4. Summary of Data Reported and Evaluation

4.1 Exposure data

Chromium in the form of various alloys and compounds has been in widespread commercial use for over 100 years. Early applications included chrome pigments and tanning liquors. In recent decades, chromium has also been widely used in chromium alloys and chrome plating.

Several million workers worldwide are exposed to airborne fumes, mists and dust containing chromium or its compounds. Of the occupational situations in which exposure to chromium occurs, highest exposures to chromium[VI] may occur during chromate production, welding, chrome pigment manufacture, chrome plating and spray painting; highest exposures to other forms of chromium occur during mining, ferrochromium and steel production, welding and cutting and grinding of chromium alloys.

Data on exposure levels are available for several specific industries and job categories covering several decades. In the past, exposures to chromium[VI] in excess of 1 mg/m^3 were found repeatedly in some processes, including chromium plating, chromate production and certain welding operations; exposures to total chromium have been even higher. Modern control technologies have markedly reduced exposures in some processes, such as electroplating, in recent years.

Occupational exposure has been shown to give rise to elevated levels of chromium in blood, urine and some body tissues, inhalation being the main route.

Nonoccupational sources of exposure to chromium include food, air and water, but the levels are usually several orders of magnitude lower than those typically encountered in occupational situations.

4.2 Experimental carcinogenicity data

Chromium[0]

Studies in rats by intratracheal, intramuscular and intrafemoral administration, in mice and rats by intrapleural and intraperitoneal administration and in mice, rats and rabbits by intravenous injections were inadequate to evaluate the carcinogenicity of *chromium metal* as a powder.

Chromium[III]

In studies in which *chromic acetate* was administered by the oral route to mice and rats and by intrapleural and intramuscular administration to rats, the incidence of tumours was not increased. In studies in which rats were administered *chromic oxide* by intrabronchial or oral routes, no increase in the incidence of tumours was observed. In experiments by intrabronchial implantation of *chromic chloride* or *chrome tan* (a basic chromic sulfate) in rats and by intraperitoneal administration of *chromic sulfate* in mice, the incidence of tumours was not increased. Many of these studies suffered from certain limitations. *Chromite ore* has been extensively tested in rats by intrabronchial, intrapleural and intrafemoral administration; no increase in the incidence of tumours was seen.

Chromium[VI]

Calcium chromate has been tested by inhalation in mice, by intratracheal administration in rats and hamsters, by intrabronchial administration and intrapleural administration in rats, by subcutaneous administration in mice, and by intramuscular administration in mice and rats. In the one study by inhalation in mice, there was an increase in the incidence of lung adenomas which was of borderline significance; in the single study by intratracheal administration and in the three studies by intrabronchial administration in rats, lung tumours were induced. No lung tumour was seen in hamsters after intratracheal instillation. Local tumours were produced in rats by intrapleural and in rats and mice by intramuscular administration of calcium chromate. *Chromium trioxide* (chromic acid) has been tested as a mist by inhalation at two dose levels in mice and as a solid by intrabronchial implantation in three studies in rats. In mice, a low incidence of lung adenocarcinomas was observed at the higher dose and of nasal papillomas at the lower dose; perforation of the nasal septum was observed at both dose levels. A few lung tumours were seen in two of the studies by intrabronchial administration in rats. *Sodium dichromate* has been tested in rats by inhalation, intratracheal, intrabronchial, intrapleural and intramuscular administration. Lung tumours, benign and malignant, were observed in the studies by inhalation and by intratracheal administration. No increase in the occurrence of local tumours was seen after intrabronchial, intrapleural or intramuscular administration. *Barium chromate* has been tested in rats by intrabronchial, intrapleural and intramuscular implantation. No increase in the occurrence of tumours was seen following intrabronchial implantation; the other studies were inadequate to allow an evaluation of the carcinogenicity of this compound. *Lead chromate* and derived pigments have been tested by intrabronchial implantation in rats without producing a significant increase in the incidence of tumours. Lead chromate and derived pigments have also been tested in rats by subcutaneous and intramuscular injection, producing malignant tumours at the site of injection

and, in one study, renal carcinomas. A study by intrapleural administration to rats could not be evaluated. No increase in tumour incidence was observed when lead chromate was administered intramuscularly to mice. A single subcutaneous injection of *basic lead chromate* produced a high incidence of local sarcomas in rats. *Zinc chromates* have been tested in rats by intrabronchial implantation, producing bronchial carcinomas, by intrapleural administration, producing local tumours, and by subcutaneous and intramuscular injection, producing local sarcomas. Two samples of *strontium chromate* were tested in rats by intrabronchial implantation, producing a high incidence of bronchial carcinomas; intrapleural and intramuscular injection of strontium chromate produced local sarcomas.

