April 23, 2024

Response to the comments of California Communities Against Toxics; Sierra Club; and Earthjustice regarding EPA's proposed health-based exposure limit for hydrochloric acid

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Response to the comments of California Communities Against Toxics; Sierra Club; and Earthjustice regarding EPA's proposed health-based exposure limit for hydrochloric acid

Recipient	**National Lime Association**
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Prepared by	**Sandra Sulsky, Debra A. Kaden, Tracy Green**

Ramboll
28 Amity Street
Suite 2A
Amherst, MA 01002
USA

T +1 413 835 4350
https://ramboll.com

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Appendices

1. Introduction

The National Lime Association (NLA) requested Ramboll Americas Engineering Solutions (Ramboll) respond to comments filed by the California Communities Against Toxics, the Sierra Club, and Earthjustice[1] regarding the US Environmental Protection Agency (EPA) proposal to use a health-based exposure limit (HBEL) for environmental hydrochloric acid (HCl). An HBEL is appropriate for substances that are deemed non-carcinogens or non-carcinogenic below certain threshold exposure levels. Ramboll assisted NLA earlier in 2024 by commenting on the science EPA cited to support the proposed HBEL, and in 2021 by providing a general evaluation of the carcinogenicity of HCl and HCl mist.[2] The main body of the current document provides a concise summary and integration of the available epidemiology and toxicology evidence to address the scientific issues raised by Earthjustice. Appendix 1 summarizes the available toxicology data. We discuss the Earthjustice comments in point-by-point fashion in Appendix 2. We have not reproduced the tables that summarize epidemiology data in appendixes to this report because we have also provided Ramboll's more detailed reports from June 2021 and February 2024 in Appendix 3 and Appendix 4, respectively. Due to the complexity of the epidemiology tables, and the methodological limitations of the studies they summarize, this information is best reviewed in the earlier reports.

2. Is Hydrogen Chloride a Carcinogen?

The fundamental question that Ramboll was originally asked was "Is HCl a carcinogen? What does the scientific literature show?" Ramboll's June 2021 and February 2024 reports (Appendix 3 and Appendix 4) detail the methods we used to address those questions, including the literature search methods and in-depth summaries of studies and reviews by authoritative bodies. In this report, we summarize those findings and address mechanisms for carcinogenicity including the roles of mutagenicity and cell proliferation in the cancer process, and implications for non-threshold and threshold exposure-response relationships. We also highlight the implications of genotoxicity in high acid settings, including its relevance to assessing risks in people. Finally, we address the Earthjustice comments dated March 11, 2024. We specifically address comments related to the science and its interpretation, and do not address legal arguments.

Epidemiology evidence

Occupational epidemiology studies provide information relevant to the health effects of environmental exposures for several reasons: 1) Occupational chemical exposures are reasonably well documented, as compared with environmental exposures that occur to the general population. 2) If identified and documented, occupational chemical exposures are sometimes quantifiable in terms of concentration and duration of exposure. 3) Even if not specifically quantified, occupational chemical exposures, when they occur, almost certainly do so at higher concentrations than the environmental exposures experienced by the general public. This is due, among other reasons, to the dilution of exposures that occur in the open vs. inside a building. Studying occupational groups exposed to a chemical at higher concentrations than are experienced by the general public is informative under the assumption that higher doses are more likely than lower doses of a chemical exposure to cause harm. If no effects are detected among those

[1] Collectively referred to as "Earthjustice" or "Earthjustice comments".

[2] Ramboll's 2021 and 2024 reports to NLA are provided in Appendix 3 and Appendix 4, respectively.

exposed at higher concentrations, it is unlikely that populations exposed at lower concentrations will experience harmful effects.

HCl is an industrial chemical that has been in use for many decades, and occupational exposure to it is both common and widespread (IARC 1992). Workplace air concentrations of HCl gas or mist have been estimated in a limited number of settings. Mean exposures ranged from <0.01 mg/m^3 to 12 mg/m^3 during acid treatment of metals, while other industrial processes produced exposures of 1 mg/m^3 or higher (cited in IARC 1992). Ambient air generally contains HCl at concentrations of 0.01 - 3 µg/m^3, roughly 1,000-fold lower than workplace concentrations (IARC 1992).

In spite of the large numbers of people who have been occupationally exposed to HCl, we identified only 16 publications describing epidemiology studies that assessed cancer risks among workers exposed to HCl.[3] The paucity of research suggests, in and of itself, that there have been few, if any, hints of increased cancer risks associated with HCl exposure in such populations.

Among the published studies we identified (see Appendix 4, February 2024 report), there were seven population-based case-control studies of cancer reported in eight publications (Farrow et al. 1989; Siemiatycki 1991; Fritschi and Siemiatycki 1996a; Fritschi and Siemiatycki 1996b; Soskolne et al. 2011; Chen et al. 2021; Ker et al. 2021; Moayedi-Nia et al. 2022). In this design, all deaths are identified in a specified population, e.g., residents of a specific city. Cases are identified as all deaths due to cancer (i.e., any type, combined into one group), or due to specific cancers. Control data are from people with other causes of death or other types of cancer, or who reside in the region being studied. Controls are matched to the cases by factors that minimally include sex and either age or calendar year at death or at diagnosis. Past occupational exposures experienced by cases and controls are determined based on their occupational histories and the two groups are compared to determine if work in a certain job or industry, or with a particular documented exposure, was more common among cases than among controls. This design can help to identify signals that suggest an occupational exposure may be associated with one or more types of cancer. The population-based case-control study design is limited by difficulties collecting detailed data on the occupational exposures of concern, and often it is not possible to collect information on non-occupational risk factors and potential confounders. If the study was not designed to evaluate a specific type of cancer, then the statistical power to detect differences in risk for relatively rare events (i.e., deaths due to a specific type of cancer) may be limited.

All of these limitations are relevant to the population-based case-control studies of HCl exposure we identified, which were published between 1989 and 2022 (Farrow et al. 1989; Siemiatycki 1991; Fritschi and Siemiatycki 1996a; Fritschi and Siemiatycki 1996b; Soskolne et al. 2011; Chen et al. 2021; Ker et al. 2021; Moayedi-Nia et al. 2022). Results from six of the seven studies (reported in seven of the eight publications) did not indicate an association between any of several types of cancer and past exposure to HCl. One study, that included only five cases, reported a nearly five-fold higher risk of lung cancer (odds ratio = 4.67, 95% confidence interval 1.34, 16.2) among those with at least 25% chance of some prior HCl exposure, but the authors were not able to determine if there had been exposures to other occupational carcinogens that might explain the association (Moayedi-Nia et al. 2022).

Well-designed case-control studies conducted within a specific plant or industry represent a more rigorous approach to determining whether occupational chemical exposure is associated with cancer risk. In this design, both cases and controls are identified from within the same worker population. This represents an

[3] Ramboll's 2024 report erroneously indicated there were 22 publications describing epidemiology studies. In fact, we summarized five toxicology publications and 13 epidemiology publications in the 2021 report (for a total of 18 publications, combined) and added three epidemiology studies published since 2021 to in the 2024 report (for a total of 16 epidemiology publications).

improvement over studies conducted in the general population because more information about the study participants is usually available. In addition, the cases and controls are, in general, more similar with respect to lifestyle and other risk factors (apart from exposure to the specific chemical(s) of interest) than may be true in studies conducted within the general population, so uncontrolled confounding is somewhat less likely to affect the study results. Case-control studies can still be hampered by incomplete or misclassified data regarding co-exposures and/or confounders, and results may be biased by flaws in the study design or by differences in the quality of information available from cases and controls (e.g., due to recall bias).

There were two occupational case-control studies described in five publications that assessed the risks of several different types of cancers associated with nominal HCl exposures (Bond et al. 1983; Bond et al. 1985; Bond et al. 1986; Bond et al. 1991; Coggon et al. 1996). The Bond et al. studies attempted to distinguish HCl from exposures to other occupational carcinogens. In their 1986 and 1991 publications, the authors reported risks of respiratory cancer deaths. Focusing on the updated analysis from 1991, none of the measures of exposure to HCl evaluated by the authors, including binary exposure status, cumulative exposure, and measures discounting recent exposures, was associated with an increase in risk of respiratory tract cancers (Bond et al. 1991). The 1985 publication reported no excess renal cancer risks associated with mixed exposures including HCl, and the 1983 publication that included 13 individuals with brain cancer presumptively exposed to HCl reported odds ratios and 90% confidence intervals[4] of 1.40 (0.70, 2.80) for hypothesis-generating comparisons with employees who had died from non-cancer causes, and 1.02 (0.81, 1.29) for comparisons with live controls.

Occupational cohort studies are generally thought to represent the strongest study design, because they approximate an experiment in which all factors other than exposure are held constant. Individuals are classified on the basis of their exposure status and the rate of health outcomes experienced among exposed individuals is compared to the rate among unexposed individuals. Compared with other study designs, this design is threatened by fewer biases that might influence the results of the study, though misclassification of exposure, lack of statistical power, and lack of information about potential confounders may still play a role in producing the results.

We identified three occupational cohort studies described in five publications that attempted to investigate associations between HCl exposure and various cancers. In all of these studies, exposures were to mixtures that included known occupational carcinogens in addition to HCl and the authors were unable to identify exposure to HCl alone or to adequately control for co-exposures to other carcinogens. The findings, therefore, cannot be attributed to HCl exposure (Beaumont et al. 1987; Steenland et al. 1988; Collins et al. 1989; Coggon et al. 1996; Marsh et al. 1999).

The sixteen epidemiology studies summarized above are described in more detail in Ramboll's previous reports (Appendix 3 and Appendix 4). In line with Ramboll's conclusions are the conclusions of multiple authoritative bodies that have also concluded that HCl is unlikely to be a carcinogen. Neither the US EPA nor the NTP have identified HCl as a chemical worthy of assessing for carcinogenicity. IARC (1992) classified HCl in Group 3 (not classifiable), the classification group representing chemicals considered least likely to present a cancer hazard. Note that IARC has only classified a single chemical as *"probably not carcinogenic to humans"* (Group 4), and they no longer use this category. OECD (2002) notes that, "In humans, no association between hydrogen chloride exposure and tumor incidence was observed." IARC also reviewed other inorganic acids in the same monograph, including "sulfuric acid and other strong

[4] 90% confidence intervals are generally reported when analyses are focused on generating hypotheses. 95% confidence intervals are generall reported when testing for causal associations.

inorganic acids" (IARC 1992) and concluded that for sulfuric acid and other strong inorganic acids, "There is sufficient evidence that occupational exposure to strong-inorganic-acid mists containing sulfuric acid is carcinogenic." IARC's overall evaluation was that "Occupational exposure to strong inorganic acid mists containing sulfuric acid is carcinogenic to humans (Group 1)" (IARC 1992), which is relevant because the conclusion is based on exposure to acid mists that must include sulfuric acid. While sulfuric acid and HCl often are found together in mixed acid exposures, the exposure contained in the mixture with the strongest relationship to the outcome (in this case, sulfuric acid) will drive the relationship for the whole mixture. This is likely the explanation for the sporadic effects observed in occupational studies of mixed acids containing HCl.

Animal bioassays

The effects of HCl exposure have also been investigated in animal studies (see Appendix 3 and Appendix 4 for further details). Overall, based on the available studies in animals, HCl exposure has not been shown to increase the incidence of tumors in animals.

An increased incidence of hyperplasia (indicative of cell proliferation) in the larynx and trachea has been reported in rats chronically exposed to HCl via inhalation: The carcinogenicity of HCl was examined in groups of 100 Sprague-Dawley rats exposed by inhalation to either gaseous HCl, formaldehyde, two types of combinations of HCl and formaldehyde, or a control group of air alone for 6 hours per day, 5 days per week over 122 weeks (Albert et al. 1982; Sellakumar 1985). Results were also compared to those for unexposed control animals. HCl concentrations were 10 ppm (14.9 mg/m^3)[5] in the HCl-only exposure. Following sacrifice, animals were examined for tissue abnormalities, including cancer, with special attention to the respiratory tract. Results of the study indicated increased incidence of hyperplasia (indicative of cell proliferation) in the larynx and trachea of animals exposed to HCl alone as compared to air controls or colony controls, but no excess cancer was observed.

Other cancer studies in experimental animals were reported by Organization for Economic Cooperation and Development (OECD 2002) – a dermal exposure study (Narat, 1925, as cited by OECD 2002) and an oral exposure study (Dyer et al., 1946 as cited by OECD 2002). No malignant tumors were reported in 99 mice dermally exposed to an unknown volume of solutions containing 3-5% HCl every 1-2 days, and then weekly for 4-6 additional weeks (total exposure duration 25-46 weeks) (Narat, 1925, as cited by OECD 2002). Dyer et al. (1946, as cited by OECD 2002) orally exposed groups of mice to a combination of HCl (1-2.5 moles per liter) and either a "control emission" (58 mice) or HCl and 1,2,5,6-dibenzanthracene (40 mice) and reported no excess cancer or pre-cancerous lesions observed in the stomachs of animals from either group exposed to HCl. OECD (2002) concluded neither study was appropriate for the assessment of carcinogenicity because of the shortcomings of the study design.

3. Is Hydrogen Chloride a Genotoxic Agent?

Mutation or genetic changes are often viewed as a first step in carcinogenicity, so various assays that examine such changes, as well as assays designed to predict such changes (collectively referred to as genotoxicity assays) may be used to predict cancer potential. To be more protective, carcinogens that are believed to have a mutagenic mode of action are generally assumed to have no threshold below which there is not some risk for cancer.

[5] Here and elsewhere, conversions from ppm to mg/m^3 assumed a molecular weight of 36.5 and 25°C, 1 atmosphere.

Such judgement is usually made based on various *in vitro* assays that examine the genotoxic potential of the test agent. These assays may be for mutation, often using bacterial or mammalian cell cultures as a test system. They may also examine the potential for DNA damage in bacterial or cell cultures exposed *in vitro*, with the understanding that DNA damage may lead to mutations. Other assays examine indications of chromosome breakage in *in vitro* systems, including sister chromatid exchange (where there are breaks and reciprocal rejoining in a pair of chromatids), or physical evidence of chromosome loss, gain, or rearrangements. Although mutation can also be examined in cells from exposed human populations, this is less frequently done (and there is no indication that this has been done for HCl).

Genotoxicity Evidence

HCl did not result in gene mutations in bacteria (*S. typhimurium strains* Ames assay strains TA 98, TA 100, TA 1535, TA 1537, TA 1538; *E. coli* strain B/Sd-4) (reviewed by OECD 2002). In mammalian cells, HCl did not result in gene mutations in one study in mouse lymphoma cell line L5178Y TK+/-, but weakly positive responses for gene mutations were found in another study using the same cell system (reviewed by IARC 1992; OECD 2002). The latter results were interpreted as being an artifact of acidic conditions (pH 6.3 in buffered cell culture medium), which resulted in cell toxicity (OECD 2002).

A qualitative predictive assay that examines cell survival in strains that have or lack the ability to repair damaged DNA had mixed results in two assays, but OECD concluded the positive finding was unrelated to DNA damage (reviewed by OECD, 2002).

HCl induced chromosome aberrations in mammalian cells in culture when concentrations were in excess of 10 mM in the cell culture media (leading to an acidic environment with a pH of 5.8) and in studies in Chinese hamster ovary cells, mouse lymphoma cells, and in insect and plant cells in a very limited set of studies. Both IARC (1992) and OECD (2002) concluded that the acidic pH is the responsible factor for these responses and that similar responses are observed for other acid substances. IARC stated "*Although only results with hydrochloric acid are reported here, similar results were obtained with other inorganic acids and with acetic acid (AK. Thilager, personal communication reported by Brusick, 1986) and lactic acid (Inga Ils & Shimada, 1974), indicating that the hydrogen ion concentration is the most important factor in experiments with acids, although specific effects of cations cannot be ruled out* (IARC 1992)*.* These concentrations would not be found environmentally and are thus not relevant for ambient air exposures to HCl. More importantly, these conditions would not be present in the human body, where the normal pH ranges between 7.35 to 7.45, with the average at 7.40 (Hopkins et al. 2024). The body includes many buffer systems to maintain that pH range, including metabolically produced carbon dioxide, phosphate buffer systems, proteins, and hemoglobin (Hopkins et al. 2024).

HCl did not induce mitotic recombination in yeast (reviewed by OECD 2002) or sister chromatid exchange in the mouse lymphoma cell line L5178Y TK+/- (reviewed by OECD 2002). A study of oral and inhalation exposure of the fruit fly *Drosophila melanogaster* strain Oregon-K exposed to hydrogen chloride at concentrations of 0.01% found sex-linked recessive lethal mutations (reviewed by OECD 2002).

Since most of the genotoxicity studies are either not published in the peer-reviewed literature or are very old and difficult to obtain, Ramboll has compiled information presented by IARC and OECD working groups (see Appendix 1). Most of these studies present clear evidence that HCl does not induce genotoxic effects, and those that appear to be positive are believed to be due to the acidic conditions of cell culture along with cytotoxicity. EPA's Cancer Guidelines (USEPA 2005) state *"…mutagenic carcinogens usually produce positive effects in multiple test systems for different genetic endpoints, particularly gene mutations and structural chromosome aberrations, and in tests performed in vivo which generally are supported by*

positive tests in vitro. Additionally, carcinogens may be identified as operating via a mutagenic mode of action if they have similar properties and SAR to mutagenic carcinogens." Thus, taken together, these studies indicate that hydrogen chloride itself is not genotoxic, although the acidic conditions it creates in cell cultures, even in the presence of buffers meant to maintain neutral pH, may lead to cytotoxicity and chromosome damage in cultured cells. These conditions are not relevant to hydrogen chloride being classified as a genotoxic agent. Indeed, such acid conditions would not occur *in vivo*, which is the important situation for carcinogenesis. This is consistent with the lack of *in vivo* evidence for cancer.

4. Does Hydrogen Chloride Induce Cell Proliferation?

In addition to mutagenic carcinogens, there are some carcinogens that are believed to act through a nonmutagenic mechanism. One such mechanism is as a result of increased cell proliferation induced under cytotoxic conditions, where damaged cells are replaced through the extensive cell growth of other, surviving cells. Such cell proliferation may lead to the possibility of replication errors in the dividing cells, leading to mutations. However, such mechanisms are believed to have a threshold concentration below which no effects are seen (Clewell et al. 2019).

Hyperplasia in animal bioassays

In the case of HCl, results from carcinogenicity studies in animals showed increased cell proliferation in the form of hyperplasia in the respiratory tract; however, there was no evidence of carcinogenicity in exposed animals (Sellakumar 1985). Furthermore, in studies where HCl was administered along with formaldehyde (Albert et al. 1982), exposures to 10 ppm (14.9 mg/m^3) HCl neither caused serious additional irritating effects nor enhanced the carcinogenicity of formaldehyde.

5. Summary and Conclusions

Based on Ramboll's review of the authoritative sources and primary scientific literature, we conclude that HCl is not a carcinogen. This is based on the limited animal bioassay studies, where there is no evidence that animals experimentally exposed to HCl have more tumors than unexposed control animals, and the epidemiological literature where there is no strong evidence of increased risk of cancer among humans who are occupationally exposed to HCl. Occupational exposures are generally higher than exposures that occur in the ambient environment, and higher exposures are more likely to lead to adverse health consequences than lower exposures. The epidemiological evidence is weak due to the limitations of the individual studies, including the inability to distinguish among exposures to a mixture of occupational and non-occupational carcinogens. Detailed discussion of the epidemiology studies is presented in prior Ramboll reports (Appendix 3 and Appendix 4).

Because of the relevance of mutation in cancer mechanism, Ramboll also examined the evidence regarding the genotoxicity of HCl. There is no evidence that HCl exposure is mutagenic to cells in culture. Rather, the limited number of studies showing chromosomal damage in mammalian cell systems are attributable to the acidic pH in the cell cultures. Many of the publications were addressing just that – the genotoxicity of acid conditions – and examined several strongly acidic chemicals. Such a situation would not occur under physiological conditions or in the environment. Ramboll presents a summary of the genotoxicity studies and the animal cancer bioassays in table form in Appendix 1.

Although we found no compelling evidence that HCl is a human carcinogen, we examined the other potential mode of action for cancer – increased cell proliferation. Although hyperplasia in the respiratory tract was observed in a rat chronic inhalation study, it did not progress to cancer. Such hyperplasia is considered a high-dose, threshold phenomenon and would not be expected at lower, non-toxic HCl exposures.

Ramboll addresses the many comments of California Communities Against Toxics, Sierra Club, and Earthjustice (referred collectively as Earthjustice) in Appendix 2 in point-by-point fashion. In this response, we only address those comments related to the science, and not those related to the law.

Overall, this report concludes that HCl is not a carcinogen, and does not contribute to the mechanisms that might be related to carcinogenicity. As such, use of a health-based exposure limit (HBEL) appears the appropriate approach to protecting human health.

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Appendix 1

Summary of available toxicology data

Table A1. Details of genotoxicity assays as presented by OECD 2002

Assay system	Test substance	Concentrations	Results	Comments	Cited References[6]
Bacterial and yeast cell assays					
Gene mutation *S. typhimurium* strains TA 98, TA 100, TA 1535, TA 1537, TA 1538 With and without metabolism system	Hydrogen chloride: 36.5-38 %	0.001, 0.01, 0.1, 1.0, 5.0 uL/plate (0.012-60 ug/plate)	Negative result was obtained in the systems	Cytotoxic at 5.0 uL/plate	Litton Bionetics, Inc. (1978) Mutagenicity evaluation of Hydrochloric acid, Final report. LBI Project No. 20893. Isquith, A., Matheson, D., and Slesinski, R. (1988) Genotoxicity studies on selected organosilicon compounds: in vitro assays. Fd. Chem. Toxic. 26, 255-261.
Gene mutation *E. coli* strain B/Sd-4 Without metabolism system	Hydrogen chloride (purity or concentration not stated)	0.00075-0.00375 %	Negative	Because survival rate varied from 0.2 to 100 % under the same condition (concentration of hydrochloric acid 0.0015 %), the negative result is questionable	Demerec, M. et al. (1951) A survey of chemicals for mutagenic action on E. coli. Am. Nat., 85, 119-136. Also reviewed by IARC
DNA damage and repair	Hydrogen chloride: 36.5-38 %	0.001, 0.01, 0.1, 1.0, 5.0 uL/plate	Negative	Cytotoxicity not stated	Litton Bionetics, Inc. (1978) Mutagenicity evaluation of

[6] As cited by OECD, 2002

Assay system	Test substance	Concentrations	Results	Comments	Cited References[6]
assay, ("rec" assay) *E. coli* strains W3110 (*po*l A+), P3078 (*pol* A-) With and without metabolism system		(0.012-60 ug/plate)			Hydrochloric acid, Final report. LBI Project No. 20893. Isquith, A., Matheson, D., and Slesinski, R. (1988) Genotoxicity studies on selected organosilicon compounds: in vitro assays. Fd. Chem. Toxic. 26, 255-261.
DNA damage and repair *E. coli* strains WP2, WP2uvrA, WP67, CM611, W3110 (*pol* A+), P3478 (*pol* A-) With and without metabolism system	Hydrogen chloride, highest technical grade available	Not stated	Ambiguous	HCl showed inhibitory activity in the WP2uvrA stain; while this response was reproducible, it was not considered adequate evidence of DNA damaging activity since the remaining WP2 deficient strains which also carried the uvrA mutation gave no indication of preferential kill at all.	McCarroll, N.E., Keech, B.H., and Piper, C.E. (1981a) An E coli microsuspension assay for the detection of DNA damage induced by direct-acting agents and promutagens., Environ. Mutagenesis, 3, 429-444.
DNA damage and repair *B. subtillis* strain H17 (arg- try-	Hydrochloric acid	Not stated	Negative		McCarroll, N.E., Keech, B.H., and Piper, C.E. (1981b) A microsuspension adaptation of the Bacillus subtilis "rec" assay.

