saturation during 96-h exposures. Diazoniums are expected to be similar to anilines with respect to their K_{ow} cutoff value for acute toxicity. This assumes that the missing fragment for NN^+ = -1.0. The acute toxicity of anilines diminishes at about a log K_{ow} = 7.0 (Veith and Broderius 1987). There are no known K_{ow} limits for chronic toxicity at this time, but it may not be much above a log K_{ow} = 10.0 for diazoniums. Future testing will determine this K_{ow} limit.

Hazard Concerns. The acute toxicity for diazoniums has been determined through SAR Analysis:

log fish 96-h LC_{50} (millimoles/L) = -2.456 - 0.331 log K_{ow}

based on a log K_{ow} for the diazonium using CLOGP Ver. 3.3 with a missing fragment for NN^+, N = 3, and R^2 = 0.98. Acute toxicity values are assumed to be valid through log K_{ow} = 8.0.

Daphnids are assumed to have similar sensitivity to fish, but green algae are expected to be more sensitive based on the use of diazoniums as fungicides.

Fate: Diazonium fungicides, e.g., Fenaminosulf, are sensitive to light but is stabilized with Na sulphite. Fenaminosulf is stable in alkaline media. Diazoniums are also used in photography, e.g., diazo reproduction paper and film. Therefore, diazoniums are expected to be subject to rapid direct and indirect photolysis under environmentally realistic conditions. Diazoniums are also expected to slowly hydrolyze to phenols.

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} < 8.0 with a missing fragment for NN^+.; no effects at saturation during 96-h exposures when log K_{ow} >= 8.0. Chronic toxicity has no known upper bound for log K_{ow}, but it is probably near 10.0 with a missing fragment for NN^+. MW must 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 >= 10.0, 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. Since diazoniums compounds are photosensitive to uv light, it is best to avoid the use of fluorescent lights in toxicity tests. If they are used, then glass filters should be used. The acute toxicity tests for fish (CFR §797.1400) and daphnids (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 not exceed 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 (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 cannot exceed the PMN's 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% active ingredients [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 (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 not exceed the aqueous solubility limit of the PMN; 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 (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, the avian acute oral 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, avian reproduction toxicity 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.

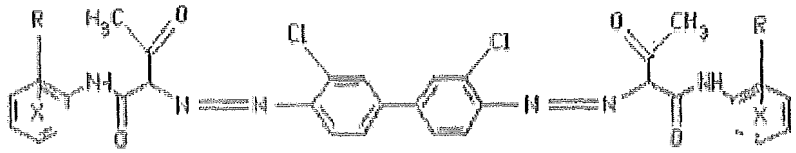
November, 1991

Category:Dichlorobenzidine-based Pigments Human Health

Environmental Toxicity

Other Names: Diarylide Pigments, DCB Pigments, Pigment Yellows

Definition: Any diazo pigment containing the substructure, dichlorobenzidine, and coupled with acetoacetanilide.



R = substituent of the coupling component

Hazard Concerns. There are oncogenicity/mutagenicity concerns for dichlorobenzidine-based pigments based on the potential release of 3,3'-dichlorobenzidine and on the presence of residual (unbound) dichlorobenzidine. DCB is a known animal carcinogen and a suspect human carcinogen. In addition, DCB is known to bioconcentrate in the tissues of aquatic organisms.

Boundaries. Concern for the intact pigment is restricted to uses at temperatures exceeding 200°C. Data submitted to the Agency under TSCA section 8(e) show that DCB pigments break down to release DCB as a vapor from colored polymers when heated to extrusion temperatures (> 200°C) and, from sheetmetal coatings during curing. Though little information exists on the biodegradation of pigments in sediments, data on other low water soluble colorants, indicate that biodegradation may occur over a period of months, possibly resulting in the release of DCB.

General Testing Strategy.

EPA's New Chemicals Program considers the following tests to be appropriate to address the potential for DCB pigments to pose a significant risk to health or the environment:

1. Monitoring data to detect the presence of DCB under actual conditions of use; temperature, dwell time, % pigment in polymer or coating, and type of polymer or coating.

2. If there are releases to water, an anaerobic biodegradation assay.

References:

Appleton HT, Sikka HC. 1980. Accumulation, elimination, and metabolism of 3,3'-dichlorobenzidine in the bluegill sunfish. Environ Sci Technol 14:50-54.

Pliss GB. 1963. On some regular relationship between carcinogenicity of aminobiphenyl derivatives and the structure of the substance. Acta Unio Int Cancrum 19:499-501.

Stula EF, Sherman H, Reinhardt CF. 1975. Experimental neoplasia in rats from oral administration of 3,3'-dichlorobenzidine, 4,4'-methylene-bis(2-chloroaniline), and 4,4'-methylene-bis(2-methylaniline). Toxicol Appl Pharmacol 32:159-176.

Stula EF, Barnes JR, Sherman H. 1978. Liver and urinary bladder tumors in dogs from 3,3-dichlorobenzidine. 1978. J Environ Pathol Toxicol 1:475-490.

