Boundaries. There are no established molecular weight boundaries for this category. Limits on chain length are inherent in the SARs.

Testing. To address ecotoxicity concerns, base set acute aquatic toxicity testing (algae: static method, daphnid and fish: flow-through method, all measured concentrations).

Tier 1. The acute aquatic base set of environmental toxicity tests will be recommended for aquatic exposures and the terrestrial base set of environmental toxicity tests (i.e., the early seeding growth test, the earthworm acute toxicity test and the soil microbial community bioassay) will be recommended for any terrestrial exposures.

Acute fish toxicity test OPPTS 850.1075

Acute daphnid toxicity test OPPTS 850.1010

Green algae toxicity test OPPTS 850.5400

Early seedling growth test OPPTS 850.4230

Earthworm acute toxicity test OPPTS 850.6200

Soil microbial community bioassay OPPTS 850.5100

Tier 2. If acute toxicity testing indicates a significant risk, then environmental fate testing in the form of aerobic biodegradation testing is recommended. Aerobic biodegradability can be determined using one of the following test guidelines:

CO_2 evolution OPPTS 835.3110

Closed bottle OPPTS 835.3110

Modified OECD screening OPPTS 835.3110

Modified MITI (I) OPPTS 835.3110

DOC die-away OPPTS 835.3110

Manometric respirometry OPPTS 835.3110

Tier 3. In addition, if acute toxicity testing indicates a significant risk, then chronic aquatic toxicity testing with fish and aquatic invertebrates will be recommended.

Fish early life stage test OPPTS 850.1400

Daphnid chronic toxicity testing OPPTS 850.1300

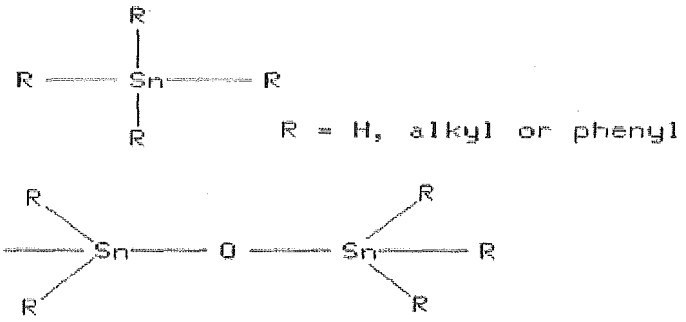
September 1988, revised September 1996

Category: Organotins Human Health

Environmental Toxicity

Definition. This category includes all mono-, di-, tri- and tetra-alkyl or phenyl organotin compounds, including organotin esters/oxides. The mode of toxic action of organotins in humans is unknown, but they are known to affect carbonate metabolism and other metabolic processes in the brain, liver, and muscle, as well as several enzymes and the oxidative activity of mitochondria. It has been suggested that general sulfhydryl binding may be responsible for the effects seen in mammals. It is assumed that these compounds need to be absorbed to be toxic, therefore, compounds with MWs > 1000 and which do not

transform to organotin compounds with MWs < 1000 will be excluded from this category. Human health and aquatic toxicity for liquid organotins is assumed to be limited by the relative octanol/water partition coefficient (a relative K_{ow} is based on the computer program, CLOGP, with C substituted for Sn). However, the limiting relative K_{ow} value is unknown. The Agency has data for an organotin with a relative log K_{ow} = 13.7 which still showed high toxicity towards fish and daphnids. Organotins which are solids at room temperature may show no toxicity at saturation at log K_{ow} values < 13.7 depending on the melting point, i.e., the higher the melting point at a given K_{ow}, the greater the likelihood that no toxicity will be observed at saturation. For solids, the no-effects-at-saturation determination has to be made on a case-by-case basis. There are no known K_{ow} limits for acute and chronic environmental toxicity at this time, but it is higher than a log K_{ow} = 13.7. Future testing will determine the K_{ow} limits.



Hazard Concerns. Tested organotins have been shown to be from moderately irritating to corrosive to the skin and eyes. Acute oral and dermal exposures can result in systemic effects, primarily neurotoxicity. Concerns for immunotoxicity are based on data on dialkyltins and trialkyltins. During a 13-week oral study in rats using dioctyltin bis (2-ethylhexylthioglycolate), effects to the thymus, spleen, lymph nodes, and bone marrow were observed. A No-Observable-Adverse-Effect-Level (NOAEL) of 1.6 mg/kg/d was derived from this study. During a 17-month feeding study in rats using bis (tri-n-butyltin)-oxide, immunoglobulin E (IgE) titers were reduced, as well as the activity of natural killer cells in the spleen, and there was reduced macrophage function. A NOAEL of 0.025 mg/kg/d was derived from this study. Based on the immunotoxicity end-point, an oral reference dose for chronic exposure (RfD) for tributyltin oxide of 3×10^{-5} mg/kg/d (IRIS 01/01/89) has been derived. Organotins are well known neurotoxins, with the tri- and tetra-substituted tins being more toxic than the mono- and di-substituted compounds. Although many tri-alkyltins show clear neurotoxic effects (eg. lesions in the hippocampus), the neurotoxic potential of di-alkyltins has not been as well defined. Available data indicate that dibutyltin and dioctyltin can produce neurotoxic effects such as reductions in brain neurotransmitter levels, alterations in spontaneous motor activity and hindlimb weakness. An effect level for neurochemical and behavioral changes following 3 days of oral administration of dibutyltin dilaurate was reported as 20 mg/kg. There are oncogenicity concerns for some of the organotins based on analogy to triphenyltin hydroxide, a group B probable human carcinogen. Therefore, the human health concerns for phenyltins will be dealt with on a case-by-case basis.

The acute aquatic toxicity for several subclasses of organotins has been determined through toxicity testing (Vighi & Calamari, 1985; Wong et al. 1982) and structure activity relationships (SAR). Organotins have been shown to be highly toxic to green algae (Wong et al. 1982). The acute toxicity of organotins is moderate to high towards daphnids (Vighi & Calamari, 1985). One datum for fish has indicated high toxicity (USEPA 1996). Organotins exhibit toxicity ranging from moderate toxicity (i.e., > 10 mg/L) to high toxicity (i.e., < 1 mg/L) depending on their K_{ow} , melting point, and MW. The higher the K_{ow}, the higher the toxicity (or the lower the EC_{50} value).

Boundaries. There are no known boundaries. The upper boundaries will be based on K_{ow} and MW. Acute toxicity expected with log $K_{ow} \leq 13.7$; chronic toxicity has no known upper bound for log K_{ow}, but it is ≥ 13.7. MW will be < 1000 for stable compounds. The environmental base set of tests will be requested for aquatic releases and the terrestrial base set of tests will be recommended for terrestrial exposures.

General Testing Strategy.

TIER 1.

A 90-day subchronic test in rodents by the oral route with special attention to the lymphoid organs (thymus, spleen, peripheral lymph nodes) and bone marrow (OPPTS 870.3100).

Neurotoxicity testing to include motor activity, a functional observational battery and neuropathology with special attention to lesions in the hippocampus (OPPTS 870.6200). This testing can be combined with the 90-day subchronic protocol cited above.

The acute aquatic base set of environmental toxicity tests will be recommended for aquatic exposures and the terrestrial base set of environmental toxicity tests will be recommended for terrestrial exposures. The acute toxicity tests for fish and daphnids should be done using the flow-through method with measured concentrations. Effective concentrations should be based on 100% active ingredients (AI) and mean measured concentrations. Measure TOC of dilution water in the control just prior to testing. Ideally, the highest treatment concentration on a mean measured concentration-basis should equal the aqueous solubility limit. Solvent can be used to assist the PMN to reach its aqueous solubility limit quicker, but cannot be used to significantly enhance the water solubility. The algal toxicity testing should be done with the static method and measured concentrations. Statistical analysis of effective concentrations at 24, 48, 72, and 96 hours should be performed. The test medium should be used with at least 0.300 mg/L EDTA as a final concentration.

