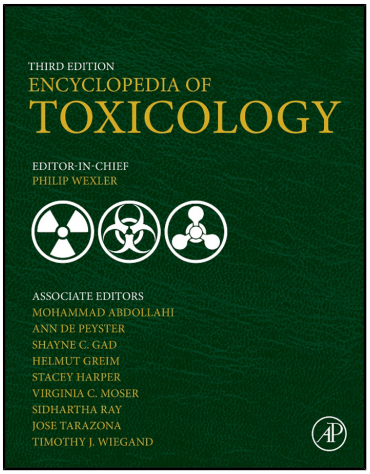

From Okoro, H.K., Fatoki, O.S., Adekola, F.A., Ximba, B.J., Snyman, R.G., 2014. Organotin Compounds. In: Wexler, P. (Ed.), Encyclopedia of Toxicology, 3rd edition vol 3. Elsevier Inc., Academic Press, pp. 720–725.
ISBN: 9780123864543

Academic Press

Organotin Compounds

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Background

The use of tributyltin (TBT) and triphenyltin (TPT) as antifouling agents on boats has been widespread because of their superior effectiveness compared to previously used copper oxide paints. TBT is a biocide and catalyst used globally. TBT compounds have particularly been used as biocides in antifouling paints and wood preservatives. TBT leachate has contaminated both marine and freshwater habitats and it has been considered to be one of the most toxic agents entering the environment. The occurrence of TBT in surface water and sediment has prompted a large number of studies on its adverse effects on nontarget organisms. By the mid-1980s, it had become widely recognized that TBT severely affects nontarget organisms. Abnormal shell thickening has been reported in the Pacific oyster *Crassostrea gigas* associated with areas of high TBT contamination. Other adverse effects of TBT on organisms include imposex in gastropods. As well as being an endocrine-disrupting agent TBT has proven to be extremely toxic to a number of aquatic organisms, in particular during sensitive early life stages. It was revealed that TBT can induce cytogenetic damage in the embryos and larvae of the marine mollusc *Mytilus edulis* and the polychaete worm *Platynereis dumerilii*. Very limited work has been done on the genotoxic potential of TBT to adult marine organisms. In algae, for instance, triorganotins had the strongest influence on their growth and the least on their chlorophyll content.

Organotin compounds (OTCs) with a benzyl radical inhibited chlorophyll production less than the OTCs with butyl and phenyl radicals. This phenomenon proves that OTCs with butyl and phenyl groups have maximum efficiency for biocide purposes. OTCs have been demonstrated to pose various adverse effects on marine organisms by causing impairment in growth, development, and reproduction, and moreover, the survival of many marine species. OTCs are used for various agricultural and industrial applications. This can lead to contamination of municipal wastewater and sewage sludge. Adverse effects of these contaminants on some biota in receiving water were similar to those found in plant effluents. As a result of these and other studies, legislation has been introduced in several countries restricting the usage of TBT. More details on the TBT legislation can be found in our previous article Okoro et al. (2011a) for further readings.

Uses

OTCs are important environmental contaminants belonging to the most widely used organometallic compounds for agricultural, industrial, and biomedicinal applications. OTCs are also used industrially as catalysts in the production of polyurethane foams and silicones. Amongst other commercial applications is the production of polyvinyl chloride (PVC) stabilizers, industrial biocides, industrial catalysts, surface disinfectants including hospital and veterinary disinfectants, surface modifying and curing agents, laundering sanitizers, rodent repellents, scintillation detectors for γ- and X-rays, ballistic additives for solid rocket engine fuels, and homophones in liquid membrane ion-selective electrodes. OTCs are also used as fungicides, miticides, molluscicides, nematicides, and ovicides. In general, the various commercial applications of OTCs gave rise to a drastic increase in the worldwide production of OTCs.

Sources of OTCs in the Environment

Due to increase in industrial application, large amounts of toxic OTCs have entered various ecosystems. Research has been largely concentrated on TBT and TPT pollutions, because these compounds directly enter the environment through industrially applied organotin biocides. But recently, there was evidence that municipal and industrial wastewater, sludge, and landfill leachates are also important sources of organotins. Physical, biological, and chemical removal mechanisms contribute to the persistence distribution of OTCs in the environment. To date, organotin research has been restricted mainly to regions having high shipping volumes, harbors and/or shipyards, because the primary ways in which organotins reach the environment are through use as antifouling agents.

