

# **NTP Research Concept: Dimethylamine Borane**

## **Project Leader**

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## **Background and Rationale**

Dimethylamine borane (DMAB) is widely used in the manufacturing of high-temperature printed electronic circuit boards, thin metal film, semiconductors and power transistors. DMAB is used as a reducing agent in a number of reactions (e.g. the reduction of aldehydes and ketones to alcohols), and as a reducing agent in the electrodeless deposition of metals (e.g. production of nanoscale gold). Production of DMAB from 1994-2002 was in the range of 10,000 – 500,000 pounds. Human exposure potential is through the various industrial production processes. With the increased production of nanoscale metals, the use may be increasing. The National Institute of Occupational Safety and Health (NIOSH) Dermatology Cross-sector Program nominated DMAB for evaluation of dermal absorption, toxicity and skin sensitization. DMAB was identified as a possible contact sensitizer and systemic toxicant and is being considered for inclusion into the NIOSH Chemical Pocket Guide. A review of the literature for adverse effects by the NIOSH-sponsored Dermal Subject Matter Expert Workgroup failed to provide sufficient scientific evidence for the group to make a recommendation on the dermal toxicity of DMAB (<http://ntp.niehs.nih.gov/go/33220>).

## **Key Issues**

Limited toxicokinetic information has been identified for DMAB in humans or animals. METEOR failed to predict the potential metabolites of this compound. However, amine borane complexes are fairly stable and this could allow for distribution to sites where neither compound would normally be transported. In an aqueous environment, DMAB could slowly dissociate into decomposition products such as boric acid, hydrogen, borates and dimethylamine. It has been suggested that the toxic effects may be associated with these decomposition products. Under certain conditions nitrosamines may be formed from dimethylamine in the presence of nitrosylating agents (nitrites, nitrogen oxides). Dimethylnitrosamine has been shown to be a carcinogen in rodents. No data on the genotoxicity of DMAB was identified.

There is very little data regarding systemic effects of the chemical following dermal exposure. There are several publications which document adverse events in workers following an accidental exposure to DMAB in an industrial setting. Four workers were exposed to liquid DMAB blown out of a pipe after improper closure of a filter. Three of the workers decontaminated immediately and reported symptoms of dizziness, nausea, vomiting and diarrhea, which resolved within 24 hours. The single worker who decontaminated 1 hour after exposure exhibited confusion and drowsiness, cognitive impairment and polyneuropathy. Neurotoxicity persisted for at least 9 months following exposure, with clinical and nerve conduction improving after 18 months. It was suggested that the neurotoxicity associated with the delayed decontamination was

indicative of dermal absorption, with resulting systemic toxicity (Tsan et al., 2005; Kuo et al., 2006). However, inhalation and oral would also be possible routes of chemical exposure in this accident.

The reported dermal LD50 value for rabbits was 210 mg/kg. For their pocket guides, NIOSH considers any compound with an LD50 < 2 g/kg body weight to have the potential for acute dermal toxicity. An acute study in rabbits suggests that the urogenital tract may also be a target tissue. No data were identified from standard repeated-dose, subchronic or chronic toxicity studies of DMAB in humans or animals. No specialty studies evaluating biological system/function specific effects of the chemical following dermal exposures were identified. DMAB had been identified as a skin irritant and potential sensitizer in multiple databases based on guinea pig studies, however the original literature reports were not available.

### **Specific Aims**

Based on effects documented following accidental exposures, it is hypothesized that DMAB is absorbed via the skin and will target the nervous system.

1. Evaluate the absorption, distribution, metabolism and excretion of DMAB following dermal administration.
2. Investigate the potential for dermal exposure to DMAB to cause systemic toxicity.
3. Investigate the potential for dermal exposure to DMAB to cause dermal hypersensitivity.

### **Proposed Approach**

The first specific aim of the proposed studies will be to evaluate the absorption, distribution, metabolism and excretion of DMAB following dermal administration. Particular attention will be paid to whether the compound forms dimethylamine or dimethylnitrosamine *in vivo*. There is a need to obtain reliable dose response information and a quantitative profile of metabolites from the toxicokinetics studies. Due to the lack of an identifiable chromophore, this compound (without radiolabeling), would not be a good candidate for absorption studies using only human skin models. However, since ADME studies will be conducted with radiolabeled compound, *in vitro* absorption studies with human skin will be conducted as an add on to the ADME. *In vitro* cytotoxicity studies using the Epiderm human skin model are also proposed to obtain information on how DMAB affects human skin. Following these studies, we will conduct a 14-day study to provide acute toxicity data. After analysis of the acute, and ADME data, we will determine the necessity to conduct subsequent toxicity studies of DMAB via a dermal route of exposure. Neurotoxicity would be evaluated as part of a 90-day toxicity study. In parallel to the ADME studies, the compound will be examined for its potential to induce genotoxicity *in vitro* and *in vivo* and dermal irritancy and hypersensitivity using the local lymph node assay and mouse ear swelling tests.

## **Significance and Expected Outcome**

Available data are inadequate to evaluate the potential toxicity of DMAB following dermal exposure. In addition, there is a need to supply publicly available data to support the skin notation that serves as the basis for the NIOSH nomination. The production of DMAB appears to be increasing because of its use in the semiconductor and nanomaterials industries. The exposure limits for this compound are based on dimethylamine. These data will be used to determine whether regulatory limits specific for DMAB are needed.

## **References**

Kuo HC, Huang CC, Chu CC, Chu NS [2006]. Axonal polyneuropathy after acute dimethylamine borane intoxication. Arch Neurol 63(7):1009-1012

Tsan YT, Peng KY, Hung DZ, Hu WH, Yang DY [2005]. Case report: the clinical toxicity of dimethylamine borane Environ Health Perspect. 113(12):1784-1786.