

SUMMARY OF DATA FOR CHEMICAL SELECTION

CHEMICAL IDENTIFICATION

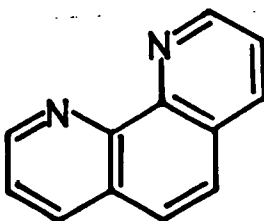
CAS Registry No.: 66-71-7

Name: o-Phenanthroline

Chem. Abstr. Name: 1,10-Phenanthroline (9 CI)

Synonyms: Ortho-phenanthroline; beta-phenanthroline;
4,5-phenanthroline; 4,5-diazaphenanthrene

Structure, Molecular Formula and Molecular Weight:



$C_{12}H_8N_2$

Mol. wt.: 180.22

Chemical and Physical Properties:

Description: White crystalline powder (1)

Melting-point: 93-94°C (monohydrate); 117°C (anhydrous)

Prepared for NCI by SRI International (2/80, rev. 6/80). Updated for NCI by Tracor Jitco/Technical Resources, Inc. under Contract No. N01-CP-41003 (5/85)

Solubility: Soluble in about 300 parts water; 70 parts benzene;
soluble in alcohol, acetone and ether (1)

BASIS OF NOMINATION TO THE CSWG

Source: Dr. Harry Klaudu (Steifel Research Institute)

Rationale: o-Phenanthroline was considered to be structurally interesting because it contains two nitrogens in the phenanthrene nucleus. It was nominated as a research chemical in order to determine the effect of the nitrogen moiety on the potential toxicological activity of the phenanthrene system.

SELECTION STATUS

CHEMICAL SELECTION WORKING GROUP

Priority: Low

Action: 2/28/80

It was postulated that o-phenanthroline might be related structurally to a "biquinoline" type of compound. It was noted that exposure to this compound would be limited. However, the CSWG selected o-phenanthroline with a low priority because it would be of scientific interest to determine the effect of this type of structure.

SUBSEQUENT ACTIVITY

The NTP Executive Committee selected o-phenanthroline for genotoxic testing only in July, 1982. Results of this test showed no mutagenic effect in Salmonella but positive induction of chromosomal aberrations and sister chromatid exchanges in Chinese hamster ovary cells in vitro.

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SELECTION STATUS

ACTION BY CSWG: (6/6/85)

Priority: Moderate

Studies Requested: Carcinogenicity

Comments: The CSWG recognized the need to determine in this compound, the effects of the ring nitrogens on the potential carcinogenic activity of the phenanthrene system. The Group noted the use of o-phenanthroline as an analytical reagent and, in particular, its use as a drying agent in a number of paints. While the material is not mutagenic in the Ames Salmonella test, it induced chromosomal aberrations and sister chromatid exchanges in Chinese hamster ovary cells. The biological effects of o-phenanthroline on DNA and RNA, both in vitro and in vivo, have been attributed in part to its ability to chelate metal ions essential for nucleic acid synthesis. o-Phenanthroline was recommended for carcinogenicity testing based on its potential for human exposure, its chemical structure, and its possible carcinogenic activity based on its limited in vitro test results.

EXPOSURE INFORMATION

Commercial Availability

o-Phenanthroline is included on the TSCA Chemical Substance Inventory, implying that it has been manufactured, imported or processed for a commercial purpose in the U.S. since January 1, 1975 (2).

Production: o-Phenanthroline was not reported to the U.S. International Trade Commission in the years 1975-1983 implying that annual production was less than 4.5×10^5 g in 1975 and less than 2.3×10^6 g in 1976-1983 (3). The largest U.S. producer (Vanderbilt Co.) reported that their production estimates of technical grade o-phenanthroline agree with the above estimates (4).

Although business has been reported to be good, the chemical is apparently becoming less popular (no volume given) as other analytical reagent methodologies (especially instrumental) become available (4).

Producers/Suppliers:

Alfa Products, Morton Thiokol Inc.
American Drug and Chemical Co.
American Research Products Co.
Carroll Products, Inc.
Chugai International Corp.
Eastern Chemical, Division of
 United Guardian Corp.
Fischer Scientific Co.
GFS Chemicals

Producers/Suppliers: (continued)

Greenwood Chemical Co.

Hach Co., Fine Chemicals Div.

Inchema Inc.

Miki Sangyo (USA), Inc.

Packfic Gateway Co.

Spectrum Chemical Mfg. Corp.

R.T. Vanderbilt Co.,

Wilshire Chemical Co. (5,6)

R.T. Vanderbilt, GFS Chemicals and Greenwood Chemical Co. are apparently the main producers of o-phenanthroline in the U.S. (4).

Technical Product Composition: o-Phenanthroline is available as a 99+% Gold Label (7). ACS reagent grade o-phenanthroline monohydrate and anhydrous o-phenanthroline have melting points of 93-94°C and 117°C, respectively (1,8). A commercially available formulation of o-phenanthroline for use with metallic driers contains 38% active ingredient in suitable organic solvents (9). The technical grade is usually shipped as a 1,10-phenanthroline solution (4).

Use Pattern: o-Phenanthroline is widely used as an analytical reagent because of its ability to form stable chelates with various metals. The iron (II)-phenanthroline complex (Ferroin) is used as a redox system in titrimetry and the detection of trace amounts of iron is based on the formation of this complex. o-Phenanthroline is also useful in the photometric determination of other metals, e.g., ruthenium, nickel and silver (10).

Industrial grade o-phenanthroline finds use in the paint and coatings industry as a paint drying accelerator for use with metallic driers (4,11).

