

***m*-Phenylenediamine**

[108-45-2]

Supplement 2009

MAK value	–
Peak limitation	–
Absorption through the skin (1990)	H
Sensitization (2008)	Sh
Carcinogenicity (1990)	Category 3B
Prenatal toxicity	–
Germ cell mutagenicity	–
BAT value	–

Sensitization

m-Phenylenediamine is an intermediate product in the production of paints and pigments. It was formerly also used as a hardener in epoxide resin systems and as a component in oxidative hair dyeing agents (CIR 1997; Kayser and Schlede 2001).

Documentation for *m*-phenylenediamine is available from 1992 (see documentation “*m*-Phenylenediamine”, 1993, a translation of the 1992 German). In this supplement the data for contact sensitization meanwhile available are summarized and evaluated.

Allergenic Effects

Effects in humans

Sensitizing effects on the skin

There are only two incompletely documented publications available for the sensitizing effects on the skin of *m*-phenylenediamine in humans; they are therefore only of limited use for this evaluation

Two years after *m*-phenylenediamine was introduced as a hardener in epoxy resin systems, a worker who did not wear protective gloves during work developed contact dermatitis on the hands. Patch testing resulted in 3+ reactions to 2% *m*-phenylenediamine, *p*-phenylenediamine and benzidine, and 2+ reactions to 2% toluidine (no other details) and 5% aniline. Although "petroleum" is given as the vehicle, petrolatum is probably the substance meant (Rudzki and Krajewska 1974). Of 38 workers who developed dermatitis as a result of contact with epoxy resins in which also *m*-phenylenediamine was used as a hardener, 8 reacted in patch tests to 2% *m*-phenylenediamine in petrolatum. Six of the 8 patients also reacted to epoxy resin. Of a further 150 patients tested with 1% *m*-phenylenediamine in petrolatum in addition to the standard series, 5 produced a reaction, 4 of them also to *p*-phenylenediamine (Rudzki et al. 1977).

In addition, in a number of studies, cross-reactions to *m*-phenylenediamine are reported in patients who probably had no previous exposure to *m*-phenylenediamine.

Two of 8 patients sensitized to *p*-phenylenediamine also produced a patch test reaction to 1% *m*-phenylenediamine in petrolatum (with 6% methyl ethyl ketone) (Basketter and Lidén 1992).

In an incompletely documented study there is some uncertainty about the number of patients who reacted to *p*-phenylenediamine (103 or 104) and were also tested with *m*-phenylenediamine, and the number of positive reactions to 2% *m*-phenylenediamine (39 or 45). Nearly all of these patients also produced a reaction to at least 1 of 5 other *m*-substituted aromatic amines tested (Rudzki et al. 1977).

Of 23 volunteers with known sensitization to *p*-phenylenediamine, who were tested with a total of 21 other amino-substituted aromatic substances, 3 also produced a 2+ reaction to 1.1% *m*-phenylenediamine in petrolatum at the readings after 24 and 48 hours, and all 3 produced at least a 2+ reaction to at least 6 other substances (Hoting et al. 1995).

Three of 16 female hairdressers sensitized to *p*-phenylenediamine reacted also to *m*-phenylenediamine (Matsunaga et al. 1989).

In another study, 21% and 53% of the tested patients with contact dermatitis from hair dyes who reacted to 1% *p*-phenylenediamine in petrolatum, reacted also to 0.1% or 1% *m*-phenylenediamine in petrolatum. However, the number of patients tested is not documented (Ishihara et al. 1985).

In another study, 28 of 40 patients who reacted to *p*-phenylenediamine also produced a reaction to 2% *m*-phenylenediamine in yellow petrolatum; 27 of the 40 patients reacted also to 2% 2,4-toluylenediamine in yellow petrolatum (Kleniewska 1975).

Apparently, the concomitant reactions to *m*-phenylenediamine and *p*-phenylenediamine are not attributable to the small amount of the para-isomer present in *m*-phenylenediamine as an impurity (Rudzki 1975).

