PRELIMINARY ENDANGERMENT ASSESSMENT
ANTRIM IRON WORKS SITE

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Prepared for
56th Century Antrim Iron Works Company

prepared. These compounds are present at levels below 1 ppb. The compounds for which toxicological data exists pose no endangerment at the concentration levels found.

While the compound lists also include chemicals for which no or inadequate toxicological data exists, the PEA concludes that the extensive expenditure of resources necessary to further evaluate these compounds is not justified in light of the toxicological data which does exist, the low concentrations, the limited receptor impact and the age of the site.

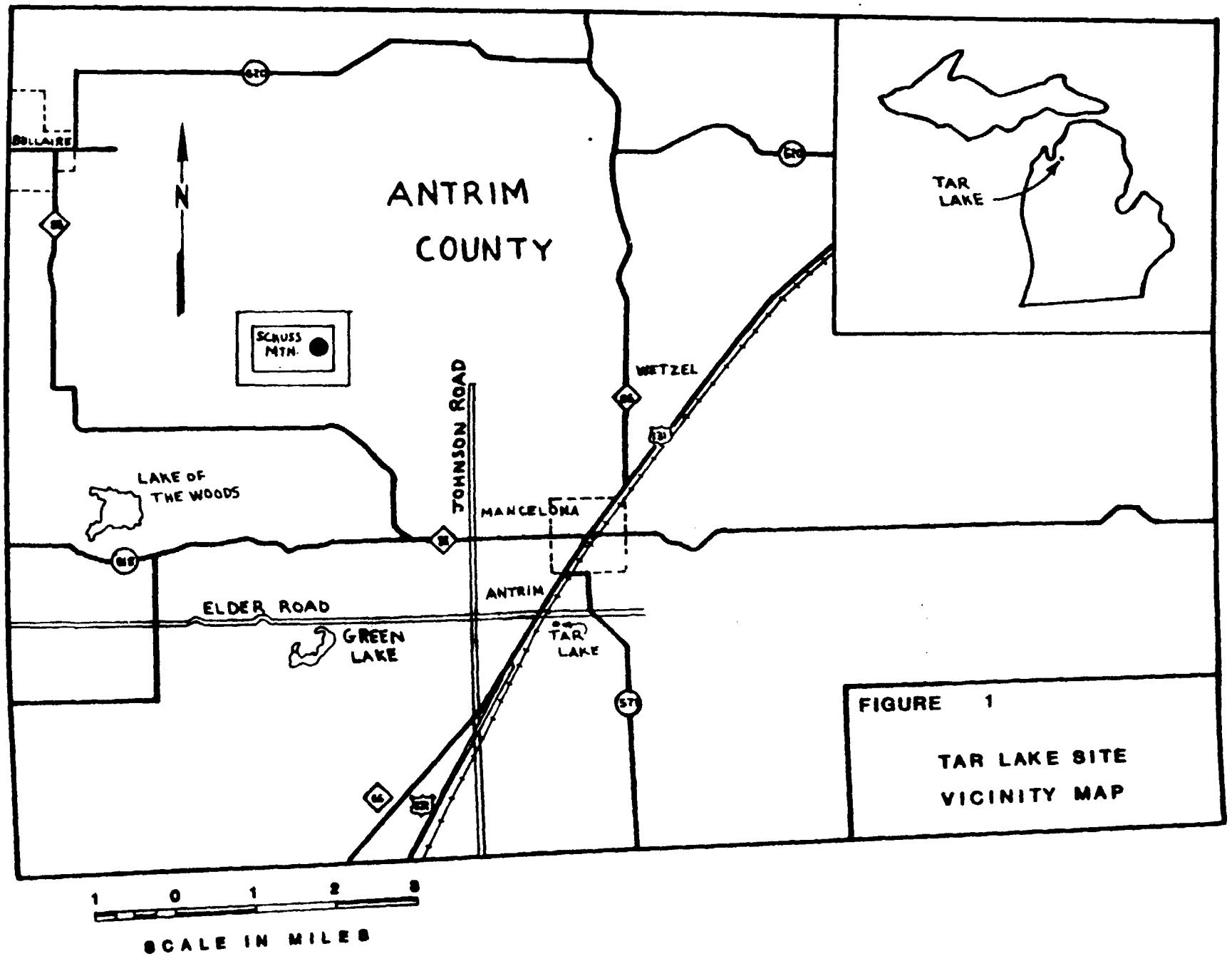


FIGURE 1

TAR LAKE SITE
VICINITY MAP

1.0 SITE HISTORY AND DESCRIPTION

1.1 Site History

The Antrim Iron Works Site is located in Antrim County, Michigan. (See Figure 1.) The site occupies 200+ acres just east of Highway 131, approximately one mile south of Mancelona, Michigan. It is situated in a rural, undeveloped area near the village of Antrim.

From 1882 (Source: Mancelona Herald, July 10, 1980 and the Mancelona Centennial Commission) to 1945, the site was the manufacturing location for companies producing iron by the charcoal method. From 1882 to 1886, the site was occupied by the John Otis Charcoal Iron Furnace Company. In 1886 the Antrim Iron Works Company (AIWC) took over the site, and in 1890, AIWC operated the world's largest charcoal furnace. AIWC produced 20,000 tons of iron annually, using hardwood charcoal made on-site in kilns. In 1910 the company began producing charcoal in sealed retorts from which crude pyroligeneous liquor was recovered. This liquor was then further processed into calcium acetate, methanol, acetone, creosote oil, and wood tar. This secondary chemical manufacturing process produced a waste equivalent to still bottoms which was discharged into a depression on site. This depression, now called Tar Lake, received annually the waste still bottoms generated from 45-50,000 cords of wood.

The furnace was closed in 1943. The chemical plant was closed in early 1944 and all AIWC operations ceased in 1945 after which the company was placed in receivership and the site was salvaged. The site received wood for tar wastes, therefore, from 1910 to 1944.

The only remaining site features are Tar Lake itself and the remains of tank supports and cooling water ditches. Tar Lake appears to have shrunk by more than 50% since the 1930's according to an evaluation of aerial photographs.

No containerized wastes are present and no record of subsequent waste discharges has been found. Moeke Lumber Company operates a lumber mill south of Tar Lake. The Township of Mancelona operated an 8-acre municipal landfill on the site for approximately eight years (1961-1969). 56th Co. has not utilized the site. The warehouses northwest of Tar Lake are used to store machinery and parts for a plant located in Mancelona, one mile north of Tar Lake.

It has been reported that Tar Lake caught fire in the 1960s and burned for an unspecified period before being extinguished by natural action.

The site itself is characterized by severe topographic relief. No permanent or intermittent streams are present and there appears to be no surface run-off from the site. In addition to Tar Lake, the site contains many large slag piles, piles of limestone, and ruins of AIWC operations. A chemical odor is present near Tar

Lake. A large sludge pile is evident on the west side of the lake. Figure 2 shows applicable site features and surrounding land. Figure 3 Shows the site in relation to local features.There have been two remedial actions to date on the site. In 1949, city water was extended to the Village of Antrim and much of the surrounding area. Local residents indicate that only a few homes continue to use groundwater. In 1984, a six foot woven-wire fence topped with barbed wire was erected to secure Tar Lake from unauthorized access.

1.2 Substances Associated with Tar Lake

The destructive distillation of hardwoods, and subsequent condensation of the gases, yields a tarry substance called pyroligneous liquor. The chemical characteristics of the liquor vary with the species of tree used. Beechwoods, for instance, yield a mixture of guaiacol and cresol (Patty's Industrial Hygiene, Volume 2a, John Wiley and Sons, New York, 1981, p. 2601) The cresol is present as a mixture of ortho, meta, and para cresols. Depending on the species of hardwood, other phenolic, cresolic, xylenolic, and pyrolic compounds may also be present. The specific chemical phenol is not present in sufficient quantities to warrant recovery. (Kirk-Othmer, Encyclopedia of Chemical Technology, Interscience Publishers, New York, 1968. Vol. 15, p.147). The pyroligneous liquor can be further refined into many compounds, "including substances now made otherwise or forgotten." (Chemical Process Industries, McGraw-Hill, New York,

p. 553) A material called 'creosote oil' was frequently prepared from hardwood liquors and subsequently refined into vanilla, perfumes, food flavorings, and spices. The compounds finding these uses are all phenolic aldehydes of the general formula R'O-R-CHO, where R is an aromatic radical and R' is a substitution group. (Note: According to the Mancelona Centennial Commission, Antrim Iron Works produced a product they called creosote oil which is assumed to be a mixture of these phenolic aldehydes.)

Phenolic ethers are also isolated from hardwood tars. These compounds have the general formula Ar-O-R, where Ar is an aryl group (aromatic) and R is any hydrocarbon. Typical phenolic ethers from hardwoods are guaiacol, isoeugenol, safrole, and estragole. These compounds are highly stable and have strong characteristic sweet odors (included in this group are clove oil, carnation oil, orangeoil, etc.) and are frequently used as perfumes and flavorings. Because of their heat stability, these compounds are also used as heat transfer agents (a modern example is DowTherm, a substitute for PCB fluids). On exposure to air, ultraviolet light, bacterial action, or oxidizing environments the ethers decompose into peroxides which then further decompose into phenolic ketones and acids which have strong, foul odors.

The third major class of chemicals isolated from hardwood tars is the benzenediols, and their esters. There are three major compounds in this group: pyrocatechol, resorcinol, and hyrdoquinone (1,2;1,3; and 1,4 benzenediol respectively). These

chemicals are water-soluble, form metal salts in alkaline solutions, and characteristically cause skin "burns" on contact. These compounds also have strong odors.

The process which produced Tar Lake is not known; however since AIWC was engaged in refining its pyroligneous waste into methanol, acetone,and acetic acid, it is reasonable to assume that Tar Lake contains the still bottoms from these processes, or 'wood tar.' Although this wood tar was apparently burned to produce steam for electricity, it is possible that wood tar production exceeded needs for the boiler and/or that wood tar was not always used as a boiler feed.

If Tar Lake does contain the still bottoms, the original constituents should be phenolic aldehydes, ethers, and diols. However auto-oxidation, ultraviolet light, weathering, bacterial action, and the 1960's fire at the lake will have created many derivative compounds, primarily stable phenolic ketones, acids, and alkyls most of which are described in the literature as having strong acrid odors. Of those compounds, the alkyl phenols appear to be primarily associated with ground water.

Positive results have been obtained using the 4-aminoantipyrine test for "phenols". This procedure detects virtually all ortho and meta substituted phenolic compounds, and some para substituted compounds; indicating that phenolic derivatives are present in groundwater downgradient from the site.

1.3 Prior Studies of the Site

Data collection prior to 1986 at the Antrim Iron Works Site and in the surrounding area has been poorly coordinated. However,

evidence of the presence of phenolic compounds in off-site private wells was suspected as early as 1929, first established in the 1940s and confirmed as recently as 1980.

A number of limited investigations of the site have been conducted since 1949. A complete list may be found in the Remedial Action Master Plan, April 30, 1984. A summary of these investigations and findings is shown below.

1949 - Eight private wells off-site were found to have "phenols" at low levels. One of the wells, according to the owner, had contained the substances "for forty years." Wells containing phenols were located west and northwest of the site. Lab reports indicate that the test method was the "Gibbs Test for Phenols."

1980 - Elevated lead levels were found in several Mancelona area wells upgradient of Tar Lake.

1980 - Analyses of Tar Lake sludge by MDNR exhibited heavy metals and phenolic compounds. Phenol tests were by Standard Methods 510B.

1982 - Monitoring wells (4) were installed at Tar Lake. Results of analyses were reported as "inconclusive." These tests were "CLP" samples by EPA Contractor.

1983 - Limited testing of Tar Lake performed by 56th Co.

Results showed positive phenol levels but no detectable heavy metals in "pore water." Phenols were measured by Standard Methods 510B.

1984 - Soil samples at the Mancelona landfill showed positive levels of lead, phenols, trichloroethylene, xylene, benzene, methylene chloride, methyl isobutyl ketone and traces of chrysotile asbestos fibers. Methods, laboratory unknown.

1985 - Analyses of on-site and off-site wells were inconclusive with regard to contaminants. On-site and regional groundwater flows were found to be north/northwest.

1988 - Ground water samples from monitoring wells and private wells were taken as part of the RI/FS. Analysis confirms presence of alkyl phenols at levels below 1 ppb per compound.

In 1986, a groundwater monitoring network was installed to monitor quality of groundwaters associated with Tar Lake. To ensure that these wells were installed and screened at depths consistent with monitoring of groundwater, a field analytical protocol was developed using colorimetric monitoring techniques for total phenols (Standards Methods Method No. 510B). The field analytical protocol was employed to monitor phenol in groundwater at various depths prior to the permanent placement of deep wells and the upgradient well. After obtaining phenol data, wells were installed in such a fashion that screens were placed at depths of

highest phenol concentration. (The field analytical procedure is fully described in the QAPP for the Field Measurements, EnSafe Document No: 1025-004-QA-001.)