Other forms of chromium

A range of *roasted chromite ores* (Cr[III/VI]), often described as mixed chromium dust, and other residue materials encountered in the early stages of bichromate production have been tested extensively in mice, rats, guinea-pigs and rabbits by inhalation and by intratracheal, intrabronchial, intrapleural and intramuscular administration. The results of these tests were generally negative, although a low incidence of local tumours was observed in rats following intrapleural or intramuscular implantation of roasted chromite ore. The studies were considered to suffer from certain inadequacies. *Chromium[IV] dioxide* was tested by inhalation in rats, producing a few lung lesions of questionable nature; the study had a number of limitations.

4.3 Human carcinogenicity data

Epidemiological studies carried out in the Federal Republic of Germany, Italy, Japan, the UK and the USA of workers in the chromate production industry have consistently shown excess risks for lung cancer. The workers in this industry may be exposed to a variety of forms of chromium, including chromium[VI] and [III] compounds.

Similarly, studies carried out in the Federal Republic of Germany, France, the Netherlands, Norway, the UK and the USA of workers in the production of chromate pigments have also consistently shown excess risks for lung cancer. Workers in this industry are exposed to chromates, not only in the pigments themselves but also from soluble chromium[VI] compounds in the raw materials used in their production. Excess risk for lung cancer has been clearly established in facilities where zinc chromate was produced, although other chromium pigments were also generally made in these plants. A small study in the UK of workers producing lead chromate pigments showed no overall excess risk for lung cancer, but a nonsignificant excess risk was seen in a subgroup of workers with lead poisoning. No data were

available on risk associated with exposure to strontium chromate or to other specific chromate pigments.

In two limited reports from the UK and in a small Italian study, excesses of lung cancer were reported in workers in the chromium plating industry. In a group of persons working in die-casting and plating in the USA, similar results were seen. These findings were confirmed in a large study of chromium platers in the UK, which demonstrated an excess risk for lung cancer in platers, particularly among those with at least ten years of employment at chrome baths. Workers in this industry have been exposed to soluble chromium[VI] compounds and possibly also to nickel.

In three reports, from Norway, Sweden and the USSR, in which ferrochromium workers were studied, the overall results with regard to lung cancer were inconclusive. The major exposure in this industry is to chromium[III] compounds and to metallic chromium, although exposure to chromium[VI] may also occur.

Cases of sinonasal cancer were reported in epidemiological studies of primary chromate production workers in Japan, the UK and the USA, of chromate pigment production workers in Norway and of chromium platers in the UK, indicating a pattern of excess risk for these rare tumours.

For cancers other than of the lung and sinonasal cavity, no consistent pattern of cancer risk has been shown among workers exposed to chromium compounds.

The results of epidemiological studies of stainless-steel welders are consistent with the finding of excess mortality from lung cancer among other workers exposed to chromium[VI], but they do not contribute independently to the evaluation of chromium since welders are also exposed to other compounds. (See also the monograph on welding.)

No epidemiological study addressed the risk of cancer from exposure to metallic chromium alone.

4.4 Other relevant data

Inhaled chromium[VI] from welding and chrome-plating aerosols is readily absorbed from the respiratory tract. The degree of absorption depends on the extent of reduction of the hexavalent form to chromium[III], which is absorbed to a much lesser extent. The same factors apply to absorption from the gastrointestinal tract, although absorption by this route is generally much less than that from the respiratory tract.

Chromium[VI] compounds may cause adverse effects to the skin, the respiratory tract and, to a lesser degree, the kidneys in humans, while chromium[III] is less toxic.

Elevated levels of sister chromatid exchange were observed in workers exposed to chromium[VI] compounds in electroplating factories in four out of six studies.

Chromosomal aberrations were found in all three studies of exposed workers; an increased frequency of aneuploidy was reported in one of these studies. The two available studies on chromium[III] were inadequate to evaluate its cytogenetic effect in humans.

Chromates enter cells more readily than chromium[III] compounds and are reduced ultimately to chromium[III]. The reduction process and the subsequent intracellular activity of reduced chromium species are important for the mechanism of toxicity and carcinogenicity of chromium[VI]. Particulate chromium[III] compounds can also enter cells by phagocytosis.

