Arsine; CASRN 7784-42-1

Human health assessment information on a chemical substance is included in the IRIS database only after a comprehensive review of toxicity data, as outlined in the IRIS assessment development process. Sections I (Health Hazard Assessments for Noncarcinogenic Effects) and II (Carcinogenicity Assessment for Lifetime Exposure) present the conclusions that were reached during the assessment development process. Supporting information and explanations of the methods used to derive the values given in IRIS are provided in the guidance documents located on the IRIS website.

STATUS OF DATA FOR Arsine

File First On-Line 03/01/1994

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	not evaluated	
Inhalation RfC (I.B.)	yes	03/01/1994
Carcinogenicity Assessment (II.)	not evaluated	

I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

I.A. Reference Dose for Chronic Oral Exposure (RfD)

Substance Name — Arsine
CASRN — 7784-42-1

Not available at this time.

I.B. Reference Concentration for Chronic Inhalation Exposure (RfC)

Substance Name — Arsine
CASRN — 7784-42-1
Last Revised — 03/01/1994

The inhalation Reference Concentration (RfC) is analogous to the oral RfD and is likewise based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. The inhalation RfC considers toxic effects for both the respiratory system (portal-of-entry) and for effects peripheral to the respiratory system (extrarespiratory effects). It is expressed in units of mg/cu.m. In general, the RfC is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily inhalation exposure of the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Inhalation RfCs were derived according to the Interim Methods for Development of Inhalation Reference Doses (EPA/600/8-88/066F August 1989) and subsequently, according to Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry (EPA/600/8-90/066F October 1994). RfCs can also be derived for the noncarcinogenic health effects of substances that are carcinogens. Therefore, it is essential to refer to other sources of information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

I.B.1. Inhalation RfC Summary

Critical Effect	Exposures*	UF	MF	RfC
Increased hemolysis, abnormal RBC morphology, and increased spleen weight **13-Week Rat and Mouse and 28-Day Hamster Inhalation Study** **Blair et al., 1990a,b**	NOAEL: 0.08 mg/cu.m NOAEL(ADJ): 0.014 mg/cu.m NOAEL(HEC): 0.014 mg/cu.m LOAEL: 1.6 mg/cu.m LOAEL(ADJ): 0.28 mg/cu.m LOAEL(HEC): 0.28 mg/cu.m	300	1	5E-5 mg/cu.m
Increased hemolysis, increased spleen weight, and impaired compensatory	NOAEL: 0.08 mg/cu.m NOAEL(ADJ): 0.014 mg/cu.m NOAEL(HEC): 0.014 mg/cu.m LOAEL: 1.6 mg/cu.m			

Critical Effect	Exposures*	UF	MF	RfC
erythropoiesis **12-Week Mouse Inhalation Study** **Hong et al., 1989**	LOAEL(ADJ): 0.28 mg/cu.m LOAEL(HEC): 0.28 mg/cu.m			

*Conversion Factors and Assumptions — Assuming 25 C and 760 mmHg, LOAEL (mg/cu.m) = 0.025 ppm x 77.93/24.45 = 0.08 x 6 hours/24 hours x 5 days/7 days = 0.014 mg/cu.m. The NOAEL(HEC) was calculated for a gas:extrarespiratory effect, assuming periodicity was attained. Because the b:a lambda values are unknown for the experimental species (a) and humans (h), a default value of 1.0 is used for this ratio. NOAEL(HEC) = NOAEL(ADJ) x [b:a lambda(a)/b:a lambda(h)] = 0.014 mg/cu.m.

I.B.2. Principal and Supporting Studies (Inhalation RfC)

Blair, P., M. Thompson, R. Morrissey et al. 1990a. Comparative toxicity of arsine gas in B6C3F1 mice, Fischer 344 rats, and Syrian golden hamsters: System organ studies and comparison of clinical indices of exposure. Fund. Appl. Toxicol. 14(4): 776-787.

Blair, P., M. Thompson, M. Bechtold et al. 1990b. Evidence of oxidative damage to red blood cells in mice induced by arsine gas. Toxicology. 63(1): 25-34.

Hong, H., B. Fowler, and G. Boorman. 1989. Hematopoietic effects in mice exposed to arsine gas. Toxicol. Appl. Pharmacol. 97(1): 173-182.

