Recommendation from the Scientific Committee on Occupational Exposure Limits for Ethyl Carbamate [Urethane]

SCOEL/SUM/172
March 2012

Employment, Social Affairs and Inclusion

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8-hour TWA	:	not feasible to derive a health-based limit (see Recommendation)
STEL (15 mins)	:	not feasible to derive a health-based limit (see Recommendation)
Notation	:	[Skin contact must be avoided because of local skin carcinogenicity]
SCOEL carcinogen group	:	A (non-threshold genotoxic carcinogen)
Risk assessments	:	see chapter 2.7.3

Substance identification:	ethyl carbamate
Synonyms	urethane, leucothane, pracarbamin (IARC 1974)
Molecular formula:	$C_3H_7NO_2$
Structural formula:	$H_2N\text{-}CO\text{-}O\text{-}C_2H_5$
EU classification:	Carc. 1B H350 May cause cancer
CAS No.:	51-79-6
EC No. :	200-123-1
INDEX No.:	607-149-00-6
Molecular weight:	89.09
Melting point:	49 °C
Boiling point:	182-184 °C
Conversion factor:	[Not volatile at room temperature]

Soluble in: water (1 g/0.5 mL), ethanol (1 g/0.8 mL), chloroform (1 g/0.9 mL), ether (1 g/1.5 mL), glycerol (1 g/2.5 mL), olive oil (1g /32 mL) (Budavari *et al* 2000).

This summary document is based on documentations of IARC (1974, 2010) and DFG (2004), supplemented by a recent literature search of SCOEL.

1. Occurrence, use and occupational exposure

The primary use of urethane has been as a chemical intermediate in the preparation of amino acids. Urethane is also used as a solubiliser and co-solvent in the manufacture of pesticides, fumigants and cosmetics, and as an intermediate for the manufacture of pharmaceuticals and in biomedical research. It was formerly used as an active ingredient in drugs prescribed for the treatment of neoplastic diseases, as a sclerosing formulation for varicose veins, as a hypnotic and a topical bactericide. It is used in veterinary medicine as an anaesthetic. Possible human exposures are via inhalation, ingestion and dermal contact (NTP 2009).

Urethane may be formed naturally as a result of fermentation. Therefore, it has been detected in a variety of fermented foods and beverages, Levels in wine and beer are usually below 100 µg/L, whereas higher levels (in the mg/L range) have been found in some spirits. Levels in food have been regulated and significantly reduced in the last 20 years (IARC 2010). For more details on urethane exposure in food, see EFSA (2007).

2. Health significance

Urethane is reasonably anticipated to be a human carcinogen based on sufficient evidence of carcinogenicity in experimental animals (IARC 1974, 2010). Experimental evidence suggests great similarities in the metabolic pathways of the activation of ethyl carbamate in rodents and humans. The formation of proximate carcinogens that are DNA-reactive are thought to play a major role in ethyl carbamate-induced carcinogenesis; this probably also occurs in human cells (IARC 2010). The contents of urethane in food have been regulated and significantly reduced in the last 20 years (IARC 2010). For more details on urethane exposure in food, see EFSA (2007). Urethane has been classified by IARC (1974, 2010) as a class 2A carcinogen, based on sufficient evidence for carcinogenicity in animals and mechanistic considerations.

2.1. Toxicokinetics/metabolism

Because of the former pharmaceutical use of urethane in the treatment of malignant disorders, its metabolism was studied already in the 1960s; early reviews are by Haddow (1963) and Mirvish (1968). An extensive summary of such studies is part of the documentation of IARC (1974).

