REACH

Hydrogen chloride

EC number: 231-595-7 | CAS number: 7647-01-0

Toxicological information

Carcinogenicity

S-01 | Summary

Administrative data

Description of key information

Hydrochloric acid did not evoke a carcinogenic response in treated rats.

Key value for chemical safety assessment

Carcinogenicity: via inhalation route

Link to relevant study records

Reference	
Endpoint:	carcinogenicity: inhalation
Type of information:	experimental study
Adequacy of study:	key study
Study period:	Not specified. Study published in 1985.
Reliability:	2 (reliable with restrictions)
Rationale for reliability incl. deficiencies:	other: Deficiencies: Food consumption not measured. Haematology, clinical chemistry and urinalysis not performed. Individual data not reported.
Qualifier:	no guideline followed
Deviations:	not applicable
Principles of method if other than guideline:	Guideline study No.: Formaldehyde and hydrogen chloride can react together to form low concentrations of bis(chloromethyl) ether (BCME The study design for the HCl- exposed group in this study is in broad agreement with, and in duration exceeds, OECD 451 (1981) if conducted as a limit test.
GLP compliance:	no
Remarks:	GLP was not compulsory at the time the study was conducted
Species:	rat
Strain:	Sprague-Dawley
Sex:	male
Details on test animals and environmental conditions:	TEST ANIMALS - Source: Charles River, Wilmington, Mass., USA - Age at study initiation: 9 weeks old - Weight at study initiation: 316 ± 16 g - Fasting period before study: not specified. - Housing:not specified - Diet (e.g. ad libitum): not specified. - Water (e.g. ad libitum): not specified. - Acclimation period: not specified. ENVIRONMENTAL CONDITIONS - Temperature (°C): not specified. - Humidity (%): not specified. - Air changes (per hr): not specified. - Photoperiod (hrs dark / hrs light): not specified. IN-LIFE DATES: not specified.
Route of administration:	inhalation
Type of inhalation exposure (if applicable):	other: Not stated, presumably whole-body
Vehicle:	unchanged (no vehicle)
Details on exposure:	GENERATION OF TEST ATMOSPHERE / CHAMBER DESCRIPTION - Exposure apparatus: Formaldehyde vapour was entrained in air by passing over a slurry of paraformaldehyde (purified trioxymethylene) in paraffin oil maintained at 75-90 °C. HCl supplied by a compressed tank. 1. Premix method: HCOH-laden air and HCl were simultaneously directed into a 13.5-litre mixing vessel. Make up air was introduced into the mixing vessel to yield an overall gas mixture flow rate of 4 litres/min. The effluent from the mixing vessel was passed directly into the air intake of exposure chamber. Since the air flow through the exposure chamber was 300 litres/min, there was a 75-fold dilution of the effluent from the mixing vessel. 2. Non-premix: each gas was fed separately into the inlet air supply of the exposure chamber. TEST ATMOSPHERE - Brief description of analytical method used: HCl and HCOH determinations were made every 0.5 hr during each 6-hour daily exposure. Hydrogen chloride quantities were determined by titration with sodium hydroxide. Formaldehyde amounts were determined by a chromatographic acid method. Since bis(chloromethyl) ether (BCME) can form from HCl and HCOH in moist air, the relevant amounts in the mixing vessel were measured by a gas chromatography/mass spectrometry method. - Samples taken from breathing zone: not specified.
Analytical verification of doses or concentrations:	yes
Details on analytical verification of doses or concentrations:	1. Combination of HCl + HCOH – premixed: HCl 1000 ppm + HCOH 800 to 1500 ppm in the reaction vessel before introduction into the 1.3 m2 exposure chamber; BCME concentrations were measured in this premix. 2. Combination of 10 ppm HCl + 15 ppm HCOH fed separately into the inlet air supply of the 1.3 m3 exposure chamber; this avoided formation of BCME due to the low concentration of gases but BCME was not measured. 3. HCOH alone 15 ppm 4. HCl alone 10 ppm 5. Sham air Mean daily measured concentrations (ppm) ± standard deviation Pre-mix Non-premix HCOH HCL HCOH HCl HCOH HCl 15.2 9.9 14.9 9.7 14.8 10.0 ± 2.3 ± 2.4 ± 2.1 ± 2.5 ± 2.1 ± 1.7 BCME: 0.1-0.4 ppb
Duration of treatment / exposure:	128 weeks
Frequency of treatment:	daily, five days per week, six hours per day
Post exposure period:	none

