

DATE: August 21, 2001

MEMORANDUM

SUBJECT: *Inorganic arsenic* - Report of the Hazard Identification Assessment Review Committee.

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THROUGH: Jess Rowland, Co-Chair
and
Elizabeth Doyle, Co-Chair
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)

TO: Norm Cook, Chief
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Antimicrobial Division (7510C)

PC Code: 06801, 006802, 013505

On August 21, 2001, the Health Effects Division's Hazard Identification Assessment Review Committee (HIARC) evaluated the toxicology data base of **Inorganic Arsenic**, established the toxicological endpoints for incidental residential oral exposure as well as occupational exposure risk assessments. The HIARC also established the appropriate relative bioavailability of arsenic after oral administration (water vs. soil) that can be used for Chromated Copper Arsenate (CCA) CCA risk assessment. The Committee's conclusions are presented in this report.

Committee Members in Attendance

Members present were: W. Burnam, E. Doyle, P. Hurley, E. Mendez, D. Nixon, A. Assaad, J. Liccione, J. Rowland, J. Chen and P. Deschamp.

Also in attendance were: Doreen Aviado of the Antimicrobial Division.

Data evaluation prepared by: Steve Malish of the Antimicrobial Division.

Data Evaluation / Report Presentation :

Jonathan Chen
Toxicologist

And

Tim McMahon
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1 INTRODUCTION

In order to support a Reregistration Eligibility Document (RED) for the non-food use of arsenic (+5) as contained in the wood preservative Chromated Copper Arsenate (CCA) [PC Code 000132], on August 21, 2001, the Health Effects Division's Hazard Identification Assessment Review Committee (HIARC) evaluated the toxicology data base of **Inorganic Arsenic**, established the toxicological endpoints for incidental residential oral exposure as well as occupational exposure risk assessments. The HIARC also established the appropriate relative bioavailability of arsenic after oral administration (water vs. soil). The Committee's conclusions are presented in this report.

2 HAZARD IDENTIFICATION

2.1 Acute Reference Dose (RfD)

Arsenic, as contained CCA, is not listed for food use. Therefore, an acute RfD is not required.

2.2 Chronic Reference Dose (RfD)

Arsenic, as contained CCA, is not listed for food use. Therefore, a chronic RfD is not required.

2.3 Occupational/Residential Exposure

2.3.1 Short-Term Incidental Oral (1-30 days) Exposure

Study Selected:

Franzblau, A. and Lilis, R. 1989. Acute Arsenic Intoxication from Environmental Arsenic Exposure. Archives of Envir. Health. 44(6). 385-390. MRID 45496802. and

Mizuta, N. et al. 1956. An Outbreak of Acute Arsenic Poisoning Caused by Arsenic-Containing Soy-Sauce (Shoyu). A Clinical Report of 220 Cases. Bull Yamaguchi Med Sch 4(2-3):131-149. MRID 45496803.

Executive Summary:

Franzblau (1989) reported 2 cases of subchronic (2 months) arsenic intoxication resulting from ingestion of contaminated well water (9-10.9 mg/L) sporadically (once or twice a week) for about 2 months. Acute gastrointestinal symptoms, central and peripheral neuropathy, bone marrow suppression, hepatic toxicity and mild mucous membrane and cutaneous changes were presented. The calculated dose was 0.03 - 0.08 mg/kg/day based on a body weight of 65 Kg and ingestion of from 238 to 475 ml water/day.

Mizuta (1956) reported a poisoning incident involving the presence of arsenic [probably calcium arsenate] contained in soy-sauce. The duration of exposure was 2-3 weeks. The arsenic content was estimated at 0.1 mg/ml. Out of 417 patients, the authors reported on 220 (age not specified for all patients). The age of the 46 patients with age information range from 15 - 69. An early feature of the poisoning was appearance of facial edema that was most marked on the eyelids. Other symptoms presented included multifaceted gastrointestinal symptoms, liver enlargement, upper respiratory symptoms, peripheral neuropathy and skin disorders. In the majority of the patients, the symptoms appeared within two days of ingestion and then declined even with continued exposure. There was evidence of minor gastrointestinal bleeding (occult blood in gastric and duodenal juice). There were abnormalities in electrocardiograms (altered Q-T intervals and P and T waves). These changes were not evident on reexamination after recovery from the clinical symptoms. An abnormal patellar reflex was evident in >50% of the cases. This effect did not return to normal during the course of the investigation.

