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TOXICOLOGICAL EVALUATIONS

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TOXICOLOGICAL EVALUATION

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(3-Chloro-2-hydroxypro-pyl)trimethyl-ammonium chloride

No. 237

CAS No. 3327-22-8

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(3-Chloro-2-hydroxypropyl)trimethylammonium chloride

1 Summary and assessment

(3-Chloro-2-hydroxypropyl)trimethylammonium chloride (as QUAB 188) is of low toxicity upon single oral and dermal administration to rats (LD_{50} rat oral of commercially available solutions is 2170 to 5184 mg/kg body weight; LD_{50} rat oral of the pure substance is approx. 2800 mg/kg body weight; LD_{50} rat dermal of commercially available solutions is > 2000 mg/kg body weight). Seven-hour inhalation exposure to atmosphere saturated with (3-chloro-2-hydroxypropyl)trimethylammonium chloride produces no treatment-related effects in rats.

In rats of both sexes, repeated oral administration of (3-chloro-2-hydroxypropyl)trimethylammonium chloride at 1085 mg/kg body weight for 28 days resulted in slight morphological changes in the kidneys. No lower doses were tested and hence a *no observed effect level* was not ascertained in this study.

In the rabbit, (3-chloro-2-hydroxypropyl)trimethylammonium chloride is not, or at most slightly, irritating to the skin and eye.

When tested on guinea pig skin, (3-chloro-2-hydroxypropyl)trimethylammonium chloride has no sensitising potential.

In the Salmonella/microsome assay and the HPRT test, the substance is found to cause gene mutations both in the presence and absence of metabolic activation. In the chromosome aberration test in human lymphocytes and in the UDS test in primary rat hepatocytes, the substance also tests positive. In the mouse micronucleus test with intraperitoneal injection, (3-chloro-2-hydroxypropyl)trimethylammonium chloride proves not to be mutagenic.

In a carcinogenicity study conducted in NMRI mice receiving dermal applications of (3-chloro-2-hydroxypropyl)trimethylammonium chloride (twice weekly) at dose levels of 0 (controls), 0.018 and 0.18 ml (equivalent to 0, 13.8 and 138 mg/mouse) for 89 weeks (females) and 105 weeks (males), slightly increased hyperkeratosis and acanthosis at the application site we-

re noted and attributed to a minimal irritation potential of the substance. In the male mice of the high dose group, there was a statistically significant increase in the incidence of bronchioloalveolar tumours (adenomas and carcinomas) which was higher than those in historical controls.

In humans, no harmful effects have been observed in connection with the handling of the chemical at a production plant.

(3-Chloro-2-hydroxypropyl)trimethylammonium chloride is a substance on the third-priority list of the European Union. The Rapporteur Member State is Finland. In the Federal Republic of Germany, the Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area ("MAK-Kommission") of the Deutsche Forschungsgemeinschaft will investigate the possibility of establishing a MAK value for the chemical as well as the necessity for classification of its carcinogenic potential.

2 Name of substance

2.1	Usual name	(3-Chloro-2-hydroxypropyl)trimethylammonium chloride
2.2	IUPAC name	3-Chloro-2-hydroxy-N,N,N-trimethyl-1-propanaminium chloride
2.3	CAS No.	3327-22-8
2.4	EINECS No.	222-048-3

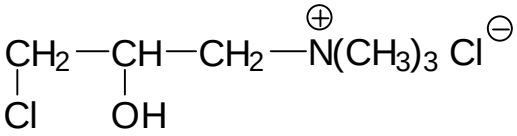
3 Synonyms, common and trade names

Ammonium(2-chloro-2-hydroxypropyl)trimethyl chloride
(3-Chlor-2-hydroxypropyl)trimethylammoniumchlorid
3-Chloro-2-hydroxypropyltrimethylammonium chloride
CHTP
CHTPMAC
Dextrosil KA

