NITROAROMATICS
Test Plan for m-Nitrotoluene

CAS No. 99-08-1

Monocyclic Aromatic Amines and Nitroaromatics Panel
American Chemistry Council
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Member companies in the Monocyclic Aromatic Amines and Nitroaromatics Panel are Albemarle Corporation, Bayer Corporation, Buffalo Color Corporation, and First Chemical Corporation.

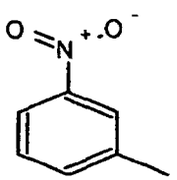
I. INTRODUCTION

The Monocyclic Aromatic Amines and Nitroaromatics Panel was organized under the American Chemistry Council to participate in the Environmental Protection Agency's High Production Volume (HPV) Challenge Program (the HPV program). The member companies are committed to making existing test data publicly available for products in these two categories and developing any additional screening level data needed to meet HPV program endpoints on health and environmental effects, fate, and physiochemical properties.

In consideration of animal welfare concerns to minimize the use of animals in the testing of chemicals, the Panel has performed an extensive literature search for all published and unpublished data and has evaluated the adequacy of the data. This document summarizes the existing test data for m-nitrotoluene, a monocyclic nitroaromatic compound included in the HPV program. A condensed robust summary document has been prepared and is included in this submission. The document is "condensed" to exclude entries in the official European Chemical Bureau IUCLID file that are not relevant to endpoints addressed in this submission. The robust summary document references all the studies summarized below.

II. SUMMARY OF M-NITROTOLUENE DATA

Figure 1. m-Nitrotoluene
CAS number 99-08-1



Manufacturing, Use, and Exposure Information for m-Nitrotoluene

m-Nitrotoluene is used in organic synthesis, specifically in the synthesis of dyes, toluidines, nitrobenzoic acids, and explosives. Mixed nitrotoluene isomers are manufactured by the reaction of toluene with nitric acid, using a sulfuric acid catalyst. The meta isomer is separated by distillation. Because this chemical is used only as an intermediate, human and environmental exposure is limited. The potential for exposure occurs in the workplaces of the manufacturers and their customers. The ACGIH TLV® TWA exposure limit is 2 ppm (11 mg/m^3) with a skin

notation. The OSHA PEL is 5 ppm (30 mg/m^3) with a skin notation, and the German MAK limit is also 5 ppm (28 mg/m^3) with a skin notation. The NIOSH IDLH (immediately dangerous to life and health) concentration is 200 ppm. The US manufacturer uses and recommends both personal protective equipment and engineering controls to limit exposure. If air concentrations are above 2 ppm and less than 50 ppm, a NIOSH approved full-face respirator with canisters or cartridges specifically approved for use with organic vapors is recommended as a minimum. If greater than 50 ppm, a self-contained breathing apparatus should be used. If the atmospheric concentration is unknown, a supplied air respirator is recommended. To prevent skin contact, use of supported neoprene gloves for routine work and butyl rubber gloves when there is a probability of liquid contact is recommended. A butyl rubber full body suit may be needed depending on exposure potential. To prevent eye contact, chemical goggles should be used. If splashing is possible, a full-face shield is recommended.

Summary of Test Data

Test data are available for all HPV endpoints for m-nitrotoluene. Testing of another nitrotoluene isomer, p-nitrotoluene, is underway and will be applied to this isomer. The existing data are reviewed below. The IUCLID document contains a summary of all available information on this chemical, and a condensed robust summary has information from the most relevant studies for the HPV endpoints.

Physical and Chemical Properties

m-Nitrotoluene is a liquid at room temperature, and has a relative density of 1.157. The boiling point is 232°C at atmospheric pressure, and the reported vapor pressure ranges from 10 hPa at 89.7°C to 0.199 hPa at 20°C. It is considered moderately soluble in water (419 mg/l @20°C). The log of the octanol-water partition coefficient is 2.45, which indicates a low potential for bioaccumulation. This low potential was confirmed in bioaccumulation studies in fish. These data are sufficient to describe the physical and chemical properties of this chemical for the HPV program.

Fate

If released into water, biodegradation will be a major removal process. Evaporation from water will also be significant, as will photolysis in surface waters. Since m-nitrotoluene has no hydrolyzable groups, loss from water may occur through evaporation or photodegradation in the absence of biota. The estimated Henry's Law constant suggests that m-nitrotoluene is slightly volatile. However, the photodegradation half-life is sufficient to account for essentially all of the 18% loss of m-nitrotoluene over the 8-day period of the water stability study. The initial rate of photolysis has been shown to be similar at pH values of 3 and 11. Therefore, further studies of water stability at various pH values are not needed. m-Nitrotoluene is not readily biodegradable, but is inherently biodegradable. A ready biodegradability study found less than 10% biodegradation in 28 days, while biodegradation after acclimation of sludge was 75% after 14 days and 93% after 28 days. A review of all three nitrotoluene isomers concluded that in natural waters, biodegradation and photolysis are the main degradation routes. [Nitrotoluenes (Methylnitroenzenes), BUA Report 41, April 1989, p. 29.] In this same review, the authors concluded, "Nitrotoluenes can only be degraded by adapted bacteria. They must be regarded as not readily biodegradable". (Ibid, p. XII). Adsorption to sediments is expected to be low. In air, reaction with hydroxyl radicals is expected to be negligible. In soils, adsorption is predicted to be low, and leaching is expected to be significant. Evaporation from dry soils is expected to be low. For HPV Program purposes, there are sufficient data for m-nitrotoluene to characterize its fate.