Remarks:	Deviations from protocol: see section on 'Any other information on materials and methods incl. tables' Basis: other:
No. of animals per sex per dose:	100 males/group
Control animals:	other: yes, clean air only (plus colony control)
Details on study design:	not specified.
Positive control:	not specified.
Observations and examinations performed and frequency:	DETAILED CLINICAL OBSERVATIONS: Yes - Time schedule: daily MORTALITY: Yes - Time schedule: daily BODY WEIGHT: Yes - Time schedule for examinations: measured and recorded monthly. FOOD CONSUMPTION : - Food consumption for each animal determined and mean daily diet consumption calculated as g food/kg body weight/day: No - Compound intake calculated as time-weighted averages from the consumption and body weight gain data: No FOOD EFFICIENCY: - Body weight gain in kg/food consumption in kg per unit time X 100 calculated as time-weighted averages from the consumption and body weight gain data: No WATER CONSUMPTION AND COMPOUND INTAKE (if drinking water study): No OPHTHALMOSCOPIC EXAMINATION: No HAEMATOLOGY, CLINICAL CHEMISTRY, URINALYSIS: No NEUROBEHAVIOURAL EXAMINATION: No
Sacrifice and pathology:	GROSS PATHOLOGY: Yes HISTOPATHOLOGY: Yes (see table) ORGAN WEIGHTS: No Animals were allowed to die naturally or were killed when moribund; the study continued until the last animal died (indefinite duration, full lifespan). Complete necropsy was performed on each animal and particular attention was given to the respiratory tract. All organs and the entire head were fixed in 10% neutral buffered formalin. The head was decalcified and multiple cross sections, 1.5 to 2 mm apart, were taken, beginning just behind the nostrils and extending back as far as the orbits. Histologic sections were prepared from each lobe of the lung, trachea, larynx, liver, kidneys, testes, and other organs where gross pathology was present.
Other examinations:	none.
Statistics:	Student t test on mortality; χ2 for cancer response. Tumour incidences were corrected for mortality using a life-table method (Sacks, 1959) and log-rank analysis (Peto et al, 1977). References: Sacks, R. (1959): Life table technique in the analysis of response time data from laboratory experiments in animals. Toxicol Appl.Pharmacol. 1 203-227. Peto, R., Pike, M.C. et al (1977) Design and analysis of randomised clinical trials requiring prolonged observation of each patient. Brit.J.Cancer 35 1-39
Clinical signs:	effects observed, treatment-related
Mortality:	mortality observed, treatment-related
Body weight and weight changes:	effects observed, treatment-related
Food consumption and compound intake (if feeding study):	not examined
Food efficiency:	not examined
Water consumption and compound intake (if drinking water study):	not examined
Ophthalmological findings:	not examined
Haematological findings:	not examined
Clinical biochemistry findings:	not examined
Urinalysis findings:	not examined
Behaviour (functional findings):	not examined
Organ weight findings including organ / body weight ratios:	not examined
Gross pathological findings:	effects observed, treatment-related
Histopathological findings: non-neoplastic:	effects observed, treatment-related
Histopathological findings: neoplastic:	effects observed, treatment-related
Details on results:	CLINICAL SIGNS AND MORTALITY Swelling in the anterior portion of the nose was often seen in the early stages of tumour development. In later stages the swelling was enlarged, penetrated the nasal bone, and was at times ulcerated. The rates of mortality of the different groups were not different up to 32 weeks; however, a higher rate of mortality was evident at that time in the group receiving the premix HCl and HCOH. Statistical analysis showed significant difference in this group compared with both non-premix group and HCOH alone. There were no statistical differences between the mortality in the hydrogen chloride and air control groups.

BODY WEIGHT AND WEIGHT GAIN
Both combined exposure groups (premix and not premix) showed a marked decrease in weight after 16 weeks as did the group receiving HCOH alone. No difference compared to controls was noted in the HCl alone group.

GROSS PATHOLOGY AND HISTOPATHOLOGY:
The primary lesions in animals receiving HCOH-HCl combination or HCOH were found in the nasal cavity. These included rhinitis, ranging from mild to severe, exudation in the lumen of the nasal cavity, necrosis, and desquamation of respiratory epithelial cells in the respiratory epithelium that covers the naso-maxillary turbinates and the nasal septum. The olfactory epithelium in ethmoidal turbinates often showed an inflammatory reaction with seropurulent exudates filling the lumen.

The cut surface of swelling in the anterior portion of the nose noted also in life showed friable, cheesy material, which was mostly keratin formation.

