HEALTH EFFECTS OF PROJECT SHAD CHEMICAL AGENT:

BIS HYDROGEN PHOSPHITE

[CAS # 3658-48-8]

Prepared for the National Academies
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Health Effects of Bis Hydrogen Phosphite
This report deals primarily with the biological health challenges engendered by the agent that is the subject of the report. Nevertheless, this report also incorporates, by reference and attachment, a supplement entitled "Psychogenic Effects of Perceived Exposure to Biochemical Warfare Agents".

The supplement addresses and describes a growing body of health effects research and interest centered upon the psychogenic sequelae of the stress experienced personally from actual or perceived exposure to chemical and biological weaponry. Because awareness of exposure to agents in Project SHAD logically includes the exposed person also possessing a perception of exposure to biochemical warfare agents, the psychogenic health consequences of perceived exposure may be regarded as additional health effects arising from the exposure to Project SHAD agents. This reasoning may also apply to simulants and tracers. Therefore, a general supplement has been created and submitted under this contract to address possible psychogenic effects of perceived exposure to biological and chemical weaponry.

Because such health effects are part of a recent and growing public concern, it is expected that the supplement may be revised and expanded over the course of this contract to reflect the actively evolving literature and interest in the issue.
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I. EXECUTIVE SUMMARY

Bis hydrogen phosphite (BHP), more commonly termed bis(2-ethylhexyl) hydrogen phosphite in the scientific literature, bears the chemical formula $\text{C}_{16}\text{H}_{35}\text{O}_{3}\text{P}$. It is identified by the Chemical Abstracts Service (CAS) Registry Number 3658-48-8. Bis hydrogen phosphite appears as a colorless liquid with a faint odor. It is commonly used as a lubricant additive to prevent corrosion. In Project SHAD, it served as a chemical warfare agent simulant.

No published human studies of any kind, or experimental studies of carcinogenicity, genotoxicity, and reproductive toxicity of bis hydrogen phosphite are known. (There is a 1986 study suggesting that compounds with a 2-ethylhexyl moiety may have a tendency to cause liver cancer in female mice but it did not specifically address bis hydrogen phosphite.) Nevertheless, the Toxicology Division of the U.S. Army Chemical Warfare Laboratories performed several animal studies in acute and subacute exposure to bis hydrogen phosphite in the late 1950s. The tests also evaluated cholinesterase inhibition through a red blood cell assay.

The study concluded overall that acute oral and ocular exposure was “relatively innocuous” as also was a cumulative oral exposure of 70 days (Joffe 1958). It found, however, a significant degree of toxic reaction to inhalational, cutaneous, and intraperitoneal and intravenous exposure. The study nevertheless dismissed concerns regarding the latter two pathways because of the unlikely administration of the chemical through those routes into humans.

Inhalational exposure of rats and guinea pigs to saturated vapor and mist suggested that both one-time and cumulative exposure could cause significant respiratory distress and tissue injury. Dermal exposure caused a coagulative necrosis on the epidermis and dermis, with repeated exposure inhibiting regeneration. Human skin exposure, reported from accidental hand contact with bis hydrogen phosphite, also induced cases of dermatitis. An assay aimed at cholinesterase inhibition was also performed, testing for any inhibition in exposed rabbits and dogs. No effect was found.

Psychogenic effects specifically of bis hydrogen phosphite are not reported. General psychogenic effects of perceived exposure to agents of chemical and biological warfare are examined in the supplement “Psychogenic Effects of Perceived Exposure to Biochemical Warfare Agents.”

