

THE UNIVERSITY  
of NORTH CAROLINA  
at CHAPEL HILL



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

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<sup>a</sup> University of North Carolina, Chapel Hill, USA

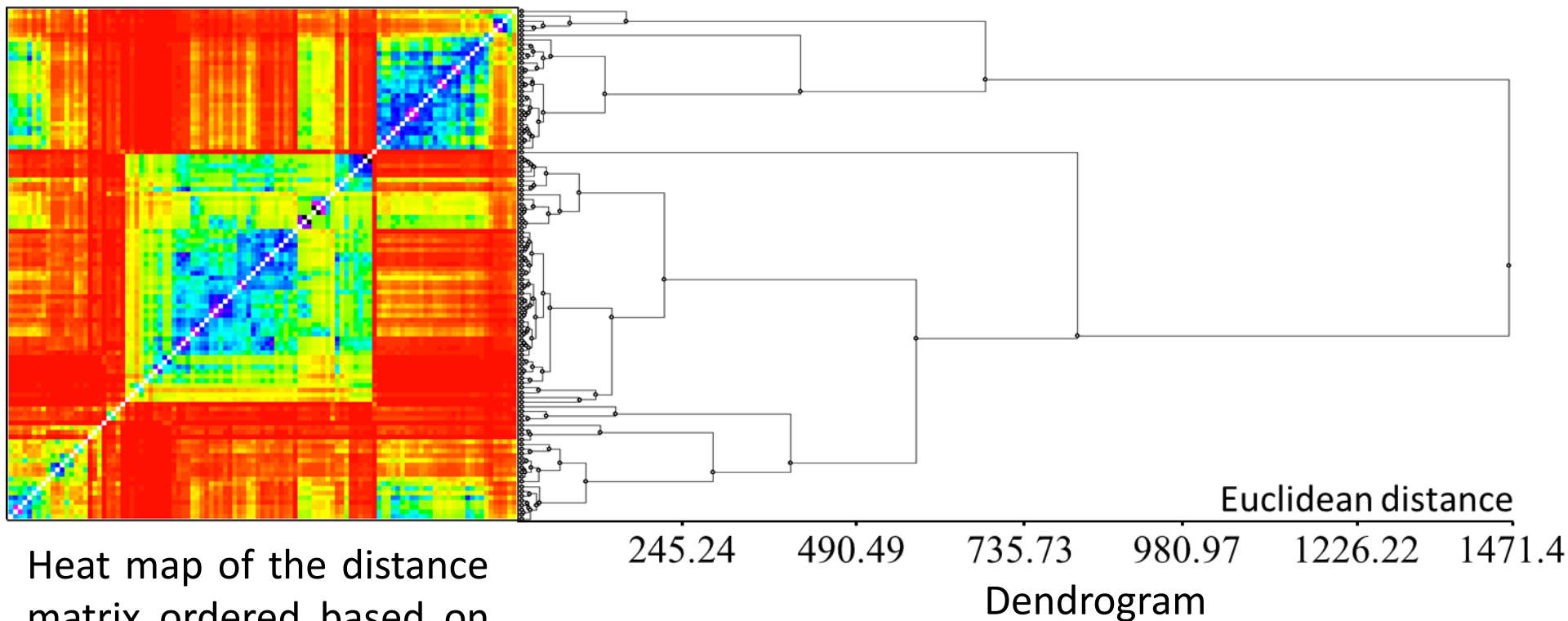
<sup>b</sup> Federal University of Goiás, Goiás, Brazil

<sup>c</sup> North Carolina State University, Raleigh, USA

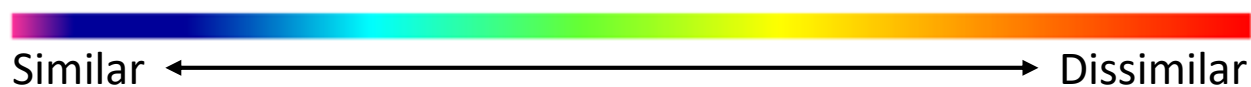
<sup>d</sup> ILS NIEHS, RTP, USA

**CLUSTER ANALYSIS OF  
HUMAN SKIN SENSITIZATION  
DATASET**

No. of compounds = 109



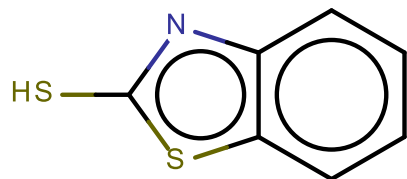
Heat map of the distance matrix ordered based on the clustering and colored\* using structural similarity.



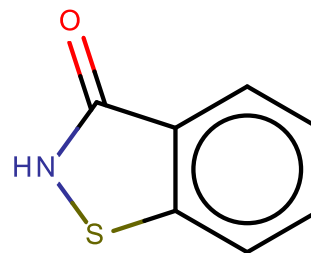
# CLUSTER 1

4

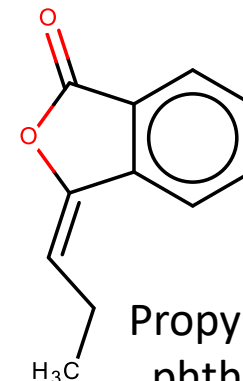
Conflicting experimental annotation between duplicates



