Orthanilic Acid
[88-21-1]

Review of Toxicological Literature

Prepared for

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EXECUTIVE SUMMARY

The nomination of orthanilic acid [88-21-1] to the ICCEC is based on the limited amount of toxicological information available for this chemical. Orthanilic acid is produced as a byproduct in the manufacture of sulfanilic acid (the para isomer), and as a mixture with sulfanilic and metanilic acids by treating aniline with fuming sulfuric acid. It is also considered to be an impurity in the sulfanilic acid used in industry. No data on current production or import volumes were located for orthanilic acid. The only reported use for orthanilic acid is in the manufacture of dyes. Aminobenzenesulfonic acid (CASRN 30179-49-8) is mentioned in 36 records indexed by Chemical Abstracts. It is possible that the generic CASRN has been used to represent a mixture of isomers, which would probably include orthanilic acid. Uses described include binders for activated carbon-containing air filter units and anilinesulfonic acid-based cement dispersants, as a stabilizer in electroless (i.e., chemical, not electrolytic) gold coating, as a copolymer in dispersants for heat-resistant drilling muds, in a capacitor electrolyte, and as a porous support for the enzyme catalyst for industrial production of high-fructose corn syrup.

No data on environmental occurrence of orthanilic acid were located, but reports on biodegradation of the compound indicate that it is probably found in the industrial wastes from the high-volume use of aromatic sulfonates to produce detergents, dyes, and additives to products such as inks and engine oils.

The only data available on the chemical disposition of orthanilic acid was that it inhibited the enzymatic conjugation of 1-chloro-2, 4-dinitro-benzene with glutathione through its ability to bind directly to this protein.

Orthanilic acid had a positive inotropic (relating to muscle contraction/ tension) effect in *in vitro* guinea pig heart preparations.

Orthanilic acid was reported as weakly positive for the induction of gene mutations in *Salmonella typhimurium* strain TA98 without metabolic activation only (TA100, TA97, TA98, and TA1535 were tested with and without metabolic activation). However, it was reported as negative for mutagenicity in another *S. typhimurium* study.

No short-term, chronic, reproductive, carcinogenicity, or immunotoxicity studies of orthanilic acid were located.

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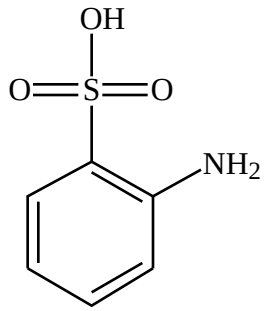
1.0 BASIS FOR NOMINATION

The nomination of orthanilic acid [88-21-1] to the ICCEC is based on the limited amount of toxicological information available for this chemical.

2.0 INTRODUCTION

Orthanlilic Acid (CASRN 88-21-1)



2.1 Chemical Identification

Orthanilic acid ($C_6H_7N0_3S$, mol. wt. = 173.19) is also called:

Benzenesulfonic acid, 2-amino- (9CI)	Aniline-2-sulfonic acid
Benzenesulfonic acid, o-amino- (8CI)	Aniline-o-sulfonic acid
1-Aminobenzene-2-sulfonic acid	o-Anilinesulfonic acid
2-Aminobenzenesulfonic acid	Anilino-2-sulfonic acid
2-Aminobenzenesulphonic acid	Anilino-o-sulfonic acid
o-Aminobenzenesulfonic acid	Anilino-o-sulphonic acid
o-Aminophenylsulfonic acid	o-Sulfanilic acid

2.2 Physical-Chemical Properties

Property	Information	Reference
Physical State	Minute hexagonal	Budavari (1996)
Melting Point, °C	320; decomposes at ~325	Northcott (1978) and Budavari (1996)
Dissociation Constant at 25°C (pKa)	$3.3x10^{-3}$	Budavari (1996)
Solubility:		
Water	Slowly and sparingly soluble in water. Slow crystallization from water may give a hemihydrate.	Budavari (1996)
Organic Solvents	Insoluble in ethyl alcohol and ethyl ether.	HODOC (1997)
Partition Coefficients:		
Log octanol/water	-2.95	ISHOW (1990)

Orthanilic acid rapidly reacts with NO^{2-}.

3.0 PRODUCTION PROCESSES AND ANALYSES

Orthanilic acid is produced as a byproduct in the manufacture of sulfanilic acid (the para isomer) either by baking aniline sulfate at 200-220°C, or by heating a mixture of aniline and sulfuric acid in a high boiling solvent (Foerst, 1953; cited by Marmion, 1975). Orthanilic acid is also produced as a mixture with sulfanilic and metanilic acids by treating aniline with fuming sulfuric acid between 0°C and 100°C (Northcott, 1978).

