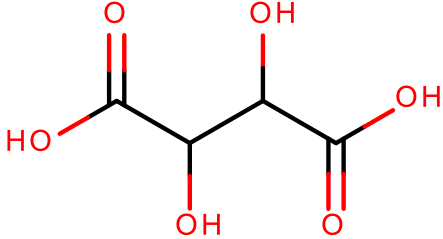
Sensitizer
Sensitizer
Sensitizer

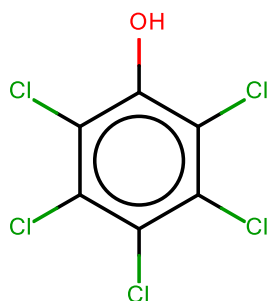
Non-sensitizer
Sensitizer
Sensitizer

Non-sensitizer
Non-sensitizer
Non-sensitizer

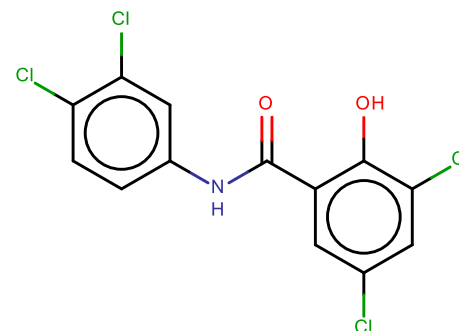
CLUSTER 21

24

	 <p>Thioglycerol</p>	 <p>Glycerol</p>	 <p>Isopropanol</p>
Human	Sensitizer	Non-sensitizer	Non-sensitizer
LLNA	Sensitizer	Non-sensitizer	Non-sensitizer
QSAR	Non-sensitizer	Non-sensitizer	Non-sensitizer
	 <p>Propylene glycol</p>	 <p>Tartaric acid</p>	
Human	Non-sensitizer	Non-sensitizer	
LLNA	Non-sensitizer	Non-sensitizer	
QSAR	Non-sensitizer	Non-sensitizer	



Pentachlorophenol



3,3',4',5-Tetrachlorosalicylanilide

Human

Sensitizer

Sensitizer

LLNA

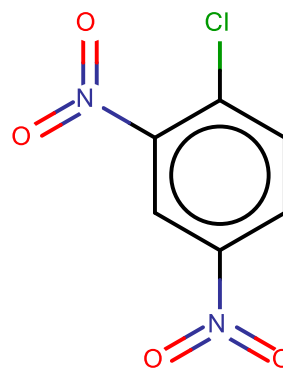
Sensitizer

Sensitizer

QSAR

Sensitizer

Sensitizer



2,4-Dinitrochlorobenzene

Human

Sensitizer

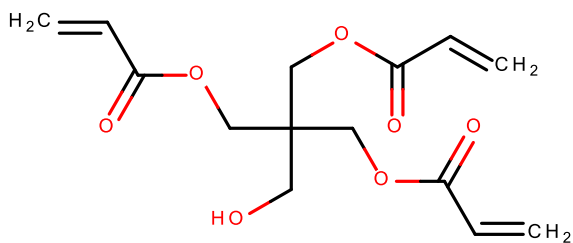
LLNA

Sensitizer

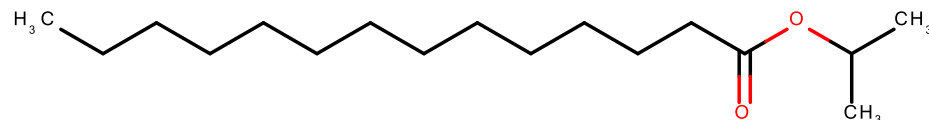
QSAR

Sensitizer

Conflicting experimental annotation between duplicates



Pentaerythritol triacrylate



Isopropyl myristate

Human

Sensitizer

Non-sensitizer

LLNA

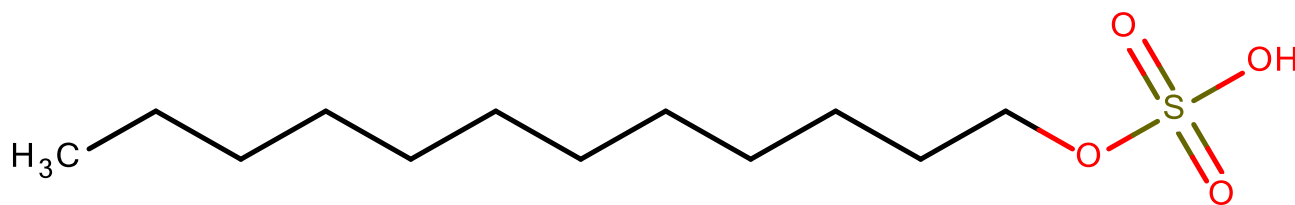
Non-sensitizer

Sensitizer

QSAR

Sensitizer

Non-sensitizer



Sodium lauryl sulfate

Human

Non-sensitizer

LLNA

Sensitizer

QSAR

Non-sensitizer