There is no reported antidote to any of the effects of bis hydrogen phosphite. The Registry of Toxic Effects of Chemical Substances (RTECS) categorizes bis hydrogen phosphite as a “primary irritant,” for which standard medical emergency procedures should be performed, e.g. removal from the area of contact; monitoring and ventilating the victim; irrigating or washing the locus of contact, etc., as appropriate (RTECS 2004).
Bis hydrogen phosphite is barely treated in secondary sources. Where it does, the discussion may be overly dismissive of risk. One Project SHAD information site declares flatly and conclusively that the substance is not carcinogenic. Actually, published studies of human carcinogenicity are unknown, as are animal studies on the same subject. Nor are there found published genotoxicity studies. A commercial distributor advertises for sale bis hydrogen phosphite as “harmless” despite its irritant qualities and absent long-term data (Pfaltz & Bauer 1997). The Hazardous Substance Data Bank (HSDB) does not even report the main animal toxicology studies that have been published.
II. BACKGROUND DATA

Identification & Physical Chemistry

Project SHAD Chemical Agent Name: Bis Hydrogen Phosphate

Structure

\[
\begin{align*}
\text{H}_3\text{C} & \quad \text{OH} \\
\text{O} & \quad \text{P} \\
\text{O} & \quad \text{H}_3\text{C} \\
\text{H}_3\text{C} & \quad \text{CH}_3 \\
\end{align*}
\]

CAS#: 3658-48-8

More Commonly Appearing Name: Bis (2-Ethylhexyl) Hydrogen Phosphate

Abbreviation: BHP (Project SHAD)

Alternate Names: Phosphonic acid, bis (2 - ethylhexyl) ester (used by RTECS); D-2-ethylhexyl phosphate; Chelex H 8; Di - 2 - ethylhexyl hydrogen phosphite; Di - 2 - ethylhexyl phosphite; Bis (2 - ethylhexyl) hydrogen phosphite; Bis (2 - ethylhexyl) phosphite; Bis (2 - ethylhexyl) phosphonate; Bis (2 - ethylhexyl) phosphonic acid; Diisooctyl phosphite

Chemical Formula: C_{16}-H_{35}-O_3-P

Molecular Weight: 306.48

Boiling Point: 163 deg C @ 3 mm Hg

Sources: (HSDB 2004a, RTECS 2004, Joffe 1958)

Bis hydrogen phosphite appears as a colorless liquid with a faint odor. Its water solubility is very low and its vapor pressure is also low (Joffe 1958; HSDB 2004a; RTECTS).

Use & Manufacture

Bis hydrogen phosphite is commonly used as a lubricant additive to prevent corrosion. Between 0.1 and 1 million pounds of bis hydrogen phosphate are produced yearly in the

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United States (HSDB 2004a). In Project SHAD, bis hydrogen phosphite served as a chemical warfare agent simulant (DeploymentLINK 2004).

**Toxicokinetics**

Examination of the toxicokinetics of bis hydrogen phosphite has not been found in the literature.
III. TOXICITY PROFILES

Overview

There are few studies on the toxicity of bis hydrogen phosphite. No published studies of human effects (aside from a passing anecdotal reference) or other clinical data were found. Nor were any human, or animal studies of the carcinogenicity, genotoxicity, and reproductive toxicity found. Nevertheless the Toxicology Division of the U.S. Army Chemical Warfare Laboratories did perform several acute and subacute animal studies in the late 1950s (Joffe 1958).

The published results of those tests, along with some additional acute testing done by the Albright & Wilson Co. in 1984, have provided toxicological information and animal dose values for various routes of exposure (Joffe 1958; RTECS). The Army tests also evaluated cholinesterase inhibition through a red blood cell assay. Insofar as data exist, the toxicity of bis hydrogen phosphate, at least in acute oral and ocular exposures, appears relatively low but the substance is irritating and harmful to lung and skin tissue at high doses (Joffe 1958). RTECS labels bis hydrogen phosphite a “primary irritant” (RTECS 1997).

Lethal doses in animals occurred through several exposure pathways, including the cutaneous. The firm of Albright and Wilson performed some acute animal studies in 1984 that appear to confirm the low oral and ocular risks (Joffe 1958; RTECS).

