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Toxicity of tin

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Synonyms: tin, organotin, metal, toxicity

Definition

Tin (Sn, from *stannum*) is the 49th most abundant element in the Earth's crust, where it occurs primarily as a mineral containing tin dioxide (SnO₂). In its elemental form tin is a soft, silver-white metal which is relatively inert towards air and water. Tin is a main group metal (atomic number 50) and appears in its inorganic and organic compounds in two oxidation states: +2 and the more stable +4. While elemental tin and the inorganic tin compounds are considered relatively non-toxic, the more lipid-soluble organic tin species exhibit a variety of distinct toxic reactions. Generally, tri-substituted (R₃SnX) and disubstituted (R₂SnX₂) organotins are more toxic than mono-substituted (RSnX₃) tin species. Toxicity decreases with increasing alkyl chain length independent on the counter ions (Gajda and Jancsó, 2010).

Exposure

Human exposure to tin arises from the release of the metal and its compounds from natural and anthropogenic sources. Elemental tin is used in alloys such as brass or bronze, in pewter and in soldering materials. Inorganic tin compounds are largely employed as intermediates for the synthesis of organotin compounds and in electrolytes for plating tin and tin al-

loys. They are also found in pigments and glazes, in cosmetics, dental care products, coloring agents and food additives. Organotin compounds are widely utilized as stabilizers for PVC, as homogenous catalysts for polyurethane foam formation and silicone vulcanization, for glass coating, as pesticides (fungicides, insecticides, acaricides), antifouling agents, wood preservatives, disinfectants, and rodent repellants. Some of the applications of organotin compounds have been discontinued because of their high toxicity, particularly in aquatic environments (ATSDR 2005; Gajda and Jancsó, 2010). Naturally occurring organotin compounds are methylated tin species formed from inorganic tin by the action of bacteria present in soil and marine sediments (Dopp et al., 2004, Hirner and Rettenmeier, 2010). The most important source for human exposure to tin is the uptake from food contaminated by tin compounds (seafood, food products in tin-lined cans) and from contact with household products. Data on human exposure to inorganic and organotin compounds is however limited. Evidently, tin is not an essential element for humans (ATSDR 2005).

Toxicokinetics

Inorganic and organic compounds can be absorbed to some extent by inhalation, ingestion, or dermal penetration. Organotin compounds are more readily taken up than inorganic compounds by any of these routes with absorption increasing with higher degrees of alkylation. Absorbed tin is distributed throughout the body. In postmortem samples tin has been found in kidney, liver, lung, brain, and bone tissue with the highest concentration measured in the latter tissue. The metabolism of inorganic tin compounds have not been investigated as yet. Organic tin compounds are successively dealkylated/dearylated according to animal and in vitro studies. Dealkylation products may be hydroxylated and/or conjugated with glutathione and further metabolized to mercapturic acid derivatives. Feces and to a lesser extent urine are the major routes of tin excretion. Most tin compounds, particularly the inorganic species, are eliminated rather rapidly, but small amounts are stored in

bones for up to a few months. While inorganic and organic tin compounds can be transferred across the placenta, the uptake of these compounds through breastfeeding has not yet been demonstrated (Appel 2004; ATSDR 2005).

Mechanisms of action

The toxic effects of organotin compounds result from interactions of the alkyl and aryl moieties with cell membranes and the intracellular reactivity of the alkyltin cation. Basically, the effects can be categorized in Ca^{2+} -dependent and Ca^{2+} -independent reactions. Organotin compounds disturb Ca^{2+} homeostasis by increasing free intracellular Ca^{2+} concentration, which among others affects signaling pathways, induces apoptosis and promotes depolymerisation and desintegration of cytoskeletal and nuclear proteins. Ca^{2+} -independent are coordinative and covalent binding to proteins leading to inhibition of enzymes involved in energy production and drug metabolism and in the regulation of transmembrane gradients. Increased neuronal release of and/or decreased neuronal uptake of neurotransmitters and decreased expression of neural cell adhesion molecules induced by trimethyltin, and suppressed T-cell-mediated immune response by butyltin compounds are also among the toxic reactions caused by organotin compounds.

Although there are many reports describing the potential toxicity of organotins in human and mammals, the critical target molecules for the toxicity of organotin compounds remain unclear. Recently, organotin compounds including TBT and TPT were identified as nanomolar agonists for retinoid X receptor (RXR) and peroxisome proliferator-activated receptor (PPAR) gamma, which are members of the nuclear receptor superfamily. TBT and TPT are potent activators of these nuclear hormone receptors (RXR, $\text{PPAR}\gamma$) and they

promote adipocyte differentiation, suggesting that these organotins might contribute to the development of metabolic diseases (Nakanishi T, 2008).