1-Propanaminium, 3-chloro-2-hydroxy-N,N,N-trimethyl chloride
QUAB 188
QUAT 188
Reagens-S-CFZ
Servon XRK
Trimethyl(2-hydroxy-3-chloropropyl)ammonium chloride
Verolan KAF

4 Structural and molecular formulae

4.1 Structural formula



4.2 Molecular formula $C_6H_{15}Cl_2NO$

5 Physical and chemical properties

5.1	Molecular mass, g/mol	188.12	
5.2	Melting point, °C	< –15	(Degussa, 1991)
5.3	Boiling point, °C	110	(EC, 1996)
5.4	Vapour pressure, hPa	15 (at 20 °C)	(EC, 1996)
5.5	Density, g/cm³	1.152 (60% (w/w) in aqueous solution)	(Degussa, 1991)
		1.163 (65% (w/w) at 20 °C)	(EC, 1996)
		1.17 g/ml (65% (w/w) at 20 °C)	(EC, 1996)
5.6	Solubility in water	Miscible (at 20 °C)	(EC, 1996)
5.7	Solubility in organic solvents	Soluble in alcohol (ca. 15%), insoluble in hydrocarbons and chlorinated hydrocarbons	(Degussa, not dated)
5.8	Solubility in fat	No information available	
5.9	pH value	ca. 3–6 (at 20 °C)	(EC, 1996)

5.10	Conversion factor	1 ml/m³ (ppm) ≙ 7.69 mg/m³ 1 mg/m³ ≙ 0.13 ml/m³ (ppm) (at 1013 hPa and 25 °C)

6 Uses

Used for quaternisation of compounds containing hydroxyl, amino and other functional groups; in the synthesis of cationic bipolymers, e.g. from starch, cellulose, guar, gelatine, proteins and of synthetic polymers, e.g. polyacrylic acid, acrylamide-acrylic acid copolymers, polyaminoamides, polyethylene imide, polyvinyl alcohol; in the textile industry (cationic modification of textile fibres such as cellulose and viscose; Degussa, 1991, not dated).

7 Experimental results

7.1 Toxicokinetics and metabolism

No information available.

7.2 Acute and subacute toxicity

Acute toxicity

(3-Chloro-2-hydroxypropyl)trimethylammonium chloride (QUAB 188, original liquid; no further details; probably 60%) was investigated in male and female Sprague-Dawley rats (initial weight 100 to 105 g; age at study initiation was 38 and 42 days, respectively) with regard to acute toxicity following oral administration (by gavage). Per dose, groups of 10 males and 10 females were treated (dose separation factor 1.21). Clinical signs of toxicity, food consumption and body weights were recorded. All animals (both those which died intercurrently and those sacrificed at the end of the study) were autopsied and examined macroscopically. The LD_{50} was calculated according to Litchfield and Wilcoxon. For the males, an oral LD_{50} (7 days) of 4.15 ml (approx. 4781 mg)/kg body weight was found for the original liquid used, while the value ascertained for the females was 4.05 ml (approx. 4666 mg)/kg body weight. The minimum lethal dose was 3.83 ml (ap-

prox. 4412 mg)/kg body weight in both sexes. This is equivalent to an LD_{50} of approx. 2800 mg/kg body weight for pure (3-chloro-2-hydroxypropyl)trimethylammonium chloride, assuming that the test formulation contained 60% of the pure chemical. The clinical signs of intoxication included sedation, ataxia, miosis, dyspnoea, tonic-clonic convulsions, reduced food intake and, at higher dose levels, lying on the abdomen or side as well as tremors. Deaths occurred after 30 minutes to 3 hours. The survivors no longer showed any signs of impairment 48 hours after administration. Gross pathology revealed no specific findings (Degussa, 1977 a).

Male and female rats were given single doses of (3-chloro-2-hydroxypropyl)trimethylammonium chloride (no indication, whether aqueous solution or pure substance) of up to 2000 mg/kg body weight by oral gavage. The observation period was 14 days. Whereas there were no deaths among the males, one of the females given 2000 mg/kg body weight died. Therefore, the oral LD_{50} was reported as > 1000 < 2000 mg/kg body weight (no further details; Dow Chemical, 1984 d).