Arsine gas is a potent hemolytic agent and a recognized industrial hazard. Typical cases of acute poisonings, predominantly in workers accidentally exposed, resulted in hemoglobinuria, jaundice, and hemolytic anemia. The rapid and unique hemolysis caused by arsine can progress to oliguric renal failure, which can be fatal without proper therapy (Levinsky et al., 1970; Fowler and Weissberg, 1974). It has been reported that a half-hour exposure to 25-50 ppm can be lethal (Blackwell and Robins, 1979). Hemolytic anemia, however, is the most consistent clinical finding in humans. Observed hemolytic effects in humans are consistent with effects observed in laboratory animals and include increased Hgb concentrations; reticulocytosis; leukocytosis; and altered RBC morphology characterized by basophilic stippling, anisocytosis, poikilocytosis, red-cell fragments, and ghost cells (Levinsky et al., 1970; Fowler and Weissberg, 1974; Wald and

Becker, 1986). Species differences are expected to be relatively few with respect to hematologic effects for this direct-acting hemolytic agent. This was confirmed in a series of comparative toxicity studies in B6C3F1 mice, Fischer 344 rats, and Golden Syrian hamsters (Blair et al., 1990a; Hong et al., 1989).

Although the reactive form of arsine and the specific sequence of events that precede hemolysis are not fully known, the general mechanism of RBC damage caused by arsine is understood. In vitro studies (Blair et al., 1990b) show that the concentration of reduced glutathione falls during incubation with arsine. It is likely that this is due to an oxidized metabolite of arsine because arsine does not lyse RBCs in the absence of molecular oxygen (Blair et al., 1990b; Pernis and Magistretti, 1960). Maintenance of glutathione in the reduced state via the hexose monophosphate shunt in erythrocytes is essential for the maintenance of sulfhydryl groups in membrane proteins and Hgb. With oxidation and cross-linking of sulfhydryl groups on Hgb, denaturation of the protein occurs and aggregates of the precipitated molecule bind to the inner surface of the red cell membrane (Heinz bodies). In the process of preventing the oxidation of Hgb, glutathione levels are decreased and may not be adequate to inhibit membrane sulfhydryl oxidation (Jacob and Jandl, 1962). Both the formation of Heinz bodies and membrane sulfhydryl oxidation increase the fragility of the cell membrane and predispose cells to fragmentation (Weed and Reed, 1966). Hematologic effects observed in exposed animals by Blair et al. (1990a,b) and Hong et al. (1989), such as increased hemosiderosis, Heinz bodies, low RBC counts, low Hgb concentrations, and low HCTs, would be consistent with this pathogenesis.

Blair et al. (1990a) exposed 8-10-week-old (90-105-g) Fischer 344 rats (15-16/sex/group) 6 hours/day for 14 consecutive days and 5 days/week for 4 and 13 weeks. Exposure concentrations were 0, 0.025, 0.5, or 2.5 ppm arsine (equivalent to 0, 0.08, 1.6, or 8.0 mg/cu.m, respectively) for the 13-week study and 0, 0.5, 2.5, and 5.0 ppm for the other studies. Duration-adjusted concentrations for the 13-week study were 0.014, 0.28, or 1.4 mg/cu.m for the low-, mid-, and high-exposure groups, respectively. Blood and tissue samples were collected 1 and 3 days after the final exposure for rats exposed over 14 days and 4 weeks, respectively. Samples were collected 3 and 4 days after the final exposure for rats exposed over 13 weeks. In addition, interim samples were collected in the 13-week study to monitor the time course of hematologic changes.

In addition, Blair et al. (1990a) exposed 8-10-week-old (20-30-g) B6C3F1 mice (15-16/sex/group) 6 hours/day for 1 day (females only), 14 consecutive days, and 5 days/week for 13 weeks. Exposure concentrations were 0, 0.025, 0.5, or 2.5 ppm arsine (equivalent to 0, 0.08, 1.6, or 8.0 mg/cu.m, respectively) for the 13-week study and 0, 0.5, 2.5, and 5.0 ppm for the other studies. Duration-adjusted concentrations for the 13-week study were 0.014, 0.28, or 1.4 mg/cu.m for the low-, mid-, and high-exposure groups, respectively. Mice exposed for a single day were sacrificed 0, 1, 2, 4, or 7 days after exposure to track postexposure recovery. Mice

exposed for 14 days were sacrificed 1 or 2 days after the final exposure, whereas mice exposed for 13 weeks were sacrificed 3 or 4 days after the final exposure.