The compound is rapidly metabolised. For instance, in mice dosed with ^{14}C-labelled urethane, 90% of the radioactivity dose was excreted within 24 h as $^{14}CO_2$ in the expired air. In rats, rabbits and humans (patients with multiple myeloma treated with urethane) identified urinary excretion products were the parent compound, urethane (0.55-1.7% of the dose administered), and the metabolites *N*-hydroxy-urethane (0.02-0.15%), acetyl-*N*-hydroxy-urethane (0.1-0.6%), ethyl mercapturic acid (0.1-0.2%) and *N*-acetyl-*S*-ethoxy-carbonylcysteine (0.9-2.1%). In general, it appears that the metabolism of urethane is quantitatively similar across species. *N*-Hydroxyurethane is also excreted as glucuronide conjugate. Its rate of elimination was reported to be lower in newborn than in adult mice, which was attributed to a lack of microsomal esterase (for details, see IARC 1974).

A specific aspect that has attracted attention is the metabolic activation of urethane, via a quantitatively minor pathway, to reactive metabolites that bind to DNA and form adducts, such as 7-(oxoethyl)guanine, 1,N^6-etheno-adenine, 3,N^4-ethenocytosine and N^2,3-etheno-guanine (for review, see Barbin 2000). These DNA-adducts are identical

to those resulting from vinyl chloride (Bolt 2005). The pathway of activation involves two oxidative steps, both catalysed by CYP2E1: (i) desaturation of ethyl carbamate to vinyl carbamate, followed by (ii) epoxidation of the double bond to vinyl carbamate epoxide (Guengerich and Kim 1991; see *Figure 1*).

Quantitatively, the specific DNA-adduct forming potency of urethane has been found to be 2-4 fold lower than that of vinyl chloride, based on comparative experiments in young and adult mice (Fernando *et al* 1996).

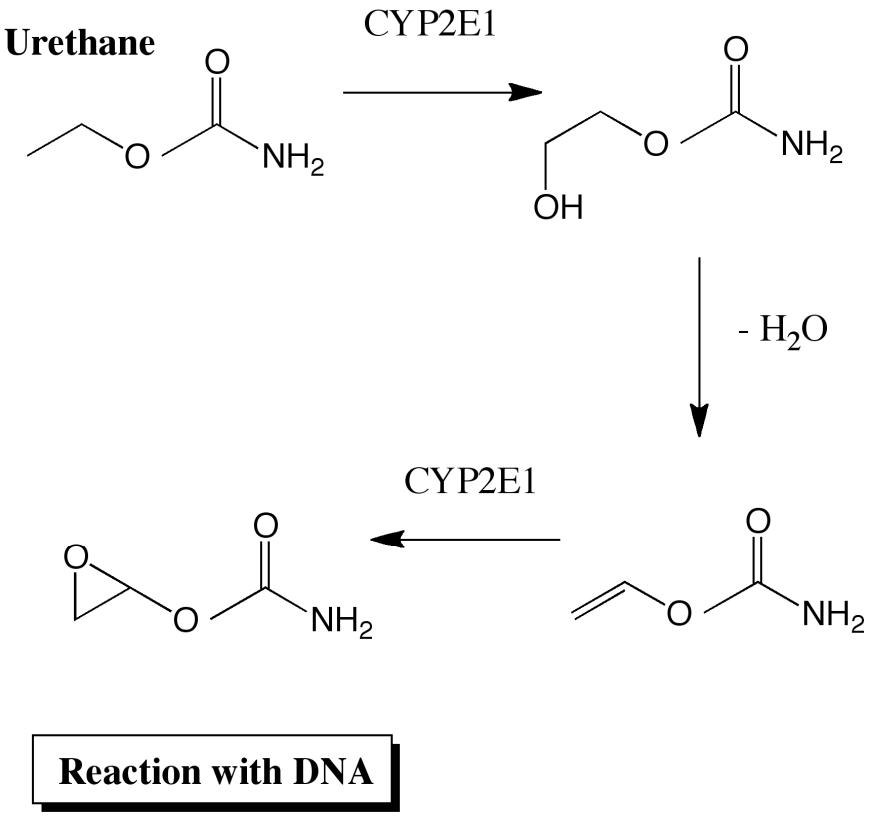

Figure 1. Proposed metabolic sequence in the biological activation of urethane (Guengerich and Kim 1991, Barbin 2000).

