ISOPROPYL ALCOHOL MANUFACTURE BY THE STRONG-ACID PROCESS

Isopropyl alcohol and isopropyl alcohol manufacture (strong-acid process) were considered by previous IARC Working Groups in 1977 and 1987 (IARC, 1977, 1987). Since that time, new data have become available, which have been incorporated in this *Monograph,* and taken into consideration in the present evaluation. A separate *Monograph* on 'Mists from Strong Inorganic Acids' – updating earlier evaluations on this agent (IARC, 1992) – appears elsewhere in this volume.

1. Exposure Data

1.1 Manufacturing processes

Isopropyl alcohol has been called the first petrochemical (IARC, 1992). It can be prepared via three different methods: indirect hydration of propylene, direct hydration of propylene, and catalytic hydrogenation of acetone. Indirect hydration, also called the sulfuric-acid process, was the only method used to produce isopropanol worldwide until the first commercial direct-hydration process was introduced in 1951. Each method has its advantages and disadvantages. For example, direct hydration is less corrosive than indirect hydration mediated by sulfuric acid. However, the direct method requires a pure propylene feed, in contrast to the indirect process, which can use a dilute, refinery stream (Lee *et al.*, 2003).

In the indirect-hydration process, propylene is reacted with sulfuric acid to produce mono- and diisopropyl sulfates, which are then hydrolysed to isopropanol. In the two-step strong-acid process, separate reactors are used for the propylene-absorption phase and the hydrolysis of the sulfate esters. The reaction occurs at high sulfuric acid concentration (> 80% wt) and low temperature (e.g. 20–30 °C). The weak-acid process is conducted in a single step at lower acid concentration (60–80% wt) and higher temperature (60–65 °C) (Logsdon & Loke, 2001).

1.2 Human exposure

1.2.1 Occupational exposure

CAREX (CARcinogen EXposure) is an international information system on occupational exposure to known and suspected carcinogens, based on data collected in the European Union (EU) from 1990 to 1993. The CAREX database provides selected exposure data and documented estimates of the number of exposed workers by country, carcinogen, and industry (Kauppinen *et al.*, 2000). No results for isopropanol were reported. For data on EU workers exposed to strong inorganic acid mists containing sulfuric acid, see the *Monograph* on Mists from Strong Inorganic Acids in this volume.

From the National Occupational Exposure Survey (1981–83) it was estimated that approximately 4.7 million workers (including approximately 2.1 million women) in the United States of America (USA) were potentially exposed to isopropanol (NIOSH, 1990). No specific information on the numbers of workers exposed during isopropanol production was provided.

Although no data were available on exposure measurements at the workplace during isopropanol production, potential exposures from the indirect-hydration process include propylene, sulfuric acid, isopropanol, diisopropyl and isopropyl hydrogen sulfates, diisopropyl ether, propanal, acetone, sulfur oxides, polymeric oils and residues. In the past, benzene was used as an azeotroping agent to remove water from 'wet isopropanol', but nowadays diisopropyl ether or cyclohexane are preferentially used for this purpose (IARC, 1992; Papa, 2000; Logsdon & Loke, 2001).

2. Cancer in Humans

In *IARC Monographs* Supplement 7 it was concluded that there was *sufficient evidence* in humans for the carcinogenicity of work in the manufacture of isopropyl alcohol by the strong-acid process and *inadequate evidence* for the carcinogenicity of exposure to isopropyl alcohol and isopropyl oils (IARC, 1987). The carcinogenic hazards to humans of work in the manufacture of isopropyl alcohol by other methods, and of exposure to diisopropyl sulfate were not evaluated. The evaluation was based on an increased incidence of cancer of the paranasal sinuses observed in workers at factories where isopropyl alcohol was manufactured by the strong-acid process. The risk for laryngeal cancer may also have been elevated in these workers.

In *IARC Monograph* Volume 54 (IARC, 1992) an evaluation was made of exposure to mists from strong inorganic acids. The epidemiological data on isopropanol production in that *Monograph* are updated and reviewed elsewhere in the present volume, and partly overlap with the information given below.

