

**TITLE**

Comment on MDBGN/DBDCB, the European baseline series, and EU legislation

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**CONFLICT OF INTEREST**

The authors have no conflict to disclose.

**AUTHOR CONTRIBUTIONS**

**Carola Lidén:** Conceptualization; writing – original draft; writing – review and editing (equal)

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To the Editor,

The paper “Should methyldibromo glutaronitrile continue to be used in the European baseline Series? A REIDAC national cross-sectional study” by Mercader-García et al.<sup>1</sup> describes continued and relatively high prevalence of positive patch test reactions to methyldibromo glutaronitrile (MDBGN; CAS number 35691-65-7) in Spain, and difficulties in establishing the relevance of these reactions. The authors question continued use of MDBGN in the European baseline series. Unfortunately, their description of European Union (EU) legislations determining use of MDBGN and labelling is, to a large extent, incorrect and misleading. This is worrying as it coincides with current marketing strategy by industry who are again promoting use of this biocidal (preservative) substance.

The preferred name of MDBGN in non-cosmetic products is 1,2-dibromo-2,4-dicyanobutane (DBDCB) (also, dibromodicyanobutane) and in the European Chemicals Agency (ECHA) dataset 2-bromo-2-(bromomethyl)pentanedinitrile; in the following discussion MDBGN/DBDCB is used.

Experts on contact allergy and readers of *Contact Dermatitis* are generally well informed about legislation on the use of preservatives in cosmetic products, including the ban on MDBGN/DBDCB, while knowledge of legislations concerning other product types (Table 1) is often deficient.

#### **Where is MDBGN/DBDCB banned or permitted?**

In Europe, MDBGN/DBDCB was permitted as preservative **in cosmetic products** during 1983 - 2007. In 2005, the EU banned its use in leave-on cosmetic products, and in 2007 banned it in rinse-off cosmetic products owing to its skin sensitizing properties. There was an unacceptably high frequency of allergic reactions, which were ignored by industry who failed to determine ‘safe’ conditions of use of the preservative. The maximum allowed concentration of MDBGN/DBDCB in cosmetic products was 0.1%. This is equal to the expected highest concentration for use in biocidal products according to the Biocidal Products Regulation (BPR) (Table 1).

Mercader-García et al. write: “Considered a type-6 biocide, it can only be used as a preservative for water-based decorative paints applied by brush or roller indoors since 2015”<sup>1</sup>. This is incorrect; paint was just an example in the assessment report when MDBGN/DBDCB was reviewed for authorisation as existing active substance for use in biocidal products. Product-type 6 (PT6) means preservatives for products during storage. The European Commission authorised MDBGN/DBDCB for continued use in biocidal products of PT6, without further restrictions except labelling according to Classification, Labelling and Packaging (CLP) Regulation ((EC) No 1272/2008)) (Table 1). The Commission may also, according to BPR Article 15, review the approval of an active substance and amend the conditions of approval.

PT6 is one of 22 biocidal product-types in Biocidal Products Regulation (BPR, Regulation (EU) 528/2012). MDBGN/DBDCB may be used in all PT6 sub-categories, including washing and cleaning fluids, paints and coatings, metal working fluids, glues and adhesives (Table 1). It was previously allowed to be used under transitional rules in five additional product-types, however, withdrawn by the manufacturer in 2008 or 2013 (Table 1).

For medicinal products and medical devices, MDBGN/DBDCB is implicitly permitted, provided the products meet the general standards on risk vs benefit (Table 1).

#### **Where can label information be expected?**

Mercader-García et al. stated that they assessed relevance of positive patch test reactions based on label information. Very few products are, however, required to have such information.

According to the CLP regulation, no hazard labelling or supplementary label information will be generated on chemical products (mixtures) if the maximum concentration of a substance classified as Skin Sens. 1 is < 0.1%, the suggested conditions mentioned in the Biocidal Committee opinion on MDBGN/DBDCB (Table 1).

A harmonised (binding) classification of MDBGN/DBDCB as skin sensitizer H317 is still lacking. This means that, irrespective of actual concentrations in products, there are no legally binding (enforceable) requirements, neither on classification nor labelling, until the substance has been formally classified under CLP. Currently, 1520 notifications (self-classification by industry) of MDBGN/DBDCB have been made to the Classification and Labelling Inventory; only 57% of the notifications include Skin Sens 1, H317, none as Skin Sens 1A. A relevant classification based on human data would be Skin Sens. 1A, with a lower specific concentration limit.