Physicochemical Properties

OTCs are organic derivatives of tin (Sn^{4+}) characterized by the presence of covalent bonds between three carbon atoms and a tin atom. They are designated as mono, di, tri, and tetraorganotin compounds. OTCs conform to the following general formula: (n-C_4H_9) SnX_2, chemically represented by the formulas $RSnX_3$, R_2SnX_2, R_3SnX, and R_4Sn, where R is any alkyl or aryl group and X is an anionic species. The nature of X influences the physicochemical properties, notably the relative solubility in water and nonpolar solvent and the vapor pressure. They are reported to be stable at temperatures up to 200 °C, thermal decomposition has no significance under environmental conditions, ultraviolet (UV) radiation, strong acids, and electrophilic agents readily cleave the tin–carbon (Sn–C) bonds. Generally, the solubility of OTCs in water decreases with increasing number and length of the organic substituent.

Partition Behavior in Water, Sediment, and Soil

OTCs are of concern, because of their high toxicity, widespread use, direct input into the environment, and their relatively high

Encyclopedia of Toxicology, Third Edition, 2014, 720–725

persistence. The OTCs enter the aquatic system by many routes. Triorganotin compounds have low aqueous solubility and low mobility and are easily adsorbed onto suspended particulate matter (SPM). The concentrations of hepatic butyltin reported in aquatic animals collected from the Seta Inland Sea, Japan, were as high as 10 000 ng g^{-1}, whereas the levels in crustaceans taken from the Japanese coastline ranged from 110 to 5200 ng g^{-1}. Evidence exists to show that legislation introduced to govern the use of TBT in antifouling paints has reduced aquatic concentrations of this contaminant. TBT was often found in water at concentrations that could cause chronic toxicity in a sensitive species. OTCs have been found to exhibit higher concentrations in the surface microlayer of freshwater than in subsurface water. TPT in water and sediments exhibits concentrations similar to that of TBT.

The deposition of SPM leads to the accumulation of considerable amounts of trisubstituted organotins and their degradation products in sediments. Several studies have been conducted on organotin pollution of river, lake, and harbor sediments. TBT concentrations are the highest in the inner harbor and in the upper ca. 10 cm sediment layer. This indicates that there is a risk of TBT mobilization from the sediment surface, which may be exacerbated by the frequently disturbed harbor environment. TPT acetate and TPT hydroxide have increasingly been used as soil treatment fungicides worldwide to treat a variety of crops. Such treatments have resulted in increasing levels of TPT acetate and TPT hydroxide in soils. Few studies have been conducted in which the abundance and persistence of TPT in soil have been measured. TPT is photolytically degraded in soils only if it is near the soil surface, where light can penetrate. Existing data on OTCs in seawater and sediment are presented in Tables 1 and 2.

Degradation

The degradation of the organotins in the environment may be defined as a progressive loss of organic groups from the Sn

Table 1 Butyltin compounds in seawater (ng Sn l^{-1}) reported for several regions of the world

Sampling location	*Year*	*MBT*	*DBT*	*TBT*
American harbors and marinas				
West and East coast, Canada	1995	<d.1[a], −460	<d.1, −270	<d.1, −500
Asian and Oceania harbors and marinas				
Coast, Korea	1997–98	<d.1–13.4	<d.1–22.3	<d.1, –4.5
North coast of Kyoto, Japan	2003	2.5–23	2.1–13	3.9–27
European harbors and marinas				
South Western coast, Spain	1993	<d.1. –51	6.8–20	9.1–79
South Eastern coast, France	1998	–	–	<0.015–0.12
Coastal waters, Greece	1998–99	<d.1. –19	<d.1. –159	<d.1.–70
North Western coast, Spain	Not provided	0.8–11.6	0.3–33.7	0.4–196.6

[a]Below detection limit.

Adapted from Okoro, H.K., Fatoki, O.S., Adekola, F.A., Ximba, B.J., Snyman, R.G., 2011b. Human exposure, biomarkers and fate of organotins in the environment. Rev. Environ. Contam. Toxicol. 213, 27–54.