Aquatic Base Set

Acute fish toxicity test OPPTS 850.1075

Acute daphnid toxicity test OPPTS 850.1010

Green algae toxicity test OPPTS 850.5400

Terrestrial Base Set

Early seedling growth test OPPTS 850.4230

Earthworm acute toxicity test OPPTS 850.6200

Soil microbial community bioassay OPPTS 850.5100

TIER 2.

If acute aquatic toxicity testing indicates a significant risk, the following environmental fate testing is recommended to determine aerobic biodegradability using one of the following test guidelines:

CO_2 evolution OPPTS 835.3110

Closed bottle OPPTS 835.3110

Modified OECD screening OPPTS 835.3110

Modified MITI (I) OPPTS 835.3110

DOC die-away OPPTS 835.3110

Manometric respirometry OPPTS 835.3110

TIER 3.

If acute toxicity testing and environmental fate testing continue to indicate a significant risk, then chronic aquatic toxicity testing with fish and aquatic invertebrates is recommended with flow-through methods and measured concentrations. Effective concentrations should be based on 100% active ingredients (AI) and

mean measured concentrations. Conduct statistical analysis of effective concentrations at days 7, 14, 21, and 28. Measure TOC of dilution water in the control just prior to testing. Ideally, the highest treatment concentration on a mean measured concentration-basis should be equal at the aqueous solubility limit. Solvent can be used to assist the PMN to reach its aqueous solubility limit quicker, but cannot be used to significantly enhance the water solubility. The 7-d fish early life stage (ELS) toxicity test cannot be substituted for the 28-d ELS toxicity test and the 7-d daphnid chronic toxicity test cannot be substituted for the 21-d toxicity test because Van Leeuwen et al. (1990) have demonstrated that the 7-d ELS toxicity test underestimated the chronic toxicity of anilines measured by the 28-d ELS toxicity test by >5.3 times when the NOECs were compared (see Table VII in Van Leeuwen).

Chronic Aquatic Toxicity

Fish early life stage test OPPTS 850.1400

Daphnid chronic toxicity testing OPPTS 850.1300

References.

8E-594.

Tributyltin oxide. Bis-(tri-n-butyltin)-oxide. (1988, December). Gesellschaft Deutscher Chemiker - Advisory Committee on Existing Chemical of Environmental Relevance (BUA). BUA Report 36.

USEPA 1996. United States Environmental Protection Agency (1996). The Office of Pollution Prevention andToxics (OPPT) premanufacture notification (PMN) ECOTOX database: a confidential business information (CBI) collection of environmental toxicity data from new chemical submissions under Sec. 5 of the Toxic Substances Control Act (TSCA). Washington, DC: Environmental Effects Branch, Health and Environmental Review Division (7403), OPPT, USEPA. OPPT contact is V. Nabholz, 202-564-8909.

Van Leeuwen, C.J., Adema, D.M.M., & Hermens, J. (1990). Quantitative structure-activity relationships for fish early life stage toxicity. Aquatic Toxicology, 16, 321-334.

Vighi, M., & Calamari, D. (1985). QSARs for organotin compounds on Daphnia magna. Chemosphere, 14, 1925-1932.

WHO 1980. World Health Organization Environmental Health Criteria 15. Tin and organotin compounds: A preliminary review. Geneva: WHO pp. 59-62.

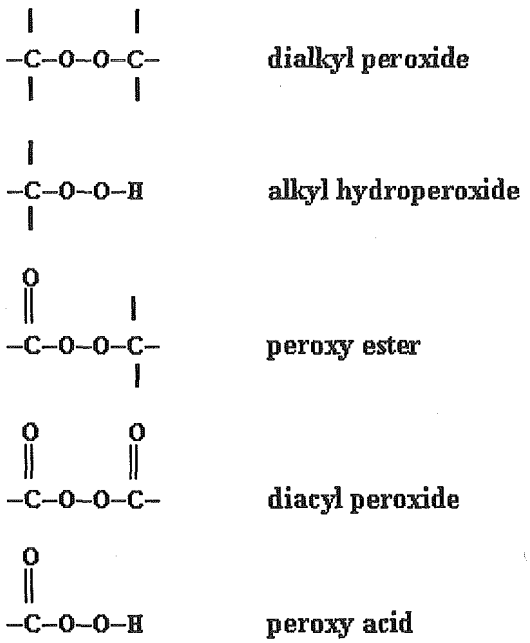
Wong, P.T.S., Chau, Y.K., Kramar, O., & Bengert, G.A. (1982). Structure-toxicity relationship of tin compounds on algae. Canadian Journal of Fisheries and Aquatic Sciences, 39, 483-488.

April 1991, revised September 1996

Category: Peroxides Human Health (case-by-case)

Environmental Toxicity

Definition. Any molecular structure containing one or more of the following functional groups is considered to be a member of the class:



The category of peroxides is a small one (<0.2% of all new chemicals). The "typical" peroxide in the new chemical program is a discrete (class I) chemical with a molecular weight of <500.

Hazard Concerns. EPA had previously identified hazard concerns for the possible carcinogenicity of new chemicals falling into the peroxide category based on available evidence. EPA has reviewed test data developed by the Society of the Plastics Industry (SPI) and others on the peroxide category of chemicals and concludes that available information does not support continued identification of peroxides as a new chemical category presenting concerns for possible carcinogenicity. EPA will continue to evaluate the potential health concerns for new chemical peroxides that are notified but, with this change, will not apply a category understanding as regards potential carcinogenicity. While the assessment of potential human health hazard concerns will be conducted on a case-by-case basis, this modification does not affect EPA's approach to environmental hazard concerns which will continue to be identified for members of this category.

Boundaries. There are no established boundary conditions for review of peroxides.

General Testing Strategy.

The New Chemicals Program considers the following tests to be appropriate to address ecotoxicity concerns for peroxides:

1. Base-set ecotoxicity testing to include fish (40 CFR 797.1400), daphnids (40 CFR 797.1300), and algae (40 CFR 797.1050).

2. Environmental fate testing including, as appropriate, melting point (40 CFR 796.1300) or boiling point (40 CFR 796.1220), water solubility (40 CFR 796.1840 or 796.1860), log K_{ow} (40 CFR 796.1550, 796.1570, or 796.1720), vapor pressure (40 CFR 796.1950), hydrolysis (40 CFR 796.3500), direct and indirect photolysis (40 CFR 796.3765), and aerobic biodegradation by any of the following test guidelines-

Modified Sturm Test 40 CFR 796.3260

Closed Bottle Test 40 CFR 796.3200

Modified OECD Screening Test 40 CFR 796.3240

Modified MITI Test (I) 40 CFR 796.3220

Modified AFNOR Test 40 CFR 796.3180

September, 1988; revised June, 1994; revised April, 2001

Category: **Persistent, Bioaccumulative, and Toxic (PBT) Chemicals** Health/Environmental Toxicity

Environmental Fate

Definition. PBT chemical substances possess characteristics of persistence (P) in the environment, accumulation in biological organisms (bioaccumulation (B)), and toxicity (T) that make them priority pollutants and potential risks to humans and ecosystems. Prominent examples of PBT chemical substances include the insecticide, DDT and polychlorinated biphenyls (PCBs). This PBT category includes the boundary conditions, such as fish bioconcentration/bioaccumulation factors and environmental persistence values, that would determine inclusion in (or exclusion from) the category, and standard hazard and fate tests to address P, B, and T concerns for the chemical substances fitting the category description. For background information and discussion of this PBT category, see http://www.epa.gov/oppt/newchems/pubs/pbtpolcy.htm, and the proposed (October 5, 1998; 63 FR 53417) and final (November 4, 1999; 64 FR 60194) "Category for Persistent, Bioaccumulative, and Toxic Chemical Substances" published in the US Federal Register.