Human Exposure: The National Occupational Hazard Survey (12) provides an estimate of the number and types of occupations which could be exposed to o-phenanthroline based on production and use patterns in 1970. The projections are as follows:

Occupation	Estimated Plants	Estimated Plants
Chemists	230	1,411
Chemical Technicians	172	640
Electrical and Electronic Engineering Tech.	55	328
Managers and Administrators, N.E.C.	68	68
Painters, Construction and Maintenance	96	133
Stationary Engineers	5	27
Mixing Operatives	256	1,225
Stationary Firemen	350	1,399
Machine Operatives, Misc. Specified	115	2,857
Miscellaneous Operatives	16	205
Vehicle Washers and Equipment Cleaners	16	32
TOTAL		8,324

The NCI/SRI Mark II data base estimated human exposure to o-phenanthroline at 2.8×10^2 g/yr, owing to dermal exposure to paints (13).

Regulatory Status: No regulatory information for o-phenanthroline was found in the literature or data bases searched (14). No occupational standard has been established by OSHA.

EVIDENCE FOR POSSIBLE CARCINOGENIC ACTIVITY

Human Data: No epidemiological studies or case reports examining the relationship between exposure to o-phenanthroline and human cancer were found in the literature (15).

Animal Data: o-Phenanthroline is neither on test currently nor scheduled for testing in a standard carcinogenesis bioassay (20).

o-Phenanthroline has been reported to be inactive in inducing tumors in mice following topical application and to exert an inhibitory effect on ethionine carcinogenesis in rats following oral administration. These experiments are discussed briefly in the following paragraphs.

In the single limited experiment reported in PHS-149, 20 mice received 10 weekly skin applications of a 10% solution of o-phenanthroline in acetone alternated at 3- to 4-day intervals with 18 weekly applications of a 0.5% solution of croton oil in acetone. No tumors were observed in the animals when the experiment was terminated at 19 weeks (21).

o-Phenanthroline has been shown to exhibit a protective effect in rats against liver tumor induction by ethionine. o-Phenanthroline (0.05%) was administered orally in the diet of 15 CFN female rats concomitantly with dl-ethionine (0.3%) for eight months. An 81% incidence each of cholangiofibrosis and hepatocellular carcinoma was observed in rats receiving ethionine only in the diet, compared to incidences of 26% and 6%, respectively, in rats receiving ethionine plus o-phenanthroline. No pathological changes were observed in the livers of five rats receiving 0.10% o-phenanthroline alone in the diet for 7.5 months (22).

In Vitro Tests:

Currently Accepted Prescreens: No tests were found in the literature of o-phenanthroline using in vitro systems that are currently being developed and validated as prescreens for carcinogenicity (15).

The NTP has, however, found that o-phenanthroline is not mutagenic in Salmonella but does cause chromosomal aberrations and sister chromatid exchanges in Chinese hamster ovary cells in vitro (24).

Other Evidence: The ability of o-phenanthroline to alter or inhibit DNA and RNA synthesis both in vitro and in vivo, and to inhibit cell growth has been attributed in part to its ability to chelate metal ions essential for nucleic acid synthesis (25). Inhibition of growth or DNA synthesis by o-phenanthroline or by metal complexes of the chemical (e.g., zinc complexes) has been observed in Escherichia coli (26), Staphylococcus aureus (27), yeast, fungi, viruses (28) and mammalian cells such as HeLa (28), L1210 leukemic cells, normal human lymphocytes (29), and CCRF-CEM human lymphoblasts (28). In several of these studies, the addition of metal ions (e.g., Zn^{2+} , Cu^{2+}) reversed the effects of o-phenanthroline on growth inhibition (28) or DNA synthesis (29).

Studies in mice in vivo have demonstrated that o-phenanthroline and the zinc complex inhibit RNA and DNA synthesis in the spleen and DNA synthesis in the liver, and increase the formation of hepatic RNA (25, 30, 31).

Metal complexes of o-phenanthroline have been shown to compete with ethidium bromide for intercalation sites on calf thymus DNA, but no

definitive evidence of any covalent binding was found (32).
o-Phenanthroline also has been reported to bind to HeLA cell DNA and Rous sarcoma virus RNA (33).

o-Phenanthroline, in the presence of a reducing agent and copper, causes the degradation of double stranded DNA. The concentrations of o-phenanthroline which are effective are the same order of magnitude as those resulting in inhibition of DNA and RNA polymerases, reverse transcriptase and terminal transferase (34).

Metabolism: No information specifically on the metabolism of o-phenanthroline was found in the literature (14,35,36,37).

Studies in animals have shown that o-phenanthroline can affect the activity of the liver mixed function oxidase system. Acute administration of the chemical in rats resulted in a significant decrease of cytochrome P-450 and a pronounced inhibition of liver microsomal enzymes involved in drug oxidation (e.g., aniline hydroxylase) (38). In contrast, chronic administration of the chemical resulted in the induction of the liver microsomal system with a subsequent increase in the activity of the liver mixed function oxidases (39). Low concentrations of the chemical have been shown to enhance microsomal NADPH-dependent lipid peroxidation in rat liver while higher concentrations (20 nM) strongly inhibit peroxidation. The stimulatory effects of the chemical were enhanced in the presence of Fe^{2+} , indicating that a metal complex may act as the activator (40).

Structure/Activity Relationships: o-Phenanthroline is an N-heterocyclic analog of the polycyclic aromatic hydrocarbon (PAH) phenanthrene. A number of carbocyclic and heterocyclic PAHs derived from phenanthrene have demonstrated carcinogenic activity in animals. These include benzo(a)pyrene, dibenz(a,h)anthracene, benzo(h)naphtho(1,2-f)quinoline and 4,11-diazadibenzo(b,def)chrysene (41).

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