2.2. Acute toxicity

At high acute doses, urethane has a narcotic effect. This is used in animal experimentation and in veterinary medicine at a g/kg dose range. The minimum effective narcotic dose in mice has been experimentally determined to be 2 g/kg (Levin 1956).

2.3. Irritation and corrosivity

There are no data indicative of locally irritating or corrosive properties of urethane.

2.4. Sensitisation

There are no published data on sensitisation.

2.5. Repeated dose toxicity

2.5.1. Human data

Urethane has been used in medical practice as a hypnotic agent at the end of the nineteenth century and was discontinued after barbiturates became available. It was also tested for treatment of cancers, or used as a co-solvent in water for dissolving water-insoluble analgesics used for post-operation pain. A clinical trial with urethane in patients with leukaemia (32 cases) and other types of somatic cancer (13 cases) involved oral administration of urethane in doses of 1-6 g/day for 5 to 109 days. The total dose varied by patient from 26 to 390 g of urethane. Nausea, vomiting and diarrhoea were reported as common side effects. Leukopenia was observed in patients with somatic tumours, while the observed sharp fall in white cell counts was considered a beneficial effect in patients with leukaemia. These health effects were reversible after the treatment with urethane was discontinued. When urethane was administered intramuscularly, dizziness and drowsiness were also reported (IARC 2010).

2.5.2. Animal data

Urethane is known to induce acute toxic reactions in rodents. In female C57BL/6J mice receiving subcutaneous injections of 4 mg/kg urethane for 12 days, spleen and thymus weights and circulating leukocyte counts were depressed (Luebke *et al* 1987). The immuno-competence of dosed mice was severely compromised, as measured by the delayed hypersensitivity reaction. Female B6C3F1 mice receiving a total dose of 4 mg/kg urethane by intraperitoneal injection in 14 days also had lower spieen and thymus weights than the controls, but peripheral blood cell counts were not affected (Luster *et al* 1982). The hypnotic and anaesthetic properties of urethane suggest a possibility of neuropharmacological effects, which may become significant when the chemical is co-administered with ethanol. Various toxic effects were reported in the National Toxicology Program (NTP) 13-week drinking water or 5% ethanol studies in rats and mice (NTP 1996). Increased lethality was observed in rats receiving urethane in excess of 300 mg/kg. Urethane was much more toxic in mice receiving more than 1 000 mg/kg, and many in the 300 mg/kg group died before the end of the study. Animals in higher dose groups had lower body weights, reduced water consumption, and exhibited thinness, abnormal posture, and ruffled fur. Leukopenia (primarily lymphocytopenia) was also observed in rats and mice receiving urethane in doses as low as 20 mg/kg. In separate 4-week and 2-year studies, male and female B6C3F1 mice were administered 4-10 mg/kg of urethane in drinking water or 5% ethanol (NTP 2004). No adverse effects on body weight or water consumption were noted at 4 weeks, but increased lethality and decreased body weights were observed in high-dose groups of the 2-year study.

2.6. Genotoxicity

Urethane is genotoxic, mutagenic and clastogenic, especially in the presence of metabolic activation. Plausible mechanisms are induction of DNA damage by its metabolite(s) (for details, see 2.2) and increase in cell proliferation in target tissues (IARC 2010).

2.6.1. In vitro

Urethane is clearly mutagenic *in vivo* in Drosophila, where it induces sex-linked recessive lethal mutations and reciprocal translocations in germ cells. The results of in vitro clastogenicity tests with urethane in mammalian systems vary among assays; the (infrequent) positive responses appeared most often with high doses of urethane tested

with exogenous metabolic activation in specific cell types under stringent conditions. Most of the data indicate that urethane is inefficient in causing point mutations in mammalian cells *in vitro*. Some reports indicate that urethane can cause DNA damage in mammalian cells *in vitro* and *in vivo*. Urethane and/or its metabolites are able to bind to nucleic acids *in vivo*. A limited number of studies was performed to assess clastogenicity of urethane in human cells *in vitro*. Studies showed that urethane can induce sister chromatid exchanges in human lymphocytes, or cause DNA damage (measured as unscheduled DNA synthesis) in human fibroblasts *in vitro*. However, it was reported that urethane neither induces micronuclei in human lymphocytes, nor causes chromosomal aberrations *in vitro*. Furthermore, no effect of urethane on gene mutations was observed in human lymphoblastoid cell line (for details, see IARC 2010).

