

6. SUMMARY OF DATA REPORTED AND EVALUATION

6.1 Exposure data

A wide range of metals and their alloys, polymers, ceramics and composites are used in surgically implanted medical devices and prostheses and dental materials. Most implanted devices are constructed of more than one kind of material (implants of complex composition). Since the early 1900s, metal alloys have been developed for these applications to provide improved physical and chemical properties, such as strength, durability and corrosion resistance. Major classes of metals used in medical devices and dental materials include stainless steels, cobalt–chromium alloys and titanium (as alloys and unalloyed). In addition, dental casting alloys are based on precious metals (gold, platinum, palladium or silver), nickel and copper and may in some cases contain smaller amounts of many other elements, added to improve the alloys' properties.

Orthopaedic applications of metal alloys include arthroplasty, osteosynthesis and in spinal and maxillofacial devices. Metallic alloys are also used for components of prosthetic heart valve replacements, and pacemaker casings and leads. Small metallic parts may be used in a wide range of other implants, including skin and wound staples, vascular endoprostheses, filters and occluders. Dental applications of metals and alloys include fillings, prosthetic devices (crowns, bridges, removable prostheses), dental implants and orthodontic appliances.

Polymers of many types are used in implanted medical devices and dental materials. Illustrative examples are silicones (breast prostheses, pacemaker leads), polyurethanes (pacemaker components), polymethacrylates (dental prostheses, bone cements), poly(ethylene terephthalate) (vascular grafts, heart valve sewing rings, sutures), polypropylene (sutures), polyethylene (prosthetic joint components), polytetrafluoroethylene (vascular prostheses), polyamides (sutures) and polylactides and poly(glycolic acids) (bioresorbables).

Ceramic materials based on metal oxides (alumina, zirconia) find use in joint replacements and dental prostheses. Other materials based on calcium phosphate are used as bone fillers and implant coatings. Pyrolytic carbon applications include heart valves and coatings for implants. Composites are used mainly in dental fillings.

Although precise numbers are not available, many millions of people worldwide have implanted devices, which may remain in place for years.

Foreign bodies, such as bullets and pellets from firearms and metallic fragments from explosions, may penetrate and remain in human tissues for long periods of time. Internal exposure to constituents, including lead (from bullets and pellets) and depleted uranium (from shell and missile fragments), may result.

6.2 Human carcinogenicity data

Sixteen case reports have described neoplasms originating from bone or soft connective tissue in the region of metal implants. An analytical study did not report an increased risk for soft-tissue sarcoma after metal implants. No association with dental amalgam was found in a case-control study in Australia.

The 30 case reports of breast cancer following silicone implants for cosmetic breast augmentation appear unlikely to correspond to an excess of breast cancer. All five cohort studies involving a total of more than 18 000 women treated with surgical prostheses made of silicone (or polyurethane-coated silicone) for cosmetic breast augmentation conducted in Canada, Denmark, Sweden and the United States consistently found no evidence of increased risk of breast cancer. The combined results of the four largest cohort studies show a 25% reduction in risk. Similar results were reported by a large case-control study including more than 2000 cases and 2000 controls in the United States. All cohort studies were based on subjects exposed to implanted silicone at an early age, usually between the ages of 30 and 40 years, so that the number of breast cancer cases observed in each study was relatively small. Except for the case-control study in the United States, only limited allowance was made for potential confounding factors, although no clear evidence has emerged as to the relevance of any such factor to a possible association between implanted silicone and breast cancer risk.

Three of the studies considered the issue of latency, with observation periods of up to 10 years or more, but even in the group of women with follow-up of 10 years or more, there was no suggestion of increased risk. The risk of cancer following surgical implantation of silicone prostheses for breast reconstruction after breast cancer was considered in a study in France. The results of this study suggest no excess risk of second primary breast or other cancer, distant metastases, local recurrence or death from breast cancer. The reduced risks for breast cancer found in the cohort and case-control studies are unlikely to be due to chance, and no bias that would explain these findings has been identified. Four cohort studies of women with surgical breast implants in Denmark, Sweden and the United States reported on cancers at sites other than the breast. None of these studies found an increased risk for all cancers combined. Two studies reported increased risk for lung cancer, but these results were based on a total of only nine observed cases. For no other cancer site was there consistent evidence of an increased risk, although the statistical power to detect an increased risk of rare neoplasms, including soft-tissue sarcomas, was small.

