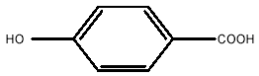
WORKPLACE ENVIRONMENTAL EXPOSURE LEVEL®

OARS WEEL

4-Hydroxybenzoic Acid (2016)

I. IDENTIFICATION[1–4]

Chemical Name: 4-Hydroxybenzoic acid
Synonyms: p-hydroxybenzoic acid, para-hydroxybenzoic acid, 4-Hydroxybenzenecarboxylic acid; 4-carboxyphenol, p-salicylic acid
CAS Number: 99-96-7
Molecular Formula: $C_7H_6O_3$
Structural Formula:



II. CHEMICAL AND PHYSICAL PROPERTIES[1,2,4]

Physical State: solid, white crystalline powder
Odor description and threshold: Not available
Molecular Weight: 138.13
Conversion factors: 1 ppm = 5.65 mg/m^3; 1 mg/m^3 = 0.18 ppm
Melting Point: 214-217 °C (338 °F).
Boiling Pt: 216.2 °C (421.2 °F)
Vapor Pressure: 2.9 x 10^{-6} mm Hg at 100 °C (212 °F), 1.9 x 10^{-7} mm Hg at 100 °C[4]
Saturated Vapor Concentration: 3.8 x 10^{-3} mm Hg at 100 °C (212 °F)
Specific gravity: 1.46
Vapor Density (air = 1): 4.76
Flammability Limits: LFL and UFL - Not available
Flash Point: Not available
Solubility: 6.0 g/L @ 25°C in water; soluble in diethyl ether, acetone. very slightly soluble in cold water. Freely soluble in alcohol. slightly soluble in chloroform. practically insoluble in carbon disulfide.
Stability and Reactivity: Stable in water at pH, 7 and 9. Incompatible with oxidizing agents, reducing agents
Partition coefficient (Log Pow): 1.37 pK1= 4.582, pK2= 9.23

III. USES[1,4]

Used as an intermediate for dyes, fungicides, cosmetics, and drugs; as a food preservative, corrosion inhibitor, anti-oxidant, and emulsifier; as a component in the manufacture of polyester; and as a constituent of liquid crystal polymers.

IV. ANIMAL TOXICITY DATA

A. Acute Toxicity

1. Lethality Data

Species	Route	LD_{50}
Rat	Oral	340 mg/kg[1,5]
Rat	Oral	6,000 mg/kg[1]
Rat (SD strain)	Oral	>5,000 mg/kg[3]
Mouse	Oral	2,200 mg/kg[1]

SD strain rats exposed to greater than 5,000 mg/kg showed no remarkable differences in body weight or deaths, one-half of animals displayed small red kidney foci at post-mortem.[3]

2. Eye Irritation

100 µg of a 25% solution of 4-hydroxybenzoic acid applied to conjunctivae of rabbits produced corneal opacity, conjunctival redness, and chemosis which were not reversible within 8 days. It was considered to be a moderate eye irritant.[1] 100 µg of a 100% solution of 4-hydroxy-benzoic acid applied to conjunctivae of rabbits produced severe corneal burning and opacity and was considered to be corrosive to the eyes of rabbits.[3]

3. Skin Absorption

Dermal absorption in Fischer 344 female rats was very low (2 %). The major portion of the dose not absorbed dermally in 24 hr was washed from the skin. (see also section on toxicokinetics).[1]

4. Skin Irritation

New Zealand white rabbits 4-Hydroxybenzoic acid (500 mg) was applied to the clipped skin with occlusive dressing for 24 hours and evaluated approximately at 24, 48 and 72 hours, and 8 days. Mild erythema and edema were observed. Erythema was reversible within 8 days but edema was not. 4-HT was considered to be slightly irritating to skin.[1]

5. Skin Sensitization

Guinea pig maximization test (Dunkin Hartley strain) 10 animals (4 controls) were inducted intradermally with a 1.0% solution and topically with a 20% solution six to eight days later. After 12-14 days, all animals were challenged with a 20% solution. Mild positive response above controls (20%) was produced.[1,6]

In a local lymph node assay four female mice (CBA/Ca strain) were inducted by daily topical application of 2.5-15.0% for three consecutive days. Five days after the initiation of exposure, [3H] methyl thymidine was injected and the labelling in lymph node cells was measured. The ratio of labelling incorporation by test lymph node cells to that recorded for control lymph node cells, (T/C) ratio was 0.6-1.5 (more than 3.0 is positive).[6] Therefore, the results of the assay were negative.

