

Chemical Information Profile

for

***o*-Phthalaldehyde
[CAS No. 643-79-8]**

**Supporting Nomination for Toxicological Evaluation by the
National Toxicology Program**

April 2007

Prepared by
Integrated Laboratory Systems, Inc.
Research Triangle Park, NC
Under Contract No. N01-ES-35515

Prepared for
National Toxicology Program
National Institute of Environmental Health Sciences
National Institutes of Health
U.S. Department of Health and Human Services
Research Triangle Park, NC
<http://ntp.niehs.nih.gov/>

Data Availability Checklist for o-Phthalaldehyde [643-79-8]

Abbreviations: H = human; L = *Lepus* (rabbit); M = mouse; R = rat

Note: No judgement of whether the available data are adequate for evaluation of these endpoints in the context of human health hazard or risk assessment has been made.

ENDPOINT	H	M	R	L
ADME				
Absorption				
Distribution				
Metabolism			✓	
Excretion			✓	
Acute Toxicity (up to 1 week)				
Dermal				✓
Inhalation				
Injection		✓		
Ocular				
Oral			✓	
Subchronic Toxicity (1 to <26 weeks)				
Dermal				
Inhalation				
Injection				
Oral			✓	
Chronic Toxicity (≥26 weeks)				
Dermal				
Inhalation				
Injection				
Oral				
Synergism/Antagonism				
Synergistic effects				
Antagonistic effects				
Cytotoxicity				
Cytotoxic effects		✓	✓	
Reproductive Toxicity				
Fertility effects			✓	
Maternal effects			✓	
Paternal effects				

ENDPOINT	H	M	R	L
Developmental Toxicity				
Developmental abnormalities			✓	
Embryonic/fetal effects			✓	
Newborn effects				
Carcinogenicity				
Dermal				
Inhalation				
Oral				
Anticarcinogenicity				
Anticarcinogenic effects				
Genotoxicity				
Cytogenetic effects			✓	
Microbial gene mutation			✓	
Gene mutation <i>in vitro</i>		✓	✓	
Gene mutation <i>in vivo</i>			✓	
Germ cell effects				
Neurotoxicity				
Behavioral activity				
Motor activity				
Immunotoxicity				
Immunotoxic effects*	✓			
Mechanistic Data				
Target Organs/Tissues			✓	
Endocrine modulation				
Effect on enzymes	✓			
Modes of action				
Effect on metabolic pathways				
Structure-Activity Relationships	✓	✓	✓	✓

*assays conducted in guinea pigs

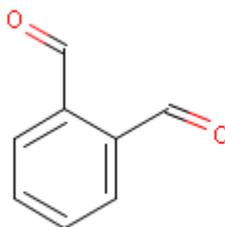
***o*-Phthalaldehyde Nomination Summary**

Chemical Name: *o*-Phthalaldehyde

CAS RN: 643-79-8

Formula: C₈H₆O₂

Molecular Wt.: 134.132



Basis for Nomination: *o*-Phthalaldehyde (OPA) is nominated by the National Institute for Occupational Safety and Health for toxicological characterization based on the limited availability of toxicological data and its increasing use as an alternative to glutaraldehyde in the sterilization of dental and medical equipment. OPA is marketed, sold, and used as a "safe" replacement for glutaraldehyde for high-level disinfection of heat sensitive dental and medical devices. Marketing literature, a recent Canadian survey (J Hosp Infec 59, 4-11, 2005), and local anecdotal information indicate that the use of OPA is widespread and on the rise. The NIOSH National Occupational Exposure Survey states that 3253 workers were potentially exposed to OPA in 1981-1983 in several industries other than healthcare. No other exposure information (including limits) is available. During that same period over 318,362 workers were potentially exposed to glutaraldehyde in the healthcare field alone. It is reasonable to assume that more than 300,000 healthcare workers may be exposed to OPA today. The disinfecting mechanism of OPA is considered to be similar to glutaraldehyde which kills organisms by the binding of the aldehyde to the cellular wall. Despite this similarity, their molecular structures are different. Glutaraldehyde is a straight-chained hydrocarbon and OPA is a benzene ring based structure. OPA has been approved for anti-microbial pesticide use (indoor only) by the U.S. EPA, and for disinfecting medical devices by the U.S. FDA. The safety of OPA relative to glutaraldehyde is based on its greater efficacy as a disinfectant. This allows it to be used at lower concentrations, which contributes to a lower vapor pressure. These two factors should result in reduced air concentrations of OPA relative to glutaraldehyde when used under similar conditions. In its 2006 *Best Practices for the Safe Use of Glutaraldehyde in Health Care*, OSHA lists OPA as an alternative to glutaraldehyde. OSHA notes that "consideration should be given to whether the alternative is safe for employees," but provides no information indicating that OPA is a safe alternative to glutaraldehyde. Neither OSHA nor the U.S. EPA has promulgated rules regarding proper use and safe exposure levels of OPA. There are virtually no peer-reviewed toxicological data in the open literature for OPA. Both the U.S. EPA and U.S. FDA have received unpublished animal toxicity reports, which are protected, in part, as confidential business information. Based on summary information in Material Safety Data Sheets and statements on the internet, it appears that OPA is not mutagenic in bacterial tests, but causes chromosomal aberrations in mammalian cell assays. It is not a developmental toxicant and is moderately toxic in subchronic toxicological studies. While no data are available for review, OPA has been noted as positive in the guinea pig maximization test and the mouse local lymph node assay. Consistent with this, a few human case reports indicate that OPA can cause mucous irritation, respiratory symptoms and IgE-mediated hypersensitivity reactions. In one report (J Allergy Clin Immunol 114, 392-397, 2004), four patients

experienced nine episodes of anaphylaxis after a urology practice switched from using glutaraldehyde to OPA for disinfecting their cystoscopes. Another report (J Allergy Clin Immunol 117, 1500-1501, 2006) related OPA to irritation of the eyes, skin, and nose resulting in stinging, excessive tearing, coughing and sneezing. It was also concluded to be a potential skin and respiratory sensitizer that may cause dermatitis with prolonged or repeated contact and may aggravate pre-existing bronchitis or asthma. These studies are limited in scope, but suggest that OPA may pose similar occupational hazards to those of glutaraldehyde. However, data are needed to define and document the potential hazard posed to healthcare workers handling OPA so that appropriate guidelines and protections can be put into place.

A. Chemical Information

Molecular Identification

Chemical Name: *o*-Phthalaldehyde (OPA)

CAS RN: 643-79-8

Synonyms: 1,2-Benzenedialdehyde; 1,2-Benzenedicarboxaldehyde (9CI); 1,2-Diformylbenzene; 1,2-Phthalaldehyde; 2-Formylbenzaldehyde; Benzene-1,2-dicarbaldehydel; *o*-Benzenedicarbaldehyde; Benzenedicarboxaldehyde; *o*-Diformylbenzaldehyde; NSC 13394; OP 100S; OP 100SF; Phthalaldehyde (6CI, 8CI); *o*-Phthaldialdehyde; Phthalic aldehyde; *o*-Phthalic aldehyde; Phthalic dialdehyde; Phthalic dicarboxaldehyde; Phthalidicarboxaldehyde; Phtharal

Trade Names: Cidex-OPA[®]

Hill Formula: C₈H₆O₂

Line Formula: OC-C₆H₄-CO

Smiles Notation: C1=CC=C(C(=C1)C=O)C=O

PubChem CID: [4807](#)

InChI: 1/C8H6O2/c9-5-7-3-1-2-4-8(7)6-10/h1-6H

Molecular Weight: 134.132

Purity of Commercial Products: Cidex-OPA[®] (0.56% phthalaldehyde, 99.45% water and <1% unspecified substances [said to be "inert" on safety data sheet]) supplied as a "ready to use" preparation ([WATCH subgroup, 2003](#)). OPA also listed with active ingredients in Ucarcide P200 Antimicrobial (99.8%) and Cidex O.P.A. Antimicrobial (99.7%) ([Scorecard Database, 2005](#)).

