5. Summary of Data Reported and Evaluation

5.1 Exposure data

Cobalt is widely distributed in the environment, occurring in the earth's crust mainly in the form of sulfides, oxides and arsenides. Cobalt metal is used to make corrosion- and wear-resistant alloys used in aircraft engines (superalloys), in magnets (magnetic alloys) and in high-strength steels and other alloys for many applications. Cobalt metal is added to metallic carbides, especially tungsten carbide, to prepare hard metals (two-phase composites; also known as cemented carbides) for metal-working tools. Cobalt is also used to manufacture cobalt-diamond grinding tools, cobalt discs and other cutting and grinding tools made from cobalt metal. Other uses of cobalt compounds include catalysts, batteries, dyes and pigments and related applications. Occupational exposure to cobalt occurs pre-

dominantly during refining of cobalt, in the production of alloys, and in the hard-metal industry where workers may be exposed during the manufacture and maintenance of hard-metal tools and during the use of diamond-cobalt tools.

5.2 Human carcinogenicity data

Several reports addressing cancer risks among workers in hard-metal production facilities in France provide evidence of an increased lung cancer risk related to exposure to hard-metal dust containing cobalt and tungsten carbide. The risk appears to be highest among those exposed to unsintered rather than sintered hard-metal dust. There is evidence for an increasing lung cancer risk with increasing duration of exposure in analyses which took into account potential confounding by smoking and other occupational carcinogens.

An earlier and smaller study of workers exposed to cobalt and tungsten carbide in the hard-metal industry in Sweden found increased mortality from lung cancer in the full cohort, with a higher risk among those with longer duration of exposure and latency. The study provides limited confirmation due to the small number of exposed lung cancer cases, the lack of adjustment for other carcinogenic exposures and the absence of a positive relationship between intensity of exposure and lung cancer risk.

The study of workers in hard-metal factories in France also allowed estimation of lung cancer risk in relation to exposures to cobalt in the absence of tungsten carbide. A twofold increased lung cancer risk was observed. However, no exposure–response relationships were reported and the results were not adjusted for other occupational carcinogens or smoking. Another study in the cobalt production industry in France reported no increase in risk of lung cancer mortality among cobalt production workers, but the study was limited by very small numbers.

5.3 Animal carcinogenicity data

Cobalt sulfate heptahydrate as an aqueous aerosol was tested in a single study by inhalation exposure in male and female mice and rats. Increased incidences of alveolar/bronchiolar neoplasms were seen in both sexes of both species. There was also an increase in adrenal pheochromocytomas in female rats. It was uncertain whether a marginal increase in pheochromocytomas in male rats was caused by cobalt sulfate.

Cobalt metal powder was tested in two experiments in rats by intramuscular injection and in one experiment by intrathoracic injection, and in rabbits in one experiment by intraosseous injection. All the studies revealed sarcomas at the injection site.

A finely powdered cobalt–chromium–molybdenum alloy was tested in rats by intramuscular injection and produced sarcomas at the injection site. In two other experiments in rats, coarsely- or finely-ground cobalt–chromium–molybdenum alloy implanted in muscle, or pellets of cobalt–chromium–molybdenum alloy implanted subcutaneously, did not induce sarcomas. Implantation in the rat femur of three different cobalt-containing alloys, in the form of powder, rod or compacted wire, resulted in a few local sarcomas. In another

experiment, intramuscular implantation of polished rods consisting of three different cobalt-containing alloys did not produce local sarcomas. In an experiment in guinea-pigs, intramuscular implantation of a cobalt–chromium–molybdenum alloy powder did not produce local tumours.

Intraperitoneal injection of a cobalt–chromium–aluminium spinel in rats produced a few local malignant tumours, and intratracheal instillation of this spinel in rats was associated with the occurrence of a few pulmonary squamous-cell carcinomas.

Interpretation of the evidence available for the carcinogenicity of cobalt in experimental animals was difficult because many of the reports failed to include sufficient details on results of statistical analyses, on survival and on control groups. Furthermore, such statistical analyses could not be performed by the Working Group in the absence of specific information on survival including fatality due to the neoplasms. Nevertheless, in the evaluation, weight was given to the consistent occurrence of tumours at the site of administration and to the histological types of tumours observed. However, intramuscular or subcutaneous injection of relatively inert foreign materials into rats is known to result in malignant tumours at the injection site, therefore limiting the interpretation of the results.

