General Remarks on the Substances Considered

This fifty-fourth volume of *IARC Monographs* covers strong inorganic acids and some other industrial chemicals. Two of the agents were evaluated previously: diethyl sulfate (IARC, 1974, 1987) and 1,3-butadiene (IARC, 1986, 1987). Manufacture of isopropanol by the strong-acid process has already been evaluated as an exposure circumstance (IARC, 1977, 1987).

Selection of topics

Selection of strong inorganic acids as the main subject of this volume was prompted by the publication of several epidemiological studies that suggested that exposure by inhalation to mists and vapours of strong inorganic acids was associated with excess risk for laryngeal and other respiratory-tract cancers. These studies led to the hypothesis that acidity itself could exert a carcinogenic effect. The first monograph in this volume addresses that question and investigates the plausibility of the hypothesis by examining the evidence from studies of some of the many industries in which strong acids are used.

An acid may be defined as a substance with the potential to donate a hydrogen ion, although it may not exhibit its acidic properties in certain media (e.g., hydrochloric acid in pure benzene). In water, acids dissociate to varying degrees, donating their hydrogen ions to water molecules to produce the hydronium ion (H_3O^+) and the anion. The strength of an acid is usually measured by the pK_a value, which is the negative logarithm (to the base 10) of the acid ionization (dissociation) constant, K_a, for the reaction. The stronger the acid, the lower the pK_a value. Some acids, like sulfuric (H_2SO_4) and phosphoric (H_3PO_4), can donate more than one hydrogen ion; these acids have separate ionization constants for the loss of each hydrogen ion. A distinction must be made between a *solution of a strong acid* and a *strongly acidic solution*. A solution of a strong acid, for example, may be very dilute and not strongly acidic (pH close to neutrality, pH 7), and a weaker acid at a high concentration may give a highly acidic solution (low pH). In mechanistic terms, it remains to be established whether biological effects from strong inorganic acids are due to hydrogen ion concentration (which is not specific to the acid in question) or to the molecular species and its interactions in organisms.

The impact of inhaled acidic agents on the respiratory tract depends upon a number of interrelated factors. These include physicochemical characteristics, e.g., gas *versus* aerosol; particle size (small particles can penetrate deeper into the lung); water solubility (more soluble agents are more likely to be removed in the nose and mouth); free hydrogen ion concentration (more acidic agents have greater effects); and the buffering capacity of the overall airway and of the local deposition site. It is also conceivable that a specific anion can directly or indirectly modulate acute effects.

Given the general lack of information on the particle size of aerosols involved in occupational exposures to acids, it is difficult to identify their principal deposition site within the respiratory tract. Estimation of changes in the pH of the mucus is therefore problematic, as diffuse deposition would challenge the buffering capacity much less than would deposition of large particles at local sites.

It is difficult to separate the effects of pH and of changes in osmolarity since exposures to low pH may alter osmolarity by changing the concentrations of ionized and nonionized species and, thus, induce reactions that do not occur at neutral pH (Scott *et al.*, 1991). Data from assays for genotoxic activity *in vitro* suggest that eukaryotic cells are susceptible to genetic damage when the pH falls to about 6.5. Cells from the respiratory tract have not been examined in this respect. Mucus secretion may protect the cells of the airways from direct exposure to inhaled acidic mists, just as mucus plays an important role in protecting the gastric epithelium from its autosecreted hydrochloric acid. In considering whether pH itself induces genotoxic events *in vivo* in the respiratory system, comparison should be made with the human stomach, in which gastric juice may be at pH 1–2 under fasting or nocturnal conditions, and with the human urinary bladder, in which the pH of urine can range from < 5 to > 7 and normally averages 6.2. Furthermore, exposures to low pH *in vivo* differ from exposures *in vitro* in that *in vivo* only a portion of the cell surface is subjected to the adverse conditions, so that perturbation of intracellular homeostasis may be maintained more readily than *in vitro*.

The industries considered were selected because they involve particularly heavy use of inorganic acids: manufacture of isopropanol, synthetic ethanol, phosphate fertilizers, lead batteries, soap and detergents, sulfuric acid and nitric acid and those industries involving treatment of metals with acids. Because sulfuric acid is the principal strong inorganic acid used in these industries and is the acid on which most epidemiological data were available, it is discussed in detail in the monograph on occupational exposures to strong acid mists and in an appendix to that monograph. Sulfur trioxide is included in the same monograph because it is directly and rapidly converted to sulfuric acid when it comes into contact with water.

Sulfur dioxide is reviewed separately because it is a major contributor to atmospheric acidity and is an important industrial chemical. It dissolves slowly in water. Aqueous solutions of sulfur dioxide may contain bisulfites, sulfites and metabisulfites, depending on their acidity, temperature and ionic strength; sulfite and bisulfite are also metabolites of sulfur dioxide. Because of their close relationship with sulfur dioxide, some of these compounds are included in the monograph on this agent.

Hydrochloric acid is a strong inorganic acid which is formed when gaseous hydrogen chloride dissolves in water. Exposures may thus occur both to the gas and to hydrochloric acid mists. As it is also industrially important and data are available on cancer in experimental animals, this acid was considered in a separate monograph.

Diethyl sulfate and diisopropyl sulfate are relevant to an evaluation of the carcinogenicity of acids because they may occur simultaneously with sulfuric acid mists in the manufacture of isopropanol and synthetic ethanol. Monographs on these two substances are therefore included.