2.0 IDENTIFICATION AND QUANTIFICATION OF SITE CONTAMINANTS

2.1 Identity of Substances Detected

Prior studies of Tar Lake indicated that phenolic compounds and possibly heavy metals were likely substances to be found in groundwaters on the site. However prior analyses had failed to yield positive data for phenols, except for colorimetric procedures for "phenolic compounds." The colorimetric tests, although considered as screening tests only, had shown phenolic concentrations ranging from 3 ppb in groundwater to 64 ppb. Therefore an analytical procedure was developed for the purpose of identifying and quantifying these phenolic compounds. A description of the development procedure and the analytical protocol itself may be found in Quality Assurance Project Plan, EnSafe Document 1025-004-QA-003, October, 1987. The procedure employed was a resin extraction adsorbtion of 15.0 l samples with subsequent GC/MS analysis for acid extractable organic compounds. The procedure has a nominal detection limit of 0.8 ppb.

Preliminary screening of Tar Lake groundwater samples during protocol development indicated that the samples probably contained mixtures of various phenolic compounds. This was confirmed during full implementation of the procedure. Table 2 is a summary of the results obtained. Although the procedure had a nominal detection limit of 0.8 ppb, the laboratory was able to approximate concentrations of some species to a level of 0.05

ppb. While a 300% error is possible with this approximation, the report does provide some identification data as well as the approximate level of concentration.

The laboratory reported that most positive phenols in Tar Lake groundwater were C2 and C3 alkyl phenols with some samples showing species of higher molecular weight. The laboratory reported that "No phenols were identified that were substituted with other than alkyl groups."

A list of predicted compounds was then prepared using CRC Handbook of Chemistry and Physics, 68th edition, 1987, CRC Press, Boca Raton, FL. to obtain lists of known compounds meeting the criteria of C2 through C12 alkyl phenols. Table 2 is the list of these phenol compounds.

In addition to the special analytical protocol employed for the phenolic acid extractable compounds, analyses were conducted for volatile organic compounds, semivolatile organic compounds, metals, and cyanide. Results of these analyses are displayed in Tables 3 through 5.

The volatile analyses were negative for chemical species except for one well which showed positive values at less than 10 ppb for benzene and toluene . This same well showed an estimated positive value for napthalene. This combination of compounds appears to be the result of gasoline contamination of the well or the sample. Since these compounds do not appear in other wells they are not further addressed in the Preliminary Endangerment Assessment.

The semivolatile organics analyses were generally negative except for monitoring wells six and seven which were positive for 2,4-dimethyl phenol at 57 and 59 ppb respectively. Quality assurance reviews indicate that these reported data represent multiple alkyl phenols rather than the single species 2,4-dimethyl phenol however.

Metals data, summarized in Table 6, are generally representative of the localized groundwater conditions of Antrim County. Positive values for lead were obtained in six wells in a range of 4.5 to 7.5 ppb. Well 16 upgradient of Tar Lake itself had the highest reported lead value at 32 ppb. Although lead has been reported in association with Tar Lake, the data do not confirm this association. Therefore lead has not been addressed in the PEA.

A review of all metals data indicates a second source area near Tar Lake that affects water quality in Wells 11, 12, 14, and 15. The second source affects potassium/calcium/sodium ratios. Conductivity values in these wells also support the potential for a second source. The Mancelona landfill located just upgradient of these wells is the most likely source.

Two positive values were obtained for cyanide, 66 and 178 ppb respectively in Wells 12 and 15. These values are also being linked to the landfill. Since Tar Lake affected wells were negative for cyanide, this parameter is not further addressed in the PEA.

In summary, the Tar Lake substances of concern are alkyl phenols, principally C2 and C3 alkyl phenols.

2.2 Substance Concentrations

Table 1 provides a summary of the approximate concentrations of the various alkyl species. For purposes of the Preliminary Endangerment Assessment, a concentration of 0.5 ppb was used for the Health Assessments as this is the approximate concentration of the most common species.

There is testimonial evidence that these concentrations may be lower now than in the past. Interviews were conducted with persons who have lived in the affected areas for more than 50 years. These individuals uniformly indicated that the "chemical water" was worse in the past. Generally they appeared to be making this assessment based on subjective indicators of taste and odor.

2.3 Analytical Methodology and Quality Assurance

A complete description of the analytical methodology used and the field and laboratory quality assurance may be found in the Quality Assurance Project Plan for the Antrim Iron Works Site.

3.0 ENVIRONMENTAL FATE AND TRANSPORT

3.1 Physical-chemical Properties

Relevant data for the alkyl phenols in environmental settings is generally not available from scientific literature. Adsorption coefficients, photodegradation rates, decomposition rates, and transformations in environmental media are not available for most of the compounds. Nevertheless considerable evidence exists that the still bottoms which comprise Tar Lake are undergoing degradation; as the volume and area of the lake have decreased dramatically in size since AIWC operations on the site ceased. The relative relationship of biological and physical/chemical degradation phenomena are unknown.

Table 7 contains a summary of data available for these compounds.

One shared characteristic of these compounds is very low threshold odor limits. Literature values for odor threshold range from 1 ppb to 25 ppb.

3.2 Prediction of Fate and Transport

It is assumed for purposes of the PEA that the alkyl phenols identified in ground water wells downgradient from Tar Lake have in fact originated at the lake. Several scenarios by which this may happen have been advanced. They include direct contact with underlying groundwater, leachate from still bottoms in the lake, and leachate from degraded tars at the edges of the lake.

TABLE 7

Physical/Chemical Properties of
Some Alkyl Phenols

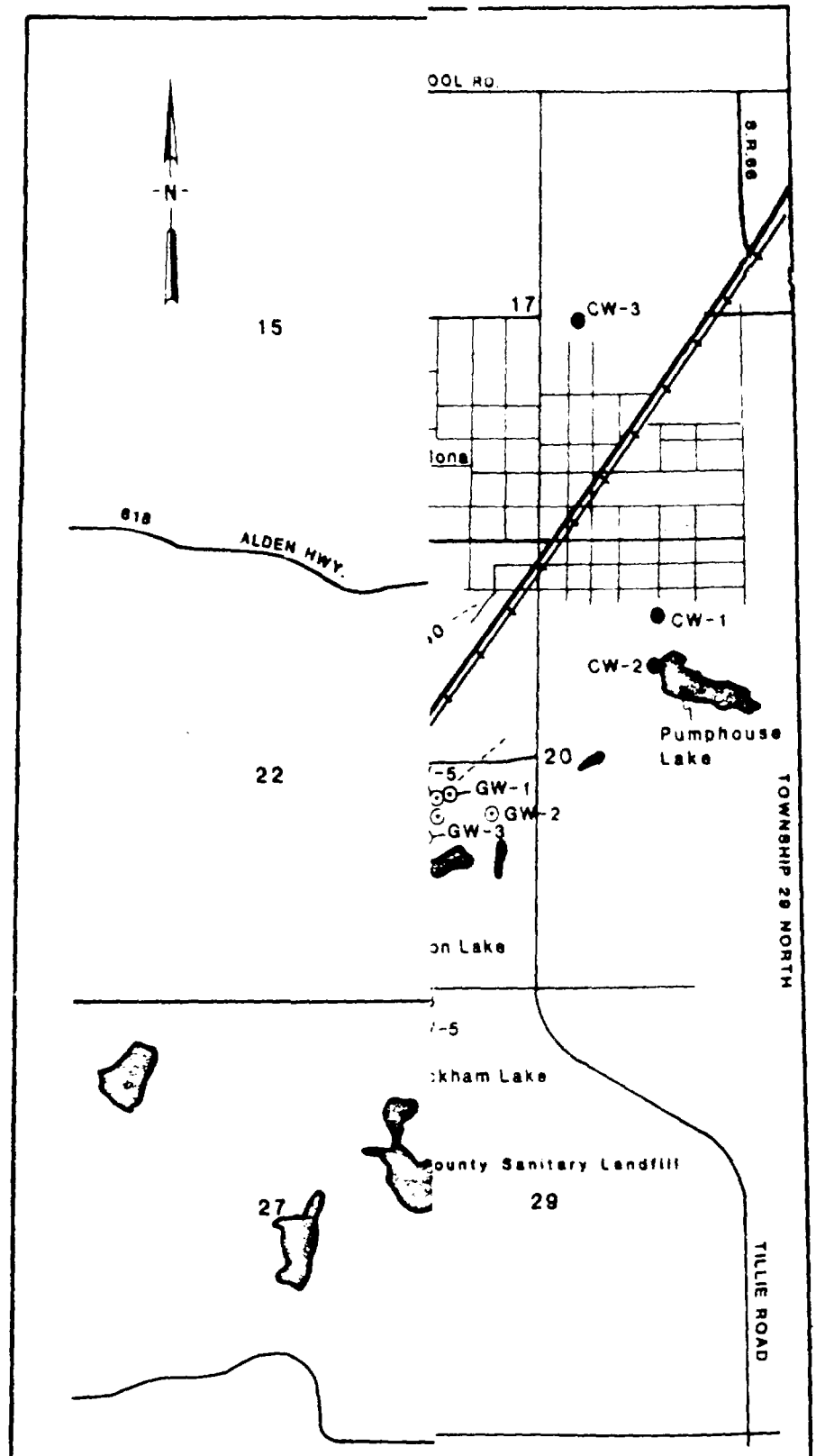
Compound	Molecular Weight	b. p. °C	Taste Threshold mg/l	Water/Odor Threshold mg/l	Sp. Gravity	log P_{oct}
2,3-dimethyl phenol	122.17	217	0.03	0.5	1.036	—
2,4-dimethyl phenol	122.17	211	0.5	0.4	1.036	—
2,5-dimethyl phenol	122.17	212	0.5	0.4	0.971	—
2,6-dimethyl phenol	122.17	203	0.5	0.4	—	2.36
3,4-dimethyl phenol	122.17	225	0.05	1.2	1.023	—
3,5-dimethyl phenol	122.17	219	—	5.0	—	2.35
O-ethyl phenol	122.17	197	0.03	0.3	1.037	—
P-ethyl phenol	122.17	218	0.01	0.6	—	2.66
P-tert-butyl phenol	150.21	236	—	—	0.908	3.31
2,6-di-t-butyl phenol	206.33	253	—	—	0.914	—
2,6-di-t-butyl,4 methyl phenol	220.36	265	—	1.0	1.048	—

Source: Verschueren, Karel. Handbook of Environmental Data on Organic Chemicals, 2nd ed. Van Nostrand Reinhold Company, New York, 1983

Note: Odor Thresholds shown are water soluble thresholds. Air odor thresholds for these compounds range from).01 mg/m^3 to 0.0002 mg/m^3.

The site is located in a severe topographic depression from which surface water from precipitation cannot exit by overland flow. The surface of Tar Lake is partially to fully covered in a layer of fresh water seasonally.

Regional groundwater flow is to the west. Figure 4 is a regional map of the area showing groundwater elevations from 1984 observations. The map is color coded to show wells reported by their owners to exhibit "chemical water." Some of these wells are reported by their owners to have begun to exhibit problems before 1929. Therefore it is assumed that for purposes of the PEA, the Antrim Iron Works Site is the source of groundwater complaints in this area and that the source of these complaints is alkyl phenols at concentrations below 1 ppb.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-N-
15
17
CW-3
lons
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TILLIE ROAD
CITY WELL LOCATION
WATER WELL LOCATION
WATER WELL LOCATION
MW MONITOR WELL
PW PRIVATE WELL
CW CITY WELL
GW GULF + WESTERN MONI
SECTION LINE
ERIAL ENGINEERS, INC.
NCINNATI, OHIO
ATER WELL INVENTORY,
IRONWORKS SITE
RIM, MICHIGAN
APPROVED BY:
PROJECT NO 024-84-170

4.0 TOXICOLOGICAL PROPERTIES

4.1 Human and Animal Toxicity

Appendix 1 contains a summary of toxicological information on the alkyl phenols from Table 3. This data was compiled by a detailed literature search in: Chemical Abstracts, 1966-1988; Med Line, 1975-1988; Tox Line, 1965-1988; and various toxicological compendia. Each citation found in these references was reviewed in the individual paper. In some cases, no toxicological references were found. In some other cases conflicting data was found in the literature indicating that some of this data is unreliable. A large portion of the early data on some of these compounds is also in Russian. In some cases where acute data was found, there were no corresponding chronic investigations.

After summarizing the available toxicological data, a toxicological health assessment has been made for each compound for which there is sufficient data. This assessment may be found at the end of each such compound list as "Health Assessment." [The Health Assessments were made by E.M. Bellet, Ph.D., toxicologist associated with Chemical Consultants International, Inc. Dr. Bellet's resume is attached as Appendix 2.]

None of the compounds has been found to be carcinogenic or teratogenic. Some have been found to be tumorigenic at very high

doses. Most are toxic to fish at concentrations 100 times their occurrence in Tar Lake groundwater. Several are skin irritants and all generally exhibit organoleptic qualities.

4.2 Human Health Standards and Criteria

Health based standards and criteria do not exist for most of these alkyl phenol compounds. Several standards have been established for "phenols" as a class of compounds however.

Levels for discharge of "phenols" have been set under the Clean Water Act. The compound 2,4-dimethyl phenol is regulated at 40 CFR 414 for discharge at 47 ppb maximum daily limit and 19 ppb maximum monthly average.

The Food and Drug Administration has set maximum limits for several of the higher molecular weight alkyl phenols which are used as accelerators and antioxidants in food products.

The most recent review of chronic toxicity for the compound phenol was a review by the Environmental Protection Agency (53 FR 18024-18032) for the purpose of establishing regulatory levels and chronic toxicity reference levels for RCRA. In that review, the Agency proposed a 1 mg/l chronic toxicity reference level for phenol.