Acute toxicity

The acute toxicity of inorganic tin compounds is rather low. Following ingestion of canned food contaminated by tin, nausea, vomiting and diarrhea have been reported. Stomachaches, anemia, and liver and kidney disorders may occur if larger amounts of inorganic tin are ingested. In contrast, organotin compounds exhibit a considerably more pronounced toxicity following acute or subacute exposure. Reported effects include skin and eye irritation, respiratory irritation, gastrointestinal effects, and neurological sequelae. Lethal cases have occurred both after acute inhalation exposure to a mixture of trimethyltin and dimethyltin vapors and after acute oral ingestion of trimethyltin. Treatment of staphylococcus infections with a drug contaminated with triethyltin iodide (the so-called Stalinon[®] affair) caused about 100 deaths in France in 1954. Neurological symptoms (headache, photophobia, altered consciousness, and convulsions) occurred about four days after the intoxication and partially continued in the surviving patients for several years.

Chronic toxicity of inorganic tin

There are only few reports on chronic toxic effects of inorganic tin compounds. Chronic inhalation exposure to stannic oxide dust or fumes may cause stannosis, a benign form of pneumoconiosis. Gastrointestinal symptoms may occur after repeated ingestion of inorganic tin compounds. Signs of anemia and gastrointestinal distension are effects observed after chronic exposure of animals to inorganic tin compounds.

Chronic Toxicity of Organotin Compounds

Neurotoxicity

As indicated by the accidental, sometimes lethal intoxication cases in France in 1954, neurotoxicity is an important toxicological endpoint of certain organotin compounds. Particularly trimethyl and triethyltin are potent neurotoxins, however, symptoms of neurotoxicity (encephalopathy) have also been found after exposure to dimethyltin (Michalke et al. 2009). In addition to the clinical signs and symptoms such as headaches, photophobia, altered consciousness, and convulsions, reported in the intoxication cases, morphological alterations have been demonstrated in various brain regions. Following exposure to trimethyltin neuronal necrosis have been found in areas of the limbic system, particularly in the hippocampus. Behavioral changes such as aggression, memory loss and unresponsiveness may result. As observed in the French cases, triethyltin ingestion caused brain and cord swelling characterized by fluid accumulation between myelin layers, splitting of the myelin sheets and formation of intramyelin vacuoles. Similar findings were obtained in animal studies when the respective short-chain alkyltin compounds were administered. The mechanisms of neurotoxic action of trimethyl- and triethyltin have not yet been elucidated in detail. One hypothesis is that small amounts of trimethyltin may inhibit the ability of astrocytes to maintain a transmembrane K^+ gradient causing an imbalance between neuronal inhibition/excitation.

Immunotoxicity

The immune system is a primary target of the butyl- and octyltin-induced toxicity as shown in numerous animal studies, however, adverse immunological effects have not been reported in exposed humans. Immunological alterations observed in rats after administration of tributyltin oxide involve the depletion of lymphocytes in the thymus and a reduced size and weight of this organ. It seems to be a direct and selective action of tributyltin oxide on the lymphocytes, whereas dialkyltins appear to interfere with the proliferation of the thymo-

cytes. Acute immunotoxic effects require daily doses as high as >2 mg/kg in the rats, the impairment of specific and nonspecific resistance to infections may occur already at daily doses as low as 0.25 mg/day if applied long-term.

Hematological Effects

Anemia as indicated by a decreased hemoglobin concentration has been observed after subchronic or chronic oral exposure of rats to dibutyltin dichloride, tributyltin oxide, or dioctyltin dichloride. Based on the finding that tributyltin oxide administration led to increased reticulocyte counts and reduced iron concentrations in serum it has been suggested that the organotin compound interferes with hemoglobin synthesis, either by suppressing iron uptake or by fostering iron loss. It appears unlikely that environmental levels of organotin compounds are high enough to cause hematological effects in humans.

Reproductive and developmental toxicity

Effects of organotin compounds on human reproduction and development have not been investigated yet. In rats and mice, administration of di- and tributyl- and of triphenyltin compounds in daily doses of >3 mg/kg during gestation days 7-9 induced pregnancy failure, pre- and postimplantation losses, resorptions and stillbirths. In male rats, exposure to tributyltin in daily doses of 10 mg/kg affected reproduction by causing histologic alterations in seminal vesicles and epididymis and reduced sperm counts. Embryotoxic and teratogenic effects, mainly cleft palate and facial malformations, have also been observed after exposure of rat embryos to organotins. There is still uncertainty whether these effects only occur secondary to maternal toxicity.

The observed effects on reproduction and development have been related to the interference of organotin compounds with the synthesis of sex hormones, resulting in an androgen/estrogen imbalance which affects sexual maturation. In in vitro studies in human chorioncarcinoma cells tributyl- and triphenyltin compounds markedly enhanced estradiol