Additives in Commercial Products: Cidex-OPA[®]: potassium phosphate salts (phosphate buffer), benzotriazole (corrosion inhibitor), D&C Green #5 (green dye), citric acid, and Versenal 120 (chelating agent) ([Rideout, 2003](#))

Impurities in Commercial Products: Phthalic anhydride, phthalide, and 2-carboxybenzaldehyde detected after 6 months storage in high-density polyethylene containers (Dynamac Corp., 1990)

Mammalian Metabolites: Phthalaldehydic acid [119-67-5], 2-hydroxymethylbenzoic acid [612-20-4], and phthalic anhydride [85-44-8]

Biodegradation Products: Phthalide [87-41-2] (by *Euglena gracilis* Z) (Noma et al., 1991)

Environmental Transformation: OPA was reported as a photodegradation product of 2-naphthoic acid in the presence of titanium dioxide ([Muneer et al., 2005](#)); also identified as one of the photodegradation products from irradiation of benz[*a*]anthracene in the presence of organic constituents (9,10-anthraquinone, 9-xanthone, and vanillin) of atmospheric aerosols (Jang and McDow, 1997). OPA may also be formed by ozonolysis of remediated PAH-contaminated soils and wastewaters (Sarasa et al., 1998; Seibel et al., 1995). Cidex-OPA[®] formulated at 0.55% has a 14-day usage life and a 2-year closed bottle shelf life ([Rideout, 2003](#)).

Physical-Chemical Properties

Physical State: 99% Technical formulation: pale yellow to yellow crystalline solid at 20 °C (Dynamac Corp., 1990; [WATCH subgroup, 2003](#)); Cidex-OPA[®] Solution: light-blue clear liquid ([Advanced Sterilization Products, 2005](#))

Specific Gravity or Density: 99% Technical formulation: 0.63±0.10 g/mL at 20 °C (Dynamac Corp., 1990); Cidex-OPA[®] Solution: 1.0003 g/cc ([Advanced Sterilization Products, 2005](#))

Boiling Point: 266.2±23 °C @ 760 mm Hg [calculated] (Registry, 2006); Cidex-OPA[®] Solution: 100 °C ([Advanced Sterilization Products, 2005](#))

Vapor Pressure: 99% Technical formulation: 0.0052 mm Hg (6.9×10⁻¹ Pa) @ 21 °C (Dynamac Corp., 1990; [Rideout, 2003](#); [WATCH subgroup, 2003](#))

Solubility: 99% Technical formulation: 3 g/100 mL diisopropyl ether, 5 g/100 mL deionized water, 20 g/100 mL chloroform, and 20 g/100 mL acetone at 20 °C (Dynamac Corp., 1990). [OPA assumes three forms in aqueous solution: unhydrated, monohydrated, and cyclic hemiacetal (Bover et al., 2003).]

Log P = Log K_{ow}: 0.51 (Leo, 1982)

Bioconcentration Factor(s) (species): 1.44 @ pH 1-10 @ 25 °C [calculated] (Registry, 2006)

B. Exposure Potential

U.S. Annual Production

1986-1998: No reports

2002: 10,000 – 500,000 pounds

(U.S. EPA, 2006 [[U.S. EPA IUR database](#); search by casno = 643798])

Worldwide Annual Production

Not available

Production Processes

Various processes reported.

- Pure benzaldehyde and chloroform heated with potassium hydroxide solution then acidified with dilute hydrochloric acid and cooled to yield phthalaldehyde colorless powder ([Chaudhuri, 1942](#))
- Ozonization of naphthalene in alcohol followed by catalytic hydrogenation (86.5% yield) ([Sajtos, 1988 pat.](#))
- Oxidation of:
 - phthalan by nitrogen monoxide in acetonitrile with *N*-hydroxyphthalimide as catalyst yielded 80-90% OPA ([Ishii and Nakano, 2001 pat.](#))
 - α -dichloro-*o*-xylene with aqueous nitric acid and vanadium pentoxide as catalyst with 76-99.6% yield ([Yoshinaka and Doya, 1982 pat.](#))
 - *o*-xylylene oxide and/or *o*-xylylene glycol with nitric acid solution yielded 35-72% after OPA purification ([Nakai, 2004 pat.](#))
 - *o*-phthaldehyde tetraalkyl acetals using an electrochemical technique ([Degner, 1986 pat.](#); [Giselbrecht et al., 1999 pat.](#), [2002 pat.](#))

Uses

- Disinfectant, enzyme inhibitor, indicator, and reagent ([ChemIDplus, 2004](#))
- Due to its antimicrobial efficacy and low inhalation toxicity, replacement for glutaraldehyde as a high-level disinfectant for endoscopes, thermometers, rubber and plastic equipment, and medical/surgical instruments that cannot be sterilized by heat ([Advanced Sterilization Products, 2003](#); Akamatsu et al., 2005 [PMID:[15790129](#)])
- An active ingredient in a formulation marketed as a sterilant for endoscopy equipment (O'Neil, 2006; [Rideout, 2003](#); Rutala and Weber, 2001 [PMID:[11294738](#)]; [WATCH subgroup, 2003](#))
- Measurement for cholesterol in plasma and tissue based on detection of free and esterified cholesterol following thin-layer chromatographic separation ([Rudel and Morris, 1973](#))
- Fluorescence probe for glutathione and glutathione disulfide levels, primary amines, peptides, and biological thiols (O'Neil, 2006; Senft et al., 2000 [PMID:[10805524](#)])
- Diagnostic for urea nitrogen test system ([U.S. FDA CDRH, 2006](#))
- Reagent for U.S. EPA Analytical Method 531.2 for drinking water analysis ([U.S. EPA, 2001](#))
- Intermediate in the synthesis of pharmaceuticals, medicines, and other organic compounds ([ChemicalLand 21, undated](#))
- Tanning agent in leather industry ([ChemicalLand 21, undated](#))
- Control for biofouling in a variety of applications including water treatment, pulp and paper manufacture, and oil field water flooding ([Theis and Leder, 1992 pat.](#))
- Also used in hair colorings, wood treatment, and antifouling paints ([NICNAS, 2005](#))

Occupational Exposure

The 1981-1983 National Occupational Exposure Survey reports the estimated number of workers potentially exposed to OPA was 3253 (2222 females) in 5 occupations (geologists and geodesists, clinical laboratory technologists and technicians, engineering technicians, chemical technicians, and health aides, excluding nursing) ([NIOSH, undated](#)). OPA was detected in air samples (average <10

$\mu\text{g}/\text{m}^3$) from several endoscopy units in a hospital in Italy using infrared spectroscopy and high performance liquid chromatography with UV detection ($8.4 \mu\text{g}/\text{m}^3$) (Marena et al., 2003; PMID:[12872495](#)).

Exposure Limits (Standards and Criteria): Not available

General Population Exposure

Foods and Beverages, Cosmetics, etc.: Not available

Ambient Environment: Not available

Environmental Occurrence

Natural Occurrence: Not known to occur naturally (See Section A, *Environmental Transformation*)

U.S. Environmental Releases: Not available

Concentrations in Environmental Media: Concentrations were not available. OPA was identified in samples of raw or treated drinking water in Great Britain (Fielding et al., 1981). OPA and its metabolites phthalaldehydic acid and 2-hydroxymethyl benzoic acid have been reported as biodegradation products of microorganisms (from soils, wastewaters, sediments, etc.) (e.g., Cajthaml et al., 2006 [PMID:[16403417](#)]; [Gawai et al., 2005](#); Gulyas et al., 1993; Kelley et al., 1993 [PMID:[8481006](#)]).

Regulatory Status

U.S. Environmental Protection Agency: In July 1998, Johnson and Johnson Medical Inc. cancelled their product CIDEX O.P.A. Antimicrobial [Registration No. 7078-17] as an EPA-registered pesticide ([NPIRS, 2007](#)).

Food and Drug Administration: In September 2006, three high-level disinfectants manufactured by Advanced Sterilization Products received marketing clearance: Cidex[®] OPA Concentrate (5.75% OPA, active ingredient) [510(k) No. [K032959](#)], Cidex[®] OPA Solution (0.55% OPA) [[K030004](#)], and Cidex[®] OPA Solution High-Level Disinfectant (0.55% OPA) [[K991487](#)]. [Note: K030004 is a modification for K991487.] Cidex[®] OPA Concentrate is intended for use only in the EvoTech Integrated Endoscope Disinfection System, while the other two medical devices can be used for manual processing and in automatic endoscope reprocessors ([FDA, 2006](#)).