Assay system	Test substance	Concentrations	Results	Comments	Cited References[6]
rec+), M45 (arg- try- rec-) With and without metabolism system					Environ., Mutagenesis, 3, 607-616.
Mitotic recombination Saccharomyces cerevisiae strain D4 With and without metabolism system	Hydrogen chloride: 36.5-38 %	0.001, 0.01, 0.1, 1.0, 5.0 uL/plate (0.012-60 ug/plate)	Negative	Cytotoxic at 5.0 uL/plate	Litton Bionetics, Inc. (1978) Mutagenicity evaluation of Hydrochloric acid, Final report. LBI Project No. 20893. Isquith, A., Matheson, D., and Slesinski, R. (1988) Genotoxicity studies on selected organosilicon compounds: in vitro assays. Fd. Chem. Toxic. 26, 255-261.
Mammalian cell lines					
Gene mutation Mouse lymphoma cell line L5178Y TK+/- With and without	Hydrochloric acid	Without metabolism system: 0.4, 0.5, 0.6, 0.7, 0.8 uL/mL (4.8-9.6 mM) With metabolism system: 0.8,	Negative	Cytotoxic concentrations With metabolic activation: 0.8 uL/mL (100% growth inhibition) Without metabolic activation: ~1.0 uL/mL	Litton Bionetics, Inc. (1978) Mutagenicity evaluation of Hydrochloric acid, Final report. LBI Project No. 20893. Isquith, A., Matheson, D., and Slesinski, R. (1988) Genotoxicity studies on selected organosilicon compounds: in

Assay system	Test substance	Concentrations	Results	Comments	Cited References[6]
metabolism system		1.0, 1.2, 1.4, 1.6 uL/mL (9.6-23.0 mM)		(12.5% growth inhibition at 0.8 uL/mL)	vitro assays. Fd. Chem. Toxic. 26, 255-261.
Gene mutation Mouse lymphoma cell line L5178Y TK+/- With and without metabolism system	Hydrochloric acid	With metabolic activation: pH 6.3, 6.6, 6.9, 7.2, 7.5 Without metabolic activation: pH 6.0, 6.2, 6.5, 6.7, 6.9, 7.0	Positive result at the cytotoxic condition (pH <6.2) with metabolic activation Weak positive result at the cytotoxic condition (pH 6.3) without metabolic activation.	Cytotoxicity concentrations With metabolic activation: pH <6.9 Without metabolic activation: pH $\leq$6.6	Cifone, M.A., Myhr, B., Eiche, A. and Bolcsfoldi, G. (1987) Effect of pH shifts on the mutant frequency at the thymidine kinase locus in mouse lymphoma L5178Y TK+/- cells. Mutat. Res., 189, 39-46. Also reviewed by IARC
Chromosome aberrations Chinese hamster ovary (CHO) line CHO-K1 With and without metabolism system	Hydrochloric acid	Without metabolism system: 0, 8, 10, 12, 14, 16 mM (pH 7.4, 6.1, 5.9, 5.7, 5.5, 5.3 respectively) With metabolism system: 0, 6,	Positive without metabolic activation: 14 mM (pH 5.5) Positive with metabolic activation: 8-10 mM (pH 5.8-6.0)	Cytotoxic concentrations: Without metabolic activation: 16 mM (pH 5.3) With metabolic activation: 12 mM (pH 5.5) Aim of study was to examine role of pH in inducing chromosome aberrations in CHO cells.	Morita, T., Watanabe, Y., Takeda, K. and Okumura, K (1989) Effects of pH in the in vitro chromosomal aberration test., Mutat. Res., 225, 55-60. Also reviewed by IARC

Assay system	Test substance	Concentrations	Results	Comments	Cited References[6]
		8, 10, 12 mM (pH 7.4, 6.3, 6.0, 5.8, 5.5 respectively)	Induced aberrations were almost all chromatid breaks.	pH was adjusted with sodium hydroxide, potassium hydroxide, sulfuric acid, or HCl. Authors concluded that weakly acidic media is clastogenic to CHO-K1 cells with and without metabolic activation.	
Chromosome aberrations Mouse lymphoma cell line L5178Y TK+/- With and without metabolism system	Hydrochloric acid	Without metabolism system: 0.1, 0.2, 0.4 uL/mL (1.2, 2.4, 4.8 mM) With metabolism system: 0.2, 0.4, 0.8 uL/mL (2.4, 4.8, 9.6 mM)	Negative	Cytotoxic concentrations With metabolic activation: 0.8 uL/mL (100% growth inhibition) Without metabolic activation: ~1.0 uL/mL (12.5% growth inhibition at 0.8 uL/mL)	Litton Bionetics, Inc. (1978) Mutagenicity evaluation of Hydrochloric acid, Final report. LBI Project No. 20893. Isquith, A., Matheson, D., and Slesinski, R. (1988) Genotoxicity studies on selected organosilicon compounds: in vitro assays. Fd. Chem. Toxic. 26, 255-261.
Chromosome aberration Chinese hamster ovary cells With and without	Hydrochloric acid	2.0 – 3.2 uL/mL (pH 5.00- 5.75) and control (pH 7.08)	Positive result at the cytotoxic condition (pH 5.25; 2.8 uL/mL) with metabolic activation	Cytotoxicity concentration With metabolic activation: 3.2 uL/mL (pH 5.00) Without metabolic activation: not stated	Brusick, D (1986) Genotoxic Effects in cultured mammalian cells produced by low pH treatment conditions and increased ion concentration. Environ., Mutagen., 8, 879-886.

Assay system	Test substance	Concentrations	Results	Comments	Cited References[6]
metabolism system			Negative result without metabolic activation.		The study was presented by Dr. A.K. Thilager of Sitek Research Laboratories at the 16th Annual Meeting of the Environmental Mutagen Society in Las Vegas, Nevada, 1985.
Sister chromatid exchange Mouse lymphoma cell line, L5178Y TK+/- With and without metabolism system	Hydrochloric acid Purity 36.5-38 %	Without metabolism system: 0.1, 0.2, 0.4 uL/mL (1.2, 2.4, 4.8 mM) With metabolism system: 0.2, 0.4, 0.8 uL/mL (2.4, 4.8, 9.6 mM)	Negative	Cytotoxic concentration: With metabolic activation: 0.8 uL/mL (100% growth inhibition) Without metabolic activation: ~1.0 uL/mL (12.5% growth inhibition at 0.8 uL/mL)	Litton Bionetics, Inc. (1978) Mutagenicity evaluation of Hydrochloric acid, Final report. LBI Project No. 20893. Isquith, A., Matheson, D., and Slesinski, R. (1988) Genotoxicity studies on selected organosilicon compounds: in vitro assays. Fd. Chem. Toxic. 26, 255-261.
In vivo					
Sex-linked recessive lethal mutation Drosophila melanogaster strain Oregon-K	Hydrochloric acid	5mL in a bottle of 125 mL volume, conc. 0.01%	Positive	Authors conclude "All combinations [of combinations of formaldehyde, formic acid, acetic acid and hydrochloric acid] were mutagenic and showed a mutation pattern from which it is concluded that in feeding experiments spermatocytes I are	Stumm-Tegethoff, B.F.A. (1969) Formaldehyde-induced mutations in Drosophila melanogaster independence of the presence of acids. Theor. Appl. Genet., 39, 330-334.

Assay system	Test substance	Concentrations	Results	Comments	Cited References[6]
Inhalation exposure				especially sensitive to the pairs of chemicals tested. In vapour experiments all germ cell stages were found to be susceptible."	
Sex-linked recessive lethal mutation Drosophila melanogaster strain Oregon-K Oral exposure	Hydrogen chloride	0.01%	Positive	Authors conclude "All combinations [of combinations of formaldehyde, formic acid, acetic acid and hydrochloric acid] were mutagenic and showed a mutation pattern from which it is concluded that in feeding experiments spermatocytes I are especially sensitive to the pairs of chemicals tested. In vapour experiments all germ cell stages were found to be susceptible."	Stumm-Tegethoff, B.F.A. (1969) Formaldehyde-induced mutations in Drosophila melanogaster independence of the presence of acids. Theor. Appl. Genet., 39, 330-334.

Table A2 – Summary of Animal Cancer Studies

Citation	Animal species	Exposure Route	Exposure Duration	Exposure levels	NOAEL	LOAEL	Endpoint	Comments
Sellakumar et al. 1985 and Albert et al. 1982	Rat	inhalation	6 hours/day, 5 days/week, for 122 weeks	0 or 10 ppm (14.9 mg/m^3)	None	10 ppm	Hyperplasia in the larynx and trachea. No malignant tumors reported.	Albert et al. 1982 reports interim results at 84 weeks and Sellakumar et al. 1985 reports full study results.
Narat 1925	Mice	dermal	Every 1-2 days until skin lesions occurred then weekly for 4-6 weeks; total exposure duration was 25-46 weeks.	unknown volume of solutions containing 3-5% HCl	NA	NA	No malignant tumors reported	OECD concluded the study was not appropriate for the assessment of carcinogenicity due to lack of negative controls and brief exposure period.
Dyer et al. 1946	Mice	oral	Unknown	0 or 1-2.5 moles per liter HCl	NA	NA	No cancer or pre-cancerous lesions observed in the stomach of animals	OECD concluded the study was not appropriate for the assessment of carcinogenicity due to lack of inconsistent strain, short exposure duration, and single exposure concentration.
NOAEL, no observed adverse effect level; LOAEL, lowest observed adverse effect; NA – Not applicable								

Table A3. From IARC 1992

Table 6. Genetic and related effects of hydrochloric acid

Test system	Result[a]		Dose[b] or pH	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
ECR, *Escherichia coli*, (B/Sd–4/1,3,4,5) reverse mutation streptomycin^R	–	0	15.0000	Demerec *et al.* (1951)
ECR, *Escherichia coli*, (B/Sd–4/3,4) reverse mutation streptomycin^R	–	0	15.0000	Demerec *et al.* (1951)
VFC, Chromosomal aberrations, *Vicia faba* root tips	+	0	pH 4.3	Bradley *et al.* (1968)
*Chromosomal aberrations, *Sphaerechinus granularis* spermatozoa	+	0	pH 6.0	Cipollaro *et al.* (1986)
*Chromosomal aberrations, *Spathosternum prasiniferum* spermatocytes *in vivo*	+	0	pH 4	Manna & Mukherjee (1966)
CIC, Chromosomal aberrations, Chinese hamster CHO cells *in vitro*	+	+	380.0000	Morita *et al.* (1989)
G5T, Gene mutations, mouse lymphoma L5178Y cells, *tk* locus	(+)	+	0.0000	Cifone *et al.* (1987)

[a] +, positive; (+), weakly positive; –, negative; 0, not tested; ?, inconclusive (variable response in several experiments within an adequate study)
[b] In-vitro tests, μg/ml; in-vivo tests, mg/kg bw
*Not displayed on profile

Appendix 2

Response to specific Earthjustice comments

Earthjustice makes numerous claims that neither reflect the body of the scientific literature, nor EPA's approach to assessing risks to HCl. Below, Ramboll summarizes and responds to these claims.

1. The Earthjustice comments (page 6) state: "In the supplemental proposal, EPA does not provide substantial evidence that HCl is not carcinogenic or, indeed, even attempt to provide any showing at all. For this reason alone, issuing a HBEL for HCl would be unlawful and arbitrary."

   There is ample evidence that HCl is not carcinogenic, as presented in this report and supporting prior reports submitted by Ramboll. We encourage EPA to incorporate this evidence into their response to Earthjustice.

2. The Earthjustice comments (page 6) state "…Thus, EPA seeks to bypass the fact that it lacks substantial evidence to show that HCl is not a carcinogen by now claiming it is irrelevant whether HCl is a carcinogen and the agency does not have to make any such showing."

   Ramboll believes that there is sufficient evidence that HCl is not a carcinogen, and that EPA should present that evidence and **then** argue, that since it is impossible to prove a negative, that even if HCl were a carcinogen, there is reason to believe there would be a threshold.

3. The Earthjustice comments (page 8) state "Likewise, EPA makes no attempt to reconcile its apparent current position that the lack of research into whether HCl is a carcinogen is irrelevant, 89 Fed. Reg. at 9,092, with its previous finding that the lack of conclusive research is a reason not to issue a HBEL for HCl, 75 Fed. Reg. at 32,031…"

   Ramboll has summarized research into whether HCl is a carcinogen (see this report and supporting prior reports) and the body of evidence supports the conclusion that HCl is not a carcinogen.

4. The Earthjustice comments (page 8) state: "…EPA next claims "[a]n important consideration when determining if a carcinogen has a threshold is whether it is mutagenic." 89 Fed. Reg. at 9,092…. EPA does not and cannot claim that mutagenicity is the sole test for whether a pollutant has a threshold, either for cancer or any other health harm."

   In fact, EPA clearly does consider lack of genotoxicity an important consideration for carcinogenicity determination, stating:

   > *When cancer effects are not found in well-conducted animal cancer studies in two or more appropriate species and other information does not support the carcinogenic potential of the agent, these data provide a basis for concluding that the agent is not likely to possess human carcinogenic potential, in the absence of human data to the contrary. This default option about lack of cancer effects has limitations. It is recognized that animal studies (and epidemiologic studies as well) have very low power to detect cancer effects. Detection of a 10% tumor incidence is generally the limit of power with standard protocols for animal studies (with the exception of rare tumors that are virtually markers for a particular agent, e.g., angiosarcoma caused by vinyl chloride). In some situations, the tested animal species may not be predictive of effects in humans; for example, arsenic shows only minimal or no effect in animals, whereas it is clearly positive in humans. Therefore, it is important to consider other information as well; absence of mutagenic activity or absence of carcinogenic activity among structural analogues can increase the confidence that negative results in animal studies indicate a lack of human hazard. (USEPA 2005)*

Furthermore, EPA states:

> *A nonlinear approach should be selected when there are sufficient data to ascertain the mode of action and conclude that it is not linear at low doses and the agent does not demonstrate mutagenic or other activity consistent with linearity at low doses. Special attention is important when the data support a nonlinear mode of action but there is also a suggestion of mutagenicity. Depending on the strength of the suggestion of mutagenicity, the assessment may justify a conclusion that mutagenicity is not operative at low doses and focus on a nonlinear approach, or alternatively, the assessment may use both linear and nonlinear approaches. (USEPA 2005)*

5. The Earthjustice comments (page 8) state: "Furthermore, far from providing "substantial evidence" that HCl is not mutagenic, EPA makes clear that the current evidence regarding whether HCl is mutagenic is outdated, and at best, equivocal."

   The evidence related to the genotoxicity is clear that most of the findings were negative and that the sporadic positive findings were due to the highly acidic environments (pH <6 and more often <5.5) in the cell cultures, despite buffers present in the media. These acidic conditions were always cytotoxic, which may also cause artifacts. In their summary of the genotoxicity, IARC (1992) stated:

   > *Hydrochloric acid induced chromosomal aberrations in Vicia faba, in grasshopper (Spathostemum prasiniferum) spermatocyes (by injection), in sea urchin spermatozoa and in cultured Chinese hamster ovary (CHO) cells. There was a threshold in the aberration response to increasing hydrochloric acid concentration. The effect in CHO cells was observed in the absence of rat Liver S9 preparations at a nominal hydrochloric acid concentration of 14 mM (pH 5.5) but was greater in the presence of S9, when a nominal hydrochloric acid concentration of 10 mM (pH 5.8) was required (Morita et al., 1989). The greater effect of pH in the presence of S9 was due to generation of substances from S9 at low pH, as demonstrated in experiments in which the pH of medium containing S9 was lowered to 0.9 and readjusted to 7.2 before the cells were exposed. A similar effect was observed in the absence of S9 in medium submitted to this cycle of pH changes with hydrochloric acid (suggesting that clastogens may be generated in serum-containing culture medium at low pH) (A.K. Thilager, reported by Brusick, 1986). Although only results with hydrochloric acid are reported here, similar results were obtained with other inorganic acids and with acetic acid (A.K. Thilager, personal communication reported by Brusick, 1986) and lactic acid (Ingalls & Shimada, 1974), indicating that the hydrogen ion concentration is the most important factor in experiments with acids, although specific effects of cations cannot be ruled out. (IARC 1992)*

   Similarly, the Organization for Economic Cooperation (OECD 2002) concluded:

   > *While consistent negative results have been obtained in the bacterial systems, positive results have been obtained in the non-bacterial systems. The positive results were observed at high concentration, but they were considered to be artifacts due to low pH.*

   In vitro experiments are sensitive to pH variations, as the cells are often adversely impacted by highly acidic or basic conditions. (This is the reason that pH buffers are always present in cell culture media for mammalian cell culture.) Both IARC (1992) and OECD (2002) cite a workshop

report by Brusick (1986, as cited by IARC 1992) where the mutagenic effects of low pH and high osmotic levels on cultured mammalian cells were documented.

6. The Earthjustice comments (page 9) state: "Indeed, apart from a 1992 study in "bacteria," the only studies EPA can identify indicate that HCl is mutagenic in mammals. Id. EPA seeks to discount these studies by claiming – without providing any citation whatsoever – that some unidentified research that these results were caused by exceptionally high doses of HCl. Fed Reg. at 9092. EPA's citation-free and unsubstantiated critique of the only mammalian evidence it has – evidence showing that HCl is mutagenic – scarcely amounts to a demonstration with substantial evidence that HCl is not carcinogenic…"

   See response provided above in point 5. The study EPA was referring to was a report from a workshop on this topic held at an Environmental Mutagen Society meeting (Brusick 1986). It is cited by both IARC (1992) and OECD (2002), both of which had additional information from Dr. Brusick when their working groups met.

7. The Earthjustice comments (page 9) state: "EPA's attempt to rely on "[a]nother important consideration," the mechanisms that can cause cancer, is similarly flawed. 89 Fed, Reg at 9092, EPA states that increased cell proliferation and tissue enlargement, known as hyperplasia, can lead to cancer. Id. Then, however – just as with mutagenicity – EPA seeks to discount its own evidence by arguing that the same study did not show that HCl did not cause the rats to get cancer. Id. But it is EPA's argument that hyperplasia, as a purported "mechanism" of cancer, is relevant to whether HCl is a pollutant for which a cancer threshold exists. EPA's only evidence is that HCl does cause hyperplasia. Therefore, EPA's hyperplasia argument scarcely demonstrates with substantial evidence that HCl is not a threshold pollutant. As for EPA's claim that the study does not demonstrate HCl causes cancer, it is irrelevant. It is EPA's burden to demonstrate with substantial evidence that HCl does not cause cancer. Sierra Club, 895 F3d at 10-11. EPA does not claim that its 1995 rat study provides such evidence, or could it. Id."

   There are no studies in the scientific literature clearly demonstrating that HCl causes cancer. Although cell proliferation might lead to cancer, which may be why EPA discussed it, demonstrating cell proliferation on its own does not necessarily indicate an agent is a carcinogen. USEPA (2005) states:

   > *Many, but not all, mutagens are carcinogens, and some, but not all, agents that induce cell proliferation lead to tumor development.*

   This analysis is meant to differentiate carcinogenic agents that operate through a genotoxic versus nongenotoxic mode of action, and not to identify carcinogens.

8. The Earthjustice comments (page 9) state: "EPA next claims to have "similarly recognized the existence of a threshold of exposure for hyperplasia and resulting cancer outcomes from exposure to chloroform. 89 Fed Reg. at 9092-9092 The agency claims "[c]hloroform was labeled as likely to be carcinogenic to humans under high-exposure conditions that cause hyperplasia. However, the EPA concluded that chloroform is not likely to be carcinogenic to humans under exposure conditions that do not cause hyperplasia."

   The EPA used this argument to derive a threshold-based Reference Concentration (RfC) for chloroform. With respect to HCl, EPA stated that the Agency was "mindful of" the Court determination that the rulemaking record had not shown that HCl was not a carcinogen. The Agency therefore had to show that HCl exerted its health effect, whether cancer or noncancer,

through a non-linear threshold. The EPA therefore sought to show that HCl was not a mutagen and that the critical health impact with respect to potential cancer was increased cell proliferation. They used chloroform, which EPA has classified as a "probable human carcinogen" based on chronic animal study findings, and noted

> *… chloroform is likely to be carcinogenic to humans by all routes of exposure under high-exposure conditions that lead to cytotoxicity and regenerative hyperplasia in susceptible tissues (U.S. EPA, 1998a,b). Chloroform is not likely to be carcinogenic to humans by any route of exposure under exposure conditions that do not cause cytotoxicity and cell regeneration. (USEPA 2001).*

9. Earthjustice continues (page 10) by stating: "Although EPA did not find that chloroform is a threshold pollutant, as the agency now inaccurately suggests, it did find the chloroform is a probable carcinogen based on evidence that it causes hyperplasia. https://iris.epa.gov/ChemicalLanding/&substance_nmbr=25. EPA also has evidence that HCl causes hyperplasia. 89 Fed. Reg. at 9092. Thus, EPA's new arguments about HCl are not "similar" to those underlying the chloroform finding, id. To the contrary, EPA discounts the finding that HCl caused hyperplasia because the study did not also show that HCl caused cancer. Nowhere does EPA explain why, if it believes hyperplasia is a mechanism for carcinogenicity sufficient to demonstrate that chloroform causes cancer even without an independent direct finding that chloroform causes cancer, it does not reach the same conclusion for HCl."

   EPA found that chloroform was a potential carcinogen because:

   > *"… it caused tumors (emphasis added) in several chronic animal bioassays, with significant increases in the incidence of liver tumors in male and female mice and significant increases in the incidence of kidney tumors in male rats and mice (U.S. EPA, 1994, 1998c). When examining the biology of the tumor production, the occurrence of tumors is demonstrably species-, strain-, and gender-specific, and has only been observed under dose conditions that caused cytotoxicity and regenerative cell proliferation in the target organ"* (USEPA 2001).

   EPA then continues by explaining why they believe it is a threshold carcinogen due to:

   - the majority of available studies being negative with limitations such as excessive doses or cytotoxicity in many of the positive studies,
   - suspected saturation of the primary metabolism pathway, via CYP2E1, at higher doses, with reductive metabolism which can lead to free radical formation at higher doses[7], and
   - regenerative cell proliferation following hepatotoxicity and nephrotoxicity at the higher doses.

   Thus, EPA's use of chloroform as an analogy is not to say that HCl works just like chloroform, but to demonstrate that some carcinogens are dependent on a threshold mode of action.

10. The Earthjustice comments (page 10) state: "Further, EPA states only that HCl causes hyperplasia in rats. 89 Fed. Reg. at 9092. It does not claim to have identified any level below which HCl does not cause hyperplasia in rats, let alone people. Thus, even if EPA identified a threshold below

[7] Note, IARC (1992) suggests that at the higher concentrations of HCl, after glutathione is depleted, chloroform is metabolized to phosgene. Thus, it may be a combination of altered Phase 1 metabolic pathways, as well as altered Phase 2 metabolism.

which chloroform did not cause hyperplasia – which it has not – that situation would not be "similar[]," id."

While it is true that due to their study design, neither Albert et al. (1982) nor Sellakumar (1985) identify an exposure where hyperplasia did not occur – since they only examined a single exposure concentration – that does not negate the finding of hyperplasia at high concentrations. In fact, the study designs of these two bioassays were meant to investigate whether concurrent exposures to HCl would enhance the carcinogenicity of formaldehyde at high exposure concentrations (it did not), as well as to investigate whether exposure to HCl induced cancer in the rat nose (it did not). By design, the experiments were to high concentrations of both chemicals. The first publication (Albert et al. 1982) presented preliminary results and the second publication (Sellakumar 1985) included longer follow-up periods. They demonstrated that not only did co-exposure to 10 ppm HCl and formaldehyde not enhance the carcinogenicity of formaldehyde in nasal tissues, but it also did not cause additional irritating effects in the co-exposure scenario. Hyperplasia (but not squamous metaplasia) was evident in the HCl-only group.

11. The Earthjustice comments (page 12) state: "The [2005 Carcinogenic Risk Assessment] Guidelines make clear that nonlinear or threshold approaches should not be employed in the absence of an established mode of action…. EPA has not met its own standard in its current analysis, in the absence of a toxicological risk assessment that evaluated HCl for its carcinogenic potential."

    While it is true that linear extrapolation is used as a default approach, in the case of HCl there is not good evidence that HCl causes cancer. Furthermore, it does not appear that HCl, under physiological conditions, would induce genotoxicity.

12. The Earthjustice comments (page 15) criticize EPA for considering HCl to have a non-linear mode of action in the absence of a formal determination that HCl is a carcinogen.

    However, using hyperplasia (even when there is only a LOAEL available and not a NOAEL), EPA was taking a cautious approach as if to say that even if HCl were a carcinogen, it would need to work via a non-genotoxic mechanism, which would have a threshold.

13. The Earthjustice comments (pages 15-16) state: "Very few studies have explored either genotoxicity or carcinogenicity, and yet the absence of such data does not support the conclusion of an existing threshold."

    There are, however, some studies and they do not support a finding of carcinogenicity.

14. The Earthjustice comments (page 16) state: "Very few studies have explored either genotoxicity from the few identified studies evaluating genotoxicity, at least two identified concentrations at which HCl was found to induce a response: in a 1981 study, the Escherichia coli DNA-repair assay was positive at a concentration of 25 ug/well as well as a separate study finding chromosomal nondisjunction induced at "a concentration of 100 ppm in Drosophila melanogaster in 2008."

    As discussed in Appendix 1, there have been more than these two studies, and very few studies reported any positive findings. Among those that did (such as the two studies cited by Earthjustice) the study authors generally found that the results were either inconsistent or due to the acidity of the conditions (which would not occur under physiological conditions). The *E. coli* study cited by Earthjustice (McCarroll et al 1981a as cited OECD 2002) showed inhibitory activity in the WP2uvrA stain; however, while this response was reproducible, it was not considered

adequate evidence of DNA damaging activity since the remaining WP2 deficient strains which also carried the uvrA mutation gave no indication of preferential kill.