2-Mercaptobenzothiazole



Benzisothiazolone



Propylidene phthalate

Human  
LLNA  
QSAR

Sensitizer

Sensitizer

Sensitizer

Sensitizer

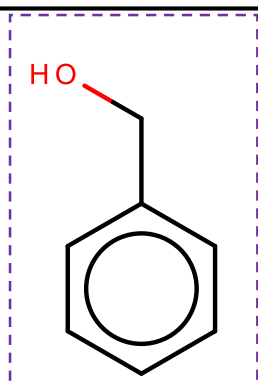
Sensitizer

Sensitizer

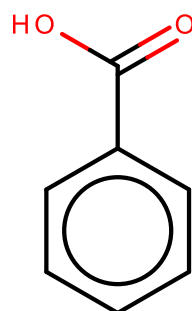
Sensitizer

Sensitizer

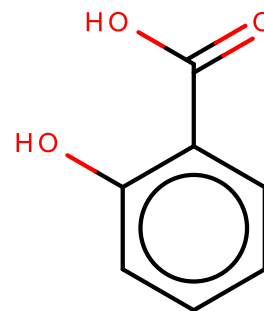
Non-sensitizer



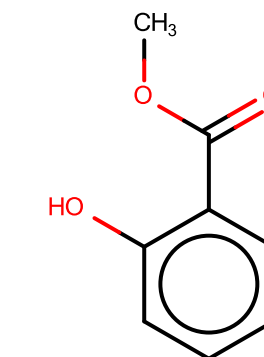
Benzyl alcohol



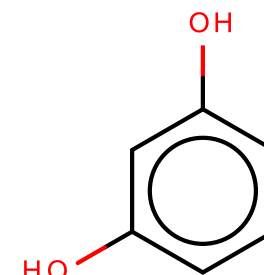
Benzoic acid



Salicylic acid



Methyl salicylate



Resorcinol

Human  
LLNA  
QSAR

Sensitizer

Non-sensitizer

Non-sensitizer

Non-sensitizer

Non-sensitizer

Non-sensitizer

Non-sensitizer

Sensitizer

Sensitizer

Sensitizer

Non-sensitizer

Non-sensitizer

Non-sensitizer

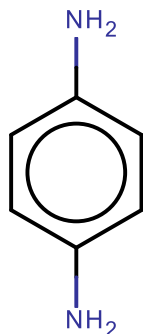
Non-sensitizer

Non-sensitizer

# CLUSTER 2 - AROMATIC AMINES

5

Human  
LLNA  
QSAR

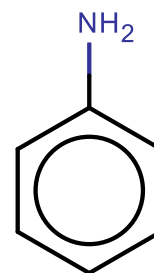


4-phenylenediamine

Sensitizer

Sensitizer

Sensitizer

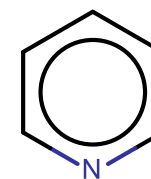


Aniline

Sensitizer

Sensitizer

Sensitizer

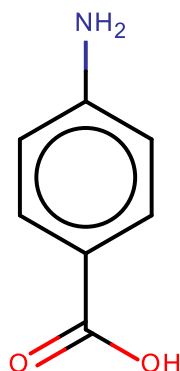


Pyridine

Sensitizer

Sensitizer

Sensitizer

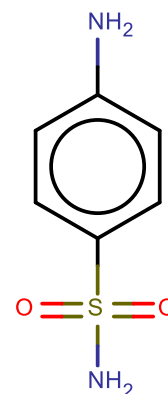


*p*-aminobenzoic acid

Non-sensitizer

Non-sensitizer

Sensitizer

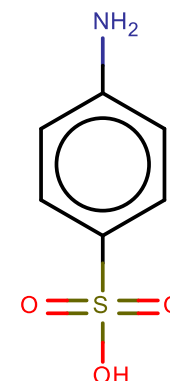


Sulfanilamide

Sensitizer

Non-sensitizer

Sensitizer



Sulfanilic acid

Non-sensitizer

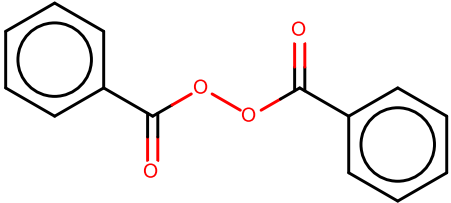
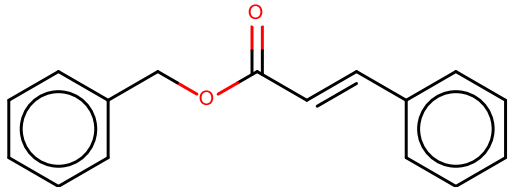
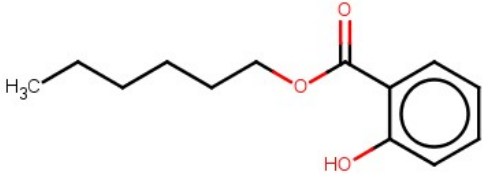
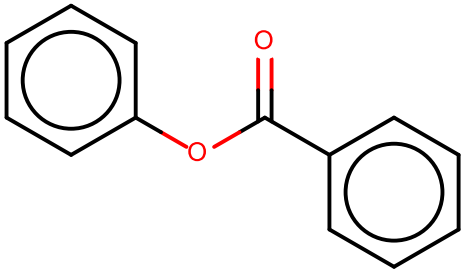
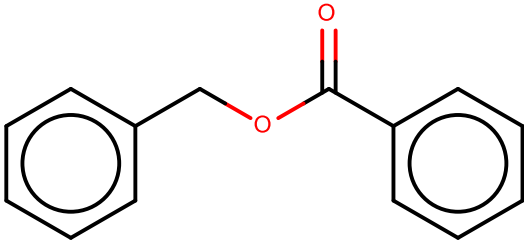
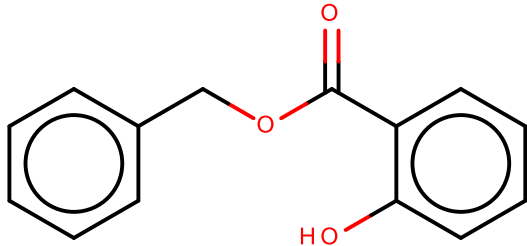
Non-sensitizer

Sensitizer

Human  
LLNA  
QSAR

# CLUSTER 3 - ESTERS OF BENZOIC ACID

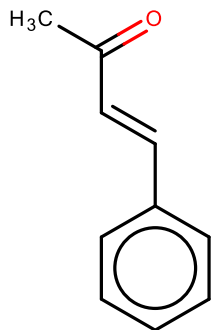
6

			
	Benzoyl peroxide	Benzyl cinnamate	Hexyl salicylate
Human	Sensitizer	Non-sensitizer	Non-sensitizer
LLNA	Sensitizer	Sensitizer	Sensitizer
QSAR	Non-sensitizer	Non-sensitizer	Non-sensitizer
			
	Phenyl benzoate	Benzyl benzoate	Benzyl salicylate
Human	Sensitizer	Non-sensitizer	Non-sensitizer
LLNA	Sensitizer	Sensitizer	Sensitizer
QSAR	Sensitizer	Non-sensitizer	Non-sensitizer

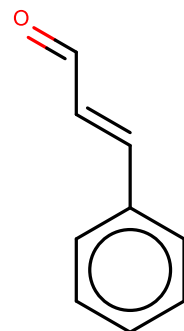
# CLUSTER 4 - CINNAMYL DERIVATIVES

7

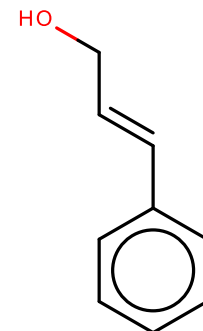
Conflicting experimental annotation between duplicates



Benzylidene acetone



Cinnamic aldehyde



Cinnamyl alcohol

Human

Sensitizer

Sensitizer

Sensitizer

LLNA

Sensitizer

Sensitizer

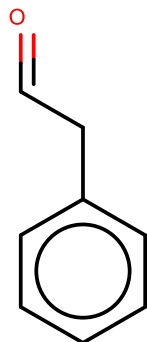
Sensitizer

QSAR

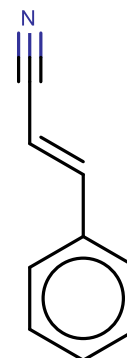
Non-sensitizer

Sensitizer

Sensitizer



Phenylacetaldehyde



Cinnamyl nitrile

Human

Sensitizer

Sensitizer

LLNA

Sensitizer

Non-sensitizer

QSAR

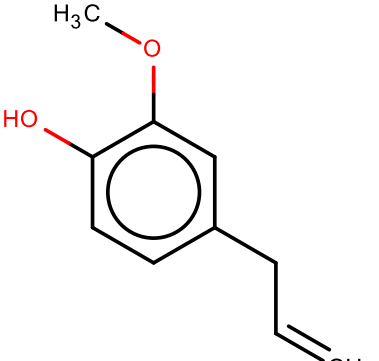
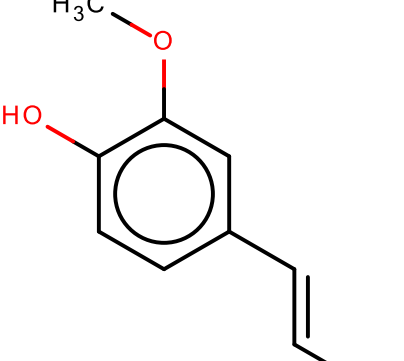
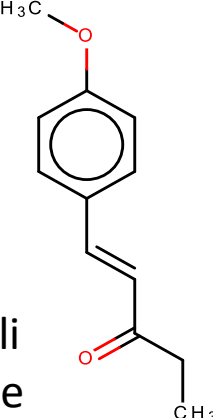
Non-sensitizer

