5. Summary of Data Reported

5.1 Exposure data

Ethyl carbamate may be formed naturally as a result of fermentation and has been detected in a variety of fermented foods and alcoholic beverages. Ethyl carbamate can also be made commercially by various reactions with ethanol. It was formerly used in medical practice as a hypnotic agent, for the treatment of cancer, in particular multiple myeloma, or in analgesics. There is no evidence that ethyl carbamate is currently used in human medicine. It is used as an anaesthetic in veterinary medicine.

The levels of ethyl carbamate in wine and beer are usually below 100 µg/L, whereas higher levels (in the milligram per litre range) have been found in some stone-fruit spirits. Levels in foods have been regulated and significantly reduced during the past 20 years.

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

In many studies, mice treated orally with ethyl carbamate demonstrated an increased incidence 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 haemangiomas and haemangiosarcomas, Harderian gland adenomas or carcinomas and angiomas. Subcutaneous administration of ethyl carbamate to adult and newborn mice induced significant increases in the incidence of lung adenomas and hepatomas, respectively. Topical application of ethyl carbamate to mice resulted in a significant increase in the incidence of lung adenomas

and mammary gland carcinomas. Mice exposed by inhalation to ethyl carbamate had an increased incidence of lung adenocarcinomas, leukaemias and uterine haemangiomas. Intraperitoneal administration of ethyl carbamate to adult mice resulted in a significant increase in the incidence of 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 ethyl carbamate developed an increased incidence of lung tumours, hepatomas and ovarian tumours. Mice born after pre-conception exposure of the sires to ethyl carbamate had an increased incidence of pheochromocytomas and adrenal gland tumours.

In one study, oral administration of ethyl carbamate to mice deficient in CYP2E1 resulted in a lower incidence of liver haemangiomas and haemangiosarcomas, lung bronchioalveolar adenomas and carcinomas, and Harderian gland adenomas than that in mice proficient in CYP2E1. In other studies, when the administration of ethyl carbamate was accompanied by topical application of the tumour promoter, 12-*O*-tetradecanoylphorbol-13-acetate, the incidence of skin papillomas and squamous-cell carcinomas was significantly increased. When the treatment with ethyl carbamate was followed by topical application of croton oil, a significant increase in the incidence of skin papillomas resulted. Topical application of ethyl carbamate to mice previously treated with 7,12-dimethylbenz[*a*]anthracene resulted in a significant increase in the incidence of skin tumours.

Rats treated orally with ethyl carbamate had an increased incidence of Zymbal gland carcinomas and mammary gland carcinomas.

Hamsters treated orally with ethyl carbamate showed an increased incidence 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 ethyl carbamate.

The carcinogenicity of ethyl carbamate has been compared with that of *N*-hydroxyethyl carbamate, 2-hydroxyethyl 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*-hydroxyethyl 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*-hydroxyethyl 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 12-*O*-tetradecanoylphorbol-13-acetate, induced skin papillomas in female mice; vinyl carbamate epoxide was significantly more active than vinyl carbamate.

Subcubcutaneous injection of ethyl carbamate or *N*-hydroxyethyl 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*-hydroxyethyl carbamate into three different strains of mice, with or without promotion by topical application of croton oil, induced skin and/or lung tumours; ethyl carbamate had similar or greater activity than *N*-hydroxyethyl carbamate.

Intraperitoneal injection of ethyl carbamate or vinyl carbamate, with or without promotion by 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 *HRas2*, 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-hydroxyethyl carbamate induced lung adenomas in male strain A mice; ethyl carbamate was more potent than 2-hydroxyethyl 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.

These data indicate that, although *N*-hydroxyethyl carbamate and 2-hydroxyethyl-carbamate are carcinogenic, they probably do not make a significant contribution to the carcinogenicity of ethyl carbamate. The data are also consistent with a metabolic activation pathway in which ethyl carbamate is oxidized to vinyl carbamate, which is subsequently oxidized to vinyl carbamate epoxide.

5.4 Mechanistic and other relevant data

Ethyl carbamate is metabolized predominantly by CYP2E1, which generates metabolites (vinyl carbamate and vinyl carbamate epoxide) that are probably proximate carcinogens. The pathways for the metabolism of ethyl carbamate are similar in rodents and humans. Interactions between ethanol and ethyl carbamate are complex.

The data are too scant to make a comprehensive evaluation of the toxic effects of ethyl carbamate in humans.

At high doses, ethyl carbamate exhibits toxic effects on the central nervous system, the gastrointestinal tract, the spleen and the thymus in experimental animals. Lower doses lead to long-term effects on the spleen and the thymus.

There is strong evidence in experimental animals for the teratogenicity of ethyl carbamate when administered during gestation. The teratogenic effects are evident in the offspring when either male or female rodents are exposed before mating or pregnancy.

The effects of ethyl carbamate on the reproductive system in mice and rats are minimal and occur only at high doses.

Ethyl carbamate is genotoxic, mutagenic and clastogenic, especially in the presence of metabolic activation.

Possible mechanisms for the carcinogenicity of ethyl carbamate are induction of DNA damage by its metabolites and an increase in cell proliferation in target tissues.