The SCOEL recommendation document covers the following substances:

<table>
<thead>
<tr>
<th>Substance name</th>
<th>EC number</th>
<th>CAS RN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crotonaldehyde (2-Butenal, mixed isomers)</td>
<td>224-030-0</td>
<td>4170-30-3</td>
</tr>
<tr>
<td>(E)-Crotonaldehyde (2-Butenal, trans isomer)</td>
<td>204-647-1</td>
<td>123-73-9</td>
</tr>
<tr>
<td>(Z)-Crotonaldehyde (2-Butenal, cis isomer)</td>
<td>-</td>
<td>15798-64-8</td>
</tr>
</tbody>
</table>

This text is not part of the official SCOEL Recommendation and is provided to give additional helpful information to the reader as regards chemicals addressed by the SCOEL Recommendation. The list is non-exhaustive and is presented for information purposes only.
Recommendation from the Scientific Committee on Occupational Exposure Limits for 2-Butenal

SCOEL/SUM/180
March 2013
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Recommendation from the Scientific Committee on Occupational Exposure Limits for 2-Butenal

| 8-hour TWA:     | -          |
| STEL (15-min):  | -          |
| Additional classification: | Skin notation |

This evaluation is based on ACGIH (2001), BUA (1993), DFG (2005), ECB (2000), IARC (1995), AEGL (2007) and IPCS (2008) and the references cited in these reviews as well as additional references from database searches (the final search performed in February 2013). As most of the available studies were performed with commercial 2-butenal, which consists of about 95% trans-2-butenal and 5% cis-2-butenal, the recommendation applies to both the pure trans isomer and the mixture of isomers.

1. Substance identification, physico-chemical properties

Chemical name: 2-Butenal
Synonyms: But-2-enal; 2-butenaldehyde; crotonaldehyde; crotonic aldehyde; ß-methylacrolein, ß-methylacrolein; 1-formylpropene
Molecular formula: C4H6O

EC No.: 224-030-0 (mixed isomers)
         204-647-1 (trans isomer)
CAS No.: 4170-30-3 (mixed isomers)
         123-73-9 (trans isomer)
         15798-64-8 (cis isomer)
Annex I Index No.: 605-009-00-9
Molecular weight: 70.09 g/mol
Conversion factors:
(20 °C, 101.3kPa)
1 ppm = 2.92 mg/m³
1 mg/m³ = 0.343 ppm

EU classification:
Flam. Liq. 2  H225  Highly flammable liquid and vapour
Muta. 2      H341  Suspected of causing genetic defects
Acute Tox. 2 H330  Fatal if inhaled
Acute Tox. 3 H311  Toxic in contact with skin
Acute Tox. 3 H301  Toxic if swallowed
STOT RE 2    H373  May cause damage to organs through prolonged or repeated exposure
STOT SE 3    H335  May cause respiratory irritation
Skin Irrit. 2 H315  Causes skin irritation
Eye Dam. 1   H318  Causes serious eye damage
Aquatic Acute 1 H400  Very toxic to aquatic life

2-Butenal is a colourless liquid with a pungent, suffocating odour. It is an α,β-unsaturated aldehyde and consequently a very reactive compound. The boiling point of the substance is 101–105 °C, and the vapour pressure is 25–43 hPa at 20 °C. The water solubility of 2-butenal is 150–181 g/l at 20 °C and the calculated log P_{OW} is 0.63. The substance has a flash point of 12.8 °C (open cup) and a density of 0.850–0.856 g/cm³ (ACGIH 2001, ECB 2000, IARC 1995, IPCS 2008).
2. Occurrence/use and occupational exposure
In the past, 2-butenal has been used mainly in the manufacture of 2-butanol, but this process has been mostly replaced by other technical syntheses. 2-Butenal has also been used in the preparation of rubber accelerators, in leather tanning, as a denaturant of ethyl alcohol, as a warning agent in fuel gases and to detect leaks in pipes. Currently, the most extensive use of 2-butenal is as an intermediate in the synthesis of sorbic acid and crotonic acid. 2-Butenal is formed during incomplete combustion and pyrolysis of organic substances, in particular during combustion of fuels in gasoline- and diesel-powered engines, wood combustion, and tobacco smoking. 2-Butenal is produced endogenously and occurs naturally in many plants, foods and beverages (Eder and Budiawan 2001, IARC 1995, IPCS 2008). Low amounts of 2-butenal has been reported, along with a variety of other aldehydes, in settled dust from indoor residences (around 1 µg/g dust) (Nilsson et al 2005).

