MINISTERIO
DE SANIDAD, CONSUMO
Y BIENESTAR SOCIAL

# SUBSTANCE EVALUATION CONCLUSION

## as required by REACH Article 48

## and

## EVALUATION REPORT

**for**

# Diallyl phthalate (DAP)

**EC No 205-016-3**

**CAS No 131-17-9**

**Evaluating Member State(s): Spain**

Dated: 19 November 2018

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# Evaluating Member State Competent Authority

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## Year of evaluation in CoRAP: 2013

Before concluding the substance evaluation a Decision to request further information was issued on: 01 September 2015.

**Further information on registered substances here:**

http://echa.europa.eu/web/guest/information-on-chemicals/registered-substances

DISCLAIMER

This document has been prepared by the evaluating Member State as a part of the substance evaluation process under the REACH Regulation (EC) No 1907/2006. The information and views set out in this document are those of the author and do not necessarily reflect the position or opinion of the European Chemicals Agency or other Member States. The Agency does not guarantee the accuracy of the information included in the document. Neither the Agency nor the evaluating Member State nor any person acting on either of their behalves may be held liable for the use which may be made of the information contained therein. Statements made or information contained in the document are without prejudice to any further regulatory work that the Agency or Member States may initiate at a later stage.

# Foreword

Substance evaluation is an evaluation process under REACH Regulation (EC) No. 1907/2006. Under this process the Member States perform the evaluation and ECHA secretariat coordinates the work. The Community rolling action plan (CoRAP) of substances subject to evaluation, is updated and published annually on the ECHA web site[1].

Substance evaluation is a concern driven process, which aims to clarify whether a substance constitutes a risk to human health or the environment. Member States evaluate assigned substances in the CoRAP with the objective to clarify the potential concern and, if necessary, to request further information from the registrant(s) concerning the substance. If the evaluating Member State concludes that no further information needs to be requested, the substance evaluation is completed. If additional information is required, this is sought by the evaluating Member State. The evaluating Member State then draws conclusions on how to use the existing and obtained information for the safe use of the substance.

This Conclusion document, as required by Article 48 of the REACH Regulation, provides the final outcome of the Substance Evaluation carried out by the evaluating Member State. The document consists of two parts i.e. A) the conclusion and B) the evaluation report. In the conclusion part A, the evaluating Member State considers how the information on the substance can be used for the purposes of regulatory risk management such as identification of substances of very high concern (SVHC), restriction and/or classification and labelling. In the evaluation report part B the document provides explanation how the evaluating Member State assessed and drew the conclusions from the information available.

With this Conclusion document the substance evaluation process is finished and the Commission, the Registrant(s) of the substance and the Competent Authorities of the other Member States are informed of the considerations of the evaluating Member State. In case the evaluating Member State proposes further regulatory risk management measures, this document shall not be considered initiating those other measures or processes. Further analyses may need to be performed which may change the proposed regulatory measures in this document. Since this document only reflects the views of the evaluating Member State, it does not preclude other Member States or the European Commission from initiating regulatory risk management measures which they deem appropriate.

[1] http://echa.europa.eu/regulations/reach/evaluation/substance-evaluation/community-rolling-action-plan

# Contents

# Part A. Conclusion

## 1. CONCERN(S) SUBJECT TO EVALUATION

Diallyl phthalate (DAP) was originally selected for substance evaluation in order to clarify concerns about:

- CMR

- Consumer use

- Exposure/Wide dispersive use

During the evaluation no further concern was identified.

The evaluation of DAP was targeted at human health endpoints.

These concerns were addressed in a decision dated 1 September 2015 requiring the Registrants to carry out a Transgenic Rodent Somatic and Germ Cell Mutation Assay (test method: EU B.58/OECD TG 488) and to provide additional information on exposure for workers and on personal protective equipment (https://echa.europa.eu/documents/10162/7f7cdb96-5fb6-4665-ba6e-a17d30965478).

## 2. OVERVIEW OF OTHER PROCESSES / EU LEGISLATION

There are no completed or ongoing processes for this substance.

## 3. CONCLUSION OF SUBSTANCE EVALUATION

The evaluation of the available information on the substance has led the evaluating Member State to the following conclusions, as summarised in the table below.