The ACGIH Threshold Limit Value for phenol on skin for a 7 or 8 hour workday is 5 ppm. The OSHA standard is also 5 ppm.

5.0 EXPOSURE ASSESSMENT

5.1 Population at Risk

The population potentially exposed to the alkyl phenols are residential and commercial water users drawing water from the affected part of the aquifer west of Tar Lake. A regional water well inventory has been conducted and identified 17 private wells in the potentially affected area. Notably certain wells within this area do not exhibit "chemical water" problems as a result of fortuitous screen placement.

All residents within the area have minimized their exposure to these compounds by obtaining alternate drinking water supplies. Municipal water supplies were brought into the area in 1949 principally as a consequence of degraded water supplies west of Tar Lake. Those homes not supplied by municipal water supplies purchase water for drinking, although some use groundwater for other purposes including bathing, dishwashing, and livestock watering. A number of residents indicated they have typically consumed degraded water in the past.

There is one small business within the affected area. This business uses groundwater for cooling and other processes.

5.2 Background Chemical Exposures

No site specific medical histories or exposure data are available.

5.3 Direct Contact Exposure

The toxicological summary (Appendix 1) reflects that many of these compounds are skin irritants, causing mild to severe skin rashes and a burning sensation on contact. However Tar Lake and the surrounding area have been fenced since 1984 to reduce the risk of direct contact exposures.

6.0 SUMMARY

A review of analytical data obtained for the Antrim Iron Works Site results in a conclusion that the substances associated with the site are alkyl substituted phenols. A predicted compound list has been created.

These compounds exist in groundwater on and off site. The only migration pathway is via groundwater. The population at risk are users of the affected aquifer west of Tar Lake.

The highest reported values for alkyl phenols is 0.5 ppb per compound. Typical concentrations are in the range of 0.05 to 0.3 ppb.

There are substantial data gaps in the toxicological literature for these compounds. However the compounds are not suspected carcinogens or teratogens. Based on available data it is concluded that they pose no endangerment at the concentrations exhibited in Tar Lake groundwater.

The toxicity of direct contact exposure has not been assessed. It is concluded however based on the skin irritation properties of the compounds that there is a risk associated with direct contact.

APPENDIX 1

TOXICOLOGICAL DATA AND

HEALTH ASSESSMENTS

FOR ANTRIM IRON WORKS SITE

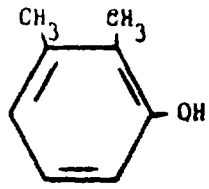
COMPOUNDS

1. 2,3-dimethylphenol

CAS 526-75-0
NIOSH ZE5500000

SYNONYMS: 2,3-xylenol; 1-hydroxy-2,3-dimethylbenzene; o-xylenol, 4-hydroxy-o-xylene

STRUCTURAL FORMULA:



TOXICITY:

ACUTE:

1. Intravenous Mouse LD_{50} is 56 mg/kg.[1,33]
2. The 24 hr. IC_{50} (Immobilization Concentration for 50% of daphnids) was found to be 0.11 mmol/liter.[2]
3. The 96-hr EC_{50} was 11.5 mg/liter for sea urchin eggs and 13 mg/liter for cod eggs.[3]

SUBCHRONIC AND CHRONIC:

OTHER HAZARDS AND OBSERVATIONS:

1. Toxic to Ascites sarcoma BP8 cells in vitro, 78% at 1 mM.[4] (This is an immunological cytotoxic test system measuring inhibition of cell growth by chemicals.)
2. The chemical was a moderate inhibitor of sheep vesicular gland prostaglandin cyclooxygenase with an I_{50} of 64 as compared to the potent inhibitor 2,4,6-trimethylphenol (I_{50} = 7uM).[52]

HEALTH ASSESSMENT: Long term data was not found. The chemical is toxic to fish. It is also a prostaglandin cyclooxygenase inhibitor. While the dimethylphenols seem to be tumorigenic, they are so at very high doses. Based upon this limited data it would be expected that the chemical would not be a health hazard at a steady state level of 0.5 ppb.

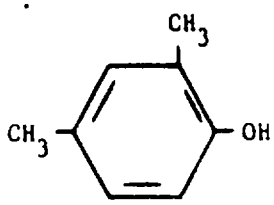
2. 2,4-Dimethylphenol

CAS 105-67-9

NIOSH ZE5600000

SYNONYMS: 2,4-xylenol; 1-hydroxy-2,4-dimethylbenzene; 4-hydroxy-1,3-dimethylbenzene; m-xylenol; m-4-xylenol; 4-hydroxy-m-xylene

STRUCTURAL FORMULA:



TOXICITY:

ACUTE:

1. Poisoning symptoms are headache, dizziness, nausea, vomiting, stomach pain, exhaustion, skin and eye irritation[5].
2. Oral Rat LD_{50} is 3200 mg/kg.[5,6]
3. Oral Mouse LD_{50} is 809 mg/kg.[5,6]
4. Dermal Rat LD_{50} is 1040 mg/kg.[5,6]
5. Dermal Mouse LD_{50} is 1040 mg/kg.[5,7]
6. Intaperitoneal Mouse LD_{50} is 183 mg/kg.[5,8]
7. Intravenous Mouse LD_{50} is 100-120 mg/kg.[5,9]
8. Three or four rats were administered 2,4-dimethyphenol by intravenous infusion (17 mg/hr) for 6 hours. At sacrifice it was noted that brain accumulated the highest amount followed by fat and liver. The chemical rapidly distributed through the body after an intravenous bolus (30 mg/kg). Plasma, liver and fat concentrations disappeared within 1 hr., whereas brain concentrations remained.[10]

9. The effect of the chemical on pulmonary toxicity was measured by intraperitoneal administration to mice at a dose of 2.27 mmol/kg. At sacrifice after 4 days, significant decrease in body weight was noted but there were no other toxic effects.[11]
10. Acute toxicity to freshwater aquatic life occurs as low as 2.12 ppm (Daphnia Magna).[5]
11. The 24 hr IC_{50} (Immobilization Concentration for 50% of daphnids) was found to be 0.09 mmol/liter.[2]
12. Flowthrough acute tests on fathead minnows for 96 hr. gave an LC_{50} of 17 mg/L.[12]
13. The LC_{50} to Bluegill was determined to be 18 mg/Liter (24 hr) and 7.8 mg/liter (96 hr).[13]
14. The 96 hr EC_{50} was 5.1 mg/liter for sea urchins eggs and 3.7 mg/liter for cod eggs.[3]
15. In a 5 minute bacterial (Photobacterium phosphoreum) EC_{50} assay the chemical reduced to 50% the light output of the bacterium at a concentration of 4.4 mg/liter.[47] (The toxic end point of this assay is the 50% reduction in luminescense of the bacterium).

SUBCHRONIC AND CHRONIC:

1. A solution of 2,4-xylenol (5 mg in benzene-25ul of a 10% solution) applied to the skin of tumor susceptible female mice twice weekly for 24 weeks produced carcinomas in 12%; results inconclusive. Possibly a tumor promoting agent.[5]
2. Acute and chronic studies of 2,4-dimethylphenol are described. At 26-30 mg/m^3 no lethal effects were noted but irritation of the mucous membrane was observed. Aerosolized (at unknown concentrations) caused death with the chemical observed to be absorbed through the lung and skin. Repeated inhalation by mice for 1 month (2 hrs daily at 23 mg/m^3) somewhat retarded growth. Functional and morphological effects, as well as respiratory activity, peripheral blood and internal organs were not altered.[14]
3. Has potential for liver and kidney damage on chronic exposure.[5]
   NOTE: These findings were found to be referencing studies in rats.[90]
4. Dermal Mouse TDLo was 16 g/kg when administered intermittantly for 39 weeks. Skin damage, fur loss, and tumor formation were noted.[5,22]
5. Chronic effects were noted in an Embryo-larval test using fathead minnows at concentrations of 1.5 to 3.2 mg/L.[12]

OTHER HAZARDS AND OBSERVATIONS:

1. Patients with contact allergy to phenolic-formaldehyde resins and 2-methyl phenol have shown simultaneous reactions to o-creosol and 2,4-dimethylphenol (unpublished results).[16]
2. Results of Ames Test was negative both with and without microsomal activation.[17,18]
3. Tested quantitatively against Salmonella typhimuirium (TA 100) and found to be non-mutagenic but was toxic at 30 umols/plate.[19]
4. Toxic to Ascites sarcoma BP8 cells in vitro, 99% at 1 mM.[4]. (This is an immunological cytotoxic test system measuring inhibition of cell growth by chemicals.)
5. The chemical was a potent inhibitor of sheep vesicular gland prostaglandin cyclooxygenase with an I_{50} of 17 as compared to the potent inhibitor 2,4,6-trimethylphenol (I_{50} = 7uM).[52]
6. After exposure to Mycoplasma pneumoniae, the chemical, at concentrations of 10^{-9}M or greater, completely prevented the morphological (loss of ciliated cells) and biochemical (decreased dehydrogenase activity) changes normally observed after exposure to the M. pneumoniae in hamster tracheal explants.[15]

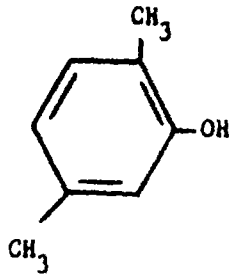
HEALTH ASSESSMENT: The chemical is a skin irritant. Subchronic inhalation and dermal studies exhibited toxicity and possible tumorigenic potential, but at very high doses. The chemical is not mutagenic, is toxic to fish and is also an inhibitor of prostaglandin cyclooxygenase. It would be expected, based upon the data, that the chemical would not be a health hazard at a steady state level of 0.5 ppb.

3. 2,5-dimethylphenol

CAS 95-87-4
NIOSH ZE5775000

SYNONYMS: 2,5-xylenol, 1-hydroxy-2,5-dimethylbenzene
4-hydroxy-p-xylene; p-xylenol

STRUCTURAL FORMULA:



TOXICITY:

ACUTE:

1. Oral Rat LD_{50} is 444 mg/kg.[20,33]
2. Oral Mouse LD_{50} is 383 mg/kg.[20,33]
3. Oral Rabbit LD_{50} is 938 mg/kg.[20,33]
4. Toxic to rainbow trout with an LC_{50} of 2.3-5.6 mg/liter in a 96 hr static test.[21]
5. The chemical is acutely toxic to fish causing 100% mortality of Daphnia at 72 hr at 0.1 mg/liter and 100% mortality to goldfish in 6 to 48 hrs at a concentration of 1 mg/liter. It is also acutely toxic to 3 species of salmon at a range of 3.12 to 6.98 mg/liter over a 3 day period in both fresh and salt water.[21]
6. The 24 hr. IC_{50} (Immobilization Concentration for 50% of daphnids) was found to be 0.09 mmol/liter.[2]
7. The 96 hr EC_{50} is 5 mg/liter for sea urchin eggs and 13 mg/liter for cod eggs.[3]

SUBCHRONIC AND CHRONIC:

1. Dermal Mouse TDLo is 4000 mg/kg after intermittant dosing at 20 weeks. Skin damage, fur loss and tumor formation were also noted.[22,33]

OTHER HAZARDS AND OBSERVATIONS:

1. Toxic to Ascites sarcoma BP8 cells in vitro, 74% at 1 mM.[4] (This is an immunological cytotoxic test system measuring inhibition of cell growth by chemicals.)
2. The chemical was a moderate inhibitor of sheep vesicular gland prostaglandin cyclooxydase with an I_{50} of 45 as compared to the potent inhibitor 2,4,6-trimethylphenol (I_{50} = 7uM).[52]

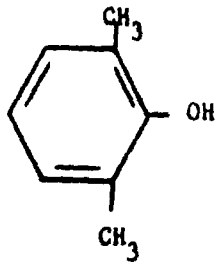
HEALTH ASSESSMENT: Subchronic dermal data exhibits toxicity and tumor formation but at very high doses. The chemical is toxic to fish and is also a prostaglandin cyclooxygenase inhibitor. It would be expected, based upon the limited data, that the chemical would not be a health hazard at a steady state level of 0.5 ppb.