In another earlier study, 41 of 60 workers who had had contact with mafenide/sulfanilamide powder among other substances, and were sensitized to para-disubstituted aromatics or had contact dermatitis, also reacted to 2,4-toluylenediamine

(in a 1% test concentration), which structurally is closely related to *m*-phenylenediamine. In addition, 24 of the 41 workers also produced a reaction to 1% *m*-aminophenol. Only 3 of the 60 persons tested reacted to 1% 2,5-toluylenediamine (Düngemann and Borelli 1966).

Overall, these studies indicate that approximately 20% to 70% of the patients sensitized to *p*-phenylenediamine can also react to *m*-phenylenediamine. On the other hand, in another study with 12 patients primarily sensitized to *p*-phenylenediamine, no reactions to 1% *m*-phenylenediamine in lanolin alcohol ointment/olive oil were observed (Schulz 1962).

Sensitization of the airways

There are no data available.

Animal Experiments

Sensitization of the skin

In a closed patch test, 10 Hartley guinea pigs were treated occlusively on the neck for induction with 1% *m*-phenylenediamine in petrolatum for 48 hours, three times a week for two weeks. The challenge treatment was carried out two weeks later by means of the occlusive application of *m*-phenylenediamine in concentrations of 0.1% and 1% to the animals' flanks. Only the 1% test preparation produced a reaction in 1 of 10 animals; no reaction to the lower concentration was observed. In pilot studies, a 10% preparation of *m*-phenylenediamine was found to produce irritation in 4 of 9 animals, whereas no irritative reactions to concentrations between 0.1% and 5% were observed on the animals' flanks (Ishihara et al. 1985).

In a publication from Russia, positive results were reported for two sensitization tests with *m*-phenylenediamine. After epicutaneous induction with 1% *m*-phenylenediamine and after intradermal induction with 50 to 400 µg *m*-phenylenediamine (no other details), 4 of 6 and 3 of 6 animals, respectively, produced a reaction when challenged with 2% *m*-phenylenediamine (ECB 2000). In a review, an earlier study was cited in which repeated application of 35% and 25% *m*-phenylenediamine to the intact or abraded skin of guinea pigs (in total 9 treatments) resulted in the development of more pronounced erythematous reactions than after the initial application (no other details), which was interpreted as an indication of sensitization (CIR 1997).

A modified open patch test and a sensitization test with intradermal induction treatment in female and male Hartley guinea pigs yielded negative results. In this study, 0.2 ml Freund's complete adjuvant (FCA) was injected into one paw of 12 animals on the first day, and 0.5 ml of a test preparation of 0.18 mmol (0.002%) *m*-phenylenediamine in water was applied non-occlusively to the neck region on the

first, third and fifth days. For intradermal induction, the same concentration of test substance in FCA was injected intradermally into one paw of 12 other animals on the fifth day, but there was no further topical application of the preparation. The challenge was carried out via the non-occlusive application of a 0.09 mmol (0.001%) aqueous test preparation to the animals' backs on day 16; none of the animals in either of the two groups produced a reaction. There were also no reactions to *o*-aminophenol, *m*-aminophenol and *p*-aminophenol or to *o*-phenylenediamine and *p*-phenylenediamine. Animals pretreated with these substances for induction likewise did not react to *m*-phenylenediamine (Dossou et al. 1985).

An earlier study with guinea pigs also yielded negative results after intradermal induction and challenge with 1% *m*-phenylenediamine (ECB 2000).

Contrary to these findings, a local lymph node assay yielded positive results. Lymphocyte proliferation was stimulated by a factor of 11.7, 15.4 and 19.2 with 2.5%, 5% and 10% preparations of *m*-phenylenediamine in acetone/olive oil (4:1), respectively. *p*-Phenylenediamine caused stimulation by a factor of 13.4, 20.4 and 19.9 at the same concentrations (Ashby et al. 1995). The *m*-phenylenediamine concentration that produced a three-fold increase in lymphocyte proliferation (EC_3 value) was determined to be 0.49% (Roberts et al. 2007).