Sensitizer

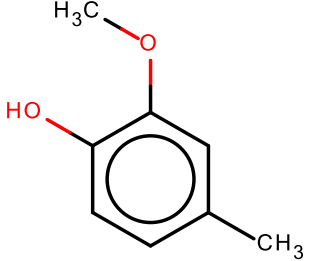
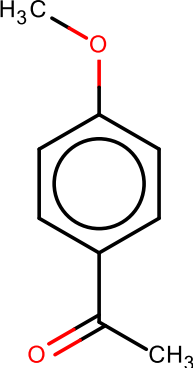
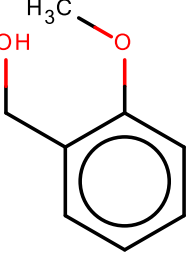
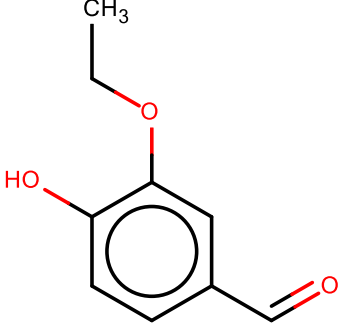
# CLUSTER 5

8

Human  
LLNA  
QSAR

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

Human  
LLNA  
QSAR

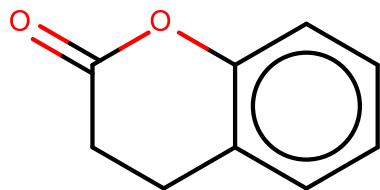
 <p>2-Methoxy-4-methylphenol</p>	 <p>4-Methoxyacetophenone</p>	 <p>Anisyl alcohol</p>	 <p>Ethyl vanillin</p>
Non-sensitizer	Non-sensitizer	Non-sensitizer	Non-sensitizer
Sensitizer	Non-sensitizer	Sensitizer	Non-sensitizer
Non-sensitizer	Sensitizer	Non-sensitizer	Non-sensitizer



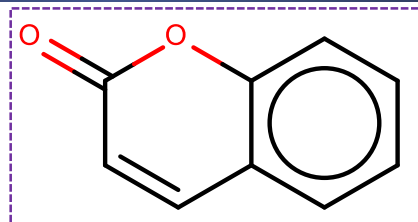
# CLUSTER 6

9

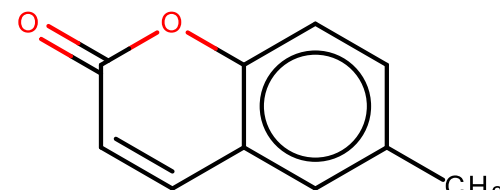
Conflicting experimental annotation between duplicates



3,4-dihydrocoumarin



Coumarin



6-methylcoumarin

Sensitizer

Sensitizer

Non-sensitizer

Sensitizer

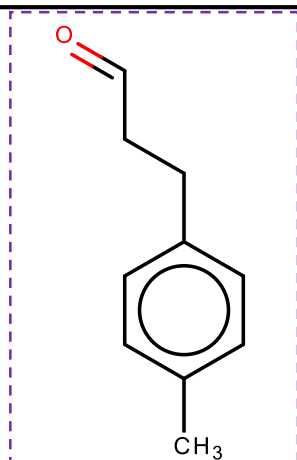
Sensitizer

Non-sensitizer

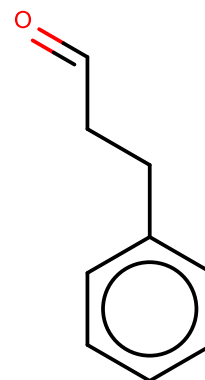
Non-sensitizer

Sensitizer

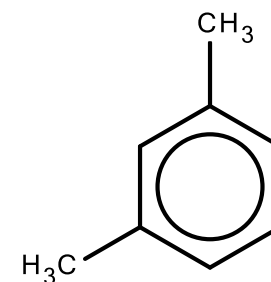
Non-sensitizer



*p*-methylhydrocinnamic aldehyde



Phenylpropionaldehyde



Xylene

Sensitizer

Sensitizer

Non-sensitizer

Sensitizer

Sensitizer

Sensitizer

Non-sensitizer

Non-sensitizer

Non-sensitizer

Human

LLNA

QSAR

Human

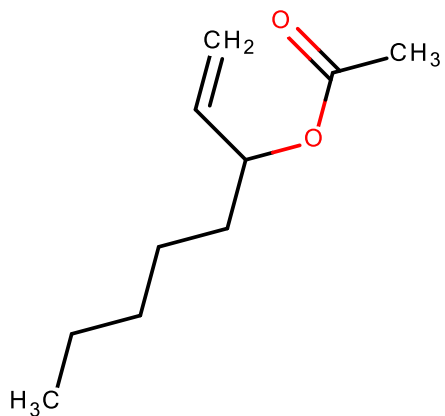
LLNA

QSAR

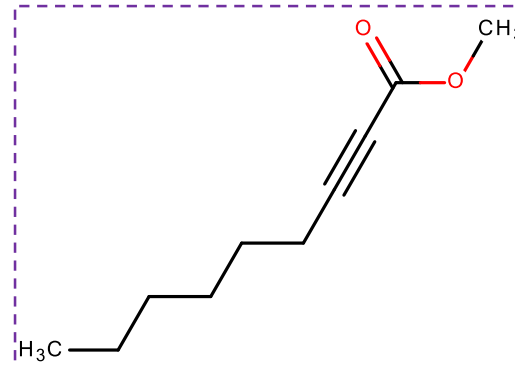
# CLUSTER 7

10

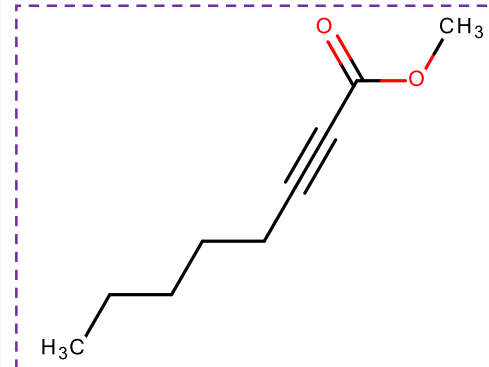
Conflicting experimental annotation between duplicates