4. 2,6-dimethylphenol

CAS 576-26-1
NIOSH ZE6125000

SYNONYMS: 2,6-xylenol

STRUCTURAL FORMULA:



TOXICITY:

ACUTE:

1. Oral Rat LD_{50} is 296 mg/kg.[20,33,67]
2. Oral Mouse LD_{50} is 980 mg/kg.[6,33]
3. Oral Rabbit is 700 mg/kg.[20,33]
4. Intravenous Mouse LD_{50} is 80 mg/kg.[9]
5. Dermal Mouse is 920 mg/kg.[6,33]
6. Dermal Rabbit is 1000 mg/kg.[23,33]
7. Acute LD_{50} values for rats and mice were 406 and 450 mg/kg, respectively. Cyanosis, hypervolemia of stomach and peritoneum, and lung hemorrhages were noted in lethally poisoned animals. Inhalation of 270 mg/m^3 for 2 hr. by mice and 4 hr. by rats disturbed breathing and caused spasmatic shaking and agitation. Recovery was 3 to 4 days. Activity threshold was 56 mg/m^3.[24]
8. The oral LD_{50} value of 2,6-dimethylphenol and MeOH were found to be 406 and 5628 mg/kg compared to 310 mg/kg for a mixture of 70:30, respectively. Similar potentation was noted in inhalation studies.[25]

9. Topical application of 0.1 ml/20cm^2 caused hyperemia, followed by erythema and ulceration in rats, guinea pigs and rabbits. The skin LD_{50} for rats was 2325 mg/kg.[24]
10. Intraperitoneal Mouse is 150 mg/kg.[26,33]
11. Primary Eye in Rabbit: was irritating at 100 mg.[23,33]
12. Flow through acute tests on fathead minnows at 96 hr. gave LC_{50} value of greater than 27 mg/liter.[12]
13. The 96 hr EC_{50} was 1.5 mg/liter to sea urchin eggs and 4 mg/liter to cod eggs.[3]
14. The 24 hr IC_{50} (Immobilization Concentration for 50% of daphnids) was found to be 0.11 mmol/liter.[2]

SUBCHRONIC AND CHRONIC:

1. Dermal Mouse TDLo was 4000 mg/kg after intermittant dosing at 20 weeks.[22,33]
2. Moderately toxic noncumulative activity was observed by inhalation or gastric gavage to mice or rats daily for 1.5 months. Non-lethal tissue damage was observed in the liver, kidneys, and spleen. Skin resorptivity was high.[27]
3. No cumulation of daily oral doses of 5 to 90 mg/kg during 1.5 months was noted. A subacute inhalation study lasting 1 month showed decreased swimming time, lowered blood SH level, and elevated blood leukocytes.[24]

4. Administration (internal) to rats in doses of 6 and 14 mg/kg/day decreased the content of sulfhydryl groups in the serum.[28]

OTHER HAZARDS AND OBSERVATIONS:

1. Toxic to Ascites sarcoma BP8 cells in vitro, 79% at 1 mM.[4] (This is an immunological cytotoxic test system measuring inhibition of cell growth by chemicals.)
2. The chemical was a potent inhibitor of sheep vesicular gland prostaglandin cyclooxygenase with an I_{50} of 16 as compared to the potent inhibitor 2,4,6-trimethylphenol (I_{50} = 7uM).[52]

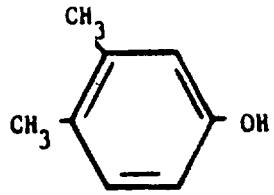
HEALTH ASSESSMENT: Subchronic dermal data exhibits minimal effects compared to the other dimethylphenols. Subchronic dermal toxicity data also exhibited minimal effects. The chemical is toxic to fish and is also a prostaglandin cyclo-oxygenase inhibitor. It would be expected, based upon the data, that the chemical would not be a health hazard at a steady state level of 0.5 ppb.

5. 3,4-dimethylphenol

CAS 95-65-8
NIOSH ZE6300000

SYNONYMS: 3,4-xylenol, 4,5-dimethylphenol, 1,3,4-xylenol

STRUCTURAL FORMULA:



TOXICITY:

ACUTE:

1. Oral Rat LD_{50} is 727 mg/kg.[67]
2. Oral Rat LDLo is 500 mg/kg.[29,33]
3. Oral Mouse LDLo is 400 mg/kg.[20,33]
4. Oral Rabbit LDLo is 800 mg/kg.[20,33]
5. Toxic to rainbow trout with an LC_{50} of 2.3-5.6 mg/liter in a 96 hr static test.[21]
6. The chemical is acutely toxic to fish causing 100% mortality of Daphnia at 72 hr at 0.1 mg/liter and to goldfish in a range of 6 to 48 hrs at a concentration of 1 mg/liter. It is also toxic to 3 species of salmon at a range of 3.12 to 6.98 mg/liter over a 3 day period in both fresh and salt water.[21]
7. The 24 hr. IC_{50} (Immobilization Concentration for 50% of daphnids) was found to be 0.15 mmol/liter.[2]
8. The 96 hr EC_{50} is 5.3 mg/liter for sea urchin eggs and 13 mg/liter for cod eggs.[3]

SUBCHRONIC AND CHRONIC:

1. Dermal Mouse TDLo is 4000 mg/kg after intermittant dosing at 20 weeks. Skin damage, fur loss, and tumor formation were also noted.[22,33]
2. Administration (internal) of 3,4-dimethylphenol to rats in doses of 0.6 and 0.14 mg/kg/day had no effect on the content of sulfhydryl groups in the serum.[28]

OTHER HAZARDS AND OBSERVATIONS:

1. Toxic to Ascites sarcoma BP8 cells in vitro, 75% at 1 mM.[4] (This is an immunological cytotoxic test system measuring inhibition of cell growth by chemicals.)
2. The chemical was a moderate inhibitor of sheep vesicular gland prostaglandin cyclooxygenase with an I_{50} of 64 as compared to the potent inhibitor 2,4,6-trimethylphenol (I_{50} = 7uM).[52]

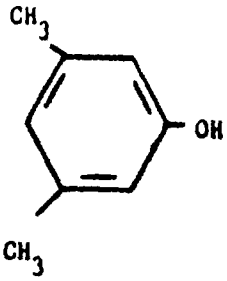
HEALTH ASSESSMENT: Subchronic dermal data exhibits toxicity and tumor formation but at very high doses. The chemical is toxic to fish and is also a prostaglandin cyclooxygenase inhibitor. It would be expected, based upon the limited data, that the chemical would not be a health hazard at a steady state level of 0.5 ppb.

6. 3,5-dimethylphenol

CAS 108-68-9
MIOSH ZE6475000

SYNONYMS: 3,5-xylenol, 1-hydroxy-3,5-dimethylbenzene
1,3,5-xylenol

STRUCTURAL FORMULA:



TOXICITY:

ACUTE:

1. Oral Rat LD_{50} is 608 mg/kg.[20,33]
2. Oral Mouse LD_{50} is 477 mg/kg.[20,33]
3. Oral Rabbit LD_{50} is 1313 mg/kg.[20,33]
4. The chemical is a severe irritant to rabbit skin at 420 mg/kg.[38]
5. Eye toxicity to rabbit was severe at 726 ug.[30,33]
6. Acute and chronic studies of 3,5-dimethylphenol are described. At 4 mg/m^3 no lethal effects were noted but irritation of the mucous membrane was observed.[14]
7. The Oral LD_{50} to Redwinged Blackbird is reported to be greater than 113 mg/kg with a Repellancy Index, R_{50}, equal to 1.00%.[31]
8. The 24 hr. IC_{50} (Immobilization Constant for 50% daphnids) was found to be 0.18 mmol/liter.[2]
9. The 96 hr. EC_{50} is 14 mg/liter for sea urchin eggs and greater than 30 mg/liter for cod eggs.[3]

SUBCHRONIC AND CHRONIC:

1. Dermal Mouse TDLo is 4000 mg/kg after intermittant dosing at 20 weeks. Skin damage, fur loss, and tumor formation were also noted.[22,33]

OTHER HAZARDS AND OBSERVATIONS:

1. Toxic to Ascites sarcoma BP8 cells in vitro, 44% at 1 mM.[4] (This is an immunological cytotoxic test system measuring inhibition of cell growth by chemicals.)
2. Tested quantitatively against Salmonella typhimurium (TA 100) and found to be non-mutagenic but was toxic at 30 umol/plate.[19]
3. The chemical did not induce mutations in the Ames Test, with or without microsomeal oxidation, did not induce gene conversion in yeast or chromosome damage in RL_4 cells.[45]
4. The chemical was a poor inhibitor of sheep vesicular gland prostaglandin cyclo-oxygenase with an I_{50} of 370 as compared to the potent inhibitor 2,4,6-trimethyl-phenol (I_{50} = 7uM).[52]

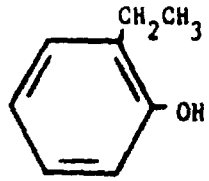
HEALTH ASSESSMENT: Subchronic dermal data exhibits toxicity and tumor formation but at very high doses. The chemical is toxic to fish and is also a prostaglandin cyclooxygenase inhibitor. It would be expected, based upon the limited data, that the chemical would not be a health hazard at a steady state level of 0.5 ppb.

7. 2-Ethylphenol

CAS 90-00-6
NIOSH SL4025000

SYNONYMS: o-ethylphenol, phlorol

STRUCTURAL FORMULA:



TOXICITY:

ACUTE:

1. Oral LD_{50} to the mouse is reported as 600± 10 mg/kg.[32]

SUBCHRONIC AND CHRONIC:

1. Dermal mouse TDLo was reported to be 3100 mg/kg after intermittant administration for 12 weeks. Neoplastic effects were noted.[22]
2. Action in humans was reported to be similar but less severe than phenol.[33]

OTHER HAZARDS AND OBSERVATIONS:

1. Toxic to Ascites sarcoma BP8 cells in vitro, 77% at 1 mM.[4] (This is an immunological cytotoxic test system measuring inhibition of cell growth by chemicals.)
2. The chemical was a poor inhibitor of sheep vesicular gland prostaglandin cyclooxygenase with an I_{50} of 105 as compared to the potent inhibitor 2,4,6-trimethylphenol (I_{50} = 7uM).[52]

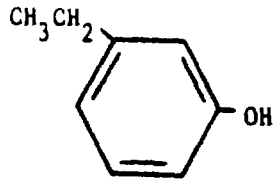
HEALTH ASSESSMENT: Subchronic dermal data exhibits toxicity and tumor formation but at very high doses. In humans it is reported to be similar but less severe than phenol, which is a skin irritant and irritates mucous membranes. The chemical also inhibits prostaglandin cyclooxygenase. It would be expected, based upon the limited data, that the chemical would not be a health hazard at a steady state level of 0.5 ppb.

8. 3-Ethylphenol

CAS 620-17-7
NIOSH

SYNONYMS: m-ethylphenol

STRUCTURAL FORMULA:



TOXICITY:

ACUTE:

SUBCHRONIC AND CHRONIC:

OTHER HAZARDS AND OBSERVATIONS:

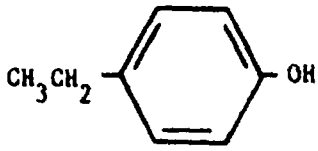
1. Toxic to Ascites sarcoma BP8 cells in vitro, 38% at 1 mM.[4] (This is an immunological cytotoxic test system measuring inhibition of cell growth by chemicals.)

9. 4-Ethylphenol

CAS 123-07-9
NIOSH

SYNONYMS: p-ethylphenol

STRUCTURAL FORMULA:



TOXICITY:

ACUTE:

SUBCHRONIC AND CHRONIC:

OTHER HAZARDS AND OBSERVATIONS:

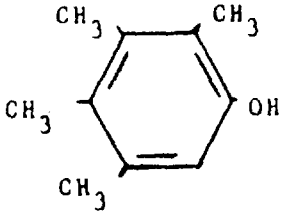
1. Toxic to Ascites sarcoma BP8 cells in vitro, 91% at 1 mM.[4] (This is an immunological cytotoxic test system measuring inhibition of cell growth by chemicals.)

10. 2,3,4,5-tetramethylphenol

CAS 488-70-0
NIOSH

SYNONYMS:

STRUCTURAL FORMULA:



TOXICITY: No Citations Found

ACUTE:

SUBCHRONIC AND CHRONIC:

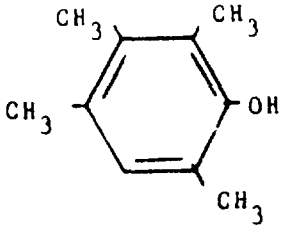
OTHER HAZARDS AND OBSERVATIONS:

11. 2,3,4,6-tetramethylphenol

CAS 3238-38-8
NIOSH

SYNONYMS: isodurenol

STRUCTURAL FORMULA:



TOXICITY: No Citations Found

ACUTE:

SUBCHRONIC AND CHRONIC:

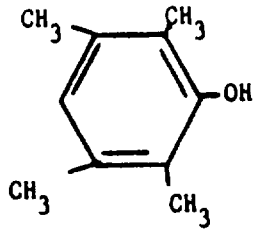
OTHER HAZARDS AND OBSERVATIONS:

12. 2,3,5,6-tetramethylphenol

CAS 527-35-5
NIOSH

SYNONYMS:

STRUCTURAL FORMULA:



TOXICITY:

ACUTE:

SUBCHRONIC AND CHRONIC:

1. The evaluation of the prevention of benzo(a)pyrene forestomach tumor induction in mice was evaluated by feeding 0.03 mmol/gm of 2,3,5,6-tetramethylphenol and measuring T/C. The T/C was 79, where T/C is the ratio between the number of mice with tumors in treated animals (T) divided by controls(C).[34]

OTHER HAZARDS AND OBSERVATIONS:

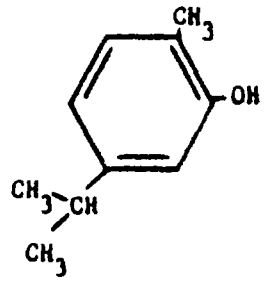
1. The chemical was a potent inhibitor of sheep vesicular gland prostaglandin cyclooxygenase with an I_{50} of 14 as compared to the potent inhibitor 2,4,6-trimethylphenol (I_{50} = 7uM).[52]

13. 2-Methyl-5-isopropylphenol

CAS 499-75-2
NIOSH FI1225000

SYNONYMS: 5-isopropyl-o-creosol, 2-hydroxy-p-cymene; 2-p-cymenol; isothymol; o-thymol; 2-(m-hydroxy-p-methylphenol) propane, carvacrol