TSCA Section 8(e) Documents:

8EHQ-0490-0962 INIT

8EHQ-0590-0962 SUPPL

8EHQ-0690-0962 FLWP

8EHQ-0790-0962 SUPPL

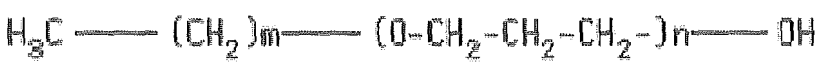
8EHQ-0890-0962 SUPPL

March, 1994

Category: <u>Dithiocarbamates</u> Environmental Toxicity

This category includes N,N-dialkyldithiocarbamates (DDC); ethylenebisdithiocarbamates (BDC); and their metal salts which include but are not limited to zinc, sodium, iron, manganese, copper, lead, mercury, silver and selenium. The alkyl groups of the DDCs generally include, methyl through butyl, but may be larger. This category also includes the degradation products of DDC and BDC which may include disulfide moieties, sulfide moieties, thiourea moieties, urea moieties, polymeric sulfide moieties, dithizaole-3-thiones, cyclic thioureas and cyclic ureas as indicated in the generic environmental hazard assessment.

alkyl ethoxylate



alkyl propoxylate

Hazard Concerns: Many members of this category are commercial insecticides, fungicides, disinfectants, rodenticides, antioxidants, slimicides, algalicides, bactericides and heavy metal chelators. Their mode of toxic action apparently results from interference with metallo-enzymes in living cells; the toxicity has been attributed to either DDCs and BDCs or their degradation products. All of the known dithiocarbamates are acutely toxic to fish, algae and bacteria at < 10 mg/L, and to aquatic invertebrates at < 1 mg/L. Chronic toxicity to fish and aquatic invertebrates ranges from 0.001 to 2 mg/L and 0.011 to 0.111 mg/L, respectively. In general, the SARs for the dithiocarbamates and their degradation products are sigmoidal with acute and chronic toxicity increasing with increasing Kow. The sigmoidal relationship between Kow and toxicity of the dithiocarbamates is very poor statistically. Consequently, toxicity predictions will be made using either the closest analog or averaging data for the two closest analogs which bracket the dithiocarbamate under question. The SAR for the degradation products is much more robust and a series of SARs will be used to predict acute toxicity of degradation products toward fish, daphnids and Photobacterim phosphoreum; and chronic toxicity toward fish, daphnids and green algae.

Boundaries: There are no known lower boundaries. The upper boundaries are based on K_{ow} and MW. When the log Kow value is < 5 mg/L, 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 between 5 and < 19, only chronic toxicity testing will be recommended. When the log K_{ow} is $\geq$ 19 (CLOGP), no testing will be requested because no toxic effects at saturation will be expected. Generally, members of this category will have MWs of less than 1000.

General Testing Strategy

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 terrestrial exposures.

Tier 2. If acute toxicity testing indicates a significant risk, then chronic toxicity with fish and aquatic invertebrates will be recommended as well as aerobic biodegradation testing.

Aerobic biodegradability can be determined using one of the following test guidelines, listed in approximate 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

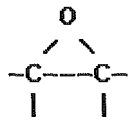
Modified AFNOR test 40 CFR 796.3180

August 1989; revised November 1995

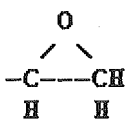
Category: Epoxides Human Health

Environmental Toxicity

Definition. Any molecular structure containing one or more epoxy groups is considered to be a member of the category:



Hazard Concerns. Health concerns for epoxides are for cancer and reproductive effects based on data for several analogous chemicals. There is greater concern for primary epoxides,



than for epoxides with substitutions on both of the epoxy carbons. Environmental toxicity is a function of the octanol-water partition coefficient. Compounds with log P's >5 act as neutral organics producing simple

narcosis, but at lower log P's, epoxides display toxicity greater than that predicted for simple narcotics. A QSAR (quantitative structure-activity relationship) to predict the environmental toxicity of epoxides is under development.

Boundaries. Structures with epoxy equivalent weights of ≥1,000 are presumed not to pose a hazard under any conditions. Concerns are confined to those species with molecular weights <1,000. Health concerns are restricted to species with molecular weights <500 if exposure is limited to the dermal route.

Testing. To address health concerns the following tests are usually recommended for members of this class: (1) a lifetime cancer bioassay by the expected route of exposure, and (2) a 90-day subchronic with attention to pathology of the reproductive organs. To address ecotoxicity concerns, base set acute aquatic toxicity testing (algae: static method, daphnid and fish: flow-through method, all measured concentrations).

September, 1988

Category: Esters Environmental Toxicity

This category includes all esters, polyesters, vinyl esters, allylic esters, propargylic esters, aliphatic esters, aromatic esters, carboxylic acid esters, and sulfonate esters. These compounds need to be absorbed to be toxic, therefore, compounds with MWs > 1000 will be excluded from this category. Acute toxicity for esters 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 => 5.0, esters show no effects at saturation during 96-h exposures (Veith et al 1984). 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 acute toxicity will be observed at saturation. For solids, the no-effects-at-saturation point has to be determined on a case-by-case basis. The K_{ow} limit for chronic toxicity is set at a log K_{ow} = 8 for liquid esters. For solid esters, chronic toxicity testing will determine this K_{ow} limit.

Hazard Concerns. The toxicity for simple esters has been determined through SAR Analysis (Clements 1988). Esters are known to be more toxic than neutral organic chemicals, and this excess toxicity decreases with increasing K_{ow}. The toxicity for vinyl esters, allylic esters, and propargylic esters is expected to be greater than for simple esters. Again, the additional excess toxicity of these vinyl esters, allylic esters, and propargylic esters is expected to decrease with increasing K_{ow}.

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 melting point.

Boundaries. There are no known lower boundaries. The upper boundaries will be based on K_{ow} and MW. Acute toxicity is expected when log K_{ow} < 5.0; no effects at saturation during 96-h exposures when log K_{ow} > 5.0. The upper boundary for chronic toxicity is 8.0. 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 > 5.0, chronic toxicity testing with fish and daphnids will be recommended.

Fate: Esters are subject to both abiotic and biotic hydrolysis, i.e., ester hydrolysis, and aerobic biodegradation. Aerobic biodegradation is expected to be the dominant route of transformation in the environment.

