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TOXICOLOGICAL EVALUATIONS

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TOXICOLOGICAL EVALUATION

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Carbamic acid butyl ester No. 273

CAS No. 592-35-8

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Carbamic acid butyl ester

Within the homologue series of aliphatic esters of carbamic acid, carbamic acid ethyl ester (urethane; CAS No. 51-79-6) with its marked mutagenic and carcinogenic effects clearly occupies a special position. Carbamic acid ethyl ester has therefore been placed in category 2 of carcinogenic compounds in the European Union and should be regarded as carcinogenic to humans. The explanation for its special position is that carbamic acid ethyl ester is the only compound of this type that is capable of forming a vinyl compound and, subsequently, an epoxide. Although only few studies are available on the metabolism of carbamic acid butyl ester, it can be excluded with a high degree of certainty that the chemical undergoes similar activation to yield mutagenic or carcinogenic metabolites.

1 Summary and assessment

In animal studies with oral or intravenous administration, 30 to 35% of the administered dose of carbamic acid butyl ester was excreted in urine, less than 1% in faeces and 61 to 64% as CO_2 in the exhaled air within 24 hours following administration, independently of the route of administration. After intravenous administration, the half-life of elimination from plasma was 0.96 hours. In rats, the metabolite N-hydroxycarbamic acid butyl ester has been detected in urine after intraperitoneal administration.

Based on the available acute toxicity study in rats, carbamic acid butyl ester is found to be harmful upon oral administration (LD_{50} rat oral 690 mg/kg body weight). Following acute intraperitoneal injection, the LD_{50} for mice is between 200 and 400 mg/kg body weight, while it is 540 mg/kg body weight following acute subcutaneous injection. In addition to unspecific signs of intoxication, the clinical signs observed after oral administration include difficulty in breathing, motor disturbances and reduced reflexes.

In the rabbit, carbamic acid butyl ester is not irritating to the skin, while it is severely irritating to the eye.

There are reports that carbamic acid butyl ester had a sensitising effect on the guinea pig skin in a Magnusson and Kligman maximisation test. However, the study is inadequate with respect to documentation and therefore

can not serve as a basis for final evaluation of the chemical’s skin-sensitising potential. The carbamate class of substances is not suspected of causing skin sensitisation.

In vitro, the Salmonella/microsome assay on *Salmonella typhimurium* and *Escherichia coli* gives no indications in the absence or presence of metabolic activation that carbamic acid butyl ester has mutagenic properties. Two gene mutation tests on *Escherichia coli* (resistance to bacteriophage T, reversion from streptomycin dependence to independence) have given a negative and a weakly positive result. In vivo, acute intraperitoneal injection of carbamic acid butyl ester into mice resulted in only transient, low binding to DNA from liver, kidneys and lungs, whereas no binding was detected in DNA from the dermis and epidermis. On the basis of existing studies, it is not possible to deduce a genotoxic potential for carbamic acid butyl ester.

The studies conducted so far to investigate the carcinogenic potential of carbamic acid butyl ester in mice after oral, intraperitoneal and subcutaneous administration do not meet current requirements with respect to experimental setup, scope and documentation. In those studies, carbamic acid ethyl ester (urethane) was also investigated in parallel. In all studies, tumour incidence rates were significantly increased by administration of carbamic acid ethyl ester, whereas treatment with carbamic acid butyl ester did not increase tumour incidence. Only in the case of one study conducted in female mice, which again was not valid, was intraperitoneal injection reported to have caused an increase in mammary tumour incidence. The overall conclusion is that a carcinogenic potential can not be excluded on the basis of the existing invalid studies. However, the chemical does not appear to have a relevant carcinogenic potential.

In an exploratory embryotoxicity and teratogenicity study in the Syrian hamster, single intraperitoneal administration of carbamic acid butyl ester on day 8 of gestation did not lead to an increase in the incidence of external or skeletal malformations. Due to the insufficient number of animals, the unusual route of administration and the unusual day of foetal examination, the study can not be used for the purpose of evaluation.

2 Name of substance

2.1	Usual name	Carbamic acid butyl ester
2.2	IUPAC name	Carbamic acid butyl ester
2.3	CAS No.	592-35-8
2.4	EINECS No.	209-751-0

3 Synonyms, common and trade names

AI3-28289
Butyl carbamate
n-Butyl carbamate
n-Butylcarbamat
Butylurethan
n-Butylurethan
Carbamic acid, butyl ester
Carbamidsäurebutylester
Carbamidsäure-butylester
Carbamidsäure-n-butylester
Carbaminsäurebutylester
Carbaminsäure, butyl-ester

4 Structural and molecular formulae

4.1 Structural formula

$$H_2N-\overset{\overset{\displaystyle O}{\|}}{C}-O-CH_2-CH_2-CH_2-CH_3$$

4.2 Molecular formula $C_5H_{11}NO_2$

5 Physical and chemical properties

5.1	Molecular mass, g/mol	117.15	
5.2	Melting point, °C	51	(Hoechst, 1988 a)
		53	(Lide and Frederikse, 1996)
		54	(Fuks and Hartemink, 1973; Jäger et al., 1986)

5.3	Boiling point, °C	204 (decomposition) (Lide and Frederikse, 1996) 204 (at 1013 hPa) (Jäger et al., 1986) 113 (at 24 hPa) (Hoechst, 1988 a) 108 (at 14 hPa) (Lide and Frederikse, 1996)
5.4	Vapour pressure, hPa	No information available
5.5	Density, g/cm³	0.972 (at 52 °C) (Hoechst, 1988 a)
5.6	Solubility in water	1 g/l (at 20 °C) (Hoechst, 1991) 25.8 g/l (at 37 °C) (Houston et al., 1974)
5.7	Solubility in organic solvents	Soluble in alcohols, esters and ketones (Hoechst, 1988 a) High solubility in ethanol, low solubility in chloroform (Lide and Frederikse, 1996)
5.8	Solubility in fat	Dissolves well in fat (Hoechst, 1988 a) Partition coefficient n-octanol/water, log P_{ow}: 0.85 (measured) (Houston et al., 1974) log P_{ow}: 0.88 (calculated) (EC, 1996)
5.9	pH value	–
5.10	Conversion factor	1 ml/m³ (ppm) ≙ 4.79 mg/m³ 1 mg/m³ ≙ 0.209 ml/m³ (ppm) (at 1013 hPa and 25 °C)

6 Uses

Intermediate in the manufacture of synthetic resins (Hoechst, 1991).