Detergents are the only chemical products that require label information with the name of all preservatives irrespective of concentration or classification. This is according to the Detergents Regulation (Table 1).

MDBGN/DBDCB in medicinal products for human use (e.g., as a preservative in transdermal formulations, including gels and patches *containing* an active substance) and for veterinary use if used as an active substance (e.g., as an antimicrobial in animal shampoo) shall be stated on the label (Directives on medicinal products for human use, and for veterinary use, Table 1). It has not yet been clarified whether such label information is required for medical devices (e.g., occlusive dressings *without* an active substance) (Regulation on medical devices, Table 1). The need for full labelling of the chemical composition of medical devices in contact with the human body has recently been highlighted<sup>2</sup>.

### **Increasing Industry interest in MDBGN/DBDCB**

The consumption of MDBGN/DBDCB in Europe declined during recent years. The ‘epidemic’ of contact allergy to MDBGN/DBDCB resulted from absence of effective risk management of its use in cosmetic products. Industry interest is, however, growing again. Lanxess AG (Cologne, Germany) (<https://lanxess.com/>) submitted the dossier on MDBGN/DBDCB to the Biocidal Active Substance Review Programme (Table 1). The company is currently launching a global campaign marketing four brands (Biochek, Preventol, Tektamer and Veriguard) with several MDBGN/DBDCB-containing in-can preservatives (corresponding to PT6) for use in various products, including adhesives, aqueous paints, coatings, dispersed pigments, household products, inks, latex emulsions, pigment slurries, polishes, polymer emulsions, printing fluids, starch, textile chemicals, and waxes. Lanxess’ key argument is that MDBGN/DBDCB “allows to avoid hazard statement H317 (May cause an allergic skin reaction.) on the container” (<https://lanxess.com/en/Media/Press-Releases/2020/10/An-even-wider-product-portfolio-for-the-manufacturing-of-high-quality-coatings>; and <https://lanxess.com/en/Products-and-Solutions/Events/Virtual-Days-EMEA/April-20-Tuesday---Coatings-And-Construction/DBDCB-%E2%80%93-An-alternative-to-overcome-regulatory-challenges-for-preservation-in-Europe>).

We fear that an increasing number of various products containing MDBGN/DBDCB as an in-can preservative (PT6) will be placed in the market in Europe, and that MDBGN/DBDCB will be undisclosed if not classified (see above).

## Patch testing with MDBGN/DBDCB

Various substances, concentrations, and patch test systems have been used for the diagnosis of contact allergy to MDBGN/DBDCB. Some authors, when unable to confirm current relevance based on label information, have suggested that most reactions are irritant, doubtful, false-positive or of only past relevance<sup>1,3-7</sup>.

Some authors have even recently suggested to delete MDBGN/DBDCB from the European baseline series<sup>1,3,4</sup>, and it has been decided by the American Contact Dermatitis Society to remove the substance from its core allergen series<sup>6</sup>, despite relatively high prevalence of contact allergy<sup>1,8-10</sup>. We consider that omitting the substance from the baseline series, instead of tracking exposure more efficiently, will harm surveillance and prevention of skin sensitization and allergic contact dermatitis.

## Conclusions

We conclude that use of MDBGN/DBDCB in the EU is regulated, but that its use is largely undisclosed (in labelling of chemical products and medical devices) owing to insufficiently protective legislation. This is alarming, particularly when industry currently is promoting increased use. Undisclosed use creates severe obstacles to sensitized individuals who need to avoid exposure, and to dermatologists when patch testing, diagnosing, and informing patients.

It is essential that information on presence of MDBGN/DBDCB in products that get into contact with the skin is easily available to consumers, employees, dermatitis patients and healthcare professionals. The Cosmetics Regulation and Detergents Regulation are positive examples on best practice of how to provide ingredient information. Corresponding ingredient information on biocides in other product types is much needed.

Harmonised and relevant classification of MDBGN/DBDCB as skin sensitizer is urgent. Considering the experience of the recent MDBGN/DBDCB-contact allergy epidemic, Skin Sens. 1A would be the most relevant. We urge ECHA, the Biocidal Committee, and EU member states to act promptly for protection of the health of consumers, workers, and patients with dermatitis.