Blair et al. (1990a) also exposed 8-10-week-old (130-150-g) Golden Syrian hamsters (15-16/sex/group) to 0, 0.5, 2.5, or 0.5 ppm arsine (equivalent to 0, 1.6, 8.0, or 16 mg/cu.m, respectively), 6 hours/day, 5 days/week (duration- adjusted to 0.28, 1.4, or 28 mg/cu.m) for 4 weeks. Blood samples were collected 3 and 4 days after the final exposure.

Histopathology and packed cell volumes (PCV) determinations were performed on all animal species. Histopathologic examinations were performed for 31 male and 29 female tissues. Respiratory tract tissues examined included the nasal cavity (three sections), esophagus, lungs, and bronchi. Hematological measurements were conducted only in the rats at interim time points (1, 3, and 11.5 days) and 3 and 4 days postexposure. Amino levalinic acid dehydratase (ALAD) activity in RBCs was assayed in all three species to determine the effects of arsine on the heme synthetic pathway.

Microscopic examinations revealed no pathology of the nasal cavity or lower respiratory tract in any of the species studied. Treatment-related lesions, as discussed below, were noted only in the spleen (all species), liver (mice only), and bone marrow (rats only). No clinical effects were reported in any of the species.

In rats, enlarged spleens and significantly increased relative spleen weights ($p < 0.05$) were observed in the 0.5- and 2.5-ppm males and females at 28 and 90 days. Despite a 3-day recovery period, male and female rats exposed to 0.5 ppm arsine for 28 or 90 days experienced an average increase in relative spleen weight of approximately 50% over controls. Increased hemosiderosis and extramedullary hematopoiesis in the spleen and bone marrow, as well as hyperplasia of bone marrow, were present in the high-concentration rats. Significantly decreased RBC counts, Hgb concentrations, and HCTs were present in blood collected at 80 or 81 days of exposure in all exposed females and in 0.5- and 2.5-ppm exposed males. The mean corpuscular volume (MCV) and mean corpuscular hemoglobin (MCH) were elevated significantly in male and female rats of the mid- and high-concentration groups, whereas platelet count increased only in the high-concentration group. Increased ALAD activity and reduced PCV occurred in the mid- and high-concentration groups. Increased ALAD activity is consistent with the increase in the number of immature RBCs observed by Hong et al. (1989) and supports the existence of a compensatory, regenerative response to RBC hemolysis at the lowest (0.025 ppm) arsine exposure level.

In mice, intracanalicular bile stasis was reported in the liver of 2.5-ppm males and females, and increased relative liver weight was reported in the 2.5-ppm males. The male and female mice exposed to 2.5 ppm and the males exposed to 0.5 ppm exhibited an elevated relative spleen weight after 90 days of exposure to arsine. Relative spleen weight increase over controls in the

males exposed to 0.5 ppm was 75% after 14 days and 32% after 90 days exposure. This corresponded to histopathological findings of enlarged, darkened spleens with increased hemosiderosis and extramedullary hematopoiesis at these exposure levels. Mean PCVs were decreased in all exposure groups of female mice (6/group) subjected to 90 days exposure and a 4-day recovery period. However, little significance is placed on these results given the small number of animals involved and the fact that no change relative to controls was observed in female mice given 90 days exposure and a 3-day recovery period. In addition, a PCV effect was seen only in males at the 2.5-ppm (90-day) exposure level. Amino levalinic acid dehydratase activity was significantly increased in the 0.5-ppm male and female mice at 14 days, but not at 90 days. Increased ALAD activity was sustained for 90 days at the 2.5-ppm exposure level.

Similar effects were observed in Golden Syrian hamsters exposed to 0, 0.5, 2.5, or 5.0 ppm arsine, 5 days/week, for 28 days. The PCV was reduced significantly in the high-concentration group for both females and males. Spleen weights of the mid- and high-exposure groups (males and females) were markedly increased relative to controls. Amino levalinic acid dehydratase activity was significantly increased at all exposure levels for males and at the mid and high levels for the females. Splenomegaly similar to that observed in the rats and mice was observed in both females and males of the mid- and high-exposure groups.

