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IARC Monographs on the Evaluation of Carcinogenic Risks to Humans

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Cobalt in Hard Metals and Cobalt Sulfate, Gallium Arsenide, Indium Phosphide and Vanadium Pentoxide

Summary of Data Reported and Evaluation

METALLIC COBALT PARTICLES (WITH OR WITHOUT TUNGSTEN CARBIDE)

Cobalt metal with tungsten carbide (Group 2A)
Cobalt metal without tungsten carbide (Group 2B)
Cobalt sulfate and other soluble cobalt(II) salts (Group 2B)

For definition of Groups, see Preamble Evaluation.

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Metallic cobalt
CAS No.: 7440-48-4

Cobalt sulfate heptahydrate
CAS No.: 10026-24-1

Tungsten carbide
CAS No.: 12070-12-1

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 predominantly 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 implan-tation of polished rods consisting of three different cobalt-containing alloys did not produce local sarcomas. In an experiment in guinea-pigs, intramuscular implan-tation 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)*.

For definition of the italicized terms, see Preamble Evaluation.

Previous evaluation: Vol. 52 (1991)

Synonyms

Metallic cobalt
- C.I. 77320
- Cobalt element
- Cobalt-59

Cobalt sulfate heptahydrate
- Cobalt monosulfate heptahydrate
- Cobalt(II) sulfate heptahydrate
- Cobalt(II) sulfate (1:1), heptahydrate

Tungsten carbide
- Tungsten carbide (WC)
- Tungsten monocarbide
- Tungsten monocarbide (WC)

GALLIUM ARSENIDE
(Group 1)

For definition of Groups, see Preamble Evaluation.

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CAS No.: 1303-00-0

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Gallium arsenide is extensively used in the microelectronics industry because of its photovoltaic properties. Gallium arsenide is produced as high purity single crystals and cut into wafers and other shapes which are used primarily for integrated circuits and optoelectronic devices. Exposure to gallium arsenide occurs predominantly in the microelectronics industry where workers are involved in the production of gallium arsenide crystals, ingots and wafers, grinding and sawing operations, device fabrication and sandblasting and clean-up activities.

5.2 Human carcinogenicity data

See Introduction to the Monographs on Gallium Arsenide and Indium Phosphide. Studies of Cancer in Humans.

5.3 Animal carcinogenicity data

Gallium arsenide was tested for carcinogenicity in a single study by chronic inhalation exposure in mice and rats. In female rats exposed to the highest concentration, significantly increased incidences of alveolar/bronchiolar neoplasms, benign pheochromocytoma of the adrenal medulla and mononuclear-cell leukaemia were observed. There was no evidence of carcinogenic activity in male rats, or in male or female mice.

Gallium arsenide was tested by intratracheal instillation in male hamsters and showed no carcinogenic response. However, due to inadequacies in design and reporting, the study did not contribute to this evaluation.

5.4 Other relevant data

Gallium arsenide has low solubility. There is in-vitro and in-vivo evidence that gallium arsenide releases gallium and arsenic moieties.

Uptake from the gastrointestinal tract is low. In inhalation studies, lung retention of inhaled gallium arsenide has been shown to be influenced by toxic effects from gallium arsenide itself. Tissue burdens are highest in the lung. Concentrations of gallium and arsenic in blood and serum remain low in long-term inhalation studies. Concentrations of gallium in testes show evidence of accumulation, but at a much lower level than in the lung. After intratracheal instillation of gallium arsenide, data indicate slower elimination and higher serum concentrations of gallium compared with arsenic.

The most prominent toxic effect of gallium arsenide is pulmonary inflammation, which may occur after a single intratracheal dose. Gallium arsenide and gallium nitrate inhibit the activity of δ-aminolevulinic acid dehydratase.

Immunological effects of exposure to gallium arsenide include inhibition of T-cell proliferation and decrease of both humoral and cellular immune response. These effects are partly due to the arsenic moiety.

Testicular toxicity was observed in rats and hamsters exposed to gallium arsenide by intratracheal administration, while animals treated with arsenic trioxide and indium arsenide did not show these effects. In inhalation studies with gallium arsenide, decreased epididymal weights and reduced sperm mobility were observed. A number of reproductive toxic effects were reported following exposure of pregnant rodents to gallium arsenide. These effects were more severe in mice than in rats.

Based on limited data, gallium arsenide does not show genotoxic activity.

5.5 Evaluation

There is *inadequate evidence* in humans for the carcinogenicity of gallium arsenide.

There is *limited evidence* in experimental animals for the carcinogenicity of gallium arsenide.

Overall evaluation

Gallium arsenide is *carcinogenic to humans (Group 1)*.