Out of the large number of patients with orthopaedic implants of complex composition (metal with bone cement with or without polyethylene), a total of 35 cases have been reported of malignant neoplasms arising from the bone or the soft tissue in the region of an implant. Fourteen cohort studies of patients following total knee or total hip replacement from six countries were performed to investigate cancer incidence in these populations. Two of the studies from Finland and two studies from Sweden were partially overlapping. One study included only patients with metal-on-metal implants, five studies included only patients with polyethylene-on-metal implants, while the

remaining studies included patients with mixed or unspecified types of implant. One study showed a small increase in overall cancer incidence, while the remaining studies showed overall decreases. Four of these studies suggested an excess risk for specific cancers, including Hodgkin's disease, non-Hodgkin lymphoma, leukaemia and kidney cancer. However, results of the other studies were not consistent with this observation. In one small cohort study from Denmark of patients with a finger or hand implant, an increased risk of lymphohaematopoietic cancer was observed. Additionally, two case-control studies, one including cases with soft-tissue sarcoma and the other including lymphoma and leukaemia, were carried out in the United States. The latter overlaps with one of the cohort studies. Neither of these studies showed an association with the presence of implants of complex composition. Most of the studies did not have information on possible confounding variables such as immunosuppressive therapy or rheumatoid arthritis for the lymphomas and analgesic drugs for kidney cancer. The follow-up in most of the studies may have been too short to evaluate cancer occurring many years after exposure; in some studies with longer follow-up, the numbers of long-term survivors were low.

Thirteen cases of breast cancer and one case of plasmacytoma have been reported in patients with cardiac pacemakers. Ten cases of different neoplasms have been reported at the site of non-metallic foreign bodies. Eight cases of sarcoma have been reported at the site of vascular grafts. No conclusions can be drawn from these case reports.

Twenty-three cases of sarcomas, twenty-three cases of carcinomas and seven cases of brain tumours have been reported at the site of metallic foreign bodies, mainly bullets and shrapnel fragments.

6.3 Veterinary studies

Despite the large number and variety of both metallic and non-metallic internal fixation devices used in dogs in recent decades, only about 60 cases of sarcomas, primarily of bone, have been reported. In addition, four cases of sarcomas at the site of other foreign bodies have been reported in dogs. One case-control study found no association between metallic implants used to stabilize fractures in dogs and the development of bone or soft-tissue tumours.

In contrast, at least 563 cases of vaccine-associated sarcomas in cats have been reported in just six years, with an estimated annual incidence of 1–13 per 10 000 vaccinated cats. Vaccine-associated sarcomas have been mostly associated with administration of recently introduced feline vaccines containing adjuvant. Tumours that develop at vaccination sites are morphologically different from those that develop at non-vaccination sites. A cohort study found that cats developed sarcomas in a shorter time at sites used for vaccination than at non-vaccination sites and that there was an increased risk for sarcoma development with increased numbers of vaccines at a given site.

6.4 Animal carcinogenicity data

Chromium metal powder was tested in rats by intramuscular and intrarenal administration, in mice and rats by intrapleural and intraperitoneal administration, in rats and rabbits by intraosseous implantation and in mice, rats and rabbits by intravenous injection. No increase in tumour incidence was observed in these studies, although most studies had limitations in design, duration or reporting.

Cobalt metal powder was tested in rats by intramuscular or intrathoracic injection, producing sarcomas at the injection site. Studies in rats by intrarenal injection and in rabbits by intraosseous injection had limitations in design, duration or reporting.