Hazard Concerns. Generally, PBT chemical substances are chemical substances that partition to water, sediment or soil and are not removed at rates adequate to prevent their bioaccumulation in aquatic or terrestrial species, with the potential to pose a risk via food chain toxicity.

Boundaries. The following table summarizes specific identification criteria and associated process for use in evaluating new chemical PBT substances.

NEW CHEMICALS PROGRAM

PBT CATEGORY CRITERIA AND PROCESS

	TSCA Section 5 Action	
	5(e) Order/Significant New Use Rule (SNUR)	Ban Pending Testing
	Exposure/release controls included in order; testing required	Deny commercialization; testing results may justify removing chemical from "high risk concern"
Persistence (transformation half-life)	>2 months	>6 months
Bioaccumulation* (Fish BCF or BAF)	≥1000	≥5000
Toxicity	Develop toxicity data where necessary, based upon various factors, including concerns for P, B, other physical/chemical factors, and toxicity.	

*Chemicals must also meet criteria for MW (<1000) and cross-sectional diameter (<20, or <20 x 10^{-8} cm). BCF of 1000 and 5000 are equivalent to log Kow of 4.2 and 5, respectively.

General Testing Strategy

***Tier 1.* Based upon SAR and professional judgment, the Agency identifies a new chemical substance as a possible PBT chemical substance.**

Log Kow — Liquid chromatography (OPPTS 830.7570/OECD 117) or generator column

	(OPPTS 830.7560) method
Ready biodegradability	Ready biodegradability (OPPTS 835.3110/OECD 301) 6 methods (choose one, or an equivalent test): DOC Die-Away, CO_2 Evolution, Modified MITI (I), Closed Bottle, Modified OECD Screening, Manometric Respirometry *or* Sealed-vessel CO_2 production test (OPPTS 835.3120)
Hydrolysis in water (if, based upon SAR, susceptibility to hydrolysis is suspected)	OPPTS 835.2110 (OECD 111)
Results	If the measured log Kow is <4.2 or if the test chemical passes the ready biodegradability test (i.e., not persistent in the environment), no further PBT-related testing is required. If the measured log Kow is greater than or equal to 4.2 and the chemical does not pass the ready biodegradability test, the chemical would require tier 2 testing. If hydrolysis testing is conducted and results in a half-life of <60 days, further testing may not be needed, but the need for testing must be determined after consideration of factors specific to the case, such as physical/chemical properties, persistence and bioaccumulative qualities of hydrolysis products, and the nature of the expected releases.

***Tier 2.* Biodegradability and Bioaccumulation**

Biodegradability	Shake-flask die-away test (OPPTS 835.3170) or an equivalent test.
Bioaccumulation	Fish bioconcentration test (OPPTS 850.1730/OECD 305), or an equivalent test). Measured BCF should be based on 100 percent active ingredient and measured concentration(s).
Results	If the measured biodegradation half-life is >60 days and measured BCF is >1000, tier 3 testing will be required. If only one condition is met, releases and exposure are further considered to determine if additional testing is required.

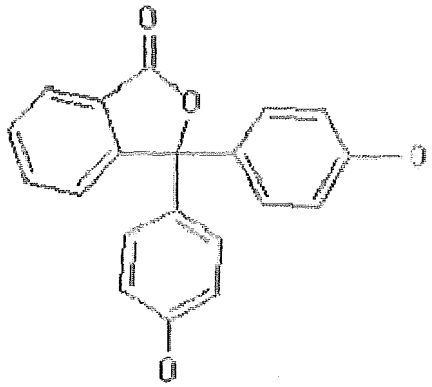
Tier 3.* *Toxicity/advanced environmental fate testing.

Human health toxicity	Combined repeated dose oral toxicity with the reproductive/developmental toxicity screening test (OECD No. 422) in rats. Other health testing will be considered where appropriate.
Environmental fate	Sediment/water microcosm biodegradation test (OPPTS 835.3180).
Chronic environmental toxicity	Fish (rainbow trout) and daphnids should be tested according to 40 CFR 797.1600 (same as OPPTS 850.1400/OECD 210) and 40 CFR 797.1330 (same as OPPTS 850.1300/OECD 202), respectively. Additional testing to evaluate other biota (e.g., avian, sediment dwelling organisms) or other effects (e.g., endocrine disrupting potential) will be considered where appropriate.

November, 1999

Category: Phenolphthaleins Human Health

Definition. Any chemical containing the phenolphthalein structure is considered to be a member of the category.



Hazard Concerns. The health concern for phenolphthalein and derivatives of phenolphthalein is for cancer based on the NTP cancer study (NTP report TR-465, November 1996) for phenolphthalein with administration via the diet. There was clear evidence of carcinogenic activity in male F344/N rats based on markedly increased incidences of benign pheochromocytomas of the adrenal medulla and of renal tubule adenomas and adenomas or carcinomas (combined). There was some evidence of carcinogenic activity in female F344/N rats based on the increased incidences of benign pheochromocytomas of the adrenal medulla in the 12,000 ppm group and of benign or malignant pheochromocytomas (combined) in the 12,000 and 25,000 ppm groups. There was clear evidence of carcinogenic activity in male $B6C3F_1$ mice based on increased incidences of histiocytic sarcomas and of malignant lymphomas of thymic origin. There was clear evidence of carcinogenic activity in female $B6C3F_1$ mice based on increased incidences of histiocytic sarcomas, malignant lymphomas of all types, lymphomas of thymic origin, and benign sex-cord stromal tumors of the ovary.

Boundaries. No boundaries currently defined.

Testing. EPA considers the following tests to be the most appropriate for phenolphthalein derivatives found to pose an unreasonable risk to human health:

Tier 1:

Comparative dermal and oral absorption study in rats (OPPTS 870.7485, "Metabolism and pharmacokinetics")

In vitro Chromosome aberrations study in Chinese hamster ovary cells with phenolphthalein as an additional positive control (OPPTS 870.5375, "In vitro mammalian cytogenetics")

Log Kow test (OPPTS 830.7550)

Water solublility for both lactone and acid form (OECD 105)

Ready biodegradability (OPPTS 835.3110)

Tier 2:

2-year carcinogenicity study in mice (OPPTS 870.4200, "Carcinogenicity")

April, 1998

Category: Phenols Environmental Toxicity

Definition. This category includes phenols (i.e., monophenols), polyhydroxy phenols, and polyphenols. It is assumed that these compounds need to be absorbed to be toxic, therefore, compounds with MWs > 1000 will be excluded from this category. Acute toxicity for phenols which are liquids at room temperature

is known to be limited by the octanol/water partition coefficient (K_{ow}). Above a log K_{ow} value of about 7.38, phenols are expected to show no effects at saturation during 96-h exposures (Veith and Broderius 1987). Phenols which are solids at room temperature may show no toxicity at saturation at lower K_{ow} values depending on the melting point, i.e., the higher the melting point at a given K_{ow}, the greater the likelihood that no toxicity will be observed at saturation. For solids, no effects at saturation has to be demonstrated on a case-by-case basis. There are no known K_{ow} limits for chronic toxicity at this time, but it may not be much above a log K_{ow} = 9.0 for liquid phenols. Future testing will determine this K_{ow} limit.

