5. Summary of Data Reported and Evaluation

5.1 Exposure data

Cadmium is found at low concentrations in the Earth's crust, mainly as the sulfide in zinc-containing mineral deposits. Since the early twentieth century, it has been produced and used in a variety of applications in alloys and in compounds. Among the important compounds of cadmium are cadmium oxide (used in batteries, as an intermediate and catalyst and in electroplating), cadmium sulfide (used as a pigment), cadmium sulfate (used as an intermediate and in electroplating) and cadmium stearate (used as a plastics stabilizer).

Occupational exposure to cadmium and cadmium compounds occurs mainly in the form of airborne dust and fume. Occupations in which the highest potential exposures occur include cadmium production and refining, nickel–cadmium battery manufacture, cadmium pigment manufacture and formulation, cadmium alloy production, mechanical plating, zinc smelting, soldering and polyvinylchloride compounding. Although levels vary widely among the different industries, occupational exposures generally have decreased in the last two decades.

Urinary and blood cadmium concentrations are generally much lower in non-occupationally exposed people, for whom the most important sources of exposure are cigarette smoking and, especially in polluted areas, eating certain foods (e.g. rice). Acidification of cadmium-containing soils and sediments may increase the concentrations of cadmium in surface waters and crops.

5.2 Human carcinogenicity data

Following a report of the occurrence of prostatic cancers in a small group of workers employed before 1965 in a plant manufacturing nickel–cadmium batteries in the United

Kingdom, a series of cohort analyses were undertaken, which did not confirm the excess among the remaining workers; however, an increase in mortality rates from lung cancer was detected. A small cohort working in the same industry was studied in Sweden: no excess of prostatic cancer was detected, but a nonsignificant increase in mortality from lung cancer was found among workers who had the longest duration of employment and latency.

Two small copper–cadmium alloy plants were studied in the United Kingdom. The rate of mortality from lung cancer was increased in one of them but decreased in the other. A case–control analysis of lung cancer did not show any association with exposure to cadmium. No increase in mortality from prostatic cancer was found in these two plants, while in a similar plant in Sweden a nonsignificant excess was detected.

Excess mortality from lung cancer was reported among workers employed in a US cadmium recovery plant, and a dose–response relationship was demonstrated between estimated cumulative exposure to cadmium and lung cancer risk. The latter was unlikely to be due to confounding by cigarette smoking and persisted among workers employed after 1940, when little arsenic was present in feedstock. Excess mortality from prostatic cancer was found initially, but the relative risk diminished and became nonsignificant with further follow-up.

In a large cohort of workers from 17 cadmium processing plants in the United Kingdom, decreased mortality from prostatic cancer was observed, while that from lung cancer was increased in the overall cohort and there were suggested trends with duration of employment and with intensity of exposure. The increase in lung cancer risk was stronger in the small proportion of workers with high cadmium exposure. Confounding by concomitant exposure to other cancer determinants, including arsenic, was not controlled for. Excess mortality from stomach cancer, which was not related to intensity of cadmium exposure, was also reported among these workers.

A number of early studies reported an increased risk for prostatic cancer among cadmium workers, but the results of later studies were not consistent. Early and recent studies provide consistent evidence that the risk for lung cancer is increased among workers exposed to cadmium.

Constraints that influence the assessment of both lung and prostatic cancer risk are that the number of long-term, highly exposed workers is small, the historical data on exposure to cadmium are limited, particularly for the non-US plants, and the ability to define and examine a gradient of cumulative exposure varies across studies. Additionally, for cohort studies, prostatic cancer poses special difficulties in that it is subject to the possibility of detection bias. Confounding by cigarette smoking in relation to lung cancer was addressed directly only in the study from the USA, but some other studies provided analyses based on internal comparisons, which are not likely to be affected by this problem. Control of the confounding effect of co-exposure to other metals, particularly arsenic and nickel, was limited; however, the analyses in which an attempt was made to distinguish US cadmium-exposed workers with different levels of exposure to arsenic indicated that the increase in lung cancer risk was unlikely to be explained by exposure to arsenic.

5.3 Animal carcinogenicity data

Cadmium chloride, cadmium sulfate and cadmium acetate have been tested by oral administration in several studies in mice and rats. Most of the studies were inadequate for an evaluation of carcinogenicity. Two adequate studies on cadmium chloride in rats are available. In one study with controlled dietary zinc levels in male rats, cadmium chloride produced dose-related increases in the incidences of leukaemia, interstitial-cell tumours of the testis and proliferative lesions of the prostate. In another study on cadmium chloride in rats, in which zinc levels in diet were not controlled, no increase in tumour incidence was seen.

In two inhalation studies in rats, malignant lung tumours were produced by cadmium chloride, cadmium sulfide/sulfate, cadmium sulfate and cadmium oxide fume and dust at low levels of exposure for short durations. In one study in rats by intratracheal instillation, malignant pulmonary tumours were produced by cadmium sulfide and cadmium chloride, but not by cadmium oxide. In one inhalation study in mice of cadmium chloride, cadmium sulfide/sulfate, cadmium sulfate and cadmium oxide fume and dust, some groups exposed to cadmium oxide fume or dust had increased incidences of lung tumours. In one inhalation study in hamsters of cadmium chloride, cadmium sulfide/sulfate, cadmium sulfate and cadmium oxide fume and dust, no increase in the incidence of lung tumours was found.

