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# **4-Methylpent-3-en-2-one**

(CAS No: 141-79-7)

Health-based Reassessment of Administrative Occupational Exposure Limits

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Committee on Updating of Occupational Exposure Limits,  
a committee of the Health Council of the Netherlands

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No. 2000/15OSH/104, The Hague, March 30, 2004

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## 1 Introduction

The present document contains the assessment of the health hazard of 4-methylpent-3-en-2-one by the Committee on Updating of Occupational Exposure Limits, a committee of the Health Council of the Netherlands. The first draft of this document was prepared by MA Maclaine Pont, M.Sc. (Wageningen University and Research Centre, Wageningen, the Netherlands).

In February 1998, literature searched in the databases Medline, Toxline, and Chemical Abstracts covering the periods 1966 until February 1998, 1981 until October 1997, and 1937 until December 1997, respectively, and using the following key words: mesityl oxide or 141-79-7 or 3-penten-2-one, 4-methyl- and isotopic compounds.

In December 1998, the President of the Health Council released a draft of the document for public review. Comments were received by the following individuals and organisations: A Aalto (Ministry of Social Affairs and Health, Tampere, Finland) and P Wardenbach, Ph.D. (Bundesanstalt für Arbeitsschutz and Arbeitsmedizin, Dortmund, Germany). These comments were taken into account in deciding on the final version of the document.

An additional literature search in Toxline and Medline in October 2003 did not result in information changing the committee's conclusions.

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## 2 Identity

|                    |   |   |
|--------------------|---|---|
| name               | : | 4-methylpent-3-en-2-one   |
| synonyms           | : | mesityl oxide; isobutenyl methyl ketone; isopropylidene acetone; methyl isobutenyl ketone; 2-methyl-2-penten-4; methyl 2,2-dimethylvinyl ketone |
| molecular formula  | : | C <sub>6</sub> H <sub>10</sub> O  |
| structural formula | : | (CH <sub>3</sub> ) <sub>2</sub> C=CH-CO-CH <sub>3</sub>   |
| CAS number         | : | 141-79-7  |

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### 3 Physical and chemical properties

|                                |   |  |
|--------------------------------|---|--|
| molecular weight               | : | 98.14  |
| melting point                  | : | -53°C  |
| boiling point                  | : | 130°C  |
| flash point                    | : | 29°C (open cup); 31°C (closed cup)   |
| vapour pressure                | : | at 20°C: 1.3 kPa   |
| solubility in water            | : | slightly soluble (at 20°C: 3 g/100 mL)   |
| log P <sub>octanol/water</sub> | : | 1.37 (estimated)   |
| conversion factors             | : | at 20°C, 101.3 kPa: 1 mg/m <sup>3</sup> = 0.24 ppm<br>1 ppm = 4.09 mg/m <sup>3</sup> |

Data from ACG91, NLM03, <http://esc.syrres.com>.

4-Methylpent-3-en-2-one is an oily, colourless liquid with an odour that has been described as honey-like or peppermint-like. It can form peroxides. It reacts vigorously with oxidation products and many other compounds. It affects many synthetic materials and copper (NLM03). Odour thresholds of 0.068 and 1.84 mg/m<sup>3</sup> (0.02 and 0.44 ppm) have been reported (Amo83, Rut86).

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### 4 Uses

4-Methylpent-3-en-2-one is used as a solvent for synthetic rubber, vinyl chloride-acetate copolymers, cellulose esters and ethers, oils, gums, resins, lacquers, inks, and stains; in ore flotation, paint removers, and as an insect repellent (ACG91).

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### 5 Biotransformation and kinetics

Based on its physical chemical properties, the dermal flux of 4-methylpent-3-en-2-one through human skin was calculated to be 1.05 mg/cm<sup>2</sup>/h (Fis90).

The committee did not find other data on the biotransformation and kinetics of 4-methylpent-3-en-2-one.

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## 6 Effects

### Human data

Citing a material safety data sheet, ACGIH stated that the probable human response in a 5-minute exposure to 100 ppm (ca. 410 mg/m<sup>3</sup>) is predicted to be eye and mucous membrane irritation, with difficult breathing, headache, and vertigo (ACG91).