A further LD_{50} value found in rats after oral administration of (3-chloro-2-hydroxypropyl)trimethylammonium chloride as a suspension in corn oil followed by a 14-day observation period was reported as 2170 mg/kg body weight. The clinical signs of toxicity were piloerection, abnormal body position and abnormal gait, lethargy, reduced respiratory rate, pallor of the extremities and salivation (no further details; Dynamit Nobel, 1982).

The acute oral toxicity of (3-chloro-2-hydroxypropyl)trimethylammonium chloride (20% aqueous solution) was investigated in groups of 5 male and 5 female rats. The observation period was 14 days. Doses of 14.4, 17.3, 20.7 and 24.8 ml/kg body weight were administered. Within a few minutes after administration, the animals became lethargic. Additional clinical signs included diarrhoea, tremor and convulsions. Deaths occurred between 90 and 120 minutes after administration. The survivors recovered after 20 hours. Macroscopic examination of the survivors revealed no treatment-related findings. The LD_{50} was given as 5184 mg/kg body weight (no further details; CFZ, 1977).

Another LD_{50} value found in rats after oral administration of (3-chloro-2-hydroxypropyl)trimethylammonium chloride (no further details of the test substance used) was reported as 3.20 ml/kg body weight (approx. 3686

mg/kg body weight in a 60% solution). The study was conducted in accordance with the OECD guidelines. Within one hour after administration, the animals showed sedation, signs of ataxia and exophthalmos. In addition, convulsions and coma were observed, particularly in animals given 2.38 ml/kg body weight or more. Deaths only occurred within one hour after administration (no further details; Servo Delden, 1982).

In an acute dermal toxicity study, undiluted (3-chloro-2-hydroxypropyl)trimethylammonium chloride (as QUAB 188) was applied to the shorn dorsal skin of male and female Wistar rats (77 to 122 days old, weighing 249 to 314 g and 174 to 207 g, respectively). The volume of substance applied was 2.0 ml/kg body weight (equivalent to 2348 mg/kg body weight). The observation period was 14 days. No systemic toxicity was noted during this period of time. There were no deaths. In isolated cases, body weight development was slightly retarded. At the application sites, scab and scale formation was observed 4 days after application but this was reversible within the observation period. The dermal LD_{50} was therefore found to be > 2348 mg/kg body weight (Degussa, 1986).

In Charles River rats, a further LD_{50} value for dermal application was reported as > 2000 mg/kg body weight (OECD guideline No. 402; no further details; HRC, 1987 a).

Four albino rats underwent 7-hour inhalation exposure to atmosphere saturated with (3-chloro-2-hydroxypropyl)trimethylammonium chloride (nominal concentration 12.05 mg/l) at room temperature. No treatment-related effects on appearance, behaviour, food consumption or survival rate were observed. The investigator considered it unlikely, however, that adequate vapour exposure was attained. The nominal concentration was calculated by sample weight differences before and after exposure. This most probably represented the loss of water from the aqueous solution of (3-chloro-2-hydroxypropyl)trimethylammonium chloride, since the chemical itself is not volatile (no further details; Dow Chemical, 1984 d).

Young adult white mice (strain, age and weight unspecified) were given a single subcutaneous injection of the substance dissolved in 0.8% saline solution. The investigators reported an LD_{50} value of 510 mg/kg body weight (no further details; Hunt and Taveau, 1909).