Hazard Concerns. The acute and chronic toxicity for phenols can be predicted through SAR Analysis. SARs are available for fish 96-h LC50, daphnid 48-h LC50, green algal 96-h EC50, fish chronic value (ChV), daphnid ChV, and algal ChV. Members of this category exhibit toxicity ranging from low toxicity (i.e., > 100 mg/L) to high toxicity (i.e., < 1 mg/L) depending on their K_{ow}, MW, and substitutions (e.g., dinitrophenols).

Dinitrophenols are known to be more toxic than predicted by these SARs (see the category for polynitroaromatics).

Fate: Phenols are subject to indirect photolysis under environmentally realistic conditions.

Boundaries. There are no known lower boundaries. The upper boundaries will be based on K_{ow} and MW. Acute toxicity expected with log K_{ow} < 7.38; no effects at saturation during 96-h exposures when log K_{ow} >= 7.38. Chronic toxicity has no known upper bound for log K_{ow}, but it is probably near 9. MW will be < 1000. The environmental base set of tests will be requested for aquatic releases and the terrestrial base set of tests will be recommended for terrestrial exposures. When the log K_{ow} is >= 7.38, chronic toxicity testing with fish, daphnids, and green algae will be recommended.

General Testing Strategy

I. Release to Aquatic Ecosystems:

Tier 1. The aquatic base set of environmental toxicity tests will be recommended for aquatic exposures. The acute toxicity tests for fish (40 CFR 797.1400) and daphnids (40 CFR 797.1300) will be done using the flow-through method with measured concentrations; effective concentrations will be based on 100% active ingredients (AI) and mean measured concentrations; measured TOC of dilution water in the control; the highest treatment concentration on a nominal-basis should equal the aqueous solubility limit; and solvent can be used to assist the PMN to reach its aqueous solubility limit quicker, but cannot be used to artificially enhance the water solubility of the PMN beyond its aqueous solubility limit.

The algal toxicity testing (40 CFR 797.1050), should be done with static methods; measured concentrations; effective concentrations based on 100% AI and mean measured concentrations; statistical analysis of effective concentrations at 24, 48, 72, and 96 hours; test medium with at least 0.300 mg/L EDTA as a final concentration; the highest treatment concentration on a nominal-basis equal to the aqueous solubility limit; and solvent can be used to assist the PMN to reach its aqueous solubility limit quicker, but cannot be used to artificially enhance the water solubility of the PMN beyond its aqueous solubility limit.

If there is no significant risk from the PMN after the results of the environmental base set have been integrated into the risk assessment, then no further testing is recommended. However, if there is a significant risk, then go to Tier 2.

Tier 2. Direct and Indirect Photolysis Screening Test (40 CFR 796.3765). If t½ ≤ 2 days, go to Tier 3; if t½ > 2 days, go to Tier 4.

Tier 3a. If t½ ≤ 2 days and photolysis products are known and/or identified, then assess photolysis products for environmental hazards.

Tier 3b. If t½ ≤ 2 days and photolysis products are not known and/or identifiable, then prepare a stock solution of PMN using the standard humic-containing solution described in the direct and indirect

photolysis screening test [40.796.3765 (b)(2) and (c)(2)], expose to sunlight for at least 6 half-lives (t½), and test photolysis products for toxicity with most sensitive species from environmental base set. For example, the most sensitive species from the environmental base set has an EC50 value = 2.0 mg PMN/L (based on 100% AI, therefore, prepare a 5.0 mg PMN per liter stock solution based on 100% AI using the standard humic-containing solution. This stock solution is exposed to sunlight for at least 6 half-lives to ensure that all of the PMN has been photolyzed, and then this stock solution is used to retest the most sensitive aquatic species to determine if the photolysis products of the PMN are more or less toxic that the PMN.

Tier 4. Fish chronic toxicity testing, i.e., fish early life stage (ELS) toxicity testing (40 CFR 797.1600), with flow-through methods; measured concentrations; effective concentrations based on 100% AI and mean measured concentrations; statistical analysis of effective concentrations at days 7, 14, 21, and 28; measured TOC of dilution water in the control; the highest treatment concentration on a nominal-basis should be set at the aqueous solubility limit; solvent can be used to assist the PMN to reach its aqueous solubility limit quicker, but cannot be used to artificially enhance the water solubility of the PMN beyond its aqueous solubility limit; and the 7-d ELS stage toxicity test cannot be substituted for the 28-d ELS toxicity test because Van Leeuwen et al (1990) have demonstrated that the 7-d ELS toxicity test underestimated the chronic toxicity of anilines measured by the 28-d ELS toxicity test by >5.3 times when the NOECs were compared (see Table VII in Van Leeuwen);

Daphnid chronic toxicity testing (40 CFR 797.1330), with flow-through methods; measured concentrations; effective concentrations based on 100% AI and mean measured concentrations; statistical analysis of effective concentrations at days 7, 14, and 21; measured TOC of dilution water in the control; the highest treatment concentration on a nominal-basis should be set at the aqueous solubility limit; solvent can be used to assist the PMN to reach its aqueous solubility limit quicker, but cannot be used to artificially enhance the water solubility of the PMN beyond its aqueous solubility limit; and the 7-d daphnid chronic toxicity test cannot be substituted for the 21-d toxicity test

because Van Leeuwen et al (1990) have demonstrated that the fish 7-d ELS toxicity test underestimated the chronic toxicity of anilines measured by the fish 28-d ELS toxicity test by >5.3 times when the NOECs were compared (see Table VII in Van Leeuwen).

Aerobic biodegradability according to any one of the following test guidelines (listed in order of preference):

Aerobic Aquatic Biodegradation 40 CFR 796.3100

Modified Sturm Test 40 CFR 796.3260

Closed Bottle Test 40 CFR 796.3200

Modified OECD Screening Test 40 CFR 796.3240

Modified MITI Test (I) 40 CFR 796.3220

Modified AFNOR Test 40 CFR 796.3180

II. Release to Terrestrial Ecosystems: The terrestrial base set of environmental toxicity tests (i.e., the early seeding growth test, the earthworm toxicity test and the soil microbial community bioassay) will be recommended for terrestrial exposures. Chronic toxicity testing for terrestrial organisms include: the plant whole life cycle test, the plant uptake test, and the soil microbial community bioassay.

References.

Van Leeuwen CJ, Adema DMM, and Hermens J. 1990. Quantitative structure-activity relationships for fish early life stage toxicity. Aquatic Toxicology 16:321-334.

Veith GD and Broderius SJ. 1987. Structure-toxicity relationships for industrial chemicals causing type (II) narcosis syndrome. In Kaiser KLE (ed), QSAR In Environmental Toxicology -II, p 385-391. Reidel Publishing Company.

July, 1991

Category: Phosphates, Inorganic

Definition. This category includes all inorganic soluble forms of phosphates, such as, phosphoric acid [PO4H3 or OP(=O)(O)O] and its salts or phosphate salts, pyrophosphates, polyphosphates, and organic and inorganic forms of phosphorous that can be oxidized to phosphates rapidly. Inorganic forms of phosphonic acid (H2PO3 or OP(=O)O) are not included in this category because monopotassium phosphonic acid [13977-65-6] has been shown not to be an algal nutrient, not to be a replacement for phosphate in algal growth medium, and not to cause exponential growth of green algae.

