# 2. RELEVANCE TO PUBLIC HEALTH

## 2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO BENZIDINE IN THE UNITED STATES

Benzidine is a crystalline solid that may be grayish-yellow, white, or reddish-gray in color. It is a synthetic chemical with low volatility and is moderately soluble in water and organic solvents. In the past, benzidine was primarily used for the manufacture of dyes, especially azo dyes in the leather, textile, and paper industries. Benzidine is no longer produced for commercial sale or imported in the United States. In 1973, OSHA regulations effectively banned U.S. production of benzidine. Any benzidine production must be for captive consumption (in-house use by the producer only), and it must be maintained in closed systems under stringent workplace controls.

Generally, ATSDR believes that the primary route of human exposure to benzidine at hazardous waste sites is by ingestion of contaminated media, and to a much lesser extent, by dermal contact with contaminated soil. Benzidine has been found in at least 28 of the 1,585 current or former NPL sites. It was identified in surface water collected at 5 sites, groundwater collected at 10 sites, soil samples collected from 9 sites, and sediment samples collected from 4 of these 28 NPL hazardous waste sites. Benzidine was not detected in air at any of the NPL hazardous waste sites. No data are available on the levels of benzidine in body tissues or fluids for those living near hazardous waste sites or for the general population, but as previously indicated, since benzidine is no longer produced or used commercially in the United States, occupational exposures and exposures to the general population are expected to be low. Exposure to benzidine through most food products is highly unlikely; however, impurities found in certain food dyes can be metabolized to benzidine once inside the body. No data were located regarding dietary intake of benzidine. There are no studies that specifically addressed the health effects of exposure to benzidine in children or immature animals; therefore, it is unknown whether children differ from adults in their susceptibility to health effects from benzidine. There do not appear to be unique exposure pathways to benzidine for children.

## 2.2 SUMMARY OF HEALTH EFFECTS

Information on the toxicity of benzidine in humans is derived mainly from studies of individuals exposed in the workplace. Exposures in such settings have been assumed to have been mainly via inhalation and dermal contact. The toxicity of benzidine has been investigated in animals by the oral route. Cancer is the principal and best documented toxic effect of benzidine in both humans and animals. Humans and dogs develop primarily cancer of the bladder, whereas rodents develop primarily liver cancer. Relatively little information is available on the noncancer effects of benzidine. Dermal and immunological effects have been reported in workers exposed to benzidine, and animal studies have reported hepatic, renal, immunological, and neurological effects. The immunological alterations in the workers were subtle, and none of the subjects exhibited signs of infection at the time of the study. Few studies were located regarding reproductive or developmental toxicity of benzidine in humans or animals. A single, somewhat limited epidemiological study failed to detect any evidence of elevated rates for birth defects in residents living near a Superfund site contaminated with benzidine. However, the extent of actual exposure (if any) to benzidine was not determined. The only animal data, from an acute intraperitoneal study in mice, did not reveal any adverse effects of benzidine on sperm morphology. As detailed in Section 2.3 and Chapter 3, the overall quality of the noncancer database is inadequate and the relevance of these observations to human health is unclear. Therefore, the section below focuses only on the health effect of major concern for benzidine, cancer.

**Cancer.** Epidemiological evidence is currently sufficient to qualitatively establish that benzidine is a human bladder carcinogen following long-term occupational exposure. Some studies have observed benzidine-associated increased risks for cancer at one or more other human tissue sites as well (i.e., stomach, kidney, central nervous system, oral cavity, larynx, esophagus, liver, gallbladder, bile duct, and pancreas). The evidence for benzidine-induced cancer in sites other than the bladder, however, is not as strong as for bladder cancer. Reasons for this include the small number of cases among the populations studied, which diminishes the power of the statistical analyses, and inconsistency between studies regarding tumor sites. The occurrence of liver and kidney cancer has some biological plausibility based on what is known about the mechanisms of benzidine carcinogenicity (see Section 3.5.2). The exposure pathways in the workplace are not known with certainty, but most probably involve a mixture of inhalation and dermal routes. While no studies were located on cancer in humans after oral exposure to benzidine itself, oral exposure to benzidine-based dyes has been reported to increase the risk of bladder cancer in Japanese kimono painters.