Based on the consumption of the arsenic in the contaminated soy-sauce, the pattern of soy-sauce consumption and on measured urinary arsenic levels, the authors estimate consumption of arsenic at 3 mg/day. Although the body weight was not reported, the EPA assumes an average body weight of 55 kg in the Asian population. The estimated exposure was, therefore, 0.05 mg/kg/day and was considered the LOAEL. **The LOAEL=0.05 mg/kg/day (edema of the face; gastrointestinal, upper respiratory, skin, peripheral and neuropathy symptoms).**

The data from these two reports suggest that oral exposure to inorganic arsenic at 0.05 mg/kg/day for a few weeks will cause adverse effects.

Dose and Endpoint for Risk Assessment: The **LOAEL = 0.05 mg/kg/day** based on edema of the face, gastrointestinal, upper respiratory, skin, peripheral and neuropathy symptoms

Comments about Study/Endpoint:

The effects seen after short-term arsenic exposure (appearance of edema, gastrointestinal or upper respiratory symptoms) differ from those after longer exposure (symptoms in skin and nervous system). Some of the short-term effects after tended to subside gradually from the 5th day of the illness, despite continuous intakes of the poison. In contrast, symptoms of peripheral neuropathy appeared in some subjects or individuals even after the cessation of arsenical intake. Therefore, based on following reasons, in addition to the 10X intraspecies variation, an additional 10X uncertainty factor is applied.

- (1). Lack of the NOAEL in the case report and no other data to support a NOAEL for the short-term effects;
- (2). Concern of the severity of the effects such as the irreversible

- peripheral neuropathy in some individuals; and
- (3). Effects seen after short-term exposure are different from those seen after longer-term exposure. The transient nature of the short-term effects masks continued accumulation of effects with repeated exposure, and some effects may appear even after the cessation of arsenic intake

Therefore, a total MOE of 100 is required (10x for intraspecies variation and 10x for using an LOAEL and the reasons stated above. No factor for interspecies differences is required).

2.3.2 Intermediate-Term Oral (1- 6 months) Exposure

Study Selected: Same as Short-Term Incidental Oral (1-30 days) Exposure

MRID No.: 45496802 and 45496803.

Executive Summary: Same as Short-Term Incidental Oral (1-30 days) Exposure

Dose/Endpoint for Risk Assessment: Same as Short-Term Incidental Oral (1-30 days) Exposure

Comments about Study/Endpoint: Same as Short-Term Incidental Oral (1-30 days) Exposure

2.3.3 Dermal Absorption

Study Selected: Wester, R. C., Maibach, H. I., Sedik, L. et al. 1993. In vivo and in vitro percutaneous absorption and skin decontamination of arsenic from water and soil. Fund. Appl. Toxicol. 20:336-340. MRID 45496801.

MRID No.: NA

Executive Summary: Wester et al. (1993) studied the percutaneous absorption of arsenic acid (H_3AsO_4) from water and soil both *in vivo* using rhesus monkeys and *in vitro* with human skin. *In vivo*, absorption of arsenic acid from water (loading $5 \mu\text{l}/\text{cm}^2$ skin area) was $6.4 \pm 3.9\%$ at the low dose ($0.024 \text{ ng}/\text{cm}^2$) and $2.0 \pm 1.2\%$ at the high dose ($2.1 \mu\text{g}/\text{cm}^2$). Absorption from soil (loading $0.04 \text{ g soil}/\text{cm}^2$ skin area) *in vivo* was $4.5 \pm 3.2\%$ at the low dose ($0.04 \text{ ng}/\text{cm}^2$) and $3.2 \pm 1.9\%$ at the high dose ($0.6 \mu\text{g}/\text{cm}^2$). Thus, *in vivo* in the rhesus monkey, percutaneous absorption of arsenic acid is low from either soil or water vehicles and does not differ appreciably at doses more than 10,000-fold apart. Wester et al. (1993) also reported that for human skin, at the low dose, 1.9% was absorbed from water and 0.8% from soil over a 24-h period.