C. Toxicological Information

Summary: OPA residue from inadequate rinsing of transesophageal echocardiography probes, colonoscopes, etc. has been associated with exacerbation of asthma and bronchitis; allergic reactions; anaphylaxis; and chemical burns and/or irritation. Dermal hypersensitivity, lower respiratory symptoms, and eye irritation due to splashes of OPA solutions have also been reported. In rats, an oral LD₅₀ of 121 mg/kg was calculated for the technical grade and >5000 mg/kg for the ~0.56% OPA solution. The dermal LD₅₀ in rabbits was >2000 mg/kg for both formulations. When administered as a single oral dose to rats, OPA caused deaths at high doses (>50 mg/kg); symptoms included ataxia, respiratory irregularity, prostration, piloerection, and damage to the stomach and intestines. In a 90-day study, male and female rats exhibited severe damage to the gastrointestinal tract and increases in white blood cells, total leukocyte counts, segmented neutrophils, and monocytes; only males had decreased levels of protein, albumin, and globulin (NOEL=5 mg/kg/day). There were no changes in the number of live or dead fetuses, corpora lutea, resorption, fetal weight, external examination, or examination of the soft tissue in female rats given OPA on gestation days 6-15. In dams that died, clinical signs were similar to those reported for subchronic studies (e.g., moderate to severe distended stomach and/or intestines, depressions in stomach, mottled liver, foci on liver, and dark lungs). Delayed skeletal development in fetuses was attributed to maternal toxicity. OPA was cytotoxic to *Salmonella typhimurium* strains but not mutagenic. It did not induce mutation in mouse lymphoma nor Chinese hamster ovary (CHO) cells but did induce chromosome aberrations and sister chromatid exchanges in CHO cells. It was also negative for unscheduled DNA synthesis in rat hepatocytes and chromosome aberrations in rat bone marrow cells. OPA is reported to inactivate numerous enzymes by cross-linking with cysteine and lysine residues at the active sites of the enzyme.

General Toxicity

Human Studies

- Cidex-OPA[®] Solution may cause eye, skin, and respiratory irritation. Ingestion may cause irritation and discoloration of the mouth, esophagus, and other digestive tract tissues, as well as gastrointestinal irritation, nausea, vomiting, and diarrhea ([Advanced Sterilization Products, 2005](#)).
- A recent toxicity assessment indicated OPA is a potential dermal and respiratory sensitizer (Rideout et al., 2005; PMID:[15571847](#)).
- Cidex-OPA[®] package inserts note that exacerbation of asthma and bronchitis have been reported; allergic reactions to OPA in nine urology patients were reported to Advanced Sterilization Products, a Johnson & Johnson Company (Sokol, 2004; PMID:[15316522](#)).
- Residual Cidex-OPA[®] Solution from disinfection of transesophageal echocardiography (TEE) probes was implicated as the cause of gray-green perioral stains observed on the cardiac surgery patients; staining faded within a few hours (Streckenbach and Alston, 2003 *lett.*). Aerodigestive tract chemical burn injury was also noted in a patient in whom a Cidex-OPA[®]-treated TEE probe was used (Venticinque et al., 2003; PMID:[14570634](#)).
- Numerous reports of chemical burns and/or irritation from inadequate rinsing of TEE probes, colonoscopes, cystoscopes, etc.; dermal hypersensitivity and lower respiratory symptoms (asthma, wheezing, pneumonia, etc.) from inadequate ventilation; and eye irritation due to splashes, have been received by the U.S. FDA Center for Devices and Radiological Health (see MAUDE database: <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfMAUDE/search.CFM>).

Animal Studies: Cidex-OPA[®] Solution is not a primary skin irritant but is a moderate primary eye irritant ([Advanced Sterilization Products, 2003](#); Rideout et al., 2005 [PMID:[15571847](#)]).

Chemical Disposition, Metabolism, and Toxicokinetics

Absorption and Clearance: Not available

Human Studies: Not available

Animal Studies

- In male rats [strain not specified in abstract] given [¹⁴C]phthalaldehyde intratracheally (i.t.) or orally (Ohtawa et al., 2001):
 - The radioactivity $C_{(max)}$ = 0.8 hour and 1.7 hours, respectively.
 - The initial phase i.t. half-life ($t_{1/2}$) = 6 hours and the $t_{1/2}$ of the elimination phase was 94 hours.
 - The carcass, urinary, and fecal values at 72 hours after i.t. dosing were 41%, 44%, and 11%, respectively. Thus, at least 43% of the original dose was absorbed.
 - The major urinary metabolites (78% of the total urinary radioactivity) were phthalaldehydic acid (33%), two unknowns (33% and 8%), and phthalic anhydride (4%).
 - The oral $t_{1/2}$ was similar to that for i.t.; however, the carcass contained only 2% of the total radioactivity at 72 hours and the urine and feces contained 43% and 50%.
- Aldo-keto-reductases are responsible for phthalaldehydic acid metabolism (e.g., AKR7A2 and AKR7A5) and are present in numerous tissues of various species, including humans (e.g., [O'Connor et al., 1999](#); [Hinshelwood et al., 2002](#)).
- The metabolism of phthalidyl prodrugs to phthalaldehydic acid and 2-(hydroxymethyl)benzoic acid has been well studied in patients, volunteers, and animals. The metabolite phthalaldehydic acid is metabolized to 2-(hydroxymethyl)benzoic acid (about 70% conversion) by humans and several laboratory species (e.g., Shiobara, 1977 [PMID:[888448](#)]; Shiobara and Ogiso, 1979).
- Orally administered phthalaldehydic acid was converted to 2-(hydroxymethyl)benzoic acid more extensively by rats (85.6-91.1% of 100 mg/kg bw) than mice (69.2% of 100 mg/kg bw), rabbits (69.5% of 100 mg/kg bw), dogs (75.1% of 30 mg/kg bw) or one male human (76.2% of 50 mg/kg bw). Rats dosed at 100 mg/kg also convert isophthalaldehydic acid (97.5%), isophthalaldehyde (58.0%), terephthalaldehydic acid (87.4%), and terephthalaldehyde (76.3%) to their corresponding isophthalic acid and terephthalic acid (Shiobara, 1977 [PMID:[888448](#)]).

Chemical Information Profile for *o*-Phthalaldehyde

- Liver slices from mice, rabbits, and monkeys *in vitro* showed minor conversion of phthalaldehydic acid to phthalic acid, but liver slices from rats and dogs did not. No conversion to phthalic acid was observed with kidney slices. Reduction in blood followed the order rat >> human > dog > mouse > rabbit blood, a pattern that differed from that observed with intact animals. Conversion by liver slices closely paralleled conversion *in vivo* (Shiobara and Ogiso, 1979).
- Phthalaldehydic acid and 2-(hydroxymethyl)benzoic acid are metabolites of several drugs such as talampicillin (phthalidyl ampicillin) that contain an ester linkage to 3-hydroxyphthalide (Budavari, 1996 [monograph on talampicillin]). 3-Hydroxyphthalide is the lactol form of phthalaldehydic acid and may exist in equilibrium with it depending on the solvent and temperature (Wheeler et al., 1957). The human metabolism of these drugs has been well studied.

Acute Exposures

LC₅₀/LD₅₀ Values: i.p. LD₅₀ = 27 mg/kg [mice] (Caujolle et al., 1956)
99.8% pure, technical grade
oral LD₅₀ = 121 mg/kg [rats] ([WATCH subgroup, 2003](#))
dermal LD₅₀ > 2000 mg/kg [rabbits] ([WATCH subgroup, 2003](#))
Cidex-OPA[®] Solution
oral LD₅₀ > 5000 mg/kg [rats] ([Advanced Sterilization Products, 2005](#))
dermal LD₅₀ > 2000 mg/kg [rabbits] ([Advanced Sterilization Products, 2005](#))

Route: oral
Species: rat (Sprague-Dawley; 5/sex)
Dose/Duration: 25, 50, 100, 250, or 500 mg/kg (single dose); 99.8% pure OPA
Observation Time: not provided
Effects: gross necropsy: extensive damage to stomach and intestines at ≥50 mg/kg; treatment-related deaths within 4 days of dosing; ataxia, decreased activity, diarrhea, respiratory irregularity, and urinary incontinence—disappeared within a week.
Source(s): [WATCH subgroup \(2003\)](#)

Route: oral (gavage)
Species: rat (Sprague-Dawley; 5/sex/dose)
Dose/Duration: 0, 10, 50, or 100 mg/kg (single dose); 99.7% pure OPA
Observation Time: not provided
Effects: death at mid dose (1/15 males and 1/15 females) and high dose (5/20 males and 7/20 females); lethargy, difficulty in breathing, prostration, piloerection, crusty nose or eyes, clear secretions around nose or mouth, and gasping
Source(s): [WATCH subgroup \(2003\)](#)

Route: dermal
Species: rabbit (New Zealand white; 5/sex)
Dose/Duration: 2000 mg/kg to shaved skin under occlusion for 24 hrs; 99.8% pure OPA
Observation Time: 14 days
Effects: skin damage at contact site; severe eschar in all animals; no deaths, signs of systemic toxicity, or significant changes in body weight
Source(s): [WATCH subgroup \(2003\)](#)

Subchronic Exposures

Route: oral (gavage)
Species: rat (strain not given; 10-15/sex)

Chemical Information Profile for *o*-Phthalaldehyde

Dose/Duration: 0, 0.5, 5, or 50 mg/kg/day for 90 days [Note: high dose reduced to 25 mg/kg/day starting day 11 in females due to large number of deaths within first 10 days]

Observation Time: not provided

Effects: high-dose animals only: treatment-related deaths (12/15 males and 10/15 females); severe damage to the gastrointestinal tract; increased number of total leukocytes, and segmented neutrophils in males and females (indicative of inflammatory condition), and in white blood cells and monocytes in males; decreased total protein (20%), albumin (22%), and globulin levels (23%) in males only. [Note: reduced absolute weight of thymus, heart, kidney, and testes not considered to be OPA-related.]