The findings of cancer in humans are supported by observations that inhalation or oral exposure to benzidine can induce mammary and liver tumors and leukemia in rats, and that oral exposure can induce liver and bile duct cancer in hamsters; liver, Harderian gland, uterine, lung, and reticulum cell cancers in mice; and bladder cancer in dogs. Although particular target organs seem species-specific and probably related to differences in metabolism, benzidine appears capable of inducing cancer in most species by most routes of exposure. There is no evidence to suggest that the carcinogenicity of benzidine is route-dependent.

The mechanism of carcinogenicity of benzidine has been studied extensively and is thought to involve the formation of reactive intermediates as a result of metabolic transformations of benzidine. These reactive intermediates are thought to produce DNA adducts, which may initiate carcinogenesis by producing mutations that become fixed before DNA can be repaired. For further details on the mechanism of benzidine carcinogenicity, see Section 3.5.2, Mechanisms of Toxicity. Susceptibility to bladder cancer has been linked to slow acetylator type of the NAT2 N-acetyltransferase gene. Research conducted in recent years, however, has shown that slow acetylators are not at increased risk for bladder cancer, relative to fast acetylators (see Section 3.10 for further details).

The Department of Health and Human Services (DHHS) and the EPA have determined that benzidine is a known human carcinogen. The International Agency for Research on Cancer (IARC) has determined that benzidine is carcinogenic to humans.

## 2.3 MINIMAL RISK LEVELS

### *Inhalation MRLs*

No inhalation MRLs were derived for benzidine because of lack of sufficient inhalation data for any duration category. The only noncancer information regarding inhalation exposure in humans comes from epidemiological reports of altered natural killer cell function and of changes in values of T lymphocyte subpopulations in exposed workers. The utilization of these studies for MRL development is limited by exposure to other aromatic amines and lack of exposure concentration data. In animals, the only study providing quantitative inhalation data focused on carcinogenic effects with no data on noncancer end points.

### *Oral MRLs*

No oral MRLs were derived for benzidine because of inadequate data, as detailed below. Acute studies by the oral route were limited to studies examining mortality in animals and to a study that reported potential immunotoxicity in mice exposed to an unspecified dose of benzidine. Some intermediate-duration studies were available that described cardiovascular, hepatic, renal, hematological, immunological, or weight-loss effects. However, those studies are inadequate for derivation of an intermediate oral MRL because they did not provide quantitative data; most had inadequate design and/or incomplete reporting of the results (i.e., no controls, dose at which the effect was seen was not identified, only one dose level was tested, high mortality). Several studies provided data on effects after chronic-duration exposure in animals, but were considered inadequate for derivation of a chronic oral MRL. For example, brain vacuolization, a serious effect that precludes its use for MRL derivation, was seen in mice exposed to approximately 1.8 mg/kg/day, the lowest dose tested in another study. Weight loss, liver foci (which may represent preneoplastic lesions), hemosiderin pigmentation of the spleen, and bile duct hyperplasia have been reported in mice after chronic-duration oral exposure to benzidine doses between approximately 2.5 and 11 mg/kg/day. All of these effects occurred at dose levels higher than the one that caused brain vacuolization. A marginally significant ($p<0.10$) increase in proteinaceous kidney casts in female mice was reported, but not the specific dose at which the effect was observed. Liver cirrhosis was observed in several rabbits orally exposed for up to 3.5 years; however, only a summary of the data was presented. Recurring renal cystitis was the only treatment-related systemic effect observed in seven dogs exposed for 5 years, but incomplete reporting of the results precluded establishing with certainty the dose level at which this effect occurred.