2.1 Cohort studies

See also Section 2.1.3 in the *Monograph* on Mists from Strong Inorganic Acids in this volume.

Two cases of nasal sinus cancer and two cases of laryngeal cancer had occurred among an unspecified number of workers at a Baton Rouge, Louisiana, USA, isopropyl alcohol-production plant by about 1950 (Eckardt, 1974; Hueper, 1966). Subsequent analyses considered isopropyl alcohol workers in combination with employees in ethanol production and other production units (Lynch *et al.*, 1979; Hanis *et al.*, 1982; see Table 2.1, available at http://monographs.iarc.fr/ENG/Monographs/vol100F/100F-27-Table2.1.pdf). At this plant, a nested case–control study of workers in isopropyl alcohol manufacturing and others ascertained 50 cases of upper respiratory tract cancer among employees and former employees who had worked during at least 10–15 years. The study made use of an unidentified non-company tumour registry (see Table 2.1, on-line). Cases and controls were assessed for exposure to sulfuric acid and other agents; those with high exposure to sulfuric acid had a significantly elevated odds ratio (OR) of 5.2 (95%CI: 1.2–22.1) for pharyngeal, nasal sinus, or laryngeal cancer (Soskolne *et al.*, 1984).

Six cases of cancer occurred in the 1970s at an isopropyl alcohol-production unit in the USA, which began operation in 1943 and had employed 600 workers through 1976 (Fishbein, 1976). Mortality through 1978 was studied among 433 isopropyl alcohol-manufacturing workers in this facility (see Table 2.1, on-line): two buccal cavity/pharyngeal cancer deaths were reported (Enterline, 1982). Subsequent studies of workers

at this plant did not include data on the mortality experience of isopropyl alcohol-manufacturing workers (Enterline *et al.*, 1990; Marsh *et al.*, 1991).

Among 182 workers employed 1928–50 in another isopropyl alcohol-production unit in the USA, a statistically significant excess of sinus cancer occurred (four cases) (Hueper, 1966; Weil *et al.*, 1952). Subsequently, a case–control study that used reported lymphohaematopoetic cancer deaths as the cases was conducted. Workers ever having had exposure to alkyl sulfates, including diisopropyl sulfate, were at elevated risk for non-Hodgkin lymphoma (8 deaths; OR, 5.1; $P < 0.05$) (Ott *et al.*, 1989). A later mortality study analysed isopropyl alcohol-manufacturing workers together with ethyl alcohol-manufacturing workers at the same and another facility ($n = 1031$) (Teta *et al.*, 1992). Excesses of cancers of the larynx, buccal cavity and pharynx were observed, but based on very small numbers. There was one death due to sinus cancer (see Table 2.1, on-line).

Among 262 men employed in an isopropyl alcohol-manufacturing unit in the United Kingdom, nine cancer deaths had occurred by 1980, including one from nasal sinus cancer, corresponding to a 50-fold increased risk (see Table 2.1, on-line; Alderson & Rattan, 1980)

No further cancer mortality or incidence studies specifically updating any of these cohorts in isopropyl alcohol manufacture have been conducted, and no studies of other isopropyl alcohol-manufacturing plants have appeared in the scientific literature.

2.2 Case–Control Studies

Hu *et al.* (2002) conducted a study of carcinoma of the kidney (renal cell) in eight Canadian provinces. From cases and population-based cancer-free controls, data were collected on exposures during one year or more to 17 substances, including isopropyl oil. The OR – adjusted for age, province of residence, education, body-mass index, pack-years of cigarettes smoked, alcohol, and meat consumption – was 1.6 for men (95%CI: 1.0–2.6) and 1.2 for women (95%CI: 0.4–3.5) (see Table 2.2, available at http://monographs.iarc.fr/ENG/Monographs/vol100F/100F-27-Table2.2.pdf).

Pan *et al.* (2005) conducted a similar study of cancer of the brain in eight Canadian provinces. Likewise, from cases and population-based cancer-free controls, data were collected on occupational exposures during one year or more to 18 substances, including isopropyl oil. Exposure to this type of oil was associated with an elevated but not significantly increased risk for brain cancer (see Table 2.2, on-line).