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; the highest treatment concentration on a nominal-basis should not exceed the aqueous solubility limit; and solvent can be used to assist the ester to

reach its aqueous solubility limit quicker, but cannot be used to artificially enhance the water solubility of the ester beyond its aqueous solubility limit.

The algal toxicity test (40 CFR §797.1050) should be done with the static method; 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 should not exceed the aqueous solubility limit of the ester; and solvent can be used to assist the ester to reach its aqueous solubility limit quicker, but cannot be used to artificially enhance the water solubility of the ester beyond its aqueous solubility limit.

If there is no significant risk from the ester 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 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

If there is no significant risk from the ester after the results of the aerobic 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 (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; the highest treatment concentration on a nominal-basis should not exceed the aqueous solubility limit of the tested chemical; solvent can be used to assist the ester to reach its aqueous solubility limit quicker, but cannot be used to artificially enhance the water solubility of the ester 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). Both anilines and esters are more toxic than predicted based on narcosis alone, i.e., both esters and anilines have excess toxicity due to a more specific mode(s) of toxic action. A seven day exposure may not allow enough time for this excess toxicity to be expressed either because of not enough exposure and/or not enough time for metabolic activation.

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; the highest treatment concentration on a nominal-basis should not exceed the aqueous solubility limit of the ester; solvent can be used to assist the ester to reach its aqueous solubility limit quicker, but cannot be used to artificially enhance the water solubility of the ester above its aqueous solubility limit; and the 7-d daphnid chronic toxicity test cannot be substituted for the 21-d toxicity test (Van Leeuwen et al 1990).

II. Release to Terrestrial Ecosystems: The terrestrial base set of environmental toxicity tests (i.e., the early seeding growth test, the earthworm toxicity test, the avian acute oral 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, the avian reproductive toxicity test, and the soil microbial community bioassay.

References.

Clements, RG (editor). 1988. Estimating toxicity of industrial chemicals to aquatic organisms using structure-activity relationships. EPA-560-6-88-001. Washington, DC: Environmental Effects Branch, Health and Environmental Review Division, Office of Toxic Substances (TS-796), United States Environmental Protection Agency. Available from the National Technical Information Service, Springfield, VA 22161, PB89-117592.

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, DeFoe D, and Knuth M. 1984. Structure-activity relationships for screening organic chemicals for potential ecotoxicity effects. Drug Metabolism Reviews 15(7):1295-1003.

November, 1991

Category: <u>Ethylene Glycol Ethers</u> Human Health

Definition. The ethylene glycol ether category is defined as follows:

$R\text{-}(OCH_2CH_2)_n\text{-}OR'$

$n = 1, 2, \text{ or } 3$

R = alkyl C_7 or less or phenyl or alkyl substituted phenyl

R' = H or alkyl C_7 or less or any group that can be chemically or metabolically removed to yield a glycol ether

Hazard Concerns. Short-chain ethylene glycol ethers are absorbed by all routes of exposure and have caused irritation of skin, eyes, and mucous membranes; hemolysis, bone-marrow damage, and leukopenia of both lymphocytes and granulocytes; direct and indirect kidney damage; liver damage, immunotoxicity, and central nervous system (CNS) depression. Short-chain ethylene glycol ethers are also developmental and reproductive toxicants. 2-Phenoxyethanol is known to cause hemolysis and eye irritation.

Boundaries. There is evidence that developmental toxicity is reduced going from the methyl to the butyl ether, and that it is reduced going from the ethylene glycol to the triethylene glycol. However, there is still a concern for maternal toxicity as reflected in developmental and subchronic toxicity studies. The systemic toxicity of longer-chain glycol ethers and alkylphenyl glycol ethers is uncertain because data are not available. The alkyl chain length of C_7 or less was chosen as a boundary for short-chain ethylene glycol ethers based on the available data.

<u>General Testing Strategy</u>

The New Chemicals Program considers the following tests to be the most appropriate for ethylene glycol ethers with sufficient exposure to potentially pose an unreasonable risk:

Tier 1 - Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screen Test (OECD Guideline 422). If signs of hematuria are seen red and white blood cell counts should be taken 2 days later except for female animals during pregnancy and lactation.

Tier 2 - The need for further testing would be determined by the results of Tier 1. This could include any of the following tests.

Prenatal Developmental Toxicity via the most appropriate route (40 CFR 799.9370)

2-Generation Reproduction Study via the most appropriate route (40 CFR 799.9380)

90-Day Subchronic Study via the most appropriate route (40 CFR 799.9346 - inhalation route; 870.3250 - dermal route; 870.3150 - oral route)

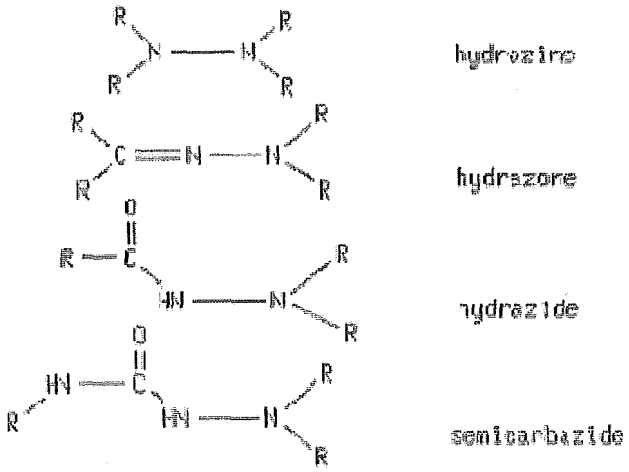
Immunotoxicity Study via the most appropriate route (OPPTS 870.7800)

June 1992, revised December 1997

Category: **Hydrazines and Related Compounds** Human Health

Environmental Toxicity

Definition: Any structure containing one or more of the following groups is considered to be a member of the category:



R is unlimited except by molecular weight

Hazard Concerns: Concerns for carcinogenicity and chronic effects to liver, kidney, and blood are based on data for a number of hydrazines and related chemicals. In humans, hydrazine, itself, may affect the central nervous system, liver, and kidneys. The toxic effects of hydrazine exposure to humans may range from mild skin and eye irritation, and skin sensitization, to severe irritation and burns, pulmonary edema, CNS depression, as well as liver and kidney damage, which can lead to death. Hydrazine may also present a serious hazard to plant life and aquatic organisms. Ecotoxicity concerns are based on structure activity relationships (SAR) using data for a number of hydrazines and hydrazides. Hydrazine itself (N_2H_4), is known to be acutely toxic to aquatic organisms at low levels, algae at < 100 ppb, 200 ppb for fish, and 30 ppb for daphnids.

Boundaries: There are no established boundaries for this category. The "typical" new chemical member of the category is a discrete (class I) chemical with a molecular weight <500. There is a greater concern for chemicals with few substitutions on the functional group than for those with multiple substitutions.

General Testing Strategy

EPA considers the following tests to be appropriate to address health and ecotoxicity concerns:

1. Lifetime cancer bioassay by the expected route of exposure in two species of rodents (40 CFR 798.3300).

2. 90-Day subchronic in one species of rodent by the expected route of exposure to assess effects to the liver, kidney, and blood (40 CFR 798.2650).

3. Base-set ecotoxicity testing to include fish (40 CFR 797.1400) using the flow-through method, daphnids (40 CFR 797.1300) using the flow-through method and algae (40 CFR 797.1050) using the static method, all measured concentrations.

Results of the acute ecotoxicity testing may trigger chronic fish (40 CFR 797.1600) and daphnid (40 CFR 797.1350) testing.

4. 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) and hydrolysis (40 CFR 796.3500). For aromatic hydrazines and related compounds, the following additional testing is recommended; direct and indirect photolysis (40 CFR 796.3765), and aerobic biodegradation.

Aerobic biodegradability can be determined using <u>one</u> of the following test guidelines, listed in approximate 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

References.

1. Bhide, S.V., R.A. D'Souza, M.M. Sawai, & K.J. Ranadive (1976). International Journal of Cancer 18: 530.

2. Biancifiori, C (1970). Journal of the National Cancer Institute 44: 943.

3. Biancifiori, C (1971). Lav. 1st Anat. Istol. Pat., Univ. Studi Perugia 31: 5.

4. Biancifiori, C., E. Bucciarelli, D.B. Clayson, & F.E: Santilli (1964). British Journal of Cancer 18: 543.

5. Hydrazine-RM2 Exit Document. OPPT Office Director's Meeting, Monday, December 13, 1993.

6. Juhasz, J., J. Balo, & B. Szende (1966). Nature (London) 210: 1377.

7. Juhasz, J., J. Balo, & B. Szende (1967). Z. Krebsforsch 70: 150.

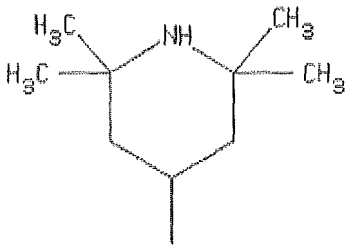
8. Toth, B. (1969). Journal of the National Cancer Institute 42: 469.

9. Toth, B. (1972). International Journal of Cancer 9: 109.

September, 1988; revised June, 1994, revised October 1995.

Category: Hindered Amines Human Health

Definition. The category is at present not well defined. A "typical" new chemical hindered amine of concern has two or more hindered amine functional groups, usually the 2,2,6,6-tetramethyl-4-piperidinyl group, and is used as a UV light stabilizer.



Hazard Concerns. Health concerns for the category are based on data submitted to the Agency under §8(e) of TSCA for Tinuvin 144 and Chimassorb 944. The data indicate that these hindered amines, and presumably hindered amines similar in structure, are toxic to the immune system, liver, blood, the male reproductive system, and the G.I. tract.

Boundaries. The boundaries of the category are not well defined. Tinuvin 144 has a molecular weight of 685, whereas Chimassorb 944 is a polymer with a number average molecular weight well in excess of 1,000. As a consequence, there is at present no molecular weight cutoff for hindered amines of concern to the new chemical program.

It is assumed that there is little or no dermal absorption of problematic hindered amines because of their high molecular weights. Consequently, hindered amines in the new chemical program are only of concern if there is significant inhalation exposure associated with their manufacture, processing, or use.

General Testing Strategy

For hindered amines found to pose a potentially unreasonable risk, a 90-day oral subchronic test in rats is the recommended test. We have requested that emphasis be placed on hematology, the immune system, and on the male reproductive system.

June 1990; revised March 1995

Category: Imides Environmental Toxicity

This category includes all imides and maleimides. Substitutions may be aliphatic, aromatic, and/or halogens. The mode of toxic action of imides is unknown, but halogenated imides are used as microbial pesticides, specifically, fungicides, bactericides, slimicides, and algicides. 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 imides which are liquids at room temperature is assumed to be limited by the octanol/water partition coefficient (K_{ow}), and the limiting K_{ow} value for acute toxicity is assumed to be about 5.0. The limiting value for chronic toxicity is assumed to be about 8.0. Imides which are solids at room temperature may show no toxicity at saturation at log K_{ow} values < 5.0 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.