STRUCTURAL FORMULA:



TOXICITY:

ACUTE:

1. Oral Rat LD_{50} is 810 mg/kg.[33,35]
2. Oral Cat LDLo is 100 mg/kg.[33,36]
3. Oral Rabbit LDLo is 100 mg/kg.[33,38]
4. Intravenous mouse LD_{50} is 80-100 mg/kg.[9]
5. Dermal Rabbit LDLo is 2700 mg/kg.[33,38] (Note: At this dose immediate irritation was noted. Complete necrosis, sloughing and scar formation followed. The rabbit died after 72 hr.)
6. Dermal Rabbit LD_{50} is greater than 5 gm/kg.[39]
7. Severe irritant to Rabbit dermally after 24 hrs. when applied full strength.[33,39]
8. Subcutaneous Rabbit LDLo is 1000 mg/kg.[33,36]
9. Subcutaneous Frog LDLo is 75 mg/kg.[33,36]

SUBCHRONIC AND CHRONIC:

OTHER HAZARDS AND OBSERVATIONS:

1. A maximization test (sensitization) was carried out on 31 human volunteers at 4% in petrolatum. No sensitization reactions were noted.[40]
2. Carvacrol applied to the intact shaved abdominal skin of the mouse was not absorbed within 2 hr.[39]
3. Carvacrol exhibited papaverine like antispasmodic action on the isolated small intestine of the mouse.[39]
4. Carvacrol exhibited moderate cytotoxic effects in HeLa cells.[39]
5. Carvacrol was given GRAS status by FEMA in 1965 and is approved for Food use by the FDA. 21CFR 172.515.[39]

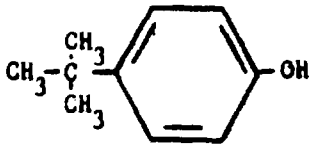
HEALTH ASSESSMENT: The chemical is a severe irritant to the skin of rabbits. It is not a human sensitizer. No long term toxicity was found. However, the chemical is on the GRAS list (FEMA) and is approved for food use by the FDA. At levels of 0.5 ppb, steady state, it is not expected that this chemical would pose a health hazard.

14. 4-tert-butylphenol

CAS 98-54-4
NIOSH SJ8925000

SYNONYMS: p-tert-butylphenol; 4-(1,1-dimethylethyl) phenol; 1-hydroxy-4-tert-butylbenzene

STRUCTURAL FORMULA:



TOXICITY:

ACUTE:

1. Oral Rat LD_{50} is 5660 mg/kg.[23,33]
2. Oral Mammal LD_{50} is 1500 mg/kg.[42]
3. Dermal Rabbit LD_{50} is 2520 mg/kg.[33,41]
4. Dermal Mammal LD_{50} is 1580 mg/kg.[42]
5. Intraperitoneal Mouse LD_{50} is 78 mg/kg.[8]
6. Applied full strength to intact or abraided rabbit skin for 24 hr. under occlusion the chemical was irritating.[43]
7. The chemical is a severe eye irritant to rabbits at 454 mg.[23,33]
8. The chemical is a severe eye irritant when administered for 24 hrs. at 50 ug.[33,44]
9. One drop of a 23% solution of p-tert-butylphenol in oil was applied to a shaved interscapular region of mice for a period of 12-17 min. Convulsions followed, and all mice died after 55-180 minutes. Guinea pigs exhibited dermatitis followed by an increase of pigmentation of the skin when treated similarly. Dogs after an intramuscular dose of 7.5 mg of a 0.5% solution of p-tert-butylphenol exhibited decolorization of the hair.[46]

10. In a 5 minute bacterial (Photobacterium phosphoreum) EC_{50} assay, p-t-butylphenol reduced to 50% the light output of the bacterium at a concentration of 0.21 mg/liter.[47] (The toxic end-point of this assay is the 50% reduction in luminescence of the bacterium).

SUBCHRONIC AND CHRONIC:

1. Several cases of contact leukoderma were reported from 2 factories in Spain where the etiological agent was p-tert-butylphenol.[48]
2. Vitiligo was detected in 54 of 198 men exposed to p-tert-butylphenol during its manufacture. Screening for other possible associated disorders revealed mildly abnormal liver-function tests in 6 workers, liver biopsy confirmed liver damage.[49]
3. Guinea pigs treated dermally for 3 weeks with a 5% solution of p-t-butylphenol exhibited mild toxicity and when treated with a 10% solution exhibited severe toxicity.[50]
4. Fifteen (15) 6 week old male Syrian golden hamsters were fed a diet containing 1.5% p-tert-butylphenol for 20 weeks. The chemical strongly induced hyperplasia and tumorous lesions in the forestomach.[51]

5. The evaluation of the prevention of benzo(a)pyrene forestomach tumor induction in mice was evaluated by feeding 0.03 mmol/gm of 4-tert-butylphenol and measuring T/C. The T/C was 60, where T/C is the ratio between the number of mice with tumor in treated animals (T) divided by controls (C).[34]

OTHER HAZARDS AND OBSERVATIONS:

1. A maximization test was carried out on 25 human volunteers applying the chemical at 1% in petrolatum. No sentization was observed.[43]
2. The chemical did not induce mutations in the Ames Test, with or without microsomal oxidation, did not induce gene conversion in yeast or chromosome damage in RL_4 cells.[45]

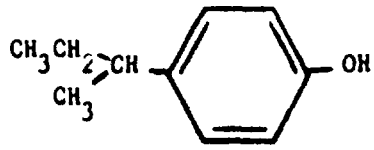
HEALTH ASSESSMENT: The chemical is a skin and severe eye irritant to rabbits. Dermally (23% solution) it was lethal to mice. Leukoderma and Vitiligo were reported in humans exposed to the chemical during its manufacture or formulation. The chemical is toxic orally to hamsters but at high doses. The chemical is not a human sensitizer and is not a mutagen. Long term data are lacking but it would be expected that the chemical would not be a health hazard at a steady state level of 0.5 ppb.

15. p-sec-butylphenol

CAS 99-71-8
NIOSH SJ8924000

SYNONYMS: 4-sec-butylphenol; 4-(1-methylpropyl) phenol

STRUCTURAL FORMULA:



TOXICITY:

ACUTE:
1. Intraperitoneal Mouse LD_{50} is 66 mg/kg.[8,9]
2. Intravenous Mouse LD_{50} is 40-60 mg/kg.[9]
3. Moderately toxic via the oral route.[33]

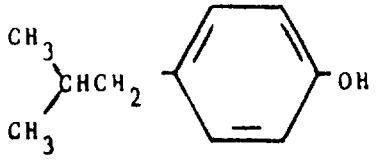
SUBCHRONIC AND CHRONIC:

OTHER HAZARDS AND OBSERVATIONS:

16. p-isobutylphenol

CAS 4167-74-2
NIOSH

SYNONYMS: 4-isobutylphenol; 4-(2-methylpropyl)phenol

STRUCTURAL FORMULA: 

TOXICITY: No Citations Found

ACUTE:

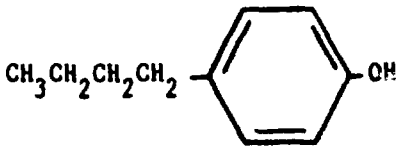
SUBCHRONIC AND CHRONIC:

OTHER HAZARDS AND OBSERVATIONS:

17. p-butylphenol

CAS 1638-22-8
NIOSH SJ8922500

SYNONYMS: 4-n-butylphenol

STRUCTURAL FORMULA: 

TOXICITY:

ACUTE:

SUBCHRONIC AND CHRONIC:

1. The Dermal TDLo to mice was 3840 mg/kg when the chemical was administered for 12 weeks intermittantly.[22]

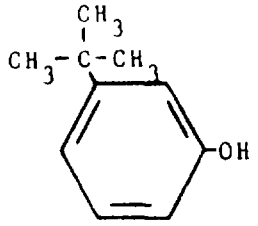
OTHER HAZARDS AND OBSERVATIONS:

18. m-tert-butylphenol

CAS 585-34-2
NIOSH

SYNONYMS: 3-(1,1-dimethylethyl)phenol;
3-hydroxy-1-tert-butylbenzene

STRUCTURAL FORMULA:



TOXICITY: No Citations Found

ACUTE:

SUBCHRONIC AND CHRONIC:

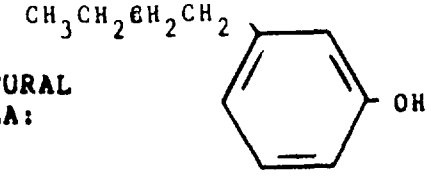
OTHER HAZARDS AND OBSERVATIONS:

19. m-butylphenol

CAS 4074-43-5
NIOSH

SYNONYMS: 3-butylphenol

STRUCTURAL FORMULA:



TOXICITY: No Citations Found

ACUTE:

SUBCHRONIC AND CHRONIC:

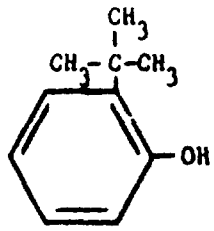
OTHER HAZARDS AND OBSERVATIONS:

20. o-tert-butylphenol

CAS 88-18-6
NIOSH

SYNONYMS: 2-(1,1-dimethylethyl)phenol; 2-tert-butylphenol.

STRUCTURAL FORMULA:



TOXICITY:

ACUTE: 1. The effect of the chemical on pulmonary toxicity was measured by intraperitoneal administration to mice at a dose of 2.27 mmol/kg. At sacrifice after 4 days, no significant signs of toxic effects were noted.[11]

SUBCHRONIC AND CHRONIC: 1. The prevention of benzo(a)pyrene forestomach tumor induction in mice was evaluated by feeding 0.03 mmol/gm o-t-butylphenol and measuring T/C. T/C was 60, where T/C is the ratio between the number of mice with tumor in treated animals (T) divided by controls(C).[34] The chemical, by comparison, did inhibit benzo(a)pyrene-induced neoplasia.

OTHER HAZARDS AND OBSERVATIONS:

1. The chemical was a moderate inhibitor of sheep vesicular gland prostaglandin cyclooxygenase with an I_{50} of 56 as compared to the potent inhibitor 2,4,6-trimethylphenol (I_{50} = 7uM).[52]
2. The chemical was administered at 42 nmol/kg of diet to female mice to evaluate its effect on its ability to induce in vivo changes in hepatic monooxygenase and detoxication enzyme activities, and to act as monooxygenase inhibitors when added in vitro. The chemical did not induce cytochrome P-450 or monoxygenase activity, but increased GSH transferase activity 2 fold.[53]

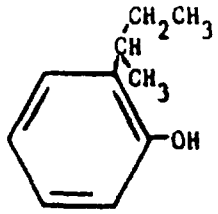
HEALTH ASSESSMENT: Long term studies are not available. The chemical had no acute effects on the lung, is a prostaglandin monooxygenase inhibitor, and does induce detoxifying enzymes in mice. It somewhat prevents benzo(a)pyrene forestomach tumor induction in mice. The data is very limited, but even so, it would not be expected that at a steady state level of 0.5 ppb the chemical would pose a health hazard.

21. o-sec-butylphenol

CAS 89-72-5
NIOSH

SYNONYMS: 2-sec-butylphenol, 2-(1-methylpropyl)phenol

STRUCTURAL FORMULA:



TOXICITY:

ACUTE:

1. The Oral Rat LD_{50} is 2700 mg/kg.[33,45]
2. The Intravenous Mouse LD_{50} is 60-80 mg/kg.[8,9,33]
3. The chemical was severely irritating dermally to the rabbit at 500 mg/kg after 24 hrs.[33,44]
4. The chemical was severely irritating to the eye of the rabbit at 50 ug after 24 hrs.[33,44]

SUBCHRONIC AND CHRONIC:

OTHER HAZARDS AND OBSERVATIONS:

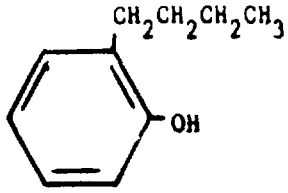
1. The chemical was a moderate inhibitor of sheep vesicular gland prostaglandin cyclooxygenase with an I_{50} of 52 as compared to the potent inhibitor 2,4,6-trimethylphenol (I_{50} = 7uM).[52]
2. The chemical was negative in the Salmonella typhimuirium assay both with and without microsomal activation.[17]

22. o-butylphenol

CAS 3180-09-4
NIOSH SJ8922500

SYNONYMS: 2-n-butylphenol

STRUCTURAL FORMULA:



TOXICITY:

ACUTE:

SUBCHRONIC AND CHRONIC:

1. The Dermal Mouse TDLo was 3840 mg/kg when administered for 12 weeks intermittantly.[22]

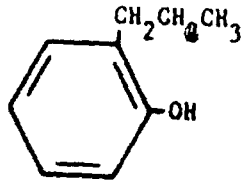
OTHER HAZARDS AND OBSERVATIONS:

23. 2-propylphenol

CAS 644-35-9
NIOSH SM8600000

SYNONYMS: o-propyphenol

STRUCTURAL FORMULA:



TOXICITY:

ACUTE:

1. Oral Rat LD_{50} is approximately 500-514 mg/kg.[33,54,67]
2. The chemical is cited by Aldrich to be toxic and irritating.[55]

SUBCHRONIC AND CHRONIC:

1. The chemical administered in chronic, subacute doses to rats decreased erythrocyte number and hemoglobin, and also impaired the functional activity of the liver (slightly) and thyroid gland.[56]
2. Oral administration of 1/5 LD_{50} to rats, 6 times a week for 60 days, had little or no effect upon liver polygonal cells and no effect on liver enzymes in the hyaloplasm.[57]
3. Oral administration of 0.2, 2 or 20 mg/kg to rats daily for 6 months produced dose dependent histological and histochemical changes in the liver, kidneys, spleen, thymus and adrenals. Adverse effects were also observed on the immune system.[54]

OTHER HAZARDS AND OBSERVATIONS:

4. The chemical was a moderate inhibitor of sheep vesicular gland prostaglandin cyclooxygenase with an I_{50} of 71 as compared to the potent inhibitor 2,4-6-trimethylphenol (I_{50} = 7uM).[52]

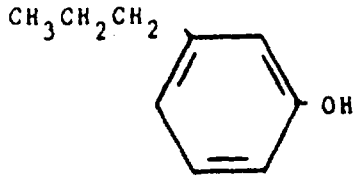
HEALTH ASSESSMENT: Subchronic oral doses, at high levels, produced liver toxicity. The data is very limited; however, the levels used which produced the toxicity were higher than would be encountered through exposure to a steady state level of 0.5 ppb. It is not expected that this chemical would be a health hazard.