Source(s): [WATCH subgroup \(2003\)](#)

Note: NOEL = 5 mg/kg/day ([Advanced Sterilization Products, 2005](#))

Chronic Exposures

Not available

Synergistic/Antagonistic Effects

Not available

Cytotoxicity

Cytotoxic to *Salmonella typhimurium* strains TA98, TA100, TA102, TA104, TA1535, and TA1537 with and without metabolic activation, Chinese hamster ovary (CHO) cells with and without metabolic activation, mouse lymphoma cells, and rat hepatocytes ([WATCH subgroup, 2003](#)).

Reproductive and Developmental Toxicity

Human Studies: Not available

Animal Studies: No change was observed in the number of live or dead fetuses, corpora lutea, resorption, fetal weight, external examination, or examination of the soft tissue of fetuses of female rats given 10-40 mg/kg bw OPA (route not provided) on gestation day 6-15. At the high dose, fetal skeletons had increased occurrence of unossified vertebral centrum, unossified or incompletely ossified sternbrae, and bent and/or wavy ribs; however, this was likely due to maternal toxicity and not developmental toxicity. In all treated groups, the clinical signs of toxicity were similar to those reported in the 90-day study (see *Subchronic Exposures*). Body weights and water consumption were significantly lower in high-dose rats, and food consumption was significantly lower in mid- and high-dose groups compared to controls. Treatment-related deaths also occurred in dams at 10 and 40 mg/kg doses. Dead rats had moderate to severe distended stomach and/or intestines, depressions in stomach, mottled liver, foci, and dark lungs ([WATCH subgroup, 2003](#)).

Carcinogenicity

Not available

Anticarcinogenicity

Not available

Genetic Toxicity

Microbial Gene Mutation: 99% Pure OPA: negative in *S. typhimurium* strains TA98, TA102, TA104, TA1535, and TA1537 with or without metabolic activation ([WATCH subgroup, 2003](#))

Human Studies (*in vitro* and *in vivo*): Not available

Animal Studies (*in vitro* and *in vivo*)

Gene Mutation: 99-99.7% Pure OPA: negative for mutation at the thymidine kinase locus in mouse lymphoma cells and the HGPRT locus in CHO cells with and without metabolic activation; negative for unscheduled DNA synthesis in rat hepatocytes (Harbell, 1988; [WATCH subgroup, 2003](#))

Cytogenetic Effects: 99-99.7% Pure OPA: induced chromosome aberrations and sister chromatid exchanges in CHO cells with and without metabolic activation; negative for chromosome aberrations in rat bone marrow cells ([WATCH subgroup, 2003](#))

Germ Cell Effects: Not available

Neurotoxicity

Not available

Immunotoxicity

Human Studies

- Since 1999, when Cidex-OPA[®] was first marketed, anaphylaxis-like reactions (nausea, penile swelling, hives, eyes irritation, anaphylactic shock, etc.) have been reported in 24 of ~1 million patients undergoing urological procedures; in all cases, instruments were manually processed ([MHRA, 2004](#)).
- In four patients undergoing cystoscopy for reevaluation of bladder cancer, nine episodes of severe anaphylaxis (which included urticaria, angioedema, penile itching/edema, laryngeal edema, etc.) were reported following the procedure (usually after the fourth or fifth time). Skin tests showed OPA to be the cause (Sokol, 2004; PMID:[15316522](#)).
- In two male patients diagnosed with bladder cancer and undergoing surveillance cystoscopy, prick tests showed an association between OPA and urticaria, angioedema of the genitals, and anaphylaxis (Joshi and Rosenfeld, 2004 abstr.).
- Anaphylaxis was reported in a 25-year-old woman after laryngoscopy for a vocal cord papilloma; skin tests and *in vitro* histamine release tests identified OPA and serum IgE as the mediators (Suzukawa et al., 2006 lett.).
- The first case of occupational bronchial asthma and contact dermatitis, reported in a nurse working in an endoscopy unit, was linked to OPA exposure (latency period of 9 and 12 months, respectively); OPA air concentrations ranged from 1.2-2.0 ppb. Both were no longer seen when the nurse was transferred to another workplace ([Fujita et al., 2006](#)).

Animal Studies: Negative results were obtained for Cidex-OPA[®] (containing 0.56% OPA) in a guinea pig Buehler assay; however, no definite conclusions were drawn regarding OPA's sensitization potential due to study limitations ([WATCH subgroup, 2003](#)). The manufacturers of Cidex-OPA[®] Solution reported it a nonsensitizer in a dermal sensitization test with guinea pigs ([Advanced Sterilization Products, 2003](#)).

D. Mechanistic Data

Target Organs/Tissues

Human: Not available

Animal: Stomach, intestines, respiratory tract, skin

Endocrine Modulation

Not available

Effect on Enzymes

Human: OPA inhibited ADP-induced change in platelet shape and aggregation without interacting with adenylate cyclase (Puri and Colman, 1991; PMID:[1910292](#)).

Animal: Reported to inactivate/inhibit several enzymes in different species:

Rabbit

- *p*-xylene hydroxylase, benzphetamine *N*-demethylase activities and cytochrome P-450 (without NADPH) in pulmonary and hepatic microsomes (Patel, 1979)
- sarcoplasmic reticulum Ca²⁺-ATPase, and pyruvate kinase in skeletal muscle (Abramson et al., 2001 [PMID:[11437355](#)]; Yilmaz and Ozer, 1990 [PMID: [2337353](#)])
- decreased ATPase affinity for ATP and phosphorylation and dephosphorylation rates of ATPase [no effect on the rates of Ca²⁺ binding or transport] in skeletal muscle ([Khan et al., 1996](#))

Cow

- succinic semialdehyde reductase from bovine brain (Cho et al., 1996; PMID:[8612746](#))
- beef liver glutamate dehydrogenase (Pandey et al., 1996; PMID:[8652617](#))

- adenosine cyclic 3',5'-monophosphate dependent protein kinase from bovine skeletal muscle (Puri et al., 1985a; PMID:[3936543](#)) and guanosine cyclic 3',5'-monophosphate dependent protein kinase from bovine lung (Puri et al., 1985b; PMID:[3002444](#))
- Pig – lactate dehydrogenase from heart and α -amylase from pancreas (Ueyama et al., 1995 [PMID:[7787301](#)]; [Zheng et al., 2003](#))
- Sheep – 6-phosphogluconate dehydrogenase from liver (Giovannini et al., 1997; PMID:[9315293](#))
- Chicken – liver mitochondrial phosphoenolpyruvate carboxykinase ([Chen et al., 1991](#))
- Pigeon – liver fatty acid synthetase (Mukherjee and Katiyar, 1999; PMID:[10549164](#))
- Other Systems:** OPA also inhibited enzyme function in bacteria (α -amylase from *Bacillus subtilis*) and fungi (glutathione reductase from yeast) (Pandey and Katiyar, 1996 [PMID:[9204403](#)]; Ueyama et al., 1995 [PMID:[7787301](#)]).

Modes of Action

Human: Not available

Animal: Inactivation of enzyme function by OPA generally occurs from the formation of isoindole due to the cross-linking of OPA with a cysteine and lysine residue at the active sites of the enzyme (see sources above in *Effects on Enzymes*). OPA also inactivated cytochrome C *in vitro* which is involved in electron transport. The suggested mechanism of activity was amino group crosslinking on membrane polypeptides and reaction with enzyme free amino groups important for their normal function (White and Elliott, 1980; PMID:[6248181](#)).

