Strong inorganic acid mists containing sulphuric acid

Gezondheidsraad
Health Council of the Netherlands

Aan de Staatssecretaris van Sociale Zaken en Werkgelegenheid
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Onderwerp : Aanbieding advies 'zwavelzuurnevels'
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Mijnheer de Staatssecretaris,

Bij brief van 3 december 1993, nr DGV/BMO-U-932542, verzocht de Staatssecretaris van Welzijn, Volksgezondheid en Cultuur namens de Minister van Sociale Zaken en Werkgelegenheid de Gezondheidsraad om gezondheidskundige advieswaarden af te leiden ten behoeve van de bescherming van beroepsmatig aan stoffen blootgestelde personen.

In dat kader bied ik u hierbij een advies aan over de kankerverwekkende eigenschappen van sterke anorganische zure nevels die zwavelzuur bevatten. Dit advies is opgesteld door de Commissie WGD van de Gezondheidsraad en beoordeeld door de Beraadsgroep Gezondheid en Omgeving.

Ik heb dit advies vandaag ter kennisname toegezonden aan de Minister van Volksgezondheid, Welzijn en Sport en de Minister van Volkshuisvesting, Ruimtelijke Ordening en Milieu.

Hoogachtend,

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Strong inorganic acid mists containing sulphuric acid

Evaluation of the carcinogenicity and genotoxicity

Dutch Expert Committee on Occupational Standards,
a committee of the Health Council of the Netherlands

to:

the Minister and State Secretary of Social Affairs and Employment

No. 2003/07OSH, The Hague, April 15, 2003

The Health Council of the Netherlands, established in 1902, is an independent scientific advisory body. Its remit is "to advise the government and Parliament on the current level of knowledge with respect to public health issues..." (Section 21, Health Act).

The Health Council receives most requests for advice from the Ministers of Health, Welfare & Sport, Housing, Spatial Planning & the Environment, Social Affairs & Employment, and Agriculture, Nature Preservation & Fisheries. The Council can publish advisory reports on its own initiative. It usually does this in order to ask attention for developments or trends that are thought to be relevant to government policy.

Most Health Council reports are prepared by multidisciplinary committees of Dutch or, sometimes, foreign experts, appointed in a personal capacity. The reports are available to the public.

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Inhoud

Samenvatting

Op verzoek van de Minister van Sociale Zaken en Werkgelegenheid beoordeelt de Gezondheidsraad de kankerverwekkende eigenschappen van stoffen waaraan mensen tijdens de beroepsuitoefening kunnen worden blootgesteld. In het voorliggende rapport neemt de Commissie WGD van de Raad, die deze beoordelingen verricht, anorganische zure nevels die zwavelzuur bevatten onder de loep. De commissie heeft haar oordeel gegoten in door de Europese Unie aangegeven termen.

De commissie concludeert dat anorganische zure nevels die zwavelzuur bevatten, kankerverwekkend zijn voor de mens (vergelijkbaar met EU categorie 1). Deze kankerverwekkende zure nevels zijn volgens de commissie niet-stochastisch genotoxisch*.

* Dit betekent dat een gezondheidskundige advieswaarde kan worden afgeleid, gebruikmakend van een methode die rekening houdt met een drempelwaarde. Een dergelijke advieswaarde wordt niet afgeleid voor genotoxische kankerverwekkende stoffen. In dit laatste geval schat de commissie het extra kankerrisico middels een lineaire extrapolatiemethode.

Executive summary

At request of the Minister of Social Affairs and Employment, the Health Council of the Netherlands evaluates the carcinogenic properties of substances at the workplace and proposes a classification with reference to the EU-directive. The Dutch Expert Committee on Occupational Standards performs this evaluation. The present report contains an evaluation by the committee on the carcinogenicity of strong inorganic acid mists containing sulphuric acid.

The committee concludes that strong inorganic acid mists containing sulphuric acid are known to be carcinogenic to humans (comparable with EU category 1). These inorganic acid mists act by a non-stochastic genotoxic mechanism*.

* This means that an occupational exposure limit can be derived using a threshold model. Such an exposure limit cannot be derived for genotoxic carcinogens. In the latter case, the committee estimates additional lifetime cancer risks using a linear extrapolation model as a default method.

Chapter 1

Scope

1.1 Background

In the Netherlands a special policy is in force with respect to occupational use and exposure to carcinogenic substances. The Minister of Social Affairs and Employment has asked the Health Council of the Netherlands to study the carcinogenic properties of substances and to propose a classification with reference to an EU-directive (annex A and F). This task is carried out by the Council's Dutch Expert Committee on Occupational Standards, hereafter called the committee.

The evaluation of the carcinogenicity of a substance is based on IARC* evaluations. The original publications are not reviewed and evaluated in the text of the report, but the overall conclusion of the IARC on the carcinogenic properties is included (annex D).

In addition to classifying substances with respect to their possible carcinogenicity according to the EU Guidelines, the committee also assesses the genotoxic properties of the substances in question. The committee expresses its conclusions in the form of standard sentences (annex E).