2.6.2. In vivo - Human data

There are no published data of studies in humans.

2.6.3. In vivo - Animal data

Results from *in vivo* somatic cell assays with urethane in mammalian species are generally positive. Chromosomal aberrations, sister chromatid exchanges, gene mutations, DNA damage and micronuclei were induced with a wide range of doses and in a large number of experimental model organisms (mice, rats, hamsters) and tissues (liver, bone marrow and lungs). Classical clastogenic effects such as chromosome aberrations are less dose-dependent than sister chromatid exchanges. In studies that also assessed the ability of urethane to induce cancer, a poor correlation was found between carcinogenicity and clastogenicity of urethane. Urethane is also able to induce point mutations in somatic cells *in vivo* (for details, see IARC 2010).

2.7. Carcinogenicity

2.7.1. Human data

No adequate human studies of the relationship between exposure to urethane and human cancer have been reported (NTP 2009, IARC 2010).

2.7.2. Animal data

(according to the summary evaluation of IARC 2010)

In many studies, mice were treated orally with urethane. This resulted in increased incidences of lung adenomas, carcinomas and squamous-cell tumours, lymphomas (mainly lymphosarcomas), mammary gland adenocarcinomas, carcinomas and adenoacanthomas, leukaemias, forestomach squamous-cell papillomas or carcinomas, heart haemangiosarcomas, liver haemangiosarcomas, Harderian gland adenomas or carcinomas and angiomas.

Subcutaneous administration of urethane to adult and newborn mice induced significant increases, respectively, in the incidences of lung adenomas and hepatomas.

Topical application of urethane to mice resulted in a significant increase in the incidence of lung adenomas and mammary gland carcinomas.

Mice exposed by inhalation had an increased incidence of lung adenocarcinomas, leukaemias and uterine haemangiomas.

Intraperitoneal administration of urethane to adult mice resulted in a significant increase in lung adenomas, hepatomas and skin papillomas. Similar treatment in newborn mice induced lymphomas, lung adenomas, hepatomas, Harderian gland tumours and stromal and epithelial tumours of the ovary.

Mice exposed transplacentally to urethane developed an increased incidence of lung tumours, hepatomas and ovarian tumours.

Mice born after pre-conceptual exposure of the fathers to urethane had an increased incidence of pheochromocytomas and adrenal gland tumours.

In one study, oral administration of urethane to mice deficient in CYP2E1 resulted in a lower incidence of liver haemangiomas and haemangiosarcomas, lung bronchio-alveolar adenomas and carcinomas, and Harderian gland adenomas compared to mice proficient in CYP2E1.

In other studies, when the administration of urethane was accompanied by topical application of the tumour promoter, 13-*O*-tetradecanoylphorbol acetate, the incidences of skin papillomas and squamous-cell carcinomas were significantly increased. When the treatment with urethane was followed by topical application of croton oil, a significant increase in the incidence of skin papillomas resulted.

Topical application of urethane to mice previously treated with 7,12-dimethyl-benz[a]anthrancene resulted in a significant increase in the incidence of skin tumours.

Rats treated orally with urethane had increased incidences of Zymbal gland carcinomas and mammary gland carcinomas.

Hamsters treated orally with urethane showed increased incidences of skin melanotic tumours, forestomach papillomas, mammary gland adenocarcinomas, liver hepatomas, liver and spleen haemangiomas, and thyroid, ovarian and vaginal carcinomas.