5.4 Other relevant data

The absorption rate of inhaled cobalt-containing particles is dependent on their solubility in biological fluids and in macrophages. In humans, gastrointestinal absorption of cobalt has been reported to vary between 5 and 45% and it has been suggested that absorption is higher in women than in men. Cobalt can be absorbed through intact human skin. It does not accumulate in any specific organ, except in the lung when inhaled in the form of insoluble particles. High concentrations of cobalt in blood are found in workers exposed to cobalt, in uraemic patients and in persons taking multivitamin preparations. Most of the absorbed cobalt is excreted in the urine within days, but a certain proportion is eliminated slowly, with half-life values between 2 and 15 years. Cobalt ions bind strongly to circulating proteins, mainly albumin. Cobalt concentrations in blood and/or in urine can be used in biological monitoring to assess individual exposure. After inhalation of metallic cobalt particles with tungsten carbide, toxic effects (alveolitis, fibrosis) occur at the site of contact and deposition. These effects are caused by the particles themselves and by solubilized cobalt ions. Systemic effects outside the respiratory tract are unlikely to be due to the particles. The main non-malignant respiratory disorders caused by inhalation of metallic cobalt-containing particles are bronchial asthma (any cobalt compounds) and fibrosing alveolitis (cobalt metal mixed with tungsten carbide or with microdiamonds). Fibrosis alveolitis, also known as hard-metal lung disease, is characterized pathologically as a giant-cell interstitial pneumonia; there is no evidence that it is caused by cobalt metal alone or cobalt salts. Non-respiratory toxic effects of cobalt include stimulation of erythropoiesis, and toxicity in the thyroid and the heart. Cobalt has skin-sensitizing properties, which may lead to contact dermatitis or airborne dermatitis.

In animals, it has been demonstrated that the health status of the lung affects the rate of clearance and retention of cobalt-containing particles. Smaller particles show a higher dissolution rate than larger ones. When mixed with tungsten carbide, the absorption and subsequent excretion of intratracheally-instilled cobalt-metal particles is greatly enhanced.

In experimental animals, various cobalt compounds cause a variety of toxic effects in the respiratory tract (pulmonary oedema, acute pneumonia), thyroid, erythropoietic tissue, myocardium and reproductive organs. A mixture of cobalt-metal particles and tungsten carbide caused effects that were much more severe than those observed with cobalt metal alone. Specific surface chemistry and increased production of reactive oxygen species at the site of mutual contact between cobalt and tungsten carbide are likely to play a role in this phenomenon. Cobalt-metal particles are weak inducers of reactive oxygen species *in vitro*, but this effect is greatly enhanced by the presence of tungsten carbide particles.

Exposure by inhalation to cobalt oxide, cobalt chloride or cobalt sulfate gives rise to a spectrum of inflammatory and proliferative changes in the respiratory tract in animals. Biochemical effects include increased levels of oxidized glutathione and stimulation of the pentose phosphate pathway, both of which are indicative of oxidative stress.

Reproductive effects of cobalt chloride include teratogenic effects in mice, and growth retardation and reduced postnatal survival in rats. Decreased fertility, testicular weights and sperm concentration have also been observed in mice. Inhalation of cobalt sulfate also gave rise to decreased sperm motility and increased sperm abnormality in mice, but not in rats.

In vitro, cobalt has been shown to induce various enzymes involved in the cellular response to stress and to interfere with cell-cycle control.

The results of genotoxicity assays with a variety of cobalt salts demonstrate the mutagenic potential of these salts both *in vitro* and *in vivo*. Moreover, from experiments performed with a mixture of cobalt and tungsten carbide particles, there is strong evidence that the mixture is mutagenic *in vitro*. It was also demonstrated to be mutagenic *in vivo* in rat lung cells.

5.5 Evaluation

There is *limited evidence* in humans for the carcinogenicity of cobalt metal with tungsten carbide.

There is *inadequate evidence* in humans for the carcinogenicity of cobalt metal without tungsten carbide.

There is *sufficient evidence* in experimental animals for the carcinogenicity of cobalt sulfate.

There is *sufficient evidence* in experimental animals for the carcinogenicity of cobalt-metal powder.

There is *limited evidence* in experimental animals for the carcinogenicity of metal alloys containing cobalt.

There is *inadequate evidence* in experimental animals for the carcinogenicity of cobalt–aluminum–chromium spinel.

Overall evaluation

Cobalt metal with tungsten carbide is *probably carcinogenic to humans (Group 2A)*.

A number of working group members supported an evaluation in Group 1 because: (1) they judged the epidemiological evidence to be sufficient, leading to an overall evaluation in Group 1; and/or (2) they judged the mechanistic evidence to be strong enough to justify upgrading the default evaluation from 2A to 1. The majority of working group members, who supported the group 2A evaluation, cited the need for either sufficient evidence in humans or strong mechanistic evidence in exposed humans.

Cobalt metal without tungsten carbide is *possibly carcinogenic to humans (Group 2B)*.

Cobalt sulfate and other soluble cobalt(II) salts are *possibly carcinogenic to humans (Group 2B)*.