3. Health significance
3.1. Toxicokinetics
2-Butenal is formed endogenously during lipid peroxidation and forms protein and DNA adducts in animals and humans (IPCS 2008).

3.1.1. Human data
2-Butenal-protein adducts have been found in the brains of patients with Alzheimer’s disease (Kawaguchi-Niida et al 2006) and in human skin (Hirao and Takahashi 2005). 2-Butenal–DNA adducts have been detected in human liver (Nath & Chung 1994), leukocytes and mammary glands (Nath et al 1996), and in oral tissues (Chung et al 1999). 2-Butenal has been detected in human milk (AEGL 2007).

3.1.2. Animal data
No data concerning the inhalation or dermal route were available. However, low dermal LD₅₀ values indicate significant skin absorption (Section 3.2.2). After oral exposure of rats to carbon-14 labelled 2-butenal in doses of 0.7–35 mg/kg, over 90 % of the substance was absorbed and rapidly metabolised; 60–78 % of the radioactivity was excreted in urine and breath within 12 hours of dosing, and after 72 hours, this increased to 82–86 %. Approximately 7 % was eliminated via faeces (ECB 2000, AEGL 2007). Following intravenous injection, 40 % of the dose was eliminated within 6 hours in urine, 33 % in exhaled air (as CO₂) and < 1 % in faeces. The metabolites were not identified, the urine contained traces only of 2-butenal and 2-butenolic acid (ECB 2000, DFG 2005).

2-Butenal is suspected to be metabolised mainly in the liver by oxidation to 2-butenolic acid, which is further degraded in the fatty acid metabolism. 2-Butenal reacts in vitro with cellular thiol groups in proteins and glutathione. After subcutaneous injection in rats, 3-hydroxy-methyl-propylmercapturic acid (6–15 % of the administered dose of 53 mg/kg) and small amounts of 2-carboxyl-1-methyl-propylmercapturic acid were the metabolites identified in the urine (ECB 2000, DFG 2005).

DNA and protein adducts have been found endogenously and after exogenous administration of 2-butenal in almost all investigated tissues (skin, liver, lung, kidney, intestinal epithelial cells) from rats and mice (Nath & Chung 1994, Eder et al 1996, 1999, Nath et al 1996).
3.1.3. Biological monitoring
There were no data available.

3.2. Acute toxicity
3.2.1. Human data
No reports on acute intoxications were available. The strong odourous and irritative properties of 2-butenal may limit exposure to higher concentrations, thereby avoiding other toxic effects (Henschler 1981).

3.2.2. Animal data
The inhalation LC₅₀ (4 hours) in rats was 69–100 ppm. Acute inhalation of high concentrations produced signs of irritation and neurotoxicity. Deceased animals revealed haemorrhagic rhinitis, proliferative lesions in the bronchioles, pulmonary congestion and pulmonary oedema as well as haemorrhages of the lung, liver, heart and kidneys (BUA 1993, Rinehart 1967).

The oral LD₅₀ values were 206–300 mg/kg in rats and about 100 mg/kg in mice. The dermal LD₅₀ was 128–170 mg/kg in rabbits and 25 mg/kg in guinea pigs (BUA 1993, ECB 2000).

3.2.3. In vitro data
The gene expression profile and cytotoxicity of normal human bronchial epithelial cells was examined after exposure to 2-butenal at 40 or 80 μM for 3 or 6 hours using microarrays technology. The gene expression analyses revealed that several biological processes representing cytotoxicity and tissue injury were dysregulated, including inflammatory responses, exogenous metabolism, cell cycle, heat shock responses and antioxidant responses (Liu et al 2010a).

Another study with human bronchial epithelial cells performed by the same group showed that 2-butenal at 10–120 μM caused decreases of intracellular reduced glutathione levels and increases of reactive oxygen species in a dose-dependent manner. 2-Butenal induced cell death by apoptosis, which gradually transitioned to necrosis at higher concentrations. Additional studies suggested that the 2-butenal-induced apoptosis was activated in a caspase-dependent way (Liu et al 2010b).