24. 3-propylphenol

CAS 621-27-2
NIOSH

SYNONYMS: m-propylphenol

STRUCTURAL FORMULA:



TOXICITY: No Citations Found

ACUTE:

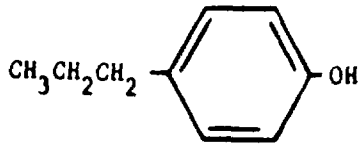
SUBCHRONIC AND CHRONIC:

OTHER HAZARDS AND OBSERVATIONS:

25. 4-propylphenol

CAS 645-56-7
NIOSH SM8610000

SYNONYMS:

STRUCTURAL FORMULA: 

TOXICITY:

ACUTE:
1. Oral Rat LD_{50} is 500 mg/kg.[33,54]
2. The chemical is cited by Aldrich to be toxic and irritating.[55]

SUBCHRONIC AND CHRONIC:
1. The chemical administered in chronic, subacute doses, to rats decreased erythrocyte number and hemoglobin and also impaired the functional activity of the liver and thyroid gland.[56]
2. Oral administration of 1/5 LD_{50} to rats, 6 times a week for 60 days, inhibited the functioning of the liver polygonal cells but had no effect on the liver enzymes in the hyaloplasm.[57]
3. Oral administration of 0.2, 2 or 20 mg/kg to rats daily for 6 months produced dose dependent histological and histochemical changes in the liver, kidneys, spleen, thymus and adrenals. Adverse effects were also noted on the immunological system.[54]

OTHER HAZARDS
AND OBSERVATIONS:

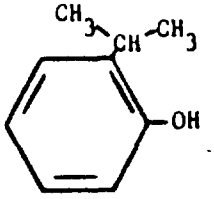
HEALTH ASSESSMENT: Subchronic oral doses, at high levels, produced liver toxicity. The data is very limited; however, the levels used which produced the toxicity were higher than would be encountered through exposure to a steady state level of 0.5 ppb. It is not expected that this chemical would be a health hazard.

26. 2-isopropylphenol

CAS 88-69-7
NIOSH SL5900000

SYNONYMS: o-isopropylphenol, 2-(1-methylethyl)phenol; o-cumenol

STRUCTURAL FORMULA:



TOXICITY:

ACUTE:
1. The Intravenous Mouse LD_{50} is 100-120 mg/kg.[9]
2. Listed by Aldrich as toxic.[55]

SUBCHRONIC AND CHRONIC:

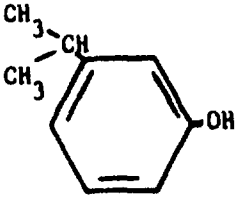
OTHER HAZARDS AND OBSERVATIONS:

27. 3-isopropylphenol

CAS 618-45-1
NIOSH SL5800000

SYNONYMS: m-cumenol, m-isopropylphenol;
3-(1-methylethyl) phenol

STRUCTURAL FORMULA:



TOXICITY:

ACUTE: 1. Oral Mouse LD_{50} is 1630 mg/kg.[58]

SUBCHRONIC AND CHRONIC:

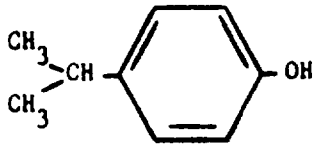
OTHER HAZARDS AND OBSERVATIONS:

28. 4-isopropylphenol

CAS 99-89-8
NIOSH SL5950000

SYNONYMS: p-isopropylphenol

STRUCTURAL FORMULA:



TOXICITY:

ACUTE:
1. Oral Mouse LD_{50} is 875 mg/kg.[33,58]
2. Intraperitoneal Mouse LD_{50} is 250 mg/kg.[33,59]
3. Intravenous Mouse, LD_{50} is 40-60 mg/kg.[9,33]

SUBCHRONIC AND CHRONIC:

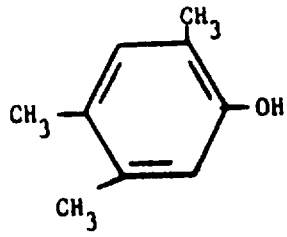
OTHER HAZARDS AND OBSERVATIONS:

29. 2,4,5-trimethylphenol

CAS 496-78-6
NIOSH

SYNONYMS:

STRUCTURAL FORMULA:



TOXICITY:

ACUTE:

SUBCHRONIC AND CHRONIC:

OTHER HAZARDS AND OBSERVATIONS:

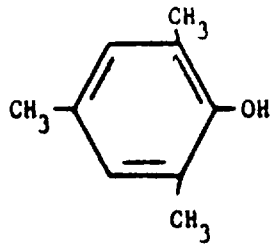
1. Tested quantitatively against Salmonella typhimuirium (TA98) and was negative as a mutagen but was toxic at 30 umol/plate.[19]
2. Toxic to Ascites sarcoma BP8 cells in vitro, 88% at 1 mM.[4] (This test is an immunological cytotoxic test system measuring inhibition of cell growth by chemicals.)

30. 2,4,6-trimethylphenol

CAS 527-60-6
NIOSH

SYNONYMS: Mesitol

STRUCTURAL FORMULA:



TOXICITY:

ACUTE:

1. The 24 hr. IC_{50} (Immobilization Concentration for 50% of daphnids) was found to be 0.20 mmol/liter.[2]
2. The effect of the chemical on pulmonary toxicity was measured by intraperitoneal administration to mice at a dose of 2.27 mmol/kg. At sacrifice after 4 days, significant decrease in body weight was noted but there was no effect on lung weight.[11]

SUBCHRONIC AND CHRONIC:

1. Ten Male Sprague-Dawley rats were administered 5.44 mmol/100g of feed for 3 weeks. The chemical did not induce hemorrhaging.[60]

OTHER HAZARDS AND OBSERVATIONS:

1. The chemical was highly inhibitory to sheep vesicular gland prostaglandin cyclooxygenase with an I_{50} of 7 uM. Inhibition of arachidonate induced platelet aggregation was greater than for

indomethacin when assayed using a 2 min preincubation of inhibitor with platelets.[52]

2. The chemical was tested against female Albino guinea pigs in the Guinea pig Maximization Test and was found to be a weak sensitizer.[16]
3. Tested quantitatively against Salmonella typhimuirium (TA98) and was negative as a mutagen but was toxic at 30 umol/plate.[19]
4. Toxic to Ascites sarcoma BP8 cells in vitro, 81% at 1 mM.[4] (This test is an immunological cytotoxic test system measuring inhibition of cell growth by chemicals.)

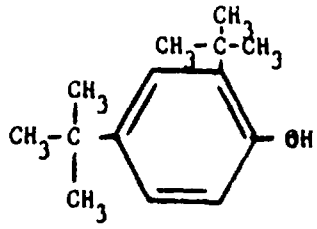
HEALTH ASSESSMENT: There was no long term data found. Oral feeding to rats did not result in hemorrhaging. The chemical was highly inhibitory to prostaglandin cyclooxygenase and was also shown not to be a mutagen. The data is very limited but from the levels evaluated it is not expected that the chemical will be a health hazard at a steady state level of 0.5 ppb.

31. 2,4-di-tert-butylphenol

CAS 96-76-4
NIOSH SK8260000

SYNONYMS: 2,4-bis(1,1-dimethylethyl) phenol

STRUCTURAL FORMULA:



TOXICITY:

ACUTE:

1. Intraperitoneal Mouse LD_{50} is 25 mg/kg.[26,33]
2. Intravenous Mouse LD_{50} is 100-120 mg/kg.[9,33]
3. Effect of the chemical on pulmonary toxicity was measured by intraperitoneal administration to mice at 2.27 mmol/kg. The chemical had no effect on body weight or lung weights at sacrifice after 4 days dosing.[11]

SUBCHRONIC AND CHRONIC:

OTHER HAZARDS AND OBSERVATIONS:

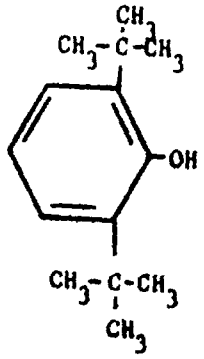
1. Five week-old female rats were administered the chemical in the diet at 0.5% for 6 days. Significant enlargement of the liver, a significant increase in cytochrome P-450 and significant increases in monooxygenase activities were noted.[61]

32. 2,6-di-tert-butylphenol

CAS 128-39-2
NIOSH SK8265000

SYNONYMS:

STRUCTURAL FORMULA:



TOXICITY:

ACUTE:

1. Oral Mouse LD_{50} is 120 mg/kg.[63]
2. Intravenous Mouse LD_{50} is 120 mg/kg.[9]
3. The effect of the chemical on pulmonary toxicity was measured by intraperitoneal administration to mice at a dose of 2.27 mmol/kg. At sacrifice after 4 days, no significant signs of toxic effects were noted.[11]

SUBCHRONIC AND CHRONIC:

1. The evaluation of the prevention of benzo(a)pyrene forestomach tumor induction in mice was evaluated by feeding 0.03 mmol/gm of 2,6-di-tert-butylphenol and measuring T/C. The T/C was 52, where T/C is the ratio between the number of mice with tumors in treated animals (T) divided by the controls (C).[34]
2. Ten Male Sprague Dawley rats were administered 5.44 mmol/100g of feed for 3 weeks. Two animals died. Hemorrhages in the epididymus, muscle, thymus, pleural

cavity, cranial cavity, and submaxillary lymph node were noted, and intragastric blood pooling was also noted.[60]

3. Hepatotoxicity of the chemical was evaluated by oral administration of 3.18 mmol/kg to mice in combination with two doses of buthionine sulfoximine (a Glutathione inhibitor). No evidence of hepatotoxicity was noted by measurement of Serum Glutamic Pyruvic Transaminase or liver calcium.[62]

OTHER HAZARDS AND OBSERVATIONS:

1. The chemical did not induce mutations in the Ames Test, with or without microsomal oxidation, did not induce gene conversion in yeast or chromosome damage in RL_4 cells.[45]
2. The chemical was administered at 42 nmol/kg of diet to female mice to evaluate its effect on its ability to induce in vivo changes in hepatic monooxygenase and detoxication enzyme activities and to act as monooxygenase inhibitors when added in vitro. The chemical caused a marked increase in liver weight, doubled cytochrome P-450 levels, induced a 5 fold increase in hepatic glutathione transferase activity and was found to be a relatively moderate protector.[53]

4. The chemical markedly increased the activity of cholinesterase in the blood of rats and mice at 1/3 the LD_{50}. In in vitro studies the chemical stimulated the activity of cholinesterase.[63]
5. The ability to induce drug metabolizing enzymes was evaluated in rats at 150 mg/kg/day for 7 days. The chemical had no effect on liver weight or enzyme activities.[65]

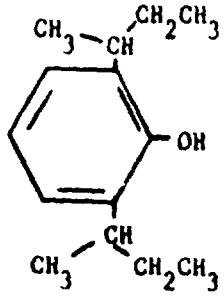
HEALTH ASSESSMENT: No evidence of hepatotoxicity was found in oral administration to mice. Short term administration to rats resulted in mortality and toxic effects. The chemical when fed to mice does markedly induce detoxifying enzymes. The chemical was not a mutagen. The chemical at 0.5 ppb steady state would not be expected to be a health hazard.