7 Experimental results

7.1 Toxicokinetics and metabolism

In vivo

Male Wistar rats (Porton strain; weighing 300 g) were administered a single intravenous or oral dose (given intraduodenally using a syringe with a long

blunted needle) of ^{14}C-labelled carbamic acid butyl ester at 5 µmol/kg body weight (equivalent to approx. 0.6 mg/kg body weight) in physiological saline solution. Within 24 hours after intravenous and oral dosing, 29.9 and 34.6% of the administered radioactivity was excreted in the urine, less than 1% the in faeces and 64.2 and 60.8% as CO_2 in the exhaled air, respectively. Less than 5% of the radioactivity excreted in urine represented unchanged test substance. Urine and plasma contained detectable amounts of at least two polar metabolites (oxidation products; no further details). Following intravenous injection, the plasma elimination half-life for carbamic acid butyl ester was found to be 0.96 hours, the steady-state volume of distribution being 583 ml/kg body weight. The suggested metabolic pathways are shown in Figure 1 (Sargent et al., 1982 a).

Figure 1. Suggested metabolic pathways for carbamic acid butyl ester (based on Sargent et al., 1982 a)

$CH_3(CH_2)_3O^{14}C(=O)NH_2$
Carbamic acid butyl ester

[Oxidation] → $CH_3(CH_2)_3O^{14}C(=O)NHOH$
N-Hydroxycarbamic acid butyl ester
H_2O → $^{14}CO_2$ + $CH_3(CH_2)_3OH$ Butanol + NH_2OH Hydroxylamine

[Oxidation] → $CH_3(CH_2)_2CH(OH)O^{14}C(=O)NH_2$
Carbamic acid hydroxybutyl ester
→ $CH_3(CH_2)_2CHO$ Butanal + $NH_2{}^{14}COOH$ Carbamic acid
→ $^{14}CO_2 + NH_3$

Esterase → $^{14}CO_2$ + $CH_3(CH_2)_3OH$ Butanol + NH_3

Female rats (body weight approx. 200 g) received a single intraperitoneal injection of carbamic acid butyl ester at a dose level of 300 or 400 mg/kg body weight. Urine was collected during the first 2 days after administration (24-hour collection periods), and the urinary amounts of unchanged test substance (urinary recovery rate 65%) and of the metabolite, N-hydroxy-carbamic acid butyl ester (urinary recovery rate approx. 100%), were determined. In the first and the second 24-hour period after administration, between 0.8 and 1.1%, respectively, of the administered dose was recovered in the urine as unchanged test substance while between 0.06 and 0.09%, respectively, was found as N-hydroxycarbamic acid butyl ester (no further details; Boyland and Nery, 1965).

The absorption of carbamic acid butyl ester was studied in situ in 4 male Porton rats (weighing 200 to 250 g) following administration (by cannulation) of [^{14}C-carbonyl]-carbamic acid butyl ester at approx. 13 mg/kg body weight into the colon. The animals were starved for 20 hours prior to dosing. The absorption rate constant ($K_a = (\ln 2)/t_{½}$; 0.0574 ± 0.0028 minute^{-1}) was calculated from the half-life of disappearance of the test substance from the colon lumen, which was approx. 12 minutes. Twenty minutes after administration, 0.89% of the dose was found in the colon wall (Wood et al., 1978).

In rats which had free access to food and water, an in-situ study on the intestinal absorption of carbamic acid butyl ester at initial concentrations of 0.1 mM (equivalent to 11.7 µg/ml) and 10 mM (equivalent to 1171.5 µg/ml) in the lumen gave respective absorption rate constants ($K_a = (\ln 2)/t_{½}$) of 0.186 and 0.175 minute^{-1}, as calculated from the half-life of approx. 4 minutes for the disappearance of the test substance from the intestinal lumen. Thirty minutes after administration, 0.94% of the dose was found in the intestinal wall (Wood et al., 1979).

In a further in-situ study on the gastric and intestinal absorption of carbamic acid butyl ester in male rats (Porton strain; body weight 190 to 210 g) with free access to food and water, an initial gastric concentration of 10 µmol/ml (equivalent to 1171.5 µg/ml) gave respective gastric and intestinal absorption rate constants ($K_a = (\ln 2)/t_{½}$) of 0.0077 and 0.175 minute^{-1}, as calculated from the respective half-lives of approx. 90 and 4 minutes for the disappearance of the test substance from the gastric and the intestinal lumen. Absorption from the stomach and the intestine was found not to be pH-dependent (Houston et al., 1974).

When female Wistar rats (3 or 4 rats/concentration; weighing 180 to 230 g) were treated in situ with [^{14}C]-carbamic acid butyl ester by intravesicular instillation of 0.5, 5.0 and 50 µmol/kg body weight (equivalent to approx. 0.06, 0.6 and 6 mg/kg body weight, respectively) into the urinary bladder, the respective half-lives for the disappearance of the test substance from the bladder were ascertained as 9.9 ± 2.2, 10.8 ± 0.2 and 11.1 ± 1.7 minutes. Absorption of carbamic acid butyl ester via the urinary bladder took place by passive diffusion. Only approx. 3 minutes after intravesical instillation of 5.0 µmol/kg, carbamic acid butyl ester equivalent was detected in plasma at levels of approx. 1 nmol/ml. After 17 minutes the plasma levels of carbamic acid butyl ester equivalent were approx. 3.5 nmol/ml, and from approx. 32 to 150 minutes after administration, the plasma levels reached a maximum (approx. 4 to 5 nmol/ml; as determined graphically from plots). Thirty minutes after instillation of 5.0 µmol/kg, 0.64 ± 0.37% of the administered dose was found to be bound to the bladder wall (Bridges et al., 1979; Sargent et al., 1979).

In vitro

In an in-vitro study on the intestinal absorption of carbamic acid butyl ester (10, 25 and 50 mM) from the isolated ileum of male Porton rats, it was found that irrespective of the concentration used, 6.6%/cm² ileum/hour was absorbed and that 1.27%/cm² ileum was bound to tissue at 1 hour. No metabolites were detected, and the recovery rate for carbamic acid butyl ester averaged 95 ± 3.45% (Houston et al., 1974).

In vitro, carbamic acid butyl ester binds to cytochrome P-450 in liver microsomes prepared from phenobarbital-induced male Wistar rats. Upon one-hour incubation at 37 °C, the unconjugated ω-1-hydroxylation product and small amounts of CO_2 were identified as metabolites (Sargent et al., 1982 b).