1.2 Committee and procedures

The present report contains an evaluation by the committee of the carcinogenicity of strong inorganic acid mists containing sulphuric acid. The members of the committee

* International Agency for Research on Cancer.

are listed in annex B. The committee consulted two additional experts, Prof dr G Mohn and dr M Nivard, both working at Department of Radiation Genetics and Chemical Mutagenesis of the University of Leiden, with respect to the genotoxic data. The first draft of this report was prepared by M Willems, from the TNO Nutrition and Food Research in Zeist, by contract with the Ministry of Social Affairs and Employment.

In 2000, the President of the Health Council released a draft of the report for public review. The individuals and organisations that commented on the draft are listed in annex C. The committee has taken these comments into account in deciding on the final version of the report.

1.3 Data

The evaluation of the carcinogenicity of strong inorganic acid mists containing sulphuric acid has been based on an IARC evaluation (IARC92). Where relevant, the original publications cited by IARC were reviewed and evaluated in the text.

In addition, literature has been retrieved from the CD ROMs of Toxline, and Medline, covering the period 1985 to December 2002.

Chapter 2

Strong inorganic acid mists containing sulphuric acid

2.1 Introduction

Chemical name	:	sulphuric acid
CAS registry number	:	7664-93-9
EINECS number	:	231-639-5
Synonyms	:	oil of vitriol, sulfuric acid, spirit of sulphur, battery acid, dipping acid, electrolyte acid, fertilizer acid, hydrogen sulphate, matting acid, Nordhausen acid.
Appearance	:	colourless (pure) to dark brown, oily, hygroscopic liquid, with no odour.
Occurrence	:	sulphuric acid is a liquid that is present in air primarily as aerosol (mists) under normal working conditions; the compound may also be present as vapour.
Use	:	as a raw material in the manufacture of synthetic fertilizers, nitrate explosives, dyes, other acids, parchment paper, glue, purification of petroleum, and pickling of metal. It is used in refining of mineral and vegetable oils, as an electrolyte of lead-acid storage batteries, and in laboratories for qualitative and quantitative analyses.
Chemical formula	:	H_2SO_4
Molecular weight	:	98.08 g/mol
Boiling point	:	315-338 ^{o}C; decomposes at 340 ^{o}C into sulphur trioxide and water.
Melting point	:	10 ^{o}C (anhydrous acid)
Vapour pressure	:	< 0.04 kPa at 20 ^{o}C; 0.13 kPa at 146 ^{o}C
Vapour density (air = 1)	:	3.4
Solubility	:	miscible with water and alcohol

Conversion factor	:	1 ppm = 2.7 mg/m^3 1 mg/m^3 = 0.37 ppm
EU Classification (100% solution)	C:	corrosive substance.
	R35:	causes severe burns.
	S1/2:	keep locked up and out of reach of children.
	S26:	in case of contact with eyes rinse immediately with plenty of water and seek medical advice.
	S30:	never add water to this product.
	S45:	In case of accident or if you feel unwell, seek medical advice immediately (*show the label where possible*).

See Kri93, Mer89, IPC00

2.2 IARC conclusion

In 1992, IARC concluded that there was sufficient evidence that occupational exposure to strong inorganic acid mists containing sulphuric acid is *carcinogenic to humans* and classified the compound in Group 1 (IARC92). The conclusion of IARC was solely based on human data.

2.3 Human data

2.3.1 IARC data

IARC evaluated numerous epidemiological studies. Only those studies, which are relevant for the present evaluation, are described below. In all these studies, mists of sulphuric acid were the predominant exposure, but in none of these studies atmospheric levels were presented.

In a cohort study of US chemical workers in an isopropanol manufacture, using the strong-acid method with sulphuric acid, a highly significant excess risk for cancer of the paranasal sinuses was observed, when compared to US proportional mortality rates (Weil *et al*., 1952).

In one large cohort study, undertaken by the US National Institute for Occupational Safety and Health (NIOSH), Beaumont *et al*. (1987)*, Steenland and Beaumont (1989)* and Steenland *et al*. (1988)* reported on the mortality patterns of 1,165 male steelworkers exposed to sulphuric acid and other acid mists in three steel-pickling operations. Of those workers, 722 had been exposed only to sulphuric acid. The

* See IARC evaluation from 1992 (IARC92).

investigators found a highly significant excess risk for laryngeal and lung cancer. The risk calculations were adjusted for smoking.

Soskolne *et al*. (1984)* performed a nested case-control study of workers at a refinery and chemical plant in the United States. Fifty incident cases were compared with 175 matched controls. The odds ratios (OR) for cancer, especially laryngeal cancer, were increased for workers with exposure to sulphuric acid compared with controls (laryngeal cancer: moderate exposure level, OR 4.6 (95% CI 0.83-25.35); high exposure level, OR 13.4 (95% CI 2.08-85.99). The ratios were adjusted for the effects of tobacco, previous history of ear, nose and throat diseases and alcoholism.

The same investigators performed a population-based case-control study in Canada (Soskolne *et al*., 1992)*, in which 183 incident males cases of laryngeal cancer and 183 matched control cases were compared for exposure to sulphuric acid. Retrospective assessment of exposure to sulphuric acid was based on job period, occupation, job title, and employer for each job held by a subject. Omitting exposures in the five years prior to diagnosis, the investigators found a significant dose-response effect, with an odds ratio of 2.52 (95% CI 0.80-7.91) for short duration-low exposure through 6.87 (95% CI 1.00-47.06) for long duration-higher exposure. The results were controlled for tobacco and alcohol use.