Subacute toxicity

Groups of 10 male and 10 female Sprague-Dawley rats received 7-day treatment with (3-chloro-2-hydroxypropyl)trimethylammonium chloride (as QUAB 188, original liquid; no further details; probably 60%) at daily oral doses of 0 (controls), 2.61, 3.16 and 3.83 ml/kg body weight (equivalent to 0, approx. 1800, 2180 and 2640 mg/kg body weight, respectively). At the highest dose level, clinical signs of intoxication were seen during the first 3 days of treatment, including sedation, ataxia, miosis, dyspnoea, tonic-clonic convulsions, reduced body weights and reduced food consumption as well as deaths which occurred within 60 minutes after administration (5 male and 6 female rats). At the mid dose level, retardation in body weight development was seen in association with reduced food consumption. Macroscopically, no changes were observed at study termination (Degussa, 1977 b).

(3-Chloro-2-hydroxypropyl)trimethylammonium chloride (as QUAB 188, 69.57% pure, 28.44% water, 1.14% 1,3-bis-trimethylammoniumpropanol-2-dichloride, 0.63% 2,3-dihydroxypropyltrimethylammonium chloride) was administered by oral gavage to 5 male and 5 female Wistar rats (initial weight 146 to 165 g and 130 to 147 g, respectively) at 1085 mg/kg body weight per day for 28 days (OECD guideline No. 407). Five males and 5 females which were given tap water served as controls. As of day 2 of the study, the treated animals exhibited clinical signs of toxicity including salivation, soft faeces and alopecia. The death of two females on the second day of the study was considered not to be treatment-related, and the animals were replaced by spare animals. During the study, there were no differences compared with controls as regards body weight development and food consumption. Examination of the reflexes, eyes, teeth and hearing showed no abnormalities. The haematological parameters determined at the end of the study and urinalysis results were without changes. In the males of the group given the test substance, the glucose levels were slightly decreased. The relative kidney weights, as compared with the controls, were slightly but statistically significantly increased in the male rats only. No macroscopic changes were observed. Histopathologically, both sexes of the test substance group exhibited changes in the kidneys, which consisted in fine diffuse vacuolation of proximal tubular cells of the inner cortical and outer medullary regions as well as slight tubular cell hyperplasia and hypertrophy with occurrence of polyploid nuclei and single abnormal mitoses. In the in-

vestigators' overall evaluation, the findings were considered to be minor. A *no observed effect level* was not ascertained in this study (Degussa, 1990).

7.3 Skin and mucous membrane effects

Skin irritation studies

In order to determine the primary skin irritancy of (3-chloro-2-hydroxypropyl)trimethylammonium chloride (as QUAB 188, a 60% solution in water), the substance was tested on the shorn intact and scarified dorsal skin of rabbits in accordance with OECD guideline No. 404. Groups of 3 female albino rabbits (white Himalayan, weight 2.8 kg, age approx. one year) received occlusive dermal applications of 0.5 ml test substance for 4 hours. Skin condition was assessed 1, 24, 48 and 72 hours after the end of exposure and scored according to the Draize method. Single application of the test substance to the skin of rabbits did not cause erythema or oedema in any one of the animals (primary irritation index 0.0). The substance thus exhibited no irritant effect on the skin of rabbits in this study design (Degussa, 1982 a).

In another study, which was designed according to Hazardous Substances, Part 191, Section 11, FDA, Washington, 1965, the potential of (3-chloro-2-hydroxypropyl)trimethylammonium chloride (no indication of purity) to cause skin irritation was investigated in the intact and the scarified dorsal skin of 6 male and 6 female rabbits. Exposure to 0.5 ml test substance under occlusive cover lasted for 24 hours. Immediately as well as 48 hours after removal of the patch, the skin reaction was assessed. No skin reactions were observed at all (Degussa, 1977 c).

In a Draize test, 55% (3-chloro-2-hydroxypropyl)trimethylammonium chloride produced very mild skin irritation in 2 out of 6 New Zealand white rabbits when applied to the scarified skin, the effect being reversible after 72 hours (no further details; CFZ, 1977).

In a skin irritation study with 4-hour semi-occlusive application according to Directive 84/449/EEC, B.4, (3-chloro-2-hydroxypropyl)trimethylammonium chloride proved to be not irritating to rabbit skin (no further details; CFZ, 1994).