Following incubation of isolated rat hepatocytes with radiolabelled carbamic acid butyl ester for one hour, there was no detectable covalent binding of the metabolites in the hepatocytes (no further details; Sargent et al., 1982 a).

7.2 Acute and subacute toxicity

In a study on the acute oral toxicity of carbamic acid butyl ester which was conducted in Wistar rats in accordance with OECD guideline No. 401, the LD_{50} was found to be 690 mg/kg body weight for female rats. The males

were only tested at one dose level (500 mg/kg body weight), a dose which was not lethal. Males and females showed unspecific signs of toxicity in addition to difficulty in breathing, motor disturbances and reduced or absent righting and paw pinch reflexes. In addition, a few females were observed to have diarrhoea, splayed legs, clear lacrimation and noses with bloody encrustations. All clinical signs were reversible within 8 days after administration. Development of body weight was normal in the animals surviving the 14-day observation period. Deaths occurred up to day 5 following administration. Necropsy of the animals which died revealed macroscopic changes in the spleen (marked reduction in size), lung (dark spots), gastrointestinal tract (filled with test substance and light yellow to reddish-brown liquid, positive test for blood) and bladder (filled to bursting with dark liquid, positive test for blood). The animals which were sacrificed at the end of the observation period showed no macroscopically visible changes (Hoechst, 1988 a).

For mice (Carworth Farms CFW), an LD_{50} of 400 mg/kg body weight was ascertained following acute intraperitoneal administration of carbamic acid butyl ester. The observation period was 10 days. Carbamic acid butyl ester exhibited anaesthetising to general anaesthetic activity (anaesthesia lasting approx. 2 hours and ½ hour at 400 and 200 mg/kg body weight, respectively, and slight loss of co-ordination occurring at 100 mg/kg body weight; Skipper et al., 1948).

In a further study investigating the acute intraperitoneal toxicity of carbamic acid butyl ester in CF_1 mice (Carworth Farms), the approximate LD_{50} was in the range from 200 to 300 mg/kg body weight when propylene glycol was used as a solvent, while it was > 1000 mg/kg body weight when water was the solvent (observation period 7 days; no further details; Doull et al., 1962).

Following acute subcutaneous injection of carbamic acid butyl ester into male Hall mice (body weight 25 ± 1 g), the LD_{50} was determined as 540 mg/kg body weight. The observation period was 24 hours. Carbamic acid butyl ester caused narcosis of short duration (approx. 2 hours) in the mice (Pound, 1967).

7.3 Skin and mucous membrane effects

In a skin irritancy study carried out in accordance with OECD guideline No. 404, 3 New Zealand rabbits (weighing 2.9 to 3.3 kg) underwent expo-

sure to 500 mg carbamic acid butyl ester (mixed into a paste with 0.18 ml polyethylene glycol 400) by semi-occlusive application to a depilated area of intact skin of approx. 25 cm² on the dorsal part of the trunk. The test substance was approx. 94% pure (impurities: 5.5% dibutyl carbonate, 0.6% n-butanol). The exposure period was 4 hours. Following exposure, any remaining chemical was carefully removed from the skin with lukewarm tap water. The effects were assessed 30 to 60 minutes and 24, 48 and 72 hours after removal of the adhesive dressing. From 30 minutes to 24 hours after removal of the patch, one animal showed very mild erythema. At 48 hours after patch removal none of the animals had signs of irritation. Based on these results, the substance was evaluated as not irritating to the skin (Hoechst, 1988 b).

In a mucous membrane irritation study carried out in accordance with OECD guideline No. 405, 3 New Zealand rabbits (weighing 2.1 to 3.3 kg) each had a single 100 mg dose of carbamic acid butyl ester instilled into the conjunctival sac of the left eye. The untreated eye served as the control. Assessment of the eyes was carried out 1, 24, 48 and 72 hours and 7 days following instillation. After 24 hours, 72 hours and 7 days, the cornea was examined in addition. From 1 to 72 hours after instillation, the iris was reddened in all of the animals. One hour to 7 days after instillation, the animals' conjunctivae were slightly swollen to swollen, the eyelids being more than half-closed, and there was hyperaemia which ranged from marked hyperaemia of some of the blood vessels to a diffuse, intense red colour. The animals' corneas exhibited diffusely opaque to mother-of-pearl-like areas. The signs of irritation were accompanied by clear or white and slimy ocular discharge. From 24 to 72 hours following instillation, the animals' conjunctivae at times exhibited white discoloration and haemorrhage. Seven days after instillation, all animals were observed to have early or advanced stages of vascularisation. Based on these results, the substance was evaluated as severely irritating to the eye (Hoechst, 1988 c).

7.4 Sensitisation

The sensitisation potential of carbamic acid butyl ester was studied in 20 female Hartley guinea pigs in the Magnusson and Kligman maximisation test. Intracutaneous induction was carried out with a formulation containing 5% test substance in ethanol, whereas for dermal induction a 25% solution

of test substance in ethanol (70%) was used. Dermal challenge was carried out 14 days after induction by percutaneous injection of a solution containing 0.2 or 1% test substance in ethanol (70%) into the shorn left flank of each of 10 animals/concentration (no information given on controls). The concentrations used for the challenge were lower than the threshold concentration of 2% which was evaluated as causing minimal irritation in a preliminary study. Twenty-four and 48 hours after removal of the patch, irrespective of the challenge concentration, sensitisation scores of 3 and 2 on a 5-point scale were ascertained (no information given on the number of animals showing a reaction or on the definitions of the degrees of sensitisation; Matsushita et al., 1977).

7.5 Subchronic and chronic toxicity

No information available.

7.6 Genotoxicity

7.6.1 In vitro

Carbamic acid butyl ester was tested for its mutagenic potential in the Salmonella/microsome assay (standard-plate incorporation test) using *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, TA 1537 and TA 1538 as well as *Escherichia coli* WP2uvrA in the absence and presence of metabolic activation (S-9 mix from Aroclor 1254-induced rat liver). The test substance was approx. 94% pure (impurities: 5.5% dibutyl carbonate, 0.6% n-butanol). Per concentration 3 plates were used. The test was repeated in independent experiments with concentrations ranging from 4 to 5000 µg/plate. Carbamic acid butyl ester was devoid of bacteriotoxicity at concentration levels of up to 10000 µg/plate. There were no indications of mutagenic activity either with or without metabolic activation (Hoechst, 1988 d).