3.3. Irritation and corrosivity
3.3.1. Human data
The odour threshold (detection) of 2-butenal is in the range of 0.035–0.2 ppm. Human studies on odour and irritation are summarised in Table 1.

Sim and Pattle (1957) exposed 12 volunteers to 4.1 ppm 2-butenal. After 30 sec of exposure, lacrimation appeared, but the eye irritation did not increase with increasing exposure duration. At 15 min exposure duration, the substance was highly irritating to all exposed mucosal surfaces, especially those of the nose and upper respiratory tract. The activity levels of the test subjects were not provided and there was co-exposure to cigarette smoke. In a study by Rinehart (1967), cited by AEGL (2007), inhalation exposure of 2–3 volunteers to 45 ppm was very disagreeable within less than 30 sec and caused conjunctival irritation. Exposure to a concentration of 15 ppm for up to 30 sec was detectable (strong odour), but not irritating to the eyes. Fannick (1982) studied the effects in workers exposed to a mean of 0.56 ppm (range < 0.35–1.1 ppm) 2-butenal for < 8 hours and reported occasional minor eye irritation. The workers
### Table 1. Human data on odourous and irritative properties of 2-butenal (adapted from AEGL 2007).

<table>
<thead>
<tr>
<th>Exposure level (ppm)</th>
<th>Exposure duration</th>
<th>Effects</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.035–0.2 0.037–1.05 0.12</td>
<td>Undefined (few seconds)</td>
<td>Odour threshold. Secondary sources, descriptions of most original studies unavailable.</td>
<td>Verschueren 1996, Ruth 1986, Amoore and Hautala 1983</td>
</tr>
<tr>
<td>0.038</td>
<td>Undefined (few seconds)</td>
<td>Subjects exposed multiple times. Roughly half of them detected odour at this level.</td>
<td>Tepikina et al 1997</td>
</tr>
<tr>
<td>0.17</td>
<td>1 min</td>
<td>Odour detection and/or irritation, exposure via mask, undefined analytical method.</td>
<td>Trofimov 1962</td>
</tr>
<tr>
<td>0.56</td>
<td>&lt; 8 hours</td>
<td>Occasional eye irritation, concentration up to 1.1 ppm, co-exposure to other chemicals.</td>
<td>Fannick 1982</td>
</tr>
<tr>
<td>4.1</td>
<td>15 min</td>
<td>Marked respiratory irritation, lacrimation after 30 sec, co-exposure to cigarette smoke.</td>
<td>Sim and Pattle 1957</td>
</tr>
<tr>
<td>3.5–14</td>
<td>Undefined</td>
<td>Irritation sufficient to wake a sleeping person. &quot;Irritating within 10 sec&quot;; no further details.</td>
<td>Fieldner et al 1954</td>
</tr>
<tr>
<td>3.8</td>
<td>10 sec</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7.3</td>
<td>Undefined (seconds?)</td>
<td>Very sharp odour and strong irritation to the eye and nose; no experimental details.</td>
<td>Dalla et al 1939</td>
</tr>
<tr>
<td>8 14 (nose) 19 (eyes)</td>
<td>Undefined (few seconds)</td>
<td>Irritation threshold; methods used to determine or define “irritation” not given.</td>
<td>Ruth 1986, Amoore and Hautala 1983</td>
</tr>
<tr>
<td>15</td>
<td>&lt;30 sec</td>
<td>Lab workers “sniffed” 2-butenal. Odour strong but not intolerable; no eye discomfort.</td>
<td>Rinehart 1967</td>
</tr>
<tr>
<td>45–50</td>
<td></td>
<td>Odour strong, pungent, and disagreeable. Burning eye sensation but no lacrimation.</td>
<td></td>
</tr>
</tbody>
</table>