33. 2,6-di-sec-butylphenol

CAS 5510-99-6
NIOSH

SYNONYMS:

STRUCTURAL FORMULA:



TOXICITY:

ACUTE:

1. The Oral Rat LD_{50} is 1320 mg/kg.[33,44]
2. The Intraperitoneal Mouse LD_{50} is 25 mg/kg.[26]
3. The Intravenous Mouse LD_{50} is 60 mg/kg.[9,33]
4. The chemical is a severe skin irritant when applied to the rabbit for 24 hours.[44]
5. The chemical is a severe eye irritant when applied to the rabbit eye at 50 ug for 24 hours.[33,44]
6. The effect of the chemical on pulmonary toxicity was measured by intraperitoneal administion to mice at a dose of 2.27 mmol/kg. At sacrifice after 4 days, no significant signs of toxic effects were noted.[11]

SUBCHRONIC AND CHRONIC:

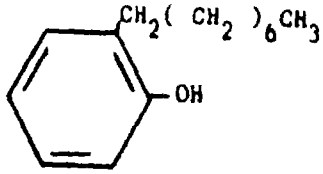
OTHER HAZARDS AND OBSERVATIONS:

34. o-octylphenol

CAS 949-13-3
NIOSH

SYNONYMS:

STRUCTURAL FORMULA:



TOXICITY:

ACUTE: 1. No toxicity data was found on the ortho derivative. However, Rohm and Haas reports that-"there is no acute oral LD_{50} for octyl phenol." Further-"octyl phenol in a neat or diluted state is a severe, rapid acting irritant to the eyes of rabbits. Octyl phenol has an extremely low vapor pressure at room temperature, therefore, the likelihood of toxic effects by inhalation is remote. No chronic inhalation studies have been carried out." It should be noted that the octyl phenol supplied by Rohm and Haas is 90% monosubstituted, of which 98% is the para-isomer with the remainder being the ortho-isomer.[64]

SUBCHRONIC AND CHRONIC:

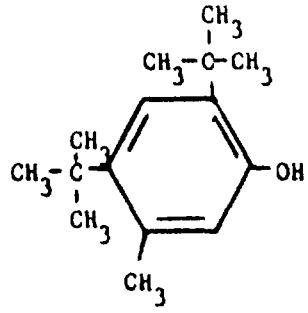
OTHER HAZARDS
AND OBSERVATIONS:

35. 2,4-di-tert-butyl-5-methylphenol

CAS 497-39-2
NIOSH

SYNONYMS: 2,4-bis(1,1-dimethylethyl)-5-methylphenol

STRUCTURAL FORMULA:



TOXICITY:

ACUTE:

1. Oral Mouse LD_{50} is 1420 mg/kg.[33,38]
2. Not significantly irritating to rabbit skin at 4.5 gm/kg after 24 hrs.[38]
3. The chemical was "dangerously" irritating to the mucous surface of the rabbit eye at 40% in ethylene glycol after 72 hrs.[38]

SUBCHRONIC AND CHRONIC:

OTHER HAZARDS AND OBSERVATIONS:

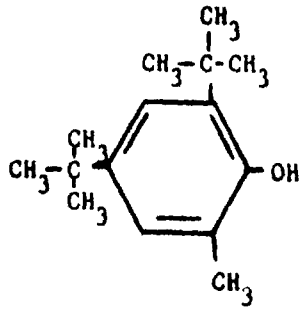
1. The ability to induce drug metabolizing enzymes was evaluated in rats at 150 mg/kg/day for 7 days. The chemical significantly increased the concentration of aminopyrine demethylase activity.[65]

36. 2,4-di-tert-butyl-6-methylphenol

CAS 616-55-7
NIOSH

SYNONYMS:

STRUCTURAL FORMULA:



TOXICITY:

ACUTE:

SUBCHRONIC AND CHRONIC:

OTHER HAZARDS AND OBSERVATIONS:

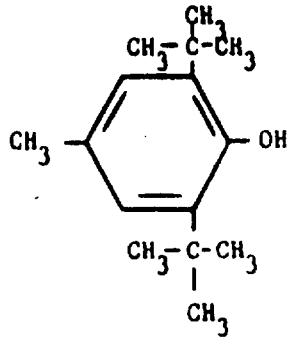
1. The ability to induce drug metabolizing enzymes was evaluated in rats at 150 mg/kg/day for 7 days. The chemical significantly increased liver weight and aminopyrine demethylase activity.[65]

37. 2,6-di-tert-butyl-4-methylphenol

CAS 128-37-0
NIOSH GO7875000

SYNONYMS: Butylated hydroxytoluene; 2,6-di-tert-butyl-p-creosol; 2,6-di-tert-butyl-1-hydroxy-4-methylbenzene; 4-methyl-2,6-di-tert-butylphenol; 4-hydroxy-3,5-di-tert-butyltoluene

STRUCTURAL FORMULA:



TOXICITY:

ACUTE:

1. Oral Rat LD_{50} is 890 mg/kg.[33,68] (Also reported to be 1700 mg/kg for female rats and 2000 mg/kg for male rats.[72])
2. Oral Mouse LD_{50} is 1040 mg/kg.[33,38] (Also reported to be 2400 mg/kg for male mice.[73])
3. Oral Cat LD_{50} is 940 mg/kg.[33,69]
4. Oral Rabbit LD_{50} is 2100 mg/kg.[33,69]
5. Oral Guinea Pig LD_{50} is 10,700 mg/kg.[33,69]
6. Intraperitoneal Mouse LDLo is 250 mg/kg.[70]
7. The chemical was moderately irritating to rabbit skin at 500 mg after 48 hrs.[33,71]
8. The chemical was severely irritating to the eye of the rabbit at 100 mg after 24 hr.[33,44]
9. The chemical is a mild human skin irritant at 500 mg after 48 hrs.[33,71]
10. Maximum acceptable daily intake for man is 0.0 to 0.5 mg/kg.[72]

SUBCHRONIC AND CHRONIC:

1. Rats were administered the chemical at 0.05 to 1.35% in the diet for 110 days. Weight gain was inhibited in groups receiving the 1.35% concentration. Increases in liver weights and thyroid gland and histological changes in kidney and liver appeared concentration dependent.[73]
2. Administration of 0.0125 to 0.8% of the chemical in the diet to rats for 25 weeks produced dose-dependent increases in the liver and caused some histological changes in the liver and kidney.[75]
3. The chemical was administered to rats by gavage at doses of 0, 25, 250, or 500 mg/kg/day for up to 28 days and also at daily doses of 1000 and 1250 mg/kg for up to 4 days (sublethal dose). The sublethal dose induced centrilobular necrosis within 48 hr., whereas after 7 to 28 days for the other doses, in a dose related fashion, hepatomegaly and at the highest dose progressive periportal hepatocyte necrosis were noted. The persistent and active nature of the lesions in rats dosed with 500 mg/kg for 28 days combined with evidence of cell damage at doses equivalent to those associated with

hepatic tumors (250 mg/kg) suggests that chronic liver cell damage may be involved in their etiology. There is no evidence that the chemical causes liver damage at a dose level of 25 mg/kg/day. This is several hundred times higher than normal human intake.[79]

4. No increase in relative liver size and only moderate proliferation of the smooth endoplasmic reticulum of infant and juvenile monkeys was observed when the chemical was administered at 500 mg/kg/day for 1 month.[83]
5. Male and female mice were administered 0, 5, 10, 20 or 30 mg of the chemical in DMSO topically 3 times weekly for 4 weeks. Between the 4th and 8th day respiratory distress with mortality was noted. At autopsy, congestion and enlargement of the lung were found. Effects were more pronounced in female mice. No pulmonary alterations were observed in Syrian golden hamsters or rats exposed to the chemical by dermal application 3 times weekly for 4 weeks at a dose of 480 mg in hamsters or 240 mg in rats.[86]
6. Rats were administered the chemical intraperitoneally at 640 and 1024 mg/kg once daily for 7 days. Mean body weights were all lower than controls after 7 days. Plasma prothrombin indexes were depressed. Congestion and edema were observed.[87]

7. Groups of 57 male and female Wistar rats were fed 0.25 or 1% of the chemical in the diet for 104 weeks. Treated rats of both sexes exhibited reduced body weight gain, relative spleen weight and white blood cell count while in males there was also a reduction in serum triglyceride. No significant histological changes were noted in the liver or haematopoietic system to explain the observed increased relative liver weight and total blood cholesterol in both sexes. Tumors were found in the liver, pancreas, mammary glands, uterus, pituitary gland and adrenal glands but the incidence was not different from controls. No carcinogenic effect of the chemical was observed.[76]
8. Rats and mice were fed the chemical in the diet at either 3000 or 6000 ppm for 105 weeks (rats) or 107 to 108 weeks (mice). Alveolar carcinomas or adenomas occurred in female mice in the low dose group. No significant tumor incidence was noted in either male or female rats over controls. The chemical was concluded not to be carcinogenic.[77]
9. Mice received intraperitoneal injections of the chemical for 8 weeks and were sacrificed at 24 weeks after the first injection. At a total dose of 6 gm/mouse the chemical was not considered to be carcinogenic.[74]

10. Mice were orally administered the chemical at 1% and 2% in the diet of $B6C3F_1$ mice for 104 weeks. In male mice administered the chemical the incidence of either a hepatocellular adenoma or a focus of cellular alteration in the liver increased with dose. It was concluded that the chemical was tumorigenic in the liver of $B6C3F_1$ male mice.[78]
11. The chemical enhanced the effect on mouse lung tumor development when administered with urethan or 3-methylcholanthrene.[80]
12. The hepatotoxicity of rats fed 2-acetylaminofluorene was greatly inhibited when the diet was supplemented with 0.5% of the chemical.[81]
13. The chemical inhibited in a dose dependent manner the hepatocarcinogenesis of concurrently fed N-2-fluorenylacetamide.[82]

OTHER HAZARDS AND OBSERVATIONS:

1. The chemical was nonmutagenic when tested against male and female rats and mice in Salmonella and mammalian cell assays.[84,85]
2. Pregnant mice were fed the chemical in the diet at 0.5% (w/w) throughout pregnancy. Effects on cholinesterase and isoenzymes were noted in the brains of newborns. There were behavioral effects noted over controls at 30 days of age: sleep,

aggression, exploratory retiex and a reduction in weight. The TDLo was given as 12,600 mg/kg.[91]

3. The chemical was fed to mice at 0.1 and 0.5% in the diet throughout pregnancy. At 0.1% of the diet the chemical had no effect on the reproductive capacity of the mice.[92]
4. The chemical was administered at 500 mg/kg body weight/day in the diet of F_0 male and female rats from 6 weeks of age until weaning of the F_1 (12 week growth, gestation period and lactation period). This way the F_1 animals were dosed via the placenta, milk and diet to 21 days of age. Decreased weight gain in both F_0 and F_1 were noted. Effects on F_1 occurred mainly during the lactation period; visual and auditory, locomotor coordination and some developmental effects were noted.[93]
5. The effects of the chemical were examined in rats fed the chemical throughout their development at levels of 0, 0.125, 0.25 or 0.5% (w/w) in the diet. The chemical at 0.5% reduced the body weights of dams and offspring during early development and increased offspring mortality. Eyelid opening, surface-righting and limb-coordination in swimming in males were among the neurobehavioural characteristics affected[88] The LDLo was reported to be 18 gm/kg in this study.[33]

6. The chemical was identified in cord blood of an infant with a lumbosacral meningomyelocele.[89]

HEALTH ASSESSMENT: The chemical is acutely not very toxic but is moderately irritating to the skin and severely irritating to the eye of the rabbit and is also a human skin irritant. The maximum acceptable daily intake for humans is 0.0 to 0.5 mg/kg. Subchronic studies in mice and rats exhibited liver toxicity and possible tumor formation. At dose levels of 25 mg/kg/day for 28 days, no liver damage was noted. This level is several hundred times higher than would normally be ingested. In monkeys no severe liver toxicity was observed when administered 500 mg/kg/day for 30 days. While toxicity was observed in the mice, the chemical was not found to be carcinogenic when administered to mice at 0.25 or 1% of the diet for 104 wks or intraperitoneally for a total dose of 6 gm/mouse. Yet, in another chronic study the chemical was found to be carcinogenic in the liver of male mice at a dose of 2% of the diet. In reproduction studies in rats and mice, effects on offspring were noted but only at very high doses. Therefore, based upon the data and the fact that the ADI is 0.5 mg/kg, at a level of 0.5 ppb, steady state, the chemical would not be expected to be a health hazard.