1-Octen-3-yl acetate



Methyl 2-nonynoate



Methyl 2-octynoate

Sensitizer

Sensitizer

Sensitizer

Non-sensitizer

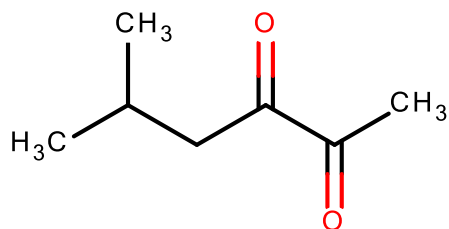
Sensitizer

Sensitizer

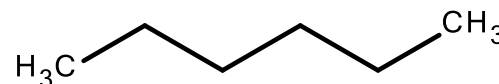
Non-sensitizer

Sensitizer

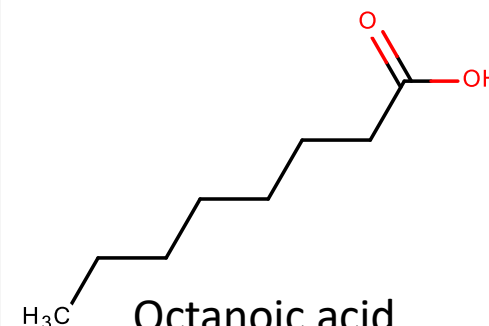
Sensitizer



Methylhexanedione



Hexane



Octanoic acid

Sensitizer

Non-sensitizer

Non-sensitizer

Sensitizer

Non-sensitizer

Non-sensitizer

Non-sensitizer

Non-sensitizer

Non-sensitizer

Human

LLNA

QSAR

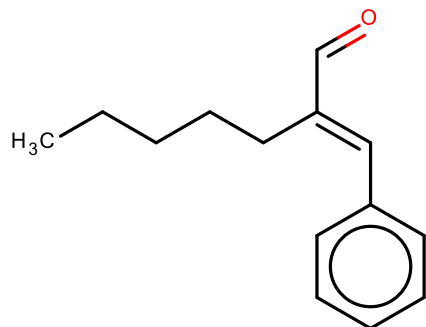
Human

LLNA

QSAR

# CLUSTER 8 - CINNAMYL DERIVATIVES

11

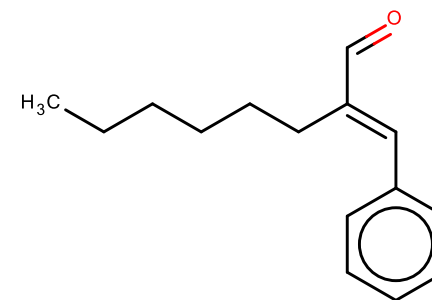


$\alpha$ -amylcinnamic aldehyde

Non-sensitizer

Sensitizer

Non-sensitizer

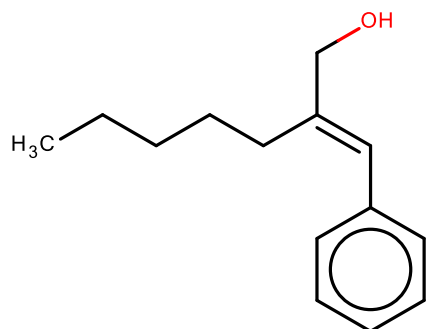


Hexyl cinnamic aldehyde

Non-sensitizer

Sensitizer

Non-sensitizer

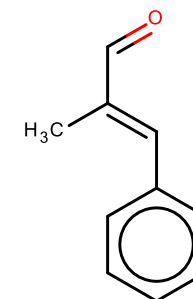


$\alpha$ -amylcinnamyl alcohol

Sensitizer

Non-sensitizer

Non-sensitizer



$\alpha$ -methyl cinnamic aldehyde

Non-sensitizer

Sensitizer

Non-sensitizer

Human

LLNA

QSAR

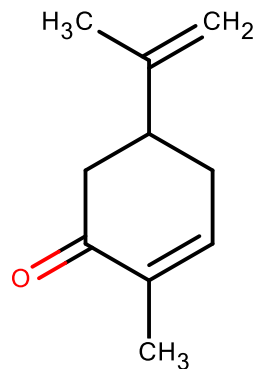
Human

LLNA

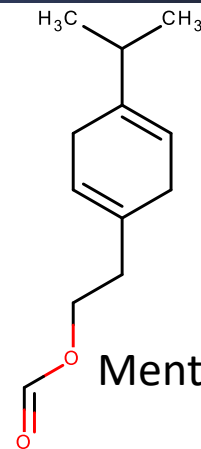
QSAR

# CLUSTER 9 - TERPENES

12



Carvone



Menthadiene-7-methyl formate

Human

Sensitizer

Sensitizer

LLNA

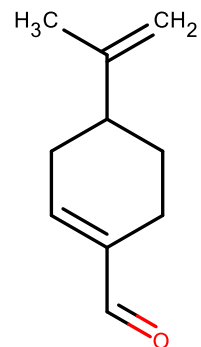
Sensitizer

Non-sensitizer

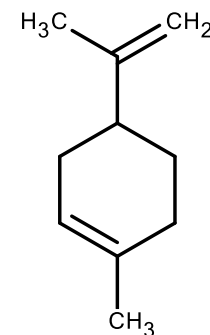
QSAR

Non-sensitizer

Non-sensitizer



Perillaldehyde



*d*-Limonene

Human

Sensitizer

Non-sensitizer

LLNA

Sensitizer

Sensitizer

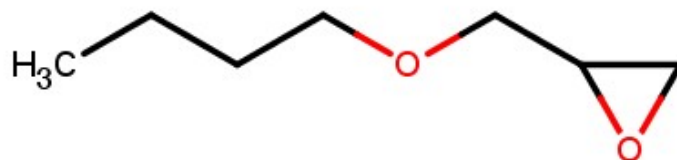
QSAR

Sensitizer

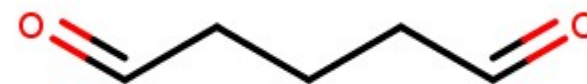