Twenty-four-hour (covered or uncovered) contact of (3-chloro-2-hydroxypropyl)trimethylammonium chloride with the skin of albino rabbits caused only slight reddening. Ten applications caused severe redness, moderate swelling and a moderate to severe burn. No adverse systemic effects were observed (no further details; Dow Chemical, 1984 d).

Studies on mucous membrane effects

Three albino rabbits (females aged 7 to 10 months, weighing 2.7 to 3.0 kg, white Himalayan) each had 0.1 ml of the substance (60% in water) instilled into the conjunctival sac of one eye (OECD guideline No. 405). At 1, 24, 48 and 72 hours following instillation, the eyes were ophthalmologically examined with the aid of a slitlamp, and any changes in the cornea, iris or conjunctivae were scored according to the Draize scale. Single instillation of the substance into the conjunctival sac caused slight changes in the conjunctivae, while the cornea and iris remained unaffected. One hour after application, the conjunctivae displayed hyperaemia and hypersecretion. After 24 hours, the hyperaemia had increased and, in addition, eyelid swelling was seen, which was partly associated with ectropion of the lid. After 3 days, the findings had not yet cleared up completely. The substance was evaluated by the investigators as being non-irritating to the rabbit eye (Degussa, 1983).

The eye irritation potential of (3-chloro-2-hydroxypropyl)trimethylammonium chloride (as QUAB 188, no indication of purity) was investigated in 3 male and 3 female rabbits in a study designed according to Hazardous Substances, Part 191, Section 12, FDA, Washington, 1965. A 0.1 ml aliquot of QUAB 188 was instilled into one eye as the original liquid and as 50%, 25% and 12.5% formulations in distilled water. At 5, 15 and 30 minutes as well as at 1 hour, 2, 4, 24, 48 and 72 hours following instillation, the eyes were examined by slitlamp. There were concentration-dependent changes in the conjunctivae. The undiluted original liquid induced erythema, oedema and hypersecretion, which all cleared up after 24 hours. At the 50% concentration level, the reactions were less pronounced and were reversible after only one hour. The 25% formulation caused only mild erythema and oedema, which were also reversible after one hour. The 12.5% formulation was tolerated without reactions (Degussa, 1977 d). The test substance thus proved to be mildly irritating to the eye.

Following instillation of (3-chloro-2-hydroxypropyl)trimethylammonium chloride into the eyes of albino rabbits, the substance essentially proved non-irritating. Up to 10 days after instillation, there were no indications of injury to the cornea (no further details; Dow Chemical, 1984 d).

In two further studies on mucous membrane effects, (3-chloro-2-hydroxypropyl)trimethylammonium chloride was evaluated as being a mild irritant. In a Draize test carried out with 55% test substance, 1 out of 6 rabbits displayed slight reddening of the conjunctivae, which was reversible after 48 hours. In a study according to OECD guideline No. 405, the substance was evaluated as a mild irritant (no further details; CFZ, 1977; HRC, 1987 b).

7.4 Sensitisation

In order to assess the skin-sensitising potential of (3-chloro-2-hydroxypropyl)trimethylammonium chloride (as QUAB 188, 69.32% solution of a 98.55% pure solid), a Magnusson and Kligman maximisation test was conducted in male and female Pirbright White guinea pigs (OECD guideline No. 406). A group of 5 and a group 3 animals/sex served as the test and control groups, respectively. Intracutaneous induction was carried out with a formulation containing 0.5% test substance in physiological saline, whereas for dermal induction 100% test substance was used. Three weeks after intracutaneous induction, the challenge was carried out with a 30% formulation of the substance. Neither the treated animals nor the controls exhibited any skin changes. (3-Chloro-2-hydroxypropyl)trimethylammonium chloride therefore proved not to have any sensitising effects on the skin of guinea pigs (Degussa, 1993).