Dermal Absorption Factor: 6.4% based on in vivo dermal absorption results derived

from the Rhesus monkey study (Wester et al., 1993)

Comments about Study/Endpoint:

The value of 6.4% dermal absorption was chosen based on the use of non-human primates for derivation of this value and the fact that this was a well-conducted study. It is observed in the study that a higher dose on the skin resulted in lower dermal absorption as noted above, but the data suggests sufficient variability in the absorption such that use of the 6.4% dermal absorption value is sufficiently but not overly conservative.

Two studies were also considered in the meeting:

- (1). Williams, KD. 1989. Dermal absorption of arsenic acid in male rats. Hazleton laboratories America, HLA 6120-127, Jan 15, 1989, MRID 41141602. Unpublished.

Williams (1989) studied the dermal absorption of arsenic acid (H_3AsO_4) from water *in vivo* with male Charles River (Crl:CD (SD) Br) rats. Dermal doses of 0 (control), 0.3 and 10.0 mg/rat [1.2 mg/kg and 40.3 mg/kg], (0.03 and 1.0 mg/cm²) of arsenic acid (75% a.i.) dermally in a volume of 0.1 ml of distilled water) applied to 10 male rats for up to 24 hours (1, 4, 10 and 24 hours). The test sites was covered with a non-occlusive cover. Residue on washed skin ranged from 18 to 23.8% of the low dose and 5.2 to 15.7% of the high dose. Adsorption of less than 1% of the applied dose as calculated by the arsenic acid equivalents contained in the urine at 24 hours.

- (2). Dutkiewicz T. 1977. Experimental studies on arsenic absorption routes in rats. Environmental Health Perspectives 19: 173-177.

Dutkiewicz (1977) studied the absorption of pentavalent inorganic arsenic via intravenous, intracheal, gastrointestinal and skin applications with Wistar rats. Arsenic in the form of sodium arsenate (Na_2HAsO_4) was used as a carrier and labelled with arsenic-74. For the dermal absorption study, the tails of female Wistar rats were immersed for one hour in 0.01, 0.1 or 0.2 M sodium arsenate solutions. The animals were sacrificed after 1, 2, 5, 24, 72, 120, 168 and 240 hours. Arsenic was determined in the bowels, muscles, bones, skin (skin of tails separately), liver, kidney, lungs, spleen, heart, blood and hair. Adsorption of less than 0.1% of the applied dose as calculated by comparison of the measured activity of the sample with the standard solutions.

Because there is evidence that the arsenic metabolism in rat and human differ, the results of these two rat studies are not appropriate to be used for dermal absorption factor determination.

2.3.4 Short-Term Dermal (1-30 days) Exposure

Study Selected: Same as Short-Term Incidental Oral (1-30 days) Exposure

MRID No.: 45496802 and 45496803

Executive Summary: Same as Short-Term Incidental Oral (1-30 days) Exposure

Dose and Endpoint for Risk Assessment: See Short-Term Incidental Oral (1-30 days) Exposure

Comments about Study/Endpoint.: See Short-Term Incidental Oral (1-30 days) Exposure above.

2.3.5 Intermediate-Term Dermal (1-6 Months) Exposure

Study Selected: Same as Short-Term Incidental Oral (1-30 days) Exposure

MRID No.: 45496802 and 45496803

Executive Summary: Same as Short-Term Incidental Oral (1-30 days) Exposure

Dose and Endpoint for Risk Assessment: See Short-Term Incidental Oral (1-30 days) Exposure

Comments about Study/Endpoint.: See Short-Term Incidental Oral (1-30 days) Exposure above.

2.3.6 Long-Term Dermal (Several Months to Life-Time) Exposure

Study Selected: Tseng, W.-P., Chu, H.M., How, S.W., et al. 1968. Prevalence of skin cancer in an endemic area of chronic arsenicism in Taiwan. J. Natl. Can. Inst. 40(3):453-463. [as cited in U.S. EPA IRIS, Arsenic, Inorganic 1998 and U.S. EPA Special Report, 1988].