Nickel metal powder was tested by inhalation exposure in mice, rats and guinea-pigs, by intratracheal instillation in rats and Syrian hamsters, by intramuscular injection in rats and hamsters and by intrapleural, intraperitoneal, intraosseous and intrarenal injection in rats. It was also tested by intravenous injection in mice and rats. Nickel metal pellets were tested by subcutaneous administration in rats. The studies by inhalation exposure were inadequate for an evaluation of carcinogenicity. After intratracheal instillation of nickel, significant numbers of squamous-cell carcinomas and adenocarcinomas of the lung were observed in rats; one adenocarcinoma of the lung was observed in hamsters. Intrapleural injections induced sarcomas in rats. Subcutaneous administration of nickel metal pellets induced sarcomas in rats; intramuscular injection of nickel powder induced sarcomas in rats and hamsters; and intraperitoneal injections induced local carcinomas, mesotheliomas and sarcomas in rats. No significant increase in the incidence of local kidney tumours in rats was seen following intrarenal injection. Studies by the intraosseous and intravenous routes were inadequate for evaluation.

Titanium metal was tested in rats by intramuscular implantation of rods and by intraosseous administration of powder, rods or wire. No local tumours occurred.

Most *nickel-based alloys* that have been tested for carcinogenicity in animals are not actually used in clinical devices, and carcinogenicity data are not available for a number of alloys which are commonly used, including nickel–titanium.

Metal alloys containing a preponderance of *nickel* in combination with varying amounts of chromium, iron, gallium, copper, aluminium and manganese have been tested as powder or pellets by subcutaneous or intraperitoneal administration to rats and by intratracheal administration to hamsters. In these studies, local sarcomas were consistently found at the injection site in the treated animals and were absent in vehicle controls. One of the nickel-based alloys (which contained approximately 66–67% nickel, 13–16% chromium and 7% iron) was tested independently by two laboratories, using different species (hamsters and rats) and different routes of administration (intratracheal and intraperitoneal). In both studies, local tumours were seen in proportion to the dose of alloy. Local tumours were also observed in two bioassays in which rats received identification ear tags made of an alloy that contained 67% nickel, 30% copper, 2% iron and 1% manganese.

Most other nickel-containing alloys tested as powder and rods in rats by intramuscular, intraperitoneal, intrarenal and intraosseous administration gave negative or

equivocal results for induction of tumours at the injection site. One study in hamsters by intratracheal administration of an alloy powder containing approximately 27% nickel, 39% iron and 16% chromium also gave negative results.

One clinically relevant alloy, Ni₃₅Co₃₅Cr₂₀Mo₁₀ (MP35N alloy), gave negative results for carcinogenicity when tested in two studies by intramuscular implantation in rats as rods, but produced local sarcomas in one study following intramuscular administration to rats as a powder.

Titanium-based alloys were tested in rats by intramuscular administration of rods and by intraosseous administration of rods and intra-articular administration of wear-debris. No local tumours were observed at the injection site in these experiments, except in one study by intraosseous administration in which a titanium/aluminium/vanadium alloy implanted into the femur as hemi-cylinders produced a high incidence of local tumours, especially where there was loosening of the implant.

Cobalt-based alloys were tested in rats by intramuscular administration. Local tumours were induced by a powder (particle size, 0.1–1 µm) in horse serum but not by dry powders (particle size, 0.5–50 and 100–250 µm) or by polished rods. No local tumours were observed in guinea-pigs following intramuscular injection of cobalt as a dry powder (particle size, 0.5–50 µm). A low incidence of local tumours was observed in rats following intraosseous administration of two cobalt-based alloys given as powder or wire. Local tumours did not occur following intraosseous implantation of rods of two other cobalt-containing alloys. No local tumours occurred in rats following intra-articular administration of a cobalt alloy powder.

Stainless steels containing 13–17% chromium were tested by intratracheal administration of powder to hamsters, intrabronchial administration of wire to rats and by intramuscular administration of rods and discs to rats and intraosseous administration of rods and powder to rats. No local tumours were observed, except in rats receiving stainless steel discs.

Thin foils of silver, gold, platinum, tin, steel, Vitallium (CoCrMo alloy) and tantalum were tested by subcutaneous implantation in rats. All of these foils produced local sarcomas.

In one study in rats, subcutaneous implantation of discs of aluminium oxide ceramic produced local sarcomas. In a few studies in mice and rats, local sarcomas were observed following subcutaneous implantation of glass sheets.