were exposed to other chemicals (e.g. acetic acid and acetaldehyde, but 2-butenal was likely the most irritant among these chemicals (AEGL 2007). Trofimov (1962) reported a threshold for mucosal irritation in humans of 0.17 ppm. In this experiment, volunteers inhaled 2-butenal vapour through a mask for 1 min; it was not specified how the vapour was generated or how the concentrations were measured. Factors taken into account were odour detection and irritation of the eyes and mucous membranes of the nose and trachea; it was not specified on which of these endpoints the estimated irritation threshold was actually based (AEGL 2007). Amoore and Hautala (1983) reported irritation thresholds of 14 ppm and 19 ppm for nose and eyes, respectively. The irritation threshold was 8 ppm in a study by Ruth 1986, cited by AEGL 2007.
A mixture of 7.5 % 2-butenal and 4 % sodium lauryl sulphate was a primary irritant in an aluminium patch test in 19 of the 33 test persons (Coenraads et al 1975). Dermal exposure to 0.12 % 2-butenal in plant oil (24 hours) was irritating to the human skin (Bainova and Madzhunov 1984).

There are 8 case reports of corneal injury due to exposure to unknown amounts of liquid 2-butenal. Healing was complete within 48 hours (ACGIH 2001).

### 3.3.2. Animal data

#### Skin

Dermal exposure of rabbit skin to 2-butenal produced irritation and inflammation (ECB 2000).

#### Eyes

2-Butenal was highly irritating to the rabbit eye, causing severe damage (ECB 2000).

#### Respiratory tract

The RD$_{50}$ values (concentrations causing a 50 % depression of the respiratory rate due to sensory irritation of the respiratory tract) in Swiss Webster and B6C3F1 mice were 3.5 ppm and 4.9 ppm, respectively. The RD$_{50}$ in F-344 rats was 23.2 ppm (Steinhagen and Barrow 1984, Schaper 1993). Trofimov (1962) reported a threshold for mucosal irritation in rabbits and cats of 17 ppm and 3.1 ppm, respectively.

André et al (2008) found that aqueous extracts of cigarette smoke (CSE), 2-butenal, and acrolein all mobilised Ca$^{2+}$ in cultured guinea pig jugular ganglia neurons and promoted contraction of isolated guinea pig bronchi in a similar fashion. The responses were abolished by a TRPA1-selective antagonist and by the aldehyde scavenger glutathione but not by the TRPV1 antagonist capsazepine or by ROS scavengers. Treatment with CSE or aldehydes increased Ca$^{2+}$ influx in TRPA1-transfected cells, but not in control HEK293 cells, and promoted neuropeptide release from isolated guinea pig airway tissue. The effect of CSE and aldehydes on Ca$^{2+}$ influx in dorsal root ganglion neurons was abolished in TRPA1-deficient mice. The results indicate the aldehydes as the main causative agents in cigarette smoke that cause neurogenic inflammation via TRPA1 stimulation.

### 3.4. Sensitisatation

#### 3.4.1. Human data

One case of allergic dermatitis is known. This person was occupationally exposed to dimethoxane, which hydrolyses to 2-butenal. A patch test revealed a positive reaction 72 hours following dermal exposure to a 1 % solution of 2-butenal in water or olive oil. Exposure to a 0.1 % solution did not provoke a reaction (Shmunes and Kempton 1980).

A mixture of 7.5 % 2-butenal and 4 % sodium lauryl sulphate was a primary irritant, but was not sensitising in a patch test with 33 subjects (Coenraads et al 1975).

#### 3.4.2. Animal data

A study regarding the sensitising properties of 2-butenal by NTP is completed (NTP 2012). According to other authors (BUA 1993, ECB 2000; without further details), the result of this study is “not sensitising”.

March 2013
3.5. Repeated dose toxicity

3.5.1. Human data
Human data on the effects of repeated exposure were not available.

3.5.2. Animal data

Inhalation
Valid animal studies on the effects of repeated inhalation exposure were not available. There is a poorly reported study by Voronin et al (1982), indicating alterations of motor activity and blood haemoglobin content of rats and mice continuously exposed to concentrations of 1.2 mg/m$^3$ (0.4 ppm) and above for 3 months.

Oral
Rats and mice (10 animals per sex and group) were gavaged with 2-butenal in doses of 0, 2.5, 5, 10, 20 and 40 mg/kg/day on 5 days/week for 13 weeks (Wolfe et al 1987). There was a dose-related increase in mortality and inflammation of the nasal cavity in rats (but not in mice) at doses of 5 mg/kg/day and above (NOAEL 2.5 mg/kg/day). Lesions of the forestomach were produced in rats at doses of 10 mg/kg/day and above (dose-related) and in mice of the highest dose group. These data are only presented as an abstract.