Tumours in the nasal cavity were seen in all three groups receiving HCl-HCOH or HCOH alone while none of the other groups, including animals receiving HCl alone, developed tumours in the nasal cavity. The number of nasal tumours in the group administered combined HCl-formaldehyde without premixing, was not different to formaldehyde alone or with premixing. Formaldehyde therefore appeared to be the causative agent. No metastatic lesions were found in other segments of the respiratory tract or in other organs. There were no remarkable differences in the latency among groups. A number of other kinds of tumours were noted in all the groups, without any significant difference noted between treated and control groups.

For more details see Tables.

Relevance of carcinogenic effects / potential:	Hydrochloric acid did not evoke a carcinogenic response in treated rats.
Dose descriptor:	NOAEL
Effect level:	< 10 ppm
Sex:	male
Basis for effect level:	other: see 'Remark'
Remarks on result:	other: Effect type: carcinogenicity (migrated information)

Tables with results are attached.

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noted in the HCl alone group.

Clinical signs were related to development of tumours in the nasal cavity: swelling in the anterior portion of the nose in the early stages of tumour development while in later stages the swelling enlarged, penetrated the nasal bone, and at times ulcerated.

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IARC, 1992 (International Agency for Research on Cancer. Monographs on the Evaluation of Carcinogenic Risks to Humans, vol. 54, Occupational Exposures to Mists and Vapours from Strong Inorganic Acids, and Other Industrial Chemicals, pp 189-211„) noted that study design did not maximise HCl exposure. The applicant in turn notes non-neoplastic histology in the respiratory tract of HCl-treated rats demonstrates a degree of toxicity (withprobably not far different to the tested dose). The study duration (entire lifespan of all rats) is rigorous, group size (100 males) meets guideline requirements since no gender-related differences would be anticipated. Although this duration of study may be subject to confounding by geriatric changes, tumours appeared sufficiently early in affected groups that the results are clear and conclusions entirely appropriate. The absence of treatment-related tumours among rats exposed to HCl for this duration is highly reassuring.

Mucosal changes found in the laryngeal-tracheal segments of rats exposed for up to 128 weeks

Observation	Premixed HCl-HCOH	Non-premixed HCl-HCOH	HCOH	HCl	Air	Colony control
No. examined	100	100	100	99	99	99
Larynx						
Hyperplasia	11	22	21	22	2	2
Squamous metaplasia	10	15	4	0	0	0
Trachea						
Hyperplasia	18	32	21	26	6	2
Squamous metaplasia	9	8	7	0	0	0

Lesions and tumours found in the nasal mucosa of rats exposed for up to 128 weeks

Observation	Premixed HCl-HCOH	Non-premixed HCl-HCOH	HCOH	HCl	Air	Colony control
No. examined	100	100	100	99	99	99
Rhinitis	74	75	74	81	72	70
Epithelial or squamous metaplasia	54	53	57	62	51	45
Squamous metaplasia	64	68	60	9	5	6
Polyps or papillomas	13	11	10	0	0	0

Squamous cell carcinoma	45	27	38	0	0	0
Adenocarcinoma	1	2	0	0	0	0
Mixed carcinoma	0	0	1	0	0	0
Fibrosarcoma	1	0	1	0	0	0
Esthesioneuroepithelioma	1	0	0	0	0	0

Conclusions: Daily exposure of rats to gaseous hydrochloric acid at the concentrations of 10 ppm, 6 hours a day, 5 days per week up to 128 weeks did not affect the survival or body weight of exposed animals. A higher incidence of hyperplasia of the larynx and trachea was noted at histopathology, compared to air and colony control groups. No serious irritating effects in the nasal epiththelium were obeserved. None of the treated animals developed any preneoplastic or neoplastic lesions indicating a lack of carcinogenic activity.

Endpoint conclusion

Endpoint conclusion:	no adverse effect observed
Dose descriptor:	NOAEC
	15 mg/m³
Study duration:	chronic
Species:	rat

Carcinogenicity: via dermal route

Endpoint conclusion

Endpoint conclusion:	no study available

Additional information

As explained in the chapter for kinetic and additionally elsewhere, Hydrogen chloride is in aqueous conditions fully dissociated, where the individual anions are systemically and abundantly present in normal physiological circumstances. Homeostatic mechanisms assures that the concentrations of H+ (pH) and that of the anion concentrations Cl- and HCO2- are strictly controlled. Absorption via oral route can be compared with the natural production of 2-3 litre gastric juice containing high levels of HCl (can be as high as 0.1M) excreted by parietal cells in the stomach lining of the fundus. Systemic pH balance is controlled via kidney and lung activity (controlling CO2 and HCO3- balance).