The spot and fluctuation tests carried out in *Escherichia coli* WP2uvrA without metabolic activation also gave no indications that carbamic acid butyl ester (purity not specified) possessed any mutagenic activity. Concentrations of 5 to 10 mg/plate (spot test) and 0.6 mg/ml (fluctuation test) were used. Parallel studies on carbamic acid ethyl ester (purity not specified) also gave negative results (Pai et al., 1978, 1985).

Similarly, a gene mutation test (resistance to bacteriophage T) carried out in *Escherichia coli* B gave no indications that carbamic acid butyl ester (purity not specified) possessed any mutagenic activity. The chemical was used at a concentration of 0.8 or 0.9% (the information given in the two publications differs), the incubation period ranging from 0.6 to 2.5 hours in 5 independent runs. In a parallel study, carbamic acid ethyl ester (purity not specified) was tested at a concentration of 5% with incubation periods ranging from 0.5 to 2.5 hours, and gave positive results (no further details; Latarjet et al., 1949; Latarget et al., 1988).

In a study conducted in the streptomycin-dependent strains B/Sd-4/1,3,4,5 and B/Sd-4/3,4 of *Escherichia coli* (back-mutation from streptomycin dependence to nondependence), carbamic acid butyl ester (purity not specified) concentrations of 0.5 to 0.8% showed weak mutagenic activity, according to the investigators' interpretation. The incubation period was 3 or 3.5 hours, and the bacteriotoxic range was identified (the respective survival rates at 0.5 and 0.8% were 86 and 4.9% of the negative control). By contrast, carbamic acid ethyl ester (purity not specified) proved positive at concentrations of 3.5 to 7% and incubation periods of 3 to 4.5 hours (Demerec et al., 1951).

7.6.2 In vivo

Male Crackenbush mice were given 10 mg/mouse carbamic acid butyl ester (labelled with ^{14}C at the C_1 position of the alkyl group; 6 µCi) as a single intraperitoneal injection. This was equivalent to a dose of approx. 333 mg/kg body weight, based on an average body weight of approx. 30 g. At different time points (3, 6, 9, 12 and 24 hours) after administration, groups of 8 animals/time point of assessment had the DNA from the lungs, liver and kidneys extracted by a modified phenol method, after which the DNA binding of carbamic acid butyl ester was determined with the aid of radioactivity measurements. The binding of butyl ester to DNA extracted from liver, kidney and lung was detected to be merely transient and low, reaching a maximum by 3 hours after administration (liver and kidney: approx. 10 and 6.6 dpm/mg DNA, respectively; lung: activity not given). After 9 to 12 hours, only minimal to no DNA binding was detectable. Analogous studies were conducted with 1-^{14}C-, 2-^{14}C- and carbonyl-^{14}C-carbamic acid ethyl ester. At 12 hours, maximum radioactivity levels were found in the liver with

1-^{14}C- and 2-^{14}C-carbamic acid ethyl ester (328 ± 24 dpm/mg DNA and 267 ± 24 dpm/mg DNA, respectively), whereas only 26 ± 2 dpm/mg DNA was measured with carbonyl-^{14}C-carbamic acid ethyl ester. Even after 24 hours, radioactivity was still detectable with 1-^{14}C- and 2-^{14}C-carbamic acid ethyl ester. Therefore, carbamic acid ethyl ester exhibited significant binding to liver DNA, but the carbonyl carbon atom was not involved in the DNA binding (Lawson and Pound, 1973).

In a further study carried out to investigate the DNA binding of carbamic acid butyl ester, male Crackenbush mice received a single intraperitoneal dose of 10 mg/mouse carbamic acid butyl ester (labelled with ^{14}C at the C_1 position of the alkyl group; 6 µCi; equivalent to approx. 308 mg/kg body weight, based on an average body weight of 33 g). At 3, 6, 12 and 24 hours following administration, groups of 6 animals/time point of assessment had the DNA extracted from the dermis and epidermis. No DNA binding of carbamic acid butyl ester could be detected with the aid of radioactivity measurements. By contrast, the comparative studies with the ethyl ester showed maximum binding after 12 hours, with binding being greater in the dermis than in the epidermis (dermis 490 µmol/g DNA, epidermis 164 µmol/g DNA). Pretreatment with croton oil (single topical treatment with 0.25 ml of a 0.15-percent solution in acetone) 16 hours prior to intraperitoneal administration of carbamic acid butyl ester was associated with transient detectable DNA binding. The respective levels of DNA-associated specific activity measured in the epidermis and dermis 12 hours after administration of carbamic acid butyl ester were 228 and 210 µmol/g DNA, while they were 95 and 75 µmol/g DNA at 24 hours. When the skin was pretreated with croton oil prior to intraperitoneal administration of carbamic acid ethyl ester this caused binding in the dermis to double compared with non-pretreated animals (887 µmol/g DNA), and in the epidermis, binding was 5 times as high as in non-pretreated animals (842 µmol/g DNA; Pound and Lawson, 1976).

When carbamic acid butyl ester was administered intraperitoneally to male Wistar rats (weighing 250 to 300 g) at 1000 mg/kg body weight, the activity of Mg^{2+}-dependent RNA polymerase was not inhibited in cell nuclei isolated from lung tissue one hour after administration. By contrast, carbamic acid ethyl ester inhibited the activity of Mg^{2+}-dependent RNA polymerase by approx. 50% in comparative studies, maximum inhibition being reached one hour after administration. Twenty hours after administration, activity levels

of Mg^{2+}-dependent RNA polymerase were back within the normal range. Mn^{2+} + $(NH_4)_2SO_4$-dependent RNA polymerase was not affected by carbamic acid ethyl ester (Eker, 1975).

7.7 Carcinogenicity

Male and female Swiss mice (3 months old; 50 mice/group) were given 0.2% carbamic acid butyl ester, 0.01% carbamic acid ethyl ester or 0.2% carbamic acid butyl ester plus 0.01% carbamic acid ethyl ester in their drinking water for 16 weeks. A relatively large number of animals died in the course of the study, which could not be evaluated due to autolysis (no further details). At necropsy of the survivors at the end of an 8-week treatment-free observation period, pulmonary tumours were found in 11 out of 24 animals of the carbamic acid butyl ester group (on average one tumour/tumour-bearing animal), in 18 out of 18 animals given carbamic acid ethyl ester (on average 19 tumours/tumour-bearing animal) and in 52 out of 63 animals (on average 6.3 tumours/tumour-bearing animal) in the group which was treated with carbamic acid butyl ester plus carbamic acid ethyl ester. According to the investigators, 1 or 2 tumours/animal corresponded to the spontaneous tumour rate (no further details; in particular, no details of untreated control animals, systemic effects or histopathological findings; Lespagnol et al., 1969).