In one study, hepatocellular adenomas and carcinomas and adenocarcinomas of the lung were observed in monkeys treated orally with urethane.

The carcinogenicity of urethane (ethyl carbamate) has been compared with that of its metabolites *N*-hydroxy-ethyl carbamate, 2-hydroxy-ethyl carbamate, vinyl carbamate and/or vinyl carbamate epoxide in mice and rats after oral, dermal, subcutaneous, intramuscular and/or intraperitoneal administration. Oral administration of ethyl carbamate or *N*-hydroxy ethyl carbamate, followed by topical application of croton oil, induced skin and lung tumours in male and female mice; ethyl carbamate was significantly more potent than *N*-hydroxy-ethyl carbamate. Topical application of ethyl carbamate or vinyl carbamate, followed by promotion with croton oil, induced skin and lung tumours in female mice; vinyl carbamate was significantly more active than ethyl carbamate. Topical application of vinyl carbamate or vinyl carbamate epoxide, with or without promotion by 13-*O*-tetradecanoylphorbol acetate, induced skin papillomas in female mice; vinyl carbamate epoxide was significantly more active than vinyl carbamate. Subcutaneous injection of ethyl carbamate or *N*-hydroxy-ethyl carbamate induced lung adenomas in two strains of mice; ethyl carbamate demonstrated greater activity. Intramuscular injection of vinyl carbamate or vinyl carbamate epoxide into female rats caused sarcomas at the injection site; vinyl carbamate epoxide was more potent. Intraperitoneal injection of ethyl carbamate or *N*-hydroxy-ethyl carbamate into three different strains of mice, with or without promotion with topical application of croton oil, induced skin and/or lung tumours; ethyl carbamate had similar or greater activity than *N*-hydroxycarbamate. Intraperitoneal injection of ethyl carbamate or vinyl carbamate, with or without promotion with topical application of croton oil, induced skin papillomas, lung adenomas and/or carcinomas, liver tumours

(hepatomas), thymic lymphomas and/or Harderian gland tumours in CD-1, A/J, $B6C3F_1$, C3H, C57BL, $B6CF_1$, $CB6F_1$-Tg Hras 2 and $CB6F_1$ non-Tg Hras 2, $B6D2F_1$ and/or $B6CF_1$ mice; vinyl carbamate was typically more potent. Intraperitoneal injection of vinyl carbamate or vinyl carbamate epoxide induced lung adenomas in female A/J mice and liver tumours (hepatomas) in male $B6C3F_1$ mice; vinyl carbamate epoxide was more active than vinyl carbamate. Intraperitoneal injection of ethyl carbamate or 2-hydroxy-ethyl carbamate induced lung adenomas in male strain A mice; ethyl carbamate was more potent than 2-hydroxy-ethyl carbamate. Intraperitoneal injection of ethyl carbamate or vinyl carbamate into male and female rats induced liver and ear duct carcinomas and neurofibrosarcomas of the ear lobe; vinyl carbamate showed more activity than ethyl carbamate (IARC 2010).

All together, the data are consistent with a metabolic activation pathway in which urethane (ethyl carbamate) is oxidised to vinyl carbamate, which is subsequently oxidised to the ultimately DNA-reactive agent, vinyl carbamate epoxide (see also 2.1).

2.7.3. Risk assessments

Against the background of residues of urethane found in food (see chapter 1), EFSA (2007) has performed a recent carcinogenic risk assessment. Based on the published experimental carcinogenicity data, a BMDL value (Benchmark Dose Level, based on a 10% incidence of alveolar and bronchiolar neoplasms in male and female mice) of 0.3 mg/kg bw per day was determined. For the case of urethane as a food contaminant, a Margin of Exposure (MOE) approach was used. As the normal dietary urethane exposure (excluding alcoholic beverages) was assessed to be in the ng/kg bw range, the resulting MOE of >10 000 was considered sufficient to conclude that this was safe.