Two other Magnusson and Kligman maximisation tests of (3-chloro-2-hydroxypropyl)trimethylammonium chloride on guinea pig skin also gave negative results (no further details; Chem-Y, 1979; HRC, 1988).

7.5 Subchronic and chronic toxicity

In a dose-finding study for a carcinogenicity study with dermal application (see Section 7.7), undiluted (3-chloro-2-hydroxypropyl)trimethylammonium chloride (as QUAB 188) and an aqueous ethanolic solution thereof were applied to the dorsal skin of mice for 3 months. Neither local nor systemic

effects were observed. The maximum volume applied was 0.20 ml (no further details; Degussa, 1997).

7.6 Genotoxicity

7.6.1 In vitro

The results of the mutagenicity tests carried out with (3-chloro-2-hydroxypropyl)trimethylammonium chloride are presented in detail in Table 1 below.

In Salmonella/microsome assays, (3-chloro-2-hydroxypropyl)trimethylammonium chloride gave predominantly positive results in *Salmonella typhimurium* strain TA 1535 with and without metabolic activation (C.P.C., 1976; Degussa, 1979, 1982 b, 1984; HRC, 1981; Hüls, 1984; Dow Chemical, 1984 a). Positive results were also reported for *Salmonella typhimurium* strain TA 100, with and without metabolic activation (Degussa, 1979, 1982 b; HRC, 1981). Only one Salmonella/microsome test with preincubation, in which a pH value of 5.5 was measured, showed no mutagenic effect for (3-chloro-2-hydroxypropyl)trimethylammonium chloride (HRC, 1982). In the HPRT test on CHO-K_1-BH_4 cells of the Chinese hamster, (3-chloro-2-hydroxypropyl)trimethylammonium chloride was found to test positive with and without metabolic activation (Dow Chemical, 1984 b). A chromosome aberration test in human lymphocytes also produced positive results in the presence and absence of metabolic activation. In the UDS assay in rat hepatocytes, (3-chloro-2-hydroxypropyl)trimethylammonium chloride was found to cause DNA damage (Dow Chemical, 1984 c).

Beginning of Table 1

Table 1. In-vitro genotoxicity tests with (3-chloro-2-hydroxypropyl)trimethylammonium chloride

Test system	Concentration range tested (µg/plate)[1)]	Metabolic activation system	Results[2)]		Reference
			with metabolic activation	without metabolic activation	
1. Gene mutation					
1.1 Gene mutation tests in bacteria					
1.1.1 Salmonella/microsome assay as standard-plate incorporation test					
Salmonella typhimurium TA 98, TA 100, TA 1535, TA 1537, TA 1538	1.58–5000, not bacteriotoxic up to 5000	S9 mix from Aroclor 1254-induced rat liver	positive (TA 1535)	positive (TA 1535)	Degussa, 1984