Overall, there is evidence from epidemiological studies that exposure of humans during the manufacture of isopropyl alcohol by the strong-acid process causes cancer of the nasal sinuses, based on three cohort studies. The evidence is inadequate to draw conclusions on other cancer sites.

3. Cancer in Experimental Animals

No data were available to the Working Group.

4. Other Relevant Data

4.1 Absorption, distribution, metabolism, and excretion

4.1.1 Humans

The kinetics of the toxic effects of inhaled acid mists on the respiratory tract depend on several interrelated factors, which include whether exposure occurs to a gas or an aerosol; the particle size, with small particles being more able to penetrate deeply into the lung (Martonen *et al.*, 1985; Jarabek *et al.*, 1989; US EPA, 1989); the solubility in water, with agents of higher solubility

being more likely to be deposited in the nose and mouth; the free hydrogen ion concentration; the breathing rate and pattern; the buffering capacity of the mucosal layer of the airways and the local deposition site (Utell *et al.*, 1989); and the presence of other chemicals carried along with the aerosol particle.

Acid mists that contain particles with a diameter of up to a few micrometers will be deposited in both the upper and lower airways. It is difficult to identify the principal site of deposition within the respiratory tract. For example, 90% of an aerosol of sulfuric acid (mass median aerodynamic diameter of particles, 5 μm) to which lead-acid battery workers are exposed, would be deposited in the extra-thoracic region of the respiratory tract, whereas only 50% of an aerosol with 2-μm particle size would be deposited in that same portion of the respiratory tract. This relationship between size and deposition renders estimation of the changes in pH of the mucus problematic, as diffuse deposition challenges the buffering capacity much less than does deposition of large particles at local sites (Gamble *et al.*, 1984; Jarabek *et al.*, 1989).

Assuming an average particle size of 1 μm and exposure concentrations of 0.4–1 mg/m^3, Amdur *et al.* (1952) showed that on average 77% of an inhaled aerosol of sulfuric acid was retained in the airways of exposed human subjects. Martonen *et al.* (1985) demonstrated that the hygroscopic growth of particles (≤ 1 μm) of several inorganic acids within the respiratory tract depended on temperature, humidity, particle size, respiratory characteristics and the hygroscopic nature of the acid.

The breathing pattern (i.e. mouth *vs* nose breathing, with normal augmentation through the mouth) also influences deposition. For all particle sizes, the dose deposited regionally below the nasopharynx is higher for mouth breathers. The effect of mouth breathing is most evident from the increasing deposition in the oropharynx, larynx and upper trachea (Jarabek *et al.*, 1989).

In the moist environment of the respiratory tract, sulfur trioxide – the anhydride of sulfuric acid – reacts instantaneously with water to form sulfuric acid (IARC, 1992); therefore, the toxicology of sulfur trioxide would be expected to be the same as that of sulfuric acid.

The medical condition called Barrett's oesophagus provides supporting evidence for an association between exposure to an acidic environment and cancer. Barrett's oesophagus refers to a metaplastic change of the lining of the lower end of the oesophagus, which is thought to be caused by chronic exposure to acid from gastric reflux. Genetic polymorphisms associated with an inflammatory response, DNA repair and chemical detoxication are all associated with the presence or progression of the condition. Changes in gene expression have been seen in metaplastic cells as a result of chronic inflammation, which could be due to genetic changes, epigenetic changes or modifications to signalling pathways (Shaheen & Richter, 2009).

4.1.2 Experimental systems

Generally, with respect to acid aerosol deposition similar effects were observed in animals. Regional deposition of sulfuric acid aerosols in experimental animals is also dependent on particle size (e.g. Dahl *et al.*, 1983). However, animal species differ from humans with regard to the dimensions and architecture of the respiratory tract, and deposition patterns of aerosols may vary accordingly (Jarabek *et al.*, 1989). A study in anaesthetized dogs showed that production of ammonia by the respiratory tract partially neutralizes acid aerosols, but larger-size aerosols are neutralized less efficiently than smaller-size aerosols (Larson *et al.*, 1982).

