# Survey of Chemical Substances in Consumer Products

Survey No 13, 2002

# Mapping of Chemical Substances from Sanitary Towels

Jane Pors, MSc
René Fuhlendorff, MSc

**Danish Environmental Protection Agency**
Danish Ministry of the Environment

# 1 Content

# 2 Introduction

September 2001 MILJØ-KEMI, Dansk Miljø Center A/S was assigned to carry out a project from the Danish Environmental Protection Agency titled:

- ***Mapping of Chemical Substances in Sanitary Towels***

The project is part of a larger investigation of different consumer products titled:

- ***Mapping of Chemical Substances in Consumer Products***

The Danish Environmental Protection Agency had prepared a project proposal (6th August 2001, HSHA/SDO12) that formed the background for contents and scope of the project.

The background for the Danish Environmental Protection Agency's (hereinafter called EPA) investigation is that the market for sanitary towels is vast as to volume and number of different products. Furthermore, it is a market characterized by extensive development due to production technical improvements, trends, and consumer demands.

EPA is interested in a mapping of the chemical substances in the hygiene products as they represent products that are close to skin and the mucous membrane or in some cases in direct contact with the mucous membrane. Furthermore, the exposure takes place over a period of time.

Project leaders for the Danish Environmental Protection Agency were Henriette Seiler Hansen and Anette Ejersted.

The products included in this report have been made anonymous. The product references are stated in appendix B.

Toxicological profiles for some of the other components are given in the report: "Mapping of Chemical Substances in Tampons" performed for the Danish Environmental Protection Agency by MILJØ-KEMI, Danish Environmental Center, job no 201259-72-184 of 19th December 2002.

# 3 Scope

EPA has requested the project to include both sanitary towels and panty liners.

## 3.1 Selection of hygiene products

### 3.1.1 Purchase of products

A large selection of stores – groceries, supermarkets, perfumeries, discount chains, and pharmacies have been visited. A random selection of different brands of hygiene products was purchased to investigate further.

### 3.1.2 Selection of hygiene products for the project

The selection of products was made in co-operation with EPA. The hygiene products were chosen to represent:

- Products made from different raw material
- Cheap and expensive products
- Product made by different manufacturers
- Products with special effect or appearance

According to the wishes of EPA a total of eight products were included in the project.

## 3.2 Chemical analysis

The chemical analyses of the sanitary towels include the following compound groups:

- Colophony
- Organic tin compounds
- Selected acrylates
- Selected phenol compounds
- GC/MS screening

According to the supplier's information no optical brightener has been added at production of the sanitary towels. Furthermore, most products do not contain chloric bleach. It has therefore only been assessed relevant to perform a chemical analysis of the products where there are doubts on the use of bleach. Besides, a potential existence of optical brightener is assessed visually at UV illumination.

Only one of the products was added dye. It was found unnecessary with further analyses of this colour.

## 3.3 Toxicological profile

From the analysis results performed by MILJØ-KEMI, Dansk Miljø Center A/S Dansk Toksikologi Center (DTC) has suggested single components where a toxicological profile could be prepared.

The final selection was carried out in co-operation with Anette Ejersted from EPA.

A total of 12 components were selected:

- Butenylidenbenzene (indicator for the group of biphenyl derivates)
- Methylethylidenbenzene (indicator for the group of biphenyl derivates)
- Bicyclopentyl 1-1'-dien (indicator for the group of bicyclopentyldienes)
- Bicyclopentyl 2-2'-dien (indicator for the group of bicyclopentyldienes)
- Dihydrotrimethylphenylindene (indicator for the group of indene derivates)
- Abietic acid
- Colophony
- Diethylhexyladipate (DEHA)
- Diethanolamine (DEA)
- Triethanolamine (TEA)
- Butyl hydroxytoluene (BHT)
- Acetophenon

The toxicological profiles for some of the other components are given in the report "Mapping of Chemical Substances in Tampons" performed for the Danish Environmental Protection Agency by MILJØ-KEMI, Danish Environmental Center, and job number 201259-72-184 of 19 December 2001.

# 4 Analytic methods

## 4.1 Sample preparation

Primarily the paper or the glue covering were removed. Thereafter all hygiene products were cut into pieces of approximately 0.5 x 0.5 cm.

Another sample preparation was performed as a part sample of the hygiene products were split in a back solely consisting of back and glue. "The front" consists of the rest of the towel. The split was carried out as accurate as possible; however, part of the core was often stuck to the back making a total split impossible. Following the split the samples were cut into pieces of approximately. 0.5 x 0.5 cm.

## 4.2 GC/MS screening (acrylate, phenol compounds, and other extractable organic compounds)

A number of sanitary towels corresponding to approximately 5 g of the product is extracted with dichloromethane added internal standard by Soxhlet extraction for 16 hours. A part sample of the extract is taken and analysed directly at combined gas chromatography and mass spectrometry (GC/MS) by scanning over a larger mass area. The content is calculated to relevant standards (acrylates and phenols) or internal standards (others).

The analysis is carried out as double identification. The limit of detection for the GC/MS screening varies from approximately 0.5 to 10 mg/kg depending on the chemical components:

| Component | Limit of detection |
|---|---|
| Acrylates 1,5 | 0.5 mg/kg |
| Acetophenon | 0.4 mg/kg |
| Isopropyllaurat | 0.5 mg/kg |
| Acryl acid ester | 0.5 mg/kg |
| Unidentified phthalate | 0.5 mg/kg |
| Butylated hydroxytoluene (BHT) | 0.5 mg/kg |
| Diethylhexyladipat (DEHA) | 2.5 mg/kg |
| Phenols | 0.5-1.5 mg/kg |
| Glycerol tricaprylat and isomer | 10 mg/kg |
| Biphenyl and indene | 5 mg/kg |
| Aliphatic, unsaturated, and cyclic hydrocarbons | 5 mg/kg |

## 4.3 Colophony

A part sample of the Soxhlet extract (see section 4.4) is evaporated to dryness, resolved in methanol and water (90:10), and analysed at combined liquid chromatography and mass spectrometry (LC/MS-DAD).

The analysis is carried out as double identification. The limit of detection is 0.5 mg/kg.

## 4.4 Organic tin compounds

A part sample of known weight and area is taken and extracted with acetic acid in methanol. The extract is shaken in aqueous medium and derivatized at an extractive derivative analysis with sodium tetraethyl borate and pentane. Isooctane is added to the organic phase, concentrated, and analysed at combined gas chromatography and mass spectrometry (GC/MS) at selective ion monitoring of the components in question. The content is calculated to the relevant standards.

The analysis is carried out as double identification. The limit of detection depends on the single component and is stated in the table below. The unit is µg organotin cation/kg.

| Component | Limit of detection |
|---|---|
| Monobutyltin (MBT) | 10 |
| Dibutyltin (DBT) | 5 |
| Tributyltin (TBT) | 5 |
| Tetrabutyltin | 10 |
| Monooctyltin | 10 |
| Dioctyltin | 10 |
| Tricyclohexyltin | 30 |
| Triphenyltin | 5 |

## 4.5 Ethanolamines

A part sample of the product with known weight is taken and extracted with demineralised water. The extract is analysed at ion chromatography detection by means of conductivity (IC).

The analysis is carried out as double identification. The limit of detection is 0.1 mg/kg for monoethanolamin, 1.0 mg/kg for diethanolamin, and 1.5 mg/kg for triethanolamin.

## 4.6 Optical brightener

All suppliers have stated that their products did not contain optical brightener. Instead of making an analysis this fact was verified by a total division of the products and an ultra-violate illumination. This method can provide false positive results as other substances may have fluorescent abilities, however, not false-negative results. In case there are fluorescent substances these will be detected at the test.

## 4.7 Bleach

A part sample is extracted with Milli-Q water, followed by a N,N-diethyl-p-phenylendiamin (DPD) titration and re-titration with iron (II)-solution. The analysis includes the following components: hypochlorite and chlorine dioxide.

Interfering components include other oxidizing components.

The analysis is carried out as double identification. The limit of detection is 2 mg/kg.

# 5 Results

## 5.1 Supplier data

All manufactures of the selected hygiene products have been contacted by MILJØ-KEMI, Dansk Miljø Center A/S in order to obtain information on the composition. All manufactures have answered a questionnaire and supplied data sheets on the products.

### 5.1.1 Selection of hygiene products for the project

The selection of hygiene products included in the project was made in co-operation with Henriette Seiler Hansen of the Danish Environmental Protection Agency. The total number of products was decided by EPA.

The below mentioned table states name, a brief product description, and manufacture/supplier. The description is made from the suppliers' information. A table containing additional information is enclosed as appendix A.

Table 1. Products included in the project.

| Description | | | | Manufacture/ supplier |
|---|---|---|---|---|
| **Type** | **Surface** | **Core** | **Barrier layer** | |
| Thick Sanitary towel | Non-woven | Cellulose | PE | A |
| Thin sanitary towel | Non-woven PP | Cellulose SAP | PE | B |
| Thin sanitary towel with wings | PP | Cellulose med latex SAP | PE | C |
| Thin sanitary towel for thong | Non-woven PP | Cellulose | PE | D |
| Combined sanitary towel and panty liner | Non-woven PP | Cellulose SAP | PE | D |
| Thin sanitary towel | PE | Cellulose SAP Rayon | PE | E |
| Panty liner | PE/PP | Cellulose SAP | PE | E |
| Thick sanitary towel | Cotton | Cellulose | PE | F |

PE: polyethylene, PP: polypropylene, SAP: polyacrylate.

## 5.2 Analytic results

### 5.2.1 Organic tin compounds

Table 2 states the result of the analyses for organic tin compounds. The limits of detection are given in section 4 "***Analytic methods***".

Table 2. The results of organic tin compounds. The results are stated in μg organotin cation/kg. Two results per product indicate double identification.

| | 1 | | 2 | | 3 | | 4 | | 5 | | 6 | | 7 | | 8 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Monobutyltin (MBT) | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Dibutyltin (DBT) | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Tributyltin (TBT) | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Tetrabutyltin | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Monooctyltin | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Dioctyltin | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Tricyclohexyltin | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Triphenyltin | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |

-: Means less than the limit of detection.

### 5.2.2 Ethanolamines

The MEA analysis was interference affected for single products. The limit of detection is thereby raised.

Table 3. Results for ethanolamines. The results are stated in mg/kg. Two results per product indicate double identification.

| | 1 | | 2 | | 3 | | 4 | | 5 | | 6 | | 7 | | 8 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Monoethanolamin | - | - | - | - | * | * | * | * | * | * | * | * | * | * | * | * |
| Diethanolamin | - | - | 13 | 7.5 | * | * | - | - | - | - | - | - | - | - | - | - |
| Triethanolamin | 6.8 | 7.5 | - | - | 2.3 | 2.2 | 9.6 | 7.7 | 1.8 | 1.9 | - | - | - | - | - | - |

-: Means less than the limit of detection.
*: A detection of monoethanolamin/diethanolamin respectively is impossible due to interference.

### 5.2.3 Acrylates and phenol compounds

Table 4 states the result of the analyses for the selected acrylates and the phenol compounds.

Table 4. Results of acrylates and phenol compounds. The results are stated in mg/kg. Two results per product indicate double identification. The limit of detection is 1.5 mg/kg for all components.

| | 1 | | 2 | | 3 | | 4 | | 5 | | 6 | | 7 | | 8 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Acrylates**: | | | | | | | | | | | | | | | | |
| Methylacrylate | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Ethylacrylate | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Butylacrylate | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Butylmethacrylate | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Tert-butyl acrylate | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Ethylendiacrylate | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Ethylhexylmethacrylate | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Hydroxypropylacrylate | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| 1,6-hexadioldiacrylate | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Diethylenglycoldiacrylate | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| **Phenols**: | | | | | | | | | | | | | | | | |
| Phenol | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| 2-ethylphenol | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| 2,3-dimethylphenol | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| 2,4-dimethylphenol | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| 3,4-dimethylphenol | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| 3,5-dimethylphenol | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| 2-methoxyphenol | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| 3-methoxyphenol | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| 2,6-dimethoxyphenol | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| 2,6-diisopropylphenol | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| 2,6-bis(1,1-dimethylethyl)phenol | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| 2-(1,1-dimethylethyl)-4-methyl phenol | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Bisphenol A | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |

-: Means less than the limit of detection.

### 5.2.4 Colophony and GC/MS screening

Table 5 states the result of the analyses for colophony and the GC/MS screening.

As colophony is a natural substance it consists of many related compounds where abietic acid is predominant.

It was not possible to quantify the compound group separately for the group of biphenyl- and indene compounds, as they are multi compounds that co-eluat with aliphatic and cyclic hydrocarbons. Both compound groups are therefore quantified collectively.

Table 5. Results of colophony and the GC/MS-screening of sanitary towels and panty liners. The results are stated in mg/kg. Two results indicate double identification.

| | 1 | | 2 | | 3 | | 4 | |
|---|---|---|---|---|---|---|---|---|
| Colophony | 4.0 | 4.3 | 11 | 12 | 22 | 21 | 1.2 | 0.4 |
| Acetophenon | - | 0.8 | - | - | - | - | - | - |
| Isopropyllaurat | - | - | - | - | - | - | - | - |
| Acryl acid ester of unknown chain length | - | - | - | - | - | - | - | - |
| Unidentified phthalate | 1.1 | 1.6 | - | - | - | 2.4 | 12 | 31 |
| Butylhydroxytoluene (BHT) | 2.5 | 0.9 | - | 0.5 | - | - | - | - |
| Diethylhexyladipate | - | - | 47 | 120 | - | - | - | - |
| 2,4-bis(1,1)-dimethylethylphenol | 0.9 | 0.5 | - | - | - | 1.3 | - | 1.0 |
| Glycerol tricaprylate | 52 | 99 | - | 30 | - | 50 | - | 49 |
| Isomer of glycerol tricaprylate | 63 | 100 | - | 26 | - | 35 | - | 63 |
| Biphenyl- and indene compounds | * | * | - | - | - | - | - | - |
| Aliphatic, unsaturated, and cyclic hydrocarbons | 7200 | 4500 | 17000 | 16000 | 13000 | 17000 | 7400 | 8500 |

-: Means less than the limit of detection.
*: Indicates content. The amount is quantified with the group of aliphatic, unsaturated, and cyclic hydrocarbons.

