
# Risk Management Option Analysis Conclusion Document

**Substance Name:** [4-[α-[4-(dimethylamino)phenyl]benzylidene]cyclohexa-2,5-dien-1-ylidene]dimethylammonium acetate (malachite green acetate)

**EC Number:** 255-288-2

**CAS Number:** 41272-40-6

**Authority:** NL-CA

**Date:** October 2017

## Cover Note

*This substance was picked up in a project on dyes that are used to colour fabric (for clothing). CCH issues were identified that may shed further light on the reprotoxic characteristics of the substance. CLH for at least skin sensitization and aquatic toxicity is suggested as follow-up risk management measure to accommodate the further regulation of this substance in the context of a more broad restriction on skin sensitizing agents in textile that is under development by the SE-CA.*

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# Foreword

The purpose of Risk Management Option analysis (RMOA) is to help authorities decide whether further regulatory risk management activities are required for a substance and to identify the most appropriate instrument to address a concern.

RMOA is a voluntary step, i.e., it is not part of the processes as defined in the legislation. For authorities, documenting the RMOA allows the sharing of information and promoting early discussion, which helps lead to a common understanding on the action pursued. A Member State or ECHA (at the request of the Commission) can carry out this case-by-case analysis in order to conclude whether a substance is a 'relevant substance of very high concern (SVHC)' in the sense of the SVHC Roadmap to 2020[1].

An RMOA can conclude that regulatory risk management at EU level is required for a substance (e.g. harmonised classification and labelling, Candidate List inclusion, restriction, other EU legislation) or that no regulatory action is required at EU level. Any subsequent regulatory processes under the REACH Regulation include consultation of interested parties and appropriate decision making involving Member State Competent Authorities and the European Commission as defined in REACH.

This Conclusion document provides the outcome of the RMOA carried out by the author authority. In this conclusion document, the authority considers how the available information collected on the substance can be used to conclude whether regulatory risk management activities are required for a substance and which is the most appropriate instrument to address a concern. With this Conclusion document the Commission, the competent authorities of the other Member States and stakeholders are informed of the considerations of the author authority. In case the author authority proposes in this conclusion document further regulatory risk management measures, this shall not be considered initiating those other measures or processes. Since this document only reflects the views of the author authority, it does not preclude Member States or the European Commission from considering or initiating regulatory risk management measures which they deem appropriate.

[1] For more information on the SVHC Roadmap: http://echa.europa.eu/addressing-chemicals-of-concern/substances-of-potential-concern/svhc-roadmap-to-2020-implementation

## 1. OVERVIEW OF OTHER PROCESSES / EU LEGISLATION

Malachite green acetate is not allowed to be used as veterinary medicine when the animals are used for human consumption, and contact with food should be avoided (EFSA website: http://www.efsa.europa.eu/en/press/news/afc050912).

The related substance Malachite green chloride is allowed in the biocide regulation 98/8/EG. Two other related substances Malachite green hydrochloride and malachite green oxalate are not allowed to be used in cosmetics.

## 2. CONCLUSION OF RMOA

| **Conclusions** | **Tick box** |
|---|---|
| Need for follow-up regulatory action at EU level: | |
| *Harmonised classification and labelling* | X |
| *Identification as SVHC (authorisation)* | |
| *Restriction under REACH* | |
| *Other EU-wide regulatory measures* | X (CCH) |
| Need for action other than EU regulatory action | |
| No action needed at this time | |

Serious Compliance issues may be identified, depending on the actual yearly imported volume into the EU.

Harmonized classification and labelling under CLP is concluded to be an appropriate follow-up risk management measure. This first step is needed to allow for further evaluation of a possible restriction for Malachite green acetate as dye in articles with a close contact to humans and possibility of washing off to run into the environment. Furthermore, CLH is needed to trigger further regulatory measures regarding its use in cosmetics (similar to the other Malachite greens) and for the environment under the Water Framework Directive.

No conclusions can be drawn yet on a possible need for Authorization or Restriction. Substance evaluation may be considered to obtain better insight in consumer exposure and to possibly further clarify its hazard properties.

One could consider to prepare and Annex VI dossier for harmonized Classification of MGA for Skin Sensitization. However, as the above described potential further actions on this substance may be (strongly) influenced by the possible outcome of a CCH, it is concluded to revisit this substance again once this further information from the CCH, e.g. on reproduction toxicity, will become available.

