



NICNAS Existing Chemicals Information Sheet

Methyldibromo Glutaronitrile (MDBGN) CAS No: 35691-65-7

June 2009

Introduction

MDBGN is used as a preservative and biocide in a range of consumer products in Australia. At the time of writing, these products include those intended to be in contact with the skin such as cosmetics, personal care products and skin care products (hand wipes) and those not intended for skin contact such as adhesives and coatings.

Due to skin sensitisation potential, MDBGN has been the subject of two European Union (EU) Scientific Committee on Consumer Products (SCCP) opinions on safe levels of use in cosmetics. NICNAS conducted a review of the human health hazards of MDBGN and of current regulatory controls. This Information Sheet contains the summarised findings from the human health hazard assessment report on MDBGN and subsequent regulatory action. The health hazard assessment report is also available separately from the NICNAS website¹.

Chemical Identity

Common name:	Methyldibromo glutaronitrile (MDBGN)
Structural formula:	$\begin{array}{c} \text{Br} \\ \\ \text{NC} - \text{C} - \text{CH}_2\text{CH}_2\text{CN} \\ \\ \text{CH}_2\text{Br} \end{array}$
CAS registry number:	35691-65-7
IUPAC chemical name:	1,2-dibromo-2,4-dicyanobutane

MDBGN is an off-white to tan crystalline powder.

Import, Manufacture and Use of Methyldibromo Glutaronitrile in Australia

In 2007, NICNAS called for information on the use of MDBGN in Australia. The call for information confirmed the use of MDBGN in consumer products. MDBGN was imported in mixtures and as a raw chemical for local formulation. It was found in products that varied from adhesives and coatings to personal care products including sunscreens, shampoos, shower gels and wet-wipe hand towels. MDBGN was reported to be present in shower gels and shampoos at concentrations between 0.003 and 0.004% and in sunscreens at 0.04%. There was limited information on final use concentrations in other products.

¹ http://www.nicnas.gov.au/Publications/CAR/Other/Methyldibromo_Glutaronitrile_PDF.pdf

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Exposure to Methylidibromo Glutaronitrile

In the mid 1980s, MDBGN began to be used as a preservative in cosmetics. The first case reports of contact sensitivity to MDBGN preserved cosmetics were reported in the late 1980s and early 1990s. Several research groups have demonstrated subsequently that the prevalence of contact sensitivity to MDBGN in various European countries has increased since the early 1990s. Animal studies have demonstrated that MDBGN is a sensitising agent. In Australia, allergy clinics have reported cases of allergy (combined prevalence of 0.7%) associated with the use of MDBGN as a preservative, most commonly in hand cleaners.

Summary of Key Health Issues

MDBGN has low acute dermal and inhalation toxicity in animals. It is moderately toxic via the oral route. MDBGN is a severe eye irritant, a skin irritant and a skin sensitiser. MDBGN is not genotoxic or carcinogenic. MDBGN is neither a reproductive nor a developmental toxin at doses not associated with maternal toxicity.

Current Regulatory Status

MDBGN is listed in the Australian Inventory of Chemical Substances (AICS).

MDBGN will be listed in the Standard for the Uniform Scheduling of Drugs and Poisons (SUSDP) under the following:

- Appendix C for preparations intended to be in contact with the skin, including cosmetic use,
- Schedule 6 for all other uses, and
- Appendix F Part 3, requiring labelling with Warning Statement 28 – “Repeated exposure may cause sensitisation” and Safety Directions 1, 4 and 7 – “Avoid contact with eyes”, “Avoid contact with skin” and “Wash hands thoroughly after use”.

To accommodate existing product stocks, this listing in the SUSDP will become effective from 1 January 2010².

Health and Safety Information

The major sources of information for the health hazards of MDBGN are previously published reports of the Cosmetic Ingredient Review (CIR) Expert Panel (1996), the United States Environmental Protection Agency (USEPA) R.E.D. Facts (1996) and the National Toxicology Program (NTP) Technical Report (2008). Three opinions by the Scientific Committee on Cosmetic Products and Non-Food Products Intended for Consumers (SCCNFP) (2002) and the Scientific Committee on Consumer Products (SCCP) (2005 and 2006) and literature searches conducted until March 2007 also provided relevant supplementary studies.

Animal Data

MDBGN is readily absorbed following oral and dermal administration.

Acute Toxicity

MDBGN is moderately toxic by the oral route in rats. The LD₅₀ value (Lethal Dose, 50%; ie. the dose that is lethal to half the animals tested) is 770 mg/kg for males and 515 mg/kg for females. It is of low toxicity by dermal (LD₅₀ >5g/kg) and inhalation (LC₅₀³ >13 mg/L) routes of exposure in rabbits and rats, respectively.

² <http://www.tga.gov.au/ndpsc/record/rr200810.htm>

³ Lethal concentration in air, that is lethal to half of the animals tested.