Table 5 continued.

| | 5 | | 6 | | 7 | | 8 | |
|---|---|---|---|---|---|---|---|---|
| Colophony | 2.3 | 2.1 | - | 13 | 12 | - | 1.2 | 4.7 |
| Acetophenon | - | - | - | 1.3 | - | - | - | - |
| Isopropyllaurat | - | - | - | - | - | - | 150 | 180 |
| Acryl acid ester of unknown chain length | 5.2 | 6.6 | - | - | - | - | - | - |
| Unidentified phthalate | - | - | 1.9 | - | 1.1 | 3.0 | - | - |
| Butylhydroxytoluene (BHT) | - | - | - | - | - | - | - | - |
| Diethylhexyladipate | - | - | - | - | - | - | - | - |
| 2,4-bis(1,1)-dimethylethylphenol | - | - | 0.6 | - | - | 1.3 | - | - |
| Glycerol tricaprylate | 53 | 99 | - | 52 | 124 | 33 | - | - |
| Isomer of glycerol tricaprylate | 31 | 82 | - | 50 | 140 | 33 | - | - |
| Biphenyl- and indene compounds | - | - | - | * | * | - | * | * |
| Aliphatic, unsaturated, and cyclic hydrocarbons | 15000 | 13000 | 18000 | 4100 | 3900 | 21000 | 32000 | 34000 |

-: Means less than the limit of detection.
*: Indicates content. The amount is quantified with the group of aliphatic, unsaturated, and cyclic hydrocarbons.

The group of biphenyl- and indene compounds originates primarily from the back of the towel for 1and 8, for which reason the components may originate from the glue on the back of the towel. Moreover, analyses of front and back of the towel respectively are not included in the project and therefore not rendered in this report.

Similarly, unidentified phthalates were detected in 1 and 8. However, these compounds only act as multi components that co-eluate with aliphatic and cyclic hydrocarbons. Both compounds have therefore been quantified collectively. The phthalates originated primarily from the back of the sanitary towels as was the case with the group of biphenyl- and indene compounds, wherefore the components may originate from the glue on the back of the towel.

### 5.2.5 Bleach

Chloric bleach has not been used at the production of several of the products. The remaining has been tested for hypochlorite and chlorine dioxide. The result is stated in table 6.

Table 6. Results of free chlorine. The results are stated in mg/kg. Two results per product indicate double identification.

| | 1 | | 2 | | 3 | | 4 | | 5 | | 6 | | 7 | | 8 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Free chlorine | * | * | - | - | * | * | - | - | * | * | - | - | - | - | - | - |

-: Means less than the limit of detection.
*: Not analysed.

### 5.2.6 Optical brightener

The following visual observations were detected at UV illumination. The investigation is carried out as single identification.

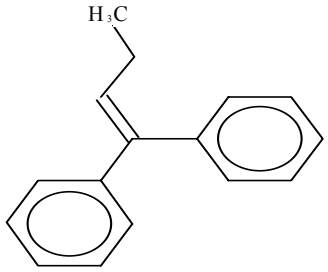
Table 7. Visual evaluation at UV-illumination of split sanitary towels.

| Product | UV-illumination |
|---|---|
| 1 | - |
| 2 | Clear marks corresponding to the glue on the back |
| 3 | Luminous areas on the layer immediately below the outer layer/surface, but not on the outer layer/surface |
| 4 | - |
| 5 | - |
| 6 | Two clear marks corresponding to the glue on the back |
| 7 | In all probability luminous areas corresponding to the glue |
| 8 | Luminous middle corresponding to the glue on the back |

-: Means that no optical brightener was visible.

# 6 Toxicological profile for 1,1'-(1-butenyliden)bis-benzene

## 6.1 Chemical identity

| | | |
|---|---|---|
| 6.1.1 | Name: | 1,1'-(1-Butenyliden)bis-benzene |
| 6.1.2 | CAS no: | 1726-14-3 |
| 6.1.3 | Molecular weight: | 208.3 |
| 6.1.4 | Molecular formula: | $C_{16}H_{16}$ |
| 6.1.5 | Structure formula: |  |



## 6.2 Regulation

| | | | |
|---|---|---|---|
| 6.2.1 | EU classification: | Not classified | (1) |
| 6.2.2 | Limit in foods: | Not allowed in food. | (2) |
| 6.2.3 | Limit in food contact materials: | Not on the provisional lists of monomers and additives notified to European Commission as substances, which may be used in the manufacture of plastics intended to come into contact with foodstuffs. | (3) |
| 6.2.4 | Limit in cosmetics: | No limitations. | (4) |

## 6.3 Physico-chemical properties

| | | | |
|---|---|---|---|
| 6.3.1 | Melting point: | 40.6 (calculated). | (5) |
| 6.3.2 | Boiling point: | 314.9 (calculated). | (5) |
| 6.3.3 | Vapour pressure: | 0,000637 (calculated). | (5) |
| 6.3.4 | Water solubility: | No data | |
| 6.3.5 | Lipid solubility: | No data | |
| 6.3.6 | Partition coefficient (log $P_{ow}$): | 4.76 (calculated). | (5) |

## 6.4 Toxicological properties

### 6.4.1 Toxicokinetic properties

#### *6.4.1.1 Uptake through skin or mucosae*

Log Kp is a measure for skin permeability. Using Potts & Guy model, the Log Kp for 1,1'-(1-butenyliden)bis-benzene can be calculated to be –0.61 cm/h. Substances with a log Kp value between –5 and 2 are categorised as having medium skin permeability. (6)

#### *6.4.1.2 Biotransformation*

No data

### 6.4.2 Acute toxicity

#### *6.4.2.1 Oral exposure*

No data

#### *6.4.2.2 Skin exposure*

No data

#### *6.4.2.3 Irritation*

No data

### 6.4.3 Subchronic/chronic toxicity

#### *6.4.3.1 Skin sensitisation*

No data

#### *6.4.3.2 Mutagenic effects*

No data

#### *6.4.3.3 Reproduction toxicity*

No data

#### *6.4.3.4 Carcinogenicity*

No data

#### *6.4.3.5 Organ toxicity*

No data

## 6.5 Conclusion

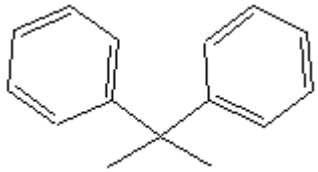
No data was available for a toxicological evaluation of 1,1'-(1-Butenyliden)bis-benzene.
The Danish EPA (Miljøstyrelsen) has informed that no QSAR data on 1,1'-(1-butenyliden)benzene are available in the Chem-X database.

## 6.6 Literature


1. Miljø- og Energiministeriets bekendtgørelse nr. 733 af 31. juli 2000 (Bekendtgørelse om listen over farlige stoffer).
2. Positivlisten: fortegnelse over tilsætningsstoffer til fødevarer. Søborg: Ministeriet for Fødevarer, Landbrug og Fiskeri, Fødevaredirektoratet; 2000.
3. European Commission. Provisional lists of monomers and additives notified to European Commission as substances, which may be used in the manufacture of plastics intended to come into contact with foodstuffs. 2001. (http://cpf.jrc.it/webpack/downloads/synoptic_internet_0401.pdf).
4. Miljø- og Energiministeriets bek. nr. 594 af 6. juni 2000 (Bekendtgørelse om kosmetiske produkter).
5. EPISuite [computer program]. v. 3.10. U.S. Environmental Protection Agency; 2001.
6. Potts RO, Guy RH. Predicting skin permeability. Pharm Res 1992;9(5):663-9.

# 7 Toxicological profile for 1,1'-(1-methylethylidene)benzene

## 7.1 Chemical identity

| | | |
|---|---|---|
| 7.1.1 | Name: | 1,1'-(1-Methylethylidene)benzene |
| 7.1.2 | CAS no: | 778-22-3 |
| 7.1.3 | Molecular weight: | 196,2914 |
| 7.1.4 | Molecular formula: | $C_{15}H_{16}$ |
| 7.1.5 | Structure formula: |  |

## 7.2 Regulation

| | | | |
|---|---|---|---|
| 7.2.1 | EU classification: | Not classified. | (1) |
| 7.2.2 | Limit in foods: | Not allowed in food. | (2) |
| 7.2.3 | Limit in food contact materials: | Not on the provisional lists of monomers and additives notified to European Commission as substances which may be used in the manufacture of plastics intended to come into contact with foodstuffs. | (3) |
| 7.2.4 | Limit in cosmetics: | No limitations. | (4) |

## 7.3 Physico-chemical properties

| | | | |
|---|---|---|---|
| 7.3.1 | Melting point: | 29 °C. | (5) |
| 7.3.2 | Boiling point: | 281 °C. | (5) |
| 7.3.3 | Vapour pressure: | 0,0045 mmHg at 25 °C (calculated). | (6) |
| 7.3.4 | Water solubility: | 5,4 mg/l (calculated). | (6) |
| 7.3.5 | Lipid solubility: | No data found. | |
| 7.3.6 | Partition coefficient (log $P_{ow}$): | 4,6 (calculated). | (6) |

## 7.4 Toxicological properties

### 7.4.1 Toxicokinetic properties

#### *7.4.1.1 Uptake through skin or mucosae*

No data found

#### *7.4.1.2 Biotransformation*

No data found

### 7.4.2 Acute toxicity

No data found

#### *7.4.2.1 Oral exposure*

No data found

#### *7.4.2.2 Skin exposure*

No data found

#### *7.4.2.3 Irritation*

No data found

### 7.4.3 Subchronic/chronic toxicity

#### *7.4.3.1 Skin sensitisation*

No data found

#### *7.4.3.2 Mutagenic effects*

No data found

#### *7.4.3.3 Reproduction toxicity*

No data found

#### *7.4.3.4 Carcinogenicity*

No data found

#### *7.4.3.5 Organ toxicity*

No data found

## 7.5 Conclusion

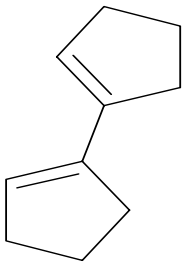
No data was available for a toxicological evaluation of 1,1'-(1-methylethylidene)benzene.
The Danish EPA (Miljøstyrelsen) has informed that no QSAR data on 1,1'-(1-methylethylidene)benzene are available in the Chem-X database.

## 7.6 Literature


1. Miljø- og Energiministeriets bekendtgørelse nr. 733 af 31. juli 2000 (Bekendtgørelse om listen over farlige stoffer).
2. Positivlisten : fortegnelse over tilsætningsstoffer til fødevarer. Søborg: Ministeriet for Fødevarer, Landbrug og Fiskeri, Fødevaredirektoratet; 2000.
3. European Commission. Provisional lists of monomers and additives notified to European Commission as substances, which may be used in the manufacture of plastics intended to come into contact with foodstuffs. 2001. (http://cpf.jrc.it/webpack/downloads/synoptic_internet_0401.pdf).
4. Miljø- og Energiministeriets bekendtgørelse nr. 594 af 6. juni 2000 (Bekendtgørelse om kosmetiske produkter).
5. Chemfinder. 2001. (http://chemfinder.cambridgesoft.com).
6. EPISuite [computer program]. v. 3.10. U.S. Environmental Protection Agency; 2001.

# 8 Toxicological profile for bicyclopentyl-1,1'-diene

## 8.1 Chemical identity

| | | | |
|---|---|---|---|
| 8.1.1 | Name: | Bicyclopentyl-1,1'-diene | |
| 8.1.2 | CAS no: | 934-02-1 | |
| 8.1.3 | Molecular weight: | 134.122 | |
| 8.1.4 | Molecular formula: | $C_{10}H_{14}$ | |
| 8.1.5 | Structure formula: |  | |

## 8.2 Regulation

| | | | |
|---|---|---|---|
| 8.2.1 | EU classification: | Not classified. | (1) |
| 8.2.2 | Limit in foods: | Not allowed in food. | (2) |
| 8.2.3 | Limit in food contact materials: | Not on the provisional lists of monomers and additives notified to European Commission as substances which may be used in the manufacture of plastics intended to come into contact with foodstuffs. | (3) |
| 8.2.4 | Limit in cosmetics: | No limitations. | |

## 8.3 Physico-chemical properties

| | | | |
|---|---|---|---|
| 8.3.1 | Melting point: | -7.33 °C (calculated) | (4) |
| 8.3.2 | Boiling point: | 193.30 °C (calculated) | (4) |
| 8.3.3 | Vapour pressure: | 0.711 mmHg, 25 °C (calculated) | (4) |
| 8.3.4 | Water solubility: | 2.44 mg/L, 25 °C (calculated) | (4) |
| 8.3.5 | Lipid solubility: | No data found. | |
| 8.3.6 | Partition coefficient (log $P_{ow}$): | 4.71 (calculated) | (4) |

## 8.4 Toxicological properties

### 8.4.1 Toxicokinetic properties

#### *8.4.1.1 Uptake through skin or mucosae*

No data found.

#### *8.4.1.2 Biotransformation*

No data found.

### 8.4.2 Acute toxicity

No data found.

#### *8.4.2.1 Oral exposure*

No data found.

#### *8.4.2.2 Skin exposure*

No data found.

#### *8.4.2.3 Irritation*

No data found.

### 8.4.3 Subchronic/chronic toxicity

#### *8.4.3.1 Skin sensitisation*

No data found.

#### *8.4.3.2 Mutagenic effects*

No data found.

#### *8.4.3.3 Reproduction toxicity*

No data found.

#### *8.4.3.4 Carcinogenicity*

No data found.

#### *8.4.3.5 Organ toxicity*

No data found.

## 8.5 Conclusion

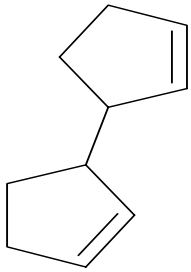
No data was available for a toxicological evaluation of bicyclopentyl-1,1'-diene.
The Danish EPA (Miljøstyrelsen) has informed that no QSAR data on bicylopentyl-1,1'-diene are available in the Chem-X database.