15. Earthjustice goes on to state (page 16): "The assessment of HCl's ability to induce a positive response in at least two separate studies provides evidence that exposure to HCl is mechanistically linked to potential genotoxic and potentially mutagenic outcomes (which cannot be ruled out)."

    In fact, the entire body of evidence points to genotoxicity being an indirect effect of the acidic conditions, which would not be present under physiologic conditions.

16. The Earthjustice comments (page 16) state: "…a fatal flaw associated with EPA's noncancer risk value for HCl" and point out the limited database.

    A limited database, particularly for a chemical which has such widespread use, does not imply that the chemical is a carcinogen.

17. The Earthjustice comments (page 17) state: "To ensure it follows the best available science, EPA should use the latest OEHHA risk exposure level ("REL") for HCl. EPA has not provided adequate rationale for choosing to ignore OEHHA's REL, which is an order of magnitude stronger than EPA's RfC."

    The chronic REL (CREL) developed by the California Environmental Protection Agency (CalEPA), of 0.009 mg/m^3 is based on the same chronic toxicity study (Sellakumar 1985) that serves as the basis for the RfC derived by EPA. While both the EPA and CalEPA toxicity values are based on the same underlying animal toxicity data and derived using similar methodologies there are significant differences in the two toxicity values with the CalEPA CREL being lower than EPA's RfC (RfC of 0.2 mg/m^3 vs. CREL of 0.009 mg/m^3). The difference in the values is related to the use of EPA's s guidance on the dosimetry adjustment of inhalation of gases (USEPA 1994). The dosimetric adjustment equation considers the surface area of all regions of the respiratory tract that are affected (i.e., extrathoracic, tracheobronchial and pulmonary). When conducting the dosimetry adjustment, CalEPA only considered the extrathoracic surface area. However, consistent with the results reported by Sellakumar et al. (1985) of increased hyperplasia in both the larynx and the trachea, EPA included the surface area of both the extrathoracic and tracheobronchial respiratory region. CalEPA notes that while extrathoracic and tracheobronchial effects were reported in rats following exposures to hydrogen chloride, the REL was based on extrathoracic effects because humans are predicted to be relatively more susceptible to the effects of hydrogen chloride in that region. However, no basis for this prediction was presented by CalEPA. The EPA guidelines recommend that when effects are observed in the mid-respiratory tract (tracheobronchial), this region should also be considered in the dosimetry adjustment calculations. Therefore, EPA's approach for the derivation of the RfC aligns with the guidelines for dosimetric adjustments following inhalation of gases and better represents the observed respiratory effects reported in the scientific literature.

18. The Earthjustice comments (page 20) state: "EPA provides no explanation for its decision to deviate from years of practice and allow acute health harm to affected communities from exposure to these chemicals." Earthjustice also comments (page 19*): The AEGL values and Emergency Response Planning Guidelines ("ERPG") values were created for emergency exposure scenarios. Levels defined for "once-in-a-lifetime, short-term exposures" and "emergency planning" for "single exposures" to chemical releases or accidents, are not appropriate tools to*

use to measure the acceptability of acute risks over a lifetime from one or more potential exposures due to an industrial source's emissions. The Science Advisory Board ("SAB") has approved use of the RELs but not the EPRGs. As the SAB has explained:

The incorporation of the available California Reference Exposure Levels (RELs) for the assessment of acute effects is a conservative and acceptable approach to characterize acute risks. The Panel has some concern with the use of the Acute Exposure Guidelines Limits (AEGLs) and Emergency Response Planning Guidelines (ERPGs) AEGL-2 and ERPG-2 values should never be used in residual risk assessments because they represent levels that if exceeded could cause serious or irreversible health effects.

The AEGL and ERPG numbers would be expected to underestimate risk. Using these numbers is likely to discount or cloak the level of risk to the maximum exposed individual.

As stated, EPA has long recognized CalEPA RELs as authoritative and regularly uses them in risk assessments. It gives no reasoned scientific explanation for refusing to use this value as the best available reference dose here. It must use the most up-to-date and best available scientific information on the risks and health effects of the HCl REL in its risk assessment. Doing so will lead to a recognition of increased acute risk from lime kiln facilities' emissions – especially if EPA is proposing to allow a staggeringly high 300 tpy of HCl emissions based on its approach outlined in the 2023 Memo.

For assessing acute risks EPA performed a screening assessment using conservative assumptions combined with reasonable worst-case exposure estimates. This screening process results in the determination that HCl emissions from facilities would pose no potential acute health risks (i.e., it "screens out" risks), or that a facility's emissions requires further assessment.

EPA's dose-response assessment for acute exposure to HCl was based on the existing recommendations of EPA's Office of Air Quality Planning and Standards (OAQPS) for hazardous air pollutants (HAPs). As noted by EPA in the 2023 memo:

> *"Depending on availability, the results from screening acute assessments are compared to both "no effects" reference levels for the general public, such as the California Reference Exposure Levels (RELs), as well as emergency response levels, such as Acute Exposure Guideline Levels (AEGLs) and Emergency Response Planning Guidelines (ERPGs), with the recognition that the ultimate interpretation of any potential risks associated with an estimated exceedance of a particular reference level depends on the definition of that level and any limitations expressed therein."*

Therefore, the results from screening acute assessments are comparable to CalEPA's Acute Reference Exposure Levels (ARELs), Acute Exposure Guideline Levels (AEGLs) and Emergency Response Planning Guidelines (ERPGs).

Following EPA's hazard quotient (HQ) approach for screening for potentially significant acute inhalation exposures, the maximum estimated acute exposure was divided by each available short-term threshold value (i.e, ARELs, AEGLs and ERPGs) to develop an array of HQ values relative to the various acute endpoints and thresholds. When none of these HQ values were greater than one, a low potential for acute risk was assumed. In those cases where HQ values above one were seen, additional information was used to determine if there was a potential for significant acute risks.

EPA noted that there were three facilities with acute screening HQ values equaling or approaching a value of 1. Each case was reviewed by examining aerial imagery of the facilities to determine the maximum offsite HQ values which resulted in a maximum acute off-site HQ equal to 0.6. EPA noted that the acute scenario was conservative and assumed there was a person present at the location and time where the maximum HQ value occurs. Therefore, EPA did not deviate from previous practice to *allow acute no health harm to affected communities.* The results from screening acute assessments were comparable to CalEPA's Acute Reference Exposure Levels (ARELs). While AEGLs and ERPGs were also considered for screening, HQ's were calculated for all available short-term threshold values.

19. The Earthjustice comments (page 20) state: "EPA should apply a default or uncertainty factor of at least 10 to account for increased risk from early-life exposures for non-cancer risk in this rulemaking and other risk assessments."

    The EPA has derived a RfC for HCl of 0.2 mg/m^3 based on the lowest adverse effect level (LOAEL) of 10 ppm (14.9 mg/m^3) reported by Sellakumar et al. (1985). The LOAEL is based on the incidence of hyperplasia reported in rats chronically exposed to HCl via inhalation, and the assumption that a threshold concentration exists below which no effects would be seen following HCl exposure. EPA applied a total uncertainty factor of 300 to the LOAEL, which included a factor of 3 for interspecies differences, 10 for intraspecies extrapolations, and 10 to extrapolate from a LOAEL to a NOAEL. The intraspecies uncertainty factor of 10 applied to the LOAEL is applied to account for variability in sensitivity to toxic chemicals among susceptible populations, which not only includes the age of the exposed population, but also sex, health status, nutrition or personal habits or genetic factors that make some people more susceptible to chemical exposure.

Appendix 3

2021 report from Ramboll to NLA

Report

June 11, 2021

Prepared for National Lime Association

EVALUATION OF THE CARCINOGENICITY OF HYDROCHLORIC ACID (HCl) AND HCl MIST

RAMBOLL Bright ideas. Sustainable change.

EVALUATION OF THE CARCINOGENICITY OF HYDROCHLORIC ACID (HCl) AND HCl MIST

Project name	**Ramboll Report on the Carcinogenicity of Hydrochloric acid (HCl) and HCl Mist**
Recipient	**National Lime Association**
Document type	**Report**
Date	**June 11, 2021**
Prepared by	**Debra A. Kaden, PhD; Carly Pavia, MS; and Sandra I. Sulsky, MPH, PhD**

Ramboll
101 Federal Street
19th Floor
Boston, MA 02110
USA

T +1 617 946 6100
https://ramboll.com

CONTENTS

APPENDICES

ACRONYMS AND ABBREVIATIONS

APCD	air pollution control device
CI	confidence interval
ENT	ear, nose and throat
HAPs	hazardous air pollutants aka air toxics
HCl	Hydrochloric acid
HCl(aq)	aqueous form of HCl
HCl(g)	gas form of HCl
IARC	International Agency for Research on Cancer
IPCS	Programme on Chemical Safety
IRIS	Integrative Risk Information System (US EPA)
MACT	maximum achievable control technology
NHL	non-Hodgkin's lymphoma
NTP	National Toxicology Program
OECD	Organisation for Economic Co-operation and Development
OR	odds ratio
ppm	parts per million
PubMed	a database containing 32 million citations developed by the National Library of Medicine
RR	relative risk
SIDS	Screening Information Dataset (OECD)
SMR	standardized mortality ratio
UADC	upper aerodigestive cancer
US EPA	United States Environmental Protection Agency
WHO	World Health Organization
yr	year

EXECUTIVE SUMMARY

Hydrogen chloride (HCl), either as a gas or dissolved in water (hydrochloric acid), is a strong corrosive acid historically used in many industrial processes. HCl has been known since the Middle Ages, and was first commercially produced in the early 1800's. Because of its many industrial uses, occupational exposure to HCl is common.

HCl has been the subject of toxicity studies in experimental animals and epidemiological studies in exposed workers. Several authoritative groups (including the World Health Organization's International Agency for Research on Cancer [IARC], the International Programme on Chemical Safety [IPCS], and the international Organisation for Economic Co-operation and Development [OECD]), have conducted evaluations of the carcinogenic potential of HCl. None of these groups have concluded that HCl is a carcinogen. Other authoritative bodies (including the US Environmental Protection Agency and the US National Toxicology Program) have chosen not to evaluate the carcinogenicity of HCl, estimating that carcinogenicity is unlikely based on its physical, chemical, and corrosive properties and the lack of evidence suggesting an association with cancer.

Ramboll US Consulting, Inc. (Ramboll) was asked by the National Lime Association to investigate the potential carcinogenicity of HCl in order to determine whether it is appropriate for US EPA to regulate HCl as a non-carcinogen by using an established health based threshold consistent with Clean Air Act § 112(d)(4). In addition to relying upon previous authoritative reviews, Ramboll did a series of additional literature searches for any new studies which might indicate HCl is a carcinogen. We employed several search strategies to make sure we uncovered any new scientific evidence that may not have been considered by previous assessments. Despite this broad search, we identified only six additional publications. This newer evidence is consistent with the earlier body of scientific evidence. In addition to direct studies of cancer associations, we also examined other supporting evidence in the form of genotoxicity studies or potential to induce cell proliferation. Taking both the epidemiological and toxicological data into account, the evidence does not indicate that HCl is a carcinogen.

IARC recognized that sulfuric acid and HCl are often found together in industrial processes. In assessing the scientific evidence for the grouping "sulfuric acid and other strong inorganic acids," IARC concluded that there was sufficient evidence associating occupational exposure to "strong-inorganic-acid mists containing sulfuric acid" with cancer. They therefore concluded that occupational exposure to strong inorganic acid mists **containing sulfuric acid** is carcinogenic to humans (i.e., a "Group 1" carcinogen) (IARC 1992). In contrast, IARC's conclusion regarding HCl was that there was **inadequate evidence** for the carcinogenicity of HCl, and they therefore assessed exposure to HCl as not classifiable as to its carcinogenicity to humans (i.e., a "Group 3"). This is relevant because the conclusion regarding acid mists is based on exposure to mixtures that must include sulfuric acid. While sulfuric acid and HCl often are found together in mixed acid exposures, the exposure contained in the mixture with the strongest relationship to the outcome (in this case, surfuric acid) will drive the relationship for the whole mixture. This is likely the explanation for the sporadic, positive associations observed in occupational studies of mixed acids containing HCl.

HCl has not been identified as a carcinogen, either by authoritative reviews or Ramboll's own search of the scientific literature, despite its long history of use. Ramboll therefore recommends that based on our review of the science and the criteria in 42 U.S.C. § 7412(d), it would be

entirely appropriate for EPA to base its standard for HCl on a health-based threshold, including an ample margin of safety.

1. INTRODUCTION

1.1 Hydrochloric Acid (HCl)

Hydrochloric acid is a strong corrosive acid that is formed when hydrogen chloride gas is dissolved in water (also known as an aqueous solution). Hydrogen chloride gas and aqueous hydrochloric acid have the same chemical formula: HCl. Chemists will designate the gas form as HCl(g) and the aqueous form as HCl(aq). For the purpose of this report, we refer to either of the physical states as HCl.

HCl is used in the production of chlorides, fertilizers, and dyes, as well as in the textile and rubber industries.[1] Commercial concentrated hydrochloric acid contains 36% to 38% hydrogen chloride in water. HCl can also be formed as a byproduct of combustion of certain fossil fuels in industrial manufacturing processes, for example from lime kilns used for manufacture of lime (CaO and MgO).

At room temperature, HCl is a nonflammable, colorless to slightly yellow gas with a pungent odor in moist air.[2,3] On exposure to air, the gas forms dense white vapors due to condensation with atmospheric moisture. When hydrogen chloride gas comes into contact with moisture, it forms hydrochloric acid. In the early twentieth century, hydrogen chloride was created by burning hydrogen gas. This method created a product of higher purity than that of the reaction between chloride salts and sulfuric acid or sodium hydrogen sulfate (IARC, 1992).

1.2 Residual Risk and Technology Review

Under Section 112 of the Clean Air Act, the Environmental Protection Agency (US EPA) regulates hazardous air pollutants (HAPs, also known as air toxics) originating from industrial facilities. There is a two-stage process for this regulation:

- In the first stage, section 112(d) requires the US EPA to develop technology-based standards, called maximum achievable control technology (MACT) standards, for each category of sources (e.g., petroleum refineries, pulp and paper mills, etc.).[4]
- In the second stage, US EPA is required under section 112(f)(2) to assess the health and environmental risks that remain after implementation of the MACT standards. If additional risk reductions are necessary to protect public health with an ample margin of safety or to prevent an adverse environmental effect, US EPA must develop standards to address these remaining risks. This second stage of the regulatory process is known as the residual risk stage. For each source category for which US EPA issued MACT standards, the residual risk stage must be completed within eight years of promulgation of the initial technology-based standard.

Also, under section 112(d)(6), US EPA must review each of the technology-based standards at least every eight years and revise it, as necessary, taking into account developments in practices, processes and control technologies. If appropriate based on the results of the risk and technology reviews, the US EPA will revise the rule. For efficiency, the US EPA includes the 112(f)

[1] https://www.epa.gov/sites/production/files/2016-09/documents/hydrochloric-acid.pdf

[2] https://www.atsdr.cdc.gov/MHMI/mmg173.pdf

[3] https://pubchem.ncbi.nlm.nih.gov/compound/Hydrochloric-acid#section=Solubility

[4] https://www.epa.gov/stationary-sources-air-pollution/risk-and-technology-review-national-emissions-standards-hazardous

and 112(d) analyses in the same regulatory package and calls the rulemakings the Risk and Technology Review.

MACT standards require the "maximum degree of [emissions] reductions" that US EPA determines "is achievable." The MACT standard is based on a minimum stringency requirement (a "floor") based on emissions levels achieved by existing sources, where the floor is based on average emission limitation achieved by the best-performing 12% of existing sources (for which the Administrator has emissions information)." Alternatively, as outlined in 42 U.S.C. § 7412(d)(4), the MACT standard may be based on a health-based threshold, assuming such a threshold has been established. This health-based threshold must include an ample margin of safety. The US EPA will not approve a health-based threshold for a MACT standard if a HAP is a carcinogen. As part of the statutory lime manufacturing risk and technology review, EPA conducted an inhalation risk assessment for HAPs emitted from lime kilns, including HCl, and found no unacceptable human health risk under worst case emissions scenarios (84 FR 48,723 (Sep. 16, 2019)).The EPA risk assessment assumed HCl is a non-carcinogen, and as such used a variety of human-health risk screening benchmarks as part of risk calculations. Ramboll therefore has undertaken this review to confirm the status of HCl as a non-carcinogen, and validate EPA's risk assessment approach.

Based on communication with the National Lime Association (via email), the gas temperature at the inlet to the air pollution control device (APCDs) is typically above 400 degrees F for most straight rotary and preheater lime kilns, and roughly 275 degrees for vertical kilns. These elevated temperatures are well above the acid dew point for HCl (typically about 130 degrees F).

Stack test data obtained from wet chemistry and vapor phase testing have also confirmed the presence of HCl as a gas in the exhaust. The vast majority of U.S. lime kilns (>95 percent) are controlled with dry APCDs. For kilns controlled with a wet scrubber, HCl emissions as mist are expected to be very low due to the solubility of HCl in water, i.e., the gas is readily absorbed in water.

1.3 Objective of this report

The objective of this report is to review and synthesize the scientific literature regarding the carcinogenicity of HCl. Ramboll based this assessment on a combination of previous assessments by authoritative bodies, as well as our own literature search.

1.4 Previous assessments of HCl carcinogenicity

HCl has been evaluated for carcinogenicity by several authoritative agencies or groups, including the World Health Organization International Agency for Research on Cancer (IARC), the Organisation for Economic Co-operation and Development (OECD), and the International Programme on Chemical Safety (IPCS). Neither the National Toxicology Program's (NTP) Report on Carcinogen (NTP, 2016) nor the US EPA's Integrative Risk Information System (IRIS) program have assessed the carcinogenicity of HCl, and neither Agency is currently evaluating the chemical (US EPA 2021a[5]; NTP, 2019[6]). For a common chemical such as HCl, this usually means that the relevant agency does not consider the evidence compelling enough to undertake a major review

[5] https://www.epa.gov/sites/production/files/2021-03/documents/iris_program_outlook_mar2021.pdf

[6] https://ntp.niehs.nih.gov/whatwestudy/assessments/cancer/ongoing/index.html

effort (US EPA, 2021b[7]; NTP, 2016a[8]; NTP 2016b).

The stated purpose of IARC reviews, published in monographs, is to identify cancer hazards, i.e., agents that are capable of causing cancer. IARC is explicit that hazards are separate from actual risks, with the latter depending on factors including exposure duration and concentration. Substances are raised for review by IARC every five years by an Advisory Group that makes its recommendations from nominations submitted by scientists and regulatory agencies. The selection is based on the availability of data and current public health priorities, as well as the existence of signals that the substance may pose a cancer hazard[9]. IARC convened a working group of experts to evaluate HCl in October 1991 and published their findings in a monograph (IARC 1992). Based on their evaluation of the occupational cohort and case-control studies and toxicological data available in 1991 (see section 2.1 for discussion of these studies), IARC concluded that there was *inadequate evidence* for the carcinogenicity of HCl in humans and that there was *inadequate evidence* for the carcinogenicity of HCl in animals. Based on these findings, IARC concluded that HCl is *not classifiable* as to its carcinogenicity in humans (Group 3). This category is used for agents, mixtures, and exposure circumstances which IARC has evaluated and found that "the evidence of carcinogenicity is inadequate in humans and inadequate or limited in experimental animals." If IARC finds *evidence suggesting lack of carcinogenicity*, "…the Working Group may add a sentence to the evaluation to characterize the agent as well-studied and without evidence of carcinogenicity." The other classifications used by IARC are *carcinogenic to humans* (Group 1); *probably carcinogenic to humans* (Group 2A) and *possibly carcinogenic to humans* (Group 2B)[9]. In its history, IARC classified only one chemical as *probably not carcinogenic to humans* (Group 4), and the Agency eliminated this category in 2019; more than half of the 1,090 chemicals it has reviewed have been classified as Group 3.[10] [11]

IARC also reviewed other inorganic acids in the same monograph, including "sulfuric acid and other strong inorganic acids" (IARC 1992). In contrast to their conclusion for HCl, their conclusion for sulfuric acid and other strong inorganic acids was that "There is *sufficient evidence* that occupational exposure to strong-inorganic-acid mists containing sulfuric acid is carcinogenic." IARC's overall evaluation was that "Occupational exposure to strong inorganic acid mists containing sulfuric acid is carcinogenic to humans (Group 1)" (IARC 1992). This is relevant because the conclusion is based on exposure to acid mists that must include sulfuric acid. While sulfuric acid and HCl often are found together in mixed acid exposures, the exposure contained in the mixture with the strongest relationship to the outcome (in this case, surfuric acid) will drive the relationship for the whole mixture. This is likely the explanation for the sporadic effects observed in occupational studies of mixed acids containing HCl.

The Organisation for Economic Co-operation and Development (OECD) Screening Information Dataset (SIDS) Initial Assessment Profile (2002) evaluated the scientific literature concerning evidence for the carcinogenicity of HCl and concluded that "In humans, no association between hydrogen chloride exposure and tumor incidence was observed." Their assessment is based on studies finding no association between HCl exposure and cancer (Albert et al., 1982; Farrow et al., 1989; Bond et al., 1986; Bond et al., 1991; Bond et al., 1993; Bond et al., 1995). OECD

[7] https://www.epa.gov/iris/basic-information-about-integrated-risk-information-system#cancer

[8] https://ntp.niehs.nih.gov/ntp/roc/process/process_508.pdf

[9] https://monographs.iarc.who.int/wp-content/uploads/2019/01/Preamble-2019.pdf

[10] https://msc.ul.com/en/resources/article/iarc-revises-preamble-and-eliminates-group-4-classification/

[11] Discussed in https://foodinsight.org/what-is-iarc/#:~:text=Of%20the%20more%20than%20900%20substances%20classified%20by,received%20a%20classification%20of%20Group%202B%20or%20higher.

stated that studies reporting associations between HCl exposures and increased risk of respiratory cancer or lung cancer could not rule out the effect of exposure to other acids or smoking habits as alternative explanations.

The International Programme on Chemical Safety (IPCS) concluded that exposure of the general population to HCl, other than during accidental releases, is minimal and almost unmeasurable (IPCS, 1982). They further stated that, on the basis of the limited information available from industrial survey data, and from the observations of controlled exposure studies, it is most unlikely that the general population is exposed routinely to any significant health risks from HCl.

2. SEARCH METHODS

2.1 Identifying Relevant Literature

In their Monograph Volume 54, published in 1992, IARC identified a total of 8 relevant epidemiological studies, including 3 cohort studies (Collins et al. 1989; Beaumont et al. 1967; Steenland et al 1988) and 5 case-control studies (Bond et al., 1983; Bond et al., 1985; Bond et al., 1986; Bond et al., 1991; and Siemiatycki, 1991). IARC also identified a single experimental animal cancer study (Sellakumar et al., 1985), which examined rats exposed by inhalation to HCl.

In their SIDS document, OECD (2002) identified many of the same studies identified by IARC (1992), as well as one additional epidemiological study (Farrow et al, 1989) and one experimental animal study (Albert et al., 1982). They also discussed two experimental animal studies (a dermal exposure study, Narat, 1925; and an oral administration study, Dyer et al., 1946) which they judged, due to study design limitations, were not appropriate for assessing carcinogenic potential.

After starting with the literature identified by the authoritative reviews (ICPS, 1082; IARC, 1992; OECD, 2002), we developed a literature search strategy consisting of three different approaches: (1) Reviewing papers published since IARC considered the carcinogenicity of HCl in 1991 that cited the relevant epidemiological studies cited in the IARC monograph vol. 54; (2) a search of epidemiological studies addressing possible associations between exposure to HCl and cancer; and (3) a targeted search of chronic (long-term) bioassays for cancer associated with HCl exposure in experimental animals. Because HCl is a common laboratory ingredient used in many experimental set-ups, a broader literature search for animal studies or *in vitro* studies would have resulted in an overwhelming number of irrelevant papers. We therefore conducted a very targeted search for additional animal studies.

Both the search of epidemiological studies examining cancer as a health endpoint and the targeted search of chronic bioassay studies for cancer in animals used PubMed, a database developed by the National Library of Medicine that includes more than 32 million citations for biomedical literature from journal articles in life sciences with a concentration on biomedicine, and online books.

2.1.1 Papers That Cited Epidemiological Papers Included in IARC or OECD

Usually, authors of journal articles cite previous relevant research in their manuscripts. Ramboll therefore conducted a search of scientific papers that cited the literature identified by IARC (1992) or OECD (2002).