Chung et al (1986) exposed 23–27 male rats for 113 weeks to 2-butenal in the drinking water at concentrations of 0, 0.6 and 6 mmol/l (42 and 421 mg/l). The higher dose produced reduced body weight gain, while survival was not affected. Nearly half of the high-dose animals had moderate to severe non-neoplastic liver lesions (fatty metamorphosis, focal necrosis, fibrosis and cholestasis) and all the remaining animals (high and low dose) developed liver cell foci (see Section 3.7.2).

Dermal
Valid animal studies on the effects of repeated dermal exposure were not available.

3.6. Genotoxicity

3.6.1. In vitro
2-Butenal induced forward and reverse mutations in bacteria (Salmonella typhimurium strains TA100, TA104, BA9) with and without metabolic activation, but only when a preincubation method or the liquid suspension technique was used. Plate incubation protocols yielded negative results.

There was no mutagenic response in the SOS chromotest in Escherichia coli PQ37 and PQ243 (DFG 2005, IARC 1995). However, when ethanol was used as solvent instead of DMSO, 2-butenal was clearly positive (PQ37). A weak SOS response was seen in S. typhimurium TA1535/pSK1002 without metabolic activation (IPCS 2008, AEGL 2007).

Exposure of primary human lymphocytes or Namalva (Burkitt’s lymphoma) cells resulted in increases of sister chromatid exchanges, chromosomal aberrations and micronuclei (Dittberner et al 1990).

In Chinese hamster ovary (CHO) hamster cells in vitro, the substance produced sister chromatid exchanges and chromosomal aberrations with or without metabolic transformation (Galloway et al 1987), but no gene mutations in a HPRT test (Foiles et al 1990).

Incubation of rat colon mucosa cells with 2-butenal resulted in DNA damage in the comet assay (Gölzer et al 1996). 2-Butenal did not induce unscheduled DNA synthesis in primary cultures of rat hepatocytes (Williams et al 1989).
The substance binds covalently to DNA of *E. coli* HB101pUC13, to calf thymus DNA and to DNA of CHO cells or human fibroblasts *in vitro*, forming cyclic adducts with deoxyguanosine (DFG 2005, ECB 2000). 1,\(N^2\)-Propano-deoxyguanosine adducts (which are produced as the main adducts also after *in vivo* exposure of animals) caused mutations in mammalian cells with a yield of about 5%, when they were incorporated in DNA plasmids and transfected into COS-7 monkey kidney cells (Fernandes et al 2005). These adducts also inhibited DNA synthesis and were mutagenic after incorporation into DNA vectors and transfection into human xeroderma pigmentosum cells (Stein et al 2006). In addition, 1,\(N^2\)-propano-deoxyguanosine adducts were capable of forming DNA crosslinks (Kozekov et al 2003, Liu et al 2006) or DNA-protein crosslinks *in vitro* (Kurtz and Lloyd 2003). Hecht et al (2001a,b) and Wang et al (2001) described the formation of several other minor adducts to deoxyguanosine after reaction of 2-butenal with calf thymus DNA.

Using the mouse lymphoma cells, Demir et al (2011) found that 2-butenal induced increased mutant frequencies at concentrations of 50 µM in the first experiment and 25 µM in the second.

**3.6.2. In vivo – Human data**

Zhang et al (2006) isolated adducts of 2-butenal with deoxyguanosine (1,\(N^2\)-propano-deoxyguanosine) from DNA of humans (not occupationally exposed to 2-butenal). These adducts were more frequently detected in lung DNA than in liver DNA and were not detectable in DNA from blood.

Nath et al (1998) found higher levels (5.5- to 8-fold) of 2-butenal-DNA adducts in gingival tissue DNA from smokers compared to non-smokers (not occupationally exposed to 2-butenal).