The Working Group noted that there were no data on cancer in humans and that gallium arsenide is, at best, a weak carcinogen in experimental animals. In reaching an overall evaluation of *Group 1*, the Working Group noted the potential for gallium arsenide to cause cancer through two separate mechanisms of action. Once in the body, gallium arsenide releases a small amount of its arsenic, which behaves as inorganic arsenic at the sites where it is distributed. (Arsenic and arsenic compounds have been evaluated as IARC Group 1, carcinogenic to humans.) At the same time, the gallium moiety may be responsible for the lung cancers observed in the study in female rats, due to the apparent resistance of rats to the carcinogenic potential of arsenic that is manifest in humans. The similarity of toxicochemical

responses observed in subchronic studies with gallium arsenide and gallium oxide adds weight to the finding that the gallium moiety is active and suggests that a carcinogenic response might be observed with other gallium compounds. The observed findings may also be a result of the combination of the two moieties.

For definition of the italicized terms, see Preamble Evaluation.

Synonym

- Gallium monoarsenide

INDIUM PHOSPHIDE
(Group 2A)

For definition of Groups, see Preamble Evaluation.

Vol.: 86 (2006) (p. 197)

CAS No.: 22398-80-7

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Indium phosphide is used in the microelectronics industry because of its photovoltaic properties. It is produced as high-purity, single crystals cut into wafers and other shapes, which are used primarily for optoelectronic devices and in integrated circuits. Exposure to indium phosphide may occur in the microelectronics industry where workers are involved in the production of indium phosphide crystals, ingots and wafers, in grinding and sawing operations and in device fabrication.

5.2 Human carcinogenicity data

See Introduction to the Monographs on Gallium Arsenide and Indium Phosphide. Studies of Cancer in Humans.

5.3 Animal carcinogenicity data

Indium phosphide was tested for carcinogenicity in a single study in mice and rats by inhalation exposure. Exposure to indium phosphide caused an increased incidence of alveolar/bronchiolar carcinomas in male mice and alveolar/bronchiolar adenomas and carcinomas in female mice and male and female rats. There was also a significant increase in the incidence of hepatocellular adenomas/carcinomas in exposed male and female mice and an increased incidence of benign and malignant pheochromocytomas of the adrenal gland in male and female rats. Other findings, which may have been exposure-related, were marginal increases in the incidences of adenomas/carcinomas of the small intestine in male mice, mononuclear-cell leukaemia in males and female rats, fibroma of the skin in male rats and carcinoma of the mammary gland in female rats. Indium phosphide was tested by intratracheal instillation in male hamsters and showed no carcinogenic response. However, due to the study design, it was not considered for evaluation.

5.4 Other relevant data

Indium phosphide has low solubility, and uptake from the gastrointestinal tract is low. Lung toxicity has been observed in long-term inhalation studies with indium phosphide. The lung tissue burden is high and elimination from the lung is very slow. In rats, concentrations of indium phosphide in blood, serum and testes could be followed for over 100 days after cessation of exposure by inhalation. The concentration of indium in the testes continued to increase, but the testicular tissue burden remained much lower than that in the lung. In various experimental systems using different routes of administration, accumulation of indium phosphide has also been demonstrated in liver, spleen and kidney. Indium is eliminated via urine and faeces.

Important toxic effects of intratracheally instilled indium phosphide particles are the induction of pulmonary inflammation, alveolar or bronchiolar hyperplasia, pneumonia and emphysema. Indium phosphide gave rise to enhanced activities of superoxide dismutase, nitric oxide synthase, cyclooxygenase and lactate dehydrogenase in bronchoalveolar lavage fluid, and to increased neutrophil and lymphocyte counts. At high doses, eosinophilic exudates and desquamation of alveolar epithelial cells were observed. Soluble indium was a potent inducer of haeme oxygenase, a marker of oxidative stress. Indium also showed inhibitory effects on protein synthesis and, at higher doses, on apoptosis.

No data were available on reproductive and developmental effects of indium phosphide in humans. Apart from slightly reduced pregnancy rates, no reproductive effects were observed in rats exposed to indium phosphide by inhalation. Mice exposed under comparable conditions were much more sensitive, showing early fetal deaths and reduced body weight gain. There is no evidence that indium phosphide is teratogenic.

Micronucleus formation was observed in male, but not in female mice exposed to indium phosphide by inhalation. No other data on genetic and related effects as a result of exposure to indium phosphide were available. An association between oxidative stress and inflammation, possibly leading to lung neoplasia has been described in rats *in vivo*. Exposure of mice to indium phosphide by inhalation for 2 years was shown to cause an increase in β-catenin somatic mutations in liver neoplasms. Indium phosphide triggers apoptosis *in vitro*.