Using the database Google Scholar, Ramboll conducted a search for any papers that cite one or more of the 9 studies identified by IARC (Sellakumar et al., 1985; Collins et al., 1989; Beaumont et al., 1967; Steenland et al., 1988; Bond et al., 1983; Bond et al., 1985; Bond et al., 1986; and Siemiatycki, 1991) or the additional epidemiological studies identified by OECD (Farrow et al., 1989). We did not perform citation searches on the experimental animal studies discussed by OECD (2002) because the Albert et al. (1982) bioassay study was superseded by the subsequent publication by the same group (Sellakumar et al., 1985), and because the two other cancer studies in experimental animals (Dyer et al., 1946; Naret, 1925) were judged by OECD (2002) as having major faults in their study design precluding conclusions to be drawn from their results.

2.1.2 PubMed Search of Epidemiological Literature

A literature search was conducted using PubMed, based on using combinations of the following search terms: "occupational"; "human"; "human exposure"; "hydrochloric acid"; "hydrogen chloride"; "carcinogenicity"; "carcinogen"; "cancer"; "epidemiology"; "cohort"; and "case-control". When searches included "cancer", clinical studies were filtered out of the search so as to remove irrelevant studies of clinical trials.

2.1.3 Targeted PubMed Search of Animal Toxicity Literature

A targeted literature search was conducted using PubMed, based on using combinations of the following search terms: "hydrochloric acid"; "hydrogen chloride"; "chronic bioassay"; and "lifetime cancer risk".

2.1.4 Exclusion criteria

Publications were excluded at the screening stage if HCl was not an exposure variable assessed in the study or if HCl exposure was not assessed in human subjects (for the search targeting epidemiological studies) or if HCl was not the test material administered to animals or the study was an aquatic toxicity study (for the search targeting chronic bioassays for cancer in experimental animals).

3. RESULTS

3.1 Literature Search Findings

The results from different steps of this search process are outlined in Figure 1 (PRISMA diagram). A total of eight epidemiological studies (Beaumont et al., 1987; Bond et al., 1983; Bond et al., 1985; Bond et al., 1986; Bond et al., 1991; Collins et al. 1989; Siemiatycki, 1991; Steenland et al., 1988) and one cancer study in experimental animals (Sellakumar et al., 1985) were included in the IARC (2002) report. A total of six epidemiological studies (Beaumont et al., 1987; Bond et al., 1983; Bond et al., 1985; Bond et al., 1986; Bond et al., 1991; Farrow et al. 1989) and four cancer studies in experimental animals (Albert et al., 1982; Dyer et al., 1946; Narat, 1925; Sellakumar et al., 1985) were cited in OECD (2002)[12]. Note, there was some overlap between these two sets of studies. Together, a total of 13 unique studies were identified– nine

[12] Note, one further publication cited by OECD (ANON, ed. 1987. Pestic. Toxic. Chem. News., 15(43), 6.) was reported only in summary form and neither the publication nor the abstract could be found. It was not included in the counts. OECD reported that all respiratory cancer cases in this study were smokers; therefore, confounding cannot be ruled out.

epidemiological and four in animals (see Appendix A).

Conducting a search of scientific publications that cite these IARC-cited or OECD-cited studies resulted in a total of 1,008 publications to screen.[13] We screened the titles and abstracts of these publications, and identified five additional papers (Coggon et al. 1996; Hathaway et al. 1997; Soskolne et al. 2011; Fritschi and Siemiatycki 1996a; Fritschi and Siemiatycki 1996b).

The PubMed searches for epidemiological publications resulted in a total of 1,934 scientific publications; after removal of duplicates and publications that had been identified through authoritative searches or citation searches, 771 unique publications remained. The targeted PubMed search of the animal toxicological literature resulted in 56 publications; after removal of duplicates and publications that had been identified through authoritative searches or citation searches, 34 unique publications remained. Overall, 805 unique publications were identified through both PubMed search strategies. We screened the titles and abstracts of these unique publications to identify 24 publications which warranted a full text screen for relevance. Only one additional relevant publication was identified from this full text screen (Tsai et al. 2016).

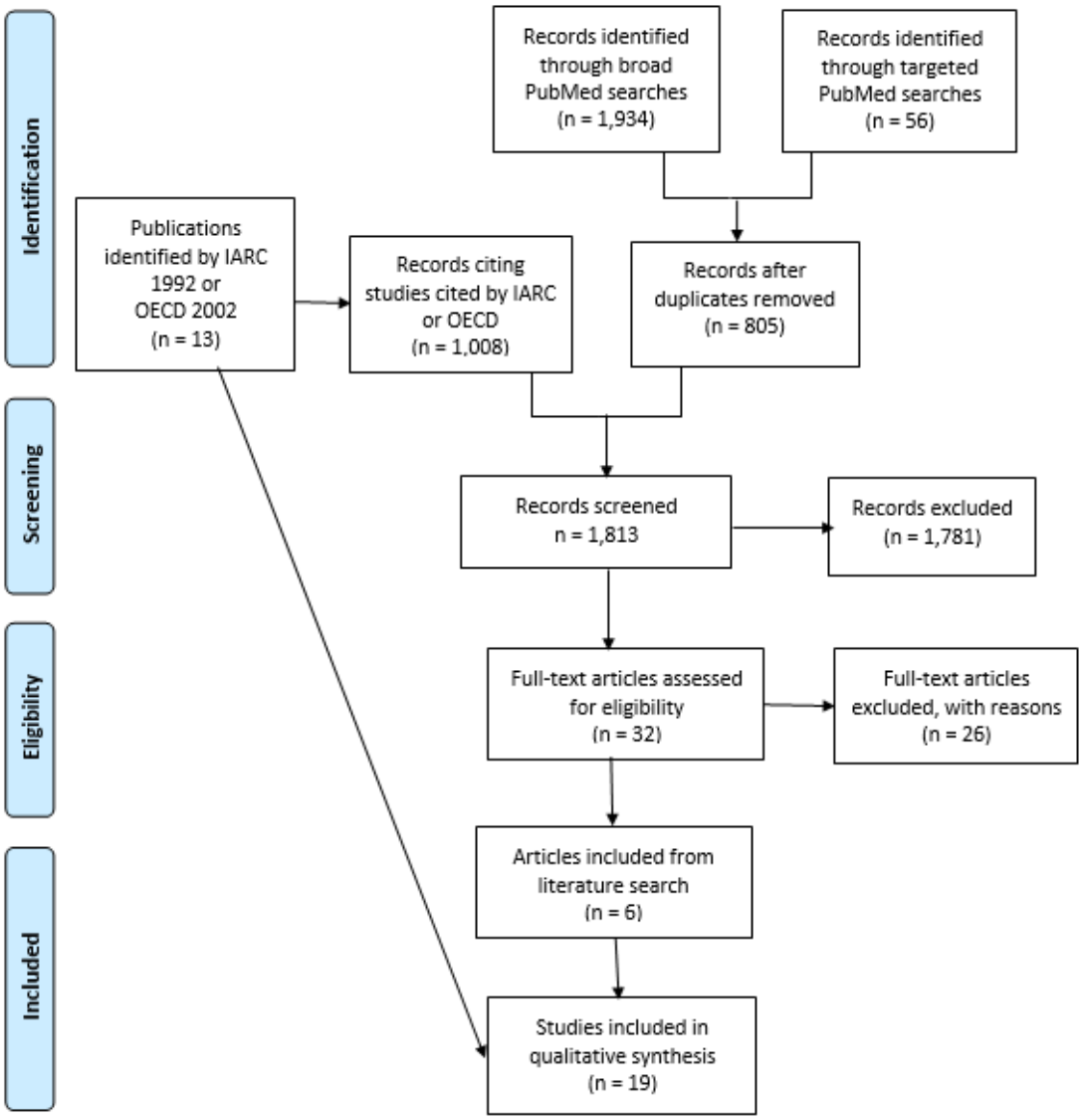
A total of 19 relevant articles were identified through the combined literature search strategy, consisting of the initial nine epidemiological studies identified by IARC and OECD and four toxicology study identified by IARC and OECD, and the six additional articles (five epidemiological studies identified through the citation search of the initial articles, and one additional article resulting from the very broad PubMed searches) (Figure 1).

3.2 Summary of Findings

The 19 relevant publications identified through this extensive literature search included: 13 epidemiological studies containing statistical analyses of the association between exposure to HCl and cancer; four publications examining cancer in experimental animals; one commentary/letter to the editor, and one review. Below is a discussion of three cohort studies (Collins et al., 1989; Beaumont et al., 1987; Steenland et al., 1988), ten case-control studies (Bond et al., 1983; Bond et al., 1985; Bond et al., 1986; Bond et al., 1991; Siemiatycki, 1991; Fritschi and Siemiatycki 1996a; Fritschi and Siemiatycki 1996b; Farrow et al. 1989; Coggon et al., 1996; Sosklone et al., 2011), and four animal toxicity studies (Sellakumar et al., 1985; Albert et al., 1982; Dyer et al., 1946; Narat, 1925). See Appendix A for list of all relevant publications. A detailed summary of the epidemiological studies, including information on study characteristics, statistical analyses, and limitations, is included in Appendix B.

[13] Among the experimental animal studies, only the Sellakumar et al. 1985 study was the subject of our search because the Albert et al., 1982 publication was superseded by the subsequent Sellakumar et al., 1985 publication, and the other two experimental animal cancer studies were very old and inadequate.

Figure 1. PRISMA Flow Diagram



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *Preferred Reporting Items for Systematic Reviews and Meta-Analyses*: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit www.prisma-statement.org.

3.3 Discussion of Individual Publications

We discuss individual studies of the carcinogenicity of HCl and HCl mists below. Further details of these studies can be found in Appendix B.

3.3.1 Epidemiological Studies

In a cohort study of steel workers involved in pickling operations, Beaumont et al. (1987) examined lung cancer mortality patterns in 1,165 workers exposed to sulfuric acid mist and other acid mists (primarily HCl mist). Jobs were categorized by acid use (sulfuric acid or other acid) and exposure potential (i.e., the likelihood of daily exposure) in order to define the following exposure categories: (1) any acid exposure (the entire exposed cohort); (2) sulfuric acid exposure only; (3) sulfuric acid only with probable daily exposure (a subset of Group 3); (4) other (not sulfuric) acid exposure only; and (5) exposure to both sulfuric acid and other acids. The analyses included those who were employed for at least 6 months in a pickling-related job with at least 1 day of work prior to 1965. Compared with men in the general U.S. population, the 189 workers with exposure to other acids (not sulfuric acid) had a statistically significant increased lung cancer mortality rate (SMR 2.24, 95% CI 1.02, 4.26) based on 9 observed deaths. When they used a more appropriate comparison to US steel workers, however, the risk estimate was lower (SMR 2.0, 95% CI 1.06, 3.78). No data on other occupational exposures or smoking habits were included in the study, and confounding by smoking status, especially, cannot be ruled out. The authors attempted several indirect adjustments for smoking, with mixed results. The authors discussed several additional limitations of the study and suggested that chance cannot be ruled out as an explanation for the results.

Steenland et al. (1988) conducted a reanalysis of 879 members of the Beaumont et al. (1987) steelworker cohort who had information related to presence or absence of diagnosis of laryngeal cancer (Steenland et al., 1988). US referent rates, calculated using national surveys of cancer incidence, were used for comparison. Most workers in the analysis were exposed to sulfuric acid, either with or without other acids. Two of the laryngeal cancer cases were exposed to acids other than sulfuric acid and three were exposed to a mixture of acids; these numbers are too small to generate reliable statistical estimates of association. The authors reported an increased risk of laryngeal cancer in steel pickler workers compared to US referent rates (RR 2.6, 95% CI 1.2, 5.0 (as reported by IARC 1992), however this includes all 9 cases across all exposure groups (sulfuric acid, other acids only, and mixture of acids). In its evaluation, the IARC (1992) working group noted that confounding by sulfuric acid could not be ruled out. The authors compared the smoking habits of their incident cancer cohort obtained from next of kin interviews with the smoking habits of the US population in 1965. They found that in their cohort "there was a similar overall prevalence of smoking compared with all United States men but cohort members who did smoke smoked more than the United States average." The authors also used methods similar to those described by Beaumont et al. (1987) to indirectly adjust for smoking habits, but residual confounding by smoking, in addition to exposure to sulfuric acid in the mixed exposure group, cannot be ruled out as an explanation for the results.

Mortality patterns were examined in a follow-up study of 8,854 workers from four Cyanimid plants in the United States and the Netherlands, where 2,293 of the workers were believed to have been exposed to the chemical acrylamide (Collins et al., 1989). Each plant had mortality patterns similar to other worker populations, and no excess mortality across all plants was observed for any of the 26 cancer sites examined. However, an excess in lung cancer (SMR 1.32) was observed in one of the four facilities studied (the Warners facility). In this facility, 11 of the 63 lung cancer deaths were in a department where there was exposure to HCl (data not presented in paper). This paper was discussed by the IARC working group (1992), who noted that no information for the expected numbers of cases in that facility was provided, making it difficult to interpret that observation.

A case-control study of brain cancer mortality at a Dow Chemical plant in Texas included an evaluation of the potential association between brain cancer and occupational exposure to HCl (Bond et al., 1983). A total of 28 former workers were identified who had died from brain cancer; 13 of these had evidence of HCl exposure based on a review of job titles. The study incorporated data from two control groups selected from the plant: Group A selected from 110 white male deaths without cancer (42 with evidence of HCl exposure based on job title) and Group B selected from a random sample of 111 employees without regard to vital status or cancer status (51 with evidence of HCl exposure). There was no statistically significant association observed between any exposure to HCl and brain tumors among workers when compared to either control group (Odds ratio (OR) 1.40, 90% CI 0.70, 2.80; OR 1.02, 90% CI 0.81, 1.29). Sub-analyses based on duration of employment focused on those who were employed for 1-4 years, as there were only four cases with 20 or more years of employment. There was no evidence of an increase in risk of brain cancer associated with HCl exposure in this subgroup (cases: n = 5, controls: n = 15; OR 2.02, 90% CI 0.5, 8.1). Note that these authors reported 90% confidence intervals, rather than the usual 95% confidence intervals, which increases the likelihood of detecting an association. This choice is usually made when the focus is on screening for potential associations and generating hypotheses to be tested in future, more rigorous studies.

Subsequently, Bond et al. (1985) published a case-control study of renal cancer mortality and exposure to HCl based in the same Dow Chemical plant, using the same study population and control groups examined earlier (Bond et al., 1983). The authors did not observe an increased risk of renal cancer in workers exposed to HCl (26 deaths from renal cancer; 12 with evidence of exposure to HCl based on job title) as compared to either control group (OR 0.90, 90% CI 0.44, 1.83 based on 44 exposed out of 92 controls; OR 0.86, 90% CI 0.40, 1.86 based on 50 exposed out of 98 controls). Cases and controls were matched on age, race, and sex, but potential confounding by exposure to other occupational chemicals was not controlled. The authors did not observe substantial differences in smoking habits between groups and therefore reported that smoking was unlikely to have been a confounder.

In a third case-control study based in the same Dow Chemical plant, Bond et al. (1986) analyzed the risk of lung cancer associated with hydrogen chloride exposure based on job title. There were 308 lung cancer deaths compared with two control groups chosen from the plant: a decedent control group and a living control group. Each contained 308 men individually matched to cases on race, year of birth $\pm$ 5 years, and year of hire. Separate results of cases with each control group were similar, so the authors pooled the control groups for greater statistical power. The authors did not observe an association between HCl exposure and lung cancer overall (exposed cases: n = 129, exposed controls: n = 245, OR 1.02, 95% CI 0.77, 1.35) or with a 15 year latency period (exposed cases: n = 108, exposed controls: n = 218, OR 0.92, 95% CI 0.68, 1.24). The authors collected information on potential confounders and noted the following to be statistically significantly associated with lung cancer risk, as expected: cigarette smoking, vitamin A intake, use of vitamin supplements, and education level. These findings lend support to the validity of the main analyses. However, due to small number of subjects available for analysis, the authors appropriately chose not to control for these potential confounders.

The Dow chemical worker population was re-evaluated again, using exposure estimates derived from job assignments, duration of exposure, and cumulative exposure (Bond et al., 1991). Analyses to estimate the risk of mortality from lung, trachea, and bronchial cancer (combined) were performed without and with a 16-year latency period and controlling for pack-years of

smoking. There was no relationship between HCl exposure and lung cancer in any of the HCl exposure groups (see Appendix B).

Coggon et al. (1996) investigated the risk of upper aerodigestive cancer mortality from exposure to mineral acid mists (HCl and sulfuric acid) in a study of steel and battery manufacture workers (Coggon et al., 1996). The authors categorized exposure as (1) no exposure to any acid mists; (2) low exposure to acid mists (<1 mg/m^3 sulfuric acid or HCl); and high exposure to acid mists ($\geq$1 mg/m^3 sulfuric acid or HCl). Based on just 15 cases, the authors reported no convincing association between exposure to mixed acid mists and upper aerodigestive cancer mortality in any category of exposure concentration and duration (see appendix B). The study also evaluated the association of "definite" exposure to mixed acid mists (HCl and sulfuric acid) and "all cancer" mortality compared to that in the national population and found no evidence of an increase in cancer mortality among the workers (full cohort SMR 0.88, 95% CI 0.79, 0.98; never exposed SMR 0.75, 95% CI 0.59, 0.91; definitely exposed SMR 0.92, 95% CI 0.79, 1.05).

Soskolne at al. (2011) examined the association between lung cancer and occupational exposure to specific acids (HCl, nitric acid, sulfuric acid, acetic acid, hydrofluoric acid, phosphoric acid, hydrocyanic acid, sulfuric dioxide, and oxides of nitrogen) in a population-based study of 178 cases and 167 controls in Toronto, Canada. Proxy interviews provided estimates of exposure concentration and frequency of exposure based on work history, which the authors used to calculate an exposure index that factored in the duration of exposure in months. There was no increase in risk of lung cancer for those "ever" exposed vs. unexposed to HCl (OR 0.98, 95% CI 0.71, 1.35) or for those with low estimated exposure vs. unexposed (OR 0.80, 95% CI 0.53, 1.22). The high exposure group had a non-statistically significant increase in risk, based on 83 cases (OR 1.24, 95% CI 0.79, 1.96) (see appendix B). The authors considered all cancers of the lip, mouth, retromolar area, nasopharynx, larynx, and nasal sinus as lung cancer for analysis.

In another population-based case-control study, this time in Montreal, Canada, Siemiatiycki (1991) examined the associations between HCl exposure and 11 different cancers (esophagus, stomach, colon, rectum, pancreas, lung, prostate, bladder, kidney, skin melanoma, and non-Hodgkin's lymphoma). The target population was men aged 35 to 70 years who were living in the Montreal metropolitan area. Cases had a histologically confirmed diagnosis of one of the selected cancer sites with the date of initial diagnosis between September 1979 and June 1985. A total of 4,576 eligible cases were ascertained. Data were analyzed using cancer controls, i.e., all cancer cases with cancers of sites other than the site being analyzed, and population controls. Population controls had no cancer diagnoses and comprised an age-stratified random sample drawn from a list of all adult Canadian citizens resident in the province that were eligible to vote. Detailed job-history interviews were conducted amongst all cancer cases to classify exposure. The authors reported that population controls were interviewed in a manner as similar as possible to the cancer cases.

Exposure to specific substances and concentration and frequency of exposure were estimated based on job categories. Based on this coding, the authors analyzed the relationships between "any exposure" and "substantial exposure" (a subset of "any exposure") to HCl and each of the 11 cancer sites, with confounding assessed separately for each cancer site. Potential confounders included age, family income, ethnic origin, birthplace, smoking, alcohol intake, coffee consumption, body mass index, and self- or proxy-respondent. After adjustment, there was no statistically significant association between 10 of the 11 cancers and exposure to HCl (see

Appendix B). The risk of non-Hodgkins lymphoma was higher among those with any exposure to HCl vs. no exposure: OR=1.5 (90% CI 1.0, 2.2) based on 90% confidence intervals, which are used in hypothesis-generating analyses because they are more likely to detect associations than the standard 95% confidence interval.

The authors also evaluated the association between HCl exposure and certain cancer sites in subsets of the population: (1) all ethnic groups, cancer controls; (2) all ethnic groups, population controls; (3) French-Canadians only, cancer controls; and (4) French-Canadians only, population controls. Analyses within each group were conducted for any and substantial exposure to HCl. From these eight sets of analyses, the authors reported results for three cancer sites: rectum, lung-oat cell, and non-Hodgkin's lymphoma (see appendix B). There was borderline statistically significant elevated risk for non-Hodgkin's lymphoma in the French-Canadian cancer controls subset (n = 18, OR 1.6, 90% CI 1.0, 2.5) and lung-oat cell cancer in the all ethnic groups cancer control subset (n = 19, OR 1.6, 90% CI 1.0, 2.6) from "any exposure" to HCl. When limited to those with "substantial exposure" to HCl, results for lung-oat cell cancer remained borderline statistically significant (n=8, OR 2.1, 90% CI 1.0, 4.5) and results for non-Hodgkin's lymphoma were not statistically significant (n = 6, OR 1.5, 95% CI 0.7, 3.2). The authors reported a statistically significantly elevated risk of rectum cancer from "any exposure" to HCl (n = 18, OR 1.9, 90% CI 1.1, 3.4) in the French Canadian population subset, but this association was smaller and not statistically significant when limited to those with "substantial exposure" to HCl (rectum: n = 5, OR 1.5, 90% CI 0.5, 3.8). The very small number of cases and wide 90% confidence intervals around these estimates do not supply convincing evidence of an association between HCl exposure and risk of rectal cancer.

Fritschi and Siemiatycki (1996a) conducted additional analyses on the association of 11 substances and non-Hodgkin's lymphoma, adjusting for age, proxy status, income, and ethnicity. Exposure was categorized as "substantial", defined as having probable or definite exposure and more than 5 years of exposure at high frequency concentration, or "non-substantial" exposure. There was no statistically significant association between occupational HCl exposure and non-Hodgkin's lymphoma at either exposure level (substantial exposure n=6, OR 1.3, 95% CI 0.5, 3.4; non-substantial exposure n=16, OR 1.6, 95% CI 0.9, 3.0). Fritschi and Siemiatycki (1996b) further evaluated exposure to several chemicals and melanoma. Risk results for HCl and melanoma were not provided, because it was "not associated with melanoma in any multivariate analyses" (Fritschi and Siemiatycki 1996b).

In a pilot study preceding the full study by Siemiatycki et al, (1991), Farrow et al. (1989) interviewed 39 male and 24 female preleukemia patients diagnosed from September 30, 1985 to September 30, 1986 for lifetime occupational exposure to specific chemicals, one of which was HCl. When compared with controls from an outpatient ear, nose and throat (ENT) surgical clinic matched to cases on age and sex, there was no meaningful difference between cases and controls (cases: n = 5, mean exposure = 21,000 hours; controls: n = 4, mean exposure = 5,000 hours). The authors did not report odds ratios for these findings, which would have been approximately 1.0 based on the nearly identical numbers of cases and controls.

3.3.2 Cancer Studies in Experimental Animals

The carcinogenicity of HCl was examined in two chronic cancer studies in rats as part of studies designed to explore the combined impacts of inhaled HCl and another irritating gas, formaldehyde (Albert et al., 1982; Sellakumar et al., 1985). This combination of gases is found in the degradation of a carcinogen, bis(chloromethyl)ether (BCME). Since formaldehyde is both an irritating gas and a carcinogen in animal inhalation studies (Swenberg et al., 1980), and HCl is also an irritating gas, the studies reported in these two publications (Albert et al., 1982; Sellakumar et al., 1985) tested whether inhalation of the combination of formaldehyde and HCl were more carcinogenic than inhalation of formaldehyde alone. Part of the controls in these tests were groups of animals exposed only to formaldehyde, or only to HCl, allowing an assessment of the carcinogenicity of HCl.

In the earlier study (Albert et al., 1982), a group of 99 eight-week old male Sprague-Dawley rats were exposed by inhalation to a mixture of 10 ppm HCl and 14 ppm formaldehyde for 6 hours per day, 5 days per week, for their lifetime. Control groups (50 rats per group) were exposed to either air introduced to the cages in the same manner as the exposed group (the "sham" control), or simply held in exposure chambers without any exposure. Authors reported benign squamous metaplasia, and two types of nasal cancer — squamous papilloma and squamous cell carcinoma — in rats exposed to the mixture of HCl and formaldehyde; these lesions were not found in the control group. This result is consistent with preciously published results obtained when rats were exposed to formaldehyde alone (Swenberg et al., 1980), and are consistent of the cancer resulting from exposure to formaldehyde.

A second experiment exposed groups of 100 nine-week old Sprague-Dawley rats to either inhaled HCl, formaldehyde, combinations of HCl and formaldehyde, or a control group of air alone for 6 hours per day, 5 days per week. This publication (Albert et al., 1982) reports interim results after 84 weeks; full results are reported in the Sellakumar et al. (1985) publication, below.