Hazard Concerns. The acute toxicity for imides and maleimides towards fish has been determined through SAR Analysis by EPA. The SAR for acute toxicity to fish is defined by the following regression equation:

log 96-h LC50 = 1.256 - 0.76 log K_{ow}

where the LC50 is in milliMoles per Liter (mM/L), N = 4, and R^2 = 0.98. The acute toxicity of imides towards daphnids is expected to be similar to that of fish, but their toxicity towards green algae is expected to be greater because of their use as microbial pesticides.

Polyimides may be more toxic than predicted using this SAR.

The toxicity of imides towards aquatic organisms can range from low (i.e., > 100.0 mg/L) to high toxicity (i.e., < 1.0 mg/L) depending on their K_{ow} and MW. The higher the K_{ow} and the lower the MW, the higher the toxicity (or the lower the EC50 value).

Boundaries.: There are no known lower log K_{ow} and MW boundaries. The upper boundaries for acute toxicity will be set at a log $K_{ow} \leq 5.0$; chronic toxicity limits will be set at a log $K_{ow} \leq 8.0$. 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.

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.

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.

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; 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; 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).

The terrestrial base set of environmental toxicity tests (i.e., the early seeding growth test [40 CFR 797.2800], the earthworm acute toxicity test [40 CFR 795.150], and the soil microbial community bioassay [40 CFR 795.3700]) will be recommended for terrestrial exposures. Chronic toxicity testing for terrestrial

organisms include: the plant whole life cycle test [40 CFR 797.2830], the plant uptake test [40 CFR 797.2850], 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.

April, 1991

Category: Diisocyanates Human Health

Definition. Any molecular structure containing two or more isocyanate groups is considered to be a member of the category for new chemical purposes:

$$R-(N=C=O)_{\geq 2}$$

Members of the class include new isocyanate monomers as well as new oligomers, polymers, prepolymers, or reaction products of existing isocyanate monomers. Most new chemical diisocyanates of concern are polymers or oligomers containing well-known diisocyanate monomers such as toluene diisocyanate (TDI) or 4,4'-methylenediphenyl diisocyanate (MDI).

Hazard Concerns. Diisocyanates are of concern for potential dermal and respiratory sensitization, and for pulmonary toxicity. Based on conflicting animal and human data for respiratory sensitization, the Agency has determined that there is presently not a reliable animal model for testing diisocyanates for potential respiratory sensitization. At this time, it is assumed that all diisocyanates may be potential human respiratory sensitizers.

Most members of the diisocyanate category have not been tested for carcinogenic potential. Though the aromatic diisocyanates [MDI, TDI, dianisidine diisocyanate (DADI)] tested positive and one aliphatic diisocyanate [hexamethylene diisocyanate (HDI)] tested negative in one species, it is premature to make any generalizations about the carcinogenic potential of aromatic versus aliphatic diisocyanates.

Boundaries. Structures with an isocyanate equivalent weight of $\geq$5,000 are presumed not to pose a hazard under any conditions. Typically, concerns are confined to those species with molecular weights <1,000.

Frequently, new chemical isocyanates are manufactured with a significant excess of isocyanate monomer. Under these circumstances, the excess monomer is usually regarded as more hazardous than the "new" chemical component, and these PMN substances are ordinarily not regulated under §5 of TSCA. For the purposes of risk assessment within the New Chemicals Program, a PMN substance is considered "existing" if more than 50% of the free isocyanate groups in the PMN substance (new chemical component + existing chemical monomer) reside on unreacted monomer(s). This does not relieve a Company, however, of any obligations to submit a PMN for the new chemical isocyanate if indeed it is not listed on the TSCA (Toxic Substances Control Act) Inventory.

General Testing Strategy. The following testing is recommended to address the potential for pulmonary toxicity and dermal sensitization.

1. Dermal sensitization (OPPTS 870.2600).

2. 90-day Subchronic inhalation toxicity test in rodents (OPPTS 870.3465).

In addition, appropriate hazard communication needs to be developed and implemented.

Health and Safety Information. The following information provides guidance in developing hazard communication and protective measures language to accompany new diisocyanate chemicals and formulations. It is based on the Agency's current understanding of the hazards associated with diisocyanates and the most effective means to limit exposure.

Warnings. Exposure to diisocyanates may cause the following human health effects: skin irritation and allergic reactions, respiratory irritation, respiratory sensitization, and lung toxicity; some diisocyanates also may cause cancer. The likelihood that these effects will occur depends on a number of factors; among them, the level of exposure, frequency of exposure, part of the body exposed, and sensitivity of the exposed individual.

Symptoms of allergic reaction and respiratory sensitization include rashes, cough, shortness of breath, asthma, chest tightness and other breathing difficulties. There is uncertainty as to the mechanism by which sensitization occurs. In sensitized individuals, exposure to even small amounts of diisocyanates (below government-recommended workplace exposure levels) may cause allergic respiratory reactions like asthma and severe breathing difficulties. It is especially important to note that contact with skin may lead to respiratory sensitization or cause other allergic reactions. In some cases, the effects of diisocyanate exposure may be immediate and life-threatening; in others, the effects may be delayed and occur hours after the exposure has ended. Repeat or prolonged exposure to diisocyanates may also cause irritation to eyes, skin, respiratory tract and lungs, as well as adverse chronic lung effects, like decreased lung capacity and function. Individuals experiencing shortness of breath, tightness in the chest or other problems breathing should seek immediate medical attention.

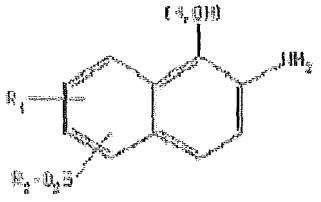
Protective Measures. In workplaces where individuals handle diisocyanates or coatings or other formulations that contain them, an industrial hygiene and safety program should be operative. Important components of this program include: hazard communication and training on safe handling practices; use of efficient and well-maintained application equipment, engineering controls and personal protective equipment; housekeeping procedures including spill prevention and cleanup practices; and, if feasible, means to measure airborne levels of polyisocyanates and diisocyanates.