6. Acute Inhalation Toxicity

No information available

B. Subacute Toxicity

In a 9-day oral study, Fisher 344 rats exposed to a diet containing 4% 4-hydroxybenzoic acid showed no histological changes in the forestomach.[7]

C. Subchronic Toxicity

4-Hydroxybenzoic acid was administered by gavage at doses of 40, 200 or 1,000 mg/kg for 45 days in males and from 14 days before mating to day 3 of lactation in females in SD (Crj: CD) rats as part of combined repeat dose and reproductive/ developmental toxicity screening test. There was no treatment related deaths. 4-Hydroxybenzoic acid induced rale and temporary salivation (sometimes accompanied by rhinorrhea) at 1,000 mg/kg and slightly at 200 mg/kg; this suggested respiratory tract irritation. There were no adverse effects on body weight change and food consumption. At necropsy, no histological and morphological changes were observed. In males there was a decrease in the percentage of lymphocytes and blood glucose levels at ≥ 200 mg/kg and decreases in total protein and increase in A/G ratio, GPT and GOT were observed at 1,000 mg/kg. These changes were significant, but not considered adverse effects by the study authors and the NOAEL for systemic toxicity was considered to be 1,000 mg/kg/day.[1]

D. Chronic Toxicity/Carcinogenicity

No information available

E. Reproductive/Developmental Toxicity

In a repeat dose screening study, 4-hydroxybenzoic acid was administered by gavage to SD (Crj: CD) rats at doses of 40, 200 or 1,000 mg/kg for 45 days in males and from 14 days before mating to day 3 of lactation in females. There were no adverse effects on copulation, fertility, maintenance of pregnancy, parturition, lactation, viability, sex ratio, body weights or morphological appearance of pups at all treated groups. The NOAEL for reproductive toxicity was considered to be 1,000 mg/kg/day.[1]

Sprague-Dawley rats at day 11 of gestation received single oral doses of 333, 667, or 1,000 mg/kg. At the high dose, 4/16 females died. At 667 and 1000 mg/kg, there were dose-related significant decreases in maternal weight gain at 24 and 48 hrs post-treatment with a corresponding decrease in litter size and litter biomass. The NOAEL was considered by the study authors to be 333 mg/kg; however, this contradicts the conclusion of a NOAEL of 1000 mg/kg in the OECD SIDS document).[1,8] No teratogenic effect was observed after subcutaneous application to rats at day 9 of gestation or intramuscular application to mice at day 9 or 12 of gestation.[1,9]

Subcutaneous administration of 5, 50, or 500 µg/100g 4-hydroxybenzoic acid in CD1 mice (n = 14) showed a dose dependent increase in amount of cornified vaginal epithelial cells and uterotrophic effect (measured by uterine weight) at the high dose especially in immature animals.[10] The positive uterotropic results were not, however, repeated in either immature B6D2F1 mice exposed subcutaneously to 4-hydroxybenzoic acid at doses of 1, 10, or 100 mg/kg bw/day for three days or Wistar rats exposed subcutaneously to 5 mg/kg bw/day for 3 days.[11]

F. Genotoxicity/Mutagenicity

1. In vitro

Ames (TA 1535, 1537, 1538, 98, 100,102,104) bacterial test: was negative (+/- S9); HPRT/V79 CHO test was negative (+/- S9); Mice (Swiss strain) micronucleus test was negative. Gene reverse mutation was negative in *S. typhimurium* TA100, TA98, TA1535, TA1537, E. *coli* strains WP2uvrA, CM611uvrA/ LEXA and WP2UVRA/PKM101 with and without metabolic activation.

2. In vivo

A chromosomal aberration test conducted at concentrations of 0, 0.18, 0.35, 0.70 mg/ml with and without metabolic activation in cultured Chinese hamster lung (CHL/IU) cells (pH-adjusted

conditions) was negative. Based on these results, 4-hydroxybenzoic acid was considered to be not genotoxic by the study authors.[1,12]

G. Metabolism/Pharmacokinetics

A toxicokinetics study performed with Fischer 344 female rats (29 days old) indicated that urinary excretion was the predominant means of elimination for 4-hydroxybenzoic acid and occurred primarily within 24 hr after intraperitoneal (i.p.) and dermal administration. (120 hr cumulative excretion after i.p. administration was 86.5 % in urine and 3.4 % in feces, and 10.2 % was detected in the carcasses of treated animals). The 120 hr cumulative excretion after dermal administration was 1.9 % in urine and 0.04 % in feces. 2 % and 0.28 % was detected in the treated skin and the carcasses of treated animals, respectively.[13–16]

Metabolism in the rat of p-hydroxybenzoic acid and its methyl, ethyl and propyl esters resulted in the appearance in the urine first of free p-hydroxybenzoic acid, followed by the glucuronide and phydroxyhippuric acid, the concentration of which increased as that of the free p-hydroxybenzoic acid /decreased.[17]

Groups of 4-8 rabbits were given 4-hydroxybenzoic acid at a dose of 100, 250, 500, 1000, or 1500 mg/kg bw by gavage every 3-7 days. Urine was collected continuously and analyzed for metabolites. The total urinary recovery of the test material ranged from 84% to 104%. Glucuronic acid and sulfate conjugates were also detected in the urine, at 10-35% and 4-7%, respectively. The concentrations of all the metabolites returned to background values within 24 hr after dosing.[18]