Groups of 100 nine-week old Sprague-Dawley rats were exposed by inhalation to either HCl[g], formaldehyde, two types of combinations of HCl[g] and formaldehyde, or a control group of air alone for 6 hours per day, 5 days per week over 122 weeks (Sellakumar et al., 1985). Results were also compared to unexposed control animals. HCl concentrations were 10 ppm (14.9 mg/m^3) in the HCl-only exposure as well as the HCl plus formaldehyde exposure group. Following sacrifice, animals were examined for tissue abnormalities, including cancer, with special attention to the respiratory tract (the site of formaldehyde-induced tumors). While hyperplasia (indicative of cell proliferation) was evident in the larynx and trachea of animals exposed to HCl alone as compared to air controls or colony controls, no excess cancer was observed. In the groups exposed to both HCl and formaldehyde, the cancer response was attributed to formaldehyde.

Two other cancer studies in experimental animals were reported by OECD (2002) – a dermal exposure study (Narat, 1925) and an oral exposure study (Dyer et al., 1946). The dermal study included 99 mice were dermally exposed to an unknown volume of solutions containing 3-5% HCl every 1-2 days until skin lesions were observed and then weekly for 4-6 additional weeks (total exposure duration 25-46 weeks) (Narat, 1925). No malignant tumors were reported, and OECD concluded that the study is not appropriate for the assessment of carcinogenicity because the of shortcomings in the study design (lack of negative control, brief exposure period). The oral study Dyer et al., 1946) included was a study designed to examine whether acids present in the stomach, such as HCl, would modify the carcinogenicity of 1,2,5,6-dibenzanthracene. In this study, groups of mice (4 different strains) were exposed to a combination of HCl (1-2.5 moles

per liter) and either a "control emission" (58 mice) or HCl and 1,2,5,6-dibenzanthracene (40 mice) through a tube inserted into their stomachs (Dyer et al., 1946). Other exposure groups without HCl were also included in the study. No excess cancer or pre-cancerous lesions were observed in the stomachs of animals from either group exposed to HCl. However, OECD concluded the study is not appropriate for the assessment of carcinogenicity because of the shortcomings of the study design (inconsistent strain, short exposure duration, single exposure concentration).

3.3.3 Reviews and Commentaries Identified

Hathaway (1997) provided a commentary that was critical of the methodological quality of studies reviewed by IARC (1992). Among other concerns, Hathaway noted small numbers of cases leading to imprecise estimates, shown by wide confidence intervals, and likely misclassification when exposure to HCl was part of a mixed exposure category. Misattribution of risks associated with exposure to some other substance that was part of the mixture could have resulted in some of the elevated point estimates reported by the authors if that other substance was carcinogenic and HCl is not. Hathaway also noted inconsistencies in reporting the number of exposed and unexposed cases in at least one study, which would affect the results given the small number of exposed cases available for analysis.

Tsai et al. (2016) conducted a review of the regulatory systems and human health effects designated by the Taiwan government under the Air Pollution Control Act. The study reviewed carcinogenic and non-carcinogenic health risks for designated air toxics. The study compiled data from international agencies such as IARC, the National Toxicology Program (NTP) of the U.S. Department of Health and Human Services, and the American Conference of Governmental Industrial Hygienists (ACGIH) and based on this data categorized HCl as non-carcinogenic.

4. DISCUSSION

4.1 Conclusions of Authoritative Reviews

The consensus opinion of multiple authoritative bodies is that HCl is unlikely to be a carcinogen. IARC classified HCl in Group 3 (not classifiable), which is the classification group used when the chemical is considered least likely to present a cancer hazard. Note that IARC has only classified a single chemical as *"probably not carcinogenic to humans"* (Group 4), and they no longer consider this category. OECD went further, stating "In humans, no association between hydrogen chloride exposure and tumor incidence was observed." IARC also reviewed other inorganic acids in the same monograph, including "sulfuric acid and other strong inorganic acids" (IARC 1992). In contrast to their conclusion for HCl, their conclusion for sulfuric acid and other strong inorganic acids was that "There is sufficient evidence that occupational exposure to strong-inorganic-acid mists containing sulfuric acid is carcinogenic." IARC's overall evaluation was that "Occupational exposure to strong inorganic acid mists containing sulfuric acid is carcinogenic to humans (Group 1)" (IARC 1992). This is relevant because the conclusion is based on exposure to acid mists that must include sulfuric acid. While sulfuric acid and HCl often are found together in mixed acid exposures, the exposure contained in the mixture with the strongest relationship to the outcome (in this case, surfuric acid) will drive the relationship for the whole mixture. This likely the explanation for the sporadic effects observed in occupational studies of mixed acids containing HCl.

ICPS did a broader assessment of potential toxicity to the general population and concluded that other than during accidental releases, it is most unlikely that the general population is exposed routinely to any significant health risks from HCl. Furthermore, neither US EPA nor the NTP have identified HCl as a chemical worthy of assessing for carcinogenicity. Thus, although HCl is a widely used chemical, no authoritative body has concluded that it poses a cancer risk. An extensive search of the primary published scientific literature identified a total of 4 publications not considered by the authoritative bodies discussed above. One of these publications is a review and one is a commentary; two publications are epidemiolocal studies. Neither alters the conclusions of the prior assessments.

4.2 Supporting Evidence

4.2.1 Evidence Regarding Genotoxicity

Mutation or genetic changes are often viewed as a first step in carcinogenicity, so various assays examining such changes, as well as assays designed to predict such changes (collectively referred to as genotoxicity assays) are often used to predict cancer potential. HCl did not induce mutations in six bacterial mutation assays or one mutation assay in yeast cells (reviewed by IARC, 1992; OECD, 2002). A qualitative predictive assay that examines cell survival in strains that have or lack the ability to repair damaged DNA had mixed results in two assays but OECD concluded the positive finding was unrelated to DNA damage (reviewed by OECD, 2002). A weakly positive response for mutations was observed in a mouse lymphoma cell assay; these results are interpreted as being an artifact of acidic conditions (pH 6.3 in buffered cell culture medium), which itself related to cell death. Other mutation assays in mammalian cell cultures were negative (reviewed by IARC, 1992; OECD, 2002). HCl induced chromosome aberrations in mammalian cells in culture when concentrations were in excess of 10 mM in the cell culture media (leading to an acidic environment with a pH of 5.8) and in a handful of studies in Chinese hamster ovary cells, mouse lymphoma cells, and in insect and plant cells in a very limited set of studies; both IARC (1992) and OECD (2002) found that the acidic pH is the responsible factor for these responses and that similar responses are observed for other inorganic acids and with acetic acid. These concentrations would not be found environmentally[14] and are thus not relevant for ambient air exposures to HCl.

4.2.2 Evidence for Inducing Cell Proliferation

In addition to mutagenic carcinogens, there are some carcinogens that are believed to act through a nonmutagenic mechanism, often by inducing extensive cell turnover which leads to the possibility of replication errors leading to mutations. However, such mechanisms are believed to have a threshold concentration below which no effects are seen. In the case of HCl, there is further evidence from the co-exposure study of Sellakumar et al. (1985), where exposure to 10 ppm HCl did not cause serious irritating effects and did not enhance the carcinogenicity of formaldehyde. Thus, there is no evidence that HCl causes the types of cell proliferation that are typically associated with nongenotoxic carcinogens.

[14] 10 mM corresponds to ~355 ppm in solution or 355 mg/Liter. In comparison, HCl concentrations in the ambient air usually do not exceed 0.01 mg/m^3 (IARC, 1992). Conservative modelling data (unpublished Ramboll report to National Lime Association, 2019), predicts that the maximum concentration of HCl in the air at the fenceline kiln would be 0.0012 mg/m^3.

4.3 Limitations of the Existing Literature (for client discussion only)

The epidemiological studies evaluated by IARC and OECD were methodologically limited. Limitations included lack of exposure verification or measurement; inadequate control for confounding exposures associated with certain cancers, small sample size or small numbers of cases, leading to lack of statistical power. In addition, many of the studies evaluated mixed exposures and mixed outcomes. The use of mixed exposure groups is particularly germane, as the mixtures often included sulfuric acid and other strong inorganic acid mists, which are classified as carcinogenic. By evaluating mixtures of HCl and these other acids, the apparent association between HCl and cancer will be inflated due to the effect of the other acids.

In spite of these weaknesses, the overall conclusion by IARC based on their review of the epidemiological data is supported by the small number of cases of cancers observed in various occupational cohorts as well as by the toxicological evidence that HCl does not have carcinogenic properties.

5. CONCLUSIONS

HCl has been assessed for carcinogenic potential by multiple authoritative bodies. After a thorough search for new studies post-dating those assessments, Ramboll concluded that the scientific evidence does not suggest it poses carcinogenic risks. In addition to direct studies of cancer associations, we also examined other supporting evidence in the form of genotoxicity studies or potential to induce cell proliferation. Taking both the epidemiological and toxicological data into account, the evidence does not indicate that HCl is a carcinogen.

IARC recognized that sulfuric acid and HCl are often found together in industrial processes. In assessing the scientific evidence for the grouping "sulfuric acid and other strong inorganic acids," IARC concluded that there was sufficient evidence associating occupational exposure to "strong-inorganic-acid mists containing sulfuric acid" with cancer. They therefore concluded that occupational exposure to strong inorganic acid mists **containing sulfuric acid** is carcinogenic to humans (i.e., a "Group 1" carcinogen) (IARC 1992). In contrast, IARC's conclusion regarding HCl was that there was **inadequate evidence** for the carcinogenicity of HCl, and they therefore assessed exposure to HCl as not classifiable as to its carcinogenicity to humans (i.e., a "Group 3"). This is relevant because the conclusion regarding acid mists is based on exposure to mixtures that must include sulfuric acid. While sulfuric acid and HCl often are found together in mixed acid exposures, the exposure contained in the mixture with the strongest relationship to the outcome (in this case, surfuric acid) will drive the relationship for the whole mixture. This is likely the explanation for the sporadic, positive associations observed in occupational studies of mixed acids containing HCl.

HCl has not been identified as a carcinogen, despite its long history of use. Ramboll therefore recommends that based on our review of the science and the criteria in 42 U.S.C. § 7412(d), it would be entirely appropriate for EPA to base its standard for HCl on a health-based threshold, including an ample margin of safety.

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APPENDIX A
RELEVANT REFERENCE LIST

Relevant Reference List

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International Agency for Research on Cancer (IARC). 1992. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Volume 54: Occupational Exposures to Mists and Vapours from Strong Inorganic Acids; and Other Industrial Chemicals. World Health Organization, Lyon.

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[c]Tsai WT. 2016. Current status of air toxics management and its strategies for controlling emissions in Taiwan. Toxics, 4(2): 8-15.

[c] Review; no new data

APPENDIX B
SUMMARY OF EPIDEMIOLOGICAL EVIDENCE

Table Appendix B: Summary of Epidemiological Evidence

Author/ Year	Industry	Study design	Pop. Size	Outcome	Exposure	Exposure Groups	# Cases	Risk Estimate	Lower 95%[a] CI	Upper 95%[a] CI	Comments (focus on potential causes of bias and/or confounding
Beaumont et al., 1987	Steel pickling	Cohort	1,165 (1,156 men; 9 women)	Lung cancer (mortality)	Sulfuric acid and other acid mists (primarily HCl)	Group 1: any acid (entire cohort)	28	SMR: 1.35	0.92	1.97	Referent group: US general population; US steel workers Two of the three facilities had consistent trends; the third facility had a small sample size and no lung cancer deaths observed. Exposure categorization was based on job category and not specific measurements of exposure level. Did not control for smoking or exposure to other potential lung carcinogens (besides coke operations). In this cohort, 2 deaths from laryngeal cancer were detected (not statistically significant)
						Group 2: sulfuric acid only	13	SMR: 1.06	0.59	1.90	
						Group 3: sulfuric acid only, probable daily exposure (subset of Group 2)	12	SMR: 1.23	0.68	2.20	
						Group 4: other acid only	9	**SMR: 2.00 (compared to other steel workers)**	**1.06**	**3.78**	
								SMR: 2.24 (compared to US population)	**1.02**	**4.26**	
						Group 5: sulfuric acid and other acid	6	SMR: 1.49	0.54	3.86	
Steenland et al., 1988	Steel pickling	Cohort	879 men	Laryngeal cancer (diagnosis)	Sulfuric acid and other acid mists	Overall analysis	9 (4 sulfuric acid only; 2 other acids only; 3 mix of sulfuric acid and other acid)	SIR (observed/expected): 2.3	--	--	Referent groups: US population and other steel workers. None of these associations were statistically significant Insufficient power to detect statistically significant changes No dose-response relationship shown IARC (1992) notes confounding by exposure to sulfuric acid could not be ruled out.
						≤5 years exposure		SIR: 1.70	--	--	
						>5 years exposure		SIR: 2.76	--	--	
						≤20 years since first exposure		SIR: 3.27	--	--	
						>20 years since first exposure		SIR: 2.03	--	--	

Author/ Year	Industry	Study design	Pop. Size	Outcome	Exposure	Exposure Groups	# Cases	Risk Estimate	Lower 95%[a] CI	Upper 95%[a] CI	Comments (focus on potential causes of bias and/or confounding
Collins et al., 1989	Acryla-mide workers	Cohort	8,854 men (2,293 exposed to acryla-mide)	Respiratory cancers mortality (lung or larynx)	Hydro-chloric acid	Acrylamide	63 in group exposed to <0.001 mg/m^3-years acrylamide (11 in a depart-ment using HCl)	No quantitative risk estimate presented for workers exposed to HCl	--	--	Subject of paper is exposure to acrylamide. It contains mention of workers in a unit with HCl exposure. Subsequent discussion by IARC (1992) notes the expected numbers for that facility were not provided.
Bond et al 1983	Chemical workers (TX)	Case-control	19,608	Brain cancer mortality	Hydrogen chloride	Hydrogen chloride and 10 other chemical categories	28 (13 exposed to HCl)	Compared to control group A (110; 42 exposed to HCl) OR: 1.40	0.70 *	2.80*	Exposure categories based on employment records and some job titles; categories were nonspecific. Exposure misclassification was possible due to lack of records in early years of company operations. Small number of cases
								Sample-based control group B (111; 51 exposed to HCl) OR: 1.02	0.81*	1.29*	
								Cases employed 1 to 4 years with matched group B controls (5 cases, 15 controls exposed) OR: 2.02	0.5*	8.1*	
Bond et al 1985	Chemical workers (TX)	Case control	19,608	Renal cancer mortality	Hydrogen chloride	Hydrogen chloride and other chemical agents	26 (12 exposed to HCl)	Compared to group A (92; 44 exposed to HCl) OR: 0.90	0.44*	1.83*	Potential unaccounted lifestyle confounders Exposure classification was based on job category and company work histories

Author/ Year	Industry	Study design	Pop. Size	Outcome	Exposure	Exposure Groups	# Cases	Risk Estimate	Lower 95%[a] CI	Upper 95%[a] CI	Comments (focus on potential causes of bias and/or confounding
								Compared to Group B (98; 50 exposed to HCl) OR: 0.86	 0.40*	 1.86*	
Bond et al., 1986	Chemical workers (TX)	Nested case-Control	19,608	Lung cancer mortality	Hydrogen chloride	Hydrogen chloride and other chemical agents	308 (237 exposed to HCl) 616 compar-ison workers, (463 exposed to HCl)	Without regard for interval prior to death: OR: 1.02	 0.77	 1.35	Exposure measurement were not available. Possible random misclassification of employee exposures Possible chance variation Possible protective role for one or more chemicals
								Excluding exposures occurring within 15 years of death OR: 0.92	 0.68	 1.24	
Bond et al., 1991	Chemical workers (TX)	Nested case-Control	19,608	Lung, trachea, bronchus cancer mortality (note, results only presented for lung cancer)	Hydrogen chloride	HCl calculated by time spent on jobs and cumulative exposure score	308 616 compar-ison workers from 2 control groups (308 each, pooled)	All dates RR: 1.0	 0.8	 1.3	Exposure was determined by job category Differences in respirator policies at plant
								Excluding exposures occurring within 15 years of death RR: 0.9	 0.7	 1.2	
						Cumulative Exposure (ppm-yr): 0.1-3.9 4.0-12.4 ≥12.5	 62 45 22	 Adj RR = 0.9 Adj RR = 1.2 Adj RR = 1.0	 0.6 0.8 0.6	 1.3 1.9 1.8	

Author/ Year	Industry	Study design	Pop. Size	Outcome	Exposure	Exposure Groups	# Cases	Risk Estimate	Lower 95%[a] CI	Upper 95%[a] CI	Comments (focus on potential causes of bias and/or confounding
Coggon et al. 1996	Steel and battery manufac-ture workers	Nested care-control	4403	Upper aerodi-gestive cancer (UADC) mortality	Acid mists (hydrochl oric and sulfuric acid)	No exposure	3 exposed cases; 18 exposed controls	OR: 1.0	--	--	Estimates based on a small number of cases Potential non-occupational and occupational confounders (tobacco, alcohol) SMRs compare mortality in the worker population with mortality in the general US population.
						Low exposure (<1 mg/m^3 sulfuric of hydrochloric acid)	2 exposed cases; 7 exposed controls	OR: 1.9	0.2	15.8	
						High exposure (≥1 mg/m^3 sulfuric or hydrochloric acid)	9 exposed cases; 43 exposed controls	OR: 1.3	0.3	5.7	
						Uncertain	1 case exposed; 5 controls exposed	OR: 1.0	0.1	12	
						No exposure	3 exposed cases; 18 exposed controls	OR: 1.0	--	--	
						Intermediate or uncertain cumulative exposure	5 exposed cases; 32 exposed controls	OR: 1.0	0.2	4.6	
						At least 5 years high cumulative exposure	7 exposed cases; 23 exposed controls	OR: 2.0	0.4	10	
				All cancer mortality	Acid mists (hydrochl oric and sulfuric acid)	Full cohort (possibly exposed, never exposed, and definitely exposed)	324	SMR: 0.88	0.79	0.98	
						Never exposed to acid mists	88	SMR: 0.74	0.59	0.91	

Author/ Year	Industry	Study design	Pop. Size	Outcome	Exposure	Exposure Groups	# Cases	Risk Estimate	Lower 95%[a] CI	Upper 95%[a] CI	Comments (focus on potential causes of bias and/or confounding
						Definitely exposed:	199	SMR: 0.92	0.79	1.05	
Soskolne et al. 2011	Male and females in Toronto, CA	Popula-tion based care-control	772	Lung cancer	10 acid categories including hydro-chloric acid	Any exposure to HCl	178 cases; 167 controls	OR: 0.98	0.71	1.35	Did not account for family history as a confounder Exposure classification
						Low exposure to HCl	95 cases; 106 controls	OR: 0.80	0.53	1.22	
						High exposure to HCl	83 cases; 61 controls	OR: 1.24	0.79	1.96	
Siemia-tycki 1991	Popula-tion-based (residents of Montreal, Canada)	Case control	3730 cancer patients	11 cancers	Hydrogen chloride	Any exposure	Esophagus (8)	OR: 1.2	0.6*	2.3*	French Canadian population to avoid confounding from ethnicity Did not carry out the analyses to rule out confounding co-exposures or occupational exposures associated with certain cancer types Potential for exposure misclassification based on interviews
							Stomach (18)	OR: 1.1	0.7*	1.6*	
							Colon (28)	OR: 0.9	0.6*	1.2*	
							Rectum (21)	OR: 1.1	0.7*	1.6*	
							Pancreas (9)	OR: 1.2	0.7*	2.2*	
							Lung (59)	OR: 0.9	0.7*	1.2*	
							Prostate (25)	OR: 0.8	0.5*	1.2*	
							Bladder (34)	OR: 1.1	0.8*	1.5*	
							Kidney (12)	OR: 1.0	0.6*	1.6*	

Author/ Year	Industry	Study design	Pop. Size	Outcome	Exposure	Exposure Groups	# Cases	Risk Estimate	Lower 95%[a] CI	Upper 95%[a] CI	Comments (focus on potential causes of bias and/or confounding
							Skin melanoma (5)[b]	OR: 0.7	0.3*	1.6*	
							NHL (22)	OR: 1.5	1.0*	2.2*	
						Substantial exposure	Esophagus (2)	OR: 1.1	0.3*	3.8*	
							Stomach (5)	OR: 0.9	0.4*	1.9*	
							Colon (15)	OR: 1.5	0.9*	2.4*	
							Rectum (6)	OR: 0.9	0.4*	2.0*	
							Pancreas (2)	OR: 0.7	0.2*	2.4*	
							Lung (20)	OR: 0.9	0.5*	1.5*	
							Prostate (11)	OR: 1.1	0.6*	2.0*	
							Bladder (13)	OR: 1.0	0.6*	1.8*	
							Kidney (3)	OR: 0.7	0.3*	1.8*	
							Skin melanoma (1)	OR: 0.4	0.1*	2.3*	
							NHL (6)	OR: 1.1	0.5*	2.3*	
						Subset analysis for these three cancer sites: Any exposure	Rectum (18)	**OR: 1.9**	**1.1***	**3.4***	
							Lung-oat cell (19)	OR: 1.6	1.0*	2.6*	
							NHL (18)	OR: 1.6	1.0*	2.5*	

Author/ Year	Industry	Study design	Pop. Size	Outcome	Exposure	Exposure Groups	# Cases	Risk Estimate	Lower 95%[a] CI	Upper 95%[a] CI	Comments (focus on potential causes of bias and/or confounding
						Subset analysis for these three cancer sites: Substantial exposure	Rectum (5)	OR: 1.5	0.5*	3.8*	
							Lung-oat cell (8)	OR: 2.1	1.0*	4.5*	
							NHL (6)	OR: 1.5	0.7*	3.2*	
Fritschi and Siemia-tycki 1996a	Popula-tion-based (residents of Montreal, Canada)	Case control	3730 cancer patients	Lymphoma and myeloma	Hydrogen chloride	Substantial exposure (those defined as probable or definite exposure and that had more than 5 years of exposure at a high frequency concentration)	6	1.3	0.5	3.4	French Canadian population to avoid confounding from ethnicity Not adjusted for other occupational exposures Potential for exposure misclassification based on interviews
						Non-substantial exposure (others not included above)	16	1.6	0.9	3.0	
Farrow et al. 1989	Popula-tion-based (Wales, UK)	Pilot case-control study	63	Myelodyspl astic syndrome (MDS)	HCl exposure	Any HCl exposure	5 exposed cases; 4 exposed controls	--	--	--	Study did not report an odds ratio. This was just an analysis to determine whether exposure was different between cases and controls based on p-value. The number of cases and controls were small and equal in the two groups. Exposure measurements were not available

[a] 95% CI unless otherwise noted

[b] An additional set of analyses was conducted (Fritschi and Siemiatycki 1996b) to expand on results and adjust for additional confounders. Authors did not present risk results for HCl and melanoma, however it was noted that HCl was not associated with melanoma in any multivariate analyses conducted.

*90% Confidence Interval

Highlighted rows indicate the same cohort

Abbreviations: CI = confidence interval; HCl = hydrochloric acid; NHL = non-Hodgkin's lymphoma OR = odds ratio; ppm = parts per million; RR = relative risk; SIR = Standardized Infection Ratio; SMR = standardized mortality ratio; UADC = upper aerodigestive cancer; yr = year

Appendix 4

2024 report from Ramboll to NLA

Erratum: Ramboll's 2024 report erroneously indicated there were 22 publications describing epidemiology studies. In fact, we summarized five toxicology publications and 13 epidemiology publications in the 2021 report (for a total of 18 publications, combined) and added three epidemiology studies published since 2021 to in the 2024 report (for a total of 16 epidemiology publications).

Document type
Report

Date
February 23, 2024

Prepared for National Lime Association

Support for public comments relevant to the US-EPA pre-proposed health-based exposure limit for HCl

RAMBOLL Bright ideas. Sustainable change.