Concentrated hydrogen chloride is corrosive to biological tissues, but at concentrations lower than those that cause corrosion or irritation, hydrogen chloride will have no effect on systemic toxicity.

Exposures to hydrogen chloride therefore can only result to local effects at sufficiently high concentrations, either by inhalation of by dermal route.

For the evaluation of possible carcinogenicity the irritation and corrosivity of HCL is of relevance for the common understanding that repeated cellular damages followed by repeated tissue repair and consequentchronic stimulation of cell growth can be an epigenetic mechanism for the development of tumours. As this is based on the mechanism of local irritation, the relevant tissues can only be those of the locally exposed respiratory system (nose, trachea, lungs) following chronic exposures via inhalation. Because it is highly soluble in water, hydrogen chloride is normally mostly deposited in the nose and other regions of the upper respiratory tract. Similarly that will be the case of aerosol exposures. Consequently, these should therefore then also be the areas to evaluate for possible higher tumour incidences in human epidemiology studies.

The results from a chronic inhalation study in rats of 10 ppm hydrogen chloride 6 hours a day, 5 days per week up to 128 weeks (Sellakumar et al, 1985) demonstrates the occurrence of limited local effects only. This chronic exposure did not affect the survival or body weight of exposed animals. Compared to air and colony control groups, only a higher incidence of hyperplasia of the larynx and trachea was noted at histopathology. No serious irritating effects in the nasal epithelium were observed. None of the treated animals developed any pre-neoplastic or neoplastic lesions indicating a lack of carcinogenic activity.

IARC evaluated Hydrochloric acid in 1992 (IARC 1992). In the same Monograph also the evaluation of occupational exposures to mists and vapours from strong inorganic acids were reported (IARC 1992). An update of the evaluation of mists from strong inorganic acids was made in in 2012, incorporating new data that had become available since then (IARC 2012).

The IACR evaluation from 1992 concluded on the basis of the available data that

- There is inadequate evidence for the carcinogenicity in humans of hydrochloric acid.
- There is inadequate evidence for the carcinogenicity in experimental animals of hydrochloric acid.

Overall evaluation: Hydrochloric acid is not classifiable as to its carcinogenicity to humans (Group 3).

IARC 2012 evaluation concludes that

- There is sufficient evidence in humans for the carcinogenicity of mists from strong inorganic acids. Mists from strong inorganic acids cause cancer of the larynx. Also, a positive association has been observed between exposure to mists from strong inorganic acids and cancer of the lung.
- There is inadequate evidence for the carcinogenicity in experimental animals of hydrochloric acid.

Overall evaluation: Mists from strong inorganic acids are carcinogenic to humans (Group 1).

The overall available data from epidemiological studies pointing at possible carcinogenicity of hydrochloric acid is actually very scarce. It basically consist of a cohort study in steel-pickling operations involving exposures from 1940's to 1960's indicating a limited increase of SMR related to hydrochloric acid of 2.24 [95% confidence interval (CI), 1.02-4.25] based on only 9 deaths in the cohort. Possible other exposures besides sulphuric acid (metaloxides, asbestos) cannot be ruled out. The information from case-control linking hydrochloric acid to cancer is also not strong, and basically actually indicates no strong relation to lung cancers. There is one case-control study (Zemła et al., 1987) pointing at a relative risk of 4.27. However, the validity of this conclusion for hydrochloric acid is very low as exposures relate to vapours of sulfuric, hydrochloric, or nitric acid, and not adjusted for possible confounding factors as smoking and alcohol.

Hydrochloric acid is non-genotoxic. The possible epigenetic mechanism upon which chronic exposure to hydrochloric acid to lead to the development of cancers, involves chronic tissue damage from local irritation or corrosive effects as result of low pH. As a consequence from exposures via inhalation this is mostly be relevant for nose and other regions of the upper respiratory tract. Studies in rat showed that chronic exposures to 10 ppm (5h/d, 5d/wk, 128 wks) only

resulted to an increased incidence of hyperplasia of the larynx and trachea compared to non-exposed animals, but no pre-neoplastic or neoplastic lesions were seen.

So consequently, in humans, when exposures are kept below irritating levels, inhalation of hydrochloric acid is NOT considered to be carcinogenic.

Justification for selection of carcinogenicity via inhalation route endpoint:
Only available chronic inhalation study

Justification for classification or non-classification

Hydrochloric acid did not evoke a carcinogenic response in treated rats. No serious irritating effects in the nasal epithelium were observed. None of the treated animals developed any pre-neoplastic or neoplastic lesions indicating a lack of carcinogenic activity.There is not sufficient information to classify hydrochloric acid as carcinogenic.