During spray applications, workers should take precautions to avoid breathing vapors, mists or aerosols. Inhalation exposures should be limited to <0.05 mg/m^3 as an 8-hour time-weighted average (TWA) for combined polyisocyanates and diisocyanates. [1] Engineering controls should serve as the first, most effective means of reducing airborne polyisocyanate and diisocyanate concentrations; an appropriate NIOSH/MSHA-approved respirator should be used as a secondary tool to lower exposures. Currently, downdraft spray booths and high-volume low-pressure (HVLP) spray guns appear to offer the most efficient technology to reduce inhalation exposures; a maintenance program should always be used to ensure optimal operating efficiencies. To limit dermal contact, individuals should wear impermeable gloves, protective clothing and goggles or glasses with side shields.

May 1990, revised July 1993, February 1995, and February, 1997

Category: ß-Naphthylamines, Sulfonated Human Health

Definition: Any new chemical whose structure is consistent with the following general structure is considered to be a member of the category of monosulfonated ß-naphthylamines:



R_1 = H, 3-, NH_2 R_2 = HO, HO_3S-CH_2-CH_2

Included in the category are azo dyes which release a sulfonated ß-naphthylamine upon reduction of azo bonds. Also included in the category are N-acetylated sulfonated ß-naphthylamines.

Hazard Concerns. Based on analogy to ß-naphthylamine *per se*, members of the class are considered potential carcinogens. A number of mono- and disulfonated ß-naphthylamines are positive in the Ames assay, and some are active in the mouse lung adenoma assay. The presence of one or two sulfonate groups or the sulfatoethylsulfone group is likely to slow systemic uptake and enhance excretion, however, the extent of these mitigating effects is unknown.

Boundaries. Concern is restricted to sulfonated ß-naphthylamines where not more than two sulfonate or sulfatoethylsulfone group(s) are on the ring distal to the ß-amino group. The Agency has sufficient data to indicate that ß-naphthylamines where a sulfonate group is on the proximal ring are unlikely to be carcinogenic.

General Testing Strategy.

The New Chemicals Program considers the following tests to be the most appropriate for mono- and di-sulfonated ß-naphthylaminesfound to pose an unreasonable risk:

- An Ames test or, for azo dyes, an Ames test with the Prival modification, and

- An unscheduled DNA synthesis test in rat hepatocytes. For azo dyes, it is necessary that the specific sulfonated ß-naphthylamine in question be isolated prior to testing.

For both tests, ß-naphthylamine is to serve as an additional positive control.

If the results of the genotoxicity testing indicate that the new chemical is genotoxic, a two- year, two-species cancer bioassay would be required.

April 1991, updated June 1999

Category: Lanthanides or Rare Earth Metals Environmental Toxicity

Definition. This category includes inorganic salts, complexes organic acids, and organometallic compounds or lanthanides or rare earth metals. There are 14 naturally-occurring lanthanides or rare earth metals:

Name Symbol MW CASRN

Lanthanum La 139 [7439-91-0]

Cerium Ce 140 [7440-45-1]

Praseodymium Pr 141 [7440-10-0]

Neodymium Nd 144 [7440-00-8]

Samarium Sm 150 [7440-19-9]

Europium Eu 152 [7440-53-1]

Gadolinium Gd 157 [7440-54-2]

Terbium Tb 159 [7440-27-9]

Dysprosium Dy 163 [7429-91-6]

Holmium Ho 165 [7440-60-0]

Erbium Er 167 [7440-52-0]

Thulium Tm 169 [7440-30-4]

Ytterbium Yb 173 [7440-64-4]

Lutetium Lu 175 [7439-94-3]

The lanthanide rare earth metals are very similar to each other. Their most important oxidation state is +3 for all. None are known to be essential to biological species. Across the lanthanide series from La to Lu, there is a general or steady decrease in their (1) atomic radii, (2) covalent radii, and (3) radii of their tripositve ions due to the addition of electrons at the 4f electron shell. This decrease in radii leads to a corresponding increase in the polarizing power of their ions and in the stability of complexes of their ions. They all have similar chemistry behaviors.

Hazard Concerns. The only toxicity data available for the lanthanide series are for La [7439-91-0]. Soluble salts of La are known to have high chronic toxicity towards fish, moderate chronic toxicity towards green algae, and low acute toxicity towards daphnids based on exposures in moderately hard water and in terms of mg La/L. Toxicity information are only available for La trichloride [10099-58-8] and La triacetate [917-70-4]. The toxicity profile for La based on available toxicity data, i.e., measured (M) and predicted (P), mg La/L (ppm La), and moderate hardness (i.e., <180.0 mg/L as $CaCO_3$) is:

fish 96-h LC50 < 1.0 P ACR10

daphnid 48-h LC50 = 160.0 M S,N BK59

green algal 96-h EC50 < 1.0 P EC50/ChV=4

fish chronic value(ChV) = 0.020 M SR12,M H104 B78

daphnid ChV = 20.0 P ACR10

algal ChV = 0.150 M S,N BK59

The lanthanides are assumed to be more toxic in soft water than hard water based on data for other heavy metals.

Boundaries. The toxicity of the lanthanide rare earth metals depends on the their physical/chemical properties and the hardness of receiving waters. The toxicity of their salts and their complexes with organic acids are expected to be related to their water solubility, their MWs, and the stability of their complexes. The toxicity of lanthanide organometallic compounds, if they exist, are expected to be related to their octanol/water partition coefficient (Kow).