Acute & Subacute Exposure

The U.S Army Chemical Warfare Laboratories study concluded that acute oral and ocular exposure was “relatively innocuous” (Joffe 1958). It found, however, a significant degree of toxic reaction to bis hydrogen phosphite during inhalation, cutaneous, intraperitoneal and intravenous exposures (Joffe 1958). (The study was to some degree dismissive of concerns regarding those pathways because of the unlikely administration of the chemical through those routes into humans.)

Toxicity values derived from the Army and Wilson & Albright Co, studies are the following (Joffe 1958; RTECS):

- Rat Oral: LD50=11.9 g/kg
- Rabbit Ocular: Conjunctivitis, resolution after 14 days, 0.25-0.1 ml
- Rat Inhalational: LC50>20g/m3
- Guinea Pig Intraperitoneal: LD50=700 mg/kg
- Mouse Intraperitoneal: LD50 = 620 mg/kg
- Rat Intraperitoneal: LD50=1.5 g/kg
- Intravenous Rabbit: LD50 =100 mg/kg
- Rabbit Dermal: LD50=4.5 g/kg

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Inhalation exposure of rats and guinea pigs over a period of 4 hours with a saturated vapor and mist suggested that both one-time and cumulative exposure could cause significant respiratory distress and tissue injury, including edema in the alveoli and respiratory tree, as well as atelectasis and emphysema. Pronounced necrosis of the bronchial epithelium with acute inflammation in the submucosa was also present. Sloughing of necrotic membranes in both the respiratory system and stomach was also observed. Only the guinea pigs experienced mortality (within several hours in the acute exposure) but both sets of animals initially responded with noticeable respiratory distress, commencing with gasping (Joffe 1958).

Exposures of guinea pigs to longer-term saturated vapor (10 week exposure to 10 mg/m$^3$) revealed similar though less severe histological signs that were not likely to be fatal (Joffe 1958).

Skin testing of rabbits caused a coagulative necrosis on the epidermis and dermis at doses of 0.0071 ml/kg (estimated as equivalent to a 5 ml dose on a human). Repeated exposure inhibited skin regeneration. Death occurred at high doses, accompanied by a “quiet lassitude” and muscle paralysis. Human dermal exposure, reported anecdotally from accidental contact with bis hydrogen phosphite in the course of the experiments, induced instances of dermatitis. Ocular damage in Draize testing of rabbits yielded a mild and passing conjunctivitis and eyelid tissue necrosis that self-resolved in less than two weeks (Joffe 1958).

Cholinesterase inhibition was tested in rabbits and dogs. Cholinesterase inhibition was evaluated via a red blood cell assay, as well as behavioral observation. The animals were given intravenous doses at a rate of 0.02 ml/kg/day and were watched for convulsion, tremor, miosis, and other appropriate indicia of pain and discomfort. No cholinesterase effect was found in the red blood cell assay or in animal behavior (Joffe 1958).

Intravenous exposure of rabbits resulted in severe lung hemorrhage and edema. Blood and fluid flowed heavily from the nostrils just prior to and after death. Intraperitoneal administration over 0.5 ml/kg led to convulsive activity followed by somnolence for about a week, after which survivors returned to normal (Joffe 1958).

A 70-day oral exposure was also determined to be relatively innocuous. No effect was seen in tested guinea pigs, which were placed on a diet of 1% bis hydrogen phosphite (Joffe 1958).

**Long-Term Sequelae**

There are no known long-term effect studies. Chronic exposure testing for non-cancer toxicity (as well as for cancer) is unknown. There were reports, cited above from the
Army study, indicating significant respiratory and stomach tissue damage from acute inhalation exposures, but studies or analyses of any long-term histological significance are not reported.

**Genotoxicity and Carcinogenicity**

No tests, case, histories, epidemiological studies or other data were found in the published literature regarding carcinogenicity or genotoxicity.