Hazard Concerns. The standard environmental toxicity profile for inorganic phosphates as P in mg P/L is:

ECOTOX: Predicted (P) and measured (M) toxicity values in mg/L (ppm) are:

fish 96-h LC50 > 100.0 P

daphnid 48-h LC50 > 100.0 P

green algal 96-h EC50 b < 0.030 P

algal 96-h EC290 b = 0.030 M S,N

fish chronic value > 10.0 P

daphnid ChV > 10.0 P

algal ChV = 0.010 M Hutchinson 1957

Predictions are based on SAR-nearest analog analysis for soluble forms of inorganic phosphates (PO4); SAR chemical class = P-O4; MW of P = 31, PO4 = 95, PO4H3 = 98; pH7; effective concentrations based on 100% active ingredients and nominal concentrations of P; hardness <24.0 mg/L as CaCO3; and TOC <2.0 mg/L;

high concern for eutrophication;

assessment factor = 10.0

concern concentration = 0.001

Phosphate phosphorus has the potential to stimulate the growth of green algae and cause algal blooms and eutrophication in freshwater and marine environments. The phosphate anion is a plant nutrient and is the major limiting nutrient in many freshwater environments. The USEPA OW WQC (USEPA 1976) states:

[W]hen such concentrations [of total phosphate phosphorus]exceed 25 µg/l at the time of the spring turnover on a volume-weighted basis in lakes or reservoirs, they may occasionally stimulate excessive or nuisance growths of algae and other aquatic plants. Algal growths impart undesirable tastes and odors to water, interfere with water treatment, become aesthetically unpleasant and alter the chemistry of the water supply. The contribute to the phenomenon of cultural eutrophication.

To prevent the development of biological nuisances and to control accelerated or cultural eutrophication, total phosphates as phosphorus (P) should not exceed 50 µg/l in any stream at the point where it enters any lake or reservoir, nor 25 µg/l within the lake or reservoir. A desired goal for the prevention of plant nuisances in streams or other flowing waters not discharging directly to lakes or impoundments is 100 µg/l

total P (Mackenthum, 1973). Most relatively uncontaminated lake districts are known to have surface waters that contain from 10 micrograms P/L (or 31 micrograms PO4H3/L) to 30 microg P/L (or 92 microg PO4H3/L) (Hutchinson, 1957).

Odum (1971) called phosphorus a major factor in the process of cultural eutrophication. Eutrophication results when nutrients, especially phosphates, are imported into aquatic ecosystems. This process is analogous to fertilizing an agricultural field. Phosphates act like a fertilizer and produce increases in the abundance of algae and other aquatic plants; eventually, they can result in excessive growths of algae (i.e., algal blooms). Excessive algae can block sunlight from reaching submerged macrophytes and other microalgae below the surface. When the algae die and fall to the bottom of slow-moving water or lakes, they are consumed by bacteria which use up available oxygen producing anaerobic conditions. Decaying algae cause odors and oxygen depletion of the water to occur with concomitant detriment to fish and aquatic invertebrates and, in turn, fishing and water-based recreational activities.

Phosphate concentrations as low as 0.050 mg P/L (ppm) or 50.0 micrograms P/L (ppb) will produce exponential growth of green algae in 96 hours (Miller et al. 1978), and phosphate concentrations from 10 to 60 micrograms P/L (ppb) were correlated to algal blooms and oxygen depletion (i.e., eutrophication) in Lake Washington, Seattle (Odum 1971). Phosphates have been severely limited or banned from detergents in 13 states, the District of Columbia, and several counties and municipalities (USEPA 1992). Sodium tripolyphosphate was one of the principal components of synthetic detergents. Freshwater green algae are clearly the most sensitive group of aquatic organisms to phosphate additions to water.

Boundaries. The boundaries for inorganic phosphate compounds depend on the release of inorganic phosphates which can be used by algae as a mineral nutrient. Any inorganic phosphate which can be used by algae as a nutrient or which transforms to release or becomes an algal nutrient is included in this category.

Testing. Based on a consideration of available data on inorganic phosphates and the physicochemical properties of these compounds, there is no need for further testing. However, if there is doubt about the availability of phosphate in a nutrient form from a PMN substance, then the algal toxicity test can be done with the PMN substance substituted for phosphate nutrient in the algal growth medium. If a PMN substance is capable of stimulating exponential growth green algae, it must be emphasized that inorganic phosphates should not be released to water because of their potential to cause eutrophication and their persistence.

Regulatory Actions.

(1) Phosphates have been severely limited or banned from detergents in 13 states, the District of Columbia, and several counties and municipalities (USEPA 1992).

(2) Water Quality Criterion, 1976 (USEPA 1976): total phosphates as phosphorus (P) should not exceed 50 micrograms p/L in any stream at the point where it enters any lake or reservoir, nor 25 micrograms P/L within the lake or reservoir.

(3) Hazard assessments of selected aqueous cleaner chemicals, USEPA (1990): OPPT recommendation to the Office of Air and Radiation: "...phosphates should never be released to water."

(4) Agency recommendation for a "nationwide elimination of the use of household laundry detergents containing phosphates." (USEPA 1992).

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March, 2000

Category: Phosphinate Esters Environmental Toxicty

Phosphinate esters are a class of organic compounds characterized by the functional group R-O-P(=O)(R)R. Phosphinate esters are metabolically active and exhibit excess aquatic toxicity in addition to narcosis. Phosphinate esters exhibit excess toxicity relative to simple esters (-C(=O)O-) and phosphate esters (-OP(=O)(O-)O-.

It is assumed that phosphinate esters need to be absorbed to be toxic, therefore, phosphinate esters with MW >1000 will be excluded from this category. Acute toxicity for phosphinate esters is known to be correlated and limited by the octanol/water partition coefficient (K_{ow}). Above a log K_{ow} value of >5.0, phosphinate esters show no effects at saturation during 96-hr exposures to fish. Phosphinate esters which are solids at room temperature may show no toxicity at saturation at lower K_{ow} values depending on the melting point, i.e., the higher the melting point at a given K_{ow}, the greater the likelihood that no toxicity will be observed at saturation. For solids, the no effects at saturation has to be determined on a case-by-case basis. There are no measured upper K_{ow} limits for chronic toxicity at this time, but it may not be much above a log K_{ow} = 8. Future testing will determine K_{ow} limits.

Hazard Concerns.

The toxicity for phosphinate esters has been determined through SAR analysis. SARs for freshwater species:

log fish 96-h LC_{50} (millimoles/L) = -1.201 -0.260 log K_{ow}

where n=2, R^2=1.0, LOGKOW (SRC)<5, MW<1000;

log daphnid 48-h LC_{50} (millimoles/L) = -1.501 -0.260 log K_{ow} where n=2, R^2=1.0, LOGKOW (SRC)<5, MW<1000;

log green algal 96-h EC_{50} (mmol/L) = -1.974 -0.332 log K_{ow}

where n=2, R^2=1.0, LOGKOW(SRC)<6.4, MW<1000, based on test data for *Pseudomonas putida*;

log fish ChV (millimoles/L) = -2.210 -0.499 log K_{ow}

where n=2, R^2=1.0, LOGKOW(SRC)<8, MW<1000, based on F96÷ACR10;

log daphnid ChV (millimoles/L) = -2.445 -0.407 log K_{ow}

where n=2, R^2=1.0, LOGKOW(SRC)<8, MW<1000, based on D48÷ACR10; and

log algal ChV (mmol/L) = -3.315 -0.223 log K_{ow}

where n=2, R^2=1.0, LOGKOW(SRC)<8, MW<1000, based on test data for *Pseudomonas putida.*

SARs for saltwater species:

log fish 96-h LC_{50} (millimoles/L) = -1.160 -0.368 log K_{ow}

where n=2, R^2=1.0, LOGKOW(SRC)<5, MW<1000; and

log mysid 96-h LC_{50} (millimoles/L) = -2,019 -0.476 log K_{ow}

where n=2, R^2=1.0, LOGKOW(SRC)<5, MW<1000.