The most important property determining the toxicity of chemicals derived from lanthanide rare earth metals is their water solubility. Water solubility cannot be estimated accurately and has to be measured. The water solubility of organometallic compounds is expected to decrease as Kow increases. There is no lower bound for Kow and the upper bound cannot be determined at this time since the Kow fragment-constant for any of the lanthanide rare earth metals are not known. In addition to solubility, MW is also an important boundary. Highly stable complexes and organometallics with MWs > 1000 are not expected to be absorbed by aquatic organisms even if they are water soluble. Therefore, only lanthanide rare earth metal-compounds with MWs < 1000 are expected to be toxic.

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 or OPPTS 850.1075) and daphnids (40 CFR §797.1300 or OPPTS 850.1010) will be done using the flow-through method; effective concentrations will be based on 100% active ingredients (ai) and mean measured concentrations; the total organic carbon (TOC) concentration of dilution water in the control must be less than 2.0 mg TOC/L; TOC must be measured in the control just prior to the start of the test; the highest treatment concentration on a nominal-basis should not exceed the aqueous solubility limit of the tested compound; solvent can be used to assist the compound to reach its aqueous solubility limit quicker, but cannot be used to artificially enhance the water solubility of the compound beyond its aqueous solubility limit; and hardness of dilution water has to be less than 180.0 mg/L as $CaCO_3$. If toxicity mitigation testing is done with humic acid, then the static method with nominal concentrations will be recommended.

The algal toxicity testing (40 CFR §797.1050 or OPPTS 850.5400), should be done with the static method; 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 no more than 0.300 mg/L EDTA as a final concentration; the TOC of the test/growth medium should be less than 2.0 mg TOC/L; TOC should be measured just prior to the start of the test; the highest treatment concentration on a nominal-basis should not exceed the aqueous solubility limit of the tested compound; and solvent can be used to assist the compound to reach its aqueous solubility limit quicker, but cannot be used to artificially enhance the water solubility of the compound beyond its aqueous solubility limit. If toxicity mitigation testing is done with humic acid, then nominal concentrations will be recommended.

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

Tier 2. Fish chronic toxicity testing, i.e., fish early life stage (ELS) toxicity testing (40 CFR §797.1600 or OPPTS 850.1400), with the flow-through method; effective concentrations based on 100% ai and mean measured concentrations; statistical analysis of effective concentrations at days 7, 14, 21, and 28; the TOC of dilution water in the control should be less than 2.0 mg TOC/L; TOC should be measured in the controls just prior to and during the test; the highest treatment concentration on a nominal-basis should not exceed the aqueous solubility limit of the tested compound; solvent can be used to assist the compound to reach its aqueous solubility limit quicker, but cannot be used to artificially enhance the water solubility of the compound beyond its aqueous solubility limit; and hardness of dilution water has to be less than 180.0 mg/L as $CaCO_3$.

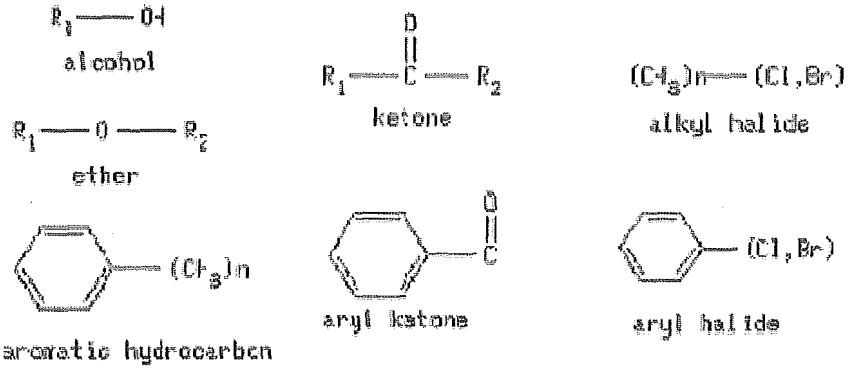
Daphnid chronic toxicity testing (40 CFR §797.1330 or OPPTS 850.1300), with the flow-through method; effective concentrations based on 100% AI and mean measured concentrations; statistical analysis of effective concentrations at days 7, 14, and 21; the TOC of dilution water in the control should not exceed 2.0 mg TOC/L; TOC must be measured in the controls just prior to and during the test; the highest treatment concentration on a nominal-basis should not exceed the aqueous solubility limit of the tested compound; solvent can be used to assist the compound to reach its aqueous solubility limit quicker, but cannot be used to artificially enhance the water solubility of the compound beyond its aqueous solubility limit; and hardness of dilution water has to be less than 180.0 mg/L as $CaCO_3$.

II. Release to Terrestrial Ecosystems: The terrestrial base set of environmental toxicity tests will be recommended for terrestrial exposures. The terrestrial base set includes: the early seeding growth test (OPPTS 850.4230), the earthworm toxicity test (OPPTS 850.6200), the soil microbial community bioassay (OPPTS 850.5100), and the avian acute oral toxicity test (OPPTS 850.2100). Chronic toxicity testing for terrestrial organisms include: the plant whole life cycle test (OPPTS 850.4150), the plant uptake test (OPPTS 850.4800), and the avian reproduction test (OPPTS 850.2300 for bobwhite quail or for mallard duck).

February, 1998

Category: Neutral Organics Environmental Toxicity

Definition. This broad category includes non-reactive non-ionizable organic chemicals such as alcohols, ketones, ethers, alkyl halides, aryl halides, and aromatic hydrocarbons.