Effect on Metabolic Pathways: Not available

Structure-Activity Relationships

Using the Chemical Asthma Hazard Assessment Program (*Hazassess*), which is based on structure-activity relationships, OPA was determined to be "undoubtedly hazardous"; a hazard index of 0.7251 was generated (range: 0.00-1.00 with 0 being very low odds and 1 being very high odds as a sensitizer). For comparison, glutaraldehyde, a known respiratory sensitizer, had a hazard index of 0.8242. Additionally, similarities between the structures of OPA and phthalic anhydride, also a known respiratory sensitizer, have been suggested; *Hazassess* generated a hazard index of 0.9984 for phthalic anhydride ([Rideout, 2003](#)).

A brief review of the toxic effects of glutaraldehyde is included since OPA is an alternative to the use of this functionally similar chemical:

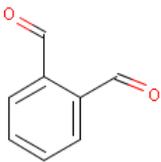
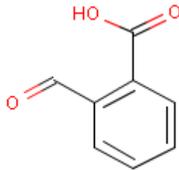
Glutaraldehyde [CAS No. 111-30-8; PubChem CID:[3485](#)] is a strong skin, eye, and respiratory irritant and can cause sensitization in humans (mainly health care workers). Cases of occupational asthma from glutaraldehyde exposure have also been reported. Several acute toxicity values are available for glutaraldehyde and include LC₅₀ values that range from 24-5000 ppm (4-hour) in rats and oral LD₅₀ values that range from 100-1300 mg/kg in mice, 89-820 mg/kg in rats, and 572-1440 mg/kg in rabbits. [Note: LD₅₀s included various aqueous solutions and other formulations.] It was negative for carcinogenicity in an NTP two-year inhalation study in male and female mice and rats and in a separate oral study of rats. The ACGIH considers glutaraldehyde not classifiable as a human carcinogen (HSDB, 2005). It was generally positive for mutagenicity in *S. typhimurium* strains TA98, TA102, TA104, and TA2638; negative in TA97, TA1535, and TA1537; equivocal in TA100; and gave mixed results in *Escherichia coli*. Glutaraldehyde was mutagenic in mouse lymphoma cells and induced unscheduled DNA synthesis. In Chinese hamster lung cells, structural and ploidy changes were observed in chromosomes in the presence and absence of metabolic activation (CCRIS, 2005). Glutaraldehyde induced sister chromatid exchange but no mutations in CHO cells (GENETOX, 1998). It induced hypersensitivity reactions in guinea pigs but none were observed in mice (NTP, 1986).

Congeners/metabolites: See Appendix

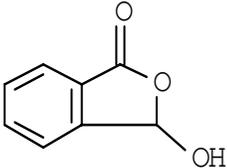
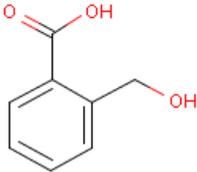
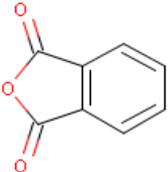
Reactive Moieties: Phthalidyl (isobenzofuranyl) moiety

Chemical Information Profile for *o*-Phthalaldehyde

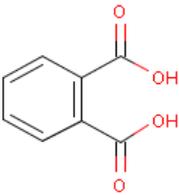
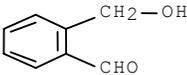
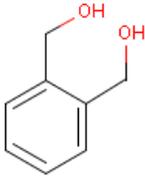
Appendix. SAR Information for Selected Metabolites and Analogs of *o*-Phthalaldehyde [CAS No. 643-79-8] ¹

Chemical Name	CAS RN & PubChem CID	CAPLUS Refs.	Structure	Physiological Activities and Other Comments
1,2-Benzenedicarboxaldehyde (9CI) (CA INDEX NAME); CIDEX OPA; <i>o</i> -Phthalaldehyde; Phthalic aldehyde	643-79-8 (CID: 4807)	2,483		The structure and synonyms for OPA are included for comparison with metabolite and analog structures and nomenclature.
<i>o</i>-Phthalaldehyde Metabolites				
Phthalaldehydic acid	119-67-5 (CID: 8406)			<ul style="list-style-type: none"> - Rat OPA metabolite (See ADME section). - Oral LD₅₀: rat = 7500 mg/kg bw; mouse = 4480 mg/kg bw (RTECS, 1997a). - Inactive up to 100 µg/mL for fungistatic activity (Grove, 1953). - Apoptotic-cytotoxicity in Chinese hamster V79 cells was inhibited by mouse aldo-keto reductase (Li et al., 2006 [CA record 145:329652]). - No hematological, biochemical, or histopathological abnormalities in rats given 300 mg/kg bw/day x 5 weeks (Shiobara, 1977). - In dogs, i.v. injection increased femoral blood flow and respiratory rate and reduced blood pressure [dose range was three times higher than that required for talampicillin, which is metabolized in dogs, rats, and humans to phthalaldehydic acid and 2-(hydroxymethyl)benzoic acid (Jeffery et al., 1978; Jones et al., 1978); the phthalidyl moiety weight is less than 30% that of talampicillin (Nozaki et al., 1975 [Japanese]; EMBASE record 77012144)].

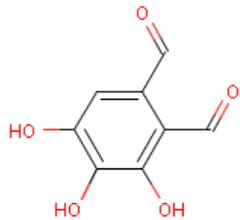
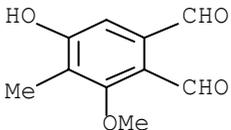
Chemical Information Profile for *o*-Phthalaldehyde

Chemical Name	CAS RN & PubChem CID	CAPLUS Refs.	Structure	Physiological Activities and Other Comments
<p>3-Hydroxyphthalide; 1(3H)-Isobenzofuranone, 3-hydroxy- (9CI) (CA INDEX NAME)</p> <p>[Note: PubChem lists phthalaldehydic acid as a synonym, but the PubChem record for phthalaldehydic acid does not list 3-hydroxyphthalide.]</p>	<p>16859-59-9 (CID: 636688)</p>	<p>72</p>		<ul style="list-style-type: none"> - Phthalaldehydic acid isomer; in equilibrium with phthalaldehydic acid in aqueous solutions (Wheeler et al., 1957). - Solution is 93.7% 3-hydroxyphthalide @ 25 °C (Bell et al., 1971 [CAPLUS record 1972:3193]); in strongly acidic or basic solutions phthalaldehydic acid predominates (Bernatek, 1960 [CAPLUS records 1968:29104 and 1962:38282]; Kagan, 1967). - Esterifies carboxylic acid moiety of drugs to give phthalidyl prodrugs (e.g., talampicillin; CID: 71447). [also used to alkylate a drug N atom to give another type of phthalide derivative (e.g., phthalidyltheophylline; CID: 147130 or 1-phthalidyl-5-fluorouracil; CID: 128467).] - Has antimicrobial and parasitocidal activities as do its aromatic and fatty acid esters (e.g., Matsugo et al., 1983 [Japanese; CAPLUS record 1984:120983]; Wheeler and Young, 1959a,b [Dow Chemical Co. patents; CAPLUS records 1959:72455 and 1960:2048]).
<p>2-(Hydroxymethyl)benzoic acid; •-Hydroxy-<i>o</i>-toluic acid</p>	<p>612-20-4 (CID: 11920)</p>	<p>82</p>		<ul style="list-style-type: none"> - Mammalian metabolite of phthalaldehydic acid (an OPA metabolite) and of several drugs that have a phthalidyl moiety (See ADME section.) [not in PubMed and/or no informative abstract in TOXLINE] - A fungal biodegradation product of benz[<i>a</i>]anthracene (Cajtham et al., 2006) and constituent of edible plants (e.g., Jun et al., 2005 [CA record 145:144260]). - Found in atmospheric emissions from waste incineration plants (Jay and Stieglitz, 1995 [TOXCENTER 1995:166109]) and in rain water (Watabe et al., 1988). - A principal rat and goat metabolite of the herbicide cinmethylin (Cinch) (CID: 91745) (Lee et al., 1988; Woodward et al., 1989) [TOXCENTER abstracts 1988:109070 and 1989:133022].
<p>Phthalic anhydride</p>	<p>85-44-9 (CID: 6811)</p>	<p>Not sought.</p>		<ul style="list-style-type: none"> - 4% of the urinary metabolites from rats 72 hours after dosing with OPA (Ohtawa et al., 2001; EMBASE record 2002098787). - Oral LD₅₀: rat ≥4020 mg/kg bw; mouse ≥2000 mg/kg bw [1530 and 1500 mg/kg bw, respectively, in ChemIDplus]. - Human inhalation exposure associated with irritation, asthmatic responses, and blood-pressure lowering (HSDB, 2005). - Teratogenic in mice at doses approaching lethality; not carcinogenic in rat or mouse 2-year bioassays; and not a dermal sensitizer in guinea pigs (HSDB, 2005) [See IRIS for a description of the NCI carcinogenesis bioassay].