Chromium[VI] compounds cross the placental barrier in greater amounts than chromium[III] compounds. Chromium trioxide increased fetal death rate, caused growth retardation and increased the frequency of skeletal deformities and of cleft palate in rodents. Developmental effects have also been reported in mice exposed to chromic chloride.

Chromium[VI] compounds of various solubilities in water were consistently active in numerous studies covering a wide range of tests for genetic and related effects. In particular, potassium dichromate, sodium dichromate, ammonium dichromate, potassium chromate, sodium chromate, ammonium chromate, chromium trioxide, calcium chromate, strontium chromate and zinc yellow induced a variety of effects (including DNA damage, gene mutation, sister chromatid exchange, chromosomal aberrations, cell transformation and dominant lethal mutation) in a number of targets, including animal cells *in vivo* and animal and human cells *in vitro*. Potassium chromate induced aneuploidy in insects, while chromium trioxide did not; various compounds induced gene mutation in insects. Potassium dichromate produced recombination, gene mutation and aneuploidy in fungi. All of these chromium[VI] compounds induced DNA damage and gene mutation in bacteria. Similar patterns were observed with zinc chromate, barium chromate, lead chromate and the derived pigments chromium orange, chromium yellow and molybdenum orange, which, however, often required preliminary dissolution in alkali or acids. A liquid chromium[VI] compound (chromyl chloride) and its vapours induced gene mutation in bacteria.

Although chromium[III] compounds were generally even more reactive than chromium[VI] compounds with purified DNA and isolated nuclei, 12 compounds of various solubilities (chromic chloride, chromic acetate, chromic nitrate, chromic sulfate, chromic potassium sulfate, chromium alum, neochromium, chromic hydroxide, chromic phosphate, chromic oxide, chromite ore and cupric chromite) gave positive results in only a minority of studies using cellular test systems, often under particular treatment conditions or at very high concentrations, which were generally orders of magnitude higher than those needed to obtain the same effects with chromium[VI] compounds. Some of the positive results could be ascribed to

contamination with traces of chromium[VI] compounds. In particular, no DNA damage was observed in cells of animals treated *in vivo* with chromic chloride, and no micronuclei were seen in cells of animals given chromic nitrate. The chromium[III] compounds tested generally did not produce DNA damage, gene mutation, sister chromatid exchange or cell transformation in cultured animal and human cells. Chromosomal aberrations were often observed with high concentrations of chromium[III] compounds. Weak effects on gene mutation and mitotic gene conversion were observed in fungi. Negative results were obtained in the large majority of tests for DNA damage and gene mutation in bacteria. Certain complexes of chromium[III] with organic ligands, which favour the penetration of chromium[III] into cells, were reported to induce DNA damage and gene mutation in bacteria and in cultured mammalian cells.

A chromium[II] compound (chromous chloride) gave negative results in in-vitro tests with animal cells (DNA damage, chromosomal aberrations and aneuploidy). A water-insoluble chromium[0] compound (chromium carbonyl) did not induce DNA damage in bacteria.

No relevant study on the genetic and related effects of metallic chromium was available to the Working Group.

4.5 Evaluation[1]

There is *sufficient evidence* in humans for the carcinogenicity of chromium[VI] compounds as encountered in the chromate production, chromate pigment production and chromium plating industries.

There is *inadequate evidence* in humans for the carcinogenicity of metallic chromium and of chromium[III] compounds.

There is *sufficient evidence* in experimental animals for the carcinogenicity of calcium chromate, zinc chromates, strontium chromate and lead chromates.

There is *limited evidence* in experimental animals for the carcinogenicity of chromium trioxide (chromic acid) and sodium dichromate.

There is *inadequate evidence* in experimental animals for the carcinogenicity of metallic chromium, barium chromate and chromium[III] compounds.

The Working Group made the overall evaluation on chromium[VI] compounds on the basis of the combined results of epidemiological studies, carcinogenicity studies in experimental animals, and several types of other relevant data which support the underlying concept that chromium[VI] ions generated at critical sites in the target cells are responsible for the carcinogenic action observed.

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[1]For definitions of the italicized terms, see Preamble, pp. 33–37

Overall evaluation

Chromium[VI] *is carcinogenic to humans* (Group 1).

Metallic chromium and chromium[III] compounds *are not classifiable as to their carcinogenicity to humans* (Group 3).