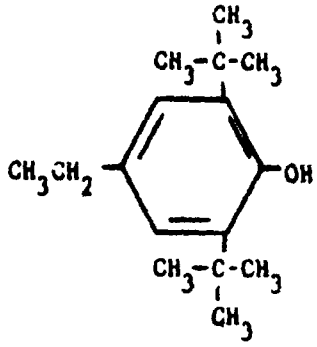
38. 2,6-di-tert-butyl-4-ethylphenol

CAS 4130-41-1

NIOSH

SYNONYMS:

STRUCTURAL FORMULA:



TOXICITY:

ACUTE:

SUBCHRONIC AND CHRONIC:

OTHER HAZARDS AND OBSERVATIONS:

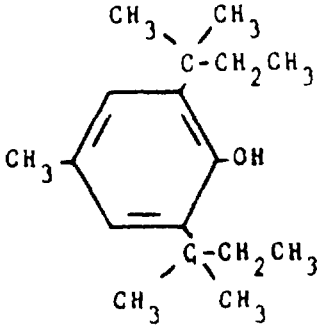
1. Hepatotoxicity of the chemical was evaluated by oral administration of 3.18 mmol/kg to mice in combination with two doses of buthionine sulfoximine (a glutathione inhibitor). Marked increases in both Serum Glutamic Pyruvic Transaminase and liver calcium are noted. The chemical causes liver injury but does not cause lung toxicity.[62]
2. The ability to induce drug metabolizing enzymes was evaluated in rats at 150 mg/kg/day for 7 days. The chemical significantly increased liver weight, the activity of hexobarbitone oxidase and aminopyrine demethylase activity.[65]

39. 2,6-bis(1,1-dimethylpropyl)-4-methylphenol

CAS 56103-67-4
NIOSH

SYNONYMS:

STRUCTURAL FORMULA:



TOXICITY: No Citations Found

ACUTE:

SUBCHRONIC AND CHRONIC:

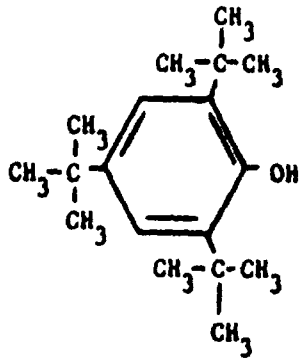
OTHER HAZARDS AND OBSERVATIONS:

40. 2,4,6-tri-tert-butylphenol

CAS 732-26-3
NIOSH

SYNONYMS: 2,4,6-tris(1,1-dimethylethyl)phenol

STRUCTURAL FORMULA:



TOXICITY:

ACUTE:

1. The effect of the chemical on pulmonary toxicity was measured by intraperitoneal administration to mice at a dose of 2.27 mmol/kg. At sacrifice after 4 days, no significant signs of toxic effects were noted.[11]

SUBCHRONIC AND CHRONIC:

1. The evaluation of the prevention of benzo(a)pyrene forestomach tumor induction in mice was evaluated by feeding 0.03 mmol/gm of the chemical and measuring T/C. The T/C was 123, where T/C is the ratio between the number of mice with tumors in treated animals (T) divided by the controls (C).[34]
2. Ten Male Sprague Dawley rats were administered 5.44. mmol/100gm of feed for 3 weeks. No deaths, and no hemorrhagic effects were noted.[60]

OTHER HAZARDS AND OBSERVATIONS:

1. Hepatotoxicity of the chemical was evaluated by oral administration of 3.18 mmol/kg to mice in combination with two doses of buthionine sulfoximine (a glutathione inhibitor). No evidence of hepatotoxicity was noted by measurement of Serum Glutamic Pyruvic Transaminase or liver calcium.[62]
2. The toxicity of the chemical was evaluated on rabbits, rats and guinea pigs. The chemical was found to be able to penetrate intact skin and caused minor changes in the activity of the nervous system along with changes in the kidneys and mucosa of the small intestine.[66]
3. Five week-old female rats were administered the chemical in the diet at 0.5% for 6 days. Significant enlargement of the liver and a significant increase in cytochrome P-450 were noted. A 10 fold increase in monooxygenase activities was noted.[61]

HEALTH ASSESSMENT: No mortality, toxic effects or hepatotoxicity were noted when the chemical was administered to rats or mice in short term studies. The chemical significantly induced detoxifying enzymes when administered to rats. The chemical would not be expected to be a health hazard at a steady state level of 0.5 ppb.

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APPENDIX 2

RESUME OF EUGENE BELLET, Ph.D

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ADDRESS: 7270 W. 98TH TERR., SUITE #100, OVERLAND PARK, KS 66212

AGE: 47 HEIGHT: 5'9" WEIGHT: 200

MARITAL STATUS: MARRIED NO. CHILDREN: 5

EDUCATION: UNIVERSITY OF CALIFORNIA, RIVERSIDE, CALIFORNIA

B.A.	1963	PHYSICS
M.S.	1969	ENTOMOLOGY
Ph.D.	1971	CHEMISTRY-TOXICOLOGY

MAJOR SUBJECTS:

ENTOMOLOGY - TOXICOLOGY, PHYSIOLOGY, BIOCHEMISTRY, ECOLOGY

CHEMISTRY - CHEMISTRY UP TO AND INCLUDING ADVANCED ORGANIC SYNTHESIS, ADVANCED ORGANOPHOSPHORUS CHEMISTRY

MATHEMATICS - UP TO AND INCLUDING MATRIX THEORY AND LINEAR ALGEBRA

PHYSICS - 27 UNITS OF GRADUATE PHYSICS, INCLUDING NUCLEAR PHYSICS, PARTICLE PHYSICS AND QUANTUM MECHANICS

SUPPORT: RECIPIENT OF ENVIRONMENTAL SCIENCES FELLOWSHIP 1967-1971

DOCTORAL THESIS: SYNTHESIS AND MODE OF ACTION OF O-(DIETHYL PHOSPHORYL) ACETOPHENONE OXIMES AND RELATED PHOSPHORAMIDATES.

WORK EXPERIENCE:

1981-PRESENT CHEMICAL CONSULTANTS INTERNATIONAL, INC.

EPA RESPONSIBILITIES INCLUDE PREPARATION OF PROTOCOLS FOR AND MONITORING OF TOXICOLOGY, ENVIRONMENTAL FATE, RESIDUE STUDIES AND ANALYTICAL METHODS TO SUPPORT TOLERANCES, NEW PRODUCTS, DATA CALL-INS. REPRESENT CLIENTS ON VARIOUS TASK FORCES. PARTICIPATION IN NEW PRODUCT DEVELOPMENT. LICENSING AND ACQUISITION OF NEW PRODUCTS.

FDA RESPONSIBILITIES INCLUDE EVALUATION AND DEVELOPMENT OF PRECLINICAL AND CLINICAL PROTOCOLS, FULL REPORTS AND SUMMARIES FOR IND's, NDA's, AND ANDA's. EVALUATION AND PREPARATION OF DRUG MASTER FILES. MONITORING CLINICAL STUDIES. PARTICIPATION IN NEW PRODUCT DEVELOPMENT PLANNING. LICENSING AND ACQUISITION OF NEW PRODUCTS.

1978-1981 BECKLOFF ASSOCIATES

VICE PRESIDENT. RESPONSIBILITIES INCLUDED EVALUATION AND DEVELOPMENT OF IND's AND NDA's. EVALUATION AND PREPARATION OF DRUG MASTER FILES. PARTICIPATION IN NEW PRODUCT DEVELOPMENT TEAM MEETINGS. DEVELOPMENT OF EUP's AND TOLERANCE SUBMISSIONS FOR PESTICIDES.

1976-1978 KALO AGRICULTURAL CHEMICALS

DIRECTOR, RESEARCH AND DEVELOPMENT. RESPONSIBLE FOR A RESEARCH GROUP OF EIGHTEEN. RESPONSIBILITIES INCLUDED DIRECTION OF FIELD GROUP; DIRECTION OF BIOLOGICAL AND CHEMICAL GROUPS; PLANNING, DEVELOPMENT AND COMPILATION OF DATA FOR VARIOUS EPA SUBMISSIONS; SEARCH FOR NEW PRODUCTS; EVALUATION OF PATENT POSSIBILITIES OF POTENTIAL NEW PRODUCTS; PROVIDED MARKETING AND SALES WITH RESEARCH SUPPORT; PROVIDED CHEMICAL PROCESS SUPPORT.

1974-1976 THE ANSUL COMPANY

MANAGER REGULATORY AFFAIRS. RESPONSIBLE FOR COORDINATING THE PLANNING OF RESEARCH, ORGANIZATION OF DATA, AND SUBMISSION OF DATA IN ORDER TO OBTAIN NEW LABELS, EXPERIMENTAL PERMITS, TOLERANCES, AND LABEL REVISIONS. RESPONSIBLE FOR THE DEFENSE OF EXISTING PRODUCTS.

ACCOMPLISHMENTS:

1. EXPERIMENTAL PERMIT AND TEMPORARY TOLERANCE FOR USE OF MONOSODIUM METHANEARSONATE ON SUGARCANE.
2. EXPERIMENTAL PERMIT FOR USE OF MONOSODIUM METHANEARSONATE ON WHEAT.
3. NUMEROUS LABEL CHANGES FOR TOBACCO SUCKERCIDES, ARSENICAL HERBICIDES.
4. FIRST APPROVED AERIAL APPLICATION OF DISODIUM METHANEARSONATE ON COTTON.
5. REVERSAL OF BAN ON ORGANOARSENICALS IN L.A. COUNTY.

1973-1974 ENVIRONMENTAL PROTECTION AGENCY

CHEMIST, CHEMISTRY BRANCH. DUTIES INCLUDED CREATING RESEARCH PROJECTS TO PROVIDE AGENCY WITH ANSWERS TO ENVIRONMENTAL QUESTIONS; WRITING CONTRACTS; REVIEWING RESEARCH PROPOSALS; EXPERIENCE IN REGISTRATION AND TOLERANCE PROCEDURES; FAMILIAR WITH GOVERNMENT REGULATIONS AS THEY RELATE TO CHEMICALS IN THE ENVIRONMENT; REVIEWING PETITIONS; DEVELOPED CONFIRMATORY METHODS FOR VARIOUS RESIDUE ANALYSES.

1971-1973 UNIVERSITY OF CALIFORNIA, BERKELEY, CA.

POSTDOCTORAL RESEARCH FELLOWSHIP UNDER DR. J.E. CASIDA. RESEARCH CENTERED AROUND ORGANOPHOSPHORUS COMPOUNDS AND OXIDATION REACTIONS. FAMILIARIZATION WITH VARIOUS TECHNIQUES IN METABOLISM AND TOXICOLOGY OF CHEMICALS. INVOLVED EXTENSIVE USE OF VARIOUS ANALYTICAL INSTRUMENTS.

SYNTHESIS OF NOVEL, EXTREMELY TOXIC MOLECULE AND ITS ANALOGS. INVESTIGATION OF MODE OF ACTION.

1965-1967 UNIVERSITY OF CALIFORNIA, RIVERSIDE, CA.

EMPLOYED ON THE STAFF OF THE ENTOMOLOGY DEPARTMENT AS A RESEARCH PHYSICIST. WORKED UNDER DR. WILLIAM E. WESTLAKE AND DR. FRANCIS A. GUNTHER DEVELOPING AND PERFECTING A MICRO-WAVE DETECTOR FOR USE IN THE RESIDUE ANALYSIS PROGRAM. PRACTICAL EXPERIENCE IN RESIDUE CHEMISTRY ACQUIRED.

1963-1965 EMPLOYED AS A BUBBLE CHAMBER ANALYST, BECAME EXPERIENCED WITH METHODS AND EQUIPMENT IN THE NUCLEAR PHYSICS PROGRAM.

PUBLICATIONS:

1. METHOD FOR OBTAINING THE EMISSION SPECTRA OF ORGANIC COMPOUNDS UTILIZING THE MICROWAVE EMISSION DETECTOR FOR GAS CHROMATOGRAPH. BULLETIN OF ENVIRONMENTAL CONTAMINATION AND TOXICOLOGY, VOL. 2, NO. 5, 1967.

2. THERMAL REARRANGEMENT OF SUBSTITUTED ACETOPHENONES O-(DIETHYL PHOSPHORYL) OXIMES AND SYNTHESIS AND BIOLOGICAL ACTIVITIES OF A SERIES OF RELATED PHOSPHORAMIDATES. JOURNAL OF AGRICULTURAL AND FOOD CHEMISTRY, VOL, 20, NO. 5, 931, 1972.

3. BICYCLIC PHOSPHORUS ESTERS: HIGH TOXICITY WITHOUT CHOLINESTERASE INHIBITION. SCIENCE, 182, 4117, 1973.

4. PRODUCTS OF PERACID OXIDATION OF ORGANOTHIOPHOSPHORUS COMPOUNDS. JOURNAL OF AGRICULTURAL AND FOOD CHEMISTRY, VOL. 22, NO. 2, 207, 1974.

5. THE HAZARD IDENTIFICATION AND ANIMAL NOEL PHASES OF DEVELOPMENTAL TOXICITY RISK ESTIMATION: A CASE STUDY EMPLOYING DINOSEB. ADVANCES IN MODERN ENVIRONMENTAL TOXICOLOGY, VOLUME XV, PRINCETON SCIENTIFIC PUBLISHING CO., PRINCETON, N.J., 1988.

PROFESSIONAL SOCIETIES: AMERICAN CHEMICAL SOCIETY, AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE.

AWARDS : RECIPIENT OF NATIONAL AERONAUTICS AND SPACE ADMINISTRATION HONORARIUM TO ATTEND THE FOURTH ANNUAL THEORETICAL BIOLOGY AND BIOPHYSICS COLLOQUIM IN MICHIGAN IN 1968.

NOMINATED TO AMERICAN MEN AND WOMEN OF SCIENCE, CHEMISTRY, 1977.

OUTSIDE ACTIVITIES: MEMBER OF THE BOARD OF DIRECTORS OF THE ALUMNI ASSOCIATION OF THE UNIVERSITY OF CALIFORNIA, RIVERSIDE, 1967-1970; VICE-PRESIDENT OF THE BOARD OF DIRECTORS, 1970-1971.

PRESIDENT OF THE BAY AREA CHAPTER OF THE U.C. RIVERSIDE ALUMNI ASSOCIATION, 1971-1972.

CHARTER MEMBER OF THE MOUNT VERNON, VIRGINIA JAYCEES, 1974.

CHAIRMAN, PUBLICATIONS COMMITTEE, 1977-1981 AMERICAN CHEMICAL SOCIETY, DIVISION OF PESTICIDE CHEMISTRY. MEMBER OF PROGRAM COMMITTEE, DIVISION OF PESTICIDE CHEMISTRY, 1983. MEMBER OF EXECUTIVE COMMITTEE, DIVISION OF PESTICIDE CHEMISTRY, 1983.

REFERENCES:

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   DEPARTMENT OF ENTOMOLOGY
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