## REFERENCES

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**TABLE 1** Brief summary of EU legislations on use and labelling focusing skin exposure and sensitization, particularly to methyl dibromo glutaronitrile (MDBGN) (INCI name), also mentioned 2-bromo-2-(bromomethyl)pentanedinitrile (DBDCB) (chemical name), CAS no. 35691-65-7. Links to legal acts or specifications<sup>a</sup>

| <b>COSMETIC PRODUCTS</b>                                                                             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Cosmetics Directive (Directive 76/768/EEC)                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|                                                                                                      | All substances (except fragrance substances) shall be listed on the label irrespective of conc.                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|                                                                                                      | MDBGN/DBDCB permitted preservative in cosmetics; max. use conc. 0.1% (1983); <a href="http://data.europa.eu/eli/dir/1983/496/oj">http://data.europa.eu/eli/dir/1983/496/oj</a>                                                                                                                                                                                                                                                                                                                                                     |
|                                                                                                      | MDBGN/DBDCB permitted in rinse-off products only, due to its skin sensitizing properties; max. use conc. 0.1% (2003); <a href="http://data.europa.eu/eli/dir/2003/83/oj">http://data.europa.eu/eli/dir/2003/83/oj</a>                                                                                                                                                                                                                                                                                                              |
|                                                                                                      | MDBGN/DBDCB not permitted in cosmetics due to its skin sensitizing properties (2007); <a href="http://data.europa.eu/eli/dir/2007/17/oj">http://data.europa.eu/eli/dir/2007/17/oj</a>                                                                                                                                                                                                                                                                                                                                              |
| Cosmetics Regulation (Regulation (EC) 1223/2009)                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|                                                                                                      | All substances (except fragrance substances) shall be listed on the label irrespective of conc.                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|                                                                                                      | MDBGN/DBDCB not permitted in cosmetics, not included in the list of preservatives allowed in cosmetic products (Annex V) (2009); <a href="http://data.europa.eu/eli/reg/2009/1223/2021-05-26">http://data.europa.eu/eli/reg/2009/1223/2021-05-26</a>                                                                                                                                                                                                                                                                               |
| <b>CHEMICALS</b>                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| Biocidal Products Directive (BPD) (Directive 98/8/EC)                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|                                                                                                      | MDBGN/DBDCB notified active substance in product-types (PTs): PT6, PT7, PT9, PT10, PT11, and PT13 <sup>b</sup> ; use permitted during a transitional period (2003); <a href="http://data.europa.eu/eli/reg/2003/2032/oj">http://data.europa.eu/eli/reg/2003/2032/oj</a>                                                                                                                                                                                                                                                            |
|                                                                                                      | Approval expired for PT13 <sup>b</sup> (2008), and for PT7, PT9, PT10, and PT11 <sup>b</sup> (2010); <a href="http://data.europa.eu/eli/dec/2008/809/oj">http://data.europa.eu/eli/dec/2008/809/oj</a> and <a href="http://data.europa.eu/eli/dec/2010/72(1)/oj">http://data.europa.eu/eli/dec/2010/72(1)/oj</a>                                                                                                                                                                                                                   |
| Biocidal Products Regulation (BPR) (Regulation (EU) 528/2012)                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|                                                                                                      | Approval of MDBGN/DBDCB renewed for PT6 <sup>b</sup> ; labelling according to CLP (2016); <a href="http://data.europa.eu/eli/reg_impl/2016/1086/oj">http://data.europa.eu/eli/reg_impl/2016/1086/oj</a>                                                                                                                                                                                                                                                                                                                            |
|                                                                                                      | Active substance factsheet:<br>– Validity of approval: start 1/1/2018, end 31/12/2027;<br>– Assessment Report: likely in-use conc. 0.01 – 0.1%;<br>– Biocidal Products Committee Opinion: max. end use conc. 0.1%, Skin Sens. 1, H317<br><a href="https://echa.europa.eu/information-on-chemicals/biocidal-active-substances/-/disas/factsheet/1226/PT06">https://echa.europa.eu/information-on-chemicals/biocidal-active-substances/-/disas/factsheet/1226/PT06</a>                                                               |
|                                                                                                      | Definitions of PT6, PT7, PT9, PT10, PT11, and PT13 <sup>b</sup> ;<br><a href="https://echa.europa.eu/regulations/biocidal-products-regulation/product-types">https://echa.europa.eu/regulations/biocidal-products-regulation/product-types</a>                                                                                                                                                                                                                                                                                     |
|                                                                                                      | Technical Agreements for Biocides, sub-division of PT6 <sup>c</sup> ; <a href="https://op.europa.eu/s/pat9">https://op.europa.eu/s/pat9</a>                                                                                                                                                                                                                                                                                                                                                                                        |
| Classification, labelling and packaging of substances and mixtures (CLP) (Regulation (EC) 1272/2008) |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|                                                                                                      | Hazard statement H317: May cause an allergic skin reaction.<br>Generic conc. limits (GCL) for classification and labelling of mixtures: Skin Sens. 1 ≥ 1.0%, 1B ≥ 1.0%, 1A ≥ 0.1%; a lower, specific conc. limit (SCL) shall be set when the GCL is not sufficiently protective; <a href="http://data.europa.eu/eli/reg/2008/1272/2021-05-10">http://data.europa.eu/eli/reg/2008/1272/2021-05-10</a> .<br>≥ 0.001% is suggested as SCL for extreme sensitizers; Guidance on the application of the CLP criteria DOI:10.2823/124801 |
|                                                                                                      | Mixtures not classified as sensitizing but containing a sensitizing substance ≥ one tenth of the conc. limit: obligatory supplemental labelling information: “EUH208 - Contains (name of sensitizing substance). May produce an allergic reaction”; <a href="http://data.europa.eu/eli/reg/2011/286/oj">http://data.europa.eu/eli/reg/2011/286/oj</a>                                                                                                                                                                              |
|                                                                                                      | No harmonised (binding) classification of MDBGN/DBDCB has yet been decided; <a href="https://echa.europa.eu/substance-information/-/substanceinfo/100.047.877">https://echa.europa.eu/substance-information/-/substanceinfo/100.047.877</a>                                                                                                                                                                                                                                                                                        |