Blair et al. (1990b) further investigated the hypothesis that hemolytic effects of arsine gas involve oxidative stress by arsine on erythrocytes, which results in denaturation of Hgb and cell lysis. B6C3F1 mice (10/sex/group) were exposed to 0, 0.025, 0.5, or 2.5 ppm arsine (equivalent to 0, 0.08, 1.6, or 8.0 mg/cu.m, respectively), 6 hours/day, 5 days/week (duration adjusted to 0.014, 0.28, or 1.4 mg/cu.m), for 13 weeks. Blood samples were collected after 5, 15, and 90 days of exposure, and hematological measurements were made. Red blood cell counts, Hgb concentrations, and HCTs were decreased in the 2.5-ppm animals (also 0.5-ppm males for Hgb concentration). Mean corpuscular volume was significantly increased in females of the 0.5-ppm group, and MCVs and MCHs were significantly increased in males and females of the 2.5-ppm group at the 90-day sacrifice. A significant increase in the mean corpuscular Hgb concentration (MCHC) and platelets also occurred in 2.5-ppm males. Some of these hematological parameters were also significantly affected on days 5 and 15 of exposure. White cell count was affected only in the earlier time points (5 and 15 days) in the high-concentration males. Methemoglobin levels were elevated significantly ($p < 0.01$) in the 2.5-ppm group after 90 days of exposure to arsine gas. Significant increases in absolute reticulocyte counts occurred in animals in the 2.5-ppm exposure groups ($p < 0.01$), and small (not statistically significant) increases occurred in the 0.5-ppm exposure groups. Morphological evaluation of RBCs revealed polychromasia, anisocytosis, poikilocytosis, increased number of Howell-Jolly bodies, and numerous acanthocytes in the 2.5-ppm animals. These effects were apparent but less severe in the 0.5-ppm group.

In another subchronic mouse bioassay, 8-week-old female B6C3F1 mice (36/group) inhaled 0, 0.025, 0.5, or 2.5 ppm arsine (equivalent to 0, 0.077, 1.54, or 7.7 mg/cu.m, respectively), 6 hours/day, 5 days/week (duration adjusted to 0.014, 0.27, or 1.37 mg/cu.m), for 12 weeks (Hong et al., 1989). Arsine in argon was introduced into the process air stream, which flowed through the mixing element and into the Rochester-type inhalation chambers. Hematology and histopathology were performed, and body and spleen weights were measured. No clinical symptoms were reported. Hematological parameters were affected (i.e., decreased RBC, Hgb concentration, and HCT; increased MCV and WBC) in a concentration-related manner. The effects were significant ($p < 0.05$) at the 2.5-ppm level for all indices. A significant ($p < 0.01$) increase in MCV and WBC was observed in mice exposed to 0.5 ppm, and MCV was increased ($p < 0.05$) in mice exposed to 0.025 ppm arsine. All blood parameters measured returned to normal by 20 weeks postexposure. Splenomegaly and increased relative spleen weight were observed after the 12-week exposure (25, 50, and 172% increased weight in the 0.025-, 0.5-, and 2.5-ppm groups, respectively). This concentration-related effect, along with the increased MCV, suggests the presence of significant extramedullary erythropoiesis in mice. By 21 days postexposure, spleen weight remained significantly elevated in the two high- concentration groups. Microscopic examination of the spleen from exposed mice revealed smaller splenic follicles, concentration-related hematopoiesis, sequestration of RBCs within red pulp, and hemosiderin accumulation within macrophages in animals of all exposure groups.