In 2000, the Dutch DECOS committee selected rat and mouse data by Port *et al* (1976) for a human cancer risk assessment, considering the length of exposure and experimental period, the presence of a control group, adequate reporting and the occurrence of tumours in various organs and tissues. Based on these data, DECOS estimated the additional lifetime cancer risk for urethane to be:

4×10^{-5} for 40 years of occupational exposure to 0.002 mg/m^3, and
4×10^{-3} for 40 years of occupational exposure to 0.2 mg/m^3 (DECOS 2000).

2.8. Reproductive toxicity

There is strong evidence in experimental animals for the teratogenicity of urethane when administered during gestation. The teratogenic effects are evident in the offspring when either male or female rodents are exposed prior to mating or pregnancy. However, the effects on the reproductive system in mice and rats are minimal in general and occur only at high doses (IARC 2010).

Many older experimental publications have reported reproductive effects of urethane using excessively high doses, obviously exceeding the Maximally Tolerated Dose (MTD). As the narcotic effect of urethane is reached at a dose of about 2 g/kg bw (see 2.2), studies are not considered here, in which only doses at or above the limit dose of 1 g/kg were assessed. For details of all studies, see IARC (2010).

Sinclair (1950) observed that female mice became infertile when urethane was injected at a dose of 240 mg/kg. Injection of 120 mg/kg urethane into pregnant mice on day 7 of gestation produced abortions and lethal central nervous system defects.

Subcutaneous administration of 1 000 mg/kg urethane to pregnant ICR/Jcl mice on day 17 of gestation caused embryonic deaths, and malformation (skeletal defects and cleft palate) in the offspring (Nomura 1975). The same author found that three subcutaneous

injections of 150 mg/kg of urethane to pregnant ICR/Jcl mice on days 9, 10 and 11 led to a significant increase in foetal malformations (Nomura 1975).

Nakane and Kameyama (1986) studied the teratogenicity of urethane in CL/ Fr mice, characterised by a high incidence of cleft lip. Pregnant CL/Fr mice (30% of their offspring have spontaneous cleft lip with associated cleft palate) were treated with various doses of urethane on different days of pregnancy. In the groups treated with 250, 500 and 750 mg/kg of urethane on day 9 of pregnancy, the frequency of cleft lip/palate decreased with the dose to 18%, 14%, and 11% of term foetuses, respectively. In the group treated with 1 000 mg/kg of urethane on day 9, the frequency of cleft lip/palate decreased to 6%, but isolated cleft palate was observed in 23% of term foetuses. Most foetuses in the same group had severe tail anomaly and showed marked loss in body weight.

Treatment of NMRI mice with a single intraperitoneal injection of 800 mg/kg of urethane on day 14 of gestation caused increased incidences of polydactylism, cleft palate and micro-ophthalmia in foetuses (Burkhard and Fritz-Niggli 1987).

The NTP 13-week study with urethane in drinking water in F344/N rats (NTP, 1996) showed that the only parameter affected after reproductive system evaluation in males was lowered epididymal spermatozoal motility and concentration in the 78- and 287-mg/kg groups. When urethane was administered in 5% ethanol vehicle, the responses were similar to drinking water vehicle. The oestrous cycle length of female rats that received 201 mg/kg urethane in 5% ethanol was longer than that of the controls. This effect was not observed with urethane in drinking water at 332 mg/kg, but only at 525 mg/kg.