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|----------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Detergents Regulation (Regulation (EC) 648/2004)                     |                                                                                                                                                                                                                                                                                                                                                     |
|                                                                      | All preservatives shall be listed on the label irrespective of conc., preferably by INCI name; <a href="http://data.europa.eu/eli/reg/2004/648/2015-06-01">http://data.europa.eu/eli/reg/2004/648/2015-06-01</a>                                                                                                                                    |
| <b>MEDICINES</b>                                                     |                                                                                                                                                                                                                                                                                                                                                     |
| Medicinal products for human use (Directive 2001/83/EC)              |                                                                                                                                                                                                                                                                                                                                                     |
|                                                                      | All active ingredients and excipients of injectable, topical, and eye preparations, and preservatives in all medicinal products must be stated on label and package leaflet; terminology: methyldibromo glutaronitrile recommended; <a href="http://data.europa.eu/eli/dir/2001/83/2019-07-26">http://data.europa.eu/eli/dir/2001/83/2019-07-26</a> |
| Veterinary medicinal products (Directive 2001/82/EC)                 |                                                                                                                                                                                                                                                                                                                                                     |
|                                                                      | Active ingredients must be stated on label and package leaflet; terminology: <i>European Pharmacopoeia</i> , INN, or other; <a href="http://data.europa.eu/eli/dir/2001/82/2009-08-07">http://data.europa.eu/eli/dir/2001/82/2009-08-07</a>                                                                                                         |
| Medical Devices (Directive 93/42/EEC) and (Regulation (EU) 2017/745) |                                                                                                                                                                                                                                                                                                                                                     |
|                                                                      | No lists on specific allowed, restricted, or banned substances. Regulation: contact with skin and sensitization risk addressed in requirements on risk assessment and labelling; further guidance documents may be needed                                                                                                                           |
|                                                                      | Directive ends 25/05/2021; <a href="http://data.europa.eu/eli/dir/1993/42/2007-10-11">http://data.europa.eu/eli/dir/1993/42/2007-10-11</a>                                                                                                                                                                                                          |
|                                                                      | Regulation shall apply from 26/05/2021; <a href="http://data.europa.eu/eli/reg/2017/745/2020-04-24">http://data.europa.eu/eli/reg/2017/745/2020-04-24</a>                                                                                                                                                                                           |

Abbreviations: conc., concentration; sens., sensitization

<sup>a</sup>Initial or consolidated legal acts.

<sup>b</sup>PT6, Preservatives for products in storage; PT7, Preservatives for surface coatings; PT9, Preservatives for fibre, leather, rubber and polymerised materials; PT10, Preservatives for construction materials; PT11, Protection products for coolants and other process water; PT13, Preservatives for fluids used in processing or cutting.

<sup>c</sup>PT6.1, Washing and cleaning fluids; PT6.2, paints and coatings; PT6.3, fluids used in paper, textile and leather production; PT6.4, metal working fluids; PT6.5, fuel; PT6.6, glues and adhesives; PT6.7, other.