Siemiatycki (1991)* performed another population-based case-control study and included cases of eleven types of histologically confirmed cancer, involving 3,730 cancer patients and 533 population controls. Thirteen percent of the entire study population were occupationally exposed to inorganic acid solutions (hydrochloric, sulphuric and nitric acids). In this group, there were two significant associations: a relative risk (RR) of 2.0 for oat-cell carcinoma of the lung (33 cases; 90% CI 1.3-2.9) and a RR of 1.7 for cancer of the kidney (32 cases; 90% CI 1.2-2.4). Some evidence for an association with exposure to sulphuric acid was found for lung cancer. No excess cancer of oesophagus, stomach, colon, rectum, pancreas, prostate or bladder, skin melanoma or non-Hodgkin's lymphoma were found.

IARC considered the studies in workers involved in the manufacture of phosphate fertilizers, lead batteries, sulphuric acid, and nitric acid to be less informative (IARC92, Ano92).

2.3.2 *Additional data*

After the IARC evaluation two case studies have been published. Houghton and White (Hou94) reported of a 65-year-old electric forklift truck driver, who developed an invasive squamous cell carcinoma in the left vocal fold in the larynx. The man did not smoke, drank alcohol only occasionally and had not been exposed to asbestos.

According to the authors, the cancer was caused to exposure to sulphuric acid fumes emanating from poorly maintained lead batteries above the driver's seat.

In another case study, a cluster is presented of three patients with nasopharyngeal carcinoma. All three patients worked in the same building of a telecommunications conveyance station in southern Taiwan with long-term exposure to sulphuric acid vapour concentrations as high as 0.18 mg/m^3. The patients had spent more time in the room where the sulphuric acid concentration was the highest compared with 19 healthy workers, working elsewhere in the same building. The authors claimed that the patients were not exposed to any other known environmental chemicals. Therefore, the authors suggested that exposure to sulphuric acid vapour may be highly associated with the development of nasopharyngeal carcinomas (Ho99).

In 1996, Coggon *et al*. (Cog96) presented the results of a cohort and a nested case-control study of upper aerodigestive tumours in men employed since 1950 at two battery plants and two steel works in the United Kingdom. The cohort included 2,678 men with definite exposure to acid mists (mainly sulphuric acid, but also hydrochloric acid), 367 with possible exposure and 1,356 who were not exposed. Mortality was compared with that of the national population. Cases of upper aerodigestive cancer were identified from death certificates and cancer registration. At the end of 1993, 93% of the men were traced, including 1,277 who had died. Among the men definitely exposed to acid mists, overall mortality was less than in the national population (SMR (standardised mortality ratio) 0.92, 95% CI 0.85-0.98), as was mortality from all cancers (SMR 0.92, 95% CI 0.79-1.05) and specifically from laryngeal cancer (SMR 0.48, 95% CI 0.01-2.70). A total of fifteen fatal cases of upper aerodigestive cancer were identified during the follow-up. When these cases were compared with controls, the excess risk was moderately increased in those who had worked for at least five years in jobs with exposure to acid mists (sulphuric acid or hydrochloric acid) (odds ratio 2.0, 95% CI 0.4-10). In 1997, Hathaway (Hat97) commented on the way the data in the previous study were presented, and concluded that the data were of limited use and produced no evidence that sulphuric acid mists may cause upper aerodigestive cancer.

In 1997, Steenland (Ste97) presented an extension of a previous follow-up study (see IARC92: publications of Steenland and/or Beaumont) for ten years (up to the end of October 1994) of a cohort of men exposed to acid mists in the steel industry in the US. The cohort consisted of 1,013 men with an average exposure of 9.2 years and with the average years of first and last exposure being 1949 and 1960, respectively. The primary exposure was to sulphuric acid mists although part of the cohort was exposed to other acid mists. Data were obtained from mailed questionnaires and telephone interviews. Fourteen cases of laryngeal cancer (six of them were still alive as of the follow-up date) were observed in the cohort while 6.4 were expected (based on US rates and adjustment

for tobacco and alcohol consumption). Except for one whose smoking status was unknown, all of these cases were current or former smokers. Seven out of these fourteen cases were daily exposed to sulphuric acid only, four to sulphuric and other acids, and three to other acids only; ten cases were exposed to sulphuric acid (Ste97).

Cocco *et al*. (Coc99) conducted a case-control study, based on the death certificates concerning gastric cancer of several million deaths in 24 states of the United States. No excess risk was associated with sulphuric acid exposure at the workplace (odds ratio 0.99 (95% CI 0.95-1.03), adjusted for all other exposures (inorganic dust, metals and nitrosamines)) and by marital and socio-economic status, and metropolitan residence).