**3.6.3. In vivo – Animal data**

A host mediated assay in CD1 mice with a single oral exposure of the animals to 8–80 mg/kg 2-butenal and simultaneous injection of *S. typhimurium* TA100 yielded a positive finding (Jagannath 1980). Oral exposure of mice (doses of 0.8–80 mg/kg, administered twice) did not induce chromosomal damage in the bone marrow micronuclei test (Mayer et al 1980). Oral exposure (1 month in drinking water at concentrations of 200 mg/l) or a single intraperitoneal injection (30 mg/kg) produced chromosomal damage in all stages of spermatogenesis and special meiotic anomalies in mice (Auerbach et al 1977, Moutschen-Dahmen et al 1975). Abnormal sperm heads, indicative of genotoxicity, were observed by Jha and Kumar (2006) in mice after a single intraperitoneal injection. The effect reached statistical significance 1 and 3 weeks after exposure at doses over 16 µl/kg and 5 weeks after exposure at the highest dose of 32 µl/kg.

A single oral high dose of 200 or 300 mg/kg 2-butenal caused an increase in DNA adducts in rat liver cells (about 3 adducts/\(10^8\) nucleotides of cyclic 1,\(N^2\)-propano-deoxyguanosine adducts, 20 hours after exposure). Lower amounts of adducts were detected in lung, kidney and large intestine. Repeated gavage to rats in doses of 1 and 10 mg/kg/day (30 applications within 6 weeks) produced a dose-dependent increase in these DNA adducts in liver cells (2.1 and 6.3 adducts/\(10^8\) nucleotides 20 hours after the last exposure). The adducts persisted partially and declined within 15 days to about 20% of the level detected 20 hours post-exposure (Eder et al 1996, 1999, Eder and Budiawan 2001). The same kind of adducts were also detected in DNA of the skin of mice treated dermally with 2-butenal at doses of 300 mg/kg (IARC 1995).
The genotoxicity of 2-butenal was evaluated by employing bone marrow and spermatocyte chromosomal aberration and dominant lethal mutation assays in Swiss albino mice. Single intraperitoneal doses of 2-butenal (8, 16 and 32 µl/kg bw) in olive oil caused dose-dependent increases in percentage aberrant metaphases in bone marrow cells. At the same doses, a dose-dependent increase in chromosomal aberrations was also seen in spermatocytes from male mice given the same doses. A lethal mutation study was performed with males given the same doses as above once daily for 5 days and then mated with untreated females. The treatment resulted in significant decreases in fertility indices, total number of implants and number of live implants per female, and increased number of dead implants per female. The percentage dominant lethal mutations increased with the dose (Jha et al 2007).

### 3.7. Carcinogenicity

#### 3.7.1. Human data

A study by Bittersohl (1974) reported 9 malignant tumours (2 squamous cell carcinomas of the oral cavity, one adenocarcinoma of the stomach, one adenocarcinoma of the caecum and 5 squamous cell tumours of the lung) among 150 workers exposed to concentrations of 1–7 mg/m³ (0.3–2.4 mg/m³) 2-butenal for 20 years. All cases were smokers. There was also exposure to acetaldehyde, butyraldehyde and higher aldehydes, to n-butanol and higher alcohols and possibly also to butadiene.

#### 3.7.2. Animal data

Chung et al (1986) exposed 23–27 male rats for 113 weeks to 2-butenal via the drinking water in concentrations of 0, 42 and 421 mg/l. Survival was not affected in any group. The incidence of hepatocellular carcinomas was 0/23, 2/27 and 0/23, and neoplastic nodules in the liver were found in 0/23, 9/27 (significant increase) and 1/23 in the control, lower and higher dose group, respectively. Liver cell foci (according to the authors precursors of hepatocellular neoplasms) were found in 1/23 controls, in 23/27 at the low dose and in 13/23 at the high dose. The increase in exposed groups was significantly different from controls but not dose-related. Ten of the high-dose animals had moderate to severe non-neoplastic liver lesions, but none of these animals developed preneoplastic lesions or tumours. The remaining 13 animals were found to have the liver cell foci without further liver lesions. The authors considered these foci as preneoplastic, however, the observed foci were mainly of the eosinophilic type. Basophilic hepatocellular foci are generally considered to be putative preneoplastic, whereas foci of the eosinophilic type are not.