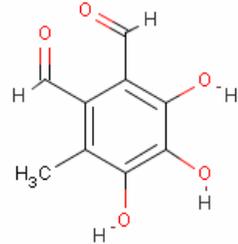
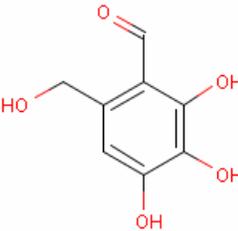
Chemical Information Profile for *o*-Phthalaldehyde

Chemical Name	CAS RN & PubChem CID	CAPLUS Refs.	Structure	Physiological Activities and Other Comments
Phthalic acid ; 1,2-Benzenedicarboxylic acid (9CI) (CA INDEX NAME)	88-99-3 (CID: 1017)	Not sought.		<ul style="list-style-type: none"> - Seldom detectable as a metabolite of phthalaldehydic acid (Shiobara and Ogiso, 1979). - Oral LD₅₀: rat = 2530 mg/kg bw (ChemIDplus). - Not mutagenic in <i>Salmonella</i>; caused only cytotoxicity in CHO cells (HSDB, 2003). - Tested in the teratogenicity FETAX assay (Bantle et al., 1999) and <i>in vitro</i> assays for inhibition of cell multiplication and of murine fetal metabolism (Karzel et al., 1989 [German]). - Induced axon-sparing lesions in the striatum when injected intrastrially in rats and evoked release of acetylcholine in striatal slices (Lehmann et al., 1985). - Activated pregnane X receptor-mediated transcription in endocrine disruptor test (Masuyama et al., 2000). - Rat metabolism reported by Williams and Blanchfield (1974)².
2-(Hydroxymethyl)benzaldehyde ³	55479-94-2 (No PubChem record)	27		<ul style="list-style-type: none"> - Possible metabolite in which one of the formyl groups of OPA is reduced to the alcohol. [Not in ChemIDplus or PubChem.] - Reported to be in equilibrium with 3-hydroxyphthalide, a cyclic hemiacetal, in aqueous media (favoring the cyclic form by 6.7:1) (Harron et al., 1981). [3-Hydroxyphthalan was not found in the Registry file; two CAPLUS records found by keyword search.] - Inactive up to 100 µg/mL for fungistatic activity (Grove, 1953).
1,2-Benzenedimethanol ³ ; <i>o</i> -(Hydroxymethyl)benzyl alcohol	612-14-6 (CID: 69153)	406		<ul style="list-style-type: none"> - Possible metabolite in which both of the formyl groups of OPA are reduced to the alcohol. - Used in organic syntheses (Google Scholar search) and included on the TSCA Inventory (ChemIDplus). - Inactive in the NCI Yeast Anticancer Drug Screen (6 assays) and in an NCI In Vivo Anticancer Drug Screen.

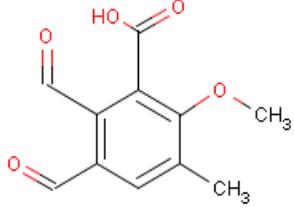
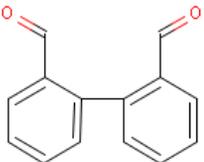
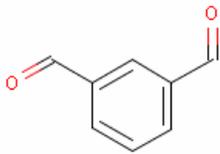
Chemical Information Profile for *o*-Phthalaldehyde

Chemical Name	CAS RN & PubChem CID	CAPLUS Refs.	Structure	Physiological Activities and Other Comments
<i>o</i>-Phthalaldehyde Analogs				
1,2-Benzenedicarboxaldehyde, 3,4,5-trihydroxy- (9CI) (CA INDEX NAME); Fomecin B	16790-41-3 (CID: 167570)	8		<ul style="list-style-type: none"> – Antibacterial compound produced as a minor metabolite by certain strains of the basidiomycetes <i>Fomes juniperinus</i> and <i>Tricholomopsis rutilans</i> (Budavari, 1996; Liberra et al., 1995). – Cytotoxic to human tumor (HeLa) cells (Liberra et al., 1995).
1,2-Benzenedicarboxaldehyde, 5-hydroxy-3-methoxy-4-methyl- (9CI) (CA INDEX NAME); Quadrilineatin	642-27-3 (No PubChem record)	9		<ul style="list-style-type: none"> – Metabolite of <i>Aspergillus quadrilineatus</i> (Birkinshaw et al., 1957). – Strongly inhibited electron transport and oxidation phosphorylation in sweet potato and mung bean mitochondria (White and Elliott, 1980). – Inactivated cytochrome C <i>in vitro</i> [suggested mechanism of action was amino group crosslinking on membrane polypeptides and reaction with enzyme free amino groups important for their normal function] (White and Elliott, 1980). – Weak activity against <i>Staphylococcus aureus</i> and <i>Escherichia coli</i> (Smith, 1957). – Not as potent an antifungal agent as related phthalaldehydes of fungal origin (Smith, 1957). – Inactive in one <i>in vivo</i> and six yeast anticancer screening assays (BioActivity Summary).

Chemical Information Profile for *o*-Phthalaldehyde

Chemical Name	CAS RN & PubChem CID	CAPLUS Refs.	Structure	Physiological Activities and Other Comments
1,2-Benzenedicarboxaldehyde, 3,4,5-trihydroxy-6-methyl- (9CI) (CA INDEX NAME); Flavipin	483-53-4 (No PubChem record)	23		<ul style="list-style-type: none"> - Metabolite of <i>Aspergillus</i> species <i>A. flavipes</i> and <i>A. terreus</i> (Raistrick and Rudman, 1956), of <i>Epicoccum nigrum</i> (Madrigal et al., 1993), and of <i>Epicoccum purpurascens</i>. - Has antimicrobial properties (Mallea et al., 1991). - Strongly inhibited electron transport and oxidation phosphorylation in sweet potato and mung bean mitochondria (White and Elliott, 1980). - Inactivated cytochrome c <i>in vitro</i> [suggested mechanism of action was amino group crosslinking on membrane polypeptides and reaction with enzyme free amino groups important for their normal function] (White and Elliott, 1980). - Screened for ability to inhibit the type I interleukin 1 receptor (Stefanelli et al., 1991).
Benzaldehyde, 2,3,4-trihydroxy-6-(hydroxymethyl)- (9CI) (CA INDEX NAME); Fomecin A (6CI, 8CI)	1403-56-1 (CID: 14964)	15		<ul style="list-style-type: none"> - I.V. LD₅₀: mouse = 50 mg/kg bw (Budavari, 1996; RTECS, 1996) [<i>The Merck Index</i> stated doses up to this value had "no apparent ill effect" (Budavari, 1996)]. - Inactive in one <i>in vivo</i> and six yeast anticancer screening assays (BioActivity Summary). - Suggested along with other polyhydroxylated aromatic compounds for use in treatment of amyloidosis and α-synuclein fibril diseases (Castillo et al., 2001 pat. [CA record 135:102574]). - Compositions containing oxy group-bearing aromatic aldehydes, including fomecin A, that are used in pharmaceuticals and cosmetics were patented by Cutanix Corporation, USA (Engles et al., 2003 pat. [CA record 139:12263]).

