GENERAL REMARKS

This forty-ninth volume of *IARC Monographs* covers chromium and its compounds, nickel and its compounds and occupational exposures in welding. Chromium and nickel are widely used as components of stainless steel and other high alloy steels. Even though mild steel is the most common material welded, a considerable proportion of welders are regularly or occasionally exposed to fumes from stainless steel containing chromium and nickel compounds.

Chromium and its compounds have been evaluated previously in the *Monographs* (IARC, 1973, 1979, 1980, 1982, 1987). The monograph on chromium and chromium compounds is, for practical purposes, divided into subsections, on the basis of the oxidation state and solubility of the compounds. The principal oxidation states of chromium are 0, III and VI; in addition, oxidation states II, IV and V occur, and sometimes the agents tested were of mixed or unknown oxidation states. The latter are described under the title 'other chromium compounds'. The compounds tested for carcinogenicity are described in more detail than other compounds of the group in sections on chemical and physical properties, production, use and occurrence. Welding of stainless steel with exposure to chromium is described in detail in the monograph on welding and is cross-referenced in the monograph on chromium and chromium compounds.

In general, stainless-steel welders (mostly fabricators) are exposed primarily to fumes that differ from those in mild-steel welding mainly in their comparatively high content of chromium and nickel. Mild-steel welders work on a variety of materials in a range of situations (e.g., shipyards, construction work), which lead to exposure to a range of particulates such as fume, grinding dust and asbestos (see IARC, 1977) and to gaseous substances (e.g., from pyrolytic decomposition of antirust paint on construction plates and the oxides of nitrogen).

Nickel and its compounds have also been evaluated previously (IARC, 1973, 1976, 1979, 1982, 1987). As for chromium, the present monograph on nickel and nickel compounds has been divided into subsections. The purpose of this subdivision was prompted by the fact that since a wide variety of nickel compounds has been tested for carcinogenicity, a grouping of data on individual nickel compounds would be useful. The studies on stainless-steel welding and on welders exposed to nickel are described in the monograph on welding. These studies are, however, cross-referenced in the monograph on nickel and nickel compounds when they are considered to contribute to the evaluation of nickel and its compounds.

Welding and welding fumes have not been evaluated previously, although some of the studies on welders are reviewed in the monographs on chromium and nickel. The chemical composition of welding fumes and gases is determined by the material being welded (e.g., mild steel, stainless steel, aluminium) and the welding technique used (manual metal arc, metal inert gas, tungsten inert gas). When painted steel is welded, the basic components of welding fumes — the metals, metal oxides and metal salts — may be accompanied by a complex mixture of other compounds. In addition to welding fumes and gases, welders are also often exposed to ultraviolet light (see IARC, 1986), to electromagnetic fields and, in some cases, to other agents originating from their work (e.g., grinding dust) or from other work carried out at the same place (e.g., asbestos in shipyards).

The epidemiological studies summarized in the monograph on welding were selected on the basis that the majority of the population under study probably consisted of welders. For example, if the occupational group studied was specified as 'welders and solderers', the study was included because the number of solderers is usually much lower than that of welders. On the other hand, studies on 'metal workers' and 'sheet metal workers' were excluded, although in these wide occupational categories there is a minority of persons who are involved in welding operations. Similarly, it is probable that the studies on 'welders' as an unspecified occupation may have included a fair number of stainless-steel welders. It should be noted that laboratory experiments with samples of welding fume may not reflect, in terms of chemical composition, human exposures during the welding process.

Solubility

Chromium and nickel compounds are often classified as 'soluble' or 'insoluble'. Such a classification can be useful for describing the physical properties and industrial applications of the various compounds, but has sometimes also been used as a crude index of bioavailability in toxicological investigations. Some confusion has arisen because the terms 'soluble' and 'insoluble' have not always been defined adequately and because a variety of test methods has been used. In the preparation of the monographs in this volume, use was made of the accepted physical definition of 'solubility' in terms of the equilibrium concentration of a single chemical substance in saturated solution in a specified solvent at a given temperature. The 'soluble fraction' of a substance or mixture is usually measured by leaching the substance for a specified time under defined test conditions, and the results obtained are highly dependent upon the precise method used. It should be noted that different forms of nominally the same compound can have very different solubilities and rates of dissolution, and the dissolution rate is affected by particle size, purity and crystallinity.