When neonatal B6C3F1 mice were injected intraperitoneally with total doses of 1.5 or 3 µmol (105 or 210 mg, split on days 8 and 15), there was no significant increase in liver tumours at 12–15 months of age (von Tungeln et al 2002). The authors suggested that this assay is not sensitive enough to detect carcinogens that induce an increase in endogenous DNA adduct formation through lipid peroxidation or oxidative stress.

In its evaluation of 2-butenal, IARC concluded that the available data were too limited to form the basis for an evaluation of the carcinogenicity to humans. The increased incidences of hepatic neoplastic nodules and altered liver-cell foci seen in the male rat drinking water study were not dose-related. The overall evaluation was Group 3, i.e. not classifiable as to its carcinogenicity to humans (IARC 1995).
3.8. Reproductive toxicity

3.8.1. Human data
Human data on reproductive or developmental effects were not available.

3.8.2. Animal data

*Fertility*

Oral exposure (one month in drinking water at concentrations of 200 mg/l or a single intraperitoneal injection (1 mg/animal, about 30 mg/kg) produced chromosomal damage in all stages of spermatogenesis and meiotic anomalies in mice (Moutschen-Dahmen *et al* 1975, Auerbach *et al* 1977, see Section 3.6.3). The study had neither positive nor negative controls but suggests that 2-butenal reaches the germ cells (IPCS 2008).

A dose-related increase in abnormal sperm heads was reported in mice treated with single intraperitoneal doses of 8, 16 and 32 µl/kg 2-butenal (6.8, 13.6 and 27.2 mg/kg). The effect reached statistical significance at doses of ≥ 16 µl/kg 1 and 3 weeks after exposure and at the highest dose of 32 µl/kg 5 weeks after exposure (Jha and Kumar 2006).

*Developmental toxicity*

Animal studies on developmental effects were not available.

4. Recommendation

*Irritation*

2-Butenal is a highly reactive and strong irritant. The RD50 values in mice are 3.5–4.9 ppm, depending on the strain (Steinhagen und Barrow 1984). Scattered human data indicate that 2-butenal is similarly irritating to humans. Thus irritation has been reported after acute exposures (seconds to minutes) at between 0.17 and 15 ppm (Table 1).

*Systemic effects*

2-Butenal is endogenously formed by lipid peroxidation. No adequate inhalation studies were available to assess the systemic toxicity. The NOAELs of subchronic and chronic animal studies with oral exposure are 2.5 and 5.9 mg/kg/day, respectively. Hepatotoxicity and inflammation of the respiratory tract were observed at higher doses (Wolfe *et al* 1987, Chung *et al* 1986).

*Genotoxicity and carcinogenicity*

2-Butenal is mutagenic *in vitro* and *in vivo*. 2-Butenal produces cyclic 1,N2-propane-deoxyguanosine and other minor deoxyguanosine adducts with DNA *in vitro* and *in vivo*. The recent study by Jha and Khumar (2006) indicates that 2-butenal reaches germ cells *in vivo*.

Data concerning carcinogenic effects are limited. The human data of Bittersohl (1974) are not useful due to the smoking status of the workers and co-exposure to other chemicals. A slight increase in liver tumours was shown in the long-term rat study by Chung *et al* (1986), but without a clear dose-response relationship (hepatocellular carcinomas in the low-dose but not in the high-dose group). In view of the genotoxic properties, a possible carcinogenic potency of 2-butenal in humans cannot be dismissed. However, the limited human and animal data are too meagre to draw definite conclusions.
Overall assessment

In conclusion, no health-based OEL can be established at the present state of knowledge.

A "skin" notation is proposed because of low dermal LD$_{50}$ values in rabbits and guinea pigs, similar to or even lower than the oral LD$_{50}$ values in rats and mice.

Only one case of allergic contact dermatitis to 2-butenal in humans is known. A controlled study with 33 subjects revealed no sensitisation and animal studies show negative results. Therefore, there is little concern for sensitisation by 2-butenal.

No data on biological monitoring were available.

The present Recommendation was adopted by SCOEL on 20 March 2013.
5. References

ACGIH, American Conference of Governmental Industrial Hygienists (2001). Crotonaldehyde. In: ACGIH, American Conference of Governmental Industrial Hygienists, Threshold limit values for chemical substances and physical agents and biological exposure indices, 2004, Cincinnati, OH.


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