Chemical Information Profile for *o*-Phthalaldehyde

Chemical Name	CAS RN & PubChem CID	CAPLUS Refs.	Structure	Physiological Activities and Other Comments
Gladiolic acid	478-05-7 (CID: 96916)			<ul style="list-style-type: none"> - Secondary metabolite of certain <i>Penicillium</i> species. - Induced hepatorenal changes in rats (treatment details not in abstract) e.g., reduction in serum albumin/glucose ratio and increase in aspartate aminotransferase, aspartate aminotransferase, total bilirubin, total cholesterol, and creatinine (El-Gendy et al., 1999 [CA record 132:147735]). - Strongly inhibited electron transport and oxidation phosphorylation in sweet potato and mung bean mitochondria (White and Elliott, 1980). - Inactivated cytochrome C <i>in vitro</i> [suggested mechanism of action was amino group crosslinking on membrane polypeptides and reaction with enzyme free amino groups important for their normal function] (White and Elliott, 1980). - Fungistatic activity (pH dependent) was slightly more effective than that of OPA (pH independent) against <i>Botrytis allii</i> [effective concentrations: 2.8 x 10⁻⁵ M (6.25 µg/mL) and 4.8 x 10⁻⁵ M (6.5 µg/mL), respectively] (Grove, 1953). - Author concluded that the adjacent free carboxyl group in gladiolic acid contributed to the activity of the <i>o</i>-formyl groups (Grove, 1953).
Diphenaldehyde; 2,2'-Diformylbiphenyl	1210-05-5 (CID: 14585)	Not sought.		<ul style="list-style-type: none"> - Structural analog of OPA identified by PubChem. - Oral LD₅₀: rat 2830 mg/kg bw (ChemIDplus). - Induced hepatotoxicity in rats (90 mg/kg bw, i.p.) after 24 hours (Yoshikawa et al., 1987). - Inactive in the NCI <i>in vivo</i> anticancer drug screen [P388 leukemia i.p. in CD2F1 (CDF1) mice (PubChem BioActivity summary for CID: 14585)]. - Major product when phenanthrene is oxidized by ozone (Yoshikawa et al., 1987).
Isophthalaldehyde; 1,3-Benzenedicarboxaldehyde [OPA isomer]	626-19-7 (CID: 34777)	744		<ul style="list-style-type: none"> - I.V. LD₅₀: mouse = 100 mg/kg bw (ChemIDplus). - I.P. LD₅₀: mouse = 824 mg/kg bw (Caujolle et al., 1956; TOXCENTER 1957:10432). - Not antitumorigenic in a mouse leukemia model (BioActivity Summary). - Inactive up to 100 µg/mL for fungistatic activity (Grove, 1953).

Chemical Information Profile for *o*-Phthalaldehyde

Chemical Name	CAS RN & PubChem CID	CAPLUS Refs.	Structure	Physiological Activities and Other Comments
Terephthalaldehyde ; 1,4-Benzenedicarboxaldehyde [OPA isomer]	623-27-8 (CID: 12173)	2,412		<ul style="list-style-type: none"> - I.P. LD₅₀: mouse = 1085 mg/kg bw (Caujolle et al., 1956; TOXCENTER 1957:10432). - LD₅₀: mouse = 1154 mg/kg bw (route not reported) (RTECS, 1997b). - Antimicrobial but no anti-tumor activity in six yeast and three mouse models (BioActivity Summary). - Inactive up to 100 µg/mL for fungistatic activity (Grove, 1953).

¹ No toxicity information was sought for the OPA analogs 2,3-naphthalenedicarboxaldehyde (CID: [96400](#)) and 2,3-anthracenedicarboxaldehyde (CID: [195906](#)), which are used in analytical chemistry to derivatize amino acids, etc., and would generate thousands of unrelated search results. Yeast anti-cancer drug screen data (six assays) are available for the anthracene analog via its PubChem record.

² No abstract available.

³ Potential OPA metabolite [inferred from 2006 review of benzaldehyde (CID: [240](#)) toxicity (Andersen, 2006; [PMID: 16835129](#)) which notes that benzaldehyde reduction to benzyl alcohol (CID: [244](#)) by NADH is catalyzed by liver alcohol dehydrogenase (Jacobs et al., 1974)].

References

- Andersen, A. 2006. Final report on the safety assessment of benzaldehyde. *Int J Toxicol*, 25(Suppl. 1):11-27. [Note that this document from the Cosmetic Ingredient Review Expert Panel does not identify any personal author and does not list the panel members.]
- Bantle, J.A., Finch, R.A., Fort, D.J., Stover, E.L., Hull, M., Kumsher-King, M., and Gaudet-Hull, A.M. 1999. Phase III interlaboratory study of FETAX. Part 3. FETAX validation using 12 compounds with and without an exogenous metabolic activation system. *J Appl Toxicol*, 19(6):447-472. Abstract from PubMed 10547627.
- Bell, R.P., Cox, B.G., and Timini, B.A. 1971. Equilibriums and kinetics in the isomerization of *o*-formylbenzoic acid. *J Chem Soc B Phys Org*, 0(11):2247-2250. Abstract from CAPLUS 1972:3193.
- Bernatek, E. 1960. Structure of the *o*-formylbenzoate ion. *Acta Chemica Scandinavica*, 14:785-788. Abstract from CAPLUS 1962:38282.
- BioActivity Summaries of NCI testing (available by links from the PubChem records for each compound): [BioActivity Summary](#) for diphenaldehyde; [BioActivity Summary](#) for fomecin A; [BioActivity Summary](#) for isophthalaldehyde; [BioActivity Summary](#) for quadrilineatin; [BioActivity Summary](#) for terephthalaldehyde.
- Birkinshaw, J.H., Chaplen, P., and Lahoz-Oliver, R. 1957. Studies in the biochemistry of micro-organisms. 102. Quadrilineatin (1:2-diformyl-5-hydroxy-3-methoxy-4-methylbenzene), a metabolic product of *Aspergillus quadrilineatus* Thom & Raper. *Biochem J*, 67(1):155-163.
- Budavari, S., Ed. 1996. *The Merck Index*, 12th ed. Merck and Co., Inc., Whitehouse Station, NJ. Monographs 256 (Fomecins), 9204 (Talampicillin), and 9214 (Talnidflumate) [from CD-ROM].
- Cajthaml, T., Erbanova, P., Sasek, V., and Moeder, M. 2006. Breakdown products on metabolic pathway of degradation of benz[*a*]anthracene by a ligninolytic fungus. *Chemosphere*, 64(4):560-564. Abstract from PubMed 16403417 and CA 145:227233.
- Castillo, G.M., Choi, P.Y., and Snow, A.D. 2001 pat. Polyhydroxylated aromatic compounds for the treatment of amyloidosis and α -synuclein fibril diseases. PCT Int Appl., Patent No. WO 2001049281. Abstract from CA 135:102574.
- Caujolle, F., Meynier, D., Auriac, P., Frajdenrach, S., and Troplent, L. 1956. Toxicity of phthalic aldehydes. *Compt rend*, 243:193301934. Abstract from TOXCENTER 1957:10432.
- ChemIDplus. 2004. Search by synonym, chemical name, CASRN, etc. at <http://chem.sis.nlm.nih.gov/chemidplus/>. Last revised on September 9, 2004.
- Dunnick, J.K., and Elwell, M.R. 1989. Toxicity studies of amphetamine sulfate, ampicillin trihydrate, codeine, 8-methoxypsoralen, alpha-methyldopa, penicillin VK and propantheline bromide in rats and mice. *Toxicology*, 56(2):123-136. Abstract from PubMed 2499954.
- El-Gendy, A.K., Saber, S., and Tohamy, A. 1999. Consequences of fungal secondary metabolites on hepatorenal changes in rats. *Afr J Mycol Biotechnol*, 7(1):57-64. Abstract from CA 132:147735.
- Engles, C.R., Fuller, B., and Pilcher, B.K. 2003 pat. Pharmaceutical and cosmetic compositions containing oxy group-bearing aromatic aldehydes. PCT Int Appl., Patent No. 2003043621. Abstract from CA 139:12263.
- Gordon, M.D., Ezzell, R.J., Bruckner, N.I., and Ascenzi, J.M. 1994. Enhancement of mycobactericidal activity of glutaraldehyde with α,β -unsaturated and aromatic aldehydes. *J Ind Microbiol*, 13(2):77-82. Abstract from CAPLUS 1995:51120.
- Grove, J.F. 1953. Gladiolic acid, a metabolic product of *Penicillium gladioli*. *Biochem J*, 54(4):664-673.
- Harron, J., McClelland, R.A., Thankachan, C., and Tidwell, T.T. 1981. Kinetic study of the reversible formation of cyclic hemiacetals from 2-(hydroxymethyl)benzaldehyde and 2-(α -hydroxyethyl)benzaldehyde. *J Org Chem*, 46(5):903-910. Internet address: http://pubs.acs.org/cgi-bin/abstract.cgi/jocea/1981/46/i05/f-pdf/f_jo00318a015.pdf?sessid=600613 (first page only). Last accessed on November 6, 2006.

Chemical Information Profile for *o*-Phthalaldehyde

HSDB (Hazardous Substances Data Bank). 2003. Phthalic acid. HSDB No. 1339. Profile last updated on March 5, 2003. Internet address (available via TOXNET on NLM): <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB>. Last accessed on November 6, 2006.

HSDB. 2005. Phthalic anhydride. HSDB No. 4012. Profile last updated on June 23, 2005. Internet address (available via TOXNET on NLM): <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB>. Last accessed on November 6, 2006.

Jacobs, J.W., McFarland, J.T., Wainer, I., Jeanmaier, D., Ham, C., Hamm, K., Wnuk, M., and Lam, M. 1974. Electronic substituent effects during the liver alcohol dehydrogenase catalyzed reduction of aromatic aldehydes. *Biochemistry*, 13(1):60-64.