Fate.

Phosphinate esters hydrolyze in water and their rate of hydrolysis is correlated with pH: the more alkaline the faster the hydrolysis. The SAR for hydrolysis is:

log hydrolysis t½ (d) = 4.325 -0.497 pH

where n=2, R^2=1.0.

At pH 7.1, the hydrolysis t½ = 6.3 days or 150 hours.

Boundaries.

MW <1000. Log K_{ow} <5.0 for acute toxicity to fish and aquatic invertebrates; log K_{ow} <6.4 for toxicity to green algae as a 96-h EC_{50}; and log K_{ow} assumed to be <8.0 for chronic toxicity to aquatic organisms, but could be higher.

General Testing Strategy.
I. Release to Aquatic Ecosystems:

Tier 1. The aquatic base set of environmental toxicity tests will be recommended for aquatic exposures. The acute toxicity tests for fish (OPPTS 850.1075) and daphnids (OPPTS 850.1010) will be done using the flow-through method with measured concentrations; effective concentrations will be based on 100% active ingredients (ai) and mean measured concentrations; measured TOC of dilution water in the control; ideally, mean measured concentrations in the highest treatment concentration should be equal the aqueous solubility limit; and solvent can be used to assist the aldehyde to reach its aqueous solubility limit quicker, but cannot be used to artificially enhance the water solubility of the test chemical significantly above its aqueous solubility limit.

The algal toxicity testing (OPPTS 850.5400), should be done with static methods; measured concentrations; effective concentrations based on 100% active ingredients (ai) and mean measured concentrations; statistical analysis of effective concentrations at 24, 48, 72, and 96 hours; test medium with at least 0.300 mg/L EDTA as a final concentration; ideally, mean measured concentrations in the highest treatment concentration should be equal the aqueous solubility limit; and solvent can be used to assist the aldehyde to reach its aqueous solubility limit quicker, but cannot be used to artificially enhance the water solubility of the test chemical significantly above its aqueous solubility limit.

If there is no significant risk from the PMN chemical after the results of the environmental base set have been integrated into the risk assessment, then no further testing is recommended. However, if there is a significant risk, then go to Tier 2.

Tier 2. Aerobic biodegradability according to either of the following test guidelines:

Ready Biodegradability OPPTS 835.3110

Sealed Vessel CO2 Production Test OPPTS 835.3120

If there is no significant risk from the PMN chemical after the results of biodegradation testing have been integrated into the risk assessment, then no further testing is recommended. However, if there is a significant risk, then go to Tier 3.

Tier 3. Fish chronic toxicity testing, i.e., fish early life stage (ELS) toxicity testing (OPPTS 850.1400), with flow-through methods; measured concentrations; effective concentrations based on 100% active ingredients (AI) and mean measured concentrations; statistical analysis of effective concentrations at days 7, 14, 21, and 28; measured TOC of dilution water in the control; ideally, mean measured concentrations in the highest treatment concentration should be equal the aqueous solubility limit; solvent can be used to assist the PMN to reach its aqueous solubility limit quicker, but cannot be used to artificially enhance the water solubility of the PMN significantly above its aqueous solubility limit; and the 7-d ELS stage toxicity test cannot be substituted for the 28-d ELS toxicity test because the 7-d ELS toxicity test may underestimate chronic toxicity measured by the 28-d ELS toxicity test when the Chronic Values are compared.

Daphnid chronic toxicity testing (OPPTS 850.1300), with flow-through methods; measured concentrations; effective concentrations based on 100% active ingredients (AI) and mean measured concentrations; statistical analysis of effective concentrations at days 7, 14, and 21; measured TOC of dilution water in the control; ideally, mean measured concentrations in the highest treatment concentration should be equal the aqueous solubility limit; solvent can be used to assist the PMN to reach its aqueous solubility limit quicker, but cannot be used to artificially enhance the water solubility of the PMN significantly above its aqueous solubility limit; and the 7-d daphnid chronic toxicity test cannot be substituted for the 21-d toxicity test because the daphnid 7-d short-term chronic toxicity test may underestimate chronic toxicity measured by the daphnid 21-d chronic toxicity test when the chronic values are compared.

II. Release to Terrestrial Ecosystems: The terrestrial base set of environmental toxicity tests (i.e., the early seeding growth test [OPPTS 850.4230], the earthworm toxicity test [OPPTS 850.6200], and the soil microbial community bioassay [OPPTS 850.5100]) will be recommended for terrestrial exposures. Chronic toxicity testing for terrestrial organisms include: the plant whole life cycle test, the plant uptake test, and the soil microbial community bioassay.

September 1996.

Category: Polyanionic Polymers (& Monomers) Environmental Toxicity

Definition.

There are two subcategories of polymers that are of concern:

- polyaromatic sulfonates - condensation products of sulfonated aromatics with formaldehyde, and

- polyacrylates with free carboxyl groups.

This category includes monomers with two or more acid groups and which act like organic acid chelators. The acid groups may include carboxylic acids, silicic acids, phosphoric acid, and sulfuric acids. These acids may also contain thiol substitutions. The acid groups on a monomer may be all of the same type of acid or may be a mixture of acids. The monomeric nucleus may include carbon, silica, oxygen, sulfur, and nitrogen, or mixtures of these elements. Members of this category must be water soluble or water self-dispersing. Molecular weights can be > 1000.

Hazard Concerns. Polyaromatic sulfonates are moderately toxic to fish, daphnids, and algae. The polyacrylates are toxic to algae only. There is no apparent relationship between charge density and toxicity, and no QSAR (quantitative structure-activity relationship) has been developed for these polymers, or the polyanionic monomers. Polyanionic monomers (as salts, e.g., Na or K salts) are moderately toxic to green algae, but show low toxicity to fish and daphnids. It is assumed that the toxicity of these compounds is due

to over-chelation of nutrient elements needed for algal growth and that this toxicity will be mitigated in the presence of Ca^{++} either added to the compound before testing or present in the growth/test medium at a hardness of about 150 mg/L as $CaCO_3$.

Boundaries. Polymers must be water-soluble. Molecular weights are generally >1,000.

General Testing Strategy

To address ecotoxicity concerns, for polycarboxylic acids (polyacrylates) and polyanionic monomers, algal testing (static methods, nominal concentrations) is recommended, in 3 separate tests: 1) the test substance as is, 2) with equivalent of calcium ion, and 3) with growth medium at 150 mg/L hardness, as $CaCO_3$). For polyaromatic sulfonates, base set aquatic toxicity testing (flow through methods, measured concentrations) in algae, daphnids, and fish is recommended.

September, 1988; revised April, 1991

Category: Polycationic Polymers Environmental Toxicity

Definition. Any polymer that exists in the environment with multiple positive charges is a member of this class. Such structures include polyamines, polyquaternary ammonium, polysulfonium, and polyphosphonium compounds.

Hazard Concerns. Members of the category are toxic to fish, invertebrates, and algae. Algae are six-fold more sensitive than fish and daphnids. It is presumed that these compounds act on the surface of organisms and need not be absorbed. Toxicity increases exponentially with increasing charge density at cationic equivalent weights of >400. At lower charge equivalent weights, toxicity does not increase. A number of QSARs (quantitative structure-activity relationships) have been developed to predict the toxicity of polycationic polymers.