## 8.6 Literature


1. Miljø- og Energiministeriets bekendtgørelse nr. 733 af 31. juli 2000 (Bekendtgørelse om listen over farlige stoffer).
2. Positivlisten: Fortegnelse over tilsætningsstoffer til fødevarer. Søborg: Ministeriet for Fødevarer, Landbrug og Fiskeri, Fødevaredirektoratet; 2000.
7. European Commission. Provisional lists of monomers and additives notified to European Commission as substances, which may be used in the manufacture of plastics intended to come into contact with foodstuffs. 2001. (http://cpf.jrc.it/webpack/downloads/synoptic_internet_0401.pdf).
3. EPISuite [computer program]. v. 3.10. U.S. Environmental Protection Agency; 2001.

# 9 Toxicological profile for bicyclopentyl-2,2'-diene

## 9.1 Chemical identity

| | | | |
|---|---|---|---|
| 9.1.1 | Name: | Bicyclopentyl-2,2'-diene | |
| 9.1.2 | CAS no: | 2690-18-8 | |
| 9.1.3 | Molecular weight: | 134.122 | |
| 9.1.4 | Molecular formula: | $C_{10}H_{14}$ | |
| 9.1.5 | Structure formula: |  | |

## 9.2 Regulation

| | | | |
|---|---|---|---|
| 9.2.1 | EU classification: | Not classified. | (1) |
| 9.2.2 | Limit in foods: | Not allowed in food. | (2) |
| 9.2.3 | Limit in food contact materials: | Not on the provisional lists of monomers and additives notified to European Commission as substances which may be used in the manufacture of plastics intended to come into contact with foodstuffs. | (3) |
| 9.2.4 | Limit in cosmetics: | No limitations. | (4) |

## 9.3 Physico-chemical properties

| | | | |
|---|---|---|---|
| 9.3.1 | Melting point: | -26.52 °C (calculated) | (5) |
| 9.3.2 | Boiling point: | 184.98 °C (calculated) | (5) |
| 9.3.3 | Vapour pressure: | 1.05 mmHg, 25 °C (calculated) | (5) |
| 9.3.4 | Water solubility: | 4.063 mg/L, 25 °C (calculated) | (5) |
| 9.3.5 | Lipid solubility: | No data found. | |
| 9.3.6 | Partition coefficient (log $P_{ow}$): | 4.45 (calculated) | (5) |

## 9.4 Toxicological properties

### 9.4.1 Toxicokinetic properties

#### *9.4.1.1 Uptake through skin or mucosae*

No data found.

#### *9.4.1.2 Biotransformation*

No data found.

### 9.4.2 Acute toxicity

#### *9.4.2.1 Oral exposure*

No data found.

#### *9.4.2.2 Skin exposure*

No data found.

#### *9.4.2.3 Irritation*

No data found.

### 9.4.3 Subchronic/chronic toxicity

#### *9.4.3.1 Skin sensitisation*

No data found.

#### *9.4.3.2 Mutagenic effects*

No data found.

#### *9.4.3.3 Reproduction toxicity*

No data found.

#### *9.4.3.4 Carcinogenicity*

No data found.

#### *9.4.3.5 Organ toxicity*

No data found.

## 9.5 Conclusion

No data was available for a toxicological evaluation of bicyclopentyl-2,2'-diene.
The Danish EPA (Miljøstyrelsen) has informed that no QSAR data on bicylopentyl-2,2'-diene are available in the Chem-X database.

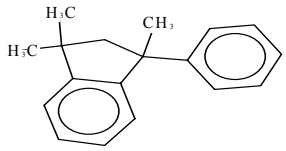
## 9.6 Literature


1. Miljø- og Energiministeriets bekendtgørelse nr. 733 af 31. juli 2000 (Bekendtgørelse om listen over farlige stoffer).
2. Positivlisten: Fortegnelse over tilsætningsstoffer til fødevarer. Søborg: Ministeriet for Fødevarer, Landbrug og Fiskeri, Fødevaredirektoratet; 2000.
3. European Commission. Provisional lists of monomers and additives notified to European Commission as substances, which may be used in the manufacture of plastics intended to come into contact with foodstuffs. 2001. (http://cpf.jrc.it/webpack/downloads/synoptic_internet_0401.pdf).
4. Miljø- og Energiministeriets bek. nr. 594 af 6. juni 2000 (Bekendtgørelse om kosmetiske produkter).
5. EPISuite [computer program]. v. 3.10. U.S. Environmental Protection Agency; 2001.

# 10 Toxicological profile for 2,3-dihydro-1,1,3-trimethyl-3-phenyl-1H-indene

## 10.1 Chemical identity

| | | | |
|---|---|---|---|
| 10.1.1 | Name: | 2,3-Dihydro-1,1,3-trimethyl-3-phenyl-1H-indene | |
| 10.1.2 | CAS no: | 3910-35-8 | |
| 10.1.3 | Molecular weight: | 236.178 | |
| 10.1.4 | Molecular formula: | $C_{18}H_{20}$ | |
| 10.1.5 | Structure formula: | | |




## 10.2 Regulation

| | | | |
|---|---|---|---|
| 10.2.1 | EU classification: | Not classified. | (1) |
| 10.2.2 | Limit in foods: | Not allowed in food. | (2) |
| 10.2.3 | Limit in food contact materials: | Not on the provisional lists of monomers and additives notified to European Commission as substances that may be used in the manufacture of plastics intended to come into contact with foodstuffs. | (3) |
| 10.2.4 | Limit in cosmetics: | No limitations. | (4) |

## 10.3 Physico-chemical properties

| | | | |
|---|---|---|---|
| 10.3.1 | Melting point: | 99.69 °C (calculated) | (5) |
| 10.3.2 | Boiling point: | 325.45 °C (calculated) | (5) |
| 10.3.3 | Vapour pressure: | 0.000693 mmHg, 25 °C (calculated) | (5) |
| 10.3.4 | Water solubility: | 0.2525 mg/L (calculated) | (5) |
| 10.3.5 | Lipid solubility: | No data found. | |
| 10.3.6 | Partition coefficient (log $P_{ow}$): | 5.91 (calculated) | (5) |

## 10.4 Toxicological properties

Trimethyl-3-phenylindan is identified as a compound in the organic acid fractions in emission extracts from diesel vehicles. The analysis was done with GC/MS. The compound was also identified as a constituent of fried chicken flavour analysed with GC/MS, and as a volatile pollutant from rubber manufacturing. (6) (7) (8)

### 10.4.1 Toxicokinetic properties

#### *10.4.1.1 Uptake through skin or mucosae*

No data found.

#### *10.4.1.2 Biotransformation*

No data found.

### 10.4.2 Acute toxicity

#### *10.4.2.1 Oral exposure*

No data found.

#### *10.4.2.2 Skin exposure*

No data found.

#### *10.4.2.3 Irritation*

No data found.

### 10.4.3 Subchronic/chronic toxicity

#### *10.4.3.1 Skin sensitisation*

No data found.

#### *10.4.3.2 Mutagenic effects*

No data found.

#### *10.4.3.3 Reproduction toxicity*

No data found.

#### *10.4.3.4 Carcinogenicity*

No data found.

#### *10.4.3.5 Organ toxicity*

No data found.

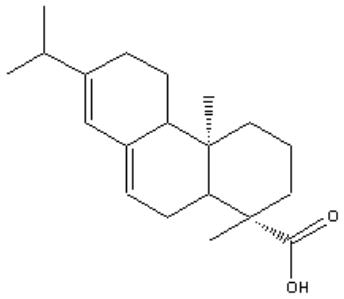
## 10.5 Conclusion

No data was available for a toxicological evaluation of 2,3-dihydro-1,1,3-trimethyl-3-phenyl-1H-indene. The Danish EPA (Miljøstyrelsen) has informed that no QSAR data on this compound is available in the Chem-X database.

## 10.6 Literature


1. Miljø- og Energiministeriets bekendtgørelse nr. 733 af 31. juli 2000 (Bekendtgørelse om listen over farlige stoffer).
2. Positivlisten: Fortegnelse over tilsætningsstoffer til fødevarer. Søborg: Ministeriet for Fødevarer, Landbrug og Fiskeri, Fødevaredirektoratet; 2000.
3. European Commission. Provisional lists of monomers and additives notified to European Commission as substances, which may be used in the manufacture of plastics intended to come into contact with foodstuffs. 2001. (http://cpf.jrc.it/webpack/downloads/synoptic_internet_0401.pdf).
4. Miljø- og Energiministeriets bekendtgørelse nr. 594 af 6. juni 2000 (Bekendtgørelse om kosmetiske produkter).
5. EPISuite [computer program]. v. 3.10. U.S. Environmental Protection Agency; 2001.
6. Williams R, Sparacino C, Petersen B, Bumgarner J, Jungers RH, Lewtas J. Comparative characterization of organic emissions from diesel particles, coke oven mains, roofing tar vapors and cigarette smoke condensate. International Journal of Environmental Analytical Chemistry 1986;26(1):27-49.
7. Tang J, Jin QZ, Shen G-H, Ho C-T, Chang SS. Isolation and identification of volatile compounds from fried chicken. Journal of Agriculture and Food Chemistry 1983;31(6):1287-92.
8. Cocheo V, Bellomo ML, Bombi GG. Rubber manufacture : sampling and identification of volatile pollutants. Am Ind Hyg Assoc J 1983;44(7):521-7.

# 11 Toxicological profile for abietic




# acid

## 11.1 Chemical identity

| | | |
|---|---|---|
| 11.1.1 | Name: | Abietic acid |
| 11.1.2 | CAS no: | 514-10-3 |
| 11.1.3 | Molecular weight: | 302.46 |
| 11.1.4 | Molecular formula: | $C_{20}H_{30}O_2$ |
| 11.1.5 | Structure formula: | |

## 11.2 Regulation

| | | | |
|---|---|---|---|
| 11.2.1 | EU classification: | Not classified | (1) |
| 11.2.2 | Limit in foods: | Not allowed in food. | (2) |
| 11.2.3 | Limit in food contact materials: | Group TDI: 1 mg/kg bw based on 90-day and 2-year oral rat studies discussed in SCF, 17th report, 1986. This report has not been available during preparation of this document. | (3) |
| 11.2.4 | Limit in cosmetics: | Permitted with no restrictions. | (4) |

## 11.3 Physico-chemical properties

| | | | |
|---|---|---|---|
| 11.3.1 | Melting point: | 173 °C | (5) |
| 11.3.2 | Boiling point: | 250 °C | (5) |

| | | | |
|---|---|---|---|
| 11.3.3 | Vapour pressure: | Approx. 3 x 10-7 mmHg at 25 °C (calculated) | (6) |
| 11.3.4 | Water solubility: | Approx. 0.09 mg/l (calculated) | (6) |
| 11.3.5 | Lipid solubility: | Soluble in chloroform | (5) |
| 11.3.6 | Partition coefficient (log $P_{ow}$): | 6.46 (calculated) | (6) |

## 11.4 Toxicological properties

### 11.4.1 Toxicokinetic properties

#### *11.4.1.1 Uptake through skin or mucosae*

Log Kp is a measure for skin permeability. Using Potts & Guy model the Log Kp for abietic acid can be calculated to be 1.05 cm/h. Substances with a log Kp value between –5 and 2 are categorised as having medium skin permeability. (7)

#### *11.4.1.2 Biotransformation*

No data

### 11.4.2 Acute toxicity

#### *11.4.2.1 Oral exposure*

No data. Presumably low acute oral toxicity, since the intravenous toxicity in mice is low (LD50 ivn. in mouse = 180 mg/kg). (8)

#### *11.4.2.2 Skin exposure*

No data. Presumably low acute toxicity when applied on skin, since the intravenous toxicity in mice is low (LD50 ivn. in mouse = 180 mg/kg). (8)

#### *11.4.2.3 Irritation*

No data

### 11.4.3 Subchronic/chronic toxicity

#### *11.4.3.1 Skin sensitisation*

Contact dermatitis may occur upon exposure to abietic acid. (9)

Abietic acid is the principal sensitiser in rosin (colophony). During a 6-month period 15 patients allergic to colophony were found. Of these 15 persons, 6 were also allergic to abietic acid. (10)

The main allergen of colophony appears to be oxidation products of abietic acid. Pure abietic acid itself is not allergenic though some authors consider it to be a major allergen in unmodified colophony. Contact sensitisation of abietic acid occurs but is uncommon. (11)

Oxidation products of abietic acid are the allergenic substances. (12)

#### *11.4.3.2 Mutagenic effects*

No data

#### *11.4.3.3 Reproduction toxicity*

No data

#### *11.4.3.4 Carcinogenicity*

No data

#### *11.4.3.5 Organ toxicity*

No data

## 11.5 Conclusion

From the limited data on this compound, the critical effect is estimated to be the sensitising potential of abietic acid. Using female hygiene products elicitates a risk of dermatitis in sensitive individuals, especially since penetration is enhanced by occlusion and irritation.
The tolerable daily intake (TDI) according to food contact materials is 1 mg/kg bw

## 11.6 Literature


1. Miljø- og Energiministeriets bekendtgørelse nr. 733 af 31. juli 2000 (Bekendtgørelse om listen over farlige stoffer). 2000;
2. 2.Positivlisten: fortegnelse over tilsætningsstoffer til fødevarer. Søborg: Ministeriet for Fødevarer, Landbrug og Fiskeri, Fødevaredirektoratet; 2000.
3. European Commission. Provisional lists of monomers and additives notified to European Commission as substances, which may be used in the manufacture of plastics intended to come into contact with foodstuffs. 2001. (http://cpf.jrc.it/webpack/downloads/synoptic_internet_0401.pdf).
4. Miljø- og Energiministeriets bek. nr. 594 af 6. juni 2000 (Bekendtgørelse om kosmetiske produkter). 2000.
5. NTP Web site. 2001. (http://ntp-server.niehs.nih.gov/cgi/iH_Indexes/ALL_SRCH_ALL_SRCH_Frames.html).
6. EPISuite [computer program]. v. 3.10. U.S. Environmental Protection Agency; 2001.
7. Potts RO, Guy RH. Predicting skin permeability. Pharm Res 1992;9(5):663-9.
8. Gosselin RE, Smith RP, Hodge HC. Clinical toxicology of commercial products. 5 ed. Baltimore.: Williams & Wilkins; 1984.
9. Klaassen CD, Amdur MO, Doull J, editors. Casarett and Doull's toxicology: the basic science of poisons. 5 ed. New York, N.Y.: McGraw-Hill: 1996.
10. Rietschel RL, Fowler jr JF, editors. Fisher's contact dermatitis. 5 ed. Philadelphia: Lippincott, Williams & Wilkins; 2001
11. de Groot AC, Weyland JW, Nater JP. Unwanted effects of cosmetics and drugs used in dermatology. 3 ed. Amsterdam: Elsevier; 1994.
12. Karlberg, A.T. Yrkesbetingad colophonyallergi: identificering av kontaktallergena ämnen i omodifierat harts. Solna: Arbetsmiljöinstitutet. Arbete och hälsa; 1990:8.