H. Other

1. Estrogenic Activity

In an *in vitro* yeast-based estrogen screening assay, 4-hydroxybenzoic acid was shown to be inactive for estrogenic activity although all other parabens tested (methyl, ethyl, propyl, butyl) indicated some degree of mild estrogenic activity.[19]

The estrogenic activity of p-hydroxybenzoic acid (PHBA) was evaluated with immature and adult ovariectomized female mice (CD1). Subcutaneous administrations of different doses of PHBA were compared with estradiol (E2), and the effects on vaginal cornification and uterotrophic activities evaluated. Different groups of animals were treated sc daily for 3 days with vehicle (corn oil, 0.3 mL/100 g), E2 (1 ug/100 g), and PHBA (0.5, 5, 50, or 500 ug/100 g). Four days after treatment, PHBA was shown to produce a dose-dependent response on vaginal cornification and uterotrophic activity in both immature and adult ovariectomized mice. The relative uterotrophic potency of PHBA (500 ug/100g) to E2 (1 ug/100 g) was 0.0011 in immature mice and 0.0018 in ovariectomized animals.[10]

2. Hypoglycemic Activity

The hypoglycemic effect of 4-hydroxybenzoic acid was studied in streptozotocin induced diabetic rats. Oral administration of 4-hydroxybenzoic acid caused a decrease in plasma glucose levels dose-dependently in the diabetic rat. The constituent did not affect serum insulin level and liver glycogen content in the diabetic model, but increased glucose consumption in normal and diabetic rats' diaphragms. These results were concluded to suggest that 4-hydroxybenzoic acid produces a hypoglycemic effect mediated by an increase in the peripheral glucose consumption.[20,21]

The possible estrogenic and hypoglycemic effects, while possibly having biological significance, are not considered to be likely significant for occupational exposure due to the routes of exposure and the intraspecies biological variation.

V. HUMAN USE AND EXPERIENCE

Although dated, the NIOSH NOES Survey (1981-1983) estimated that 2722 workers (1767 of these female) were potentially exposed to 4-hydroxybenzoic acid in the US. Occupational exposure occurred mainly through dermal contact while monitoring data indicated that the general population is exposed to 4-hydroxy-benzoic acid via inhalation of ambient air, ingestion of food, and dermal contact with products containing 4-hydroxybenzoic acid.[20] One case study concluded that occupational exposure to a variety of airborne chemicals, including 4-hydroxybenzoic acid, at a manufacturing site of epoxy resins was found to induce contact and allergic dermatitis and sensitization to bacterial and chemical allergens. No further information was provided.[5]

It was noted that 4-hydroxybenzoic acid is produced in closed systems and that occupational exposures through inhalation and the dermal route is assumed negligible. In a survey, the atmospheric concentration in-plant was not measured however the maximum exposure levels were estimated using the scenario of a single worker (body weight; 70 kg, respiratory volume; 1.25 m^3/hr) assigned to implement two bag filling operations without protection. The highest daily intake (combined EHE) was calculated at 0.067 mg/kg/day as the worst case scenario.[1]

VI. RATIONALE

4-hydroxybenzoic acid is a widely used industrial chemical, used as an intermediate in dyes, pesticides, cosmetics and drugs. It is a solid with a low vapour pressure, a high melting point and low solubility in water.

It has low acute oral toxicity in several animal species and is not genotoxic. It is considered to be slightly irritating to the skin and is a mild dermal sensitizer although is poorly absorbed dermally. It is moderately to severely irritating to the eyes.

There were no inhalation or chronic studies identified although 4-hydroxybenzene produced respiratory tract irritation and some changes to blood chemistry in male rats (statistically significant decreases in total protein and increases in A/G ratio, GPT and GOT) in subacute/subchronic studies although these effects were not correlated with histo-pathological findings or changes to organ weights. In reproductive/developmental studies, there were no significant effects observed up to the highest test dose (1000 mg/kg/day). There is, however, some evidence from a mouse study that 4-hydroxybenzene demonstrated a mild estrogenic response.

The 45 day repeat dose study is considered the critical study for setting a WEEL value. Using a worst-case approach, 1000 mg/kg/d is considered the overall LOAEL based on statistically significant (but biologically uncertain) changes to several blood parameters in male rats. In addition, the possible (but equivocal) mild estrogenic activity of 4-hydroxybenzene was also taken into consideration when recommending the WEEL of 5 mg/m^3.

VII. RECOMMENDED WEEL

8-hr time-weighted average (TWA): 5 mg/m^3

This WEEL value was originally established in 2010. No significant new literature was identified since 2010 that supports a change to the recommended WEEL value.

VIII. REFERENCES

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