In a review considering essentially the same data base as presented by IARC, Sathiakumar *et al*. (Sat97) concluded that despite several limitations (imprecise results, not adjusted for confounding factors as smoking, alcohol, and other chemical compounds) the results indicate, in aggregate, a moderate association between inorganic mists containing sulphuric acid and larynx cancer and that the data suggest a dose-response relationship. The biological plausibility and the possible mechanism of action could not be ascertained. Furthermore, the authors concluded that there was limited evidence to support a causal relationship between exposure to inorganic mists containing sulphuric acid and lung cancer. Also the data were inadequate to draw conclusions regarding the association between exposure to these mists and nasal cancer.

Greim and Reuter (Gre01) used the available carcinogenicity data to propose a new classification of carcinogenic chemicals by the German MAK commission. The authors assume that the laryngeal cancer seen in man is a result of severe local irritation caused by high concentrations of sulphuric acid aerosols and the associated increase in regenerative cell proliferation. Therefore, sulphuric acid is classified in Category 4 (Substances with carcinogenic potential for which genotoxicity plays no or at most a minor part. No significant contribution to human cancer risk is expected provided the MAK and BAT* values are observed).

2.4 Animal data

2.4.1 IARC data

No data were available to the IARC Working Group.

* MAK, Maximale Arbeitsplatz-Konzentration (maximum workplace concentration); BAT, Biologischer Arbeitsstoff-Toleranz-Wert (biological tolerance value for occupational exposures).

2.4.2 *Additional data*

In the review of Swenberg and Beauchamp a large unpublished initiation-promotion and cocarcinogenesis study by the US Environmental Protection Agency (Laskin and Sellakumar, 1978, see Swe97) was discussed. Male Syrian golden hamsters (n= 60/ group) were exposed to 100 mg/m^3 sulphuric acid mist by inhalation, for 6 hours a day and 5 days a week for the animal's lifespan. The groups were also exposed to a single (10 or 40 mg) or multiple (1 or 4 mg, 15 times) tracheal intubations of benzo(a)pyrene (BP) before or at the same time with the exposure of sulphuric acid. Control groups included air and colony control, a group exposed to sulphuric acid only, and groups treated with BP only. Laryngeal and tracheal epithelial hyperplasia was increased in hamsters exposed to sulphuric acid with and without BP intubation in the initiation-promotion experiment. No consistent differences associated with exposure to sulphuric acid were observed in the cocarcinogenesis experiment. There were no quantitative data on mortality or actual lifespan presented. However, in the initiation-promotion experiment, there were no obvious differences between the experimental groups. For the cocarcinogenesis experiment, it was reported that cumulative mortality was highest in the groups receiving BP with or without sulphuric acid. No data on body weight (gain) were presented. No neoplasms of the respiratory tract were found in any of the experimental groups exposed to sulphuric acid alone (i.e. in a total of 240 animals).

In the initiation-promotion part of this study, three benign laryngeal and tracheal tumours and two lung carcinomas were found in hamsters intubated once with 40 mg BP while one tracheal polyp was seen in the 40 mg BP plus sulphuric acid group. Following a single intubation with 10 mg BP, there was one hamster with an adenoma and a squamous cell carcinoma of the lung and another with a lung adenocarcinoma, while there was one animal with a lung adenocarcinoma when additionally exposed to sulphuric acid.

In the cocarcinogenesis part, no consistent differences were found in benign or malignant tumours in BP-exposed animals that were associated with sulphuric acid exposure. Multiple intubations of 4 mg BP caused an incidence in neoplasms of 48/60 while an incidence of 43/60 was found in animals receiving the combined BP-sulphuric acid treatment. In these groups, numbers of benign tumours were equal, but there were more carcinomas in the group receiving BP only. Multiple treatments with 1 mg BP resulted in neoplasms in 7/60 animals. A similar treatment combined with exposure to sulphuric acid resulted in a tumour incidence of 15/60. Seven additional benign tumours accounted for this increase in tumours in the sulphuric acid-exposed group. There were no differences in the time at which the tumours appeared in the two groups. Swenberg and Beauchamp concluded that this study, conducted at high exposure levels of

sulphuric acid, did not show any evidence for carcinogenic activity and equivocal evidence for cocarcinogenic or promoting activity. The committee noted that in this study no general toxic effects were observed, despite the high exposure to sulphuric acid mist, and concludes that the hamster might be a rather insensitive experimental animal in assessing carcinogenicity.

Ichinose and Sagai (Ich92) reported on the promoting and cocarcinogenic effects of sulphuric acid. Male Wistar rats were given a single intraperitoneal injection of *N-bis*(2-hydroxypropyl)nitrosamine (BHPN) at a dose of 0.5 g/kg body weight, prior to the inhalatory exposure to a mixture of 0.4 ppm nitrogen dioxide and 1 mg/m^3 sulphuric acid for 13 months. Following exposure, the animals were maintained in a clean room for another 11 months. As a result of the mixed exposure (BHPN plus nitrogen dioxide plus sulphuric acid) 3 out of the 36 animals developed lung tumours. No lung tumours occurred in the group exposed to nitrogen dioxide plus sulphuric acid only (n=36) and in the untreated controls (n=35). The numbers of lung tumours did not significantly differ among the groups. The committee is of the opinion that the presented data do not allow a conclusion on the carcinogenic effects of sulphuric acid.