Hong et al. (1989) also evaluated the effects of arsine on the hematopoietic progenitor cells in the bone marrow of mice. Erythropoiesis, as measured by quantitation of erythroid precursors in culture, revealed a significant ($p < 0.05$) bone marrow reduction of colony-forming unit erythroids/femur cells (CFU-E/femur) in the 2.5-ppm group (14%) and a slight but nonsignificant reduction in the 0.5-ppm group (10%) at 6 days postexposure. At 21 days postexposure, CFU-E/femur was not significantly reduced in the 0.5-ppm exposure group but was still reduced by 11% in the high-exposure group. Colony-forming unit granulocyte-macrophage/femur cells (CGU-GM/femur) were not affected, suggesting that erythroid precursors in the bone marrow of mice are more susceptible to arsine than granulocyte-macrophage progenitors. Because arsine reacts strongly with Hgb, it is unlikely that the arsine would survive in circulation to reach bone marrow and to interact with it directly. However, relatively high doses of arsenic have been reported to cause bone marrow suppression in humans (Hesdorffer et al., 1986).

In summary, from the Blair et al. (1990a,b) and Hong et al. (1989) studies it is apparent that there were no differences in the types of effects produced by arsine in the three species examined. Although concentration-response information is lacking for humans, similar effects have been reported in case studies, primarily involving acute occupational exposures (Hesdorffer et al., 1986; Parish et al., 1979; De Palma, 1969; Teitelbaum and Kier, 1969). One exception is that renal effects commonly observed as a consequence of acute human exposures have not been

observed following subchronic exposures to laboratory animals. However, the survival rates in all laboratory animal exposure groups were comparable with controls (i.e., the MTD was not exceeded). Thus, it is reasonable to assume that, as has been suggested by some authors (Levinsky et al., 1970), renal effects are secondary to hemolysis and would have been observed in laboratory animals at higher exposure levels. The greater susceptibility of rats to the hematologic effects of arsine may be due to the fact that mice may have a greater capability for erythrocyte regeneration because of a superior capacity for splenic extramedullary hematopoiesis (Blair et al., 1990a). The splenomegaly and increased spleen weight observed in all three species were likely the result of increased removal of damaged RBCs (fragments), hemosiderosis, and increased splenic hematopoiesis. The impact of these effects on normal splenic function is not completely known but is of concern given the reported alterations in immunocompetency of mice exposed to 2.5 ppm arsine for just 14 days (Rosenthal et al., 1989). The studies did not identify a NOAEL or LOAEL for splenomegaly; however, relative spleen weight was unchanged at the 0.025-ppm exposure level and markedly increased in mice and rats at the 0.5-ppm exposure level. With respect to RBC morphology, abnormalities consistent with those observed in humans following arsine poisonings (Fowler and Weissberg, 1974) were observed in mice at both 0.5 and 2.5 ppm. The case for impaired erythropoiesis is not as strong, but Hong et al. (1989) did identify a trend for reduced CFU-E/temur beginning at the 0.5-ppm exposure level. Thus, these studies taken together support a 0.025-ppm NOAEL (HEC = 0.014 mg/cu.m) and a 0.5-ppm LOAEL (HEC = 0.28 mg/cu.m) for increased hemolyisis, altered RBC morphology, increased spleen weight, and impaired erythropoiesis.

I.B.3. Uncertainty and Modifying Factors (Inhalation RfC)

UF — An uncertainty factor of 10 is applied to account for sensitive populations, and a factor of 3 is applied to account for interspecies extrapolation based on the use of default dosimetry adjustments and because large species differences are not expected for these direct hemolytic effects. A composite factor of 10 is applied to account for both subchronic duration extrapolation and database deficiencies, specifically the lack of a two- generation reproductive study. A reduced uncertainty factor for subchronic- to- chronic duration is applied because the principal studies do not suggest that duration of exposure is a key determinant of the critical effects (14- and 28-day exposures caused similar hematologic effects as 90-day exposures in all three species tested).

MF — None

I.B.4. Additional Studies/Comments (Inhalation RfC)

The toxicologic literature on human exposures to arsine consists principally of case studies of arsine gas poisonings in various occupational settings and investigations of health Hazards