Sensitizer

# CLUSTER 10

13



Butyl glycidyl ether



Glutaraldehyde

Human

Sensitizer

Sensitizer

LLNA

Sensitizer

Sensitizer

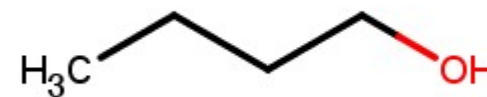
QSAR

Non-sensitizer

Sensitizer



*t*-2-hexenal



Butanol

Human

Sensitizer

Non-sensitizer

LLNA

Sensitizer

Non-sensitizer

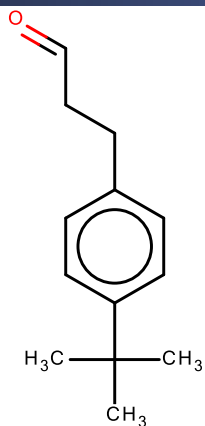
QSAR

Sensitizer

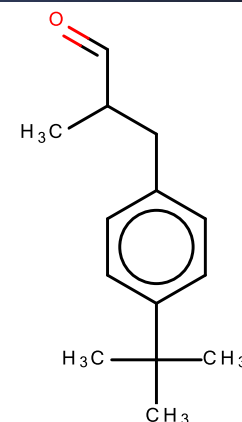
Non-sensitizer

# CLUSTER 11

14



Bourgeonal



Lilial

Sensitizer

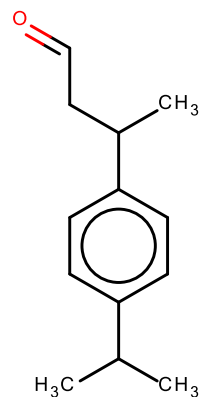
Sensitizer

Sensitizer

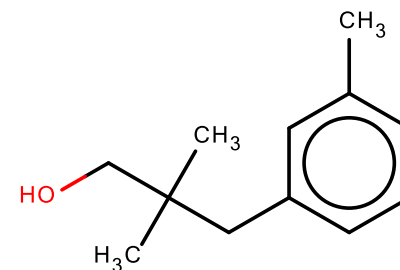
Sensitizer

Sensitizer

Sensitizer



Cyclamen  
aldehyde



Majantal

Non-sensitizer

Non-sensitizer

Sensitizer

Non-sensitizer

Sensitizer

Sensitizer

Human

LLNA

QSAR

Human

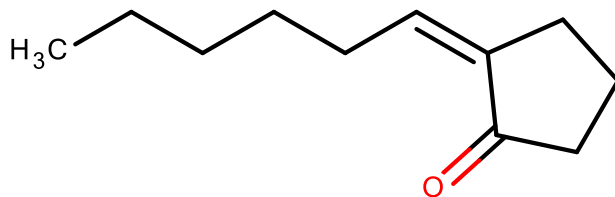
LLNA

QSAR

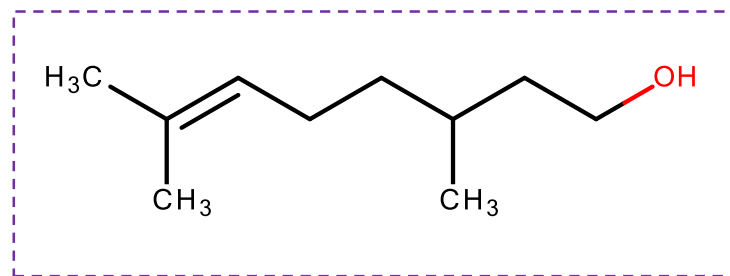
# CLUSTER 12

15

Conflicting experimental annotation between duplicates



2-Hexylidene cyclopentanone



*dl*-Citronellol

Sensitizer

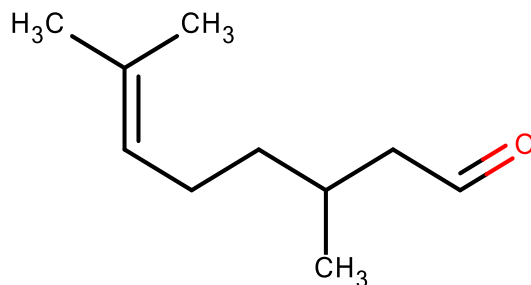
Sensitizer

Sensitizer

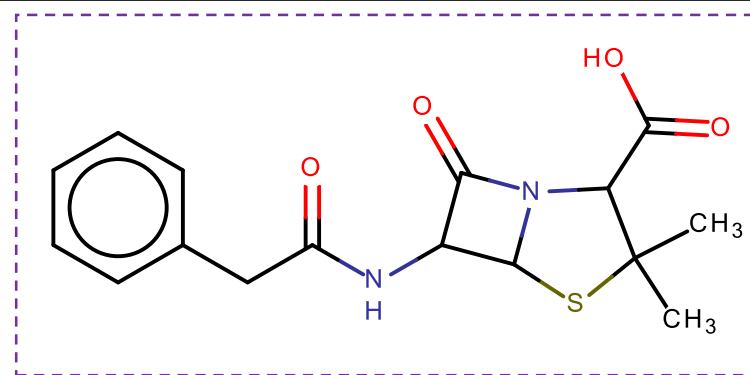
Sensitizer

Non-sensitizer

Non-sensitizer



Citronella oil



Penicillin G

Non-sensitizer

Sensitizer

Non-sensitizer

Sensitizer

Non-sensitizer

Sensitizer

Human

LLNA

QSAR

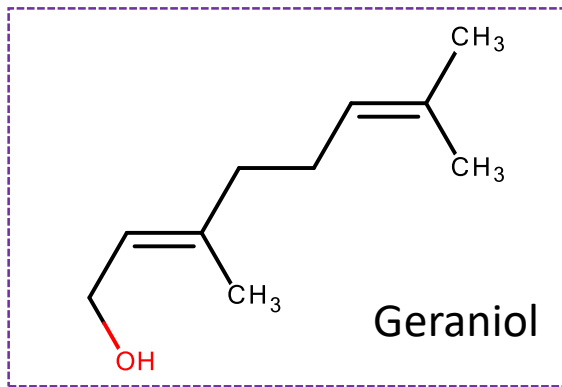
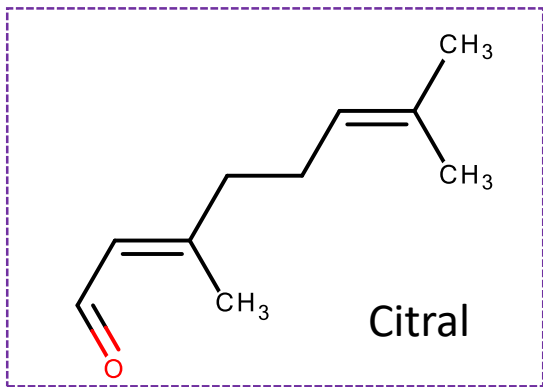
Human

LLNA

QSAR

# CLUSTER 13 - OTHER TERPENOIDS

Conflicting experimental annotation between duplicates



Human  
LLNA  
QSAR

Sensitizer

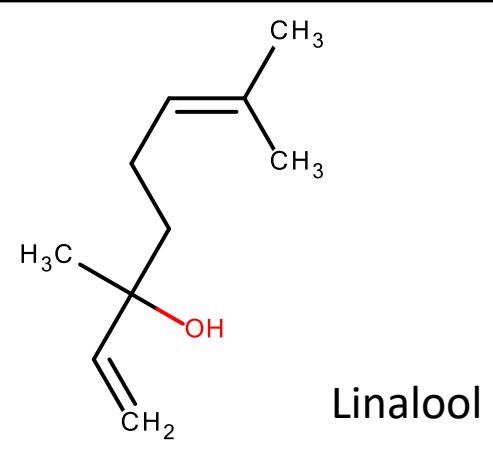
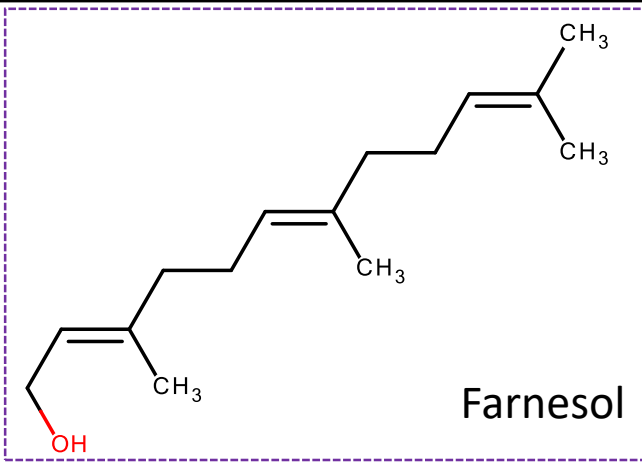
Sensitizer