In several studies, single or multiple subcutaneous injections of cadmium chloride, cadmium sulfide, cadmium sulfate and cadmium oxide and of cadmium-containing rat liver ferritin caused local sarcomas in rats. Mice appear to be generally less susceptible than rats to induction of local tumours by cadmium compounds. Cadmium powder, cadmium chloride and cadmium sulfide produced local sarcomas in rats following intramuscular administration. In a single study by intraperitoneal injection in rats, cadmium sulfide induced malignant tumours within the peritoneal cavity. Cadmium chloride in mice and rats and cadmium sulfate and cadmium-precipitated rat liver ferritin in rats produced testicular interstitial tumours after subcutaneous administration. Dietary zinc deficiency enhanced the multiplicity of cadmium-induced interstitial-cell tumours of the testis and increased the incidence of local tumours at the site of subcutaneous cadmium injections. Subcutaneous injection of cadmium chloride to rats produced tumours of the prostate but only at doses below the level that induced cadmium-induced testicular degeneration or when such degeneration was prevented by concurrent exposure to zinc. Intramuscular administration of cadmium chloride also induced prostatic tumours in rats. Subcutaneous administration of cadmium chloride increased the incidence of pancreatic tumours in rats in one study and decreased the incidence in another.

In limited studies in rats, injection of cadmium chloride into the prostate produced malignant prostatic tumours.

Administration of excess zinc by inhalation, parenteral and oral routes has been shown to reduce the carcinogenic potential of cadmium after exposure systemically or by inhalation. When combined with known carcinogens, cadmium enhanced, suppressed or had no effect on tumour incidence, depending on a complex set of circumstances including, at least in part, the dose, time sequence of administration, site of tumour and route of administration.

5.4 Other relevant data

Cadmium enters the body mainly by inhalation and by ingestion. Fractional intestinal absorption is influenced by dietary factors and increases with dietary cadmium concentration. Pulmonary fractional absorption depends partly on the solubility *in vivo* of the compound. Cadmium induces synthesis of metallothionein, a low-molecular-weight protein that binds cadmium primarily in the liver and kidney. Metallothionein production can also be induced by e.g. zinc. When metallothionein-bound cadmium is released into the blood, it is filtered through the glomeruli and then reabsorbed in the proximal tubules. In certain mammalian tissues, such as rat ventral prostate, hamster ovary and rat, mouse and monkey testis, the concentrations of metallothionein are low and its synthesis is not induced by exposure to cadmium. Most of the body burden of cadmium is retained in the kidneys and the liver. The half-life of cadmium in human kidneys is probably 10–20 years. Cadmium concentrations in whole blood are affected by both recent exposure and body burden. Excretion occurs mainly *via* the urine. Urinary excretion of cadmium by individuals without renal dysfunction primarily reflects the amount of cadmium retained in the kidneys.

The target organs for cadmium toxicity depend on the type of exposure. Inhalation of cadmium can lead to chronic obstructive airway disease. Following long-term exposure, renal tubular and glomerular dysfunction can develop. Renal function can deteriorate further, even after cessation of exposure to cadmium. Cadmium can suppress cell-mediated immune responses *in vitro*.

Parenteral administration of cadmium salts produces adverse effects on the testes, ovaries, placenta and embryo in experimental animals; many of these effects have been shown to be preventable by administration of zinc compounds. Administration of cadmium at doses that affect placental morphology or function induces fetal anaemia, growth retardation, teratogenicity and embryonic and fetal death in experimental animals. Reproductive and developmental toxicity have been reported following exposure to cadmium compounds by oral and inhalation routes, but the effects are generally much less severe than after parenteral administration.

In three of five studies, the frequencies of chromosomal aberration were increased in peripheral blood lymphocytes of workers exposed to cadmium in the metal industry, where they were usually also exposed to other metals. No effect of cadmium was observed in a limited study of workers from a Swedish alkaline battery factory. In two studies of cadmium pigment plant workers, no increase in the frequency of chromosomal aberrations was observed. No increase in the frequency of sister chromatid exchange was seen in one study of workers exposed to cadmium.

In one of two limited studies of *itai-itai* patients, increased frequency and severity of chromosomal aberrations were observed. In one study, no increase in sister chromatid exchange frequency was observed in people living in a cadmium-polluted region of Japan. In a study of subjects living in a cadmium-polluted region of China, there were small but significant increases in chromosomal aberration frequency. A significant dose–effect relationship between urinary levels of cadmium and chromosomal aberration frequency was also observed, and more severe aberration types were observed in individuals with high urinary levels of cadmium.

In those studies in which significant responses were observed, the chromosomal aberrations tended to occur in the more heavily exposed groups and were of more complex types.

Chromosomal aberrations and aneuploidy were observed in animals exposed to cadmium chloride *in vivo*. Dominant lethal mutations were generally not induced in mice.

Cadmium chloride damages DNA of human cells *in vitro*. In the few studies available, chromosomal aberrations were observed in human cells treated with cadmium sulfide but not in those treated with cadmium chloride. Indications of aneuploidy were observed in human fibroblasts after treatment with cadmium chloride.

Studies using cultured animal cells show that exposure to cadmium compounds damages genetic material. DNA strand breaks, mutations, chromosomal damage and cell transformation have been observed *in vitro*. Cadmium compounds inhibit the repair of DNA damaged by other agents, thereby enhancing their genotoxicity.

Mutations have generally not been observed in *Drosophila* or bacteria; however, a weak response was observed in some studies in bacteria and there is evidence for cadmium-induced DNA damage in bacteria.

5.5 Evaluation[1]

There is *sufficient evidence* in humans for the carcinogenicity of cadmium and cadmium compounds.

There is *sufficient evidence* in experimental animals for the carcinogenicity of cadmium compounds.

There is *limited evidence* in experimental animals for the carcinogenicity of cadmium metal.

In making the overall evaluation, the Working Group took into consideration the evidence that ionic cadmium causes genotoxic effects in a variety of types of eukaryotic cells, including human cells.

Overall evaluation

Cadmium and cadmium compounds *are carcinogenic to humans (Group 1)*.