4.0 PRODUCTION AND IMPORT VOLUMES

In 1977, orthanilic acid was produced by Eastman Kodak, Kodak Park Division (TSCAPP, 1983). Mobay Chemical Corporation and Sandoz Colors & Chemicals apparently imported the compound used in their plants. Information on production or import volumes were not provided by TSCAPP (1983), and no data on current production or import volumes were located.

5.0 USES

The only use given in the *Kirk-Othmer Encyclopedia of Chemical Technology*, 3rd edition, for orthanilic acid is in the manufacture of dyes (Northcott, 1978). Orthanilic acid is reported also to be an impurity in sulfanilic acid, an intermediate used in the manufacture of many dyes, including the certifiable colorants FD&C Yellow No. 5, FD&C Yellow No. 6, and D&C Orange No. 4 (Northcott, 1978). However, Marmion (1975) did not detect any orthanilic acid in commercial sulfanilic acid sold in the United States.

Aminobenzenesulfonic acid (CASRN 30179-49-8) is mentioned in 36 records, indexed by Chemical Abstracts, representing primarily Japanese unexamined patents. It is possible that the generic CASRN has been used to represent a mixture of isomers, which would probably include orthanilic acid. Uses mentioned include binders for activated carbon-containing air filter units (Maeda et al., 1994; Date et al., 1993 [same patent assignee for each]) and anilinesulfonic acid-based cement dispersants (e.g., Yamamoto et al., 1992; Nishimori et al., 1994; Ichihara and Hosogaya, 1996). Yoshitani et al. (1991), of Shinko Electric Industries Company, Ltd., described the use of aminobenzenesulfonic acid as a stabilizer in electroless (i.e., chemical, not electrolytic) gold plating. Other uses described in patents include in a copolymer in dispersants for heat-resistant drilling muds (Sample, 1984), and in a capacitor electrolyte in amounts of 0.1 and 0.5% (Matsushita Electrical Industrial Co., Ltd., 1972). Zhou et al. (1992) described the use of porous

anilinosulfonic acid-polystyrene polymer beads as a porous support for the enzyme catalyst for industrial production of high-fructose corn syrup.

6.0 ENVIRONMENTAL OCCURRENCE AND PERSISTENCE

Orthanilic acid was not biodegraded in samples of anaerobic aquifer slurries after 13 months (Kuhn and Suflita, 1989). Orthanilic acid was completely biodegraded, however, under conditions of the static "Zahn-Wellens" test in 21 days with a 14-day acclimatization period (Wellens, 1990).

No data on environmental occurrence were located, but the reports on biodegradation of the compound suggests that it is probably found in industrial wastes from the high-volume use of aromatic sulfonates to produce detergents, dyes, and additives to products such as inks and engine oils (Berth and Jeschke, 1989, and Cook and Leisinger, 1991; cited by Junker et al., 1994). For example, the report by Wellens (1990) on the biodegradability of orthanilic acid was from the wastewater biology laboratory of Hoechst AG.

7.0 HUMAN EXPOSURE

No data were found.

8.0 REGULATORY STATUS

No data were found.

9.0 TOXICOLOGICAL DATA

9.1 Human Data

No data were found.

9.2 General Toxicology

9.2.1 Chemical Disposition, Metabolism, and Toxicokinetics

In vitro, orthanilic acid and its N-acetylated derivatives inhibited the enzymatic conjugation of 1-chloro-2, 4-dinitro-benzene with rat liver glutathione *S*-transferase (GST) by direct binding to GST (Dierickx and Yde, 1982). It was suggested that the binding to GST of these compounds, some of which are metabolites of colorings used in human food, provides a protective function against these dyes. No other data on the chemical disposition, metabolism, or toxicokinetics of orthanilic acid in mammals were located.

9.2.2 Acute Exposure

Orthanilic acid had a positive inotropic (relating to muscle contraction/tension) effect in *in vitro* guinea pig heart preparations (Franconi et al., 1986; 1987; 1990). The heart preparations were bathed in 20 mM orthanilic acid for 60 minutes.

9.2.3 Short-term and Subchronic Exposure

No data were found.

9.2.4 Chronic Exposure

No data were found.

9.3 Reproductive and Teratological Effects

No data were found.

9.4 Carcinogenicity

No data were found.

9.5 Genotoxicity

The studies described in this section are presented in **Table 1**.

Orthanilic acid induced a weak positive increase in *his* gene mutations in *Salmonella typhimurium* (Zeiger et al., 1988). Strains TA97, TA98, TA100, and TA1535 were exposed to doses ranging from 10 to 6667 µg/plate (0.06 to 38.35 µmol/plate) using the pre-incubation method in either the presence or absence of 10% or 30% rat or hamster liver metabolic activation. The weak positive increase in revertants was observed only in strain TA98 without metabolic activation.