Support for public comments relevant to the US-EPA pre-proposed HBEL for HCl

Project name	**Support for public comments relevant to the US-EPA pre-proposed health-based exposure limit for HCl**
Recipient	**National Lime Association**
Document type	**Report**
Date	**February 23, 2024**
Prepared by	**Sandra I. Sulsky PhD; Tracy Green PhD; Debra A. Kaden, PhD**

Ramboll
28 Amity Street
Suite 2A
Amherst, MA 01002
USA

T +1 413 835 4350
https://ramboll.com

CONTENTS

APPENDICES

ACRONYMS AND ABBREVIATIONS

APCD	air pollution control device
CI	confidence interval
ENT	ear, nose and throat
HAPs	hazardous air pollutants aka air toxics
HCl	Hydrochloric acid
HCl(aq)	aqueous form of HCl
HCl(g)	gas form of HCl
IARC	International Agency for Research on Cancer
IPCS	Programme on Chemical Safety
IRIS	Integrative Risk Information System (US-EPA)
MACT	maximum achievable control technology
NHL	non-Hodgkin's lymphoma
NTP	National Toxicology Program
OECD	Organisation for Economic Co-operation and Development
OR	odds ratio
ppm	parts per million
PubMed	a database containing 32 million citations developed by the National Library of Medicine
RR	relative risk
SIDS	Screening Information Dataset (OECD)
SMR	standardized mortality ratio
UADC	upper aerodigestive cancer
US-EPA	United States Environmental Protection Agency
WHO	World Health Organization
yr	year

EXECUTIVE SUMMARY

Humans are exposed to approximately 4 million tons per year of HCl from natural sources (volcanoes, marine life, combustion of vegetation). It is found in household products such as cleaners and swimming pool additives and is formed during the burning of many plastics. HCl is considered one of the most important basic industrial chemicals. Mean air exposure to HCl in occupational settings has been estimated by IARC as ranging from <0.1 mg/m^3 to 12 mg/m^3 during acid treatment of metals, while mean exposures during other industrial processes are estimated as >1 mg/m^3. Ambient air levels of HCl typically remain below 0.01 mg/m^3.

IARC recognized that sulfuric acid and HCl are often found together in industrial processes. In assessing the scientific evidence for the grouping "sulfuric acid and other strong inorganic acids," IARC concluded that there was sufficient evidence associating occupational exposure to "strong-inorganic-acid mists containing sulfuric acid" with cancer. They therefore concluded that occupational exposure to strong inorganic acid mists **containing sulfuric acid** is carcinogenic to humans (i.e., a "Group 1" carcinogen). In contrast, IARC's conclusion regarding HCl was that there was **inadequate evidence** for the carcinogenicity of HCl, and they therefore assessed exposure to HCl as not classifiable as to its carcinogenicity to humans (i.e., a "Group 3").

Because of its wide uses in industry, tens of thousands of employees exposed to HCl have been studied and no clear signals of elevated cancer risks have emerged. This is despite the fact that many individuals classified as being exposed to HCl were actually exposed to mixtures that included recognized occupational carcinogens, including acid mists. When exposures are mixed, the substance contained in the mixture with the strongest relationship to the outcome (e.g., sulfuric acid in mixed acid mists) will drive the relationship for the whole mixture. Mixed exposures or chance are the likely explanations for the sporadic positive associations with cancer observed in occupational studies of mixed acids containing HCl. All occupational epidemiology studies published since the 1992 IARC determination are consistent with this conclusion.

The available toxicological evidence also is consistent with the human data, i.e., it does not indicate that HCl is carcinogenic or mutagenic, and there is no evidence that HCl causes the types of cell proliferation that are typically associated with nongenotoxic carcinogens. The only chronic exposure study reported increased incidence of hyperplasia (indicative of cell proliferation) in the larynx and trachea of rats exposed to 10 ppm HCl as compared to controls, but no excess cancer was observed. Hyperplasia would not be expected to progress to cancer at exposure concentrations below the threshold at which hyperplasia was reported. Two short term cancer studies in experimental animals reported that neither dermal nor oral exposures resulted in an increase in cancers. The available toxicology studies also did not provide evidence of genotoxicity or mutagenicity resulting from HCl exposures (as reviewed by Organization for Economic Cooperation and Development). Furthermore, in studies where HCl was administered along with formaldehyde, exposures to 10 ppm HCl neither caused serious irritating effects nor enhanced the carcinogenicity of formaldehyde.

The air modeling performed by US-EPA for their risk assessment is expected to contribute to an acceptable margin of safety. The default assumptions of the air model are expected to produce conservative air concentrations, and the definition of the receptor locations should produce reasonable exposure estimates for existing receptors. In addition, the chronic and acute toxicity reference values used for the risk assessment are based on the best available science.

HCl has not been identified as a carcinogen, despite its long history of use. Ramboll therefore recommends, as specified in 42 U.S.C. § 7412(d)(4), that the MACT standard for HCl be based on a health-based threshold, including an ample margin of safety.

1. INTRODUCTION

1.1 Hydrochloric Acid (HCl)

Hydrochloric acid is a strong corrosive acid that is formed when hydrogen chloride gas is dissolved in water (i.e., it is an aqueous solution). Hydrogen chloride gas and aqueous hydrochloric acid have the same chemical formula: HCl. The gas form may be designated as HCl(g), and the aqueous form as HCl(aq). For the purpose of this report, we refer to either of the physical states as HCl.

At room temperature, HCl is a nonflammable, colorless to slightly yellow gas with a pungent odor in moist air (IARC 1992; ATSDR 2014; National Library of Medicine (US), National Center for Biotechnology Information 2024; ATSDR 2002). On exposure to air, the gas forms dense white vapors due to condensation with atmospheric moisture. When hydrogen chloride gas comes into contact with moisture, it forms hydrochloric acid. Commercial concentrated hydrochloric acid contains 36% to 38% hydrogen chloride in water.

In the early twentieth century, hydrogen chloride was created by burning hydrogen gas. This method created a product of higher purity than that of the reaction between chloride salts and sulfuric acid or sodium hydrogen sulfate (IARC 1992). A widely used industrial chemical, HCl can also be formed as a byproduct of combustion of certain fossil fuels in industrial manufacturing processes, for example from lime kilns used for manufacture of lime (CaO and MgO) (IARC 1992; ATSDR 2014; ATSDR 2002). HCl can also be found in many everyday products, including household products such as cleaners and swimming pool additives (used to adjust the pH), and it is formed during the burning of many plastics. Industrial uses of HCl include pickling, electroplating metals, tanning leather, cleaning, and the production of a wide variety of products. HCl is also formed naturally in events like volcano eruptions. HCl is one of the most widely used chemicals in industrial processes, and the US Occupational Safety and Health Administration (OSHA) estimates that about 1,239,000 American workers are potentially exposed to HCl (as cited in IARC 1992). People are exposed to HCl in the ambient air, although concentrations are typically below 0.01 mg/m^3 (as cited in IARC 1992).

Based on communication with the National Lime Association (personal communication), HCl emitted from lime kilns controlled with a dry air pollution control device (APCD) is in the vapor (gas) phase. This is because the gas exit temperature (~400 degrees F) is well above any threshold where acid mist could exist[1]. This has been verified with industry stack test data obtained from wet chemistry and vapor phase testing, which confirm the presence of HCl as a gas in the exhaust. The vast majority of U.S. lime kilns (>95 percent) are controlled with dry APCDs. For kilns controlled with a wet scrubber, HCl emissions in the form of mists are expected to be very low due to the solubility of HCl in water.

1.2 Residual Risk, Technology Review, and Health-Based Exposure Limits

Under Section 112 of the Clean Air Act, the Environmental Protection Agency (US-EPA) regulates

[1] As we discuss later, the carcinogenicity evidence for acids involves acid mists specifically.

hazardous air pollutants (HAPs, also known as air toxics) originating from industrial facilities. There is a two-stage process for this regulation:

- In the first stage, section 112(d) requires the US-EPA to develop technology-based standards, called maximum achievable control technology (MACT) standards, for each category of sources (e.g., petroleum refineries, pulp and paper mills, etc.).[2]
- In the second stage, US-EPA is required under section 112(f)(2) to assess the health and environmental risks that remain after implementation of the MACT standards. If additional risk reductions are necessary to protect public health with an ample margin of safety or to prevent an adverse environmental effect, US-EPA must develop standards to address these remaining risks. This second stage of the regulatory process is known as the residual risk stage. For each source category for which US-EPA issued MACT standards, the residual risk stage must be completed within eight years of promulgation of the initial technology-based standard.

Under section 112(d)(6), US-EPA also must review each of the technology-based standards at least every eight years and revise them, as necessary, taking into account developments in practices, processes and control technologies. If appropriate based on the results of the risk and technology reviews, the US-EPA will revise the rules. For efficiency, the US-EPA includes the 112(f) and 112(d) analyses in the same regulatory package and calls the rulemakings the Risk and Technology Review.

MACT standards require the "maximum degree of [emissions] reductions" that US-EPA determines "is achievable." The MACT standard is based on a minimum stringency requirement (a "floor") based on emissions levels achieved by existing sources, where the floor is based on average emission limitation achieved by the best-performing 12% of existing sources (for which the Administrator has emissions information)."

As outlined in 42 U.S.C. § 7412(d)(4), the MACT standard may be based on a health-based threshold, assuming such a threshold has been established. The US-EPA will not approve a health-based threshold for a MACT standard if a HAP is a carcinogen. As part of the statutory lime manufacturing risk and technology review, US-EPA conducted an inhalation risk assessment for HAPs emitted from lime kilns, including HCl, and found no unacceptable human health risk under worst case emissions scenarios (84 FR 48,723 (Sep. 16, 2019)). The US-EPA risk assessment assumed HCl is a non-carcinogen, and as such used a variety of human-health risk screening benchmarks as part of risk calculations.

In its pre-proposed rule announced in the February 9, 2024 Federal Register (Vol 89, No. 28), US-EPA requested public comment on a potential health-based exposure limit (HBEL) for HCl. To regulate exposure levels using an HBEL, the chemical in question must be identified as a non-carcinogen. The specific scientific issues that the National Lime Association requested Ramboll to consider are as follows:

1. Evidence related to the potential carcinogenicity of HCl.
2. Whether the scientific community has judged there to be an established threshold for health effects associated with HCl exposure.
3. The estimated margin of safety associated with the proposed threshold.

[2] https://www.epa.gov/stationary-sources-air-pollution/risk-and-technology-review-national-emissions-standards-hazardous

2. METHODS

2.1 General approach

Ramboll reviewed and synthesized the scientific literature regarding the carcinogenicity of HCl and provided a report to NLA in June 2021. Our 2021 assessment of HCl carcinogenicity incorporated previous assessments by the World Health Organization International Agency for Research on Cancer (IARC), the Organisation for Economic Co-operation and Development (OECD), and the International Programme on Chemical Safety (IPCS) that we updated with information identified through literature searches to identify information available after the publication dates for those agency reports. We concluded that the newer evidence is consistent with the earlier body of scientific evidence, and, taking both the epidemiological and toxicological data into account, the evidence does not indicate that HCl is a carcinogen. As a follow-up to Ramboll's June 2021 report, Ramboll has undertaken the following activities:

1. To comment on the evidence related to the potential for HCl to be a carcinogen, we conducted new searches of the literature to identify any assessments of the risks associated with HCl exposure that had been conducted by authoritative bodies or that had been published in individual research studies since January 2021. This time interval deliberately overlaps with the period covered in Ramboll's previous review, in order to identify material published in early 2021 whose indexing had been delayed. We reviewed all new information to determine if it provided evidence in conflict with our prior conclusions, or if it supported our prior conclusions.
2. After incorporating new information into our prior assessment of the evidence, we abstracted all quantitative exposure data we identified to date (i.e., including sources identified for Ramboll's 2021 report) to determine if there was evidence for a threshold below which health effects were not observed (no observed adverse effect level [NOAEL]/lowest observed adverse effect level [LOAEL]). We documented this information, along with any specific health-related outcomes investigated in association with these exposure levels.
3. We developed comments on the quality, quantity, and certainty of the evidence thus summarized, and discussed the ability to consider the conclusions regarding a threshold for health effects to be "established".
4. To comment on the estimated margin of safety in US-EPA's pre-proposed rule, we reviewed US-EPA air modeling methods to verify their methods and underlying assumptions were scientifically supported. In addition, we reviewed the calculations and assumptions underlying the reference concentration values (RfC) estimated by California EPA and US-EPA to determine which approach was more appropriate.

2.2 Identifying Relevant Literature

We implemented the same search strategies documented in Ramboll's June 2021 report to NLA to verify that we were able to identify the same body of relevant literature cited in 2021 and to update those searches with material published between 2021 and February 2024. We enhanced both literature searches as described in section 2.2.2 and 2.2.3, below.

2.2.1 Updated assessments of HCl by authoritative bodies

We checked for HCl assessments by the following authoritative bodies, focusing on material published since 2021: IARC, OECD, IPCS, the US Environmental Protection Agency (US-EPA), the National Toxicology Program (NTP), the Agency for Toxic Substances and Disease Registry (ATSDR), The California Environmental Protection Agency's Office of Environmental Health Hazard Assessment (OEHHA), California Air Resources Board (CARB), The European Food Safety Authority (EFSA), and the National Institute of Health (NIH).

2.2.2 PubMed Search of Epidemiological Literature

To identify studies of humans with potential occupational exposure to HCl, we searched PubMed, using combinations of the following search terms: "occupational"; "human"; "human exposure"; "hydrochloric acid"; "hydrogen chloride"; "carcinogenicity"; "carcinogen"; "cancer"; "epidemiology"; "cohort"; and "case-control". When searches included "cancer", clinical studies were filtered out of the search to remove irrelevant studies of clinical trials. We additionally searched for epidemiology studies published since 2021 that had cited any of the literature referenced in the IARC and OECD assessments that were the initial basis of Ramboll's 2021 report.

2.2.3 Targeted PubMed Search of Animal Toxicity Literature

To identify relevant toxicological data, including animal studies and studies of mutagenicity, we searched PubMed using combinations of the following search terms: "hydrochloric acid"; "hydrogen chloride"; "chronic bioassay"; and "lifetime cancer risk". To enhance our searches of the toxicological literature, we included the terms "cancer", "carcinogenicity", and "malignant" combined with the chemical names, and we also constructed searches combining the chemical names with the terms "genotoxicity", "mutagenicity", "hyperplasia", and "cell proliferation".

2.2.4 Exclusion criteria

We excluded publications at the screening stage if HCl was not an exposure variable assessed in the study or if HCl exposure was not assessed in human subjects (for the search targeting epidemiological studies) or if HCl was not the test material administered to animals or the study was an aquatic toxicity study (for the search targeting chronic bioassays for cancer in experimental animals).

3. RESULTS

3.1 Evidence related to the potential carcinogenicity of HCl

3.1.1 Restatement of previous conclusions

In our 2021 report to NLA, Ramboll concluded there was no evidence for HCl to be a carcinogen based on a review of the assessments conducted by IARC, OECD, and ICPS and incorporating information we identified in publications post-dating those assessments. Our 2021 evaluation of the evidence included investigations of potential cancer associations based on occupational epidemiology studies, and supporting evidence in the form of genotoxicity studies and studies that assessed the potential for HCl to induce cell proliferation.

The occupational epidemiology studies (summarized in Table A1, Appendix A) were methodologically limited by their exposure assessment and categorization methods that likely resulted in exposures that combined HCl with other industrial chemicals. The use of mixed exposure groups is particularly germane, as the mixtures often included sulfuric acid and other strong inorganic acid mists, which are classified as carcinogenic. By evaluating mixtures of HCl and these other acids, any apparent association between HCl and cancer would be inflated due to the carcinogenic effect of exposure to the other acids. In spite of this confounding by mixed exposures, the results did not suggest an association with cancer.

The occupational epidemiology studies were also generally limited by inadequate control for potentially confounding, non-occupational exposures, and small numbers of cases that led to low statistical power. Based on our assessment of the available evidence, Ramboll agreed with the overall conclusion by IARC that the small number of cancer cases observed in various occupational cohorts likely represent sporadic cases and/or cases due to co-exposure by probable or known carcinogens, such as sulfuric and other acid mists.

The genotoxicity studies included in Ramboll's 2021 report either indicated no genotoxic effect of HCl, or their results were deemed due to the acidic conditions of the experiments; the concentrations of HCl that produced positive findings in these studies were higher than would be found in the environment and are not relevant for the ambient air exposures that are the subject of the proposed HBEL. Furthermore, we did not find evidence that cell proliferation – which is sometimes involved in the cancer process – is associated with HCl exposure in *in vitro* genotoxicity tests.

3.1.2 New literature: evidence related to the carcinogenicity of HCl

We did not find any relevant toxicology studies nor additional analyses published by authoritative bodies that were missing from Ramboll's 2021 report or that had been published since 2021. We identified three occupational epidemiology studies published in 2021 or later. Chen et al. (2021) conducted a case-control study in southern China based on self-reported data collected through in-person or telephone interviews. The study comprised 2,514 cases and 2,586 controls matched on age, sex, and location. Participants reported on work and health history and history of exposure to potentially confounding factors. All exposures to acids and alkalis were grouped together, thereby introducing confounding of any potential HCl association by exposure to known carcinogens. The main analysis, which adjusted for potential confounders including occupational exposure to other carcinogens, provided an elevated risk estimate for nasopharyngeal cancers (odds ratio (OR): 1.56; 95% confidence interval [CI] 1.30, 1.89). A sub-analysis that focused on participants categorized as ever or never exposed to sulfuric, hydrochloric and/or nitric acids adjusted for history of Epstein Barr virus infection provided an estimated OR for nasopharyngeal cancers of 1.63 (95% CI: 1.27, 2.09). Both estimates are very likely driven by the co-exposures to other acids that are classified as probable or known carcinogens.

In a study of 10,229 telecommunications workers (9,551 men) exposed to mixed acid mists, Ker et al. (2021) identified 52 deaths due to cancers of various types (31 cancers of the digestive system, 7 lung cancers, 5 nasopharyngeal cancers, and 9 miscellaneous cancers: 3 leukemias, 1 cervical cancer, 1 urinary cancer, 1 thyroid cancer, 1 non-pancreatic endocrine cancer, 1 immunological cancer, and 1 not specified). Note that cancer is not one disease - different types of cancers have different causes(American Cancer Society 2022). Standardized mortality ratios (SMR) estimated the risk of each type of cancer observed in the study population compared with the general population of Taiwan, where the study was conducted. All of the telecommunications

workers included in this study were exposed to mixed acids that had been previously designated as probable or known human carcinogens (sulfuric acid, hydrochloric acid, nitric acid). After controlling for age, sex, and calendar year, there was no evidence of an increased risk of nasopharyngeal cancer or lung cancer in the occupational cohort compared with the general population (i.e., SMRs adjusted for a five-year latency interval were 1.05 ($p>0.99$) and 0.76 ($p=0.59$), respectively). There were some types of cancers with SMRs greater than one, but each had only one to three cases and none of these associations were statistically significant; these are likely to represent chance findings.

Moayedi-Nia et al.(2022) published a case-control study of lung cancer nested in the Canadian CARTaGENE cohort. The authors identified 147 lung cancer cases diagnosed between 2009 and 2016 and compared their exposure histories to the exposures reported by 1,032 non-cancer controls based on the longest job held. Data were collected through telephone interviews and evaluated using CANJEM, the Canadian Job Exposure Matrix, to identify those who had no chance of exposure (never exposed), up to 25% certainty of exposure (ever), and at least 25% certainty of exposure (ever) to HCl based on job categories. After adjusting for age, smoking status, environmental tobacco smoke exposure, family history, and ever/never exposure to all other occupational lung carcinogens identified through CANJEM, participants ever occupationally exposed to HCl with at least 25% certainty had an OR of 3.79 (95% CI 1.07 – 13.41) for lung cancer compared to unexposed subjects, based on only five exposed cases (2 women and 3 men). The association was no longer statistically significant after adjustment for multiple comparisons to account for the many different potential health outcomes included in this analysis, suggesting it may have been a chance finding. There were too few cases to complete sex-stratified analyses.

3.1.3 Incorporating new information into previous conclusions for an overall assessment of evidence related to carcinogenicity of HCl

Combining the results of literature that we reviewed for Ramboll's 2021 report and this one, we found a total of 22 occupational epidemiology studies. The information included in the three occupational epidemiology studies that we identified with publication dates in 2021 or later does not alter the conclusions we reached in 2021. Taken together, the results of the available literature did not suggest that occupational exposure to HCl increased the risk of cancer.

Two of the occupational epidemiology studies provided quantitative exposure data. Bond et al. (1991) estimated cumulative and maximum average HCl exposures for subjects in a nested case-control study concerning lung cancer mortality. Compared to subjects with no estimated exposure, subjects with 2 ppm-years to 3.9 ppm-years (0.15 to 5.81 mg/m^3-year)[3], 4.0 to 12.4 ppm-years (5.96, 18.48 mg/m^3-year), and 12.5 ppm-years (18.63 mg/m^3-year) or greater showed non-statistically significant risk ratios of 0.9 (95% confidence interval 0.6 ,1.3), 1.2 (95% CI: 0.8,1.9), and 1.0 (95% CI 0.6, 1.8), respectively. There was no evidence of a trend across these groups ($chi^2 = 0.14$, $p = 0.35$). When categorized according to maximum average exposures, compared to unexposed subjects, subjects with a maximum of less than 2 ppm (2.98 mg/m^{3*}) showed a risk ratio of 0.8 (95% CI: 0.5, 1.2) and subjects with a maximum of greater than or equal to 2 ppm (2.98 mg/m^{3*}) showed a risk ratio of 1.2 (95% CI: 0.8,1.6). Neither cumulative exposures nor maximum average exposures yielded statistically significant results for any exposure level.

[3] Here and elsewhere, conversions from ppm to mg/m^3 assumed a molecular weight of 36.5 and 25°C, 1 atmosphere.

Coggon et al. (1996) reported non-statistically significant results when analyzing aerodigestive cancer mortality and maximum acid mist exposure levels. Compared to unexposed subjects, subjects ever exposed to less than 1 mg/m^3 showed an odds ratio of 1.9 (95% CI: 0.2, 15.8), and subjects exposed to 1 mg/m^3 or greater showed an odds ratio of 1.3 (95% CI: 0.3, 5.7). Notably, the maximum exposures include sulfuric acid or HCl mists rather than HCl exclusively, which is an important distinction because IARC concluded that HCl exposures other than mists were not carcinogenic. Despite this mixed exposure (mixed acid mists), the odds ratios reported by Coggon et al. (1996) were not statistically significant.

The effects of HCl exposure have also been investigated in animal studies (see Appendix, Table A2). The carcinogenicity of HCl was examined in groups of 100 Sprague-Dawley rats exposed by inhalation to either gaseous HCl, formaldehyde, two types of combinations of HCl and formaldehyde, or a control group of air alone for 6 hours per day, 5 days per week over 122 weeks (Albert et al. 1982; Sellakumar 1985). Results were also compared to those for unexposed control animals. HCl concentrations were 10 ppm (14.9 mg/m^3)[4] in the HCl-only exposure. Following sacrifice, animals were examined for tissue abnormalities, including cancer, with special attention to the respiratory tract. Results of the study indicated increased incidence of hyperplasia (indicative of cell proliferation) in the larynx and trachea of animals exposed to HCl alone as compared to air controls or colony controls, but no excess cancer was observed.

Other cancer studies in experimental animals were reported by OECD (Organization for Economic Cooperation and Development 2002) – a dermal exposure study (Narat, 1925 as cited by Organization for Economic Cooperation and Development 2002) and an oral exposure study (Dyer et al. 1946 as cited by Organization for Economic Cooperation and Development 2002). No malignant tumors were reported in 99 mice dermally exposed to an unknown volume of solutions containing 3-5% HCl every 1-2 days, and then weekly for 4-6 additional weeks (total exposure duration 25-46 weeks) (Narat,1925 as cited by Organization for Economic Cooperation and Development 2002).

Dyer et al. (1946, as cited by Organization for Economic Cooperation and Development 2002) orally exposed groups of mice to a combination of HCl (1-2.5 moles per liter) and either a "control emission" (58 mice) or HCl and 1,2,5,6-dibenzanthracene (40 mice) and reported no excess cancer or pre-cancerous lesions observed in the stomachs of animals from either group exposed to HCl. OECD concluded neither study was appropriate for the assessment of carcinogenicity because of the shortcomings of the study design.

An important consideration when determining carcinogenicity is the ability of a chemical to induce genotoxicity or mutagenicity. Genotoxic and mutagenic chemicals typically are not considered to have a threshold for their effects to occur. HCl did not induce mutations in six bacterial mutation assays nor in one mutation assay in yeast cells (reviewed by IARC 1992; Organization for Economic Cooperation and Development 2002). A qualitative predictive assay that examines cell survival in strains that have or lack the ability to repair damaged DNA had mixed results in two assays, but OECD concluded the positive finding was unrelated to DNA damage (reviewed by Organization for Economic Cooperation and Development 2002). A weakly positive response for mutations was observed in a mouse lymphoma cell assay; these results are interpreted as being an artifact of acidic conditions (pH 6.3 in buffered cell culture medium), which itself related to cell death. Other mutation assays in mammalian cell cultures were negative (IARC 1992; Organization for Economic Cooperation and Development 2002). HCl induced chromosome

[4] Here and elsewhere, conversions from ppm to mg/m^3 assumed a molecular weight of 36.5 and 25°C, 1 atmosphere.

aberrations in mammalian cells in culture at concentrations in excess of 10 mM in the cell culture media (leading to an acidic environment with a pH of 5.8) and in a handful of studies in Chinese hamster ovary cells, mouse lymphoma cells, and in insect and plant cells. IARC (1992) and OECD (2002) found that the acidic pH is the responsible factor for these responses and that similar responses are observed for other inorganic acids and with acetic acid. These concentrations would not be found environmentally and are thus not relevant for ambient air exposures to HCl.