The results of a study in which spleen cells from CBA/J mice were first incubated with the "maximum non-cytotoxic concentration" of *m*-phenylenediamine are not unequivocal. After cells were incubated with 3 μ g *m*-phenylenediamine/ml for 18 hours, CBA/J mice were twice given intraperitoneal injections of $10 \cdot 10^6$ cells at an interval of seven days. The challenge treatment was performed ten days later and consisted of a 1% *m*-phenylenediamine preparation containing hydroxyethyl cellulose applied non-occlusively to one of the animals' ears. An increase in ear thickness was found after 24 and 48 hours, and somewhat less pronounced after 72 hours. The reaction to *m*-phenylenediamine was more pronounced than the reactions in the groups treated with *o*-phenylenediamine or *p*-phenylenediamine, 2,5-toluylenediamine, *m*-aminophenol and *p*-aminophenol, 1,4-dihydroxybenzene and in the animals treated with resorcin (Kalish and Wood 1995).

According to investigations on structure–activity relationships, it was found plausible that *m*-phenylenediamine has contact sensitization potential (Fedorowicz et al. 2005).

Cross-reactions

Compared with the reactions to 1% *p*-phenylenediamine in 9 animals sensitized to *p*-phenylenediamine in a maximization test, less pronounced reactions to 5% *m*-phenylenediamine also occurred. However, the number of animals that reacted to *m*-phenylenediamine, and the severity of the reactions are not given, as, according to the authors, the reactions were not clearly readable as a result of skin discoloration produced by *m*-phenylenediamine (Li et al. 1996). According to another, incompletely documented study, none of the 4 JY-1 guinea pigs sensitized to *p*-phe-

nylenediamine in a maximization test reacted to 1% m-phenylenediamine (Shigematsu et al. 1988). The modified lymphocyte transformation tests carried out in connection with these studies using the lymphocytes of guinea pigs sensitized to p-phenylenediamine showed cross-reactions between p-phenylenediamine and m-phenylenediamine to be less common than between p-phenylenediamine and p-aminophenol, and between p-phenylenediamine and o-phenylenediamine (Li et al. 1996; Shigematsu et al. 1988).

Cross-reactions to m-phenylenediamine in guinea pigs sensitized to p-phenylenediamine were observed only occasionally also in a maximization test (a questionable positive result in 1 of 10 animals) and in a modified single injection adjuvant test (a positive result in 1 of 10 animals) (Basketter and Goodwin 1988).

Manifesto (sensitization)

For the allergenic effects of m-phenylenediamine in humans there are mainly only incompletely documented studies and findings from earlier literature describing cross-reactions in patients with known sensitization to p-phenylenediamine. A few findings suggest, however, there is also primary sensitization to m-phenylenediamine. The results from animal studies are mostly negative. As a result of methodological shortcomings or incomplete documentation in some cases, they can be included in the present evaluation only with reservations. The results of a valid local lymph node assay (LLNA) confirm the sensitizing effects of m-phenylenediamine. Also in view of the above-mentioned cross-reactions, skin sensitizing effects of m-phenylenediamine in humans appear to be plausible. m-Phenylenediamine is therefore designated with “Sh” (for substances which cause sensitization of the skin). As there are no data for the allergenic effects of the substance on the airways, it is not designated with “Sa”.