In a screening test carried out in male mice (Strain A/He; 7 to 9 weeks old; weighing 23 25 g; 16 or 32 mice/group), intraperitoneal administration of carbamic acid butyl ester at 5 mg/mouse, formulated in tricaprylin, 3 times per week for 4 weeks (total dose 60 mg/mouse) did not result in any increase in the incidence of lung tumours as compared with the vehicle control at the end of a 20-week observation period. In the carbamic acid butyl ester group, 14% of the animals developed pulmonary tumours, while the respective percentages in the tricaprylin-treated, water-treated and untreated control animals were 25, 19 and 7%. However, when carbamic acid ethyl ester was administered as a comparator, 100% of the animals had pulmonary tumours. During the study, 2 out of 16 animals of the carbamic acid butyl ester group, 4 out of 16 animals of the carbamic acid ethyl ester group and 1 out of 32, 4 out of 32 and 1 out of 32 animals from the respective control groups died (no further details; in particular, no details of systemic effects or additional histopathological findings; Shimkin et al., 1969).

Upon intraperitoneal administration of 0.25 mg/g body weight carbamic acid butyl ester in tricaprylin to male and female mice (Strain A; 10 to 12 weeks old; body weight unspecified) once per week for a period 13 weeks followed by an observation period of 2 to 3 weeks, 4 out of 33 mice (12%) had pulmonary tumours (controls 17%). The number of tumours/animal averaged 0.12 (controls 0.18). Dose levels of 0.5 and 0.375 mg/g body weight induced rapid and deep narcosis, with about 40% of the mice dying within 2 hours (no further details). Following administration of carbamic acid ethyl ester as a comparator (0.5 mg/g body weight), all 102 treated animals (100%) showed tumours. The number of tumours/animal averaged 76.9 (no further details; Larsen, 1947).

Thirty female C_3H mice (8 to 10 weeks old; weighing approx. 18 g) were given intraperitoneal injections of carbamic acid butyl ester at 6.595 mg/mouse/day, carbamic acid ethyl ester at 5 mg/mouse/day or a combination of 5 mg carbamic acid ethyl ester and 6.595 mg carbamic acid butyl ester on 6 consecutive days. The observation period was 51 weeks. A group of 30 untreated females served as controls. Those animals from the substance groups and the control group which died shortly after administration were not included in the final results of the study (no further details). There was a significant increase in the incidence of mammary tumours in the substance groups (carbamic acid ethyl ester: 12 out of 24 animals (50%); carbamic acid butyl ester: 16 out of 27 animals (59.2%); carbamic acid ethyl ester plus carbamic acid butyl ester: 17 out of 24 animals (70.8%); controls: 8 out of 22 animals (36.3%)). According to the investigators, simultaneous administration of carbamic acid ethyl ester and carbamic acid butyl ester produced an additive effect. In the group treated with carbamic acid butyl ester, 24.9% of females with mammary tumours had lung metastases, whereas in the groups given carbamic acid ethyl ester or the combination of carbamic acid ethyl ester and carbamic acid butyl ester, the respective percentages were 58.3% and 23.5% (controls 12.5%; no details of systemic effects or histopathological findings; Garcia and Guerrero, 1969).

Two-stage studies

Groups of 30 female Swiss mice (8 weeks old; weighing 20 to 28 g) received total doses of 1.17 or 5.85 mg carbamic acid butyl ester, 0.89 mg

carbamic acid ethyl ester, 0.89 mg carbamic acid ethyl ester plus 1.17 mg carbamic acid butyl ester or 0.89 mg carbamic acid ethyl ester plus 5.85 mg carbamic acid butyl ester per gram of body weight as repeated fractionated intraperitoneal doses (number of administrations not given). Subsequent to initiation, promoting treatment was administered by painting 0.5-percent croton oil (in acetone) onto the clipped skin (interscapular area) twice weekly for 45 weeks. The animals of a control group received dermal applications of croton oil for 45 weeks. After 40 weeks, skin papillomas were seen in the area of the interscapular region in 5 out of 30 animals from the group receiving 1.17 mg carbamic acid butyl ester, in 2 out of 28 animals from the group treated with 5.85 mg carbamic acid butyl ester, in 13 out of 30 animals given 0.89 mg carbamic acid ethyl ester, in 7 out of 30 animals from the group receiving 0.89 mg carbamic acid ethyl ester plus 1.17 mg of the butyl ester and in 3 out of 23 animals from the group given 0.89 mg carbamic acid ethyl ester plus 5.85 mg of the butyl ester (control group: 1 out of 29 animals). At the end of the study period of 58 to 60 weeks the animals were killed and their skin examined by microscopy. In each of the three groups which received carbamic acid ethyl ester, one tumour was identified as a squamous cell carcinoma (no further details; Garcia, 1963).

Groups of 40 male Hall mice received single subcutaneous administrations of 10 mg carbamic acid butyl ester or 25 mg carbamic acid ethyl ester per mouse. Eighteen hours prior to administration, the right side of each animal's back was treated with 25-percent acetic acid in acetone. From 2 weeks after administration of the test substance, promoting treatment was administered by giving the back 24 weekly dermal applications of 0.25 ml/animal 0.075-percent croton oil (in acetone) during a period of 26 weeks. A control group (80 animals) was treated with croton oil. The incidence of skin tumours was significantly increased relative to the control. In the group treated with carbamic acid butyl ester, 3 out of 15 survivors had a total of 5 skin tumours, whereas in the group given carbamic acid ethyl ester, there were 16 out of 30 survivors with a total of 55 skin tumours (controls: 2 out of 41 survivors had a total of 3 skin tumours). When carbamic acid butyl ester was given as a single subcutaneous injection without any promoting treatment with croton oil, no significant increase in tumour incidence was observed at study termination after 26 weeks. Following subcutaneous injection of carbamic acid ethyl ester, one animal devel-

oped a papilloma in the area of skin that had previously been treated with acetic acid (no further details; in particular, no details of systemic effects or histopathological findings; Pound, 1967).