biosynthesis along with the increase of both aromatase activity and 17-beta-hydroxysteroid dehydrogenase type I (17beta-HSD I) activity, which converts low-activity estrogen estrone to the biologically more active form estradiol. It is unclear whether these hormonal alterations are relevant to human organotin exposure. Contrary to the enhancement of aromatase activity observed in mammalian cells, tributyl- and triphenyltin compounds appeared to be potential competitive inhibitors of aromatase in gastropods. As this enzyme converts androgen to estrogen, its inhibition leads to increased androgen levels causing the irreversible sexual abnormalities called “imposex” and “intersex”, respectively. “Imposex” is a masculinisation process in female neogastropod snails, involving the development of male sex organs. The imposition of a vas deferens disrupts the oviducal structure and function preventing normal breeding activity and causing population disappearance. Oogenesis is supplanted by spermatogenesis in some species. “Intersex” is a related condition observed in littorinid mesogastropods which too become unable to lay eggs. Field evidence clearly associates these syndromes with the use of tributyltin compounds as an antifouling agent, chiefly on boat hulls. Dose-related effects can be replicated in laboratory exposures to environmentally relevant concentrations of these compounds (Matthiessen P and Gibbs PE, 1998). After organotin compounds were recognized as persistent organic pollutants with an extremely high endocrine-disrupting activity in some marine organisms, the use of these compounds was banned by the European Union in 2003 and worldwide by the International Maritime Organization.

No data are available on endocrine-related effects of short-chain alkyltins.

Genotoxicity/Carcinogenicity

Genotoxicity studies with inorganic tin compounds *in vitro* provided some positive and some negative results. Stannous chloride (SnCl_2) gave mainly negative results in bacterial tests, but caused DNA damage and sister chromatid exchanges in Chinese hamster ovary

celles (CHO) cells, and chromosomal aberrations in CHO cells and human peripheral lymphocytes. Stannic chloride (SnCl_4) was negative in bacterial test systems and in CHO cells, but induced chromosomal aberrations in human peripheral lymphocytes. The rather weak genotoxic effect of the stannous ion has been attributed to the formation of reactive oxygen species. Overall, a similar picture was obtained from in vitro and in vivo genotoxicity studies with organotin compounds. Weakly positive results were obtained in a few tests (mainly in mammalian test systems), but most investigations in bacterial and mammalian test systems turned out to be negative.

There are no studies that evaluated whether inorganic or organic tin compounds cause cancer in humans. A few animal studies showed, however, that some organotin compounds may have a carcinogenic potential which may also be of some relevance to humans. A mixture of mono-*n*-octyltin trichloride and di-*n*-octyltin dichloride induced statistically significant thymus lymphomas in female rats and generalized malignant lymphomas in rats of either sex in the highest dose-groups (Ciba-Geigy 1986). Di-*n*-butyltin diacetate caused a significant increase of hepatocellular adenomas and carcinomas in male mice, and tri-*n*-butyltin oxide significantly induced benignant hypophyseal tumors, adrenal pheochromocytomas, parathyroid adenomas, and a rare anaplastic tumor of the exocrine pancreas in male and/or female rats. Based on these studies and in view of the negligible genotoxic potential of the organotin compounds the German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area has classified *n*-butyltin and *n*-octyltin compounds as category 4 carcinogens (Substances with carcinogenic potential for which a non-genotoxic mode of action is of prime importance and genotoxic effects play no or at most a minor part provided the MAK values (Maximum concentration values) are observed (DFG, 2010). Under these conditions no contribution to human cancer risk is expected. According to the American Conference of Governmental Industrial Hygienists (AC-

GIH[®]) are all tin compounds “not classifiable as human carcinogens” (category A4). A basically identical assessment/evaluation regarding the carcinogenicity of tributyltin oxide has been made by the U.S. Environmental Protection Agency (USEPA) (“not classifiable as to human carcinogenicity”).

Regulations and Advisories

Exposure to tin and its inorganic and organic compounds has been regulated by national and international regulatory authorities to protect human health. The U.S. Food and Drug Administration (FDA) has set limits for the use of stannous chloride as a food additive and of some organic tin compounds in coatings and plastic food packaging. The use of certain organotin compounds in paints has been limited by the U.S. EPA. Several agencies have established workplace exposure limits for tin and tin compounds. The U.S. Occupational Safety and Health Administration (OSHA), the National Institute for Occupational Safety and Health (NIOSH) and the American Conference of Governmental Industrial Hygienists (ACGIH[®]) recommend workplace exposure limits of 2 mg/m³ for inorganic tin compounds (except tin oxides (OSHA and NIOSH) and tin hydride (ACGIH[®])) and of 0.1 mg/m³ for organotin compounds (except tricyclohexyltin hydroxide (NIOSH)). In contrast, the German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area has stated that there is insufficient information to establish a maximum concentration value (MAK) for tin and inorganic tin compounds. For n-butyltin and n-octyltin compounds a MAK value of 0.02 mg/m³ was established, for phenyltin compounds a MAK value of 0.002 mg/m³ and for the other organic tin compounds a MAK value of 0.1 mg/m³ (DFG 2010).

Based on No observed adverse effect levels (NOAEL) for immunological effects of tributyltin oxide in rats ATSDR derived intermediate- and chronic-duration oral Minimal risk levels (MRL) of 0.0003 mg/kg per day. For intermediate duration exposure to dibutyltin-

in chloride and inorganic tin MRLs of 0.005 mg/kg per day and 0.3 mg Sn/kg per day, respectively, have been derived. There are no MRLs available for oral exposure to methyl-, ethyl-, octyl- and phenyltin compounds and for any inhalation and dermal exposure to tin compounds. An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects over a specified duration of exposure (US Dep. Health, 2005).

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