More recently, Uleckiené and Griciuté (Ule97) used Wistar rats and CBAxC57B1 mice of both sexes, to study the carcinogenic effects of sulphuric acid in a long-term study. The rats (n=30/group/sex) were exposed to maximal tolerated doses of sulphuric acid by intratracheal installation (0.3 mL 0.6%, twice a month for 12 months) or by gastric intubation (0.5 mL 0.6%, once a week for life); one untreated group served as control (n=30/sex). Other groups were administered benzo(a)pyrene by intratracheal installation (twice a month for two months, total dose 20 mg) with or without sulphuric acid exposure to determine cocarcinogenesis. Mice (n=22-30/group/sex) received sulphuric acid water solutions by gastric intubation (0.2 mL 0.2%, once a week for life), urethane by intraperitoneal injections (twice a week, 10 injections, total dose 100mg) or a combination of these two compounds; one untreated group served as control (n=30 males and 27 females). The animals were observed for their entire life. Sulphuric acid increased the overall tumour morbidity in rats and mice. The majority of the tumours appeared in organs at the site at which sulphuric acid was installed (intratracheal installation, trachea and lungs; gastric intubation, oesophagus and forestomach) showing that it is a local acting carcinogen. The authors, furthermore, consider sulphuric acid to be a weak chemical carcinogen, because i) tumours that appeared in the respiratory tract were not numerous, ii) there were almost no malignant tumours in the first year of study, and iii) not all differences were statistically significant. The investigators also consider the compound to be a moderate cocarcinogen when administered with benzo(a)pyrene. According to the committee, the data are too limited to make this conclusion. Overall, the committee considers the study of Uleckiené and

Criciuté insufficient for evaluating the carcinogenic activity of sulphuric acid mists, because it does not meet international criteria for assessing carcinogenicity.

Swenberg and Beauchamp (Swe97) presented in their review also the results of a number of studies (using monkeys, dogs, rabbits, guinea pigs) focusing on the toxicity of air pollutants including sulphur dioxide, sulphuric acid, and ozone. Although these studies were concluded to suffer from a number of flaws with respect to duration, number of animals, and organs/tissues examined, they did not show preneoplastic or carcinogenic effects.

In a 28 day sub-acute inhalation study, female Alpk:AP_fSD (Wistar-derived) rats (n=10/group) were exposed to aerosols of sulphuric acid at concentrations of 0 (control), 0.3, 1.38 and 5.5 mg/m^3 for 5 days per week, for a period of either 5 days or 28 days. The major treatment related effect was squamous metaplasia of the larynx. The severity of the metaplasia was related to exposure duration and concentration; at 0.3 mg/m^3 sulphuric acid aerosol only minimal metaplastic change was observed after 28 days in a few animals. No effects were observed in the nasal passage or lungs (Kil02).

Overall, Swenberg and Beauchamp (Swe97) evaluated most of the carcinogenicity studies with animals in great detail. In addition, Greim and Reuter (Gre01) used the available carcinogenicity animal data to propose a new classification of carcinogenic chemicals by the German MAK commission. In both reviews, the authors concluded that all the carcinogenic studies are comprised by inadequate quality control and reporting. Overall, from the literature, it is proposed that sulphuric acid may be a tumour promoter through the mechanism of chronic tissue irritation.

2.5 Mutagenicity and genotoxicity

2.5.1 IARC data

IARC did not find data on the genetic and related effects of exposure to sulphuric acid mists in experimental *in vitro* systems; however, IARC evaluated some studies on the effects of the reduction of pH values (< 7: range between 3 and 6.7) by the strong acid.

Singer and Grunberger (1983)* reported that low pH enhances the level of depurination of isolated DNA.

Low pH did not affect the frequency of point mutations in various bacteria strains, yeast and fungi, but it induced gene conversion in *S. cerevisiae,* chromosomal aberrations in *Vicia faba* root tips and mitotic abnormalities in sea urchin.

Brusick (1986)* and Morita *et al*. (1989)* reported that low pH induced chromosomal aberrations in Chinese hamster ovary cells (pH ≤ 5.5). No chromosomal

* See IARC evaluation from 1992 (IARC92).

effects, however, were observed in rat lymphocytes. Exposure to low pH did not result in mutations in mouse lymphoma L5178Y cells (Cifone *et al*., 1987)*. In all the studies with mammalian cells, the presence of S9 significantly enhanced the effects.

2.5.2 Additional data

Based on the same data as evaluated by IARC, Swenberg and Beauchamp (Swe97) suggest that the most likely mechanisms of carcinogenicity by inorganic acid mists is related to the ability to reduce pH, which influences chromosomal integrity.

Also in a review by Soskolne *et al*. (Sos89), the pH as a modulator of mitotic activity and cell differentiation by sulphuric acid mist exposure was discussed. Based on the available data at that time, the authors expected that a decrease of pH in the extracellular matrix might cause structural/functional alterations in the mitotic apparatus, thus resulting in spindle damage and non-disjunction, and may affect gene expression and alter cell differentiation. They recommended further research to get more insight in the genetic toxicity from acidification.

No additional studies of localized pH or *in vivo* genotoxic effects of strong inorganic acid mists containing sulphuric acid are known to the committee.