## 3. NEED FOR FOLLOW-UP REGULATORY ACTION AT EU LEVEL

Malachite green acetate is produced outside Europe and imported as a substance and as a substance in articles. Most important health concerns involve respiratory and skin sensitizing effects (self classification cat. 1), reproduction toxic effects (self classification cat. 2) and aquatic acute and chronic (self classification cat. 1) effects. Based on the self-classification of structural similar Malachite green salts, MGAe may be classified as muta. (cat. 2) and carc. (cat. 2). Malachite green acetate does not meet the article 57 criteria for SVHC.

**Table: SVHC Roadmap 2020 criteria**

| | Yes | No |
|---|---|---|
| a) Art 57 criteria fulfilled? | | Not at present |
| b) Registrations in accordance with Article 10? | X | |
| c) Registrations include uses within scope of authorisation? | X | |
| d) Known uses not already regulated by specific EU legislation that provides a pressure for substitution? | X | |

Concern for MGA involves exposure of workers using the substance or using articles containing the substance, and consumers. Concern for consumers may involve the consumption of wild fish and the use of articles dyed with MGA. Furthermore, as residues of MGA are found in wild eel this may suggest that environmental exposure may be of concern. The primary source of environmental pollution of Malachite Green is represented by industrial wastewater and secondary by release during washing of dyed textile, thus the fate and pathways of MG in surface water is of primary concern.

## 3.1 Compliance issues

Based on the information available in the registration dossier, the Registration dossier for MGA may be non-compliant on the following:

1. There are serious inconsistencies with the motivation for read across between the different malachites used to comply to the information requirements in the registration dossier. In some cases, the registrant claims the 4 substances are the same and therefore read across is justified to MGA. In other cases, the registrant argues that the 4 different malachites (malachite green acetate, malachite green chloride, malachite green oxalate and leucomalachite green) are different with regard to their effects, e.g. when claiming that malachite green is not carcinogenic.

2. Malachite green acetate is indicated by the registrant as a mono-constituent substance. The Registration dossier on the other hand does suggest MGA may be regarded as a multi-constituent substance. A possible substance identity issue may therefore be identified and should be checked.

3. According to the yearly production volumes indicated by the registrant in the Registration dossier, Malachite green acetate should be registered according to the information requirements specified in Annex IX (100 – 1.000 tpa). A reproduction toxicity study is presently missing from the registration dossier.

A reproductive toxicity study is missing from the registration dossier. This study is waived but the NL-CA questions if the justification for waiving is correct, since no proper PNDT study was performed for this substance. For the tonnage band within which this substance is brought onto the EU market this study is required. Moreover, the developmental toxicity studies that are performed showed that in rabbits the substance does affect foetal development. Consequently, a concern for reproductive toxicity does exist, adding to the need to have this further information.

Further, ED-related effects are observed (see also table below), mainly on thyroid, but effects vary per study, per substance and sometimes differ between males and females, rats and mice. There seems to be an effect on reproduction affecting the fetuses, but the findings seem not conclusive. If further information would be generated, EOGRTS could

be considered with the extension of cohorts for DNT, supported by the observed effects seen on thymus. There may not be sufficient information available that would trigger extension to DIT.

| Level | | substance | Effect | Dose | Ref |
|---|---|---|---|---|---|
| Level 1 | Existing data and non-test information | | | | |
| Level 2 | *In vitro* assays providing data about selected ED mechanisms/pathways | Malachite green/leucomalachite green | Malachite green reduced proliferation capability & impaired mitochondrial activity; no effects with leucomalachite green | ? | 2005, Stammati A. |
| Level 3 | *In vivo* assays providing data about selected ED mechanisms/pathways | | | | |
| Level 4 | *In vivo* assays providing data on adverse effects on ED relevant endpoints | Malachite green oxalate administered to pregnant rabbits | Significant teratological effects at all doses in rabbits (plus abnormalities in skeleton, liver, heart and kidneys) | 5/10/20 mg/kg bw, days 6-18 of gestation | 1983, Klimisch score 2 |
| | | Malachite green, rats | Teratogenic effects ; domed heads | 10/30/100 mg/kg/day | 1991, OECD 414 |
| | | Malachite green, rats | T3 significantly higher, T4 significantly lower on day 4 and 21 | 1200ppm, female rats | OECD 407 |
| | | Leucomalachite green, rats | Decrease in T4, increase in TSH on day 4 and 21, apoptotic follicular epithelial | male rats, 1160 ppm, and 1160 and 580 ppm, | OECD 407 |

| | | | | | |
|---|---|---|---|---|---|
| | | | cells in thyroid gland | male rats | |
| Level 5 | *In vivo* assays providing more comprehensive data on adverse effects on ED relevant endpoints over extensive parts of the life cycle of the organism | Malachite green chloride | Increased incidences of thyroid gland follicular cell adenoma or carcinoma (significant at 300 ppm) and hepatocellular adenoma (significant at 600 ppm), and a dose-related increasing trend in mammary gland carcinoma in rats (only females exposed), | 300/600 ppm, female rats only, no effect in mice | Culp, 2006. Non-GLP; OECD 453 |