Aquatic Toxicity

m-Nitrotoluene was harmful to fish (96-hr LC_{50}>10<100 mg/L) and harmful or toxic (48-hr EC50>1<10 mg/L) to Daphnia. .This chemical was also harmful to algae (96-hr EC50 = 14 mg/L). The aquatic toxicity data are adequate for m-nitrotoluene to fill HPV Program endpoints.

Mammalian Acute Toxicity

m-Nitrotoluene is classified as "harmful" in most studies by single oral doses according to ANSI labeling criteria, as the majority of the reported rat oral LD_{50} values were >500 and <2000 mg/kg. It was not harmful by inhalation or by single dermal applications; no evidence of toxicity was found by these routes. No further acute toxicity testing is proposed.

Mammalian Repeated Exposure Toxicity

Oral toxicity studies in rats and mice ranging from two weeks to three months in duration have been completed on m-nitrotoluene. Both incorporation into diet and gavage were used to administer the test material. In rats, adverse effects on the blood such as increased methemoglobinemia, anemia, reticulocytosis, and spleen congestion were common at high doses. These effects are typical for nitroaromatic compounds. Other effects in rats included mild effects on the liver, hyaline droplet nephropathy in males, and effects on the male and female reproductive systems. Mice had mild, reversible effects on the liver and lung and immunotoxicity; there was no evidence of reproductive effects. The definitive subchronic toxicity studies completed to date were the three-month dietary studies in rats and mice. In rats, hyaline droplet nephropathy in males and spleen pigmentation in females occurred at dietary concentrations of 625 ppm and higher, about 46-48 mg/kg/day. Significant histopathology occurred in the spleen in both sexes at 2500 ppm (about 171 mg/kg/day) and higher doses. Decreased sperm count in males occurred only at the highest concentration, 10,000 ppm (about 661 mg/kg/day), while changes in estrus cycle length occurred only at concentrations of 5000 and 10,000 ppm (about 336 and 638 mg/kg./day, respectively). Therefore, in rats, effects on the reproductive organs occurred at higher doses than effects on most other organs. This chemical has been adequately tested for repeated exposure toxicity to fill HPV program endpoints.

Genetic Toxicity

Standard bacterial assays found no evidence of mutagenicity. In vitro cytogenetics assays in Chinese hamster ovary and lung cells were negative, but an assay using human lymphocytes was positive. Studies of unscheduled DNA synthesis in whole animals were negative. Genetic toxicity screening is adequate for m-nitrotoluene to fill HPV Program endpoints.

Developmental and Reproductive Toxicity

A combined developmental and reproductive toxicity screening study was done in rats. . Animals were dosed for 90 days prior to mating, during mating and gestation. Blood and spleen effects typical for nitroaromatic compounds were found in the parental animals, and less severe splenic toxicity was also found in the offspring at 3 months of age. There were no effects indicative of developmental toxicity and no effects on fertility or any other reproductive parameters. This study is consistent with the results of the three-month oral study in rats described above, as the dose used in this screening study was 300 mg/kg/day, slightly lower than the doses responsible for reproductive toxicity in the three-month study.

In response to comments from the EPA on the need for additional reproductive toxicity testing, the Panel plans to share costs for a reproductive toxicity study of p-nitrotoluene (CAS no. 99-99-0), an ICCA Program chemical. This study, which is using the OECD 421 protocol plus additional histopathology, has recently been completed in response to data needs in Germany, and the Panel expects to submit the completed study this year to support the database for m-nitrotoluene.

This approach will minimize the use of animals for testing. The application of data developed for p-nitrotoluene to the meta isomer is justified by the results of the National Toxicology Program (NTP) repeated dose toxicity studies completed for both of these isomers (NTP, 1992). (Toxicity studies of o-, m-, and p-nitrotoluenes (CAS Nos. 88-72-2, 99-08-1, 99-99-0) administered in dosed feed to F344/N rats and B6C3F1 mice. NTP Report TOX 23; NIH Publication 93-3346.). Both m- and p-nitrotoluene impaired testicular function, decreasing sperm counts in rats at the same dose level, 10,000 ppm. Both isomers also increased estrus cycle length at 5000 ppm.