# 12 Toxicological profile for colophony

## 12.1 Chemical identity

| | | |
|---|---|---|
| 12.1.1 | Name: | Colophony |
| 12.1.2 | CAS no: | 8050-09-7 |
| 12.1.3 | Molecular weight: | - |
| 12.1.4 | Molecular formula: | - |
| 12.1.5 | Structure formula: | - |

## 12.2 Regulation

| | | | |
|---|---|---|---|
| 12.2.1 | EU classification: | R43 | (1) |
| 12.2.2 | Limit in foods: | Not allowed in food. | (2) |
| 12.2.3 | Limit in food contact materials: | Group TDI (including Rosin and Rosin gum): 1 mg/kg bw | (3) |
| 12.2.4 | Limit in cosmetics: | Permitted with no restrictions. | (4) |

## 12.3 Physico-chemical properties

| | | | |
|---|---|---|---|
| 12.3.1 | Melting point: | 100-140 °C | (5) |
| 12.3.2 | Boiling point: | 250 °C | (5) |
| 12.3.3 | Vapour pressure: | No data | |
| 12.3.4 | Water solubility: | Not soluble | (5) |
| 12.3.5 | Lipid solubility: | Soluble in chloroform | (6) |
| 12.3.6 | Partition coefficient (log $P_{ow}$): | No data | |

## 12.4 Toxicological properties

### 12.4.1 Toxicokinetic properties

#### *12.4.1.1 Uptake through skin or mucosae*

Log Kp is a measure for skin permeability. Log Kp cannot be calculated for a mixture of substances like colophony, but using abietic acid as an example the Log Kp can be calculated to be 1.05 cm/h. Substances with a log Kp value between –5 and 2 are categorised as having medium skin permeability. (7)

#### *12.4.1.2 Biotransformation*

No data

### 12.4.2 Acute toxicity

#### *12.4.2.1 Oral exposure*

Oral LD50 in rats: 7.6-8.4 g/kg bw. (8)

#### *12.4.2.2 Skin exposure*

No data

#### *12.4.2.3 Irritation*

Adhesive tapes based on colophony frequently caused irritant plaster reactions. (9)

At body temperature rosin is rather inert, but hot rosin has produced mechanical injury to the eyelids and possibly also of the eyeglobe. Early injury was opaque cornea, with vision reduced to finger counting at 1 meter. The eyes healed gradually and after one month the vision returned to normal despite some residual corneal opacities. (10)

A plant material known as Gummi Guttae (from nineteenth century reports on experiments on rabbits), which may or may not correspond to colophony, is injurious to the eye.

### 12.4.3 Subchronic/chronic toxicity

#### *12.4.3.1 Skin sensitisation*

The main component of colophony is abietic acid, which is the principal sensitiser in rosin (colophony). During a 6-month period 15 patients allergic to colophony were admitted. Of these 15 persons, 6 were also allergic to abietic acid. (11)

Colophony is occasionally present in cosmetics and has caused dermatitis in mascara, eye shadow and rouge. (9)

Colophony is among the ten most usual causes of positive patch tests. Oxidation products of the resin acids were found to be the principal allergenic substance, and the allergenic activity was diminished by chemical reduction. (12)

Colophony may cross-react with perfume and other odoriferous substances. Colophony has been reported to cause allergy, e.g. in lipsticks, lottery tickets and paper money, and is a reported allergen in stomal dermatitis. (11)

Contact sensitisation is common. (13)

#### *12.4.3.2 Mutagenic effects*

Colophony was not mutagenic in Salmonella typhimurium strains TA 98 and TA100 with and without metabolic activation. Neither did it raise chromosome damage in CHO cells in vitro (chromosomal breaks and sister chromatid exchange (SCE)). (14)

#### *12.4.3.3 Reproduction toxicity*

No data

#### *12.4.3.4 Carcinogenicity*

No data

#### *12.4.3.5 Organ toxicity*

Groups of 10 male and 10 female rats were fed dietary levels of gum rosin (0.01, 0.05, 0.2, 1.0 and 5.0 %) for 90 days. Two similar groups received the stock diet only. No effects were seen upon growth, food intake, haematology, urinalysis, gross and microscopic histology at levels through 0.2 %. At the 5 % feeding level all animals died. At 1 % the animals showed an (8)

initial lag in weight gain and food consumption during the first two weeks. On autopsy increased liver size was observed. No microscopic pathology being seen however.

Groups of 30 male and 30 female rats were fed dietary levels of gum rosin (0.05, 0.2 and 1.0 %) for two years. Two similar control groups received the stock diet only. At the 0.05 % and 0.2 % feeding levels no effects were seen upon weight gain, food consumption, mortality, haematology and gross and microscopic pathology. At the 1 % dietary level some growth depression was noted. On autopsy increased liver size was observed. No microscopic pathology being seen however. (8)

## 12.5 Conclusion

From the limited data on colophony, the critical effect is estimated to be the sensitising potential of the compound. Using female hygiene products containing colophony elicitates a risk of dermatitis in sensitive individuals, especially since penetration is enhanced by occlusion and irritation.
The tolerable daily intake (TDI) according to food contact materials is 1 mg/kg bw.
In the studies described in section 12.4.3.5, 0.2 % dietary level of gum rosin could be assigned as a NOEL for rats and 1.0 as a LOEL. Assuming a food consumption of 20 g/day and a body weight of 200 g/rat these dietary levels equals doses of 200 and 1000 mg/kg bw/day. Using a safety factor of 10 for extrapolating from animals to humans and another 10 to protect the sensitive part of the population, the NOEL for humans would be 2 mg/kg bw/day and the LOEL 10 mg/kg bw/day.

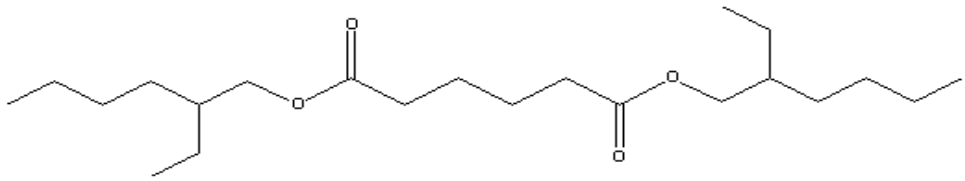
## 12.6 Literature


1. Miljø- og Energiministeriets bekendtgørelse nr. 733 af 31. juli 2000 (Bekendtgørelse om listen over farlige stoffer).
2. Positivlisten: fortegnelse over tilsætningsstoffer til fødevarer. Søborg: Ministeriet for Fødevarer, Landbrug og Fiskeri, Fødevaredirektoratet; 2000.
3. European Commission. Provisional lists of monomers and additives notified to European Commission as substances, which may be used in the manufacture of plastics intended to come into contact with foodstuffs. 2001. (http://cpf.jrc.it/webpack/downloads/synoptic_internet_0401.pdf).
4. Miljø- og Energiministeriets bek. nr. 594 af 6. juni 2000 (Bekendtgørelse om kosmetiske produkter).
5. Chemfinder 2001. (http://chemfinder.cambrigdesoft.com).
6. Documentation of the threshold limit values and biological exposure indices. Vol.3. 6 ed. Cincinnat: American Conference of Governmental Industrial Hygienists (ACGIH); 1991.
7. Potts RO, Guy RH. Predicting skin permeability. Pharm Res 1992;9(5):663-9.
8. IPCS INCHEM 2001. (http://www.inchem.org/search.html). Cronin E. Contact dermatitis. Edinburgh: Churchill Livingstone; 1980.
9. Grant WM, Schuman JS. Toxicology of the eye: effects on the eyes and visual system from chemicals, drugs, metals and minerals, plants, toxins and venoms; also systemic side effects from eye medications. 4 ed. Springfield; Thomas: 1993.
10. Rietschel RL, Fowler jr JF, editors. Fisher's contact dermatitis. 5 ed. Philadelphia.: Lippincott, Williams & Wilkins: 2001
11. Karlberg, A.T. Yrkesbetingad colophonyallergi: identificering av kontaktallergena ämnen i omodifierat harts. Solna: Arbetsmiljöinstitutet. Arbete och hälsa; 1990:8.
12. de Groot AC, Weyland JW, Nater JP. Unwanted effects of cosmetics and drugs used in dermatology. 3 ed. Amsterdam: Elsevier; 1994.
13. Athanasiou K, Lillis D. Absence of mutagenic and clastogenic action of pine-tar resin in the Salmonella/microsomal and CHO culture systems. Mutat Res 1982;103(3-6):229-32.

# 13 Toxicological profile for diethylhexyladipate

## 13.1 Chemical identity

| | | |
|---|---|---|
| 13.1.1 | Name: | Diethylhexyladipate |
| 13.1.2 | CAS no: | 103-23-1 |
| 13.1.3 | Molecular weight: | 370.57 |
| 13.1.4 | Molecular formula: | $C_{22}H_{42}O_4$ |
| 13.1.5 | Structure formula: | |



## 13.2 Regulation

| | | | |
|---|---|---|---|
| 13.2.1 | EU classification: | Not classified | (1) |
| 13.2.2 | Limit in foods: | Not allowed in food. | (2) |
| 13.2.3 | Limit in food contact materials: | No restrictions on the provisional lists of monomers and additives notified to European Commission as substances that may be used in the manufacture of plastics intended to come into contact with foodstuffs. SCF opinion: Statement on a new intake study. No opinion found. | (3) |
| 13.2.4 | Limit in cosmetics: | Permitted with no restrictions. | (4) |

## 13.3 Physico-chemical properties

| | | | |
|---|---|---|---|
| 13.3.1 | Melting point: | -67.8 °C | (5) |
| 13.3.2 | Boiling point: | 214 °C | (5) |
| 13.3.3 | Vapour pressure: | 8.5 x 10-7 mmHg at 20 °C | (5) |
| 13.3.4 | Water solubility: | 0.78 mg/l at 22 °C | (5) |
| 13.3.5 | Lipid solubility: | Soluble in most organic solvents | (5) |
| 13.3.6 | Partition coefficient (log $P_{ow}$): | 8.1 | (6) |

## 13.4 Toxicological properties

### 13.4.1 Toxicokinetic properties

#### *13.4.1.1 Uptake through skin or mucosae*

Log Kp is a measure for skin permeability. Using Potts & Guy model, the Log Kp for diethylhexyladipate (DEHA) can be calculated to be 0.77 cm/h. Substances with a log Kp value between –5 and 2 are categorised as having medium skin permeability. (7)

#### *13.4.1.2 Biotransformation*

In six male volunteers administered 46 mg deuterium labelled DEHA (approx. 0.5 mg/kg bw) in corn oil, 2-ethylhexanoic acid was the only metabolite that could be determined in the plasma. It had an elimination half-life of 1.65 h. In urine, the following metabolites were identified 2-ethylhexanoic acid (8.6 %), 2-ethyl-5-hydroxyhexanoic acid (2.6 %), 2-ethyl-1,6-hexanedioic acid (0.7 %), 2-ethyl-5-ketohexanoic acid (0.2 %) and 2-ethylhexanol (0.1 %). The half-life for elimination of all metabolites excreted in the urine averaged 1.5 h, and none of the metabolites could be detected after 36 hours. (8)

The absorption, distribution, and elimination of diethylhexyladipate were studied in mice and rats. Rats, male mice, and pregnant female mice on day 17 of gestation were administered $^{14}C$ labelled DEHA dissolved in dimethyl sulfoxide or corn oil iv or intragastrically. The DEHA was labelled on the carbonyl carbon or on the 1-hexyl carbon. The animals were killed at intervals from 5 min to 4 days after dosing, and the tissue distribution of $^{14}C$ activity was determined by whole body autoradiography. The tissue distribution of $^{14}C$ activity from carbonyl labelled DEHA was similar in all animals. Highest levels of radioactivity were observed in the body fat, liver, and kidney. $^{14}C$ activity from 1-hexyl labelled DEHA was observed in the bronchi of male mice. In pregnant mice, $^{14}C$ activity was observed in the fetal liver, intestine, and bone marrow during the first 24 hr after carbonyl labeled DEHA was given. Very little activity was found in the fetuses of mice given DEHA that were 1 hexyl labelled. No DEHA derived radioactivity was found in mice 4 days after dosing. Blood DEHA concentration in rats increased faster and was two or three times higher when the dose was given intragastrically in DMSO rather than corn oil. (5)

### 13.4.2 Acute toxicity

#### *13.4.2.1 Oral exposure*

In rats, LD50 is reported to be 9 to 45 g/kg bw (route of exposure not mentioned). Poisoning is accompanied by excitation with subsequent general inhibition, apathy, and motor coordination disorder. Hours before death, the animals were comatose. In survivors, signs of intoxication have completely disappeared in 5 to 7 days. No deaths occurred when rats were dosed with 2.5 g/kg bw. (9)

No acute effects were observed some hours after oral (5)

administration of diethylhexyladipate (13 g/kg bw) to guinea pigs. However, during the succeeding days (3-21 days) half of the animals died.

#### *13.4.2.2 Skin exposure*

After dermal application, the LD50 value for rabbit was between 8.41 and 15.1 g/kg bw. (10)

#### *13.4.2.3 Irritation*

An eye and skin irritant. (11)

Diethylhexyladipate does not irritate or irritates only slightly the skin and mucosa. (10)

Diethylhexyladipate rated 1 on rabbit eyes, on a scale from 1 to 10 (most severe injuries was rated 10) according to degree of injury observed after 24 hr, paying particular attention to condition of cornea. (12)

Skin-rabbit: 500 mg open Mild (13)

### 13.4.3 Subchronic/chronic toxicity

#### *13.4.3.1 Skin sensitisation*

Diethylhexyladipate showed no sensitizing potential (10)

#### *13.4.3.2 Mutagenic effects*

Diethylhexyladipate was not mutagenic in Salmonella typhimurium TA 1535, TA 1537, TA 1538, TA 98, and TA 100, with and without metabolic activation, or in Saccharomyces cerevisiae. (5)

#### *13.4.3.3 Reproduction toxicity*

Rats were given diethylhexyladipate in the diet from 10 weeks pre-mating up to 36 days postpartum. The treatment with 12 g/kg diet resulted in reduction of total litter weights, body weight gain of the pups, and mean litter size. Histologic examination failed to reveal changes in the pubs. (9)

A single ip administration of 0.5 to 10.0 ml/kg bw in mice produced antifertility and mutagenic effect, as indicated by reduced frequency of pregnancies and increased numbers of early fetal deaths. Reduction in the number of implantations was also noted. However, these findings were questioned since the study lacked data on the number of pregnancies per treated male and the number of corpora lutea per female.