Tseng, W.-P. 1977. Effects and dose-response relationships of skin cancer and Blackfoot disease with arsenic. Environ. Health Perspect. 19:109-119. [as cited in U.S. EPA IRIS, Arsenic, Inorganic 1998 and U.S. EPA Special Report, 1988].

MRID No.: NA

Executive Summary: In Taiwan, Tseng, (1977), Tseng, (1968) [U.S. EPA, 1998] noted that hyperpigmentation, keratosis and possible vascular complications were seen at LOAEL = 0.17 mg/L (0.014 mg/kg/day). The NOAEL = 0.009 mg/L of

water (0.0008 mg/kg/day).

The NOAEL was based on the arithmetic mean of 0.009 mg/L in a range of arsenic concentration of 0.001 to 0.017 mg/L. The NOAEL also included estimation of arsenic from food. Since experimental data were missing, arsenic concentrations in sweet potatoes and rice were estimated as 0.002 mg/day. Other assumptions included consumption of 4.5 L water/day and 55 kg body weight (Abernathy, (1989). **NOAEL** [(0.009 mg/L x 4.5 L/day) + 0.002 mg/day]/55 kg = **0.0008 mg/kg/day**. The **LOAEL** dose was estimated using the same assumptions as the NOAEL starting with an arithmetic mean water concentration from Tseng, (1977) of 0.17 mg/L. **LOAEL** = [(0.17 mg/L x 4.5 L/day)+ 0.002 mg/day]/55 kg = **0.014 mg/kg/day**. **The NOAEL = 0.0008 mg/kg and LOAEL=0.014 mg/kg/day (based on hyperpigmentation, keratosis and possible vascular complications).**

Dose and Endpoint for Risk Assessment: **The NOAEL = 0.0008 mg/kg and LOAEL=0.014 mg/kg/day (based on hyperpigmentation, keratosis and possible vascular complications).**

Comments about Study/Endpoint:

Although the exposed population is big (over 40,0000), only one ethnic population is involved in these two studies. A total MOE of 3 is applied to address the intraspecies variation.

2.3.7 Inhalation Exposure (All Durations)

Since no inhalation studies are available, committee selected the same studies as in the dermal risk assessments. Since the dose identified for inhalation risk assessments are from oral studies, route-to-route extrapolation should be as follows:

- Step I: The inhalation exposure component (i.e., $\mu\text{g a.i./day}$) using a 100% (default) absorption rate and application rate should be converted to an equivalent oral dose (mg/kg/day);
- Step II: The dermal exposure component (i.e., mg/kg/day) using 6.4 % absorption factor and application rate should be converted to an equivalent oral dose. The dose should be combined with the converted oral dose in Step I.
- Step III: To calculate the MOE's , the combined dose from Step I and II should then be compared to the oral LOAEL of 0.05 mg/kg/day for short and intermediate term exposure and the oral LOAEL of 0.0008mg/kg/day for long-term exposure.

2.3.8 Margins of Exposure for Occupational/Residential Risk Assessments

A MOE of 100 is selected for short, and intermediate-term oral, dermal and inhalation risk assessments. A MOE of 3 is selected for long-term dermal and inhalation risk assessments.

3 RELATIVE BIOAVAILABILITY

The bioavailability of absorbed inorganic arsenic is dependent on the matrix in which it is exposed to. Arsenic in drinking water is in a water-soluble form, and it is generally assumed that its absorption from the gastrointestinal tract is nearly complete. Arsenic in soils, however, may be incompletely absorbed because they may be present in water-insoluble forms or interact with other constituents in the soil. The relative bioavailability of arsenic after it is been exposed (water versus soil) was defined as the percentage of arsenic absorbed into the body of a soil-dosed animal compared to that of animal receiving an single dose of arsenic in aqueous solution. This is a route specific issue.

3.1 Relative Bioavailability (Soil vs. Water) Through Oral Route

The arsenic relative bioavailability from soils were studied in different animal models and were summarized below.