(particularly reproductive toxicity) within the microelectronics industry. After the initial demonstration of its toxicity in 1815, 454 cases of poisoning had been documented by 1974. Of 207 cases of arsine toxicity between 1928 and 1974 (4.5 cases/year), 25% were fatal (Fowler and Weissberg, 1974). Between 1974 and 1986, 24 additional cases were reported (2 cases/year) with no fatalities (Wald and Becker, 1986). This decline in case reports/year and fatalities from acute poisonings is not necessarily an indication that a problem no longer exists. Prior to 1974, anuria was a common cause of death following acute exposures to high concentrations of arsine. With the ready availability of hemodialysis, patients should not die from renal failure (Hesdorffer et al., 1986; Wald and Becker, 1986). Further, the importance of treatment via exchange transfusions (Hesdorffer et al., 1986) or some other method such as penicillamine chelation (Risk and Fuortes, 1991) for the adequate removal of arsine and significant amelioration is now recognized. Less severe cases may not cause hematuria (Risk and Fuortes, 1991) and may go unrecognized and untreated as the attending medical staff may not be aware of the possibility of arsine gas poisoning. In fact, most cases of arsine poisoning have not resulted from the manufacture or use of the gas itself, but from formation of arsine as a by-product of a chemical reaction involving a base metal, an arsenic impurity, and an acid (ACGIH, 1986).

In humans, clinical signs of acute exposures to arsine are abdominal pain, hematuria, and jaundice. Other symptoms that have been reported following acute (Wald and Becker, 1986) and subchronic exposures (Risk and Fuortes, 1991) include headache, malaise, weakness, and gastrointestinal distress accompanied by nausea and vomiting. Hemolytic anemia, however, is the most consistent clinical finding in humans. Observed hemolytic effects in humans are consistent with effects observed in laboratory animals and include increased Hgb concentrations, reticulocytosis, leukocytosis, and altered RBC morphology characterized by basophilic stippling, anisocytosis, poikilocytosis, red-cell fragments, and ghost cells (Levinsky et al., 1970; Fowler and Weissberg, 1974; Wald and Becker, 1986). Bone marrow suppression by arsenic may give the impression that no or minimal hemolysis is taking place. In a recent case, a patient did not receive immediate exchange transfusion because initial reticulocyte counts suggested that severe continuous hemolysis was not occurring (Hesdorffer et al., 1986). Hematuria is a symptom generally associated with acute exposure to arsine (Wald and Becker, 1986). However, it was not observed following longer term, presumably lower level, exposure despite the occurrence of both hepatic and renal impairment (Risk and Fuortes, 1991).

The semiconductor industry makes use of many toxic materials, including a variety of solvents, acids, and metals such as arsenic. The semiconductor manufacturing process involves extensive use of dopant gases, primarily arsine, phosphine, and diborane (LaDou, 1983; Pastides et al., 1988). The California Department of Industrial Relations reported a higher rate of occupational illness in the electronics industry between 1977 and 1980, and that the semiconductor industry accounts for a large part of the difference (LaDou, 1983). Two processes, the "photolithurgic" process and the "diffusion" process, were investigated as potential sources of general illness and

spontaneous abortions (Pastides et al., 1988). The photolithurgic process involves coating wafers with a photosensitive material containing glycol ethers and, often, xylene, toluene, and hexamethyldisilazane. The diffusion process involves heating the wafer at very high temperatures in a chamber containing arsine, phosphine, and diborane (dopants). Three groups of workers were selected for participation in this study: (1) all current workers with more than 1 month of employment in the photolithurgic area, (2) workers employed primarily in the diffusion area (but also workers from other areas exclusive of photolithurgy), and (3) administrative staff not exposed to any of the process chemicals. Spontaneous abortion ratios, defined as the number of fetal losses prior to 29 weeks gestation divided by the number of total pregnancies, were increased in both exposure groups. The spontaneous abortion ratios observed for women in the photolithurgic, diffusion, and nonexposed groups were 31.3% (5/16), 38.9% (7/18), and 17.8% (71/398), respectively. An increased relative risk of 2.18 for the diffusion group vs. the nonexposed group (95% confidence interval = 1.11-3.60) was calculated. This observation persisted even after controlling for a variety of risk factors including age at pregnancy, gravidity, consumption of caffeine during pregnancy, smoking during pregnancy, and consumption of alcohol during pregnancy. The elevated ratio among women in the photolithurgic group was not statistically significant; however, the risk of spontaneous abortion in the photolithurgic and diffusion groups relative to the nonexposed group remained consistent, regardless of which risk factors were considered. This study was subject to several limitations. First, the authors acknowledge that many semiconductor workers have exposures to chemicals found in both the photolithurgic and diffusion areas, and workers were sometimes involved in work in both areas during their tenure with the company. Second, spontaneous abortion rates were based on a small sample size (34 pregnancies in both manufacturing groups). These limitations, along with the lack of quantifiable exposure data for any individual chemical, preclude making any kind of determination regarding the role of arsine in the observed increased spontaneous abortion rate.