A study in rats showed a dose dependent increase in minor skeletal defects (slightly poorer ossification) in addition to an increased incidence of ureter abnormalities. The NOEL was found to be 28 mg/kg bw. An ADI of 0.3 mg/kg bw was calculated for this NOEL.

#### *13.4.3.4 Carcinogenicity*

A carcinogenesis bioassay was conducted by feeding diets containing 12,000 or 25,000 ppm of diethylhexyladipate to groups of 50 male and 50 female F344 rats and 50 male and 50 female B6C3F1 mice for 103 weeks. Groups of 50 undosed rats and mice of each sex served as controls. All surviving animals were killed at 104 to 107 weeks. Mean body weights of high-dose rats and mice of either sex were lower than those of the controls throughout the study. Compound administration was not associated with tumour formation in F344 rats of either sex. Hepatocellular carcinomas or adenomas occurred in mice of both sexes in a dose-related way at incidences that were (13)

significantly higher for high-dose males and for low- and high-dose females compared to the controls. When compared with the incidence in historical laboratory control mice, however, the liver tumours in male mice could not be clearly related to compound administration. Under the conditions of this bioassay, diethylhexyladipate was not carcinogenic for F344 rats. This type of tumours in rodents is connected with liposome formation, a mechanism not found in humans. Diethylhexyladipate was carcinogenic for female B6C3F1 mice, causing increased incidences of hepatocellular carcinomas, and was probably carcinogenic for male B6C3F1 mice, causing hepatocellular adenomas.

No data on carcinogenicity are available in humans. Limited evidence of carcinogenicity in animals. IARC´s evaluation: Not classifiable as to its carcinogenicity to humans (Group 3). (8)

#### *13.4.3.5 Organ toxicity*

When rats were fed diets containing diethylhexyladipate at doses equivalent to 0.16 g/kg bw/day for 90 days, no effects on growth or on liver or kidney weights or histopathologic effects were observed. However, reduced growth and altered liver or kidney weights were observed in rats receiving 2.9-4.7 g/kg bw/day for 90 days. (5)

For the rat, a NOEL (no-observed-effect level) of 610 mg diethylhexyladipate/kg bw/day is specified for a 90-day peroral intake. (10)

## 13.5 Conclusion

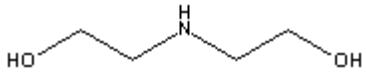
In the teratogenicity experiment mentioned above, NOEL was stated to be 28 mg/kg bw/day corresponding to an ADI of 0,3 mg/kg bw/day. A NOEL of 610 mg diethylhexyladipate /kg bw/day is specified in rats in a 90-days peroral intake study.

## 13.6 6 Literature


1. Miljø- og Energiministeriets bekendtgørelse nr. 733 af 31. juli 2000 (Bekendtgørelse om listen over farlige stoffer).
2. Positivlisten: fortegnelse over tilsætningsstoffer til fødevarer. Søborg: Ministeriet for Fødevarer, Landbrug og Fiskeri, Fødevaredirektoratet; 2000.
3. European Commission. Provisional lists of monomers and additives notified to European Commission as substances that may be used in the manufacture of plastics intended to come into contact with foodstuffs. 2001. (http://cpf.jrc.it/webpack/downloads/synoptic_internet_0401.pdf)
4. Miljø- og Energiministeriets bek. nr. 594 af 6. juni 2000 (Bekendtgørelse om kosmetiske produkter).
5. Diethylhexyladipate, (Reviewed by SRP on 5/6/2000 ). Hazardous Substances Data Bank (HSDB); National Library of Medicine (NLM). Lastest version on CD-ROM.
6. Verschueren K. Handbook of environmental data on organic chemicals. 3 ed. New York: Van Nostrand Reinhold; 1996.
7. Potts RO, Guy RH. Predicting skin permeability. Pharm Res 1992;9(5):663-9.
8. International Agency for Research on Cancer (IARC). Some industrial chemicals. Lyon: IARC; 2000. p. 157+170 (IARC monographs on the evaluation of carcinogenic risks to humans. Vol. 77)
9. Sheftel VO. Indirect food additives and polymers: migration and toxicology. Boca Raton:Lewis; 2000.
10. Beratergremium für umweltrelevante Altstoffe (BUA) der Gesellschaft deutscher Chemiker: Di-(2-ethylhexyl)adipat. Stuttgart: Hirzel; 1997. (BUA-Stoffbericht: nr. 196.)
11. Lewis sr RJ. Sax's dangerous properties of industrial materials. - 2: A-G. 9 ed. New York: Van Nostrand Reinhold; 1995.
12. Grant WM, Schuman JS. Toxicology of the eye. 4 ed Springfield (IL): Thomas;1993.
13. NTP Web site. 2001; National Toxicology Program.http://ntp-server.niehs.nih.gov/cgi/iH_Indexes/ALL_SRCH_ALL_SRCH_Frames.html).

# 14 Toxicological profile for diethanolamine

## 14.1 Chemical identity

| | | |
|---|---|---|
| 14.1.1 | Name: | Diethanolamine |
| 14.1.2 | CAS no: | 111-42-2 |
| 14.1.3 | Molecular weight: | 105,14 |
| 14.1.4 | Molecular formula: | $C_4H_{11}NO_2$ |
| 14.1.5 | Structure formula: |  |



## 14.2 Regulation

| | | | |
|---|---|---|---|
| 14.2.1 | EU classification: | Xn;R22-48/22 Xi;R38-41 | (1) |
| 14.2.2 | Limit in foods: | Not allowed in food. | (2) |
| 14.2.3 | Limit in food contact materials: | Contact with food containing nitrite should be avoided. SCF opinion: Data inadequate. | (3) |
| 14.2.4 | Limit in cosmetics: | Prohibited in cosmetic products.<br><br>In raw materials in the cosmetic product: Maximum secondary alkanolamine (dialkanolamine) content: 0.5 % (as impurities). | (4) |

## 14.3 Physico-chemical properties

| | | | |
|---|---|---|---|
| 14.3.1 | Melting point: | 28 °C | (5,6) |
| 14.3.2 | Boiling point: | 268.8 °C; 269.1 °C | (5,6) |
| 14.3.3 | Vapour pressure: | 0.00037 hPa (25 °C) | (6) |
| 14.3.4 | Water solubility: | Very soluble | (7) |
| 14.3.5 | Lipid solubility: | In benzene: 4.2 %; in ether: 0.8 %; in carbon tetrachloride: < 0.1 %; in n-heptane: < 0.1 %. | (5) |
| 14.3.6 | Partition coefficient (log $P_{ow}$): | -2.18 at pH 7.15 buffered (measured), -1.43/-1.77 (calculated) | (6) |

## 14.4 Toxicological properties

### 14.4.1 Toxicokinetic properties

#### *14.4.1.1 Uptake through skin or mucosae*

[$^{14}$C]diethanolamine was applied to 19.5 cm$^2$ of rats and covered for 48 h (no washing) or for 6 h before it was removed by washing. Absorbed [$^{14}$C]diethanolamine was determined in 48-h urine and faeces and from sampled tissues. Unwashed rats absorbed 1.4 % and washed animals 0.64 % of the dose, while the majority of [$^{14}$C]diethanolamine was recovered in the occlusive wrappings (80 %) and in the skin of the exposure site (3.6 %). The radioactivity was found in carcass, liver, or kidney but very little in urine (0.11 %), faeces or blood. (8)

#### *14.4.1.2 Biotransformation*

Diethanolamine is incorporated into membrane phospholipids and interacts with lipid metabolism in vivo, eg. by inhibiting incorporation of ethanolamine and choline into phospholipids in rat liver and kidney. (8)

Diethanolamine is metabolised by biosynthetic routes common to ethanolamine, resulting in O-phosphorylated, N-methylated and N,N-dimethylated derivatives that are incorporated as polar head groups into aberrant phospholipids which are, in turn, incorporated into critical membranes.

### 14.4.2 Acute toxicity

#### *14.4.2.1 Oral exposure*

The oral LD50 values have ranged from 0.78 to 3.5 g/kg bw in rats. Other studies have reported LD50 values 3.3 g/kg bw in mice, and 2.2 g/kg bw in rabbits and guinea pigs. Poisoning caused irritation of the oral and GI tract mucosa and motor excitation. Death occurs within 24 hours from respiratory failure. The substance has caused liver and kidney damage in animals. (10)

#### *14.4.2.2 Skin exposure*

LD50 skin rabbit: 12,200 mg/kg bw. (7)

Mild non-neoplastic lesions occurred at the site of application in the epidermis of exposed male and female rats. The incidence of acanthosis in males, hyperkeratosis and exudates in males and females were greater than those in the control animals. (11)
Dermal administration to mice was associated with increased incidences of changes of liver and kidneys, thyroid gland follicular cell hyperplasia and hyperkeratosis of the skin.

#### *14.4.2.3 Irritation*

The substance is irritating to the eyes. (9)
The liquid applied to the skin of rabbits under semiocclusion for 24 hours on 10 consecutive days caused only minor, if any, (9)

irritation.

In other studies with open applications to the ear over 14 days and ten 24 h semioccluded patch applications to the shaved abdomen, some denaturation of the ear skin was shown after ten doses and on the abdomen after three doses. The conclusion of the studies was “Moderately irritating”. Clinical skin testing of cosmetic products containing diethanolamine in concentrations above 5 % showed mild skin irritation. (12)

When 0.2 ml liquid diethanolamine was dropped in the rabbit eye and rinsed out after 15 seconds, moderate to severe conjunctival irritation and corneal injury were observed. (9)

Doses of 750 µg/24 h to rabbit eyes were severely irritating. (7)

The undiluted liquid and 40 % solutions produce severe eye burns, whereas 15 % produces only minor damage. (13)

### 14.4.3 Subchronic/chronic toxicity

#### *14.4.3.1 Skin sensitisation*

Clinical skin testing of cosmetic products containing diethanolamine in concentrations below 5% showed no skin sensitisation. (12)

#### *14.4.3.2 Mutagenic effects*

Diethanolamine was not mutagenic in 4 strains of Salmonella typhimurium in the presence or absence of metabolic activation of enzymes. In vitro cytogenic tests (chromosome aberrations and sister chromatid exchanges) were negative. Mouse lymphoma and Micronucleus tests were negative too. (11)

Diethanolamine has been demonstrated to be non-mutagenic in the Ames Salmonella typhimurium assay, with and without metabolic activation, using strains TA1535, TA1537, TA1538, TA98, and TA100; and also negative in the E. coli assay, Saccharomyces gene conversion assay, and the rat liver chromosome assay. The authors noted that the lack of mutagenic activity was in accord with the absence of electrophilic reactivity. (13)

#### *14.4.3.3 Reproduction toxicity*

Rats dosed by gavage on day 6 to 19 of gestation showed maternal effects (reduced body weight (≥ 200 mg/kg/day), increased absolute kidney weight (≥ 125 mg/kg/day), altered feed intake (≥ 200 mg/kg/day), and water intake (≥ 125 mg/kg/day)). In the pups, postimplantation mortality was elevated at ≥ 200 mg/kg/day, and early postnatal mortality was increased at ≥ 125 mg/kg/day. Pup body weight was reduced at ≥ 200 mg/kg/day. Thus, maternal and developmental toxicity NOAEL’S were 50 mg/kg/day and the LOAEL’S were 125 mg/kg/day. (14)

In a 13 weeks NTP study in rats, testicular degeneration appeared to be a direct toxic action of diethanolamine. Animals given 2,500 ppm diethanolamine in drinking water had reduced sperm motility and count. (10)

#### *14.4.3.4 Carcinogenicity*

Two-year studies with dermal application showed no evidence of carcinogenic activity in male rats administered 16, 32, or 64 mg/kg diethanolamine or in female rats administered 8, 16 or 32 mg/kg. The corresponding study on B6C3F1 mice showed increased incidence of liver neoplasms in males and females and increased incidence of renal tubule neoplasms in males. (11)

IARC has evaluated that there is inadequate evidence for the carcinogenicity in humans, and limited evidence in experimental animals for the carcinogenicity of diethanolamine. The overall evaluation is that diethanolamine is not classifiable as to its carcinogenicity to humans (Group 3). (8)

In the presence of nitrosating agents diethanolamine may give rise to N-nitrosodiethanolamine, a known animal carcinogen.