A majority of subjects experienced some degree of eye and nasal irritation at 25 and 50 ppm (ca. 100 and 205 mg/m<sup>3</sup>), respectively. One of the objectionable after-effects of this solvent was the persistent unpleasant taste that remained with many subjects for 3 to 6 hours after the exposure. Based on the unpleasant taste and nasal irritation at 50 ppm (ca. 205 mg/m<sup>3</sup>), the majority of the subjects suggested 25 ppm (ca. 100 mg/m<sup>3</sup>) to be the highest concentration that would be satisfactory for an 8-hour day (Sil46).

### Animal data

#### *Irritation and sensitisation*

4-Methylpent-3-en-2-one scored an injury grade of 5 (i.e., 0.02 mL undiluted test compound gives a score of over 5.0 points and 0.005 mL not over 5.0 points - out of a maximum of 20)\* on a scale of 1 to 10, 18 to 24 hours after instillation into the eyes of rabbits (Car46).

Referring to a data sheet, it was stated that application of 430 mg of 4-methylpent-3-ene-2-one to be mildly irritating to the skin of rabbits in an open irritation test (NIO03).

With respect to the respiratory tract, the sensory irritation in the upper part of the respiratory tract was studied by determining the concentration associated with a 50% decrease in the respiratory rate (RD<sub>50</sub>). Using male Swiss OF1 mice, the RD<sub>50</sub> for 4-methylpent-3-ene-2-one was 61 ppm (250 mg/m<sup>3</sup>) (Cea84).

#### *Acute toxicity*

Data on the acute lethal toxicity of 4-methylpent-3-en-2-one in experimental animals are summarised in Table 1.

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\* Grade 5 was also characterised as a 'severe burn from 0.005 mL' (Smy54).

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Table 1 Summary of acute toxicity studies for 4-methylpent-3-en-2-one in experimental animals.

| exposure route | species (sex)      | concentration/dose                 | effects                       | reference |
|----------------|--------------------|------------------------------------|-------------------------------|-----------|
| inhalation     | rat                | 9000 mg/m <sup>3</sup> (4 hours)   | LC <sub>50</sub>              | Izm82     |
|                | rat (male, female) | 4090 mg/m <sup>3</sup> (4 hours)   | mortality in 2-4/6            | Car49     |
|                | mouse              | 10,000 mg/m <sup>3</sup> (2 hours) | LC <sub>50</sub>              | Izm82     |
|                | mouse (male)       | 1795 mg/m <sup>3</sup> (4 hours)   | ID <sub>50</sub> <sup>a</sup> | Cea84     |
|                | guinea pig         | 8,180 mg/m <sup>3</sup> (7 hours)  | 100% mortality                | ACG91     |
| dermal         | rabbit             | 5150 mg/kg bw                      | LD <sub>50</sub>              | NIO03     |
|                | mouse              | ca. 86 mg/kg bw (0.1 mL)           | mortality in 1/10             | Har39     |
|                | mouse              | ca. 430 mg/kg bw (0.5 mL)          | mortality in 10/10            | Har39     |
| oral           | rat                | 1120 mg/kg bw                      | LD <sub>50</sub>              | ACG91     |
|                | mouse              | 710 mg/kg bw                       | LD <sub>50</sub>              | Izm82     |
|                | rabbit             | 1000 mg/kg bw                      | LD <sub>50</sub>              | ACG91     |

<sup>a</sup> ID<sub>50</sub> = median concentration that produces a 50% decrease in immobility time in a 'behavioural despair' swimming test.