Female B6C3F1 mice (36/group) inhaled 0, 0.5, 2.5, or 5.0 ppm arsine (0, 1.6, 8, or 16 mg/cu.m) 6 hours/day for 14 days (Hong et al., 1989). Concentration-related decreases in RBC count, Hgb, and HCT values were found after exposure, but values returned to normal levels by 3 weeks postexposure. Significant concentration-related splenomegaly was observed in mice. The relative spleen weight was significantly increased (38-236% increase) in all exposed groups compared to controls at 2 days postexposure and remained at 24 days postexposure (12-48% increase). Histopathology revealed a concentration- related hematopoiesis in spleens of exposed mice. To evaluate the effect of arsine on erythropoiesis, quantitation of erythroid precursors in culture were examined. In the bone marrow, colony-forming unit granulocyte- macrophage/femur cells (CGU-GM/femur) (8-13% decrease compared with control) and colony-forming unit erythroids/femur cells (CFU-E) (11-27% decrease) were significantly reduced in all exposed groups on day 2 or 3 postexposure. Values returned to normal levels after 3 weeks except for the CFU-E values in the high-concentration group (9% decrease). Therefore, the changes in hematological parameters and the reduction in CFU-E in the bone marrow suggest that fewer

bone marrow cells divide or that extramedullary erythropoiesis in sites such as spleen compensate for deficit in bone marrow cells.

Rosenthal et al. (1989) examined immunological parameters in groups of female B6C3F1 mice that inhaled 0, 0.5, 2.5, or 5 ppm arsine (0, 1.6, 8, or 16 mg/cu.m) 6 hours/day for 14 days. Marked changes in splenic cellular populations were observed in exposure groups. The percentage of splenic lymphocytes fell significantly and in a dose-related fashion in all exposure groups, from 83.4% in air controls to 45.6% in animals exposed to 5.0 ppm arsine. At the same time, there was a concomitant increase in percentages of immature erythrocytes (rubricytes). Splenic T-cell percentages were significantly decreased at all arsine concentrations, whereas the percentage of B-cells was depressed only at the 5.0-ppm exposure level. In vitro analysis showed a concentration-dependent decrease in natural killer cell and cytotoxic T-lymphocyte function (significant at the 2.5- and 5.0-ppm exposure levels). Increased susceptibility to Listeria and Plasmodium yoelii was observed at all concentrations. As previous studies have shown, these data suggest that the spleen represents a target of arsine manifested by altered cellular populations. The decreases in certain host resistance parameters suggest that arsine exposure also results in immunosuppression. For immunotoxic effects, based principally on decreased cytotoxic T-lymphocyte function and increased susceptibility to Listeria, a NOAEL of 0.5 ppm and a LOAEL of 2.5 ppm are identified from this study.

The concentration-response curve for effects from acute exposure to arsine has been shown by Peterson and Bhattacharyya (1985) to be steep. The investigators exposed B6CF1/Anl female mice (8/group) to 0, 5, 9, 11, 15, or 26 ppm arsine for 1 hour. Blood samples were taken for hematologic evaluation 1, 5, and 11 days after exposure. No alterations in HCT, erythrocyte, leukocyte, or reticulocyte levels were noted in the 5-ppm group. Significant hemolytic responses were seen in the other groups. Hematocrit values were 98.8, 80.2, 79.7, 61.4, and 21.7% of controls 1 day after exposure for the 5-, 9-, 11-, 15-, and 26-ppm groups, respectively. At the 26-ppm exposure level, all five mice that remained after the first 24-hour sampling period died within 4 days.