#### *14.4.3.5 Organ toxicity*

The maximum daily dose having no effect in rats (oral/intraperitoneal administration) over a 90 days period was 0.02 g/kg; a daily dose of 0.17 g/kg over the same period produced microscopic pathological lesions and deaths; and 0.09 g/kg caused changes in liver and kidney weights. (13)

## 14.5 Conclusion

Based on the above it is concluded, that

1. the critical acute effect is skin and eye irritation.
   NOAEL and LOAEL for skin irritation is:
   NOAEL < 5 %
   LOAEL 5 % (mild irritation)
   Doses of 750 µg/ 24 h to rabbit eyes were severely irritating.
2. The critical effect from long-term, repeated exposure is liver and kidney damage (oral/intraperitoneal administration).
   NOAEL 0.02 g/kg bw
   LOAEL 0.09 g/kg bw

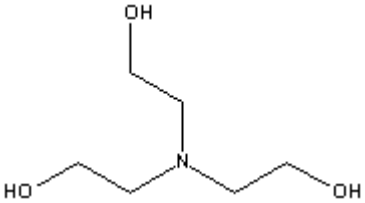
## 14.6 Literature


1. Miljø- og Energiministeriets bekendtgørelse nr. 733 af 31. juli 2000 (Bekendtgørelse om listen over farlige stoffer).
2. Positivlisten: fortegnelse over tilsætningsstoffer til fødevarer. Søborg: Ministeriet for Fødevarer, Landbrug og Fiskeri, Fødevaredirektoratet; 2000.
3. European Commission. Provisional lists of monomers and additives notified to European Commission as substances which may be used in the manufacture of plastics intended to come into contact with foodstuffs. 2001. (http://cpf.jrc.it/webpack/downloads/synoptic_internet_0401.pdf)
4. Miljø- og Energiministeriets bekendtgørelse nr. 594 af 6. juni 2000 (Bekendtgørelse om kosmetiske produkter).
5. Budavari S, editor. The Merck Index: an encyclopedia of chemicals, drugs, and biologicals. 12 ed. Whitehouse Station (NJ): Merck & Co. Inc; 1996.
6. Verschueren K. Handbook of environmental data on organic chemicals. 3 ed. New York: Van Nostrand Reinhold; 1996.
7. Lewis Sr RJ. Sax's dangerous properties of industrial materials. - 2: A-G. 9 ed. New York: Van Nostrand Reinhold; 1995.
8. International Agency for Research on Cancer (IARC). Some industrial chemicals. Lyon; IARC 2000. (IARC monographs on the evaluation of carcinogenic risks to humans. Vol 77).
9. American Conference of Governmental Industrial Hygienists (ACGIH); Documentation of the threshold limit values and biological exposure indices. Vol 1. 6 ed. Cincinnati (OH): ACGIH; 1991.
10. Sheftel VO. Indirect food additives and polymers: migration and toxicology. Boca Raton (FL): Lewis; 2000.
11. National Toxicology Program (NTP). Toxicology and Carcinogenesis Studies of Diethanolamine (CAS No.111-42-2) in F344/N Rats and B6C3F1 Mice (Dermal Studies); 1999. (http://ntp-server.niehs.nih.gov/htdocs/LT-studies/tr478.html).
12. Final Report on the Safety Assessment of Triethanolamine, Diethanolamine and Monoethanolamine. 1983. The Cosmetic Ingredient Review Program, vol. 2, No.7, 1983.
13. Clayton GD, Clayton FE, editors. Patty's industrial hygiene and toxicology. - 2: Toxicology. - Part B. 4 ed. New York: Wiley; 1994.
14. National Toxicology Program (NTP). Developmental Toxicity Screen for Diethanolamine (CAS No. 111-42-2) Administered by Gavage to Sprague- Dawley (CD) Rats on Gestation Days 6 through 19: Evaluation of Dams and Pubs through Postnatal Day 21. NTP; 1999. (http://ntp-server.niehs.nih.gov/htdocs/TT-studies/TER96001.html).

# 15 Toxicological profile for triethanolamine

## 15.1 Chemical identity

| | | |
|---|---|---|
| 15.1.1 | Name: | Triethanolamine |
| 15.1.2 | CAS no: | 102-71-6 |
| 15.1.3 | Molecular weight: | 149.19 |
| 15.1.4 | Molecular formula: | $C_6H_{15}NO_3$ |




15.1.5 Structure formula:

## 15.2 Regulation

| | | | |
|---|---|---|---|
| 15.2.1 | EU classification: | Not classified. | (1) |
| 15.2.2 | Limit in foods: | Not allowed in food. | (2) |
| 15.2.3 | Limit in food contact materials: | No restrictions on the provisional lists of monomers and additives notified to European Commission as substances which may be used in the manufacture of plastics intended to come into contact with foodstuffs: Substances for which no or only scanty and inadequate data was available. | (3) |
| 15.2.4 | Limit in cosmetics: | Field of application and/or use:<br>(a) non-rinse-off products<br>(b) other products<br><br>Max. allowed concentration in finished cosmetic products:<br>(a) 2.5 %<br><br>Other limitations and requirements:<br>(a) and (b)<br>Minimum purity: 99 %. Maximum secondary alkanolamine content (impurities): 0.5 % (concerns raw materials used in finished cosmetic products) | (4) |

## 15.3 Physico-chemical properties

| | | | |
|---|---|---|---|
| 15.3.1 | Melting point: | 21.5 °C | (5) |
| 15.3.2 | Boiling point: | 335.4 °C; 360 °C | (5) (6) |
| 15.3.3 | Vapour pressure: | 0.0000036 mmHG at 25 °C | (6) |
| 15.3.4 | Water solubility: | Readily soluble, miscible. | (7) (5) |
| 15.3.5 | Lipid solubility: | In benzene: 4.2 %; in ether: 1.6 %; in carbon tetrachloride: 0.4 %; in n-heptane: < 0.1 %. | (5) |
| 15.3.6 | Partition coefficient (log Pow): | -1.32/ -1.75 (calculated); -2.3 (measured) | (6) |

## 15.4 Toxicological properties

### 15.4.1 Toxicokinetic properties

#### *15.4.1.1 Uptake through skin or mucosae*

Data from various studies in mice and rats (1000-2000 mg/kg bw) suggest that absorption of dermally administered triethanolamine is almost complete in 24 h. (8)

#### *15.4.1.2 Biotransformation*

The biotransformation of [$^{14}$C]triethanolamine to monoethanolamine and diethanolamine was specifically investigated in mice after both intravenous and dermal treatments. Neither of the hypothetical metabolites was detected in urine, whereas more than 95 % of the radioactivity detected in urine was identified as unchanged triethanolamine. (8)

### 15.4.2 Acute toxicity

Triethanolamine is generally considered to have a low acute and chronic toxicity. Lehman (1950) states that if deleterious effects were to occur in humans from triethanolamine, these would probably be acute in nature and would be due to its alkalinity rather than an inherent toxicity. (9)

In general high doses of triethanolamine are well tolerated by rats and mice. Major sites of toxicity are liver and kidney, while skin toxicity occurs after dermal application, especially when undiluted triethanolamine is applied. (8)

In view of the low vapour pressure of , significant exposure by inhalation appears unlikely, and the chief risk would be from direct local contact of the skin or eyes with the undiluted, unneutralized fluid. (9)

#### *15.4.2.1 Oral exposure*

$LD_{50}$ oral rat: 8 g/kg bw (10)

The ingestion of several ounces can probably be tolerated by man, but unless the liquid is partly neutralized with acid, alkali burns of the mouth, pharynx and esophagus are likely. (11)
The principal toxic effect in animals has been ascribed to alkalinization (systemic alkalosis), and functional signs of transient liver injury have been described in animals after sublethal doses. Gross pathology has been limited to the GI tract in fatal oral poisonings in rats and guinea pigs.

#### *15.4.2.2 Skin exposure*

In a 24 h closed patch test the undiluted triethanolamine, 91.8 % and 88.1 % both containing slightly more than 6 % diethanolamine, were each applied to the intact skin of 3 rabbits and to the abraded skin of 3 rabbits. Exposure was 2 g/kg bw triethanolamine. The 88.1% triethanolamine elicited mild erythema and no edema and the skin returned to normal by day 6. The 91.8 % triethanolamine produced moderate erythema and no edema at 24 h and the treated sites were normal by day 10. The animals were observed for 14 days. All rabbits gained weight and none died. (12)

#### *15.4.2.3 Irritation*

Triethanolamine showed little potential for rabbit skin irritation in acute and subchronic skin irritation tests. (12)

Tested by application of a drop to rabbit eyes, it caused moderate, presumably transient injury, graded 5 on a scale of 1 to 10 after 24 h, and in another test it caused negligible irritation. (13)

In a test for vaginal mucosa irritation of a spermicidal preparation containing 1.92 % triethanolamine, the product was tested in six female rats in the same stage of estrus. The product was placed inside the vaginas of the rats daily for 3 days. On the fourth day vaginas were exposed and examined for erythema, exudates and edema. The spermicidal preparation was classified as a nonirritant to rat vaginal mucosa. (12)

Triethanolamine appeared to be without irritating effects in conc. < 5 % in most people; above this concentration (mild) skin irritation is observed. (8)

Applications of 5 or 10 % solution to rabbit or rat skin did not produce irritation, but gave evidence of skin absorption. (9)

### 15.4.3 Subchronic/chronic toxicity

#### *15.4.3.1 Skin sensitisation*

Dermal applications of undiluted triethanolamine to guinea pigs have shown no evidence of skin sensitising activities. (12)

Triethanolamine may be a sensitiser in industrial products, and cases of allergy to triethanolamine has been described for metal workers. (14)

Triethanolamine appears to be free of skin sensitization effects in its extensive use in cosmetics. (9)

#### *15.4.3.2 Mutagenic effects*

Triethanolamine was not mutagenic to Salmonella typhimurium strains, with or without metabolic activation. In vitro rat liver cells chromosome assay was negative. Drosophilia melanogaster sex-linked recessive lethal mutations were negative. (15)

#### *15.4.3.3 Reproduction toxicity*

Triethanolamine was administered as a solution in acetone to the skin of male and female rats at dose levels up to 500 mg/kg bw/day for 10 weeks before mating and then to the females during gestation and lactation. No effect on mating, fertility, or offspring growth and survival were observed. Similar studies with mice with doses up to 2000 mg/kg bw/day showed no effects of treatment. (8)

#### *15.4.3.4 Carcinogenicity*

Studies on cancer mortality or incidence among workers using metalworking fluids with ethanolamines as additives gave no results specifically in relation to triethanolamine. Studies in mice and rats with oral administration in the drinking water showed no increase in the incidence of tumours. Dermal application on rats showed no increase in the incidence of tumours either. (8)

IARC has evaluated that there is inadequate evidence in humans for the carcinogenicity, and inadequate evidence in experimental animals for the carcinogenicity of triethanolamine. The overall evaluation is that triethanolamine is not classifiable as to its carcinogenicity to humans (Group 3).

#### *15.4.3.5 Organ toxicity*

Triethanolamine was applied dermally to rats for 1 h, 5 days a week for 6 months. A 6.5 % solution showed no toxic effects. A 13 % solution caused changes in liver and central nervous system function. (12)

High purity triethanolamine was applied to the shaved backs of 10 guinea pigs in a closed patch continuous exposure test. 8 g/kg was applied daily for five days a week. Deaths occurred from 2 to 17 applications. No guinea pigs survived 17 applications. Adrenal, pulmonary, hepatic, and renal damage was observed. (12)

In a 90-d subacute feeding experiment with rats, the maximum dose producing no effect was 0.08 g/kg. Microscopic lesions and deaths occurred at 0.73 g/kg, and 0.17 g/kg produced alterations in liver and kidney weights. (9)

## 15.5 Conclusion

Based on the above it is evaluated,

1) that the human critical acute effect is irritation from direct contact with skin or the eyes with the undiluted, unneutralized fluid.
NOAEL: conc. < 5%
LOAEL: conc. = 5%

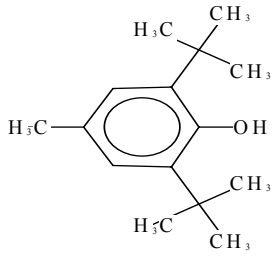
2) that the critical effect from a 90 days repeated exposure study in rats is liver and kidney damage
NOAEL 0.08 g/kg bw
LOAEL 0.17 g/kg bw

## 15.6 Literature


1. Miljø- og Energiministeriets bekendtgørelse nr. 733 af 31. juli 2000 (Bekendtgørelse om listen over farlige stoffer).
2. Positivlisten: fortegnelse over tilsætningsstoffer til fødevarer. Søborg: Ministeriet for Fødevarer, Landbrug og Fiskeri, Fødevaredirektoratet; 2000.
3. European Commission. Provisional lists of monomers and additives notified to European Commission as substances that may be used in the manufacture of plastics intended to come into contact with foodstuffs. 2001. (http://cpf.jrc.it/webpack/downloads/synoptic_internet_0401.pdf)
4. Miljø- og Energiministeriets bek. nr. 594 af 6. juni 2000 (Bekendtgørelse om kosmetiske produkter).
5. Budavari S, editor. The Merck Index: an encyclopedia of chemicals, drugs, and biologicals. 12 ed. Whitehouse Station (NJ); Merch & Co, Inc; 1996.
6. Verschueren K. Handbook of environmental data on organic chemicals. 3 ed. New York (NY): Van Nostrand Reinhold; 1996.
7. Sheftel VO. Indirect food additives and polymers: migration and toxicology. Boca Raton (FL): Lewis; 2000.
8. International Agency for Research on Cancer (IARC). Some industrial chemicals. Lyon: IARC; 2000. (IARC monographs on the evaluation of carcinogenic risks to humans. Vol. 77).
9. Clayton GD, Clayton FE, editors. Patty's industrial hygiene and toxicology. - 2: Toxicology. - Part B. 4 ed. New York: Wiley; 1994.
10. Lewis RJ. Sax's dangerous properties of industrial materials. - 3: H-Z. 9 ed. New York: Van Nostrand Reinhold; 1996.
11. Gosselin RE, Smith RP, Hodge HC. Clinical toxicology of commercial products. 5 ed. Baltimore (PA): Williams & Wilkins; 1984.
12. Final Report on the Safety Assessment of Triethanolamine, Diethanolamine and Monoethanolamine. 1983. The Cosmetic Ingredient Review Program, vol. 2, No.7, 1983.
13. Grant WM, Schuman JS. Toxicology of the eye : effects on the eyes and visual system from chemicals, drugs, metals and minerals, plants, toxins and venoms; also systemic side effects from eye medications. 4 ed. Springfield (IL): Thomas; 1993.
14. Rietschel RL, Fowler jr JF, editors. Fisher's contact dermatitis . 5 ed. Philadelphia (PA): Lippincott, Williams & Wilkins; 2001.
15. Richardson ML, Gangolli S, editors. The dictionary of substances and their effects. - 7: S-Z. Cambridge: Royal Society of Chemistry; 1994.