The dissolution process can involve physical and chemical mechanisms, and the resulting compounds in solution might be chemically different from the source compound in the test material. For example, nickel subsulfide (Ni_3S_2) can be oxidized by dissolved oxygen, entering solution as nickel sulfate (Ciccarelli & Wetterhahn, 1984). Interpretation of the results of leaching measurements can be difficult: a low result, for example, might imply either a mixture with a small soluble fraction or a pure soluble material which dissolves relatively slowly. In few cases can the results of such tests, or data on solubility, for a substance in one solvent system be extrapolated reliably to other solvent systems.

Bioavailability

'Bioavailability' is a term used to denote the fraction of a substance that is absorbed, delivered to a target site and/or is responsible for a specific toxic or carcinogenic effect. Clearly, water solubility of an agent will often be an important factor in its availability within the body. It is, however, not the only relevant determinant of bioavailability. All dissolved chromium species, for example, may not pass equally through cell membranes: chromates in solution readily cross cell membranes, while Cr[III] does not. Chromates, moreover, have a range of solubilities in water and in body fluids, and agents such as lead chromate may release very few chromate ions for passage through cell membranes. Passage through cell membranes is only one route by which an agent may reach a target within a cell: particulate compounds of chromium and nickel may be phagocytized and thus become bioavailable.

The bioavailability of a potentially carcinogenic entity that is common to other members of its class of closely related compounds is an important factor in its carcinogenic potency, as demonstrated by differences in the levels of carcinogenic response observed in experimental and epidemiological studies. Not only is sufficient delivery of metal ion important, but in excess it can produce toxic effects (e.g., inhibitory phagocytosis), limiting uptake or survival of preneoplastic cells.

The classification scheme used in the *IARC Monographs* is qualitative and is based solely on the strength of evidence from the studies considered. Because of differences in observed levels of carcinogenic response, potency, and therefore dissolution and bioavailability as well, play a role in this qualitative evaluation. Alternatively, differences in the degree of evidence may merely reflect the fact that the entity has not been adequately tested over the range of compounds in which it occurs.

Biological monitoring

Biological monitoring of chromium, nickel and welding exposures shows that absorption into the human body has taken place. Such studies were considered, but several factors, such as sampling time, toxicokinetic factors and analytical validity, were taken into account, and the Working Group did not attempt to use such data to compare absorbed doses in different exposure situations.

Availability and reporting of data

There is a paucity of evidence for and against the possible carcinogenic hazards of oral exposures to chromium or nickel compounds in foods or potable water. There is also a lack of precision in characterizing the chemical species and physical properties of the tested compounds and welding processes described in these monographs, which hinders interpretation of the data.

Adequacy of animal experiments

Chromium and nickel are major world commodities, and these metals and their compounds constitute occupational exposures, principally by inhalation, for many millions of workers. Many long-term tests for carcinogenesis have been carried out by application to internal tissues (by injection or implantation); however, few bioassays of exposure by inhalation were available for evaluation. The paucity of data on the effects of inhalation of these compounds is partially offset by evidence from studies by intratracheal and intrabronchial exposure.

Carcinogenic effect is often strongly related to duration of exposure, in both humans and animals; thus, negative results for a single application of a soluble compound in an animal experiment cannot provide reasonable evidence that an agent will not be carcinogenic under conditions of prolonged or repeated application. This fact may provide a possible explanation for some of the negative results observed. In the absence of data from studies of soluble, acutely toxic substances by prolonged inhalation, some evidence may be obtained from repeated exposure of the same target cell population, as by repeated multiple injections of a toxic nickel-containing compound into the peritoneal cavity. The requirements for the carcinogenicity testing of metals need further elaboration.

Genetic and related effects

Most of the available short-term test results have been incorporated in the text. These include the results of anchorage-independent growth assays using Syrian hamster BHK21 fibroblasts. This assay in particular demonstrated that many metal compounds can induce changes in the normal growth pattern of the cells; however, neither this assay nor that for fetal mouse cell transformation was evaluated for the final summary (Section 4.4), because technical and interpretative difficulties are associated with both of them.

Interpretation of moderately elevated lung cancer rates

Apparently moderate elevations in lung cancer rates among occupationally exposed groups may occur as a result of confounding exposures to cigarette smoke and other carcinogens. Accurate smoking histories are rarely available in epidemiological studies of industrial workers, and, due to the differences in smoking prevalences, national or even regional lung cancer rates may not provide an appropriate basis for calculating expected numbers in industrial cohort studies. Furthermore, workers in a particular industry may also be exposed to carcinogens in other occupations during their working lives. For example, in several recent industrial studies, high lung cancer rates have been reported among short-term workers, which seem unlikely to be due to the specific period of employment. In the absence of an increasing trend with duration of exposure, a relative risk for lung cancer lower than about 1.5 should be interpreted with caution, although larger excesses are unlikely to be due entirely to smoking or to other exposures.

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