2.6 Evaluation

The epidemiological data, evaluated by the committee, showed an association between exposure to strong inorganic acid mists containing sulphuric acid and laryngeal cancer. Life-style factors, such as tobacco and alcohol consumption, and other exposures were, according to the committee, only of minor influence on the association between exposure to strong inorganic acid mists and laryngeal cancer. Also the committee noted that the association with laryngeal cancer was found in various industries and occupations in which workers may be exposed to strong inorganic acid mists containing sulphuric acid. Based on these data, the committee concludes that exposure to strong inorganic acid mists containing sulphuric acid can cause laryngeal cancer.

Data from carcinogenicity studies on sulphuric acid in experimental animals are inadequate. In a large lifetime study in hamsters, the carcinogenicity of 100 mg/m^3 sulphuric acid mist was evaluated, as well as its ability to act as a promoter or co-carcinogen for benzo(a)pyrene. No evidence for carcinogenic potential was shown. Although an increase in papillomas was noticed in the benzo(a)pyrene plus sulphuric acid group, the cocarcinogenic or promoting potential was considered equivocal.

In other animal studies with among others dogs and monkeys, no evidence for carcinogenicity of sulphuric acid was found. These studies suffer, however, from a number of flaws as to duration, number of animals, organs/tissues examined, etcetera.

The committee did not find evidence that strong inorganic acid mists containing sulphuric acid causes mutations in DNA. *In vitro* data do indicate that sulphuric acid mists are clastinogenic.

Based on the *in vitro* mutagenicity and genotoxicity data, the committee considers sulphuric acid mist as a non-stochastic genotoxic agent. Most likely, a reduction of the pH is one of the biological mechanisms, by which strong inorganic acid mists containing sulphuric acid exerts its carcinogenic effect.

2.7 Recommendation for classification

The committee concludes that strong inorganic acid mists containing sulphuric acid are known to be carcinogenic to humans (comparable with EU category 1). The committee is of the opinion that these acid mists act as non-stochastic genotoxic carcinogens.*

* This means that an occupational exposure limit can be derived using a threshold model. Such an exposure limit cannot be derived for genotoxic carcinogens. In the latter case, the committee estimates additional lifetime cancer risks using a linear extrapolation model as a default method.

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A	Request for advice
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Annexes

Annex **A**

Request for advice

In a letter dated October 11, 1993, ref DGA/G/TOS/93/07732A, to, the State Secretary of Welfare, Health and Cultural Affairs, the Minister of Social Affairs and Employment wrote:

Some time ago a policy proposal has been formulated, as part of the simplification of the governmental advisory structure, to improve the integration of the development of recommendations for health based occupation standards and the development of comparable standards for the general population. A consequence of this policy proposal is the initiative to transfer the activities of the Dutch Expert Committee on Occupational Standards (DECOS) to the Health Council. DECOS has been established by ministerial decree of 2 June 1976. Its primary task is to recommend health based occupational exposure limits as the first step in the process of establishing Maximal Accepted Concentrations (MAC-values) for substances at the work place.

In an addendum, the Minister detailed his request to the Health Council as follows:

The Health Council should advice the Minister of Social Affairs and Employment on the hygienic aspects of his policy to protect workers against exposure to chemicals. Primarily, the Council should report on health based recommended exposure limits as a basis for (regulatory) exposure limits for air quality at the work place. This implies:

- A scientific evaluation of all relevant data on the health effects of exposure to substances using a criteria-document that will be made available to the Health Council as part of a specific request for advice. If possible this evaluation should lead to a health based recommended exposure limit, or, in the case of

genotoxic carcinogens, a ‘exposure versus tumour incidence range’ and a calculated concentration in air corresponding with reference tumour incidences of 10^{-4} and 10^{-6} per year.

- The evaluation of documents review the basis of occupational exposure limits that have been recently established in other countries.
- Recommending classifications for substances as part of the occupational hygiene policy of the government. In any case this regards the list of carcinogenic substances, for which the classification criteria of the Directive of the European Communities of 27 June 1967 (67/548/EEG) are used.
- Reporting on other subjects that will be specified at a later date.

In his letter of 14 December 1993, ref U 6102/WP/MK/459, to the Minister of Social Affairs and Employment the President of the Health Council agreed to establish DECOS as a Committee of the Health Council. The membership of the Committee is given in annex B.

Annex **B**

The committee

- GJ Mulder, *chairman*
  professor of toxicology; Leiden University, Leiden
- RB Beems
  toxicologic pathologist; National Institute of Public Health and the Environment, Bilthoven
- LJNGM Bloemen
  epidemiologist; DOW benelux NV, Terneuzen
- PJ Boogaard
  toxicologist; SHELL International BV, The Hague
- PJ Borm
  toxicologist; Heinrich Heine Universität Düsseldorf (Germany)
- JJAM Brokamp, *advisor*
  Social and Economic Council, The Hague
- DJJ Heederik
  epidemiologist; IRAS, University of Utrecht, Utrecht
- AAJP Mulder, *advisor*
  Ministry of Social Affairs and Employment, The Hague
- TM Pal
  occupational physician; Dutch Centre for Occupational Diseases, Amsterdam
- IM Rietjens
  professor of toxicology; Wageningen University, Wageningen.