There is, inevitably, a great deal of overlap among these monographs. Exposures to acid mists and vapours occur in industries other than those described in the first monograph; these exposures are complex, and may be accompanied by exposures to known carcinogenic agents, such as nickel compounds (see IARC, 1990), chromium[VI] compounds (see IARC, 1990), inorganic arsenicals (see IARC, 1987), soots (see IARC, 1987), coal-tars (see IARC, 1987) and polycyclic aromatic hydrocarbons (see IARC, 1983). Epidemiological studies on nickel refining, other basic metals industries, chromate production, chromium plating and nickel plating were therefore considered to be uninformative for an evaluation of acids, and only passing reference is made to these studies. Some studies of copper smelter workers that specifically address exposure to sulfur dioxide are described in detail, however, in spite of the simultaneous occurrence of other suspect agents. The monographs do not emphasize studies of environmental exposures, which are usually at a much lower level than occupational exposures and for which causal relationships are more difficult to establish.

The final monograph in this volume is on 1,3-butadiene. It is included because an up-to-date evaluation of this very important monomer was clearly required and new data had become available since it was evaluated previously (IARC, 1987).

Issues in the evaluation of epidemiological studies of occupational exposure to mists and vapours from strong acids

(*a*) *Site of cancer and mode of action*

In the epidemiological studies reviewed, cancer of the upper respiratory system occurred frequently in association with occupational exposure to mists and vapours from strong acids, either alone or in addition to cancer of the lung. This finding is biologically plausible, given that the route of entry is inhalation. Inhalation of mists from strong acids could cause rapid local reactions; thus, the sites of primary response would be in the upper respiratory tract when the particles have an aerodynamic diameter[1] of 5–30 μm and in the tracheal, bronchial and bronchiolar regions when the particles are 1–5 μm.

These observations may be important for understanding the etiology of excess cancers in the upper airways, where cancer occurrence in association with industrial exposures is quite rare.

(*b*) *Cancer incidence and mortality*

Many of the available studies addressed cancer mortality rather than incidence. It is often the case that studies on incidence are not available, since in some areas of the world there is no system to ensure enumeration of all cancer cases. When the cancers observed are those for which survival after diagnosis is quite good, however, the true magnitude of an association between exposure and the cancer may be underestimated if only mortality is studied. For example, patients diagnosed with laryngeal or oropharyngeal cancer may live for a long time after treatment and may eventually die of another disease, so that their cause of death might not reflect the fact that they had had laryngeal or oropharyngeal cancer. Further,

[1]Aerodynamic diameter is a measure of particle size which takes into account both density and aerodynamic drag.

cancers at these sites frequently produce secondary lesions in the oropharyngeal region; these can obfuscate identification of the primary site, and death may be attributed to the secondary lesion. For these reasons, studies of cancer incidence are more sensitive for detecting any excess of upper respiratory cancer in association with occupational exposures than are mortality studies.

(*c*) *Life style factors*

Information on smoking habits is often not collected in epidemiological studies of occupational groups, mainly because of cost limitations. When the target site of interest is the lung and the magnitude of the excess cancer risk is small, the possibility must be entertained that the excess was due to a greater prevalence of smoking in the occupational group than among the reference population, and not to the occupational exposure. The same explanation can apply to a small excess risk for cancer of the larynx, since smoking is a major risk factor for this disease. In several of the studies examined, however, excesses of laryngeal cancer and not of cancer of the lung were seen in relation to occupational exposure. In these cases, the Working Group considered that smoking was not a major confounder, as the principal carcinogenic effect of smoking is on the lung. In some studies, the excesses are relatively large; in others, information on smoking was available and the excess risks persisted after adjustment for smoking. The latter studies were of greatest importance in evaluating the carcinogenic risk of occupational exposures to mists and vapours from strong acids.

(*d*) *Specification of exposure and dose–response*

Particularly in respect of the occupations considered in these monographs, it is difficult to specify the exposures of workers. The names of jobs and processes are usually the only available information for linking an individual to the exposure of interest. Furthermore, such linkage is done retrospectively and in the absence of industrial hygiene measurements. No process or job in any industry involves exposure to a single chemical, and exposures to chemicals within a single process or job may be so highly correlated that it is impossible to separate their effects in regard to cancer risks in epidemiological studies. In this situation, cancer risks must be examined across industries or even across processes to determine whether there are other situations in which only one of the chemicals is common and whether cancers at the same site are occurring in workers involved in these other processes. The presence of other known carcinogens within the industry must be reviewed to eliminate any confounding of the conclusions.

To determine that the evidence is sufficient to establish the carcinogenicity of an agent, observation of a dose– or exposure–response is helpful. In most situations, past exposures of workers were not measured, and processes, chemicals and levels of exposures have changed over time. Thus, exposures are based on estimates of the relative amounts of chemicals that are associated with jobs and processes, taking account of how these amounts vary over time. Such estimates are then tied to an individual's occupational history to give a proxy measure of cumulative dose. Despite the fact that this measure is only relative and gives a highly uncertain picture of true exposures over time, it may be a more reliable comparative measure of exposure between individuals than is the use of a few contemporary measures of the agents in the work environment. Estimates that include only selected jobs and a few values for each

job can give little indication of the potential variability in exposure by job and may not represent past exposures within the industry.

Use of retrospective exposure scoring systems for estimating an exposure–response relationship is thus tenuous. Usually, no information on the appropriateness of the estimated relative ranks is available: a value of 10 may not actually represent an exposure that was 10 times one in the past; time spent in a job is used as an exposure score to estimate the incidence of cancer by 'dose'. It is not surprising that the results are most consistent when exposures are grouped categorically and cancer rates are determined on the basis of grouped data, although the sensitivity of a response based on a specific categorical grouping may be undefined.

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