Jay, K., and Stieglitz, L. 1995. Identification and quantification of volatile organic components in emissions of waste incineration plants. *Chemosphere*, 30(7):1249-1260. Abstract from TOXCENTER 1995:166109.

Jeffery, D.J., Jones, K.H., and Langley, P.F. 1978. The metabolism of talampicillin in rat, dog and man. *Xenobiotica*, 8(7):419-427. Abstract from PubMed 685291. Abstract from PubMed 685291.

Jones, K.H., Langley, P.F., and Lees, L.J. 1978. Bioavailability and metabolism of talampicillin. *Chemotherapy*, 24(4):217-226. Abstract from PubMed 348415.

Jun, H.R., Cho, I.H., Choi, H-K., and Kim, Y.-S. 2005. Comparison of volatile components in fresh and dried red peppers (*Capsicum annum* L.). *Food Sci Biotechnol*, 14(3):392-398. Abstract from CA 145:144260.

Kagan, J. 1967. The structure of phthalaldehydic acid. *J Org Chem*, 32(12):4060-4062. Abstract from CAPLUS 1968:29104. Internet address: http://pubs.acs.org/cgi-bin/abstract.cgi/jocea/1967/32/ill/f-pdf/f_jo01287a078.pdf?session=600613 (first page only).

Karzel, K., Munzenberg, K.J., and Krisinger, J. 1989. The effect of benzenecarboxylic acids—in particular mellitic acid—in *in vitro* biological system (German). *Arzneimittelforschung*, 39(1):6-11. Abstract from PubMed 2719744.

Lee, P.W., Woodward, M.D., and Stearns, S.M. 1988. *o*-Acylation as a novel conjugation pathway for cinmethylin in rats. *J Agric Food Chem*, 36(1):95-97. Abstract from TOXCENTER 1988:109070.

Lehmann, J., Ferkany, J.W., Schaeffer, P., and Coyle, J.T. 1985. Dissociation between the excitatory and "excitotoxic" effects of quinolinic acid analogs on the striatal cholinergic interneuron. *J Pharmacol Exp Ther*, 232(3):873-882. Abstract from PubMed 2983071.

Li, D., Hinshelwood, A., Gardner, R., McGarvie, G., and Ellis, E.M. 2006. Mouse aldo-keto reductase AKR7A5 protects V79 cells against 4-hydroxynonenal-induced apoptosis. *Toxicology*, 226(2-3):172-180. Abstract from CA 145:329652.

Liberra, K., Jansen, R., Wegner, U., and Lindequist, U. 1995. Fomecin B as a cytotoxic metabolite from the basidiomycete *Tricholomopsis rutilans* (Schaeff. ex. Fr.) Sing. (German). *Pharmazie*, 50(5):370-371. Abstract from PubMed 7604075.

Madrigal, C., Tadeo, J.L., and Melgarejo, P. 1993. Degradation of flavipin by *Monilinia taxa*. *Mycol Res*, 97(5):634-636. Abstract from TOXLINE (secondary source ID: BIOSIS/93/25621) via TOXNET on NLM at Internet address: <http://toxnet.nlm.nih.gov/cgi-bin/sis/search>. October 19, 2006.

Mallea, M., Pesando, D., Bernard, P., and Khoualalene, B. 1991. Comparison between antifungal and antibacterial activities of several strains of *Epicoccum purpurascens* from the Mediterranean area. *Mycopathologia*, 115(2):83-88. Abstract from PubMed 1784310.

Masuyama, H., Hiramatsu, Y., Kunitomi, M., Kudo, T., and MacDonald, P.N. 2000. Endocrine disrupting chemicals, phthalic acid and nonylphenol, activate pregnane X receptor-mediated transcription. *Mol Endocrinol*, 14(3):421-428.

Matsugo, S., Fujita, F., Takamizawa, A., Hatano, Y., Hasegawa, A., Ohta, T., and Konishi, T. 1983. An application of organic peroxides to cancer therapy. 1. Synthesis and degradation studies of organic peroxide and its antibacterial effect (Japanese). *Niigata Yakka Daigaku Kenkyu Hokoku*, 3:37-44. Abstract from CAPLUS 1984:120983.

Nozaki, Y., Kumagai, F., Takeda, M., et al. 1975. (Japanese) Pharmacological studies on talampicillin hydrochloride (Japanese). *J Jpn Assoc Infect Dis*, 49(11):781-822. Abstract from EMBASE 77012144.

Ohtawa, M., Ichimoto, S., Nakaki, R., and Sugimoto, K. 2001. Absorption and excretion of [(14)C] *ortho*-phthalaldehyde following intratracheal and oral administration to male rat. *Jpn Pharmacol Ther*, 29(9):611-621. Abstract from EMBASE 2002098787.

PubChem. Database providing substance information, compound structures, and bioactivity data. Internet address (home page): <http://pubchem.ncbi.nlm.nih.gov/>.

Raistrick, H., and Rudman, P. 1956. Studies in the biochemistry of micro-organisms. 97. Flavipin, a crystalline metabolite of *Aspergillus flavipes* (Bainier & Sartory) Thom & Church and *Aspergillus terreus* Thom. *Biochem J*, 63(3):395-406.

RTECS (Registry of Toxic Effects of Chemical Substances). 1996. RN: 1403-56-1 (Formecin A). Database produced by NIOSH; available on STN International.

RTECS. 1997a. RN: 119-67-5 (Phthalaldehydic acid). Database produced by NIOSH; available on STN International.

RTECS. 1997b. RN: 623-27-8 (Terephthalaldehyde). Database produced by NIOSH; available on STN International.

Shiobara, Y. 1977. The effect of carboxyl substituent on the metabolism of aromatic aldehydes. *Xenobiotica*, 7(8):457-468.

Shiobara, Y., and Ogiso, T. 1979. The effect of a carboxyl substituent on the metabolism *in vitro* of certain aromatic aldehydes. *Xenobiotica*, 9(3):157-164.

Smith, G. 1957. Appendix. Anti-fungal tests on quadrilineatin. *Biochem J*, 67(1):163-164.

Stefanelli, S., Corti, E., Montanini, N., Denaro, M., and Sarubbi, E. 1991. Inhibitors of type-I interleukin-1 receptor from microbial metabolites. *J Antibiot (Tokyo)*, 50(6):484-489. Abstract from PubMed 9268004.

Watabe, K., Nakanishi, T., Shishido, J., Masumoto, K., Okamoto, A., Kato, Y., and Kondo, M. 1988. Identification of some organic compounds in rain water by means of a gas chromatograph-mass spectrometer-computer system. *Eisei Kagaku*, 34(1):25-30. Search result from TOXLINE (secondary source ID: BIOSIS/88/16538) via TOXNET on NLM at Internet address: <http://toxnet.nlm.nih.gov/cgi-bin/sis/search>. Last accessed on October 31, 2006.

Wheeler, D.D., and Young, D.C. 1959a. Phthalidyl esters of aromatic acids. PA: Dow Chemical Co. Patent No. US 2877236. Abstract from CAPLUS 1959:72455.

Wheeler, D.D., and Young, D.C. 1959b (pat.). Phthalidyl esters of alkanolic acids. PA: Dow Chemical Co. Patent No. US 2897210. Abstract from CALPUS 1960:2048.

Wheeler, D.D., Young, D.C., and Erley, D.S. 1957. Reactions of phthalaldehydic acid. *J Org Chem*, 22(5):547-556.

White, G.A., and Elliott, W.B. 1980. Inhibition of electron transport and oxidative phosphorylation in plant mitochondria by gliolic acid and structurally-related aromatic *ortho* dialdehydes. *Can J Biochem*, 58(1):9-22. Abstract from PubMed 6248181.

Williams, D.T., and Blanchfield, B.J. 1974. Retention, excretion and metabolism of phthalic acid administered orally to the rat. *Bull Environ Contam Toxicol*, 12(1):109-112. Search result (no abstract) from PubMed 4433845.

Woodward, M.D., Stearns, S.M., and Lee, P.W. 1989. Metabolic fate of cinmethylin in goat. *J Agric Food Chem*, 37(3):787-791. Abstract from TOXCENTER 1989:133022.

Yoshikawa, T., Giamalva, D.H., Flory, W., Ruhr, L.P., Church, D.F., and Pryor, W.A. 1987. Toxicity of polycyclic aromatic hydrocarbons. IV. Effects of diphenaldehyde, a major product of ozonized phenanthrene, in rats. *Biochem Int*, 15(1):139-146. Abstract from PubMed 2899430.