- H Roelfzema, *advisor*
  Ministry of Health, Welfare and Sport, The Hague
- T Smid
  occupational hygienist; KLM Health Safety & Environment, Schiphol and professor of working conditions, Free University, Amsterdam
- GMH Swaen
  epidemiologist; Maastricht University, Maastricht
- RA Woutersen
  toxicologic pathologist; TNO Nutrition and Food Research, Zeist
- P Wulp
  occupational physician; Labour Inspectorate, Groningen
- ASAM van der Burght, *scientific secretary*
  Health Council of the Netherlands, The Hague
- JM Rijnkels, *scientific secretary*
  Health Council of the Netherlands, The Hague

The committee consulted two additional experts, Prof dr G Mohn and dr M Nivard, both working at Department of Radiation Genetics and Chemical Mutagenesis of the University of Leiden, with respect to the genotoxic data.

The first draft of the present advisory report was prepared by MI Willems, from the Department of Occupational Toxicology of the TNO Nutrition and Food Research, by contract with the Ministry of Social Affairs and Employment.

Secretarial assistance was provided by mrs R Aksel-Gauri.
Lay-out: mrs J van Kan.

Annex C

Comments on the public review draft

A draft of the present report was released in 2000 for public review. The following organisations and persons have commented on the draft document:

- Mr A Aalto, Ministry of Social Affairs and Health, Finland;
- Mr C Braun, Akzo Nobel, The Netherlands;
- Mr T Fry, Health and Safety Executive, United kingdom.

Annex **D**

IARC Monograph

Occupational exposures to mists and vapours from strong organic acids and other industrial chemicals (Volume 54, 1992)

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Strong inorganic acids may be present in the work environment as mists, vapours or gases. The most prevalent acids are sulfuric, hydrochloric, nitric and phosphoric acids, which may be present in a wide variety of industries, including the extraction, fabrication and finishing of metal, fertilizer production, battery manufacture and various segments of the petroleum, chemical and petrochemical industries. Millions of workers worldwide are estimated to be potentially exposed to these acids.

Sulfuric acid is the most widely used of the strong inorganic acids. Average exposures to sulfuric acid mists in pickling, electroplating and other acid treatment of metals are frequently above 0.5 mg/m^3, while lower levels are usually found in the manufacture of lead-acid batteries and in phosphate fertilizer production. Exposure to sulfuric acid also occurs during its manufacture and during the production of isopropanol, synthetic ethanol and detergents. Hydrochloric acid is used in industries that involve acid treatment of metals, where occupational exposure levels to hydrochloric acid mists and gas are frequently above 1 mg/m^3. Exposures to hydrochloric acid may also occur during its synthesis and use in various industrial processes. Pickling and other acid treatments of metal may entail occupational

exposures to nitric and phosphoric acids, but these occur less frequently than exposures to sulfuric and hydrochloric acids. Exposure to nitric acid also occurs during its manufacture and exposure to phosphoric acid in phosphate fertilizer production.

5.2 Human carcinogenicity data

An early study of isopropanol manufacture in the USA using the strong-acid process demonstrated an excess of nasal sinus cancer. Studies of one US cohort of workers in pickling operations within the steel industry showed excesses of laryngeal and lung cancer after smoking and other potential confounding variables had been controlled for. A Swedish study of a cohort of workers in steel pickling also showed an excess risk for laryngeal cancer. A nested case-control study of workers in a US petrochemical plant showed an elevated risk for laryngeal cancer among workers exposed to sulfuric acid. Of two population-based case-control studies in Canada, one of laryngeal cancer showed an increased risk for exposure to sulfuric acid, and one of lung cancer suggested an excess risk; the latter also suggested a risk associated with exposure to mixed inorganic acids. In all these studies, sulfuric acid mists were the commonest exposure, and positive exposure-response relationships were seen in two of the studies.

Additional supporting evidence was provided by one cohort study in the soap manufacturing industry in Italy, which showed an increased risk for laryngeal cancer. Studies of three US cohorts and one Swedish cohort in the phosphate fertilizer manufacturing industry showed excess lung cancer, but there was potential confounding from exposure to radon decay products in some cohorts.

5.3 Animal carcinogenicity data

No data were available to the Working Group.

5.4 Other relevant data

Acid mists containing particles with a diameter of up to a few micrometers will be deposited in both the upper and lower airways. They are irritating to mucous epithelia, they cause dental erosion, and they produce acute effects in the lungs (symptoms and changes in pulmonary function). Asthmatics appear to be at particular risk for pulmonary effects.

Significant increases in the incidences of sister chromatid exchange, micronucleus formation and chromosomal aberrations in peripheral lymphocytes were observed in a single study of workers engaged in the manufacture of sulfuric acid.

The studies reviewed examined the effects of pH values < 7 specifically. In cultured mammalian cells at pH 6.7 or below, cell transformation, gene mutation and chromosomal aberrations were induced. Mitotic abnormalities were induced in sea urchins and clastogenic effects in plants. Gene conversion was induced in yeast cells.

No point mutation was observed in fungi, yeast or bacteria. Acid pH caused depurination of isolated DNA.