One study on a general class of chemicals and their activity has concluded that the 2-ethylhexyl moiety has a propensity for inducing hepatocarcinogenesis in mice, particularly those of the female sex? (Kluwe 1987). No study that specifically addressed bis hydrogen phosphite was found in the literature.
IV. PSYCHOGENIC EFFECTS

Psychogenic effects specifically of bis hydrogen phosphite are not reported. General psychogenic effects of perceived exposure to agents of chemical and biological warfare are examined in the supplement “Psychogenic Effects of Perceived Exposure to Biochemical Warfare Agents.”
V. TREATMENT & PREVENTION

There is no reported antidote to any of the effects of bis hydrogen phosphite. The Registry of Toxic Effects of Chemical Substances (RTECS) categorizes bis hydrogen phosphite as a “primary irritant” (RTECS 1997)

Treatment for primary respiratory irritation is to move the patient to fresh air, monitor for respiratory distress and evaluate for more serious conditions, administering oxygen and assisting ventilation. Ocular exposure should be met with eye irrigation and removal to a health care facility if ill effects persist. Dermal exposure requires removal of contaminated clothing and the washing of the exposed area with soap and water. (HSDB 2004b)
VI. SECONDARY SOURCE COMMENT

Bis hydrogen phosphite is barely touched upon in secondary sources. Some material appears to be too sweeping in conclusiveness, given the rarity of published study of the agent.

A Project SHAD information site of the Department of Defense (DeploymentLINK) declares flatly that the substance is not carcinogenic, nor does it have chronic effects. “[Bis hydrogen phosphite] is not carcinogenic and there are no chronic exposure hazards,” according to the “Project 112 Glossary.” (DeploymentLINK 2004) Actually, as discussed in the previous sections, human carcinogenicity studies are not found in the published literature, nor are animal carcinogenicity or genotoxicity studies of bis hydrogen phosphite known.

A commercial distributor advertising bis hydrogen phosphite for sale labels it “harmless” despite its demonstrated significant irritant qualities and the absence of long-term and carcinogenic data. (Pfaltz & Bauer Co. 1997)

The Hazardous Substance Data Bank of the TOXNET database does not report the animal toxicology studies discussed herein despite an extensive detailing of bis hydrogen phosphite’s environmental activity. (HSDB 2004a)
Where abstracts appear, they are verbatim from the original source and presented without correction, insertion, or additional comment unless otherwise indicated.


Abstract: Chronic toxicity and carcinogenicity studies of several phthalic acid esters (PAEs) and compounds containing a 2-ethylhexyl moiety were conducted in Fischer 344 rats and B6C3F1 (hybrid) mice. The compounds studied were phthalic anhydride, di(2-ethylhexyl) phthalate, butyl benzyl phthalate, diallyl phthalate, di(2-ethylhexyl) adipate, tris(2-ethylhexyl) phosphate, and 2-ethylhexyl sulfate (sodium salt). Estimated maximum tolerable doses and fractionally lower doses of each compound were administered to groups of 50 male and 50 female rats and mice for 2 years, followed by sacrifice, necropsy, and histopathologic examination of major organs and tissues. The low toxic potencies of most of the compounds allowed for relatively high doses to be given during the chronic studies. In general, the toxic manifestations of the PAEs were closely correlated with their ester substituents. Although many of the PAEs possessed some carcinogenic activity, target sites for such effects were dissimilar, suggesting the absence of a common mode of action. In contrast, all of the 2-ethylhexyl-containing compounds studied possessed some hepatocarcinogenic activity, indicating that this moiety may have a propensity for causing hepatocarcinogenesis in mice, particularly those of the female sex. The 2-ethylhexyl compound that caused the greatest hepatocarcinogenic response in mice, di(2-ethylhexyl) phthalate, was also hepatocarcinogenic in rats. Similarly, those with a relatively greater effect in female mice were also active in male mice. Thus, sex
and species differences in 2-ethylhexyl-induced hepatocarcinogenesis in rodents are probably quantitative rather than qualitative in nature.