Sensitizer

Sensitizer

Non-sensitizer

Sensitizer



Human  
LLNA  
QSAR

Sensitizer

Non-sensitizer

Sensitizer

Non-sensitizer

Sensitizer

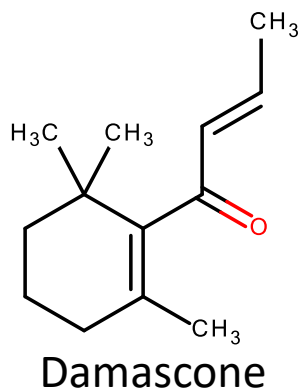
Non-sensitizer



# CLUSTER 14 - DAMASCONES

17

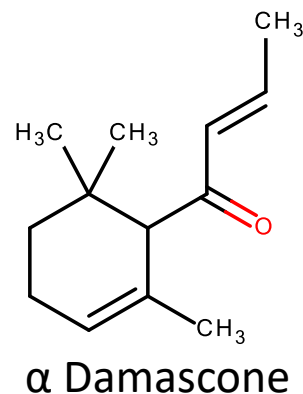
Human  
LLNA  
QSAR



Non-sensitizer

Sensitizer

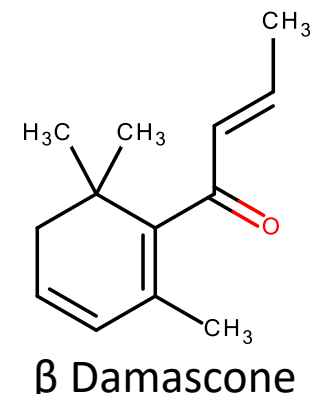
Non-sensitizer



Non-sensitizer

Sensitizer

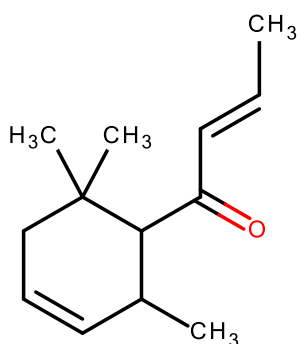
Non-sensitizer



Non-sensitizer

Sensitizer

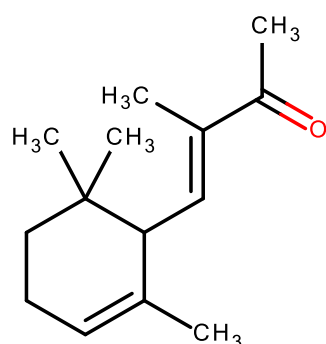
Non-sensitizer



Sensitizer

Sensitizer

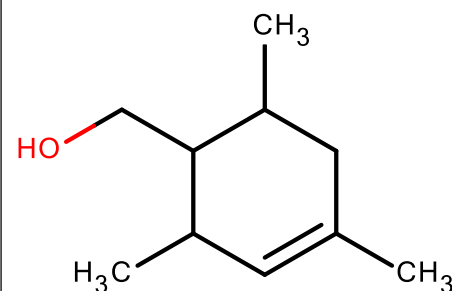
Non-sensitizer



Non-sensitizer

Sensitizer

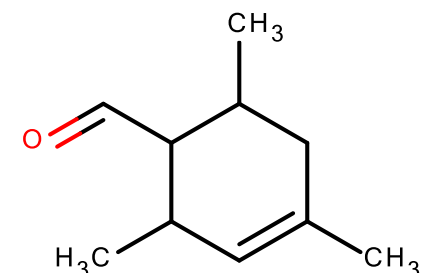
Non-sensitizer



Sensitizer

Non-sensitizer

Non-sensitizer



Non-sensitizer

Sensitizer

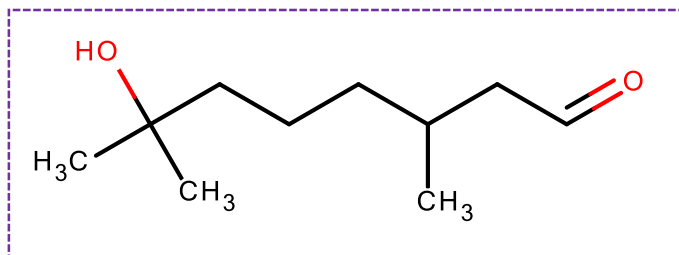
Non-sensitizer

Human  
LLNA  
QSAR

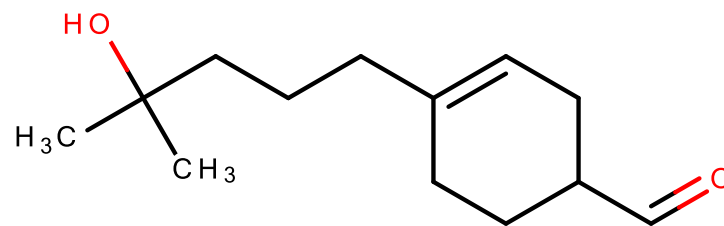
# CLUSTER 15

18

Conflicting experimental annotation between duplicates



Hydroxycitronellal



Lyral

Human

Sensitizer

Non-sensitizer

LLNA

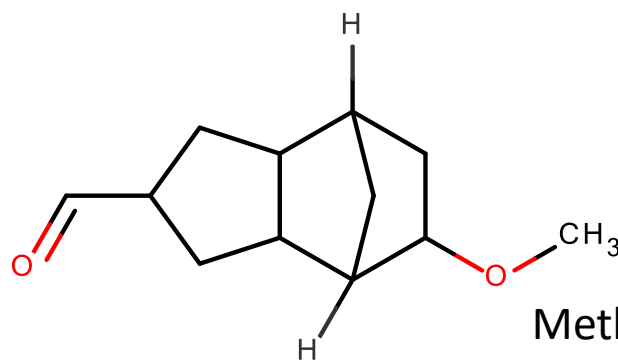
Sensitizer

Sensitizer

QSAR

Non-sensitizer

Non-sensitizer



Methoxy dicyclopentadiene carboxaldehyde

Human

Non-sensitizer

LLNA

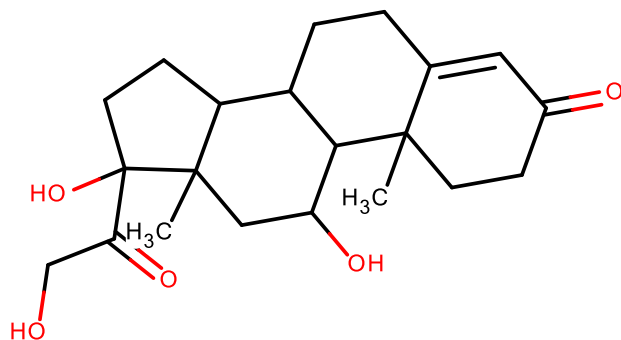