Roberts et al. 2001

The relative bioavailability of arsenic from selected soil samples was measured in a primate model. Sodium arsenate was administered to five male *Cebus apella* monkeys by the intravenous and oral routes, and urine and feces were collected over a four-day period. Pharmacokinetic behavior of arsenic and the fractions of dose excreted in urine and feces were consistent with previous observations in humans. Soil samples from four waste sites in Florida (one from an electrical substation, one from a wood preservative treatment (CCA) site, one from a pesticide application site, and one from a cattle dip vat site) were dried and sieved. Soil doses were prepared from these samples and administered orally to the monkeys. Relative bioavailability was assessed based on urinary excretion of arsenic following the soil dose compared with excretion following an oral dose of arsenic in solution. Relatively consistent bioavailability measurements were obtained among monkeys given the same soil sample. Differences in bioavailability were observed for different sites, with relative bioavailability ranging from $10.7 \pm 14.9\%$ (mean \pm SD) to $24.7 \pm 3.2\%$ for the four soil samples.

Freeman et al. 1993

The relative bioavailability of arsenic from soil samples from Anaconda, Montana was measured. After a fasting period of approximately 16 hours, prepubescent male and female SPF New Zealand White rabbits (5/sex/group) were given a single oral (capsule) administration of soil (3900ppm As) at three dose levels (0.2, 0.5, and 1.0 g of soil/kg, corresponding to 0.78, 1.95 and 3.9 mg As/kg, respectively). Control groups included

untreated controls, and an intravenous sodium arsenate group (1.95 mg As/kg). The relative bioavailability of arsenic in the soil was approximately 37 - 56 % (based on the As concentration in the excreted urine).

Freeman et al. 1995

Oral absorption of arsenic in a group of three female Cynomolgus monkeys from a soluble salt, soil, and household dust was compared with absorption of an intravenous dose of sodium arsenate (Freeman et al. 1995). Mean absolute percentage bioavailability based on urine arsenic excretion was reported at 67.6±2.6% (gavage), 19.2±1.5% (oral dust), and 13.8±3.3% (oral soil). Mean absolute percentage bioavailability based on blood arsenic levels was reported at 91.3±12.4% (gavage), 9.8±4.3% (oral dust), and 10.9±5.2% (oral soil). The relative bioavailabilities of arsenic in the dust and soil were approximately 28.4% and 20.4% respectively (based on urine).

Groen et al. 1993

Arsenic was administered as an intravenous solution (As₂O₅) or orally as As in soil to groups of six beagle dogs, and urine was collected in 24-hour fractions for 120 hours. After 120 hours, 88% ± 16% of the dose administered intravenously was excreted in the urine, compared to only 7.0 ± 1.5% excreted in the urine after oral soil administration. The calculated bioavailability of inorganic As from urinary excretion was 8.3 ± 2.0%.

USEPA Region 10, 1996

The relative bioavailability of arsenic and lead in soil or slag from the Ruston/North Tacoma Superfund Site has been studied in immature swine that received one single oral dose of soil or sodium arsenate (EPA, 1996). Following a 12 hour overnight fast, each animal was given a single administration of the appropriate test material. Solutions of sodium arsenate and lead acetate were administered separately and not mixed together prior to administration. The group receiving environmental media received a single oral administration of one of four quantities of soils at 25, 60, 100 or 150 mg soil/kg of body weight (BW) (0.04, 0.10, 0.16, or 0.24 mg As/kg BW and 0.03, 0.08, 0.14, or 0.20 mg pb / kg BW). Control groups include intravenous or gavage doses of solution arsenic, untreated controls (received aqueous vehicle only), and an intravenous sodium arsenate group (1.95 mg As/kg). Because several urine samples were lost during sampling procedure, urinary arsenic excretion was not used as a biomarker in estimating bioavailability. Based on the blood level of arsenic, the relative bioavailability of arsenic (soil versus water) in the soil was 78% (56 - 111%).