Furthermore, the presently available information may be contradictory with regard to the following:

- Dermal absorption of Malachite green (oxalate and chloride) is indicated in the registration dossier as negligible. In contrast, Oplatowska M. et al. (2011) showed migration through the skin after use of green paper towels.
- The registration dossier states that *Consumer exposure* is not relevant because the substance is not released from articles. In contrast, for the environment, the registration dossier states that the primary source of environmental pollution of malachite green is industrial waste water and the secondary most important source is release through washing of dyed textile. Therefore the fate and pathways of malachite green in surface water is of primary concern.

These elements should be considered in a Compliance check.

## 3.2 Harmonised classification and labelling

MGA is currently self classified as respiratory and skin sensitizer Cat. 1, reproductive toxicant Cat. 2 and aquatic acute and chronic toxicant Cat. 1. Consequently, Harmonized classification for these endpoints could be considered.

Investigating the possibility of proposing harmonized classification for MGA for the endpoints Aquatic toxicity (acute and chronic), Resp. and skin sensitization, reproductive toxicity and possibly also mutagenicity and carcinogenicity under CLP may be considered as a first risk management measure. Harmonized classification will support transparent communication regarding the health hazards of MGA, similar to the other Malachite salts. Harmonized classification as Skin Sens. Cat 1 would be needed for the substance to be included in the restriction proposal on Skin Sens in textiles by SE (see section 5.2.3.3). Harmonized classification may also be a first step towards further regulation of this

substance under the Water Framework Directive, and restricting its use under the Cosmetics Regulation (like is already the case for the other Malachite green salts).

Further should be noted that data on reproductive toxicity are currently missing. This new information, when requested through compliance check, could shed further light on the possible need to classify the substance as Repro Cat 1B. Awaiting CCH could therefore be considered appropriate.

# 4. TENTATIVE PLAN FOR FOLLOW-UP ACTIONS IF NECESSARY

Depending on the outcome of the CCH, further assessment is needed to identify the hazard and possible risk for this substance. Authorization and Restriction could become appropriate risk management measures. Furthermore, Substance Evaluation may be preferred to further clarify concerns.

As a follow-up of the compliance check, there is a general concern, primarily for consumer exposure to MGA but also for worker and environmental exposure. Information in the registration dossier, and obtained after contact with the registrants is insufficient to clarify this concern. Substance evaluation (SEv) could be considered to obtain further information on use and exposure. Considering consumer exposure it may particularly be relevant to the issue to more extensively survey MG release from dyed textiles not only in relation to accumulation in surface water but also in relation to human skin contact: while sweating and before and after first washing cycles.

In addition, SEv could be considered to obtain more information on reproductive toxicity where the CCH process will not deliver this information. In 2010, a RAC opinion was published on leucomalachite green, resulting in its classification for Carc. 2 and Muta. 2 (ref: ECHA/RAC/CLH-O-0000001309-75-03/A1). On developmental toxicity, RAC concludes the following: “Malachite green is classified as Repr. Cat. 3; R63, based on limited evidence of developmental toxicity in rabbits (increased resorptions in the absence of maternal toxicity, with no malformations); there is no understanding of how malachite green caused these effects.” More information could be requested through SEv.

## 4.1 Identification as a substance of very high concern, SVHC (first step towards authorisation)

No conclusions can be drawn yet on a possible need for Authorization or Restriction. When MGA will be classified in line with the other salts, the substance may meet art. 57(f) for respiratory toxicity, and, depending on the outcome of any reproduction toxicity study, might meet art. 57(c). From the data available, conclusions with regard to MGA possibly meeting the art. 57 criteria cannot be drawn yet.

## 4.2 Restriction under REACH

No conclusions can be drawn yet on a possible need for Authorization or Restriction. Based on the currently available information on production, use and exposure of MGA, there is presently no indication of a EU-broad risk for workers or consumers. Consequently, further regulatory measures under REACH in the form of a Restriction are not applicable at this moment in time. The SE-CA is developing a restriction proposal for skin sensitizing agents in textiles. Once MGA will be classified as skin sensitizer Cat. 1B in line with the present self-classification for this substance, MGA could be considered for further regulatory measures to prevent consumer exposure under the textile restriction

proposal by SE. In that case, further information on consumer exposure would be of added value to judge if there is a need to reduce the actual exposure of consumers. This information is missing from the registration dossier and could be requested through the process of Substance evaluation.