References

- Ashby J, Basketter DA, Paton D, Kimber I (1995) Structure activity relationships in skin sensitization using the murine local lymph node assay. *Toxicology* 103: 177–194
- Basketter DA, Goodwin BFJ (1988) Investigation of the prohaptent concept. Cross reactions between 1,4-substituted benzene derivatives in the guinea pig. *Contact Dermatitis* 19: 248–253
- Basketter DA, Lidén C (1992) Further investigation of the prohaptent concept: reactions to benzene derivatives in man. *Contact Dermatitis* 27: 90–97
- CIR (Cosmetic Ingredient Review) (1997) Final report on the safety assessment of m-phenylenediamine and m-phenylenediamine sulfate. *Int J Toxicol* 16, Suppl 1: 59–115
- Dossou KG, Sicard C, Kalopissis G, Reymond D, Schaefer H (1985) Method for assessment of experimental allergy in guinea pigs adapted to cosmetic ingredients. *Contact Dermatitis* 13: 226–234

- Düngemann H, Borelli S (1966) Untersuchungen zur Gruppenallergie bei aromatischen Amino-Verbindungen (Studies on group allergies of aromatic amino compounds. Test results on so-called "para group" allergies) (German). *Berufsdermatosen* 14: 281–295
- ECB (European Chemicals Bureau) (2000) *m*-Phenylenediamine. IUCILID dataset, 18th February 2000, ECB, Ispra, Italy
- Fedorowicz A, Singh H, Soderholm S, Demchuk E (2005) Structure-activity models for contact sensitization. *Chem Res Toxicol* 18: 954–969
- Hoting E, Baum C, Schulz KH (1995) Untersuchungen zur Frage der Kreuzallergenität von amino- und nitro-substituierten aromatischen Verbindungen (Studies of the question of the cross-allergenicity of amino and nitro-substituted aromatic compounds) (German). *Dermatosen Beruf Umwelt* 43: 50–58
- Ishihara M, Nogami T, Itoh M, Nishimura M (1985) Sensitization potency of dye intermediates and modifiers in guinea pigs. *Hifu* 27: 585–590
- Kalish RS, Wood JA (1995) Sensitization of mice to paraphenylenediamine and structurally-related compounds: adjuvant effects of vitamin A supplementation. *Contact Dermatitis* 33: 407–413
- Kayser D, Schlede E (Eds) (2001) *Chemikalien und Kontaktallergie – Eine bewertende Zusammenstellung* (Chemicals and contact allergy – An evaluation) (German), Urban & Vogel, München
- Kleniewska D (1975) Studies on hypersensitivity to "para group". *Berufsdermatosen* 23: 31–36
- Li Q, Inagaki H, Minami M (1996) Evaluation of cross-sensitization among dye-intermediate agents using a modified lymphocyte transformation test. *Arch Toxicol* 70: 414–419
- Matsunaga K, Hayakawa R, Suzuki M, Kawaguchi K, Ogino Y, Hirose O (1989) Allergic contact dermatitis in hairdressers and barbers. Causative factors and chemicals (Japanese). *Hifu (Skin Res)* 31, Suppl 7: 167–175
- Roberts DW, Patlewicz G, Kern PS, Gerberick F, Kimber I, Dearman RJ, Ryan CA, Basketter DA, Aptula AO (2007) Mechanistic applicability domain classification of a local lymph node assay dataset for skin sensitization. *Chem Res Toxicol* 20: 1019–1030
- Rudzki E (1975) Pattern of hypersensitivity to aromatic amines. *Contact Dermatitis* 1: 248–249
- Rudzki E, Krajewska D (1974) Primary sensitivity to metaphenylenediamine. *Contact Dermatitis Newslett* 16: 483
- Rudzki E, Krajewska D, Grzywa Z (1977) Sensitivity to *m*-phenylenediamine. *Berufsdermatosen* 25: 85–89
- Schulz KH (1962) Allergien gegenüber aromatischen Amino- und Nitro-Verbindungen (Allergies to aromatic amino and nitro compounds) (German). *Berufsdermatosen* 10: 69–91
- Shigematsu T, Ozawa N, Nakayama H (1988) in vitro study of the cross-sensitivity of hair dye using hapten-specific lymphocytes. *Contact Dermatitis* 19: 30–35

completed 27.6.2007