4.2 Genetic and related effects

4.2.1 Humans

Significant increases in the incidence of sister chromatid exchange (SCE), micronucleus formation and chromosomal aberrations in peripheral lymphocytes were detected in a study of 40 workers at a sulfuric acid plant in China, compared with 42 controls working and studying at a university in the same city as the factory. The controls were matched according to sex, age and smoking habits. The mean number of SCE/cell was 6.72 ± 0.22 for workers and 2.71 ± 0.31 for unexposed controls ($P < 0.01$); the mean frequency of micronuclei in cultivated lymphocytes was 0.168% in those from the workers and 0.071% from the control group ($P < 0.001$); and the mean frequency of several types of chromosomal aberration (including rings, translocations and di-centrics) per 100 metaphases was 0.963 for the workers and 0.227 for controls ($P < 0.01$). No positive correlation was observed between the frequency of sister chromatid exchange, micronuclei or chromosomal aberrations and length of employment of the workers. While there was no significant difference between smokers and non-smokers with regard to the frequencies of sister chromatid exchange and chromosomal aberrations, smokers among both the workers and the controls had significantly more micronuclei than non-smokers ($P < 0.001$) (Meng & Zhang 1990a, b).

4.2.2 Experimental systems

No data were available on genetic and related effects of exposures to acid mists in experimental systems; however, studies on genotoxic effects under extreme culture conditions with respect to pH have been reviewed (Scott *et al.*, 1991; Swenberg & Beauchamp, 1997).

The carcinogenic activity of sulfuric acid may be related to the genotoxicity of low pH conditions. Reduced pH environments enhance the depurination rate of DNA and the deamination rate of cytidine (Singer & Grunberger, 1983; IARC, 1992); it has been suggested that the fidelity of enzymes involved in DNA replication and repair may be reduced by low pH (Brusick, 1986). Also, low pH (5.4–6.5) is associated with induction of clastogenicity, sister chromatid exchange and chromosomal aberrations (Morita *et al.*, 1991, 1992; Morita, 1995).

Deamination of cytidine at CpG sites appears to be one of the mechanisms of mutation induction in the *p53* tumour-suppressor gene (Harris, 1993).

4.3 Toxicity relevant to carcinogenicity

Acid mists are irritating to mucous epithelia; they cause dental erosion and produce acute effects in the lungs (symptoms and changes in pulmonary function) (IARC, 1992).

Workers exposed to sulfuric acid mists had an increased incidence of symptoms and macroscopic and microscopic changes of the nasal mucosa, including squamous metaplasia and atypia, with an exposure-response relationship (Grasel *et al.*, 2003).

4.4 Synthesis

Little information on possible mechanisms of carcinogenicity of inorganic acid mists is available. The increased incidence of cancer of the paranasal sinuses in workers involved in the strong-acid process of isopropyl alcohol manufacture may be due to exposure to the strong acid mists and/or the presence of diisopropyl sulfate, an intermediate that shows sufficient evidence of carcinogenicity in experimental animals.

Available data suggest that localized low pH from inhalation of inorganic acid mists could damage DNA and lead to neoplasia. There is no evidence that would support the occurrence of DNA damage by any other mechanism of carcinogenesis.

5. Evaluation

There is *sufficient evidence* in humans for the carcinogenicity of isopropyl alcohol manufacture by the strong-acid process. Isopropyl alcohol manufacture by the strong-acid process causes cancer of the nasal cavity.

No data on carcinogenicity of strong acid mists in experimental animals were available to the Working Group.

It is plausible that areas of localized low pH from inhalation of inorganic acid mists could damage DNA and increase cancer risks. There is no evidence to support DNA-damage induction by any other mechanism as the cause of the observed cancers due to exposure to inorganic acid mists.

Isopropyl alcohol manufacture by the strong-acid process is *carcinogenic to humans (Group 1).*

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