Pregnant Fischer 344 rats and CD-1 mice were exposed to 0, 0.025, 0.5, or 2.5 ppm arsine (0, 0.08, 1.6, or 8 mg/cu.m, respectively), 6 hours/day, on gestational days 6-15 (Morrissey et al., 1990). Mice were killed on gestational day 17 and rats on gestational day 20. Significant increases in absolute and relative spleen weights were observed in the 2.5-ppm exposed mice, but no significant differences in the developmental indices were observed. In the 2.5-ppm rats, enlarged spleen was noted in >80% of the animals at necropsy (changes in spleen weight were not reported). A significant increase in the average fetal body weight per litter was evident in the 2.5-ppm group. No other developmental or reproductive effects were observed. In further experiments by these investigators, pregnant rats (13- 15/group) were exposed to 0 or 5 ppm arsine (0 or 16 mg/cu.m) during gestational days 4-15 (Morrissey et al., 1990). Exposed rats

developed splenomegaly and displayed significant changes in all hematological values (i.e., increased leukocyte and platelet counts, MCV, MCH, and MCHC; decreased RBC, Hgb concentration, and HCT) compared with those of the control group. Therefore, a NOAEL of 0.5 ppm arsine (HEC = 1.6 mg/cu.m) was determined for maternal toxicity (increased spleen weight in rats and mice), and a NOAEL of 0.5 ppm (HEC = 1.6 mg/cu.m) was determined for developmental effects (increase in average fetal body weight per litter in rats).

The ACGIH (1986) recommends a TLV-TWA of 0.05 ppm (0.2 mg/cu.m) based on hemolytic anemia.

I.B.5. Confidence in the Inhalation RfC

Study — High
Database — Medium
RfC — Medium

The studies by Blair et al. (1990a,b) and Hong et al. (1989) indicate that the most sensitive endpoints of arsine exposure in rats are increased hemolysis, altered RBC morphology, increased spleen weight, and impaired erythropoiesis. These effects result in splenic changes due to increased removal of damaged RBCs and splenic hematopoiesis. Taken together, the studies are given high confidence because the sample sizes were adequate, statistical significance was reported, critical endpoints were consistent with one another or replicated across studies, concentration-response relationships were documented, three species were investigated, and both a NOAEL and LOAEL were identified. These findings are corroborated by subacute inhalation exposure studies conducted by the same investigators. Supporting evidence also is provided by a reproductive study (Morrissey et al., 1990) in which similar effects were observed in pregnant rats exposed to arsine. The database is given medium confidence because there are three inhalation subchronic animal studies (two species) and a developmental/reproductive study that reported the same critical endpoint; however, there is a lack of data on human exposure, a lack of chronic inhalation studies, and no two-generation reproductive study. A medium confidence in the RfC follows.

I.B.6. EPA Documentation and Review of the Inhalation RfC

Source Document — This assessment is not presented in any existing U.S. EPA document.

Other EPA Documentation — U.S. EPA, 1984a,b

Agency Work Group Review — 02/11/1993

Verification Date — 02/11/1993

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the RfC for Arsine conducted in September 2002 identified one or more significant new studies. IRIS users may request the references for those studies from the IRIS Hotline at hotline.iris@epa.gov or (202)566-1676.

I.B.7. EPA Contacts (Inhalation RfC)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or hotline.iris@epa.gov (internet address).

II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — Arsine
CASRN — 7784-42-1

This substance/agent has not undergone a complete evaluation and determination under US EPA's IRIS program for evidence of human carcinogenic potential.

III. [reserved]
IV. [reserved]
V. [reserved]

VI. Bibliography

Substance Name — Arsine
CASRN — 7784-42-1

VI.A. Oral RfD References

None

VI.B. Inhalation RfC References

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VI.C. Carcinogenicity Assessment References

None

VII. Revision History

Substance Name — Arsine
CASRN — 7784-42-1

Date	Section	Description
03/01/1994	I.B.	Inhalation RfC on-line
12/03/2002	I.B.6.	Screening-Level Literature Review Findings message has been added.

VIII. Synonyms

Substance Name — Arsine
CASRN — 7784-42-1
Last Revised — 03/01/1993

- 7784-42-1
- Arsine
- UN2188
- Agent SA
- Arsenic hydride
- ARSENIC HYDRIDE (ASH3)
- Arsenic trihydride
- ARSENIURETTED HYDROGEN
- Arsenous hydride
- Arsenowodor [Polish]
- Arsenwasserstoff [German]
- Arsina [Spanish]
- HSDB 510
- Hydrogen arsenide