Table 1. In-vitro genotoxicity tests with (3-chloro-2-hydroxypropyl)trimethylammonium chloride					
Test system	Concentration range tested (µg/plate)[1)]	Metabolic activation system	Results[2)]		Reference
			with metabolic activation	without metabolic activation	
Salmonella typhimurium TA 98, TA 100, TA 1535, TA 1537, TA 1538	1000–25000, not bacteriotoxic up to 25000	S9 mix from Aroclor 1254-induced rat liver	positive (TA 100, TA 1535)	positive (TA 100, TA 1535)	Degussa, 1979
Salmonella typhimurium TA 98, TA 100, TA 1535, TA 1537, TA 1538, *Escherichia coli* WP2uvrA (pKM101)	400–124000, not bacteriotoxic up to 124000	S9 mix from Aroclor 1254-induced rat liver	positive (TA 100, TA 1535)	positive (TA 100, TA 1535)	Degussa, 1982 b
Salmonella typhimurium TA 1535, TA 1537, TA 1538	100–100000	no information	positive (TA 1535)	positive (TA 1535)	C.P.C., 1976
Salmonella typhimurium TA 98, TA 100, TA 1535, TA 1537, TA 1538	150–15000, slightly bacteriotoxic in TA 1535 from 5000	S9 mix from Aroclor 1254-induced rat liver	positive (TA 100, TA 1535)	positive (TA 100, TA 1535)	HRC, 1981
Salmonella typhimurium TA 98, TA 100, TA 1535, TA 1537, TA 1538	10–5000	S9 mix from phenobarbital-induced rat liver	no information	positive (TA 1535)	Hüls, 1984
1.1.2 Salmonella/microsome assay as preincubation test					
Salmonella typhimurium TA 98, TA 100, TA 1535, TA 1537, TA 1538	100–100000, not bacteriotoxic up to 100000	S9 mix from Aroclor 1254-induced rat liver	positive (TA 1535)	positive (TA 1535)	Dow Chemical, 1984 a
Salmonella typhimurium TA 100, TA 1535	500–15000, pH 5.5	S9 mix from Aroclor 1254-induced rat liver	negative	negative	HRC, 1982
1.2 Gene mutation tests in mammalian cells					
CHO-K_1-BH_4/HPRT test, ovarian cells of the Chinese hamster	0.09–45.5 mg/ml with S9 mix, 0.1–50 mg/ml without S9 mix, toxicity tested	S9 mix from Aroclor 1254-induced rat liver	positive	positive	Dow Chemical, 1984 b
2. Chromosome damage					
Chromosome aberration, human lymphocytes	0.016–12.0 mg/ml	S9 mix (no further details)	positive	positive	CFZ, 1984
3. DNA damage					
UDS test, rat hepatocytes	0.001–10 mg/ml, cytotoxic from 0.1 mg/ml	primary rat hepatocytes	positive	–	Dow Chemical, 1984 c

[1)] if not stated otherwise, the publications contain no cytotoxicity data
[2)] whenever specified in the references that only certain strains tested positive, these are mentioned here

End of Table 1

7.6.2 In vivo

(3-Chloro-2-hydroxypropyl)trimethylammonium chloride (as QUAB 188, 69% solution of a 99.92% pure solid) was tested for mutagenic activity in

the micronucleus test in accordance with OECD guideline No. 474. Twenty-one male and 24 female NMRI mice were given (3-chloro-2-hydroxypropyl)trimethylammonium chloride intraperitoneally as a solution in water at the maximum tolerated dose of 147 mg/kg body weight. The negative controls (18 males and 18 females) were treated with physiological saline solution, while the positive controls (18 males and 18 females) were given cyclophosphamide at 51.1 mg/kg body weight. The maximum tolerated dose elicited slight to severe clonic convulsions, decrease in muscle tone, loss of righting reflex with lateral and dorsal positions, sunken sides and stilted gait. Of the females, 5 died within the first 14 minutes after administration. At 24, 48 and 72 hours after administration, 6 male and 6 female mice of both the positive and negative control groups and at least 6 males and 6 females of the test material group were sacrificed in order to prepare bone marrow smears, and 1000 polychromatic erythrocytes were evaluated per animal (5 mice/group were scored). The number of micronuclei in the test material group was not elevated relative to the negative control group. At all of the sampling time points, the ratio of polychromatic to normochromatic erythrocytes remained unchanged. The substance thus proved to be devoid of mutagenicity under these experimental conditions (Degussa, 1992).

7.7 Carcinogenicity

In a carcinogenicity study conducted in accordance with OECD guideline No. 451, groups of 50 male and 50 female mice (strain Bor:NMRI, SPF; initial weight of the males and females 17 to 28 g and 15 to 24 g, respectively) received twice-weekly applications to the shorn dorsal skin of 0 (controls), 0.018 and 0.18 ml (3-chloro-2-hydroxypropyl)trimethylammonium chloride (as QUAB 188, 65.79% pure, 32.36% water; equivalent to 0, 13.8 and 138 mg/mouse) in 10% aqueous ethanol solution. After 89 weeks (females) and 105 weeks (males), 75% of animals were deceased, and the survivors were sacrificed. Body weight development, food consumption, reflex tests, examinations of the eyes, hearing and teeth, haematological parameters as well as organ weights did not differ from the controls. Macroscopic examination was without findings. Histopathological examination of the application site revealed a dose-related increase in hyperkeratosis and acanthosis, which according to the investigators probably reflected a mini-