USEPA Region 8, 1997

The bioavailability of arsenic in soil has been studied in juvenile swine that received daily oral doses of soil or sodium arsenate (in food or by gavage) for 15 days (EPA 1997). The soils were obtained from various mining and smelting sites and contained, in addition to arsenic at concentrations of 100-300 µg/g, lead at concentrations of 3,000-14,000 µg/g. The arsenic doses ranged from 1 to 65.4 µg/kg/day. The fraction of the arsenic dose

excreted in urine was measured on days 7 and 14 and the relative bioavailability of the soil-borne arsenic was estimated as the ratio of urinary excretion fractions, soil arsenic:sodium arsenate. The mean relative bioavailability of soil-borne arsenic ranged from 0 to 98% in soils from seven different sites (mean±SD, 45% ±32). Estimates for relative bioavailability of arsenic in samples of smelter slag and mine tailings ranged from 7 to 51% (mean±SD, 35%±27).

By carefully comparing data on the urinary and fecal recovery of arsenic after oral and intravenous dose of sodium arsenate and human, monkey was considered as an appropriate study model in evaluating the relative bioavailability of arsenic due to its similarity in excretion and G.I. absorption characteristics. The Roberts et al study also employed a variety of soil types including soil from a CCA-contaminated site. Therefore, based on the study results of Roberts et al. (2001), **a oral relative bioavailability (soil vs. water) of 25% was selected by HIARC.**

3.2 Relative Bioavailability (Soil vs. Water) Through Dermal Route

Wester et al., (1993) studied the dermal absorption of arsenic from both water and soil with Rhesus monkeys. *In vivo*, absorption of arsenic acid from water (loading 5 µl/cm² skin area) was 6.4 ± 3.9% at the low dose (0.024 ng/cm²) and 2.0 ± 1.2% at the high dose (2.1 µg/cm²). Absorption from soil (loading 0.04 g soil/cm² skin area) *in vivo* was 4.5 ± 3.2% at the low dose (0.04 ng/cm²) and 3.2 ± 1.9% at the high dose (0.6 µg/cm²). The dermal absorption of arsenic from water is not statistically different from the absorption from soil. Therefore, **a dermal relative bioavailability (soil vs. water) of 100% was selected by HIARC. In other words, via dermal exposure, the magnitude of absorption of arsenic is equal if the arsenic is in water or in soil.**

4 CLASSIFICATION OF CARCINOGENIC POTENTIAL

IRIS (1998) classified inorganic arsenic as a class A carcinogen (human carcinogen), based on sufficient evidence from human data. An increased lung cancer mortality was observed in multiple human populations exposed primarily through inhalation. Also, increased mortality from multiple internal organ cancers (liver, kidney, lung, and bladder) and an increased incidence of skin cancer were observed in populations consuming drinking water high in inorganic arsenic.

5 FQPA CONSIDERATIONS

This is a non-food use chemical (inorganic arsenic used as a wood preservative in CCA) and does not require any food tolerance. Consequently, it does not come under the Food Quality Protection Act of 1996.

6 HAZARD CHARACTERIZATION

Arsenic is an element that is present in soil, water, and food. In the environment, arsenic exists in many different forms. In water, for example, arsenic exists primarily as the inorganic forms As +3 (arsenite) and As +5 (arsenate), while in food, arsenic exists primarily in organic forms (seafood, for example, contains arsenic as arsenobetaine, a form which is absorbed but rapidly excreted unchanged). Human activities also result in the release of arsenic into the environment, such as residual arsenic from former pesticidal use, smelter emissions, and the use of chromated copper arsenicals (CCA) in the pressure-treatment of wood that is used for construction of decks, fences, playgrounds, and other structural uses.