5.5 Evaluation

There is *inadequate evidence* in humans for the carcinogenicity of indium phosphide.

There is *sufficient evidence* in experimental animals for the carcinogenicity of indium phosphide.

Overall evaluation

Indium phosphide is *probably carcinogenic to humans (Group 2A)*.

In the absence of data on cancer in humans, the final evaluation for the carcinogenicity of indium phosphide was upgraded from 2B to 2A based on the following: extraordinarily high incidences of malignant neoplasms of the lung in male and female rats and mice; increased incidences of

pheochromocytomas in male and female rats; and increased incidences of hepatocellular neoplasms in male and female mice. Of significance is the fact that these increased incidences of neoplasms occurred in rats and mice exposed to extremely low concentrations of indium phosphide (0.03–0.3 mg/m^3) and, even more significant, is the fact that these increased incidences occurred in mice and rats that were exposed for only 22 weeks (0.1 and 0.3 mg/m^3) and followed for 2 years.

For definition of the italicized terms, see Preamble Evaluation.

Synonym

- Indium monophosphide

VANADIUM PENTOXIDE
(Group 2B)

For definition of Groups, see Preamble Evaluation.

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CAS No.: 1314-62-1

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Vanadium is widely distributed in the earth's crust in a wide range of minerals and in fossil fuels. Vanadium pentoxide, the major commercial product of vanadium, is mainly used in the production of alloys with iron and aluminium. It is also used as an oxidation catalyst in the chemical industry and in a variety of minor applications. Expo-sure to vanadium pentoxide in the workplace occurs during the refining and processing of vanadium-rich mineral ores, during the burning of fossil fuels, especially petroleum, during the handling of vanadium catalysts in the chemical manu-facturing industry and during the cleaning of oil-fired boilers and furnaces. Expo-sure to vanadium can also occur from ambient air contaminated by the burning of fossil fuels and, at much lower levels, from contaminated food and drinking-water.

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

Vanadium pentoxide was tested for carcinogenicity in a single study in mice and rats by inhalation exposure. In both male and female mice, the incidences of alveolar/bronchiolar neoplasms were significantly increased, and there were also increases in male rats. It was uncertain as to whether a marginal increase in alveolar/bronchiolar neoplasms in female rats was related to exposure to vanadium pentoxide.

5.4 Other relevant data

Vanadium pentoxide is rapidly absorbed following inhalation, but poorly through dermal contact or ingestion. Elimination from the lung is initially fast, but complete only after several days. Lung retention can increase due to impaired health status of the lung. Distribution of vanadium

pentoxide is mainly to the bone and kidney.

The major non-cancer health effect associated with inhalation exposure to vana-dium pentoxide involves acute respiratory irritation, characterized as ‘boilermakers bronchitis’. This clinical effect appears to be reversible. Green coloration of the tongue is another frequently observed clinical manifestation of intoxication with vana-dium pentoxide.

Vanadium has been recognized as an essential nutritional requirement in animals of high order, but its function is not clear. Vanadium pentoxide has important effects on a broad variety of cellular processes. It stimulates cell differentiation, it causes cell and DNA injury via generation of reactive oxygen species and it alters gene expression. The many biochemical effects induced by vanadium pentoxide, such as the inhibition of a number of different enzymes, can explain many of the metabolic effects observed in experimental animals treated with this compound.

Vanadium pentoxide can pass the blood–placenta barrier. It has been reported to be teratogenic in rodents and it affects sexual development in pre-pubertal animals, the toxicity in males being greater than that in females. The reduced fertility seen in male mice was confirmed by a reduction in sperm motility *in vitro*.

Vanadium pentoxide is mutagenic *in vitro* and possibly *in vivo* in mice. It shows clasto-genic and aneugenic activity in cultured mammalian cells, the latter effect probably being due to disturbance of spindle formation and chromosome segregation. Vana-dium pentoxide has been reported to inhibit enzymes involved in DNA synthesis and repair of DNA damage. Data on genetic effects in humans exposed to vanadium pentoxide are scarce.

5.5 Evaluation

There is *inadequate evidence* in humans for the carcinogenicity of vanadium pentoxide.

There is *sufficient evidence* in experimental animals for the carcinogenicity of vanadium pentoxide.

Overall evaluation

Vanadium pentoxide is *possibly carcinogenic to humans (Group 2B)*.

For definition of the italicized terms, see Preamble Evaluation.

Synonyms

- CI 77938
- Divanadium pentaoxide
- Pentaoxodivanadium
- Vanadic acid anhydride
- Vanadin (V) oxide