Groups of 40 male Hall mice (weighing approx. 26 g at the beginning of the study) were given a single subcutaneous dose of 25 mg carbamic acid ethyl ester or a combination of 25 mg carbamic acid ethyl ester and 5, 10 or 15 mg carbamic acid butyl ester per animal. From day 7 after the injection, the animals had 0.25 ml croton oil (0.5% in acetone) painted onto the skin of the back once a week for 20 weeks (5 mg carbamic acid butyl ester group) or 0.25 ml croton oil (0.075% in acetone) applied to the skin of the back once a week for 28 weeks. At weeks 22 and 36, respectively, the animals were examined for skin tumours. The animals which had received carbamic acid ethyl ester in combination with carbamic acid butyl ester showed no increase in the incidence of skin tumours as compared with those which had received carbamic acid ethyl ester alone (the numbers of tumour-bearing animals in the groups treated with 25 mg carbamic acid ethyl ester were 7 out of 38, 19 out of 34 and 19 out of 33 having a total of 10, 42 and 43 tumours, respectively; in the group given 25 mg carbamic acid ethyl ester plus 5 mg carbamic acid butyl ester, there were 8 tumour-bearing animals out of 33 with a total of 13 tumours; in the group given 25 mg carbamic acid ethyl ester plus 10 mg carbamic acid butyl ester 5 out of 9 animals had a total of 8 tumours). All animals which had received 25 mg carbamic acid ethyl ester plus 15 mg carbamic acid butyl ester died within 24 hours. Out of the 9 survivors beyond week 40 which had received 25 mg carbamic acid ethyl ester plus 10 mg carbamic acid butyl ester, 6 mice had developed a total of 10 skin tumours, 4 mice had a total of 9 lung adenomas, one mouse had a tumour of the liver (haemangiosarcoma) and there were 2 mice with leukaemia. In the dose group which had been given 25 mg carbamic acid ethyl ester alone, out of 33 mice there were 16 mice with 24 skin tumours, 15 had 41 lung adenomas, 4 had liver tumours and 4 had leukosis (no further details; in particular, no details of systemic effects or additional histopathological findings; Pound, 1972).

In a further study in male Hall mice (body weight approx. 25 g; age approx. 7 weeks), groups of 30 mice received initiation treatment by single intraperitoneal injection of carbamic acid butyl ester at 3.4 mEq (milliequivalents)/kg body weight or carbamic acid ethyl ester at 5.6 mEq/kg body weight without croton oil pretreatment or 18 hours after pretreatment with

croton oil (single dermal application of 0.25 ml croton oil (0.075-percent in acetone)). From 3 weeks after initiation, promoting treatment was administered by dermal application to the clipped dorsal skin of 0.24 ml 0.075-percent croton oil (in acetone)/animal once weekly for 18 weeks and subsequent application of 0.24 ml 0.15-percent croton oil (in acetone) once weekly up to the 32nd week. A group of 90 animals served as untreated controls. The study was terminated 78 weeks after administration of the test substance. The yields of skin tumours, hepatomas, liver haemangiomas, lung adenomas and leukaemia are shown in Table 1. Whether pretreated with croton oil or not, the mice showed no increase in the yields of skin tumours, lung adenomas or leukaemia after administration of carbamic acid butyl ester. The number of hepatocellular tumours seen after pretreatment with croton oil was considered by the investigators to be of doubtful significance. In contrast, application of carbamic acid ethyl ester significantly enhanced the yields of all types of tumour investigated, whether the animals were pretreated with croton oil or not (Pound and Lawson, 1976).

Table 1. Tumour yields as determined 78 weeks following single intraperitoneal administration of carbamic acid butyl ester or carbamic acid ethyl ester with or without croton oil pretreatment (0.075% in acetone)

Carbamic acid ester	Pretreatment	Number of mice studied	Number of mice with					
			skin tumours	hepatomas	liver haemangiomas	hepatomas and haemangiomas	lung adenomas	leukaemia
Carbamic acid butyl ester	without	26	2 (7.7%)	2 (7.7%)	1 (3.8%)	1 (3.8%)	5 (19%)	2 (7.7%)
Carbamic acid butyl ester	with croton oil	27	3 (11%)	3 (11%)	3 (11%)	1 (3.7%)	6 (22%)	2 (7.4%)
Carbamic acid ethyl ester	without	22	8 (36.4%)	6 (27.3%)	7 (31.8%)	2 (9%)	13 (59%)	6 (27.3%)
Carbamic acid ethyl ester	with croton oil	24	10 (41.7%)	6 (25%)	6 (25%)	3 (12.5%)	18 (75%)	5 (20.8%)
Controls	–	79	10 (12.7%)	4 (5%)	3 (3.8%)	0	15 (19%)	7 (8.9%)

None of the studies conducted so far to investigate the carcinogenic potential in mice meet current requirements with respect to experimental setup, scope and documentation. In these studies, parallel investigations were carried out with carbamic acid ethyl ester (urethane), a chemical which in

the European Union has been placed in category 2 of carcinogenic substances ("substances which should be regarded as if they are carcinogenic to man"; GefStoffV, 1997). In all studies, tumour yields were significantly increased by administration of carbamic acid ethyl ester, whereas treatment with carbamic acid butyl ester was found to increase only the yield of mammary tumours.

7.8 Reproductive toxicity

Pregnant Syrian hamsters (2 or 3 hamsters/group) were given a single intraperitoneal injection of carbamic acid butyl ester at a dose level of approx. 129, 246 or 492 mg/kg body weight on day 8 of gestation. A control group of 19 pregnant females was treated with physiological saline solution. There were no deaths in the low and intermediate dose groups (0 out of 2 and 0 out of 3 pregnant females, respectively), while in the high dose group 2 out of 3 pregnant animals died. At necropsy on day 13 of gestation, the number of implantations/dam was in the range of the controls in all 3 dose groups. Embryomortality (percentage of dead or resorbed foetuses/pregnant female) was 12.5, 10.8 and 100% in the low, mid and high dose group, respectively (controls 11.1%). The live foetuses of the low and intermediate dose groups were not observed to have any external or skeletal malformations (DiPaolo and Elis, 1967). Due to the insufficient number of animals, the unusual route of administration and the unusual day of foetal examination, the study can not be used for the purpose of evaluating the teratogenic potential of carbamic acid butyl ester.

7.9 Effects on the immune system

No information available.

7.10 Neurotoxicity

No information available.

7.11 Other effects

In the deer mouse (*Peromyscus maniculatus*), an LD_{fr} of 1213 mg/kg body weight/day was ascertained following oral administration of carbamic acid butyl ester. The LD_{fr} represented the dose ingested with the feed over a 3-day test period without killing more than 50% (Schafer and Bowles, 1985).