# 16 Toxicological profile for BHT

## 16.1 Chemical identity

| | | | |
|---|---|---|---|
| 16.1.1 | Name: | BHT | |
| 16.1.2 | CAS no: | 128-37-0 | |
| 16.1.3 | Molecular weight: | 220.36 | |
| 16.1.4 | Molecular formula: | $C_{15}H_{24}O$ | |
| 16.1.5 | Structure formula: |  | |

## 16.2 Regulation

| | | | |
|---|---|---|---|
| 16.2.1 | EU classification: | Not classified. | (1) |
| 16.2.2 | Limit in foods: | As an antioxidant in animal and vegetable fats and oils: 100 mg/kg.<br>As an antioxidant in chewing gum: 400 mg/kg.<br>As an antioxidant in dietary supplements: 400 mg/kg. | (2) |
| 16.2.3 | Limit in food contact materials: | ADI: 0.05 mg/kg bw. | (3) |
| 16.2.4 | Limit in cosmetics: | Permitted with no restrictions. | (4) |

## 16.3 Physico-chemical properties

| | | | |
|---|---|---|---|
| 16.3.1 | Melting point: | 71°C | (5) |
| 16.3.2 | Boiling point: | 265 °C | (5) |
| 16.3.3 | Vapour pressure: | 0.015 mmHg at 20 °C | (6) |
| 16.3.4 | Water solubility: | 0.0004 g/l water | (7) |
| 16.3.5 | Lipid solubility: | Soluble in hydrocarbons, oils and fats at 20 °C. | (7) |
| 16.3.6 | Partition coefficient (log $P_{ow}$): | 5.1 (calculated) | (8) |

## 16.4 Toxicological properties

### 16.4.1 Toxicokinetic properties

#### *16.4.1.1 Uptake through skin or mucosae*

Metabolism of BHT in skin has been demonstrated in an experiment with application of $^{14}C$-labelled BHT to fuzzy rat skin. The percutaneous absorption was 13 % of the applied dose. (9)

#### *16.4.1.2 Biotransformation*

After oral administration of 40 mg $^{14}C$-labelled BHT to two male volunteers, about half of the ingested dose appeared in the urine within 24 hours. About 75 % was excreted in the urine at the end of the observation period (not defined). Most was excreted as the glucuronide of a metabolite. Free and conjugated BHT-acids were minor urinary components. (7) (10)

BHT was found to be metabolised to 4-hydroxy-BHT and an unknown metabolite. (9)

In rats, only traces of BHT are found in the blood and no metabolites were found 24 hours after ingestion. (9)

### 16.4.2 Acute toxicity

#### *16.4.2.1 Oral exposure*

Reported values of $LD_{50}$ (oral rat) is between 890 mg/kg bw and 5800 mg/kg bw. (11)

#### *16.4.2.2 Skin exposure*

No data found.

#### *16.4.2.3 Irritation*

Application of 500 mg/48 hours has caused mild skin irritation in humans. (12)

One case of contact urticaria from BHT-containing plastics has been reported in a 19-year old female. When a 20-min. patch test was performed with BHA and BHT in ethanol, positive allergic reactions were elicited by both substances at 1 %, while 0.1 % and 0.01 % did not evoke a reaction. (11)

### 16.4.3 Subchronic/chronic toxicity

#### *16.4.3.1 Skin sensitisation*

For a two-year period (September 1987-December 1989) 1,336 consecutive eczema patients were patch tested with BHT. The patient material consisted of all new eczema patients observed in that period, and no selection was made. Patch tests were performed with BHT in 2 % petrolatum. The patches were left on for 2 days, and readings were performed after 2 days, 3 days, and 1 week. All patch testes were negative. (11)

Three out of 112 patients referred to an outclinic for eczematous dermatitis were tested positive to BHT. The patch test was carried out with BHT 2 % pet. One case, a 24-year old female, had eczema of the hands, feet, and lips. After the eczema had subsided, she was challenged orally with 10 mg BHT and 10 mg BHA. 12 hours later, an itching vesicular eczema erupted on several fingers and the vermilion border of the lower lip. Direct skin challenge with 5 % BHT in alcohol gave symptoms after 15 minutes. Another case, a 74-year old female leg ulcer patient, had a period with irritation and redness of her oral mucosa. These symptoms subsided after withdrawal of toothpaste. Patch tests were positive to many of the constituents in the toothpaste, among them was BHT. She had probably been sensitized by topical remedies used for treatment of the leg ulcer. However, she did not present any dermatitis. (11)

One case of facial eczema was caused by BHT in lipstick. This was proved by patch testing with 1 % BHT. (11)

Two cases of allergic contact dermatitis from BHT in leg ulcer patients have been described. Both were males in their seventies. (11)

In a 4-week study, mice were applied 145, 289, 578, or 867 mg/kg bw/day (male) and 208, 415, 830, and 1245 mg/kg bw/day (female) of BHT in the vehicle DMSO. The BHT was of food additive grade with a purity >98 %. The dermal application was performed 3 times a week. The treated animals exhibited respiratory distress with subsequent dose-dependent mortality. The autopsies revealed congestion and enlargement of the lung with oozing of froth from the trachea. The NOAEL was set to 145 mg BHT/kg bw. (11)

#### *16.4.3.2 Mutagenic effects*

BHT has been tested for gene mutation in several tests. No effects have been observed in the Salmonella/microsome test on strains TA97, TA98, TA100, TA102, TA 104, TA1535, TA1537, and TA 1538 with and without metabolic activation. (9)

BHT was mutagenic in the L5178Y tk+/tk- mouse lymphoma cell forward mutation assay. (11)

Adult rat liver epithelial cell/hypoxanthine-guanine phosphoribosyl transferase test (ARL/HGPRT): In ARL cells exposed to BHT, no significant increase in TGr mutants was observed. (11)

Dominant lethal test: Male rats were dosed for 10 weeks with 0, 400, 1,333 or 4,000 mg/kg diet. Each of the 20 males from each dose group was mated with two females. 14-18 days after 1st day of breeding, females were sacrificed, and total implants, early deaths and total corpora lutea were counted. Body weight gain was depressed at the 4,000 mg/kg groups but increased at the 400 and 1,333 mg/kg doses. The test was positive in the 1,333 and 4,000 mg/kg groups because of significant increase in dead implants during the first week of breeding. (11)

Hepatocyte/DNA repair test: BHT did not induce DNA repair in rat hepatocytes exposed up to toxic concentrations. DNA repair was induced by the positive control compound 2-amino-fluorene. (11)

Chromosome aberration test and sister chromatic exchange test in Chinese hamster ovary cells were negative in the concentrations 0 and 1.6-16 g/ml, with and without metabolic activation. (11)

#### *16.4.3.3 Reproduction toxicity*

Groups of 6 female rhesus monkeys were fed either 0 or 50 mg BHT + 50 mg BHA/kg bw/day for two years. During the second year, they were mated with males that had not been dosed. The gestation period of 165 days was included in the two years. No difference between control and experimental infants were found in behaviour, weight, body length or head circumference as measured at birth, and 14, 28, 42, and 56 days after delivery. All adult animals and four infants were observed for two years after the exposure. No abnormalities attributable to the exposure could be shown. (9)

Mated pairs of Swiss-Webster mice were given either 0 % or 0.5 % BHT in the diet. The young were continued on a diet that was similar to that of their mothers. BHT treated pups had decreased sleeping, a large increase in fighting, and learning ability was severely reduced. Some previously untreated animals were fed a control diet or a 0.5 % BHT diet. They were isolated for three weeks and then tested for aggression. The BHT-fed animals were more aggressive than the controls, but the difference was not statistically significant. This suggests that the aggression effect found in the continuously fed animals is of developmental nature. (11)

#### *16.4.3.4 Carcinogenicity*

CPI mice, male and female, were fed diets containing BHT up to 5000 mg/kg diet for up to two years. No compound-related increase in liver cell carcinomas was found, but an exposure-related increase in the incidence of lung neoplasia was established on the basis of an exposure to BHT in another strain of mouse. (9)

Lung tumour promotion has been shown to be due to a specific metabolite called BHT-BuOH and it is effective at one-fourth of the dose of BHT.

B6C3F1 mice were given 0,10.000 or 20.000 mg BHT/kg diet, corresponding to 0, 1.64 or 3.48 mg/kg bw/day for male mice and 0, 1.75 or 4.13 mg/kg bw/day for female mice. The diet was maintained for 104 weeks upon which the animals underwent a 16-week recovery period prior to pathological examination. In male mice administered BHT, the incidence of mice with either a hepatocellular adenoma or a focus of cellular alteration in the liver was increased in a clear dose-response relationship. The authors state that the results of this study indicate BHT to be tumorigenic to the liver of the B6C3F1 male mouse. However, it should be noted that there was a better survival of the mice given BHT than of the controls. (11)

A clear dose-dependent response with skin carcinomas was shown in an initiation-promotion study on adult female SENCAR mice. 7,12-dimethylbenzanthracene was used as initiator and applied on their shaven backs. Ten days later, BHT-OOH, a known carboxyl metabolite, was applied with 0-20 moles/mouse twice weekly for 50 weeks. A second control group had BHT-OOH applied without initiator. Humans are also capable of metabolising BHT to BHT-OOH, but it is not known whether it can be formed in the skin or only in the liver. (11)

IARC has evaluated that BHT is not classifiable as a human carcinogen (group 3). (7)

#### *16.4.3.5 Organ toxicity*

At low doses BHT is relatively non-toxic to all mammalian species. At doses several orders of magnitude greater than those ingested by humans a variety of toxic effects have been identified including bleeding disorders and damage to heart, reproductive organs, adrenal glands, kidney and liver. In mice only, BHT also produces diffusive lung lesion. (13)

Two cases are reported where BHT in food aggravated symptoms in patients with chronic urticaria. (9)

Ingestion of 4 g of BHT caused severe epigastric cramping, generalized weakness, nausea, and vomiting followed by dizziness, confusion, and a brief loss of consciousness in a 22-year old woman. (9)

Ingestion of 80 g of BHT in safflower oil caused a feeling of light-headedness, unsteady gait, slurred speech, and a feeling of sounds and voices being "far away" in a 24-year old woman. Objective findings were dysarthria, wide based gait, a positive Romberg test, slowed mentation without thought disorder and dysmetria of the left (dominant) arm. Symptoms subsided the following day. (Reasonable doubt should be attached to the ability to ingest as much as 80 g of BHT in safflower oil). (9)

## 16.5 Conclusion

The oral $LD_{50}$ in rats is below 2000 mg/kg bw. At low doses BHT is relatively non-toxic to all mammalian species. At doses several orders of magnitude greater than those ingested by humans a variety of toxic effects have been identified. Therefore BHT is within the EC-criteria to be classified as harmful with R22. The reported sensitising effects of BHT fulfil the EC-criteria for classifying BHT as sensitising with R43.

Based on a long-time study over 50 weeks of skin tumours in mice exposed to 0-20 mol/mouse BHT-OOH twice a day and the supporting evidence of dermal metabolism, it may seem justified to suspect BHT of being a cancer promoter in skin. The EC-criteria do not leave room for such a classification, and it should be noted that the effect is highly relevant for humans, since BHT is used as an antioxidant in creams and other cosmetics.

BHT seems to be moderately toxic after oral ingestion and has shown allergenic properties in numerous human cases. Based on the above information it is concluded, that

1. The critical acute effect in humans is skin irritation (contact urticaria after a 20 minutes patch test).
   NOAEL: 0.1% BHT in ethanol.
   LOAEL: 1% BHT in ethanol.
   Critical effect:
2. The critical acute effects in mice are respiratory disorders and enlargement of the lung after dermal exposure;
   NOAEL = 145 mg/kg bw
   LOAEL = 208 mg/kg bw.

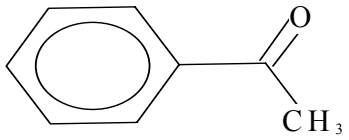
## 16.6 Literature


1. Miljø- og Energiministeriets bekendtgørelse nr. 733 af 31. juli 2000 (Bekendtgørelse om listen over farlige stoffer).
2. Positivlisten: Fortegnelse over tilsætningsstoffer til fødevarer. Søborg: Ministeriet for Fødevarer, Landbrug og Fiskeri, Fødevaredirektoratet; 2000.
3. European Commission. Provisional lists of monomers and additives notified to European Commission as substances that may be used in the manufacture of plastics intended to come into contact with foodstuffs. 2001. (http://cpf.jrc.it/webpack/downloads/synoptic_internet_0401.pdf)
4. Miljø- og Energiministeriets bekendtgørelse nr. 594 af 6. juni 2000 (Bekendtgørelse om kosmetiske produkter).
5. Chemfinder. 2001;http://chemfinder.cambridgesoft.com
6. Dutch Institute for the Working Environment; Dutch Chemical Industry Association; Chemical safety sheets: Working safely with hazardous chemicals. Dordrecht: Samson Chemical Publishers; 1991.
7. International Agency for Reserach on Cancer (IARC). Some naturally occuring and synthetic food components, furocoumarins and ultraviolet radiation. Lyon: IARC; 1986. (IARC monographs on the evaluation of carcinogenic risk of chemicals to humans vol. 40).
8. EPISuite [computer program]. v. 3.10. U.S. Environmental Protection Agency; 2001.
9. Nordisk Ministerråd. Health effects of selected chemicals to the environment. - 4: Summaries and classification proposals. Copenhagen: Nordisk Ministerråd; 1997. TemaNord; 1997:605CP – Environment)
10. Sheftel VO. Indirect food additives and polymers: Migration and toxicology. Boca Raton (FL): Lewis; 2000.
11. IUCLID (International Uniform Chemical Information Database) CD-ROM. Ispra: European Commission, Joint Research Centre, European Chemicals Bureau; 2000.
12. Lewis Sr RJ. Sax's dangerous properties of industrial materials. - 2: A-G. 9 ed. New York: Van Nostrand Reinhold; 1995.
13. Ballantyne B, Marrs TC, Syversen T, editors. General and applied toxicology. Vol. 3. 2 ed. London: Macmillan;1999.