The Ecological and Toxicological Association of Dyes Manufacturers (ETAD, unpublished study, 1989; cited by Jung et al. 1992) reported that orthanilic acid was negative for the induction of *his* gene mutations in *S. typhimurium.* Information on specific strains, dose levels, and S9 conditions were not provided.

9.6 Immunotoxicity

No data were found.

10.0 STRUCTURE-ACTIVITY RELATIONSHIPS

Orthanilic acid and *L*-cysteic acid were the only 2 of 20 taurine (2-aminoethanesulfonic acid) analogs tested that prevented the negative inotropic effect of a low-calcium medium in a dose-dependent manner (Franconi et al., 1986; 1987; 1990). However, the mechanisms of action of these three compounds in interfering with drugs with negative or positive inotropic action appeared to be different.

It has been demonstrated *in vitro* that taurine analogs that have the basic taurine structure (N-C-C-S) partially in a semi-rigid unsaturated ring structure stimulate the phosphorylation of a 44 kDa protein in the mitochondrial fraction of rat heart (Lombardini, 1994; 1996). These analogs include orthanilic acid, pyridine-3-sulfonic acid, and quinoline-8-sulfonic acid.

In addition to orthanilic acid, the aminobenzenesulfonic acids sulfanilic acid and metanilic acid inhibit the glutathione-*S*-transferase (GST)-mediated conjugation of 1-chloro-2,4-dinitrobenzene with glutathione by directly binding to GST (Dierickx and Yde, 1982).

Table 1. Genotoxicity of Orthanilic Acid

Test System	Biological Endpoint	S9 Metabolic Activation	Chemical Form, Purity	Dose	Endpoint Response	Comments	Reference
Salmonella typhimurium strains TA100, TA98, TA97, and TA1535	*his* reverse gene mutations	± 10 or 30% rat or hamster	orthanilic acid, n.p.	10 to 6667 µg/plate (0.06 to 38.35 µmol/plate) using the pre-incubation method	weak positive/ negative	Weak positive increase in revertants only in strain TA98 without S9.	Zeiger et al. (1988)
S. typhimurium, strains n.p.	*his* reverse gene mutations	conditions n.p.	orthanilic acid, n.p.	n.p.	negative	No other experimental details were provided.	ETAD (unpublished study, 1989; cited by Jung et al., 1992)

Abbreviations: n.p. = not provided

11.0 ONLINE DATABASES AND SECONDARY REFERENCES

11.1 Online Databases

Chemical Information System Files

ISHOW (Information System for Hazardous Organics in Water)
SANSS (Structure and Nomenclature Search System)
TSCAPP (Toxic Substances Control Act Plant and Production)
TSCATS (Toxic Substances Control Act Test Submissions)

DIALOG Files

359 Chemical Economics Handbook
302 Kirk-Othmer Encyclopedia of Chemical Technology, Full text
161 NIOSHTIC (Occupational Safety and Health)

Internet Databases

Code of Federal Regulations full text. 1996 versions of various titles via GPO Gate, a gateway by the Libraries of the University of California to the GPO Access service of the Government Printing Office, Washington, DC. Internet URL http://www.gpo.ucop.edu/

National Library of Medicine Databases

EMIC and EMICBACK (Environmental Mutagen Information Center)

STN International Files

BIOSIS (Biological Abstracts)
CA File (Chemical Abstracts)
CANCERLIT
CEN (Chemical & Engineering News)
CIN (Chemical Industry Notes)
CSNB (Chemical Safety News Base)
EMBASE (Excerpta Medica)
HSDB (Hazardous Substances Data Bank)
IPA (International Pharmaceutical Abstracts)

MEDLINE (Index Medicus)
PROMT (Predicasts Overview of Markets and Technology)
RTECS (Registry of Toxic Effects of Chemical Substances)
TOXLINE
TOXLIT

TOXLINE includes the following subfiles:

Toxicity Bibliography	TOXBIB
International Labor Office	CIS
Hazardous Materials Technical Center	HMTC
Environmental Mutagen Information Center File	EMIC
Environmental Teratology Information Center File (continued after 1989 by DART)	ETIC
Toxicology Document and Data Depository	NTIS
Toxicology Research Projects	CRISP
NIOSHTIC7	NIOSH
Pesticides Abstracts	PESTAB
Poisonous Plants Bibliography	PPBIB
Aneuploidy	ANEUPL
Epidemiology Information System	EPIDEM
Toxic Substances Control Act Test Submissions	TSCATS
Toxicological Aspects of Environmental Health	BIOSIS
International Pharmaceutical Abstracts	IPA
Federal Research in Progress	FEDRIP
Developmental and Reproductive Toxicology	DART

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