mal irritancy of the substance. No tumorigenic changes were observed at the application site. Histopathological examination of the inner organs revealed an increased incidence of bronchioloalveolar tumours (adenomas and carcinomas). Group comparison showed that a statistically significant difference existed only between the male mice of the high dose group and those of the control group. An increase in the incidence of bronchioloalveolar tumours was also seen in the female mice of the high dose group, but statistical significance was not reached (see Table 2).

Table 2. Incidences of lung tumours in mice following dermal application of (3-chloro-2-hydroxypropyl)trimethylammonium chloride (twice weekly) for 89 (females) and 105 weeks (males)

	Controls		(3-Chloro-2-hydroxypropyl)trimethyl-ammonium chloride			
			0.018 ml		0.18 ml	
Sex	♂	♀	♂	♀	♂	♀
Number of animals	50	50	50	50	50	50
Hyperplasia	4	0	5	2	4	3
Benign tumours	7	3	8	8	12	7
Malignant tumours	10	6	14	5	16	10
Benign and malignant tumours	17 (34%)	9 (18%)	22 (44%)	13 (26%)	28* (56%)	17 (34%)

* $p < 0.05$

The investigators conducting the study had no in-house historical control data available, for which reason the incidence of bronchioloalveolar tumours and hyperplasia were compared with published data for the same mouse strain and breeder (Bomhard, 1993). Comparison with the historical controls also showed increased incidences of bronchioloalveolar tumours (historical controls: males 27.8%; Bomhard, 1993) and hyperplasia. According to the investigators, however, study duration (105 weeks for the males) was longer than in the published controls (21 months) and could therefore have resulted in a higher background incidence of tumours. In the authors' opinion, the biological relevance of the increased incidence of lung tumours is, therefore, unclear and may represent a promoting rather than a tumour-inducing effect. (Note: In another publication (Bomhard and Mohr, 1989) on historical control data for NMRI mice from various breeders and studies of 104 weeks' duration and longer, incidences of lung tumours of 33.1% and 20.6% were reported in males and females, respectively. Nei-

ther study contains data on the incidence of hyperplasia in the lung.) In the males and females of the high dose group, there was an increased incidence of focal glandular hyperplasia in the stomach, which in the females was significant. According to the investigators, this higher incidence could have arisen from oral exposure to the test material due to licking of the application site, or may have been incidental, as glandular hyperplasia in the stomach is common in mice of this age. In the low dose group, one carcinoma and 3 adenomas were additionally found in the glandular stomach. In the absence of dose-dependency, these tumours were evaluated by the authors as not being related to the test substance. As no data were available on the plasma levels of (3-chloro-2-hydroxypropyl)trimethylammonium chloride and the actual amounts ingested, the authors considered evaluation of the stomach findings impossible. The cumulated incidences of infrequent tumours found in different organs was slightly increased in the high dose group. Since the tumour types were varied and did not affect a particular target tissue, the increase in overall incidence was considered an artificial effect which was not related to treatment (Degussa, 1997).

7.8 Reproductive toxicity

No information available.

7.9 Effects on the immune system

No information available.

7.10 Neurotoxicity

No information available.

7.11 Other effects

No information available.

8 Experience in humans

No harmful effects have been reported so far in connection with the handling of the chemical (Degussa, 1988).

9 Classifications and threshold limit values

In the Federal Republic of Germany, the Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area ("MAK-Kommission") of the Deutsche Forschungsgemeinschaft will investigate the possibility of establishing a MAK value for the chemical as well as the necessity for classification of its carcinogenic potential (DFG, 2000).

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