In vitro, carbamic acid butyl ester bound to bovine serum albumin independently of the temperatures used in the experiments (10 and 37 °C; approx. 4 to 6 binding sites/albumin molecule; Brown et al., 1982).

Carbamic acid butyl ester caused dissociation of isosafrole metabolite-cytochrome P-450 complexes at 37 °C in liver microsomes obtained from rats which had received intraperitoneal pretreatment with isosafrole (150 mg/kg body weight daily on 3 consecutive days). The protein concentration was 2 mg/ml, while carbamic acid butyl ester was used at a concentration of 1.0 mM. The binding spectra were recorded at a wavelength of 438 nm (Dickins et al., 1979).

When *Bacillus subtilis* 168i$^-$ was exposed to carbamic acid butyl ester at a concentration level of 8.5 mg/ml (18-hour incubation period at 37 °C), this led to complete inhibition of growth as a result of the extension of the lag phase (from one hour to 3 hours) and the generation time (from between 30 and 45 minutes to between 60 and 75 minutes; De Giovanni-Donnelly et al., 1967).

Liver slices (100 mg/experiment) obtained from female hooded rats, female H-strain rats and male H-strain rats (6 to 8 weeks old) were incubated for 45 minutes with N-hydroxyurethane at 0.5 µmol/g liver tissue or carbamic acid butyl ester at 10 µmol/g liver tissue. Subsequently, the N-hydroxyurethane contents were determined. The catabolism of N-hydroxyurethane was inhibited by incubation with carbamic acid butyl ester. In the female hooded rats, the amount of catabolysed N-hydroxyurethane was 0.36 µmol/g liver tissue (controls 1.5 µmol/g), whereas the respective concentrations in the male and female H-strain rats were 2.3 µmol/g (controls 2.5 µmol/g) and 1.6 µmol/g (controls 2.5 µmol/g). In the investigator's opinion, the inhibition of N-hydroxyurethane catabolism was strain-specific (Nery, 1968).

Six male Sprague-Dawley rats (weighing 125 to 175 g) underwent partial hepatectomy. Six hours after the operation, 3 animals were injected with

carbamic acid butyl ester in propylene glycol at 200 mg/kg body weight, while 3 others were given the vehicle (controls). For RNA labelling, a solution of ^{3}H-labelled orotic acid in physiological saline was injected into the portal vein at a dose of 600 µCi/kg body weight (22.2 x 10^{6} Bq/kg body weight). Eighteen hours after surgery the animals were sacrificed, and nuclear RNA synthesis was measured in the hepatocytes. RNA synthesis was not affected by the administration of carbamic acid butyl ester (Glazer, 1973).

In order to investigate the potential inhibitory effect of carbamic acid butyl ester on tumour growth, female Swiss mice (weighing 18 to 22 g) underwent subcutaneous implantation of sarcoma-180 tumour fragments (approx. 1.5 mm) into the axillary region. Twenty-four hours after tumour implantation, the animals were injected intraperitoneally with carbamic acid butyl ester, dissolved in propylene glycol, at a dose of 250 mg/kg body weight/day on 7 consecutive days. Two out of 5 animals treated in this manner died. Preliminary studies had shown 500 mg/kg body weight to be toxic. Tumour growth was determined by weighing the mice prior to tumour implantation and at the end of therapy. Carbamic acid butyl ester did not inhibit tumour growth under the conditions of this study (no further details; Stock et al., 1960).

8 Experience in humans

No harmful effects have been reported so far in connection with the production and handling of carbamic acid butyl ester (Hoechst, 1997).

According to a written communication from the Informationsverbund Dermatologischer Kliniken (IVDK, Information Network of Departments of Dermatology for the surveillance and scientific evaluation of contact allergies in Germany), carbamic acid butyl ester is not on the IVDK's list of allergens and has not been tested (IVDK, 1998).

9 Classifications and threshold limit values

No information available.

References

Boyland, E., Nery, R.
The metabolism of urethane and related compounds
Biochem. J., 94, 198–208 (1965)

Bridges, J.W., Sargent, N.S.E., Upshall, D.G.
Rapid absorption from the urinary bladder of a series of n-alkyl carbamates: a route for the recirculation of drugs
Br. J. Pharmacol., 66, 283–289 (1979)

Brown, N.A., Wilson, A.G.E., Bridges, J.W.
Chain length dependency of fatty acid and carbamate binding to serum albumin
Biochem. Pharmacol., 31, 4019–4029 (1982)

Demerec, M., Bertani, G., Flint, J.
A survey of chemicals for mutagenic action on E. coli
Am. Naturalist, 85, 119–136 (1951)

Dickins, M., Elcombe, C.R., Moloney, S.J., Netter, K.J., Bridges, J.W.
Further studies on the dissociation of the isosafrole metabolite-cytochrome P-450 complex
Biochem. Pharmacol., 28, 231–238 (1979)

DiPaolo, J.A., Elis, J.
The comparison of teratogenic and carcinogenic effects of some carbamate compounds
Cancer Res., 27, 1696–1701 (1967)

Doull, J., Plzak, V., Brois, S.J.
A survey of compounds for radiation protection
NTIS AD 277-689, pp. 1–3, 37, 108 (1962)

EC (European Commission), Existing Chemicals Bureau, Joint Research Centre, Ispra, Italy
IUCLID data set Butyl carbamate
CD-ROM, ed. I (1996)

Eker, P.
Effects of the carcinogen urethane on nuclear RNA polymerase activities
Eur. J. Cancer, 11, 493–497 (1975)

Fuks, R., Hartemink, M.A.
The acid-catalysed reaction of cyanogen chloride with aliphatic alcohols. A general synthesis of aliphatic carbamates
Bull. Soc. Chim. Belg., 82, 23–30 (1973)

Garcia, H.
Inhibition of tumorigenic action of urethane by butyl carbamate
Biologica, 34, 11–13 (1963)

Garcia, H., Guerrero, A.
Mouse mammary carcinogenesis by ethyl and butyl carbamates
Proc. Soc. Exp. Biol. Med., 132, 422–425 (1969)

GefStoffV (Gefahrstoffverordnung)
11th ed., p. 629
Carl Heymanns Verlag (1997)

Giovanni-Donnelly, De, R., Kolbye, S.M., DiPaolo, J.A.
The effect of carbamates on Bacillus subtilis
Mutat. Res., 4, 543–551 (1967)

Glazer, R.I.
Inhibition of the synthesis of nuclear RNA by urethan in regenerating liver
Biochem. Biophys. Res. Commun., 53 (3), 780–786 (1973)