As shown in Table A1 in the Appendix, tens of thousands of employees exposed to HCl have been studied, and very small numbers of cases of various types of cancers, which are expected to have different causes and risk factors, have been identified. This is in spite of the high likelihood that individuals classified as being exposed to HCl were actually exposed to mixtures that included recognized occupational carcinogens, including acid mists. Such mixed exposure groups would incorrectly assign risk to HCl if the risk were actually due to exposure to the other chemicals that co-occurred with HCl. The small numbers of cases have resulted in very unstable risks estimated with a high degree of uncertainty; in addition to the confounding effects of other exposures, chance cannot be ruled out as the cause of those findings.

HCl is a commonly used industrial chemical with a long history of use (IARC 1992). Had there been a causal association between HCl exposure and cancer, it is likely that concerns would have been raised and any potential association would have been more fully investigated. The small number of cases that have been detected in the existing research base implies HCl is likely not a carcinogen; the cases were most probably caused by co-exposures to known occupational carcinogens and/or to uncontrolled confounding by non-occupational carcinogenic exposures, such as cigarette smoking.

3.2 Has the scientific community judged there to be a threshold for health effects associated with HCl exposure?

It is logically impossible to prove a negative, i.e., that HCl does not cause cancer.

HCl currently has many industrial uses, in the production of chlorides, fertilizers, and dyes, in the steel, textile and rubber industries, in the production of numerous chemicals, making it one of the most widely used chemicals in industrial processes (IARC 1992). Given its wide use in industry, it can be inferred logically that occupational exposure to this chemical is common. Very little research on its carcinogenicity has been carried out, however, suggesting that no or few signals have emerged to indicate an elevated cancer risk associated with occupational exposure to HCl. This inference is borne out by the small numbers of cancer cases identified among the thousands of occupationally exposed individuals included in the studies we identified (Table A1 in Appendix A) and is supported by toxicological evidence indicating a lack of mutagenic or carcinogenic activity by HCl.

Some substances may produce tumors through a nonmutagenic mechanism, often by inducing extensive cell turnover which leads to the possibility of replication errors leading to mutations. However, such mechanisms are believed to have a threshold concentration below which no effects are seen. In the case of HCl, results from carcinogenicity studies in animals showed increased cell proliferation in the form of hyperplasia in the respiratory tract; however, there was no evidence of carcinogenicity (Sellakumar 1985). Furthermore, in studies where HCl was administered along with formaldehyde (Albert et al. 1982), exposures to 10 ppm (14.9 mg/m^3) HCl neither caused serious irritating effects nor enhanced the carcinogenicity of formaldehyde.

In conclusion, the available toxicological and epidemiological evidence does not indicate HCl is mutagenic or carcinogenic and there is no evidence that HCl causes the types of cell proliferation that are typically associated with nongenotoxic carcinogens. While the evidence from animal studies indicated chronic HCl exposure to 10 ppm (14.9 mg/m^3) led to increased incidence of hyperplasia, hyperplasia would not be expected to progress to cancer at exposure concentrations below the threshold at which hyperplasia was reported.

3.3 Proposed margin of safety

The US-EPA has derived a RfC for HCl of 0.2 mg/m^3 (Table 1) based on the lowest adverse effect level (LOAEL) of 10 ppm (14.9 mg/m^{3*}) reported by Sellakumar et al. (1985). The LOAEL is based on the incidence of hyperplasia reported in rats chronically exposed to HCl via inhalation, and the assumption that a threshold concentration exists below which no effects would be seen following HCl exposure. US-EPA has designated "low confidence" in the current RfC based on the study used as the basis for the RfC and the sparsity of the overall database for HCl (animal and human toxicity data). The study that serves as the basis for the RfC (Sellakumar 1985) includes only one treatment group and a control group. In addition, the supporting toxicity data includes only subchronic toxicity studies with no additional chronic or reproductive toxicity data. Based on the research completed for Ramboll's 2021 report and the review of both toxicology and epidemiology data completed from 2021 to the present, there are no additional data that could be considered by US-EPA that could increase the confidence in the RfC at this time. More studies would have to be conducted in order to increase confidence in the RfC, and they should include chronic exposures and reproductive endpoints.

The chronic REL (CREL) developed by the California Environmental Protection Agency (CalEPA), of 0.009 mg/m^3 (Table 1) is also based on the same chronic toxicity study (Sellakumar 1985) that serves as the basis for the RfC derived by US-EPA. While both the US-EPA and CalEPA toxicity values are based on the same underlying animal toxicity data and derived using similar methodologies there are significant differences in the two toxicity values with the CalEPA CREL being lower than US-EPA's RfC (RfC of 0.2 mg/m^3 vs. CREL of 0.009 mg/m^3). The difference in the values is related to the use of US-EPA's s guidance on the dosimetry adjustment of inhalation of gases (US-EPA 1994). The dosimetric adjustment equation considers the surface area all regions of the respiratory tract that are affected (i.e., extrathoracic, tracheobronchial and pulmonary). When conducting the dosimetry adjustment, CalEPA only considered the extrathoracic surface area. However, consistent with the results reported by Sellakumar et al. (1985) of increased hyperplasia in both the larynx and the trachea, US-EPA included the surface area of both the extrathoracic and tracheobronchial respiratory region. CalEPA notes that while extrathoracic and tracheobronchial effects were reported in rats following exposures to hydrogen chloride, the REL was based on extrathoracic effects because humans are predicted to be relatively more susceptible to the effects of hydrogen chloride in that region. However, no basis for this prediction was presented by CalEPA. The US-EPA guidelines recommend that when effects are observed in the mid-respiratory tract (tracheobronchial), this region should also be considered in the dosimetry adjustment calculations. Therefore, US-EPA's approach for the derivation of the RfC aligns with the guidelines for dosimetric adjustments following inhalation of gases and better represents the observed respiratory effects reported in the scientific literature.

US-EPA conducted a risk assessment to determine an HBEL for HCl for the Lime Manufacturing source category. The purpose of the assessment was to determine the level of HCl emissions that would ensure health thresholds are not exceeded with an ample margin of safety. Unit emissions

of one ton per year of HCl along with emission release parameters for each facility were used to estimate the HBEL. Inhalation exposure concentrations and potential health risks were estimated using US-EPA's Human Exposure Model (HEM4), which incorporates the American Meteorological Society/US-EPA Regulatory Model (AERMOD) dispersion modeling system (AERMOD version 22112), a Gaussian plume dispersion model for modeling point, area, and volume sources of continuous air emissions (USEPA 2005).

US-EPA provides details of the risk assessment and HBEL estimation in a memo, "Risk Approach to Assess a Health-Based Emission Limitation for Hydrochloric Acid for the Lime Manufacturing Source Category" (US-EPA Docket: EPA-HQ-OAR-2017-0015). The reported inputs for the air modeling were conservative. Unit emissions of 1 ton per year (tpy) of HCl assigned to each facility were used as input into HEM4 to estimate the maximum ambient chronic concentration, which were then scaled up by a factor of 300 to assess chronic and acute risks. A default hourly acute emissions multiplier of 10 was applied to reflect 1-hour emissions ten times the annual emissions level divided by 8,760 hours per year. Annual concentrations were estimated to assess chronic health impacts and 1-hour concentrations were estimated to assess acute health impacts.

In assessing the margin of safety for environmental HCl exposure, US-EPA calculated the chronic noncancer health hazard based on a hazard quotient (HQ), which is the estimated exposure at a location divided by a reference level (e.g., the RfC). HQs of ≤1 are not likely to cause adverse health effects, and as exposures increase above the reference level resulting in HQs >1, the potential for adverse effects increases. For assessing acute risks US-EPA performed a screening assessment using conservative assumptions combined with reasonable worst-case exposure. This screening process results in the facility being determined to pose no potential acute health risks (i.e., it "screens out"), or the facility requires further assessment. The toxicity reference values used for the risk assessment of chronic exposure were based on recommendations for HAPS (USEPA 2018). The toxicity reference values recommended by HAPs in order of priority are US-EPA RfC's and CalEPA's REL (Table 1). US-EPA's dose-response assessment for acute exposure to HCl was also based on the existing recommendations of HAPs. The results from screening acute assessments were compared to CalEPA's Acute Reference Exposure Levels (ARELs), Acute Exposure Guideline Levels (AEGLs) and Emergency Response Planning Guidelines (ERPGs) (Table 1).

Based on conservative air modeling assumptions and toxicity reference values based on the best available science and methodologies, US-EPA derived a HBEL emission level of 300 tpy of HCl. Results of the risk assessment indicated the maximum chronic non-cancer hazard from HCl emissions for this source category resulted in an HQ equal to 0.2, which is 5 times below a HQ of 1 indicating adverse chronic health effects are not likely to occur. For the acute assessment, three facilities had acute screening HQ values equaling or approaching a value of 1. EPA reported that an examination of aerial imagery of the facilities showed maximum acute off-site HQ equal to 0.6.

Overall, the air modeling performed by US-EPA for this assessment should contribute to an acceptable margin of safety. The default assumptions of the air model are expected to produce conservative air concentrations, and the definition of the receptor locations should produce reasonable exposure estimates for existing receptors. In addition, the chronic and acute toxicity reference values used for the risk assessment are based on the best available science.

4. SUMMARY AND CONCLUSIONS

Humans are exposed to approximately 4 million tons per year of HCl from natural sources (volcanoes, marine life, combustion of vegetation), as well as industrial sources, HCl is one of the most important basic industrial chemicals IARC (1992)summarized estimated mean air concentrations of HCl in occupational settings ranging from <0.1 mg/m^3 to 12 mg/m^3 during acid treatment of metals. Mean exposures during other industrial processes are estimated as >1 mg/m^3. HCl is also found in household products such as cleaners and swimming pool additives and is formed during the burning of many plastics. IARC (1992) reported that ambient air levels of HCl typically remain below 0.01 mg/m^3.

As shown in Table A1 in the Appendix, tens of thousands of employees exposed to HCl have been studied with no clear signals of elevated cancer risks emerging. This is in spite of the high likelihood that individuals classified as being exposed to HCl were actually exposed to mixtures that included recognized occupational carcinogens, including acid mists. Had there been a causal association between HCl exposure and cancer, it is likely that concerns would have been raised and any potential association would have been more fully investigated.

IARC (1992) recognized that sulfuric acid and HCl are often found together in industrial processes. In assessing the scientific evidence for the grouping "sulfuric acid and other strong inorganic acids," IARC concluded that there was sufficient evidence associating occupational exposure to "strong-inorganic-acid mists containing sulfuric acid" with cancer. They therefore concluded that occupational exposure to strong inorganic acid mists **containing sulfuric acid** is carcinogenic to humans (i.e., a "Group 1" carcinogen) (IARC 1992). In contrast, IARC's conclusion regarding HCl was that there was **inadequate evidence** for the carcinogenicity of HCl, and they therefore assessed exposure to HCl as not classifiable as to its carcinogenicity to humans (i.e., a "Group 3"). This is relevant because the conclusion regarding acid mists is based on exposure to mixtures that must include sulfuric acid. While sulfuric acid and HCl often are found together in mixed acid exposures, the exposure contained in the mixture with the strongest relationship to the outcome (in this case, sulfuric acid) will drive the relationship for the whole mixture. This is likely the explanation for the sporadic, positive associations observed in occupational studies of mixed acids containing HCl. All occupational epidemiology studies published since the 1992 IARC determination are consistent with this conclusion.

As shown in Table A2 in the Appendix, the effects of HCl exposure have also been investigated in animal studies. Results of the only chronic exposure study indicated increased incidence of hyperplasia (indicative of cell proliferation) in the larynx and trachea of rats exposed to HCl alone as compared to air controls or colony controls, but no excess cancer was observed (Sellakumar 1985). Two short term cancer studies in experimental animals were reported by OECD (Organization for Economic Cooperation and Development 2002): Neither the dermal exposure study (Narat, 1925 as cited by Organization for Economic Cooperation and Development 2002) nor the oral exposure study (Dyer et al. 1946 as cited by Organization for Economic Cooperation and Development 2002) reported any increase in cancer occurrence.

Some substances may produce tumors through a nonmutagenic mechanism, often by inducing extensive cell turnover which leads to the possibility of replication errors leading to mutations. However, such mechanisms are believed to have a threshold concentration below which no effects are seen. In the case of HCl, results from carcinogenicity studies in animals showed increased cell proliferation in the form of hyperplasia in the respiratory tract; however, there was

no evidence of carcinogenicity (Sellakumar 1985) and there was no evidence of genotoxicity or cell proliferation resulting from HCl exposures (reviewed by OECD). Furthermore, in studies where HCl was administered along with formaldehyde (Albert et al. 1982), exposures to 10 ppm HCl neither caused serious irritating effects nor enhanced the carcinogenicity of formaldehyde.

The available toxicological and epidemiological evidence does not indicate HCl is mutagenic or carcinogenic and there is no evidence that HCl causes the types of cell proliferation that are typically associated with nongenotoxic carcinogens. While the evidence from animal studies indicated chronic HCl exposure to 10 ppm led to increased incidence of hyperplasia, hyperplasia would not be expected to progress to cancer at exposure concentrations below the threshold at which hyperplasia was reported.

The air modeling performed by US-EPA for this assessment should contribute to an acceptable margin of safety. The default assumptions of the air model are expected to produce conservative air concentrations, and the definition of the receptor locations should produce reasonable exposure estimates for existing receptors. In addition, the chronic and acute toxicity reference values used for the risk assessment are based on the best available science.

HCl has not been identified as a carcinogen, despite its long history of use. Ramboll therefore recommends, as specified in 42 U.S.C. § 7412(d)(4), that the MACT standard for HCl be based on a health-based threshold, including an ample margin of safety.

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Table 1 – Toxicity Reference Values		
Toxicity Reference Value	**ppm**	**mg/m^3**
Chronic		
USEPA RfC	0.013*	0.02
CalEPA CREL	0.006	0.009
Michigan EGLE ITSL	0.013*	0.02
Acute		
AEGL-1 (1-hour)	1.8	2.7
AEGL-2 (1-hour)	22	33
ERPG-1	3	4.5
ERPG-2	20	30
CalEPA REL	1.4*	2.1
Michigan EGLE ITSL	1.4*	2.1
ACGIH TLV – Ceiling	2	3*
OSHA PEL - Ceiling	5	7
Cal/OSHA PEL – Ceiling	2	3*
Cal/OSHA PEL – 8-hour TWA	0.3	0.45

*Value was calculated based on a molecular weight of 36.5, 25°C, and 1 atmosphere.

USEPA IRIS – US Environmental Protection Agency Integrated Risk Information System

RfC – inhalation reference concentration

CalEPA (OEHHA) - the California Environmental Protection Agency's Office of Environmental health hazard Assessment

CREL – Chronic Reference Exposure Level

AEGL - Acute Exposure Guideline Levels

AEGL-1 is the airborne concentration (expressed as ppm or mg/m3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic nonsensory effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure.

AEGL-2 is the airborne concentration (expressed as ppm or mg/m^3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience irreversible or other serious, long-lasting adverse health effects or an impaired ability to escape.

ERPG - Emergency Response Planning Guidelines

ERPG-1 is the maximum airborne concentration below which it is believed that nearly all individuals could be exposed for up to 1 hour without experiencing other than mild transient adverse health effects or without perceiving a clearly defined, objectionable odor.

ERPG-2 is the maximum airborne concentration below which it is believed that nearly all individuals could be exposed for up to 1 hour without experiencing or developing irreversible or other serious health effects or symptoms which could impair an individual's ability to take protective action.

ITSL - Initial Threshold Screening Level

OSHA - Occupational Safety and Health Association

PEL - Permissible Exposure Limit

ACGIH - American Conference of Governmental Industrial Hygienists

TLV - Threshold Limit Value

TWA - Time Weighted Average

APPENDIX A
SUMMARY TABLES

Table A1. Summary of Epidemiology Studies

Citation	Industry	Study design	Pop. Size	Outcome	Exposure	Exposure Groups	Exposure Levels	# Cases	Risk Estimate	Lower 95%[a] CI	Upper 95%[a] CI	Comments (focus on potential causes of bias and/or confounding
Beaumont et al. 1987	Steel pickling	Cohort	1,165 (1,156 men; 9 women)	Lung cancer (mortality)	Sulfuric acid and other acid mists (primarily HCl)	Group 1: any acid (entire cohort)	Dose was not quantified. Dose-response relationship was based on length of employment	28	SMR: 1.35	0.92	1.97	Referent group: US general population; US steel workers Two of the three facilities had consistent trends; the third facility had a small sample size and no lung cancer deaths observed.
						Group 2: sulfuric acid only		13	SMR: 1.06	0.59	1.9	Exposure categorization was based on job category and not specific measurements of exposure level.
						Group 3: sulfuric acid only, probable daily exposure (subset of Group 2)		12	SMR: 1.23	0.68	2.2	Did not control for smoking or exposure to other potential lung carcinogens (besides coke operations).

Table A1. Summary of Epidemiology Studies

Citation	Industry	Study design	Pop. Size	Outcome	Exposure	Exposure Groups	Exposure Levels	# Cases	Risk Estimate	Lower 95%[a] CI	Upper 95%[a] CI	Comments (focus on potential causes of bias and/or confounding
Beaumont et al. 1987	Steel pickling	Cohort	1,165 (1,156 men; 9 women)	Lung cancer (mortality)	Sulfuric acid and other acid mists (primarily HCl)	Group 4: other acid only	Dose was not quantified. Dose-response relationship was based on length of employment	9	SMR: 2.00 (compared to other steel workers)	1.06	3.78	In this cohort, 2 deaths from laryngeal cancer were detected (not statistically significant)
									SMR: 2.24 (compared to US population)	1.02	4.26	
						Group 5: sulfuric acid and other acid		6	SMR: 1.49	0.54	3.86	

Table A1. Summary of Epidemiology Studies

Citation	Industry	Study design	Pop. Size	Outcome	Exposure	Exposure Groups	Exposure Levels	# Cases	Risk Estimate	Lower 95%[a] CI	Upper 95%[a] CI	Comments (focus on potential causes of bias and/or confounding
Steenland et al. 1988	Steel pickling	Cohort	879 men	Laryngeal cancer (diagnosis)	Sulfuric acid and other acid mists	Overall analysis	Dose not quantified	9 (4 sulfuric acid only; 2 other acids only; 3 mix of sulfuric acid and other acid)	SIR (observed/expected): 2.3	--	--	Referent groups: US population and other steel workers. None of these associations were statistically significant Insufficient power to detect statistically significant changes
						<5 years exposure			SIR: 1.70	--	--	
						>5 years exposure			SIR: 2.76	--	--	No dose-response relationship shown
						<20 years since first exposure			SIR: 3.27	--	--	
						>20 years since first exposure			SIR: 2.03	--	--	IARC (1992) notes confounding by exposure to sulfuric acid could not be ruled out.

Table A1. Summary of Epidemiology Studies												
Citation	**Industry**	**Study design**	**Pop. Size**	**Outcome**	**Exposure**	**Exposure Groups**	**Exposure Levels**	**# Cases**	**Risk Estimate**	**Lower 95%[a] CI**	**Upper 95%[a] CI**	**Comments (focus on potential causes of bias and/or confounding**
Collins et al. 1989	Acrylamide workers	Cohort	8,854 men (2,293 exposed to acrylamide)	Respiratory cancers mortality (lung or larynx)	Hydro-chloric acid	Acrylamide (Not exposed: <0.001 mg-m3-years vs exposed >0.001 mg-m3-years (cumulative exposure for acrylamide based on (number of days in the job * estimated daily exposure) divided by 365).	Dose not quantified for HCL	63 in group exposed to <0.001 mg/m3-years acrylamide (11 in a department using HCl)	No quantitative risk estimate presented for workers exposed to HCl	--	--	Subject of paper is exposure to acrylamide. It contains mention of workers in a unit with HCl exposure. Subsequent discussion by IARC (1992) notes the expected numbers for that facility were not provided.

Table A1. Summary of Epidemiology Studies

Citation	Industry	Study design	Pop. Size	Outcome	Exposure	Exposure Groups	Exposure Levels	# Cases	Risk Estimate	Lower 95%[a] CI	Upper 95%[a] CI	Comments (focus on potential causes of bias and/or confounding
Marsh et al. 1999	Acrylamide workers	Cohort	8508 workers	Respiratory cancers mortality	Hydro-chloric acid	Duration of exposure (yr) : Mean (SD) - 0.08 (1.02), Max-26.53	Dose not quantified for HCL	276 cases (16 exposed to HCL)	OR:1.50	0.86	2.59	The findings may be confounded by smoking as complete smoking data was not available for this subgroup exposed to HCL.
Bond et al. 1983	Chemical workers (TX)	Case-control	19,608	Brain cancer mortality	Hydrogen chloride	Hydrogen chloride and 10 other chemical categories	Dose not quantified.	28 (13 exposed to HCl)	Compared to control group A (110; 42 exposed to HCl) OR: 1.40	0.70 *	2.80*	Exposure categories based on employment records and some job titles; categories were nonspecific. Exposure misclassification was possible due to lack of records in early years of company operations. Small number of cases

Table A1. Summary of Epidemiology Studies

Citation	Industry	Study design	Pop. Size	Outcome	Exposure	Exposure Groups	Exposure Levels	# Cases	Risk Estimate	Lower 95%[a] CI	Upper 95%[a] CI	Comments (focus on potential causes of bias and/or confounding
Bond et al. 1983	Chemical workers (TX)	Case-control	19,608	Brain cancer mortality	Hydrogen chloride	Hydrogen chloride and 10 other chemical categories	Dose not quantified.	28 (13 exposed to HCl)	Sample-based control group B (111; 51 exposed to HCl) OR: 1.02	0.81 *	1.29*	Exposure categories based on employment records and some job titles; categories were nonspecific. Exposure misclassification was possible due to lack of records in early years of company operations. Small number of cases

Table A1. Summary of Epidemiology Studies												
Citation	**Industry**	**Study design**	**Pop. Size**	**Outcome**	**Exposure**	**Exposure Groups**	**Exposure Levels**	**# Cases**	**Risk Estimate**	**Lower 95%[a] CI**	**Upper 95%[a] CI**	**Comments (focus on potential causes of bias and/or confounding**
Bond et al. 1983	Chemical workers (TX)	Case-control	19,608	Brain cancer mortality	Hydrogen chloride	Hydrogen chloride and 10 other chemical categories	Dose not quantified.	28 (13 exposed to HCl)	Cases employed 1 to 4 years with matched group B controls (5 cases, 15 controls exposed) OR: 2.02	0.5*	8.1*	Exposure categories based on employment records and some job titles; categories were nonspecific. Exposure misclassification was possible due to lack of records in early years of company operations. Small number of cases

Table A1. Summary of Epidemiology Studies												
Citation	**Industry**	**Study design**	**Pop. Size**	**Outcome**	**Exposure**	**Exposure Groups**	**Exposure Levels**	**# Cases**	**Risk Estimate**	**Lower 95%[a] CI**	**Upper 95%[a] CI**	**Comments (focus on potential causes of bias and/or confounding**
Bond et al. 1985	Chemical workers (TX)	Case control	19,608	Renal cancer mortality	Hydrogen chloride	Hydrogen chloride and other chemical agents	Dose was not quantified	26 (12 exposed to HCl)	Compared to group A (92; 44 exposed to HCl) OR: 0.90	0.44 *	1.83*	Potential unaccounted lifestyle confounders Exposure classification was based on job category and company work histories
									Compared to Group B (98; 50 exposed to HCl) OR: 0.86	0.40 *	1.86*	

Table A1. Summary of Epidemiology Studies												
Citation	**Industry**	**Study design**	**Pop. Size**	**Outcome**	**Exposure**	**Exposure Groups**	**Exposure Levels**	**# Cases**	**Risk Estimate**	**Lower 95%[a] CI**	**Upper 95%[a] CI**	**Comments (focus on potential causes of bias and/or confounding**
Bond et al. 1986	Chemical workers (TX)	Nested case-Control	19,608	Lung cancer mortality	Hydrogen chloride	Hydrogen chloride and other chemical agents	Dose was not quantified. Exposure level based on ranking-low, moderate, high according to job assignment	308 (237 exposed to HCl) 616 comparison workers, (463 exposed to HCl)	Without regard for interval prior to death: OR: 1.02	0.77	1.35	Exposure measurements were not available. Possible random misclassification of employee exposures Possible chance variation
									Excluding exposures occurring within 15 years of death OR: 0.92	0.68	1.24	Possible protective role for one or more chemicals