Numerous polymeric materials have been tested for carcinogenicity in mice and rats, most frequently by subcutaneous, intramuscular or intraperitoneal injection. Many materials—cellophane, ε-caprolactone-L-lactide copolymer, polyamide (Nylon), poly(ethylene terephthalate), polyethylene, poly-L-lactide, poly(2-hydroxyethylmethacrylate), poly(methyl methacrylate), polypropylene, polystyrene, polytetrafluoroethylene, polyurethane, poly(vinyl alcohol), poly(vinyl chloride), polymethylsiloxane (silicone) film or polysilicone gum and vinyl chloride–vinyl acetate copolymers—produced sarcomas at the site of implantation with varying incidence. When several polymers were tested in rats according to the same experimental protocol, sarcoma

incidences ranged from 70% (polypropylene) to 7% (silicone). A low incidence of local tumours was seen with silicone in five separate experiments using rats.

A few experiments with various polymeric materials have been reported using small number of other animal species, such as rabbits, guinea-pigs and hamsters, with generally negative findings.

Polymeric materials with a large surface area and a flat and smooth surface morphology generally induced a significantly increased incidence of sarcomas at the site of implantation. In most studies, perforated or foam materials or textiles induced lower incidences of sarcomas in comparison with flat films. Some studies suggest that surface roughening decreases local sarcoma incidence. The diameter and number of transmembrane channels (pores) per unit surface area are critical for this trend of decrease in sarcoma incidence. Segmenting or pulverizing polymeric materials significantly decreases local sarcoma incidences, often to nil.

For biodegradable polymers, the degradation rate is critical for local tumour induction in rodents. No local tumours were observed with poly(glycolic acid), which is quickly degraded within two months, whereas local sarcomas were induced by poly-L-lactide and ϵ -caprolactone-L-lactide copolymer which degraded more slowly (the polylactide degraded but was dimensionally unchanged at 24 months; ϵ -caprolactone-L-lactide copolymer fragmented after six months).

6.5 Other relevant data

The mutagenicity and carcinogenicity of a biomaterial are influenced by the exact composition of the biomaterial or extract(s); the composition and rates of release of leachable materials into the biological environment; degradation, which may lead to the formation of compounds with different mutagenic properties or leachability; the physical environment; and the surface properties. Much of the information available for assessment is inadequate in these respects, and methods are often not validated.

Wear and corrosion of metal implants result in the generation and release of a wide range of degradation products. The composition of the material surface or particles can vary as individual components are selectively removed or chemically modified. In the case of alloys, the release of one type of metal ion can be strongly influenced by the identity of other metals in the alloy. Most studies provide inadequate characterization data, but there is potential for the release of chemical species of known mutagenicity or carcinogenicity.

Experimental studies have shown that the potential for lead toxicity as a complication of lead projectile or bullet injury appears to be related to the surface area of the bullet (the greater the surface area, the greater the absorption), the location of the bullet (muscle or joint tissues), the presence of synovial fluid and length of time that the bullet resided in the body.

Available studies are inadequate to permit reliable and accurate estimates of long-term effects of depleted uranium in humans. Because of the low specific radioactivity of depleted uranium, the long-term toxicity is thought to be due to chemical rather than radiation effects.

Inflammatory (fibrotic) reactions have been observed with several non-metallic implant materials, including silicones and polyurethanes. Depending on the physical properties of the biomaterial, its presence can be associated with implantation-site sarcomas in rodents. There are insufficient data to conclude that a genotoxic mechanism operates in solid-state carcinogenesis. There are in-vitro data demonstrating the inhibitory effects of polyurethane, polyethylene and poly(ethylene terephthalate) on gap junctional intercellular communication.

Mutagenic properties of some biomaterial extracts have been demonstrated in some studies. The compounds shown or suspected to be responsible for this are components of the biomaterial, unreacted monomers or products of secondary reactions.

Data on the local and systemic availability of chemical species have been reported for only a limited number of biomaterials. In the case of poly(ester urethane) foam, biodegradation results in the generation of 2,4-diaminotoluene. This compound induces hepatocellular carcinomas when fed to mice and rats. There is no evidence that chemical carcinogenesis due to this compound plays a direct role in the mechanism of implant-site sarcoma development. There is no convincing evidence for the biodegradation of polydimethylsiloxanes (silicones).