Boundaries. Polymers must be water-soluble or water-dispersible. Molecular weights are >300 although the typical new chemical polycationic polymer has a molecular weight in excess of 1000. EPA has been engaged in discussions with the Cationic Flocculant Producers Association in an attempt to identify and develop a set of tests on representative polycationic polymers which could better define the limits of the category.

General Testing Strategy

To address ecotoxicity concerns, for polymers with % amine nitrogen <0.7% and >0.1%: base set acute aquatic toxicity testing in algae, daphnids, and fish, plus humic acid testing in fish (20 mg/L humic acid in dilution water and 10 mg/L) is recommended. All testing uses static method, nominal concentrations. For some members of the class, a test of sorbed chemical using a benthic organism may also be recommended.

September, 1988; periodically revised.

Category: Polynitroaromatics Environmental Toxicity

This category includes all dinitroaromatics and trinitroaromatic compounds, for example, dinitrobenzenes, dinitroanilines, dinitrophenols, and dinitropyridines. Polynitroaromatics probably act by uncoupling of oxidative phosphorylation (Doull et al 1980). It is assumed that these compounds need to be absorbed to be toxic, therefore, compounds with MWs > 1000 will be excluded from this category. Acute toxicity for polynitroaromatics which are liquids at room temperature is assumed to be limited by the octanol/water partition coefficient (K_{ow}). Above a log K_{ow} value of => 7.00 (based on test data for anilines reported Veith and Broderius 1987), polynitroaromatics are not expected to show toxic effects at saturation during 96-h exposures. Polynitroaromatics which are solids at room temperature may show no toxicity at saturation at lower K_{ow} values depending on the melting point, i.e., the higher the melting point at a given K_{ow}, the

greater the likelihood that no toxicity will be observed at saturation. For solids, the no effects at saturation has to be determined on a case-by-case basis. There are no known K_{ow} limits for chronic toxicity at this time, but it may not be much above a log K_{ow} = 10 for liquid polynitroaromatics. Future testing will determine this K_{ow} limit.

Hazard Concerns. The acute and chronic toxicity for several classes of polynitroaromatics have been determined through SAR Analysis:

dinitroanilines:

fish 96-h LC50 (mM/L)= -0.027 -0.596 log K_{ow}; N=2; R^2=1.0

daphnid 48-h LC50 (mM/L)= -0.296 -0.558 log K_{ow}; N=2; R^2=1.0

fish ChV (mM/L)= -0.91 -0.661 log K_{ow}; N=2; R^2=1.0

dinitrobenzenes:

fish 96-h LC50 (mM/L)= -1.867 -0.333 log K_{ow}; N=2; R^2=1.0

daphnid 48-h LC50 (mM/L)= -0.325 -0.634 log K_{ow}; N=3;

R^2=0.86

fish ChV (mM/L)= -3.0 -0.40 log K_{ow}; N=2; R^2=1.0

daphnid ChV (mM/L) = -0.7 -0.625 log K_{ow}; N=2; R^2=1.0

dinitrophenols:

fish 96-h LC50 (mM/L)= -0.285 -0.559 log K_{ow}; N=4; R^2=0.96

daphnid 48-h LC50 (mM/L)= 0.083 -0.632 log K_{ow}; N=7;

R^2=0.85

fish ChV (mM/L)= -1.78 -0.552 log K_{ow}; N=4; R^2=1.0

daphnid ChV (mM/L) = -0.465 -0.654 log K_{ow}; N=2; R^2=1.0

Polynitroaromatics are known to be more toxic than predicted by the neutral organic SARs.

Members of this category exhibit toxicity ranging from low toxicity (i.e., > 100 mg/L) to high toxicity (i.e., < 1 mg/L) depending on their K_{ow} and MW.

Fate: Polynitroaromatics are expected to be subject to rapid direct and indirect photolysis under environmentally realistic conditions.

Boundaries.: There are no known lower boundaries. The upper boundaries will be based on K_{ow} and MW. Acute toxicity expected with log K_{ow} < 7.0; no effects at saturation during 96-h exposures when log K_{ow} >= 7.0. Chronic toxicity has no known upper bound for log K_{ow}, but it is probably near 10. MW will be < 1000. The environmental base set of tests will be requested for aquatic releases and the terrestrial base set of tests will be recommended for terrestrial exposures. When the log K_{ow} is >= 7.0, chronic toxicity testing with fish and daphnids will be recommended.

General Testing Strategy.

I. Release to Aquatic Ecosystems:

Tier 1. The aquatic base set of environmental toxicity tests will be recommended for aquatic exposures. The acute toxicity tests for fish (40 CFR 797.1400) and daphnids (40 CFR 797.1300) will be done using the flow-through method with measured concentrations; effective concentrations will be based on 100% active ingredients (AI) and mean measured concentrations; measured TOC of dilution water in the control; the highest treatment concentration on a nominal-basis should equal the aqueous solubility limit; and solvent can be used to assist the PMN to reach its aqueous solubility limit quicker, but cannot be used to artificially enhance the water solubility of the PMN beyond its aqueous solubility limit.

The algal toxicity testing (40 CFR 797.1050), should be done with static methods; measured concentrations; effective concentrations based on 100% active ingredients (AI) and mean measured concentrations; statistical analysis of effective concentrations at 24, 48, 72, and 96 hours; test medium with at least 0.300 mg/L EDTA as a final concentration; the highest treatment concentration on a nominal-basis equal to the aqueous solubility limit; and solvent can be used to assist the PMN to reach its aqueous solubility limit quicker, but cannot be used to artificially enhance the water solubility of the PMN beyond its aqueous solubility limit.

If there is no significant risk from the PMN after the results of the environmental base set have been integrated into the risk assessment, then no further testing is recommended. However, if there is a significant risk, then go to Tier 2.

Tier 2. Direct and Indirect Photolysis Screening Test (40 CFR 796.3765). If $t_{1/2} \leq 2$ days, go to Tier 3; if $t_{1/2} > 2$ days, go to Tier 4.

Tier 3a. If $t_{1/2} \leq 2$ days and photolysis products are known and/or identified, then assess photolysis products for environmental hazards.

Tier 3b. If $t_{1/2} \leq 2$ days and photolysis products are not known and/or identifiable, then prepare a stock solution of PMN using the standard humic-containing solution described in the direct and indirect photolysis screening test [40.796.3765 (b)(2) and (c)(2)], expose to sunlight for at least 6 half-lives ($t_{1/2}$), and test photolysis products for toxicity with most sensitive species from environmental base set. For example, if the most sensitive species from the environmental base set has an EC50 value = 2.0 mg PMN/L (based on 100% active ingredients [AI]), then prepare a 5.0 mg PMN per liter stock solution based on 100% AI using the standard humic-containing solution. This stock solution is exposed to sunlight for at least 6 half-lives to ensure that all of the PMN has been photolyzed, and then this stock solution is used to retest the most sensitive aquatic species to determine if the photolysis products of the PMN are more or less toxic that the PMN.