# 17 Toxicological profile for acetophenone

## 17.1 Chemical identity

| | | | |
|---|---|---|---|
| 17.1.1 | Name: | Acetophenon | |
| 17.1.2 | CAS no: | 98-86-2 | |
| 17.1.3 | Molecular weight: | 120.15 | |
| 17.1.4 | Molecular formula: | $C_6H_5COCH_3$ | |
| 17.1.5 | Structure formula: | | |




## 17.2 Regulation

| | | | |
|---|---|---|---|
| 17.2.1 | EU classification: | Classified with Xn;R22 and Xi;R36. | (1) |
| 17.2.2 | Limit in foods: | Not allowed in food. | (2) |
| 17.2.3 | Limit in food contact materials: | No restrictions on the provisional lists of monomers and additives notified to European Commission as substances that may be used in the manufacture of plastics intended to come into contact with foodstuffs. Listed as a substance for which no or only scanty and inadequate data was available. | (3) |
| 17.2.4 | Limit in cosmetics: | No limitations. | (4) |

## 17.3 Physico-chemical properties

| | | | |
|---|---|---|---|
| 17.3.1 | Melting point: | 20 °C | (5) |
| 17.3.2 | Boiling point: | 202 °C | (5) |
| 17.3.3 | Vapour pressure: | 0.99 mmHg | (5) |
| 17.3.4 | Water solubility: | 0.7 g/100 ml at 20 °C | (5) |
| 17.3.5 | Lipid solubility: | Very soluble in propylene glycol and oils | (6) |
| 17.3.6 | Partition coefficient (log $P_{ow}$): | 1.6 | (5) |

## 17.4 Toxicological properties

### 17.4.1 Toxicokinetic properties

#### *17.4.1.1 Uptake through skin or mucosae*

Acetophenon can enter the body by inhalation, ingestion or (7)

through the skin.

#### *17.4.1.2 Biotransformation*

The metabolism of acetophenon in albino rats was studied. Within 1-3 days a total dose of 100 mg/kg bw was administered intraperitonal to 8 male rats. The urine was collected up to 24 hours after the final dose and analysed. The final metabolites were mandelic acid and benzoylformic acid and other intermediates were omega-hydroxyacetophenone (o-HA), phenylglyoxal or phenylethylene glycol, and phenylglycol aldehyde. (8)

### 17.4.2 Acute toxicity

Acetophenon has been used as a anesthetic in the 19th century before less toxic substances were found. It is a hypnotic in higher concentrations. (7)

#### *17.4.2.1 Oral exposure*

Oral LD50 in rats = 815 mg/kg bw. The compound is moderate toxic by ingestion. (6)

Among healthy humans no effects were observed after ingestion of 100-300 mg acetophenon. Ingestion of 450-600 mg caused increased micturition, the pulse weakened and slowed after 5-6 hours and a slight but continuous decrease of haemoglobin was observed. The decrease was reversible but there is no information of the time. According to these results the NOEL is assumed to be 300 mg acetophenon. (8)

#### *17.4.2.2 Skin exposure*

One report of a rabbit dermal LD50 of 1,760 mg/kg bw exists but there is no data of the method or the test substance. (8)

Another study reports that mice, who had their tails immersed in acetophenon for 4 hours, all died. (8)

#### *17.4.2.3 Irritation*

Acetophenon is a skin irritant that may cause dermatitis. (6)

The application of 515 mg of acetophenon (open) to rabbit skin induced mild skin irritation. (7)

Application of two drops of saturated aqueous solution of acetophenone to eyes of rabbits caused discomfort despite prior application of local anesthetic drops. (9)

### 17.4.3 Subchronic/chronic toxicity

#### *17.4.3.1 Skin sensitisation*

No skin senzitation was observed after administration of 2 % acetophenon in petrolatum on human skin. (8)

#### *17.4.3.2 Mutagenic effects*

In Ames test on ***Salmonella typhimurium*** TA 98, TA 100, TA 1535 and TA 1537 the results were negative. The concentration of acetophenon was 8-5000 g/plate and the test included both metabolic activated cells and not activated cells. (8)

A cytogenic test on chromosomal aberrations in chinese (8)

hamster cells, testing a concentration of 0-1.2 mg acetophenon/ml cell culture, was also negative.
A DNA damage and repair assay was performed on DNA from the bacteriophage PM2. The concentration of acetophenon was 2.7 M and was performed without metabolic activation. The study investigated endonuclease-sensitive modifications and single strand breaks induced by UV (333nm) irradiation in the presence and absence of acetophenone. The test was positive. (8)

#### *17.4.3.3 Reproduction toxicity*

A teratogenicity study on rats was performed from day 10-15 of gestation. A solution of 480 mg acetophenon was applied to the skin once a day. No changes in gestation period, size of litter, weight of offspring, time for teeth and hair appearance, opening of eyes or appearance of reflexes were observed. (8)

#### *17.4.3.4 Carcinogenicity*

No data found.

#### *17.4.3.5 Organ toxicity*

Skin, eyes, respiratory tract and central nervous system are the organs most affected. (7)

## 17.5 Conclusion

Acetophenon may enter the body via absorption through skin, inhalation or ingestion. It is found to be a skin and severe eye irritant but still a solution of 2 % acetophenon in petrolatum is reported not to induce any irritation on human skin. In rabbits dermal application of 515 mg of the compound induced mild skin sensitisation, while the LD50 in rabbits is 1760 mg/kg bw. The oral LD50 in rats is found to be 850 mg/kg bw, and acetophenone is classified as Xn;R22 and Xi;R21 according to the EC criteria. However, acetophenon could also be classified as Xn;R21 “harmful by skin contact”.
The above information indicates that acetophenone is toxic by ingestion and by skin contact. No data indicate a genotoxic effect other than in the bacteriophage PM2. Since the compound is absorbed through skin and could be classified as R21 it should not be allowed in cosmetics without limitations.

(8)

Based on the above, It is concluded that;

1. the critical acute effects of ingestion of acetophenon by healthy humans are increased micturition, weakened pulse and decreased haemoglobin (reversible)

2. NOEL = 300 mg acetophenone.

3. LOAEL = 450 mg acetophenone.

## 17.6 Literature


1. Miljø- og Energiministeriets bekendtgørelse nr. 733 af 31. juli 2000 (Bekendtgørelse om listen over farlige stoffer).
2. Positivlisten: Fortegnelse over tilsætningsstoffer til fødevarer. Søborg: Ministeriet for Fødevarer, Landbrug og Fiskeri, Fødevaredirektoratet; 2000.
3. European Commission. Provisional lists of monomers and additives notified to European Commission as substances that may be used in the manufacture of plastics intended to come into contact with foodstuffs. 2001. (http://cpf.jrc.it/webpack/downloads/synoptic_internet_0401.pdf)
4. Miljø- og Energiministeriets bek. nr. 594 af 6. juni 2000 (Bekendtgørelse om kosmetiske produkter).
5. Dutch Environment Institute for the Working; Dutch Chemical Industry Association. Chemical safety sheets: working safely with hazardous chemicals. Dordrecht: Samson Chemical Publishers; 1991.
6. Lewis Sr RJ. Sax's dangerous properties of industrial materials. Vol 2: A-G. 9 ed. New York: Van Nostrand Reinhold; 1995.
7. Sittig M. Handbook of toxic and hazardous chemicals. Park Ridge (NJ): Noyes; 1981
8. European Chemicals Bureau (ECB). IUCLID (International Uniform Chemical Information Database) CD-ROM. Ispra: ECB; 2000.
9. Grant WM, Schuman JS. Toxicology of the eye. 4 ed. Springfield (IL): Thomas; 1993.

# 18 Summary and conclusion

## 18.1 Analysis

A total of eight sanitary towels and panty liners were included in the project.

GC/MS screening detected a total of eleven 11 components/groups, whereof several of the components could be identified (acetophenon, isopropyllaurate, diisooctyladipate, 2,4-bis(1,1)-dimethylethylphenol, glycerol tricaprylate, and an isomer of this). The remaining components are stated with a group nomination.

The group of biphenyl- and indene compounds originates primarily from the back of the towel for two of the products, for which reason the components may originate from the glue on the back of the towel. In the same two samples unidentified phthalates were detected that could not be quantified. Likewise, these phthalate compounds originated primarily from the back of the sanitary towels and most probably from the glue on the back of the towel.

No content of acrylates and phenol compounds could be detected in the hygiene products. Furthermore, contents of eight different organic tin compounds could not be detected.

At the analysis for ethanolamines, diethanolamines were detected in one product in a level between 8 and 13 mg/kg, while triethanolamin was detected in four products in a level between 2 and 10 mg/kg. Monoethanolamin could not be detected.

According to the suppliers' information no optical bleach has been added to any of the products. At the production of several of the products no chloric bleach have been used.

One of the products contained fluorescent areas that could be caused by a content of optical brightener. Several of the products had fluorescent areas corresponding to the glue on the back of the sanitary towel/panty liner. Where in doubt the products were tested for hypochlorite and chlorine dioxide non of which were detected.

## 18.2 Toxicological profile

A toxicological profile has been prepared for the following twelve substances.

### 18.2.1 Butenylidenbenzene

The Danish EPA (Miljøstyrelsen) has informed that no QSAR data on 1,1'-(1-butenyliden)benzene are available in the Chem-X database.

### 18.2.2 Methylethylidenbenzene

No data was found.
The Danish EPA (Miljøstyrelsen) has informed that no QSAR data on 1,1'-(1-methylethylidene)benzene are available in the Chem-X database.

### 18.2.3 Bicyclopentyl 1-1'-diene

No data was available for a toxicological evaluation of bicyclopentyl-1,1'-diene. The Danish EPA (Miljøstyrelsen) has informed that no QSAR data on bicylopentyl-1,1'-diene are available in the Chem-X database.

### 18.2.4 Bicyclopentyl 2-2'-diene

No data was available for a toxicological evaluation of bicyclopentyl-2,2'-diene. The Danish EPA (Miljøstyrelsen) has informed that no QSAR data on bicylopentyl-2,2'-diene are available in the Chem-X database.

### 18.2.5 Dihydrotrimethylphenylindene

No data was available for a toxicological evaluation of 2,3-Dihydro-1,1,3-trimethyl-3-phenyl-1H-indene. The Danish EPA (Miljøstyrelsen) has informed that no QSAR data on this compound is available in the Chem-X database.

### 18.2.6 Abietic acid

From the limited data on this compound, the critical effect is estimated to be the sensitising potential of abietic acid. Using female hygiene products elicitates a risk of dermatitis in sensitive individuals, especially since penetration is enhanced by occlusion and irritation.

The tolerable daily intake (TDI) according to food contact materials is 1 mg/kg bw

### 18.2.7 Colophony

From the limited data on colophony, the critical effect is estimated to be the sensitising potential of the compound. Using female hygiene products containing colophony elicitates a risk of dermatitis in sensitive individuals, especially since penetration is enhanced by occlusion and irritation.
The tolerable daily intake (TDI) according to food contact materials is 1 mg/kg bw.
0.2 % dietary level of gum rosin could be assigned as a NOEL for rats and 1.0 as a LOEL. Assuming a food consumption of 20 g/day and a body weight of 200 g/rat these dietary levels equals doses of 200 and 1000 mg/kg bw/day.

Using a safety factor of 10 for extrapolating from animals to humans and another 10 to protect the sensitive part of the population, the NOEL for humans would be 2 mg/kg bw/day and the LOEL 10 mg/kg bw/day.

### 18.2.8 Diethylhexyladipate

In the teratogenicity experiment mentioned above, NOEL was stated to be 28 mg/kg bw/day corresponding to an ADI of 0,3 mg/kg bw/day. A NOEL of 610 mg diethylhexyladipate /kg bw/day is specified in rats in a 90-days peroral intake study.

### 18.2.9 Diethanolamine

Based on the available data it is concluded that

1. the critical acute effecting humans is skin and eye irritation.
   NOAEL and LOAEL for skin irritation is:
   NOAEL < 5%
   LOAEL 5% (mild irritation)
   Doses of 750 μg/ 24 h to rabbit eyes were severely irritating.
2. The critical effect from long-term, repeated exposurein rats is liver and kidney damage (oral/intraperitoneal administration).
   NOAEL 0.02 g/kg bw
   LOAEL 0.09 g/kg bw

### 18.2.10 Triethanolamine

Based on the information given in section it is concluded that

1. that the critical acute effect in humans is irritation from direct contact with skin or the eyes with the undiluted, unneutralized fluid.
   NOAEL: conc. < 5%
   LOAEL: conc. = 5%
2. that the critical effect from long-term repeated oral exposure in rats is liver and kidney damage
   NOAEL 0.08 g/kg bw
   LOAEL 0.17 g/kg bw

### 18.2.11 Butylhydroxytoluene (BHT)

The oral $LD_{50}$ in rats is below 2.000 mg/kg bw and the ingestion of large single doses of BHT cause considerable disturbances in humans. Therefore BHT is within the EC-criteria to be classified as harmful with R22. The reported sensitising effects of BHT fulfil the EC-criteria for classifying BHT as sensitising with R43.

Based on the study on skin tumours in mice and the supporting evidence of dermal metabolism, it may seem justified to suspect BHT of being a cancer promoter in skin. The EC-criteria do not leave room for such a classification, and it should be noted that the effect is highly relevant for humans, since BHT is used as an antioxidant in creams and other cosmetics.

BHT seems to be moderately toxic after oral ingestion and has shown allergenic properties in numerous human cases.
Based on the available data it is concluded, that

1. The critical acute effect in humans is skin irritation (contact urticaria after a 20 minutes patch test).
   NOAEL: 0.1 % BHT in ethanol.
   LOAEL: 1 % BHT in ethanol.
   Critical effect:
2. The critical acute effects in mice are respiratory disorders and enlargement of the lung after dermal exposure;
   NOAEL = 145 mg/kg bw
   LOAEL = 208 mg/kg bw.

### 18.2.12 Acetophenone

Acetophenon may enter the body via absorption through skin, inhalation, or ingestion. It is found to be a skin and severe eye irritant but still a solution of 2% acetophenon in petrolatum is reported not to induce any irritation on human skin. In rabbits dermal application of 515 mg of the compound induced mild skin sensitisation, while the LD50 in rabbits is 1760 mg/kg bw. The oral LD50 in rats is found to be 850 mg/kg bw, and acetophenone is classified as Xn;R22 and Xi;R21 according to the EC criteria. However, acetophenone could also be classified as Xn;R21 “harmful by skin contact”.

The above information indicates that acetophenone is toxic by ingestion and by skin contact. No data indicate a genotoxic effect other than in the bacteriophage PM2. Since the compound is absorbed through skin and could be classified as R21 it should not be allowed in cosmetics without limitations.

Based on the available data it is concluded, that

1. the critical acute effects of ingestion of acetophenon are increased micturition, weakened pulse and decreased haemoglobin (reversible)
   NOEL = 300 mg acetophenone.
   LOAEL = 450 mg acetophenone.