Table 2 Butyltin compounds in sediments around the world

Sampling Location	*Year*	*MBT*	*DBT*	*TBT*
American harbors and marinas				
West and East coast, Canada	1995	<d.1[a],–330	<d.1–1100	<d.1–5100
Crystal Lake, USA	2001–03	21.3–320[b]	59–350[b]	1.5–14 000[b]
Asian and Oceania harbor and marinas				
Port of Osaka, Japan	1995–96	<d.1	<d.1	10–2100
Coast, Malaysia	1997–98	5.0–360[b,c]	3.8–310[b,c]	2.8–1100[b,c]
Great Barrier Reef World Heritage Area, Australia	1999	<d.1–1.61	<d.1–7.1	<d.1–1275
Alexandra harbor, Egypt	1999	<0.1–186	<0.1–379	1–2076
Mumbai harbor, India	2000–01	<d.1–131[c]	na	4.5–1193[c]
Fishing harbors, Taiwan	2001–04	na	na	2.4–8548[c]
Sanriku coast, Japan	2005	<d.1–3300	<d.1–3400	2–14000
West coast, France	1993	25–74	9–29	7–30
River Thames, UK	1994	12–172	12–219	1–60
Tagus Estuary, Portugal	1998–99	na	na	5.4–35[c]
North Western coast, Italy	1999–2000	<d.1	<d.1	3–27

[a]Below detection limit.
[b]Wet weight.
[c]ng organotin instead of Sn na, No data available.

Adapted from Okoro, H.K., Fatoki, O.S., Adekola, F.A., Ximba, B.J., Snyman, R.G., 2011b. Human exposure, biomarkers and fate of organotins in the environment. Rev. Environ. Contam. Toxicol. 213, 27–54.

cation. UV irradiation, biological cleavage, and chemical cleavage are the processes through which removal of the organic groups can be caused. Photolysis by sunlight appears to be the fastest route of degradation in water. OTC species are rapidly dealkylated by UV irradiation, while the TBT derivatives show much lower degradation rates. TPT is photolytically degraded in soils only if it is near the soil surface, where light can penetrate.

Bioaccumulation of OTCs

It has been reported widely that TBT is extremely toxic to marine organisms and they display a remarkable ability to accumulate this contaminant (up to $5\,g\,g^{-1}$). Differences in most experimental results reported might be due to temperature which is directly related to the assimilation and the level of feeding. OTC accumulation by higher trophic aquatic organisms proceeds through either uptake from solution alone or by a combination with diet digestion. Recent studies have shown that marine mammals and birds also accumulate high levels of toxic butyltins in various tissues and organs. Ecotoxicological implication of sludge-derived organotin pollution on soils is that bioaccumulation of these compounds in the terrestrial food web may occur measured exposure levels of OTCs, such as dibutyltin and tri-*n*-butyltin compounds in wildlife and human tissue sample that are reported in the range of 3.0–100 nm.

Human Exposure to Organotins

OTCs such as TBT and TPT have been utilized globally as biocides, agricultural fungicides, and wood preservatives as well as disinfecting agents in circulating industrial cooling water. They have also been used as antifouling paints for marine vessels. Human exposure to nonpoint sources of organotin can occur from the contaminated dietary sources (seafood, shellfish), fungicides on food crops, textiles, and industrial water systems as well as antifungal agents in wood treatment. The gastrointestinal tract is a major route by which humans are exposed to environmental chemicals. A variety of mono- and di-alkyltins are used prevalently as heat stabilizers in the manufacture of plastic and humans are exposed to them through the leaching of PVC from water pipes and PVC plastic used for packaging of food items. It has been confirmed that the organotins used in various consumer products can migrate from such products during normal use and contribute to their widespread presence in dusts from the indoor environment. Additional sources include various alcoholic beverages (port, red, and white wines). OTCs tend to accumulate in higher species including mammals in organs such as the liver, kidney, and brain. From previous exposure experiment reported in literature, it has been observed that the spectrum of potential adverse chronic systems effects of OTCs in humans is very broad and this includes primary immunosuppressive, endocrinopathic, neurotoxic, metabolic, and enzymatic activity, as well as liver, kidney, bioaccumulative, and possibly carcinogenic activity. Various sources of human exposure to OTCs are shown in Figure 1.