Cytotoxicity of freshly cured dental composite materials and bonding agents has been demonstrated. Also, the components of resin composites all cause significant toxicity in direct contact with fibroblasts. However, the hazard for the dental pulp depends on the quantities which permeate the dentin and accumulate in the pulp.

A limited number of animal studies have shown pulpal responses to acid etching and bonding agents, which indicates a possible risk of pulpal reactions in patients. Composite materials may give rise to biological effects, but microleakage and bacterial infection complicate the evaluation of pulpal effects of composites.

Clinical reports on the adverse effects of composite filling materials indicate that pulpal and mucosal reactions rarely occur.

With few exceptions, the amounts of individual chemicals to which professionals and patients are exposed from adhesive agents and composite dental filling materials seem to be insufficient to cause clear, systemic toxic effects. Some constituents of adhesive agents and composite materials may have genotoxic potential. For most compounds of dental composites, there is little information on toxicity. With the exception of methyl methacrylate, no relevant data are available to compare local concentrations of released compounds with levels that produce toxic effects.

Formaldehyde has been shown to be released from some dental polymers *in vitro*, but the levels appear to be low.

6.6 Evaluation

There is *evidence suggesting lack of carcinogenicity* in humans of breast implants, made of silicone, for female breast carcinoma.

There is *inadequate evidence* in humans for the carcinogenicity of implanted prostheses made of silicone for neoplasms other than female breast carcinoma.

There is *inadequate evidence* in humans for the carcinogenicity of non-metallic implants other than those made of silicone.

There is *inadequate evidence* in humans for the carcinogenicity of metallic implants and metallic foreign bodies.

There is *inadequate evidence* in humans for the carcinogenicity of orthopaedic implants of complex composition and of cardiac pacemakers.

No epidemiological data relevant to the carcinogenicity of ceramic implants or dental alloys of precious metals were available.

There is *sufficient evidence* in experimental animals for the carcinogenicity of implants of metallic cobalt, metallic nickel and for nickel alloy powder containing approximately 66–67% nickel, 13–16% chromium and 7% iron.

There is *limited evidence* in experimental animals for the carcinogenicity of implants of alloys containing cobalt and alloys containing nickel, other than the specific aforementioned alloy.

There is *inadequate evidence* in experimental animals for the carcinogenicity of implants of chromium metal, stainless steel, titanium metal, titanium-based alloys and depleted uranium.

There is *sufficient evidence* in experimental animals for the carcinogenicity of polymeric and metallic materials in the form of thin films, foils or sheets when implanted into connective tissues of rodents.

There is *inadequate evidence* in experimental animals for the carcinogenicity of poly(glycolic acid) implants.

There is *inadequate evidence* in experimental animals for the carcinogenicity of polymeric materials in the form of powders when inserted into connective tissues of rodents.

There is *inadequate evidence* in dogs for the carcinogenicity of metallic implants and metallic and non-metallic foreign bodies.

There is *limited evidence* in cats for the carcinogenicity of certain feline vaccines containing adjuvants.

Overall evaluation

Organic polymeric materials as a group are *not classifiable as to their carcinogenicity to humans (Group 3)*.

Polymeric implants prepared as thin smooth films (with the exception of poly(glycolic acid)) are *possibly carcinogenic to humans (Group 2B)*.

Orthopaedic implants of complex composition and cardiac pacemakers are *not classifiable as to their carcinogenicity to humans (Group 3)*.

Silicone breast implants are *not classifiable as to their carcinogenicity to humans (Group 3)*.

Metallic implants prepared as thin smooth films are *possibly carcinogenic to humans (Group 2B)*.

Implanted foreign bodies of metallic cobalt, metallic nickel and an alloy powder containing 66–67% nickel, 13–16% chromium and 7% iron are *possibly carcinogenic to humans (Group 2B)*.

Implanted foreign bodies of metallic chromium or titanium and of cobalt-based, chromium-based and titanium-based alloys, stainless steel and depleted uranium are *not classifiable as to their carcinogenicity to humans (Group 3)*.

Dental materials are *not classifiable as to their carcinogenicity to humans (Group 3)*.

Ceramic implants are *not classifiable as to their carcinogenicity to humans (Group 3)*.