In addition, Smyth et al. exposed male rats (n=10) and male and female guinea pigs (n=10) to high concentrations for short periods. Exposure to 13,000 ppm (53,170 mg/m<sup>3</sup>) caused mortality in 0, 16, 20, and 100% of the animals at 10, 15, 30, and 60 minutes, respectively. When exposed to 500, 1000, or 2500 ppm (2045, 4090, and 10,225 mg/m<sup>3</sup>), 30, 68, and 100% of the animals died after 8 hours. Results from post-mortem examination indicated narcotic death with some lung irritation (Smy42). Hart et al. exposed mice and rabbits to concentrations of 4-methylpent-3-en-2-one of 6000 to 24,000 ppm (24,540-98,160 mg/m<sup>3</sup>). In mice, eye and nose irritation were observed as well as dyspnoea, convulsions, narcosis, vasodilatation, and cyanosis. Mortality occurred in 135, 84, and 23 minutes when exposed to 6000, 13,000, and 24,000 ppm (24,540, 53,170, and 98,160 mg/m<sup>3</sup>), respectively. No organ lesions were seen upon gross post-mortem examination. For rabbits, only eye and nose irritation at exposure to 13,000 ppm (53,170 mg/m<sup>3</sup>) for 30 or 90 minutes were reported (Har39). When Ito exposed male mice (n=5/group) to concentrations of 250 to 7600 ppm (1023-31,084 mg/m<sup>3</sup>), all mice survived 6-7-hour exposure to 250 and 450 ppm (1023, 1841 mg/m<sup>3</sup>). Exposure to 1100, 1800, and 3000 ppm (4499, 7362, 12,270 mg/m<sup>3</sup>) was lethal to 1/5 (within 9.5 hours), 3/5 (within 6.5 hours), and 3/5 (within ca. 3.5 hours) animals, respectively. All animals died within ca. 1 and 2 hours at levels of 7600 and 4200 ppm (17,178 and 31,084 mg/m<sup>3</sup>), respectively (Ito69).

### *Repeated-dose toxicity*

Hart et al. exposed 10 mice daily to concentrations of 4-methylpent-3-en-2-one of 13,000 ppm (53,170 mg/m<sup>3</sup>), for 15 minutes. All animals survived 5 exposures, but after 11 exposures, 3 had died. When increasing exposure duration to 30 minutes/day, all 10 mice died within 6 days. Post-mortem examinations of the exposure-related deaths showed hepatic necrosis, pulmonary haemorrhage and oedema, renal tubular degeneration, and gastrointestinal tract distension. When 6 rabbits were exposed to this concentration, 30 minutes/day for 15 days, there was slight eye and nose irritation. Extension of exposure periods to 60 minutes/day resulted in spastic paralysis, within 10 days, and death, within 7-11 days after the onset of paralysis. Post-mortem examinations showed organ lesions similar to those found in mice (Har39). Smyth et al. exposed 10 male rats and 10 guinea pigs of both sexes to concentrations of 0, 50, 100, 250, and 500 ppm (205, 409, 1023, and 2045 mg/m<sup>3</sup>), 8 hours/day, 5 days/week, for 6 weeks. Since effects were similar in both species, Smyth et al. reported the results without making distinction between species. Nose and eye irritation were observed at 250 and 500 ppm only. Because of the high mortality rate (13/20) at 500 ppm, exposure of this group was terminated after 10 days. Death was attributed to the anaesthetic action on the circulatory and respiratory systems. All animals of the other exposure groups survived. There was no evidence of anaemia or cyanosis in any of the exposure groups. In the 250-ppm group, there were decreased body weight gain and slight albuminuria. Upon post-mortem examination, no effects were seen in the 50-ppm group. At the higher dose levels, concentration-related lung, liver, and kidney changes were observed (Smy42). Ito found leucocytosis, hypertrophy of the liver, kidney, and spleen in rats (n=5/group) due to exposure to concentrations of 4-methylpent-3-en-2-one of 300 ppm (1227 mg/m<sup>3</sup>), 2 hours/day, 6 days/week, for 1-5 weeks. In 4 rabbits exposed to 25 ppm (102 mg/m<sup>3</sup>), 4 hours/day, for 5 days, anaemia and a decrease in white blood cell counts were observed (Ito69). Brondeau et al. found a concentration-related decrease in white blood cell counts (leucopenia) without any change in differential or red blood cell counts in rats after 4-hour exposures to 18, 68, 86, and 130 ppm (74, 278, 352, 532 mg/m<sup>3</sup>), being statistically different (p<0.05) from controls at the 2 higher concentrations. This effect was adrenal dependent and Brondeau et al. regarded it as an associative response to sensory irritation (Bro90).

The committee did not find data from studies on the carcinogenicity or reproduction toxicity of 4-methylpent-3-en-2-one.

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### *Mutagenicity and genotoxicity*

4-Methylpent-3-en-2-one was negative when tested without metabolic activation using *S. typhimurium* strain TA100 (Che86).

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## **7 Existing guidelines**

The current administrative occupational exposure limit (MAC) for 4-methylpent-3-en-2-one in the Netherlands is 15 ppm (60 mg/m<sup>3</sup>), 8-hour TWA.