Toxicokinetics

TBT is acutely toxic to aquatic life at concentrations in the low nanograms per milliliter range. It can cause reproductive impairment in snails and chambering in oysters when concentrations in water are between 0.01 and $0.1\,ng\,m^{-1}$. Acute response range has been reported widely on species exposed to TBT but the kinetics and mechanism of TBT toxicity have not been thoroughly examined. The rate at which organisms bioaccumulate and eliminate a contaminant can be used to predict its biological and bioaccumulation potentials. The dual rate constant approach for a one-compartment first-order kinetic model has been used to describe bioconcentration and toxicity. The assumption in this model includes constant uptake, dose dependence, kinetics, and instantaneous mixing within the compartment. Uptake clearance and elimination rate constants are conditional and this can be affected by several biological and environmental factors such as temperature, salinity, body size, and oxygen content. In general, exposure content is proportional to the whole-body concentration meaning that it is proportional to the concentration of the toxicant at the site of action.

Mechanism of Toxicity

Organotins are known to be toxic at relatively low levels of exposure, not only to marine invertebrates but also to mammals and other animals. Organotin toxicity increases with the number of alkyl groups attached. Amongst the organotins, the most toxic ones are the trialkyltin compounds, followed by the dialkyltin and monoalkyltin compounds, with the ethyl derivative in each group being reported as the most toxic. Toxicity appears to be primarily related to relative lipophilicity in marine invertebrates such that TBT is often more toxic than dibutyltin (DBT), which is in turn more toxic than monobutyltin to certain enzyme systems. DBT is a more potent immunotoxin in fish than TBT. Moreover, trisubstituted organotins also interact with various intracellular enzymes that may lead to toxicity, mainly cytochrome P450-dependant monooxygenases, which play an important role in detoxifying xenobiotics.

Acute and Short-Term Toxicity

Acute toxicity studies involve single-dose study which is carried out to investigate the effects of a compound after oral ingestion. Acute toxicity tests in rats with single intragastric administration of TBT compounds were conducted The LD_{50} values that were obtained at the end of the experiment ranged between 94 and $224\,mg\,kg^{-1}$. The pronounced clinical symptoms posed are apathy and emaciation, and increased salivation. A study revealed that the larvae of rock shell *Haustrum haustorium* as well as the larvae of the disk abalone *Haliotis rufescens* and the giant abalone *Haliotis sorenseni* are relatively sensitive to organotins such as TBT and TPT, compared to other aquatic organisms like fish, shellfish, and other invertebrates. It is only recently that data have become available on the acute toxicity of organotin salts on adult molluscs, proving that water dissolved TBT is highly toxic. It has been reported that lethal concentrations for