Non-sensitizer

QSAR

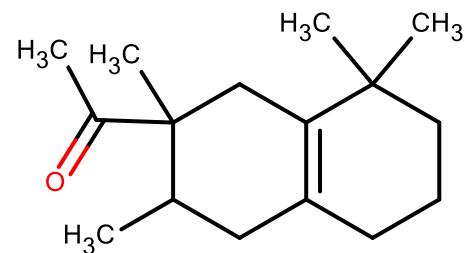
Sensitizer

# CLUSTER 16

19



Hydrocortisone



Isocyclemone E

Human

Non-sensitizer

Non-sensitizer

LLNA

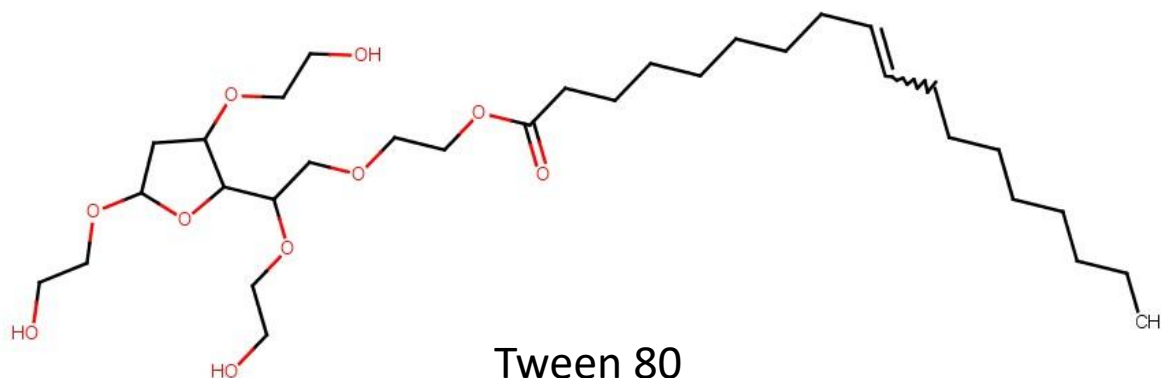
Non-sensitizer

Sensitizer

QSAR

Non-sensitizer

Sensitizer



Tween 80

Human

Non-sensitizer

LLNA

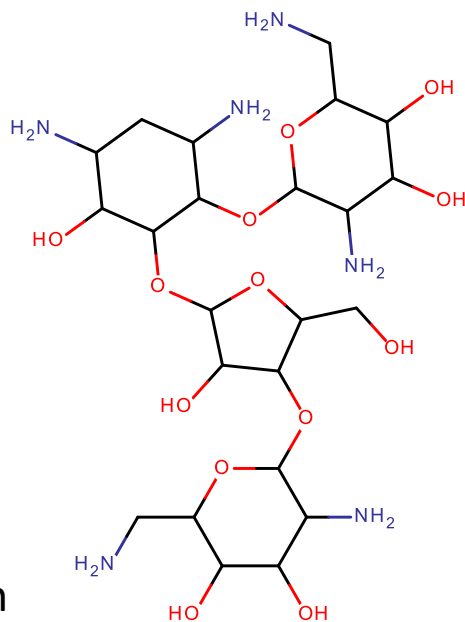
Non-sensitizer

QSAR

Sensitizer

# CLUSTER 17 - AMINOGLYCOSIDES

20

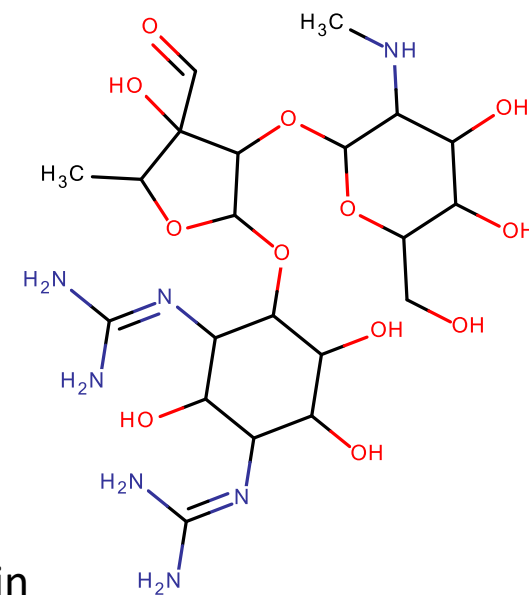


Neomycin

Sensitizer

Non-sensitizer

Sensitizer



Streptomycin

Sensitizer

Non-sensitizer

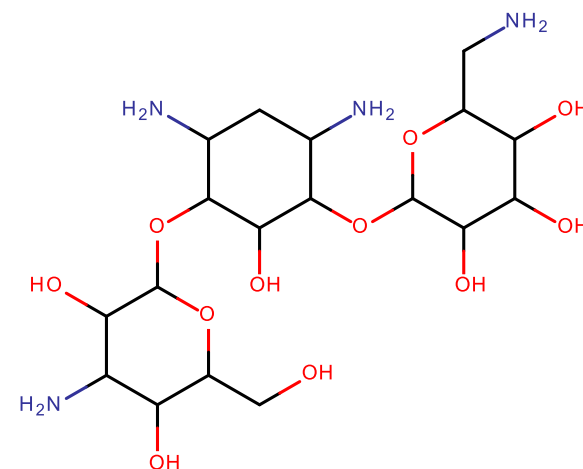
Sensitizer

Kanamycin

Sensitizer

Non-sensitizer

Sensitizer



Human

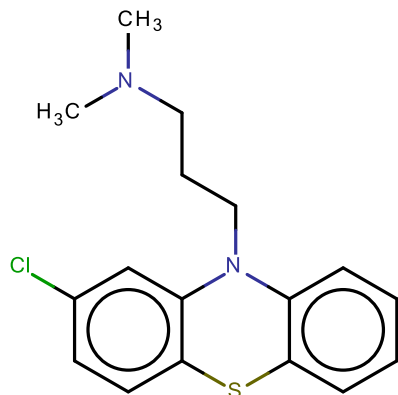
LLNA

QSAR

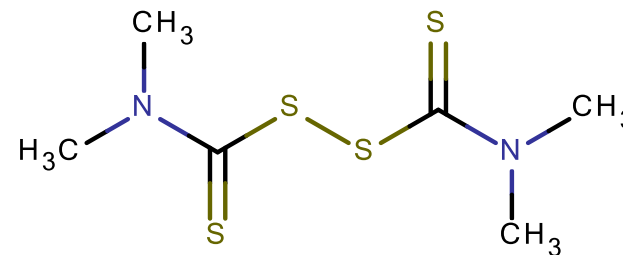
Human

LLNA

QSAR



Chlorpromazine



Tetramethylthiuram-disulfide

Human

Sensitizer

Sensitizer

LLNA

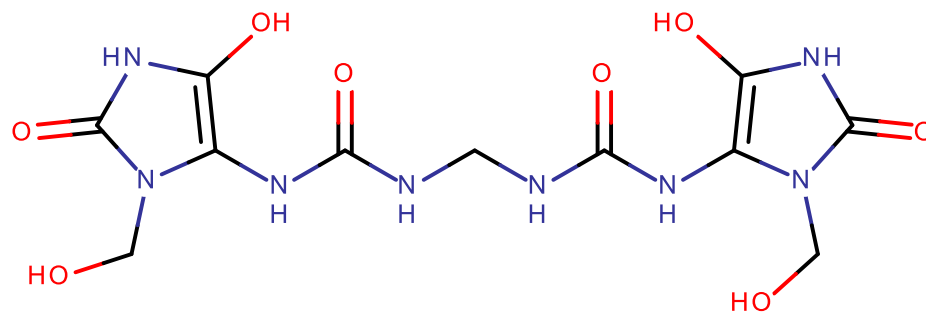
Sensitizer

Sensitizer

QSAR

Sensitizer

Sensitizer



Imidazolidinyl urea

Human

Sensitizer

LLNA

Sensitizer

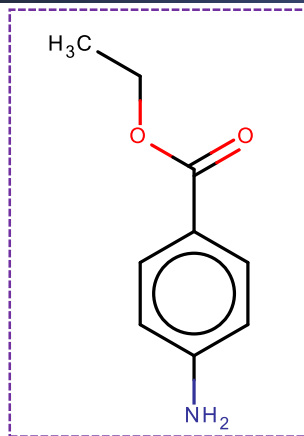
QSAR

Sensitizer

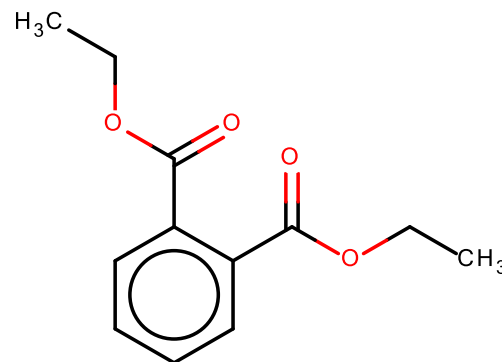
# CLUSTER 19

22

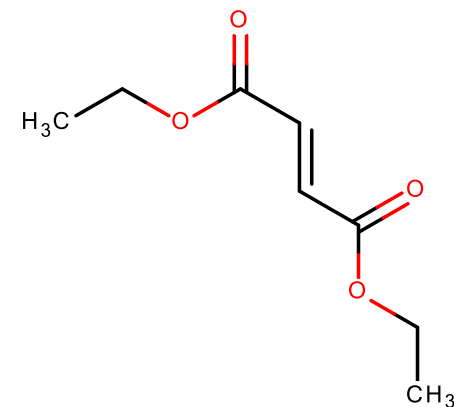
Conflicting experimental annotation between duplicates