Existing occupational exposure limits for 4-methylpent-3-en-2-one in some European countries and in the USA are summarised in the annex.

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## **8 Assessment of health hazard**

According to old studies with volunteers, a concentration of 4-methylpent-3-en-2-one of ca. 100 mg/m<sup>3</sup> (25 ppm) induces some degree of eye irritation and a concentration of ca. 205 mg/m<sup>3</sup> nasal irritation and a persistent unpleasant taste.

In experimental animals, 4-methylpent-3-en-2-one was moderately irritating to the eyes and mildly irritating to the skin of rabbits. Acute lethal toxicity data included 4-hour LC<sub>50</sub> values of 9000 mg/m<sup>3</sup> in rats and of 10,000 mg/m<sup>3</sup> in mice, a dermal LD<sub>50</sub> of 5150 mg/kg bw in rabbits, and oral LD<sub>50</sub> values of 1120 mg/kg bw in rats and of 710 mg/kg bw in mice. Death following inhalation exposure was attributed to anaesthetic action on circulatory and respiratory systems.

The committee did not find well-performed repeated-dose toxicity studies, including carcinogenicity and reproduction toxicity, of 4-methylpent-3-en-2-one. The information available showed eye and nose irritation and slight effects on body weight, lung, liver, and kidneys of rats and guinea pigs exposed to 1023 mg/m<sup>3</sup>, 8 hours/day, 5 days/week, for 6 weeks, and leucocytosis and liver, kidney, and spleen hypertrophy in rabbits exposed to ca. 100 mg/m<sup>3</sup>, 4 hours/day, for 5 days.

The committee considers the toxicological database on 4-methylpent-3-en-2-one too poor to justify recommendation of a health-based occupational exposure limit.

In view of the effects (leucocytosis; liver, kidney, spleen hypertrophy) found at 102 mg/m<sup>3</sup> in a 5-day study in rabbits (Ito69), the committee considers the



current MAC value of 60 mg/m<sup>3</sup> (15 ppm), 8-hour TWA, to be at least one order of magnitude too high.

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## Annex

Occupational exposure limits for 4-methylpent-3-en-2-one in various countries.

| country<br>- organisation   | occupational exposure<br>limit |                   | time-weighted<br>average | type of exposure<br>limit | note <sup>a</sup> | reference <sup>b</sup> |
|---|--------------------------------|-------------------|--------------------------|---------------------------|-------------------|------------------------|
|   | ppm                            | mg/m <sup>3</sup> |                          |                           |                   |                        |
| the Netherlands<br>- Ministry of Social Affairs and<br>Employment | 15                             | 60                | 8 h                      | administrative            |                   | SZW03                  |
| Germany<br>- AGS  | 25                             | 100               | 8 h                      |                           | S                 | TRG00                  |
| - DFG MAK-Kommission  | 25                             | 100               | 8 h                      |                           |                   | DFG03                  |
|   | 50                             | 200               | 15 min <sup>c</sup>      |                           |                   |                        |
| Great-Britain<br>- HSE  | 15                             | 61                | 8 h                      | OES                       |                   | HSE02                  |
|   | 25                             | 102               | 15 min                   | STEL                      |                   |                        |
| Sweden  | -                              | -                 |                          |                           |                   | Swe00                  |
| Denmark   | 10                             | -                 | 8 h                      |                           |                   | Arb02                  |
| USA   |                                |                   |                          |                           |                   |                        |
| - ACGIH   | 15                             | -                 | 8 h                      | TLV                       |                   | ACG03b                 |
|   | 25                             | -                 | 15 min                   | STEL                      |                   |                        |
| - OSHA  | 25                             | 100               | 8 h                      | PEL                       |                   | ACG03a                 |
| - NIOSH   | 10                             | 40                | 10 h                     | REL                       |                   | ACG03a                 |
| European Union<br>- SCOEL   | -                              | -                 |                          |                           |                   | EC03                   |

<sup>a</sup> S = skin notation; which mean that skin absorption may contribute considerably to body burden; sens = substance can cause sensitisation.

<sup>b</sup> Reference to the most recent official publication of occupational exposure limits

<sup>c</sup> Maximum number per shift: 4, with a minimum interval between peaks of 1 hour.