5.5 Evaluation

There is *sufficient evidence* that occupational exposure to strong-inorganic-acid mists containing sulfuric acid is carcinogenic.

Overall evaluation

Occupational exposure to strong-inorganic-acid mists containing sulfuric acid *is carcinogenic to humans (Group 1)*.

Annex **E**

Classification of substances with respect to carcinogenicity

The committee expresses its conclusions in the form of standard phrases:

Judgement of the committee	Comparable with EU class
This compound is known to be carcinogenic to humans • It is genotoxic • It is non-genotoxic • Its potential genotoxicity has been insufficiently investigated. Therefore, it is unclear whether it is genotoxic	1
This compound should be regarded as carcinogenic to humans • It is genotoxic • It is non-genotoxic • Its potential genotoxicity has been insufficiently investigated. Therefore, it is unclear whether it is genotoxic	2
This compound is a suspected human carcinogen.	3
• This compound has been extensively investigated. Although there is insufficient evidence of a carcinogenic effect to warrant a classification as 'known to be carcinogenic to humans' or as 'should be regarded as carcinogenic to humans', they indicate that there is cause for concern.	(A)
• This compound has been insufficiently investigated. While the available data do not warrant a classification as 'known to be carcinogenic to humans' or as 'should be regarded as carcinogenic to humans', they indicate that there is a cause for concern.	(B)
This compound cannot be classified	not classifiable

Annex **F**

Guideline 93/21/EEG of the European Union

4.2 Criteria for classification, indication of danger, choice of risk phrases

4.2.1 Carcinogenic substances

For the purpose of classification and labelling, and having regard to the current state of knowledge, such substances are divided into three categories:

Category 1:

Substances known to be carcinogenic to man.

There is sufficient evidence to establish a causal association between human exposure to a substance and the development of cancer.

Category 2:

Substances which should be regarded as if they are carcinogenic to man.

There is sufficient evidence to provide a strong presumption that human exposure to a substance may result in the development of cancer, generally on the basis of:

- appropriate long-term animal studies
- other relevant information.

Category 3:

Substances which cause concern for man owing to possible carcinogenic effects but in respect of which the available information is not adequate for making a satisfactory assessment.

There is some evidence from appropriate animal studies, but this is insufficient to place the substance in Category 2.

4.2.1.1 The following symbols and specific risk phrases apply:

Category 1 and 2:

T; R45 May cause cancer

However for substances and preparations which present a carcinogenic risk only when inhaled, for example, as dust, vapour or fumes, (other routes of exposure e.g. by swallowing or in contact with skin do not present any carcinogenic risk), the following symbol and specific risk phrase should be used:

T; R49 May cause cancer by inhalation

Category 3:

Xn; R40 Possible risk of irreversible effects

4.2.1.2 Comments regarding the categorisation of carcinogenic substances

The placing of a substance into Category 1 is done on the basis of epidemiological data; placing into Categories 2 and 3 is based primarily on animal experiments.

For classification as a Category 2 carcinogen either positive results in two animal species should be available or clear positive evidence in one species; together with supporting evidence such as genotoxicity data, metabolic or biochemical studies, induction of benign tumours, structural relationship with other known carcinogens, or data from epidemiological studies suggesting an association.

Category 3 actually comprises 2 sub-categories:

a substances which are well investigated but for which the evidence of a tumour-inducing effect is insufficient for classification in Category 2. Additional experiments would not be expected to yield further relevant information with respect to classification.

b substances which are insufficiently investigated. The available data are inadequate, but they raise concern for man. This classification is provisional; further experiments are necessary before a final decision can be made.

For a distinction between Categories 2 and 3 the arguments listed below are relevant which reduce the significance of experimental tumour induction in view of possible human exposure. These arguments, especially in combination, would lead in most cases to classification in Category 3, even though tumours have been induced in animals:

- carcinogenic effects only at very high levels exceeding the 'maximal tolerated dose'. The maximal tolerated dose is characterized by toxic effects which, although not yet reducing lifespan, go along with physical changes such as about 10% retardation in weight gain;
- appearance of tumours, especially at high dose levels, only in particular organs of certain species is known to be susceptible to a high spontaneous tumour formation;
- appearance of tumours, only at the site of application, in very sensitive test systems (e.g. i.p. or s.c. application of certain locally active compounds); if the particular target is not relevant to man;
- lack of genotoxicity in short-term tests in vivo and in vitro;
- existence of a secondary mechanism of action with the implication of a practical threshold above a certain dose level (e.g. hormonal effects on target organs or on mechanisms of physiological regulation, chronic stimulation of cell proliferation;
- existence of a species - specific mechanism of tumour formation (e.g. by specific metabolic pathways) irrelevant for man.

For a distinction between Category 3 and no classification arguments are relevant which exclude a concern for man:

- a substance should not be classified in any of the categories if the mechanism of experimental tumour formation is clearly identified, with good evidence that this process cannot be extrapolated to man;
- if the only available tumour data are liver tumours in certain sensitive strains of mice, without any other supplementary evidence, the substance may not be classified in any of the categories;
- particular attention should be paid to cases where the only available tumour data are the occurrence of neoplasms at sites and in strains where they are well known to occur spontaneously with a high incidence.