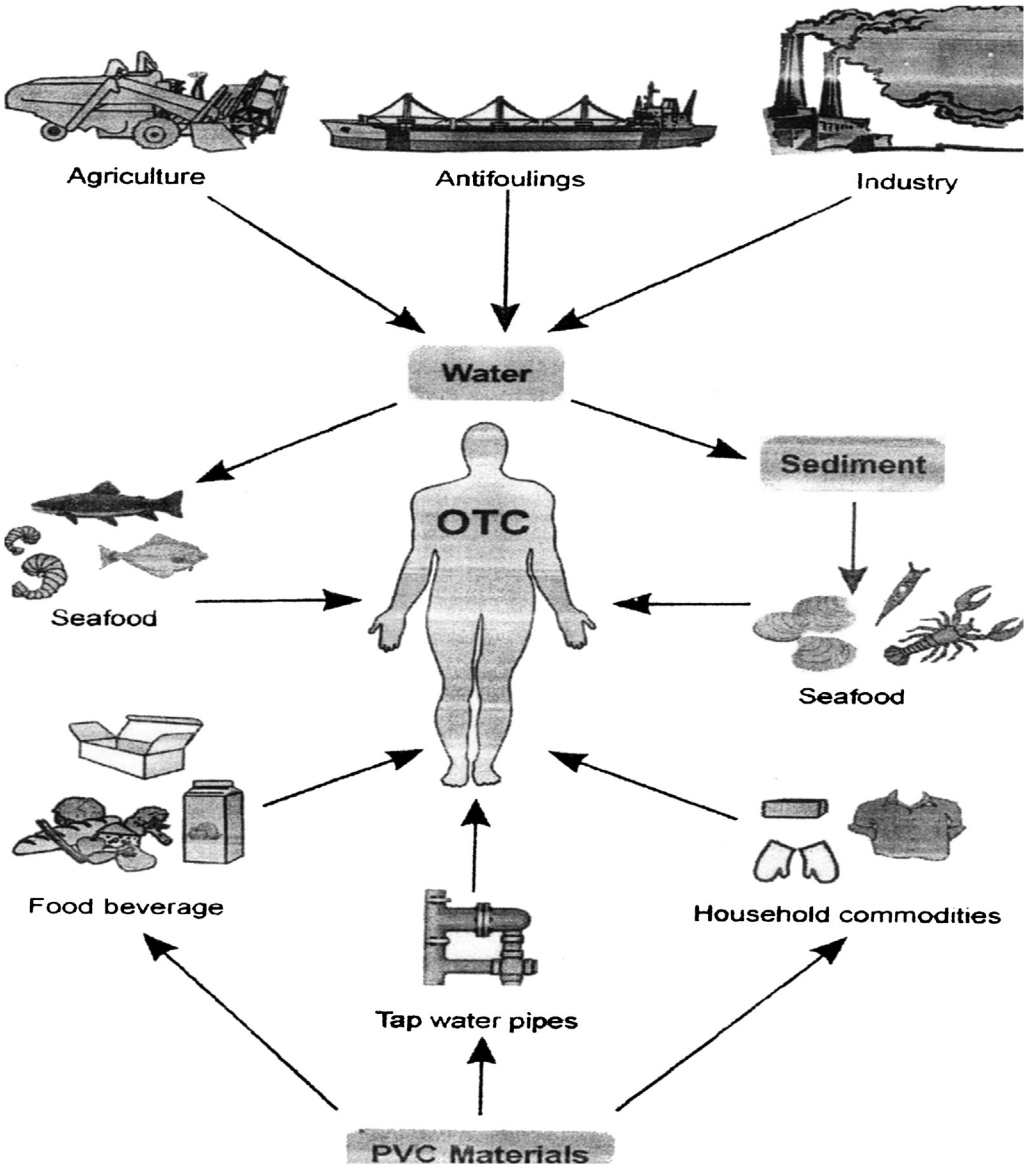

Figure 1 General sources of organotin compounds for humans. Adapted from Hoch, M., 2001. Organotin compounds in the environment: an overview. Appl. Geochem. 16, 719–743.

zooplankton are as low as 0.4 $\mu g\,l^{-1}$. Previous studies have also shown that OTCs such as dimethyltin chloride cause acute toxicity to the liver and kidneys, whereas trimethyltin chloride damages the central nervous system.

Chronic Toxicity

The first indication of the effects of TBT on nontarget molluscs was noted on Pacific oysters on the French Atlantic coast in the proximity of a large number of pleasure crafts. The main effects noted were the shell malformation of the adult oysters. Later experimental work revealed that TBT is the causative agent for shell thickening and direct mortality of larvae, since it has been observed globally that TBT concentrations in seawater were quite high near harbors all over the world. It has been confirmed that TBT can cause reproductive failure and abnormalities in shell production in the Japanese oyster. Thus it can be said that this contaminant causes the following effects in molluscs: (1) perturbation of reproduction, (2) decrease of the growth rate of juveniles, and (3) thickening of the adults' shells. Prolonged exposure to concentrations below the 48–96 h LC_{50} for molluscs can cause mortality due to bioconcentration of the pollutant. TBT is chronically toxic to adult marine bivalves at concentrations as low as 0.2 $g\,l^{-1}$ which cause 50% mortality after 180 days exposure.

Immunotoxicity

Organotins have been demonstrated to have immunotoxic and teratogenic properties in mammals. DBT is frequently appearing to be more toxic than TBT. The importance of the precise timing of exposure to DBT in induction of defects in

developing rat embryos was demonstrated. For some of a series of dialkyltin compounds, a selective action on the immune system of the rat was observed. A dose-related decrease in the weights of the thymus gland, spleen, and lymph nodes of rats fed on these compounds for several weeks was caused by dialkyltin compounds. Reduction of thymus gland weight was observed at dietary exposure concentrations as low as 5 mg DBT or dioctyltin per kg feed. Apparently, various immune functions investigated like delayed-type hypersensitivity to tuberculin, allograft rejection, graft-versus-host reaction, and resistance to *Listeria monocytogenes* infection indicated that the cell-mediated immune response was suppressed by these alkyltin compounds.

Reproductive Toxicity

TBTs and TPTs have been reported to induce toxic effects in male and female reproductive organs of rodents. A study revealed that the contaminants cause tumors in organs of rodents and it has been stated in literature that this may result in endocrine disruption. A delay was found in the completion of preputial separation after 0.5 or 15 mg of TBT was administered to male Wistar rats. It was concluded that peripubertal exposure to TBT clearly affected male sexual development. In ecotoxicological studies with snails, it was revealed that this compound interferes with the sex hormone metabolism and causes an increase in testosterone concentration. The effects of these endocrine-disrupting chemicals on the sex hormone system of mammals include effects on the male and female reproductive organs such as changes in weight of the ovaries and the testes.