Table A1. Summary of Epidemiology Studies

Citation	Industry	Study design	Pop. Size	Outcome	Exposure	Exposure Groups	Exposure Levels	# Cases	Risk Estimate	Lower 95%[a] CI	Upper 95%[a] CI	Comments (focus on potential causes of bias and/or confounding
Bond et al. 1991	Chemical workers (TX)	Nested case-Control	19,608	Lung, trachea, bronchus cancer mortality (note, results only presented for lung cancer)	Hydrogen chloride	HCl calculated by time spent on jobs and cumulative exposure score		308 616 comparison workers from 2 control groups (308 each, pooled)	All dates RR: 1.0	0.8	1.3	Exposure was determined by job category. Differences in respirator policies at plant
									Excluding exposures occurring within 15 years of death RR: 0.9	0.7	1.2	
							Cumulative Exposure (ppm-yr): 0.1-3.9 (0.15-5.81	62	Adj RR = 0.9	0.6	1.3	0.15-0.58

Table A1. Summary of Epidemiology Studies												
Citation	**Industry**	**Study design**	**Pop. Size**	**Outcome**	**Exposure**	**Exposure Groups**	**Exposure Levels**	**# Cases**	**Risk Estimate**	**Lower 95%[a] CI**	**Upper 95%[a] CI**	**Comments (focus on potential causes of bias and/or confounding**
							mg/m3-yr)					
Bond et al. 1991	Chemical workers (TX)	Nested case-Control	19,608	Lung, trachea, bronchus cancer mortality (note, results only presented for lung cancer)	Hydrogen chloride	HCl calculated by time spent on jobs and cumulative exposure score	4.0-12.4 (5.96-18.48 mg/m3-yr)	45	Adj RR = 1.2	0.8	1.9	
							>12.5 (18.63 mg/m3-yr)	22	Adj RR = 1.0	0.6	1.8	
Chen et al. 2021	Population based (residents of Guangdong and Guangzi, China)	Case-control	2,514 cases, 2,586 controls	Nasopharyngeal cancer incidence	Mixed acids and alkalis (sulfuric acid, hydrochloric acid, nitric acid, concentrated alkai, ammonia)	Ever exposed	Dose not quantified.	311	OR = 1.38	1.03	1.85	Does not consider exposure to HCl alone- only as part of a mixed acid exposure Risk estimate is no longer significant when analyzed across different dose levels No quantitative measurements of exposure

Table A1. Summary of Epidemiology Studies												
Citation	**Industry**	**Study design**	**Pop. Size**	**Outcome**	**Exposure**	**Exposure Groups**	**Exposure Levels**	**# Cases**	**Risk Estimate**	**Lower 95%[a] CI**	**Upper 95%[a] CI**	**Comments (focus on potential causes of bias and/or confounding**
												Self-reported exposures are liable to recall bias
Chen et al. 2021	Population based (residents of Guangdong and Guangzi, China)	Case-control	2,514 cases, 2,586 controls	Nasopharyngeal cancer incidence	Mixed acids and alkalis (sulfuric acid, hydrochloric acid, nitric acid, concentrated alkai, ammonia)	<8 years exposure	Dose not quantified.	109	OR = 1.53	0.89	2.64	Unclear if overlap between exposures of interest was accounted for
						8-22 years exposure		91	OR = 1.09	0.68	1.77	
						>=23 years exposure		111	OR = 1.56	0.99	2.45	
						First exposed aged >=23		101	OR = 1.37	0.84	2.25	
						First exposed aged 18-22		86	OR = 1.19	0.71	1.97	
						First exposed aged <18		124	OR = 1.56	0.99	2.47	
					Mixed acids (sulfuric acid, hydrochloric acid,	Ever exposed		176	OR = 1.63	1.27	2.09	

Table A1. Summary of Epidemiology Studies												
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					nitric acid)							
Coggon et al. 1996	Steel and battery manufacture workers	Nested case-control	4403	Upper aerodigestive cancer (UADC) mortality	Maximum exposure to acid mists (hydrochloric or sulfuric acid)	No exposure	Zero	3 exposed cases; 18 exposed controls	OR: 1.0	--	--	Estimates based on a small number of cases Potential non-occupational and occupational confounders (tobacco, alcohol) SMRs compare mortality in the worker population with mortality in the general US population.
						Low exposure	<1 mg/m3 sulfuric or hydrochloric acid	2 exposed cases; 7 exposed controls	OR: 1.9	0.2	15.8	
						High exposure	>1 mg/m3 sulfuric or hydrochloric acid	9 exposed cases; 43 exposed controls	OR: 1.3	0.3	5.7	

Table A1. Summary of Epidemiology Studies												
Citation	**Industry**	**Study design**	**Pop. Size**	**Outcome**	**Exposure**	**Exposure Groups**	**Exposure Levels**	**# Cases**	**Risk Estimate**	**Lower 95%[a] CI**	**Upper 95%[a] CI**	**Comments (focus on potential causes of bias and/or confounding**
						Uncertain	NA	1 case exposed; 5 controls exposed	OR: 1.0	0.1	12	
Coggon et al. 1996	Steel and battery manufacture workers	Nested case-control	4403	Upper aerodigestive cancer (UADC) mortality	Cumulative exposure to acid mists (hydrochloric or sulfuric acid)	No exposure	Dose not quantified.	3 exposed cases; 18 exposed controls	OR: 1.0	--	--	Estimates based on a small number of cases Potential non-occupational and occupational confounders (tobacco, alcohol) SMRs compare mortality in the worker population with mortality in the general US population.
						Intermediate or uncertain cumulative exposure		5 exposed cases; 32 exposed controls	OR: 1.0	0.2	4.6	
						At least 5 years high cumulative exposure		7 exposed cases; 23 exposed controls	OR: 2.0	0.4	10	
		Cohort		All cancer mortality	Acid mists	Full cohort (possibly	Dose not quantified.	324	SMR: 0.88	0.79	0.98	

Table A1. Summary of Epidemiology Studies												
Citation	**Industry**	**Study design**	**Pop. Size**	**Outcome**	**Exposure**	**Exposure Groups**	**Exposure Levels**	**# Cases**	**Risk Estimate**	**Lower 95%[a] CI**	**Upper 95%[a] CI**	**Comments (focus on potential causes of bias and/or confounding**
					(hydrochloric or sulfuric acid)	exposed, never exposed, and definitely exposed)						
Coggon et al. 1996	Steel and battery manufacture workers	Cohort	4403	All cancer mortality	Acid mists (hydrochloric or sulfuric acid)	Never exposed to acid mists	Dose not quantified.	88	SMR: 0.74	0.59	0.91	
						Definitely exposed		199	SMR: 0.92	0.79	1.05	
Ker et al. 2021	Office workers at a telecommunication company	cohort	10,229 workers compared to the general population of Taiwan	All cancer mortality	Mixed acids (sulfuric acid, hydrochloric acid, nitric acid)	All workers compared to the general population	Dose not quantified	All cancer: 42	SMR = 0.68	P <0.01		Comparing to a general population rather than a traditional control group opens the possibility of confounding by any unknown co-exposures than telecommunication employees are likely to encounter
									SPMR = 1.47	P 0.03		

Table A1. Summary of Epidemiology Studies

Citation	Industry	Study design	Pop. Size	Outcome	Exposure	Exposure Groups	Exposure Levels	# Cases	Risk Estimate	Lower 95%[a] CI	Upper 95%[a] CI	Comments (focus on potential causes of bias and/or confounding
Ker et al. 2021	Office workers at a telecommunication company	cohort	10,229 workers compared to the general population of Taiwan	All cancer mortality	Mixed acids (sulfuric acid, hydrochloric acid, nitric acid)	All workers compared to the general population	Dose not quantified	Lip, oral cavity, pharynx: 5	SMR = 0.50	P 0.13		All employees had employer-provided medical insurance and it is possible cancer in this population was more likely to receive a diagnosis than cancer in the general population- cancer in the general population may be underestimated by comparison
									SPMR = 1.18	P 0.83		
								Combined nasopharynx: 5	SMR = 1.05	P >0.99		Significant results are only seen for all cancers combined and not for any specific sites.
									SPMR = 2.49	P 0.11		

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Citation	**Industry**	**Study design**	**Pop. Size**	**Outcome**	**Exposure**	**Exposure Groups**	**Exposure Levels**	**# Cases**	**Risk Estimate**	**Lower 95%[a] CI**	**Upper 95%[a] CI**	**Comments (focus on potential causes of bias and/or confounding**
Ker et al. 2021	Office workers at a telecommunication company	cohort	10,229 workers compared to the general population of Taiwan	All cancer mortality	Mixed acids (sulfuric acid, hydrochloric acid, nitric acid)	All workers compared to the general population	Dose not quantified	Combined digestive system: 23	SMR = 0.69	P 0.07		No measurements of exposure- all employees are assumed to have had the same exposure and there is no information on intensity or duration
								Combined digestive system: 23	SPMR = 1.48	P 0.09		No measurements of exposure- all employees are assumed to have had the same exposure and there is no information on intensity or duration
								Stomach: 7	SMR = 1.64	P 0.28		Few cancer cases observed, limits statistical power
									SPMR = 3.24	P 0.01		

Table A1. Summary of Epidemiology Studies												
Citation	**Industry**	**Study design**	**Pop. Size**	**Outcome**	**Exposure**	**Exposure Groups**	**Exposure Levels**	**# Cases**	**Risk Estimate**	**Lower 95%[a] CI**	**Upper 95%[a] CI**	**Comments (focus on potential causes of bias and/or confounding**
Ker et al. 2021	Office workers at a telecommunication company	cohort	10,229 workers compared to the general population of Taiwan	All cancer mortality	Mixed acids (sulfuric acid, hydrochloric acid, nitric acid)	All workers compared to the general population	Dose not quantified	Colon 2	SMR = 0.80	P >0.99		This article is more concerned with demonstrating the differences between an SMR and an SPMR and less concerned with investigating a specific health effect.
									SPMR = 1.66	P 0.68		
								Rectum: 2	SMR = 1.24	P 0.96		
									SPMR = 2.59	P 0.36		
								Liver: 10	SMR = 0.49	P 0.02		
									SPMR = 1.07	P 0.87		
								Gallbladder: 1	SMR = 1.33	P >0.99		
									SPMR = 2.79	P 0.60		
								Pancreas: 1	SMR = 0.77	P >0.99		
									SPMR = 0.57	P 0.94		

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Ker et al. 2021	Office workers at a telecommunication company	cohort	10,229 workers compared to the general population of Taiwan	All cancer mortality	Mixed acids (sulfuric acid, hydrochloric acid, nitric acid)	All workers compared to the general population	Dose not quantified	Combined respiratory system: 7	SMR = 0.76	P 0.59		
									SPMR = 1.46	P 0.41		
								Cervix: 1	SMR = 5.77	P 0.32		
									SPMR = 10.79	P 0.18		
								Urinary: 1	SMR = 1.61	P 0.92		
									SPMR = 3.26	P 0.53		
								Thyroid: 1	SMR = 9.49	P 0.20		
									SPMR = 19.38	P 0.10		
								Non-pancreatic endocrine system: 1	SMR = 9.92	P 0.19		
Ker et al. 2021	Office workers at	cohort	10,229 workers	All cancer mortality	Mixed acids	All workers compared	Dose not quantified	Non-pancreatic	SPMR = 21.87	P 0.09		

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Citation	**Industry**	**Study design**	**Pop. Size**	**Outcome**	**Exposure**	**Exposure Groups**	**Exposure Levels**	**# Cases**	**Risk Estimate**	**Lower 95%[a] CI**	**Upper 95%[a] CI**	**Comments (focus on potential causes of bias and/or confounding**
	a telecommunication company		compared to the general population of Taiwan		(sulfuric acid, hydrochloric acid, nitric acid)	to the general population		endocrine system: 1				
								Unspecified site: 1	SMR = 9.77	P 0.19		
									SPMR = 22.79	P 0.09		
								Myeloid leukemia: 1	SMR = 1.16	P >0.99		
									SPMR = 2.67	P 0.62		
								Unspecified leukemia: 1	SMR = 1.44	P >0.99		
									SPMR = 3.33	P 0.52		
Moayadi-Nia et al. 2022	Population-based (residents of Quebec, Canada)	Case-cohort	1179	Lung cancer incidence	Hydrogen chloride	Exposed, low certainty (0-25% chance of exposure)	Dose not quantified.	81	OR = 0.75	0.51	1.09	Only the higher certainty category shows significant results but it is driven by a small number of cases.

Moayadi-Nia et al. 2022	Population-based (residents of Quebec, Canada)	Case-cohort	1179	Lung cancer incidence	Hydrogen chloride	Exposed, high certainty (>=25% chance of exposure)	Dose not quantified.	5	OR = 3.79	1.07	13.41	No information on intensity or duration of exposure, or other quantitative measurements Linking in the job exposure matrix is described as "low resolution" and could only connect subjects to broad categories rather than specific jobs. The higher exposure group includes individuals with exposure certainty as low as 25%- potential for misclassification across all groups. Does not appear to have controlled for co-exposures of interest. Does not control for indoor or outdoor air pollution

Table A1. Summary of Epidemiology Studies

Citation	Industry	Study design	Pop. Size	Outcome	Exposure	Exposure Groups	Exposure Levels	# Cases	Risk Estimate	Lower 95%[a] CI	Upper 95%[a] CI	Comments (focus on potential causes of bias and/or confounding
Moayadi-Nia et al. 2022	Population-based (residents of Quebec, Canada)	Case-cohort	1179	Lung cancer incidence	Hydrogen chloride	Exposed, low certainty (5-25% chance of exposure)	Dose not quantified.	13	OR = 1.08	0.56	2.05	Controls for past exposure to known lung carcinogens (such as asbestos) as a binary variable-does not take into account intensity of past exposure or if the subject was exposed to multiple known carcinogens
						Exposed, high certainty (>=25% chance of exposure)		5	OR = 4.67	1.34	16.2	
Soskolne et al. 2011	Male and females in Toronto, CA	Population based case-control	772	Lung cancer	10 acid categories including hydro-chloric acid	Any exposure to HCl	Dose not quantified.	178 cases; 167 controls	OR: 0.98	0.71	1.35	Did not account for family history as a confounder.
						Low exposure to HCl	Dose not quantified.	95 cases; 106 controls	OR: 0.80	0.53	1.22	Exposure classification
						High exposure to HCl	Dose not quantified.	83 cases; 61 controls	OR: 1.24	0.79	1.96	
Siemiatycki 1991	Population-based (residents of	Case control	3730 cancer patients	11 cancers	Hydrogen chloride	Any exposure	Dose not quantified.	Esophagus (8)	OR: 1.2	0.6*	2.3*	French Canadian population to avoid confounding from ethnicity

Table A1. Summary of Epidemiology Studies												
Citation	**Industry**	**Study design**	**Pop. Size**	**Outcome**	**Exposure**	**Exposure Groups**	**Exposure Levels**	**# Cases**	**Risk Estimate**	**Lower 95%[a] CI**	**Upper 95%[a] CI**	**Comments (focus on potential causes of bias and/or confounding**
	Montreal, Canada)							Stomach (18)	OR: 1.1	0.7*	1.6*	
								Colon (28)	OR: 0.9	0.6*	1.2*	Did not carry out the analyses to rule out confounding co-exposures or occupational exposures associated with certain cancer types
								Rectum (21)	OR: 1.1	0.7*	1.6*	
								Pancreas (9)	OR: 1.2	0.7*	2.2*	Potential for exposure misclassification based on interviews
								Lung (59)	OR: 0.9	0.7*	1.2*	
								Prostate (25)	OR: 0.8	0.5*	1.2*	
								Bladder (34)	OR: 1.1	0.8*	1.5*	
								Kidney (12)	OR: 1.0	0.6*	1.6*	
Siemiatycki 1991	Population-based (residents of	Case control	3730 cancer patients	11 cancers	Hydrogen chloride	Any exposure	Dose not quantified.	Skin melanoma (5)b	OR: 0.7	0.3*	1.6*	
								NHL (22)	OR: 1.5	1.0*	2.2*	

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	Montreal, Canada)					Substantial exposure	Dose not quantified.	Esophagus (2)	OR: 1.1	0.3*	3.8*	
								Stomach (5)	OR: 0.9	0.4*	1.9*	
								Colon (15)	OR: 1.5	0.9*	2.4*	
								Rectum (6)	OR: 0.9	0.4*	2.0*	
								Pancreas (2)	OR: 0.7	0.2*	2.4*	
								Lung (20)	OR: 0.9	0.5*	1.5*	
								Prostate (11)	OR: 1.1	0.6*	2.0*	
								Bladder (13)	OR: 1.0	0.6*	1.8*	
								Kidney (3)	OR: 0.7	0.3*	1.8*	
								Skin melanoma (1)	OR: 0.4	0.1*	2.3*	
								NHL (6)	OR: 1.1	0.5*	2.3*	
Siemiatycki 1991	Population-based (residents of Montreal, Canada)	Case control	3730 cancer patients	11 cancers	Hydrogen chloride	Subset analysis for these three cancer sites: Any exposure	Dose not quantified.	Rectum (18)	OR: 1.9	1.1*	3.4*	
								Lung-oat cell (19)	OR: 1.6	1.0*	2.6*	
								NHL (18)	OR: 1.6	1.0*	2.5*	

Table A1. Summary of Epidemiology Studies												
Citation	**Industry**	**Study design**	**Pop. Size**	**Outcome**	**Exposure**	**Exposure Groups**	**Exposure Levels**	**# Cases**	**Risk Estimate**	**Lower 95%[a] CI**	**Upper 95%[a] CI**	**Comments (focus on potential causes of bias and/or confounding**
						Subset analysis for these three cancer sites: Substantial exposure	Dose not quantified.	Rectum (5)	OR: 1.5	0.5*	3.8*	
								Lung-oat cell (8)	OR: 2.1	1.0*	4.5*	
								NHL (6)	OR: 1.5	0.7*	3.2*	
Fritschi and Siemiatycki 1996a	Population-based (residents of Montreal, Canada)	Case control	3730 cancer patients	Lymphoma and myeloma	Hydrogen chloride	Substantial exposure (those defined as probable or definite exposure and that had more than 5 years of exposure at a high frequency concentration)	Dose not quantified.	6	1.3	0.5	3.4	French Canadian population to avoid confounding from ethnicity. Not adjusted for other occupational exposures
						Non-substantial exposure (others not	Dose not quantified.	16	1.6	0.9	3	Potential for exposure misclassification based on interviews

Table A1. Summary of Epidemiology Studies

Citation	Industry	Study design	Pop. Size	Outcome	Exposure	Exposure Groups	Exposure Levels	# Cases	Risk Estimate	Lower 95%[a] CI	Upper 95%[a] CI	Comments (focus on potential causes of bias and/or confounding
						included above)						
Farrow et al. 1989	Population-based (Wales, UK)	Pilot case-control study	63	Myelodysplastic syndrome (MDS)	HCl exposure	Any HCl exposure	Dose not quantified.	5 exposed cases	--	--	--	Study did not report an odds ratio. This was just an analysis to determine whether exposure was different between cases and controls based on p-value.
								4 exposed controls				The number of cases and controls were small and equal in the two groups. Exposure measurements were not available

[a] 95% CI unless otherwise noted.

[b] An additional set of analyses was conducted (Fritschi and Siemiatycki 1996b) to expand on results and adjust for additional confounders. Authors did not present risk results for HCl and melanoma, however it was noted that HCl was not associated with melanoma in any multivariate analyses conducted.

*90% Confidence Interval

Highlighted rows indicate the same cohort

Abbreviations: CI = confidence interval; HCl = hydrochloric acid; NHL = non-Hodgkin's lymphoma OR = odds ratio; ppm = parts per million; RR = relative risk; SIR = Standardized Infection Ratio; SMR = standardized mortality ratio; UADC = upper aerodigestive cancer; yr = year

Table A2 – Summary of Toxicology Studies								
Citation	**Animal species**	**Exposure Route**	**Exposure Duration**	**Exposure levels**	**NOAEL**	**LOAEL**	**Endpoint**	**Comments**
Sellakumar et al. 1985 and Albert et al. 1982	Rat	inhalation	6 hours/day, 5 days/week, for 122 weeks	0 or 10 ppm (14.9 mg/m^3)	None	10 ppm	Hyperplasia in the larynx and trachea. No malignant tumors reported.	Albert et al. 1982 reports interim results at 84 weeks and Sellakumar et al. 1985 reports full study results.
Narat 1925	Mice	dermal	Every 1-2 days until skin lesions occurred then weekly for 4-6 weeks; total exposure duration was 25-46 weeks.	unknown volume of solutions containing 3-5% HCl	NA	NA	No malignant tumors reported	OECD concluded the study was not appropriate for the assessment of carcinogenicity due to lack of negative controls and brief exposure period.
Dyer et al. 1946	Mice	oral	Unknown	0 or 1-2.5 moles per liter HCl	NA	NA	No cancer or pre-cancerous lesions observed in the stomach of animals	OECD concluded the study was not appropriate for the assessment of carcinogenicity due to lack of inconsistent strain, short exposure duration, and single exposure concentration.

NOAEL, no observed adverse effect level; LOAEL, lowest observed adverse effect; NA – Not applicable

APPENDIX B
RELEVANT REFERENCE LIST FROM 2022 RAMBOLL REPORT

Relevant Reference List

Reviews and Assessments

International Agency for Research on Cancer (IARC). 1992. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Volume 54: Occupational Exposures to Mists and Vapours from Strong Inorganic Acids; and Other Industrial Chemicals. World Health Organization, Lyon.

The International Programme on Chemical Safety (IPCS). 1982. Environmental Health Criteria 21: Chlorine and Hydrogen Chloride. World Health Organization, Geneva, 1982.

Organisation for Economic Co-operation and Development (OECD). 2002. Screening Information Dataset (SIDS) Initial Assessment Profile for SIAM 15: Hydrogen Chloride. Downloaded from https://hpvchemicals.oecd.org/UI/handler.axd?id=e1fe4ef3-e3d4-4f3d-9a58-8bf2f8296b61. Accessed February 10, 2021.

US EPA 2005. Guidelines for Carcinogen Risk Assessment. US Environmental Protection Agency, Washington DC Downloaded from https://www.epa.gov/sites/production/files/2013-09/documents/cancer_guidelines_final_3-25-05.pdf

Publications identified by IARC (9)

Beaumont JJ, Leveton J, Knox K, Bloom T, McQuiston T, Young M, Goldsmith R, Steenland NK, Brown DP, Halperin WE. 1987. Lung cancer mortality in workers exposed to sulfuric acid mist and other acid mists. Journal of the National Cancer Institute, 79(5): 911-921.

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Siemiatycki J. 1991. Risk Factors for Cancer in the Workplace. Boca Raton, FL. CRC Press.

Steenland K, Schnorr T, Beaumont J, Halperin W, Bloom T. 1988. Incidence of laryngeal cancer and exposure to acid mists. Occupational and Environmental Medicine, 45(11): 766-776.

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Albert RE, Sellakumar AR, Laskin S, Kuschner M, Nelson N, Snyder CA. 1982. Gaseous formaldehyde and hydrogen chloride induction of nasal cancer in the rat. Journal of the National Cancer Institute, 68(4): 597-603.

[1]ANON, ed. 1987. Pestic. Toxic. Chem. News., 15(43): 6.

[1] Cannot obtain; not included in the counts

Beaumont JJ, Leveton J, Knox K, Bloom T, McQuiston T, Young M, Goldsmith R, Steenland NK, Brown DP, Halperin WE. 1987. Lung cancer mortality in workers exposed to sulfuric acid mist and other acid mists. Journal of the National Cancer Institute, 79(5): 911-921.

Bond GG, Cook RR, Wight PC, Flores GH. 1983. A case-control study of brain tumor mortality at a Texas Chemical plant. Journal of Occupational Medicine, 25(5): 377-386.

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Farrow A, Jacobs A, West RR. 1989. Myelodysplasia, chemical exposure, and other environmental factors. Leukemia, 3(1): 33-35.

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Fritschi and Siemiatycki 1996a. Lymphoma, myeloma and occupation: Results of a case-control study. International Journal of Cancer, 67(4): 498-503.

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International Agency for Research on Cancer (IARC). 1992. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Volume 54: Occupational Exposures to Mists and Vapours from Strong Inorganic Acids; and Other Industrial Chemicals. World Health Organization, Lyon.

Soskolne CL, Jhangri GS, Scott HM, Brenner DR, Siemiatycki J, Lakhani R, Gérin M, Dewar R, Miller AB, Risch HA. 2011. A population-based case-control study of occupational exposure to acids and the risk of lung cancer: evidence for specificity of association. International Journal of Occupational and Environmental Health, 17(1): 1-8.

[3]Tsai WT. 2016. Current status of air toxics management and its strategies for controlling emissions in Taiwan. Toxics, 4(2): 8-15.

[3] Review; no new data