Tier 4. Fish chronic toxicity testing, i.e., fish early life stage (ELS) toxicity testing (40 CFR 797.1600), with flow-through methods; measured concentrations; effective concentrations based on 100% active ingredients (AI) and mean measured concentrations; statistical analysis of effective concentrations at days 7, 14, 21, and 28; measured TOC of dilution water in the control; the highest treatment concentration on a nominal-basis should be set at the aqueous solubility limit; solvent can be used to assist the PMN to reach its aqueous solubility limit quicker, but cannot be used to artificially enhance the water solubility of the PMN beyond its aqueous solubility limit; and the 7-d ELS stage toxicity test cannot be substituted for the 28-d ELS toxicity test because Van Leeuwen et al (1990) have demonstrated that the 7-d ELS toxicity test underestimated the chronic toxicity of anilines measured by the 28-d ELS toxicity test by >5.3 times when the NOECs were compared (see Table VII in Van Leeuwen);

Daphnid chronic toxicity testing (40 CFR 797.1330), with flow-through methods; measured concentrations; effective concentrations based on 100% active ingredients (AI) and mean measured concentrations; statistical analysis of effective concentrations at days 7, 14, and 21; measured TOC of dilution water in the control; the highest treatment concentration on a nominal-basis should be set at the aqueous solubility limit; solvent can be used to assist the PMN to reach its aqueous solubility limit quicker, but cannot be used to artificially enhance the water solubility of the PMN beyond its aqueous solubility limit; and the 7-d daphnid chronic toxicity test cannot be substituted for the 21-d toxicity test because Van Leeuwen et al (1990) have demonstrated that the fish 7-d ELS toxicity test underestimated the chronic toxicity of anilines

measured by the fish 28-d ELS toxicity test by >5.3 times when the NOECs were compared (see Table VII in Van Leeuwen).

Aerobic biodegradability according to any one of the following test guidelines (listed in order of preference):

Aerobic Aquatic Biodegradation 40 CFR 796.3100

Modified Sturm Test 40 CFR 796.3260

Closed Bottle Test 40 CFR 796.3200

Modified OECD Screening Test 40 CFR 796.3240

Modified MITI Test (I) 40 CFR 796.3220

Modified AFNOR Test 40 CFR 796.3180

II. Release to Terrestrial Ecosystems: The terrestrial base set of environmental toxicity tests (i.e., the early seeding growth test, the earthworm toxicity test and the soil microbial community bioassay) will be recommended for terrestrial exposures. Chronic toxicity testing for terrestrial organisms include: the plant whole life cycle test, the plant uptake test, and the soil microbial community bioassay.

References.

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May, 1991

Category: Respirable, Poorly Soluble Particulates Health Only

Definition. This category includes a variety of inorganic, poorly soluble (as designated in ILSI 2000) particulates. Typically, they are oxides of various metals or nonmetals (i.e., silicon).

Boundaries. Potential for respirability--that is, if there are any particles $\leq$ 10 μ in diameter in the material being handled by workers. Summarized below are currently available test data on five different poorly soluble particulates-silica, talc, titanium dioxide, PMN 96-175 (lithium manganese oxide), and carbon black. The suitability of one or more of these analogues for a particular PMN particulate must be determined on a case-by-case basis. Risk is to be assessed by the margin of exposure method for the reason stated in the next paragraph.

Hazard Concerns

The category concerns discussed here are limited to effects on the lung as a result of inhaling the particles. Broadly, as shown in rat inhalation studies, these effects range from inflammation to fibrosis to, potentially, cancer. Because it is still not known with certainty whether high lung burdens of poorly soluble particulates can lead to lung cancer in humans via mechanisms similar to those of the rat, in the absence of mechanistic data to the contrary, it must be assumed that the rat model can identify potential carcinogenic hazards to humans. Since the apparent responsiveness of the rat model at overload is dependent on coexistent chronic active inflammation and cell proliferation, at lower lung doses in which chronic active inflammation and cell proliferation are not present, no lung cancer hazard is anticipated (ILSI 2000).

Some of the particulates may contain metals, for example, chromium, that may present other and more imminent toxicities, depending on the bioavailability of the metal ions. Thus, the toxicities of the metal components of the particulates must also be assessed, and on a case-by-case basis.

Lung Toxicity of Five Poorly Soluble Particulates

1. Fibrogenicity/Carcinogenicity of Crystalline Silica

Humans. Based on "sufficient evidence" for the carcinogenicity of inhaled crystalline silica from occupational sources, the International Agency for Research on Cancer (IARC, 1997) has classified crystalline silica as a Group 1 carcinogen in humans. According to IARC, studies of the following populations provided the least-confounded examinations of an association between silica exposure and cancer risk: gold miners, stone industry workers, granite shed and quarry workers, crushed stone industry workers, diatomaceous earth industry workers, refractory brick workers, pottery workers, and cohorts of registered silicotics. Not all of these studies demonstrated excess cancer risks; but, in view of the large number of epidemiological studies undertaken and the wide range of populations and exposure circumstances, some nonuniformity of results would be expected. In some studies, increasing risk gradients have been observed in relation to dose surrogates--cumulative exposure, duration of exposure, or the presence of radiographically defined silicosis--and, in one instance, to peak intensity exposure. For these reasons, the IARC Working Group concluded that overall, the epidemiological findings support increased lung cancer risks from inhaled crystalline silica resulting from occupational exposure.

Animals. IARC (1997) has concluded that there is "sufficient evidence" in experimental animals for the carcinogenicity of crystalline silica. A number of studies (rev.in: IARC, 1997; Woo et al., 1988; Holland, 1990) have demonstrated that, in addition to silicosis/fibrosis, pulmonary tumors are induced in rats exposed to quartz (Mini-U-Sil; a common form of crystalline silica) by inhalation, single intrapleural, intraperitoneal, and/or intratracheal administration. In a 24-month inhalation study in rats, the lowest tested dose of respirable crystalline silica particles to induce lung tumors **(Lowest Observed Adverse Effect Level, or LOAEL) was 0.74 mg/m^3.**

*** Note for Cases Using Silica as Primary Analogue:** For LOAEL doses, the Agency considers a Margin of Exposure (MOE) of 1,000 or greater as representing a low order of toxicity for health endpoints for which a threshold dose is deemed appropriate. In this instance, exposures would have to be reduced to 0.0007 mg/m^3 to achieve a MOE of 1,000, a concentration that is practically impossible to achieve. Because the LOAEL of 0.74 mg/m^3 is based on test data on pure silica and because silica is considered to be a much more potent lung toxicant than crystalline particulates containing silica, **the Agency has adopted the NIOSH REL (Recommended Exposure Level) for silica, 0.05 mg/m^3, as a NCEL[1/] (New Chemical Exposure Limit - see http://www.epa.gov/oppt/newchems/pubs/ncelmain.htm for more information) concentration that would adequately protect workers from crystalline particulates containing silica. This NCEL replaces the former one based on OSHA Permissable Exposure Limit (PEL) for silica 0.1 mg/m^3.**

2. Fibrogenicity/Carcinogenicity of Talc

Humans. Epidemiology studies suggest an association between nonfibrous talc (a finely powdered hydrous magnesium silicate) and lung cancer risk. The OSHA PEL for talc is 20 mppcf (million particles per cubic foot) and the NIOSH-recommended 8-hr TWA concentration is 2 mg/m^3.

Animals. In an NTP inhalation study (NTP TR 421, 1993), male and female F344 rats were exposed to 0, 6, or 18 mg/m^3 talc for 113 and 122 weeks, respectively. There was clear evidence of the carcinogenicity of talc in female rats based on the increased incidence of alveolar/bronchiolar adenomas and carcinomas of the lung in the **18- mg/m^3 group (LOAEL).** The **No Observed Adverse Effect Level (NOAEL) from this study is 6 mg/m^3.** The NCEL for analogous particulates would be 0.06 mg/m^3.

3. Fibrogenicity/Carcinogenicity of Titanium Dioxide (TI)