Hoechst AG, Pharma Forschung Toxikologie und Pathologie
Butylurethan – Prüfung der akuten oralen Toxizität an der Wistar-Ratte
Unpublished report No. 88.0386 (1988 a)

Hoechst AG, Pharma Forschung Toxikologie und Pathologie
Butylurethan – Prüfung auf Hautreizung am Kaninchen
Unpublished report No. 88.0167 (1988 b)

Hoechst AG, Pharma Forschung Toxikologie und Pathologie
Butylurethan – Prüfung auf Augenreizung am Kaninchen
Unpublished report No. 88.0240 (1988 c)

Hoechst AG, Pharma Research Toxicology and Pathology
Butylurethan – Study of the mutagenic potential in strains of Salmonella typhimurium (Ames test) and Escherichia coli
Unpublished report No. 88.0682 (1988 d)

Hoechst AG
AIDA-Grunddatensatz Carbamic acid, butyl ester (1991)

Hoechst AG, Werksärztliche Abteilung
Written communication to BG Chemie of 17.11.1997

Houston, J.B., Upshall, D.G., Bridges, J.W.
A re-evaluation of the importance of partition coefficients in the gastrointestinal absorption of anutrients
J. Pharmacol. Exp. Ther., 189, 244–254 (1974)

IVDK (Informationsverbund Dermatologischer Kliniken)
Written communication to BG Chemie of 28.03.1998

Jäger, P., Rentzea, C.N., Kieczka, H.
Carbamates and carbamoyl chlorides
In: Ullmann’s encyclopedia of industrial chemistry
5th ed., vol. A5, pp. 51–53, 56–58
VCH Verlagsgesellschaft mbH, Weinheim (1986)

Larsen, C.D.
Evaluation of the carcinogenicity of a series of esters of carbamic acid
J. Natl. Cancer Inst., 8, 99–101 (1947)

Latarget, R., Buu-Hoi, N.P., Elias, C.A.
Induction d'une mutation spécifique chez une bactérie par des cancérigènes hydrosolubles
Cancer J., 2, 23–29 (1988)

Latarjet, R., Elias, C., Buu-Hoi, N.P.
Production d'une mutation bactérienne par des cancérigènes hydrosolubles
C.R. Soc. Biol., 143, 776–778 (1949)

Lawson, T.A., Pound, A.W.
The interaction of carbon-14-labelled alkyl carbamates, labelled in the alkyl and carbonyl positions, with DNA in vivo
Chem. Biol. Interact., 6, 99–105 (1973)

Lespagnol, A., Adenis, L., Cazin, J.C., Driessens, J.
L'adénome pulmonaire de la souris Swiss recevant de l'uréthane. VI. Action du carbamate de butyle et d'isoamyle
C.R. Soc. Biol., 163, 2145–2147 (1969)

Lide, D.R., Frederikse, H.P.R. (eds.)
CRC Handbook of chemistry and physics
77th ed., p. 3-109
CRC Press, Boca Raton, New York, London, Tokyo (1996)

Matsushita, T., Yoshioka, M., Aoyama, K., Arimatsu, Y., Nomura, S.
Experimental study on contact dermatitis caused by fungicides benomyl and thiophanate-methyl
Ind. Health, 15, 141–147 (1977)

Nery, R.
Some aspects of the metabolism of urethane and N-hydroxyurethane in rodents
Biochem. J., 106, 1–13 (1968)

Pai, V., Bloomfield, S.F., Jones, J., Gorrod, J.W.
Mutagenicity testing of nitrogenous compounds and their N-oxidised products using trp^+ reversion in E. coli
Biol. Oxid. Nitrogen., 375–382 (1978)

Pai, V., Bloomfield, S.F., Gorrod, J.W.
Mutagenicity of N-hydroxylamines and N-hydroxycarbamates towards strains of Escherichia coli and Salmonella typhimurium
Mutat. Res., 151, 201–207 (1985)

Pound, A.W.
The initiation of skin tumours in mice by homologues and N-substituted derivatives of ethyl carbamate
Aust. J. Exp. Biol. Med. Sci., 45, 507–516 (1967)

Pound, A.W.
Tumour formation in mice by urethane administered with related carbamates
Br. J. Cancer, 26, 216–225 (1972)

Pound, A.W., Lawson, T.A.
Carcinogenesis by carbamic acid esters and their binding to DNA
Cancer Res., 36, 1101–1107 (1976)

Sargent, N.S.E., Upshall, D.G., Bridges, J.W.
Absorption of drugs from the urinary bladder
Biochem. Soc. Trans., 7, 129–130 (1979)

Sargent, N.S.E., Wood, S.G., Upshall, D.G., Bridges, J.W.
The relationship between chemical structure and the in vivo metabolism of an homologous series of n-alkyl carbamates
J. Pharm. Pharmacol., 34, 367–372 (1982 a)

Sargent, N.S.E., Upshall, D.G., Bridges, J.W.
The relationship between binding to cytochrome P-450 and metabolism of n-alkyl carbamates in isolated rat hepatocytes
Biochem. Pharmacol., 31, 1309–1313 (1982 b)

Schafer, E.W., jr., Bowles, W.A., jr.
Acute oral toxicity and repellency of 933 chemicals to house and deer mice
Arch. Environ. Contam. Toxicol., 14, 111–129 (1985)

Shimkin, M.B., Wieder, R., McDonough, M., Fishbein, L., Swern, D.
Lung tumor response in strain A mice as a quantitative bioassay of carcinogenic activity of some carbamates and aziridines
Cancer Res., 29, 2184–2190 (1969)

Skipper, H.E., Bryan, C.E., Riser, W.H., jr., Welty, M., Stelzenmuller, A.
Carbamates in the chemotherapy of leukemia. II. The relationship between chemical structure, leukopenic action, and acute toxicity of a group of urethan derivatives
J. Natl. Cancer Inst., 9, 77–88 (1948)

Stock, C.C., Clarke, D.A., Philips, F.S., Barclay, R.K.
Sarcoma 180 screening data
Cancer Res., 20 (3), 1–172 (1960)

Wood, S.G., Upshall, D.G., Bridges, J.W.
The absorption of aliphatic carbamates from the rat colon
J. Pharm. Pharmacol., 30, 638–641 (1978)

Wood, S.G., Upshall, D.G., Bridges, J.W.
Further consideration of the existence of an optimal partition coefficient for intestinal absorption of foreign compounds
J. Pharm. Pharmacol., 31, 192–193 (1979)