Hazard Concerns. Neutral organics are environmentally toxic because of their ability to produce simple narcosis in aquatic species. Toxicity is a function of the octanol-water partition coefficient. Compounds with log P's of <5 exhibit toxicity within 96 hours. At log P 5-8, toxicity is apparent only after extended exposure. Compounds with a log P >8 are not toxic at water saturation even after prolonged exposure. There are a number of QSARs (quantitative structure-activity relationships) to predict the toxicity of neutral organics.

Boundaries. The molecular weights of neutral organics of concern are generally less than 1,000. Log P is <8. QSAR predictions of toxicity are constrained by water solubility. If a predicted toxicity level exceeds water saturation, then a longer test is needed to observe toxicity.

General Testing Strategy

To address ecotoxicity concerns, base set acute aquatic toxicity testing (algae (40 CFR 797.1050): static method, daphnid (40 CFR 797.1300) and fish (40 CFR 797.1400): flow-through method, all measured concentrations).

To properly assess any human and environmental toxicity or exposure, certain environmental fate properties, such as aerobic biodegradation, need to be measured. Aerobic biodegradability can be determined using one of the following test guidelines, listed in approximate 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

The physical state and electronic charge of the PMN substance should also be reported.

For some neutral organics (e.g. ketones) direct/indirect photolysis (40 CFR 796.3765 and 796.3700) AND possibly biodegradation testing is recommended.

For some neutral organics (e.g. alkyl halides) hydrolysis testing (40 CFR 796.3510) AND possibly biodegradation testing is recommended.

September 1988; revised October 1995

Category: Nickel Compounds Human Health

Environmental Toxicity

Definition. Inorganic and organic compounds of nickel in which there is the potential for uptake of either Ni^{2+} or organonickel.

Hazard Concerns. Nickel compounds e.g., nickel refinery dust, and its major component nickel subsulfide, have been shown to be carcinogenic in humans. Some nickel compounds are known to be genotoxic. IRIS has established an oral RfD for the soluble salts of nickel of 2×10^{-2} mg/kg/d (1992) based on effects on organ weights in a two-year feeding study in rats. In the study, there was a statistically significant reduction in total body weight, higher heart-to-body weight ratios and lower liver-to-body weight ratios than controls. In addition to the effects on organ weights found in the critical two-year study, two other sensitive endpoints exist, neonatal mortality and dermatotoxicity. While no reproductive effects have been associated with nickel exposure to humans, several studies in laboratory animals have demonstrated fetotoxicity.

Soluble inorganic nickel compounds produce acute and chronic toxicity in freshwater and saltwater aquatic organisms over a wide range of concentrations but bioconcentrates only to a small degree. There are no known toxicity data for organonickel compounds.

Boundaries. Any nickel compound that will release Ni^{2+} is considered hazardous. Conversely, there are no available data to suggest that nickel compounds in which the Ni^{2+} is not released may pose a health hazard.

The boundaries for ecotoxicity of Ni^{2+} compounds depend on whether they are Ni^{2+} salts, Ni^{2+} chelates, or organonickel compounds. There is also a molecular weight boundary for strong ion pairs/complexes which is 1000.

The boundaries for organonickel compounds (e.g., K_{ow} of the organic portion) are undefined but the molecular weight boundary is expected to be 1000.

Occupational Exposure Controls. Because nickel compounds have been shown to be toxic by the inhalation/ingestion route, exposure controls that maintain airborne exposures at 0.1 mg/m^3 or below are needed (consistent with OSHA PEL TWA). In addition, since nickel compounds are also toxic by the dermal route, NIOSH approved protective gloves are also recommended.

Testing. Depending upon estimated workplace exposures and releases to water, which will be assessed on a case-by-case basis, the following testing may be recommended:

To address health effects concerns due to the toxicity of nickel and its compounds, the following tests may be recommended:

A 90-day subchronic study in rats by an appropriate route to assess systemic toxicity (OPPTS 870.3100 or 870.3250 or 870.3465)

Results of the 90-day study may trigger a lifetime bioassay in rats and mice by the inhalation route to assess potential carcinogenicity (OPPTS 870.4200)

To address ecotoxicity concerns due to toxicity of nickel and its compounds, the following base set tests may be recommended:

Acute fish toxicity test OPPTS 850.1075

Acute daphnid toxicity test OPPTS 850.1010

Green algae toxicity test OPPTS 850.5400

All tests utilize measured concentrations.

To properly assess human and environmental toxicity or exposure, certain physico-chemical or environmental fate properties need to be measured:

Water solubility OPPTS 830.7840 or 830.7860

Octanol/water partition coefficient (K_{ow}) OPPTS 830.7550 or 830.7560 or 830.7570

Vapor pressure OPPTS 830.7950 or 830.8000

Melting point-melting range OPPTS 830.7200

Boiling point OPPTS 830.7220

In addition, aerobic biodegradation by one of the following methods:

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

References.

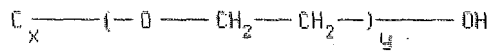
IRIS access. # 1271 (09/30/87) Nickel, soluble salts.

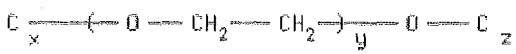
OSHA PELs (1995-1996)

September 1996

Category: <u>**Nonionic Surfactants**</u> Environmental Toxicity

Definition. Any neutral structure having surfactant activity is considered a member of this category. Many of these surfactants have the following types of structure:





Ethoxylate groups may be mixed with or be replaced by alcohol groups. Other neutral groups e.g. propoxylates, esters, halogens, may also be present.

Hazard Concerns. Acute aquatic toxicity increases exponentially with increases in the hydrophobic chain length when the number of ethoxy groups or the hydrophilic component is held constant. In addition, when the number of carbons in the hydrophobe are constant, toxicity decreases with an increasing number of ethoxylate groups. The aquatic toxicity of members of the category can be predicted by structure-activity relationship (SAR).