Additionally, the adverse effects of phenyltins include Leydig cell hyperplasia as well as morphological changes of the endometrium. The US Environmental Protection Agency (USEPA) has stated that there is a possible relationship between hormonal effects, development of pituitary and testicular tumors, and TPT. Therefore, TPT is considered to be one among the chemicals that disrupt the endocrine system. Thus, there is a need for more research to be carried out on the effects of OTCs on the endocrine system and in particular on the hormonal control of male and female reproduction.

Genotoxicity

TBT has been considered as one of the most toxic contaminants entering the environment. Its effects are of particular concern since it causes induction of reproductive abnormalities and destabilization of female prosobranch. This phenomenon is known as imposex, and is characterized by the development of male sex organs in the female gastropods. The toxic effect of TBT to the marine mollusc *M. edulis* was investigated and it was found that TBT is genotoxic to the early life stages of marine mussels. The authors found a significant increase in DNA damage when a biomarker was used to test for the genotoxic effect of TBT. They suggested that TBT could be genotoxic due to its ability to disrupt calcium homeostasis. The development and survival of an organism is often closely related to the genotoxic effects. *Mytilus edulis* and *P. dumerilii* have been used in studies on the check for genotoxic effects of TBTO. It was revealed that TBTO is toxic and genotoxic to embryo and larval stages of the two examined species. *Platynereis dumerilii* was proven to be more sensitive to TBTO than *M. edulis*. In general, relatively few studies have been done on the genotoxic potential of TBT.

Carcinogenicity

TBT has been reported widely to be carcinogenic due to its wide use as an antifouling agent. The antioxidant response in the spleen of the rockfish *Sebastiscus marmoratus* was investigated after exposure to benzo-[*a*]-pyrene and TBT. Fish were exposed to environmentally relevant concentrations of TBT and benzo-[*a*]-pyrene as well as their mixture. Biochemical analyses of the spleens were done after 7, 25, and 50 days exposure. They found that after 7 days exposure to these chemicals, induction of glutathione peroxidase (GPx) occurred. However, after 25 and 50 days exposure, inhibition of GPx activity occurred. It was concluded that TBT induces the antioxidant defense system even after short-term exposure. In another study conducted by the Institute of Public Health and Environmental Hygiene in the Netherlands, TBTO was added to the food of rats at concentration ranges between 0.5 and 50 ppm over a period of 2 years. Their findings revealed that TBTO causes pancreatic adenocarcinoma, which is a rare type of tumor in the strain of female rats used.

Symptoms and Clinical Management of Organotin Poisoning

OTCs are used as heat stabilizers in industrial and agricultural biocides. Due to the development of industry and agriculture, OTCs have been used and have become a common source of occupational poisons. OTCs have been reported to be toxic to the human liver, kidney, and the central nervous system investigated. It was found that the poisoning was mild in four patients, moderate in six, and severe in five. After hospitalization, the severe patients were given glucocorticoids intravenously, namely 500 mg methylprednisolone on the first day, followed by 160 g (second day), and 180 mg (third day), respectively. The results showed that elevated levels of blood ammonia, decreased levels of blood potassium, and metabolic acidosis are common effects among patients with organotin poisoning. They suggested that demyelination can be observed in patients with severe poisoning. The effect is reversible after suitable treatments. Manifestations of mild poisoning of organotins could include headaches, dizziness, hypodynamia, restlessness, inappetence, and nausea. Medium poisoning may include mental confusion, vomiting, hypersomnia, and affective disturbances, while severe poisoning includes twitching, mental symptoms, epilepsy, and coma.

Exposure Standards and Guidelines

According to the EPA (1997), the exposure standard and guidelines set for freshwater aquatic life was 0.063 $\mu g\,l^{-1}$, while for aquatic life it was set at 0.001 $\mu g\,l^{-1}$.

See also: Toxicity, Acute; Mechanisms of Toxicity; Environmental Toxicology; Bioaccumulation; Neurotoxicity; Pharmacokinetic and Toxicokinetic Modeling; Toxicity Testing, Carcinogenesis.

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