Humans are very sensitive to arsenic toxicity when compared with other experimental animals. Inorganic arsenic is acutely toxic, and ingestion of large doses leads to gastrointestinal symptoms, disturbances of cardiovascular and nervous system functions, and eventually death. The effects seen after short-term arsenic exposure (appearance of edema, gastrointestinal or upper respiratory symptoms) differ from those after longer exposure (symptoms of skin and neuropathy). Some of the effects after short-term exposure tended to subside gradually from the 5th day of the illness, despite continuous intakes of the poison. In contrast, symptoms of peripheral neuropathy appeared in some individuals even after the cessation of arsenical intakes. The acute oral toxicity of inorganic arsenic in humans shows lethal effects in the range of 22- 121 mg/kg, which is consistent with results of animal studies showing lethality in the range of 15-175 mg/kg. Subchronic studies with arsenic in experimental animal models have produced only generalized toxicity (i.e. weight loss, and decreased survival), while data from human exposures have shown more specific toxic effects, such as neurotoxicity and hyperkeratosis of the skin of the hands and feet (ATSDR, 2001).

Chronic toxicity studies with inorganic arsenic in experimental animals also show a lack of specific toxic effects, whereas the scientific literature that describes chronic human exposure shows a clear relationship between chronic exposure to inorganic arsenic and the development of skin cancer as well as cancers of the lung, liver, and bladder (ATSDR, 2000; NRC, 1999).

7 **DATA GAPS**
There is no data gap identified.

8 **ACUTE TOXICITY**

Acute Toxicity Summary of Arsenic Acid (75%)

Guideline	Study Type	MRID/ Data Accession No.	Results	Toxicity Category
81-1 (OPPTS 870.1100)	Acute Oral	40409001	<u>Mouse</u> LD ₅₀ = ♂ 141 mg/kg = ♀ 160 mg/kg M+F = 150 mg/kg ----- <u>Rat</u> LD ₅₀ = ♂ 76 mg/kg = ♀ 37 mg/kg M+F = 52 mg/kg	II
		26356		I
81-2 (OPPTS 870.1200)	Acute Dermal	26356	<u>Rabbit</u> LD ₅₀ = ♂ 1750 mg/kg = ♀ 2300 mg/kg	II
81-3 (OPPTS 870.1300)	Acute Inhalation	404639-02	<u>Mouse</u> LC ₅₀ = ♂ 1.153 mg/L = ♀ 0.79 mg/L M+F = 1.040 mg/L	II
81-4 (OPPTS 870.2400)	Primary Eye Irritation	26356	<u>Rabbit</u> 3/6 animals died by day 7. The 3 surviving animals were sacrificed on day 9 because of severe ocular irritation and corrosion.	I
81-5 (OPPTS 870.2500)	Primary Skin Irritation	26356	<u>Rabbit</u> At 30 minutes, all animals showed moderate to severe erythema and slight to severe edema. All animals died prior to the 24 hour observation.	I
81-6 (OPPTS 870.2600)	Dermal Sensitization	406462-01	<u>Guinea Pig</u> Not a Sensitizer	NR

9 SUMMARY OF TOXICOLOGY ENDPOINT SELECTION

The doses and toxicological endpoints selected for various exposure scenarios are summarized below.

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY
Acute Dietary	This risk assessment is not required.		
Chronic Dietary	This risk assessment is not required.		
Incidental Short- and Intermediate-Term Oral	LOAEL= 0.05 MOE = 100	Based on edema of the face, gastrointestinal, upper respiratory, skin, peripheral and neuropathy symptoms	Franzblau et al.(1989) and Mizuta, N. et al. (1956)
Dermal Short- and Intermediate-Term ^(a)	LOAEL= 0.05 MOE = 100	Same as Incidental Short- and Intermediate- Term Oral Exposure	
Dermal Long-Term ^(a)	NOAEL= 0.0008 MOE = 3	Based on hyperpigmentation, keratosis and possible vascular complications.	Tseng et al. (1968) and Tseng (1977)
Inhalation Short- and Intermediate-Term ^(c)	LOAEL= 0.05 MOE = 100	Same as Incidental Short- and Intermediate- Term Oral	
Inhalation, Long-Term	NOAEL= 0.0008 MOE = 3	Same as Dermal Long-Term Exposure	

Note:

- (a). MOE = Margin of Exposure; NOAEL = No observed adverse effect level; and LOAEL = Lowest observed adverse effect level.
- (b). The dermal absorption factor = 6.4%.
- (c). For inhalation exposure, a default absorption factor of 100% is used. Using route-to-route extrapolation to estimate the exposed dose.

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