Benzocaine



Diethyl phthalate



Diethylmaleate

Human

Sensitizer

Non-sensitizer

Sensitizer

LLNA

Sensitizer

Non-sensitizer

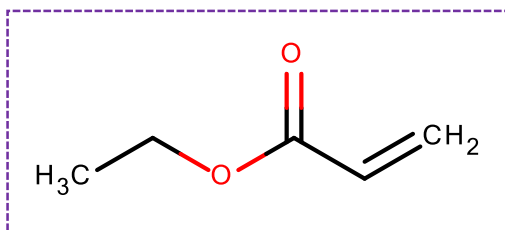
Sensitizer

QSAR

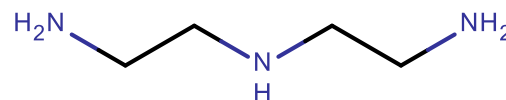
Sensitizer

Sensitizer

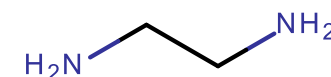
Sensitizer



Ethyl acrylate



Diethylenetriamine



Ethylenediamine

Human

Sensitizer

Sensitizer

Sensitizer

LLNA

Sensitizer

Sensitizer

Sensitizer

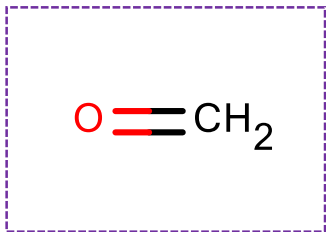
QSAR

Sensitizer

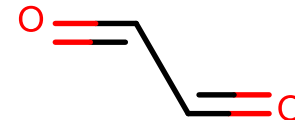
Sensitizer

Sensitizer

Conflicting experimental annotation between duplicates



Formaldehyde



Glyoxal

Human

Sensitizer

Sensitizer

LLNA

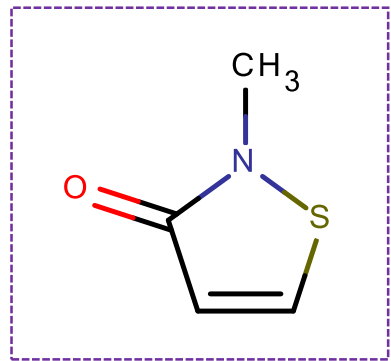
Sensitizer

Sensitizer

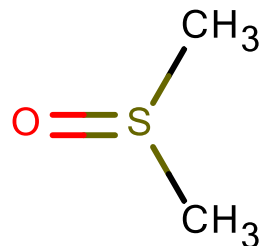
QSAR

Sensitizer

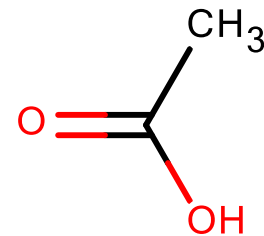
Sensitizer



Methylisothiazolinone



Dimethyl sulfoxide



Lead acetate

Human

Sensitizer

Non-sensitizer

Non-sensitizer

LLNA

Sensitizer

Sensitizer

Non-sensitizer

QSAR

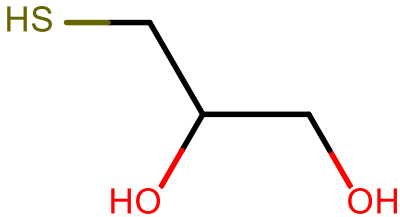
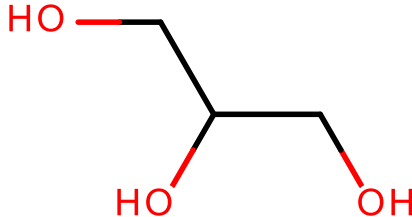
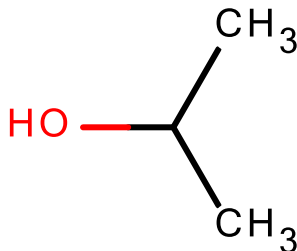
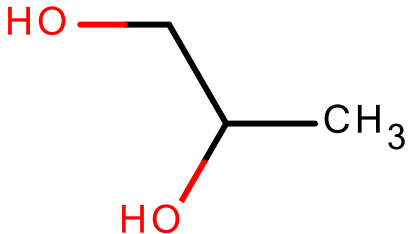
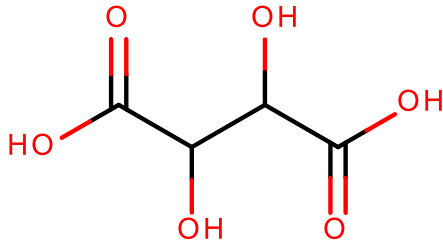
Sensitizer

Sensitizer

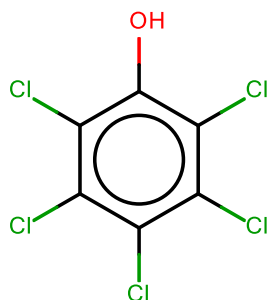
Non-sensitizer

# CLUSTER 21

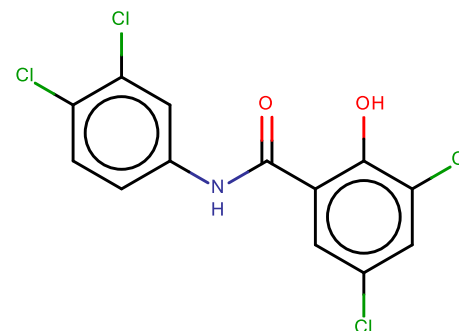
24

	 <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

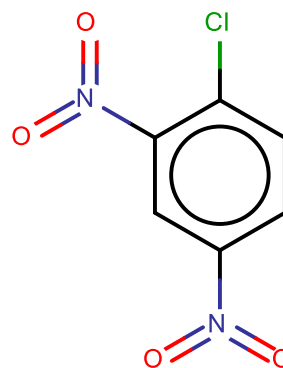
Sensitizer

Sensitizer

QSAR

Sensitizer

Sensitizer



2,4-Dinitrochlorobenzene

Human

Sensitizer

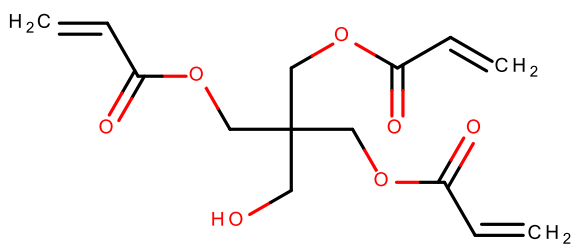
LLNA

Sensitizer

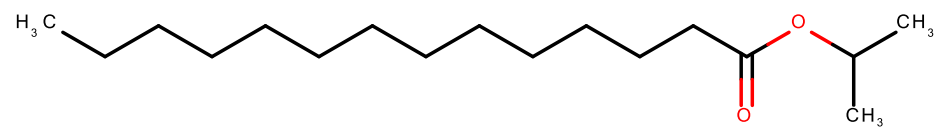
QSAR

Sensitizer

Conflicting experimental annotation between duplicates



Pentaerythritol triacrylate



Isopropyl myristate

Human  
LLNA  
QSAR

Sensitizer

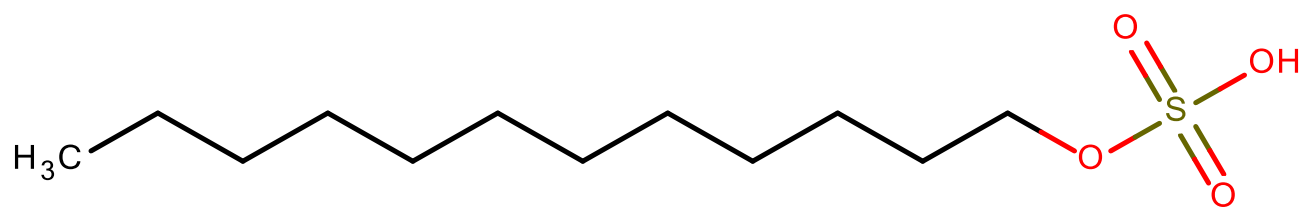
Non-sensitizer

Non-sensitizer

Sensitizer

Sensitizer

Non-sensitizer



Sodium lauryl sulfate

Human  
LLNA  
QSAR

Non-sensitizer

Sensitizer

Non-sensitizer