The NTP 13-week study with urethane in drinking water in B6C3F1 mice (NTP 1996) demonstrated that minimal to mild degeneration occurred in the testes of males administered 1 500 mg/kg. Degeneration of the seminiferous tubules, characterised by loss of germ cells and by the presence of a few to numerous spermatid giant cells within tubule lumens, was observed in five males receiving 1 500 mg/kg. The histopathologic changes in the testis were considered secondary to the debilitated condition of the mice, as these changes occurred only in mice that died early. Epididymal spermatozoal concentration was generally lower in exposed males than in the controls, and the difference was significant in the 40- and 191-mg/kg groups. Spermatozoal motility was also lower in males in the 191 mg/kg group than in the controls. In females, minimal to mild degeneration occurred in the ovaries at doses above 1 500 mg/kg. Females administered 1 500 mg/kg or above had degenerative changes of the ovarian follicles consisting of greater amounts of cell debris within developing follicles than occurred in control females. The histopathologic changes in the ovaries were considered secondary to the debilitated condition of the mice, as these changes occurred only in mice that died early. In seven females in the 511-mg/kg group, the ovaries were smaller than those of the controls as a result of decreased numbers of follicles and corpora lutea and the flattening of interstitial cells. Females that received 511 mg/kg had effectively ceased to have an oestrous cycle. In nine females, no cyclicity was demonstrated, while in the remaining female, the percentage of dioestrous smears was doubled. When urethane was administered in 5% ethanol the effects on epididymal spermatozoal concentration and motility in male mice did not seem to be enhanced. It was noted that if 5% ethanol had any effect on urethane toxicity in the male reproductive system in the mouse, the effect may have been masked due to the lower fluid, and therefore urethane, consumption in the 5% ethanol study. In females, the 5% ethanol vehicle appeared to enhance urethane-induced ovarian atrophy. Other effects detailed above for water vehicle were also observed with 5% ethanol as a vehicle.

Non-neoplastic lesions of the reproductive system in female B6C3F1 mice were assessed in the recent 2-year NTP study (NTP 2004). In the uterus of females exposed to

increasing concentrations of urethane in drinking water containing 0% or 2.5% ethanol, incidences of angiectasis (dilated vascular spaces lined by a single layer of essentially normal endothelial cells) and thrombosis occurred with positive trends, and the incidences in females exposed to 3 and 10 mg/kg of urethane were significantly increased. In female mice receiving urethane in 5% ethanol vehicle, no significant effect on these parameters was observed. Haemorrhage from large areas of uterine angiectasis was the cause of death in five females (one exposed to 3 mg/kg and four exposed to 10 mg/kg of urethane). No significant effects of urethane on the male reproductive system were reported in this study.

3. Recommendation

The toxicological concern regarding urethane is directed towards carcinogenicity. Non-neoplastic responses, including reproductive toxicity, occur only at high experimental doses, to which nowadays humans are no longer exposed.

Urethane was subject to repeated evaluation by IARC (1974, 2010). It is reasonably anticipated to be a human carcinogen, based on sufficient evidence of carcinogenicity in experimental animals. Urethane induces malignant tumours in rats and mice at a considerable multiplicity of target sites, after different modes of administration (see 2.7.2). Urethane is genotoxic, mutagenic and clastogenic, especially in the presence of metabolic activation. There is strong evidence to suggest that urethane is metabolically activated by a distinct route that leads to formation of the DNA-reactive epoxide of vinyl carbamate (see 2.1 and *Figure 1*). This epoxide gives rise to formation of specific DNA adducts, which are also formed by the human carcinogen vinyl chloride. Quantitatively, the specific DNA-adduct forming potency of urethane is about 2-4 fold lower than that of vinyl chloride, based on experiments in young and adult mice (Fernando *et al* 1996).

Considering all available data on carcinogenicity, genotoxicity and the plausible mode of action (with a strong similarity to that of the human carcinogen vinyl chloride), urethane is categorised in the SCOEL group A of genotoxic non-threshold carcinogens. A health-based Occupational Exposure Limit or Short-Term Exposure Limit cannot be derived. Occupational contact to urethane should be avoided. This is strengthened by risk assessments of DECOS (2000) and of EFSA (2007), the latter pointing to a benchmark dose level of 0.3 mg/kg bw (based on a 10% incidence of alveolar and bronchiolar neoplasms in male and female mice, see 2.7.3).

There is no literature data regarding possible skin penetration. Nevertheless, skin contact must carefully be avoided based on the local carcinogenicity of urethane to the skin.

There is no data regarding biological monitoring strategies in persons occupationally exposed to urethane.

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