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Irritation

In pure form (98%), MDBGN is a severe eye irritant. Instillation of MDBGN powder into the rabbit eye resulted in severe irritation, which persisted for at least 21 days post-instillation. Equivocal results were obtained from skin irritation tests in animal studies. However, repeat dose dermal toxicity tests reported moderate to severe erythema and slight to moderate oedema. Non-neoplastic skin lesions were also reported.

Sensitisation

Results obtained from animal studies vary according to the type of animal study. Adjuvant⁴ and non-adjuvant animal tests showed no or only minimal evidence of skin sensitising potential for MDBGN. However, results from three local lymph node assays (LLNA) and from two novel adjuvant methods for assessing skin sensitisation potential strongly suggest that MDBGN is a sensitising agent.

Repeated Dose Toxicity

In 13-week repeat feeding studies, the observed effects of MDBGN were thyroid follicular cell hypertrophy, thyroid hyperplasia, increased pigmentation of the liver and spleen and increased extramedullary haematopoiesis when administered at high doses (4000 ppm) in dogs. Follow-up studies found no significant changes in levels of thyroid hormones. While this study showed thyroid effects via the oral route, the major use of MDBGN is not intended for food use. Therefore, the level of exposure to MDBGN via the oral route is expected to be low. A No-Observed-Adverse-Effect-Level (NOAEL) of 10 ppm (0.331 mg/kg bw [body weight]) was determined for females based on diarrhoea and emesis observed at 100 ppm (3.11 mg/kg bw).

Repeated dermal application of MDBGN was associated with moderate to severe erythema and slight to moderate oedema. Non-neoplastic lesions at the application site such as epidermal hyperplasia, hyperkeratosis, parakeratosis, necrosis, and ulcers were observed. Dermal chronic active inflammation and sebaceous gland hyperplasia were also reported.

Genotoxicity

MDBGN did not show evidence of mutagenic activity in a variety of *in vitro* and *in vivo* assays, except for one assay where increased frequencies of chromosomal aberrations in Chinese hamster ovary (CHO) cells were reported. Overall, the experimental evidence indicates that MDBGN is not mutagenic.

Carcinogenicity

Two-year dermal studies conducted in rats and mice showed no evidence of carcinogenic effects with MDBGN. In the rat study, no increases in the incidence of neoplasms at the site of application were observed even though irritation and epidermal hyperplasia at the site of application were reported in all dosed animals administered with 6 or 18 mg/kg bw MDBGN. In the mouse study, dermal administration with 0.6 - 6 mg/kg bw MDBGN were not associated with any treatment-related clinical findings nor increases in the incidence of neoplasms at the site of application.

⁴ Agents that modify the effect of other agents

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Reproductive and Developmental Toxicity

In a multigenerational study, MDBGN was administered via diet to rats at dose levels up to 275 mg/kg bw for males and 360 mg/kg bw for females. No treatment related effects were seen in the parental generation. The NOAEL was determined to be 6.3 mg/kg bw for males and 7.5 mg/kg bw for females, based on effects on the spleen and changes in various organ weights seen at higher doses in F1⁵ rats. In another study, a NOAEL for developmental toxicity was determined to be 175 mg/kg bw. Available information suggests that MDBGN is neither a reproductive nor a developmental toxin at doses that are not associated with maternal toxicity.

Human Data

Sensitisation

The prevalence of MDBGN sensitivity has been monitored in numerous countries and over an extended period by routine patch testing of contact dermatitis patients. The prevalence varies significantly between countries, but this is to be expected as the use of MDBGN as a preservative is likely to vary between countries. Across all available patch test surveys (concentration range of 0.03-0.5% MDBGN), the prevalence rate of positive patch test reactions ranged from 0-11.7%, with a median prevalence rate of 2.0%. In some studies, the prevalence rate increased to up to 19.6% when 0.3% MDBGN was tested in patients sensitised to their own cosmetics. Another study also found that healed areas of skin previously affected by MDBGN contact allergy developed a more vigorous sensitisation response upon re-exposure to MDBGN. When MDBGN pre-sensitised individuals were patch tested with MDBGN at concentrations ranging from 0.0001-1%, the prevalence rate of positive reactions ranged from 7.7-92%. Available human data from diagnostic patch test surveys and elicitation studies in MDBGN sensitised individuals indicate that MDBGN is a human skin sensitiser.

International Regulatory Activities

MDBGN was permitted in the EU in rinse-off cosmetic products at a maximum concentration of 0.1% and was prohibited for use in cosmetic sunscreen products at >0.025%. However, the most recent 2006 SCCP opinion concluded that no safe levels could be identified for MDBGN in cosmetics. As a result of this most recent SCCP opinion, MDBGN has been removed from Annex VI of the EU Cosmetics Directive (List of Preservatives Which Cosmetic Products May Contain) and is no longer allowed to be used in any cosmetic products in the EU.

Regulations in the USA currently permit the use of MDBGN in cosmetics at up to 0.025% in leave-on products and 0.06% for rinse-off products.

⁵ First generation