**Table 1**

| CONCLUSION OF SUBSTANCE EVALUATION<br><br>Conclusions | Tick box |
|---|---|
| Need for follow-up regulatory action at EU level | |
| Harmonised Classification and Labelling | |
| Identification as SVHC (authorisation) | |
| Restrictions | |
| Other EU-wide measures | |
| No need for regulatory follow-up action at EU level | **X** |

As a result of the substance evaluation decision dated 1 September 2015, the Registrant has updated his dossier including the results of the requested study on mutagenicity and revised the exposure assessment part. The new information and revised exposure assessment clarified previous issues on hazard, exposure and risk management, thereby removing the concerns addressed in the substance evaluation decision.

# 4. FOLLOW-UP AT EU LEVEL

## 4.1. Need for follow-up regulatory action at EU level

### 4.1.1. Harmonised Classification and Labelling

The Registrant has self-classified the substance as Acute Tox. 4 (H332: Harmful if inhaled) and Skin Sens. 1B (H317: May cause an allergic skin reaction). Taking into account the information available, the eMSCA supports these self-classifications.

According to CLP Regulation, harmonized classification and labelling for hazard classes/differentiations other than CMR and respiratory sensitization can be proposed if a justification demonstrating the need for action at EU level is provided. In this particular case, effects on human health are correctly identified in the registration dossier through the self-classification, and operational conditions and risk management measures at the workplace are considered to be sufficient to control the risks derived from dermal exposure to DAP. Therefore, the eMSCA does not consider a proposal for harmonized classification as a priority.

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

Not applicable.

### 4.1.3. Restriction

Not applicable.

### 4.1.4. Other EU-wide regulatory risk management measures

Not applicable.

# 5. CURRENTLY NO FOLLOW-UP FORESEEN AT EU LEVEL

## 5.1. No need for regulatory follow-up at EU level

**Table 2**

| REASON FOR REMOVED CONCERN<br><br>The concern could be removed because | Tick box |
|---|---|
| Clarification of hazard properties/exposure | X |
| Actions by the registrants to ensure safety, as reflected in the registration dossiers (e.g. change in supported uses, applied risk management measures, etc.) | |

The following concerns have been concluded in the scope of substance evaluation:

Mutagenicity

A Transgenic Rodent Somatic and Germ Cell Mutation Assay (TGR assay) was required by ECHA decision during the substance evaluation process of DAP since initial grounds for concern related to suspected mutagenic potential were confirmed.

Following the substance evaluation decision, a transgenic rodent somatic and germ cell mutation (TGR) assay (OECD TG 488) was conducted according to GLP with DAP (Unnamed report, 2016). Mutation frequency was assessed in liver, bone marrow and forestomach. Furthermore, the Registrant decided to perform an additional *in vivo* micronucleus assay (OECD TG 474) on peripheral blood in combination with the TGR assay, with the intention of clarify the uncertainty concerning the equivocal result obtained in an *in vivo* chromosome aberration assay in bone marrow cells (Shelby and Witt, 1995).

The results obtained showed that DAP did not induce gene mutations or micronucleus formation in male transgenic mice under the experimental conditions.

Although statistically significant increases in the mutant frequency (MF) were observed at the intermediate dose group (200 mg/kg bw/d) in the liver in the TGR assay, this difference was within the acceptable range calculated from historical data for the negative control group and did not show dose-dependency. The mutant frequency in the forestomach and bone marrow did not show any differences. In the micronucleus assay a significant increase in the incidence of micronucleated reticulocytes (MNRET) was noted at the 400 mg/kg bw/d. However, no dose-response relationship was observed and authors considered that this increase was marginal and within the acceptable range from historical data for the negative control group, based on another report cited in the literature. For these reasons, the effects were considered spontaneous and not biologically relevant.

In summary, taking into account the results obtained from both gene mutation and micronucleus assays, it seems to be enough evidence to indicate that DAP is not able to cause gene mutations or chromosomal aberrations *in vivo*. For this reason, it is considered that the concern has been clarified and neither further information nor harmonized classification is required.

Worker exposure assessment

In the substance evaluation decision notified to the Registrant, a higher tier (Tier 2) exposure assessment for workers was requested, since the Registrant were not able to prove that dermal exposure to DAP was adequately controlled in exposure scenarios 1-3. In addition, glove specific information was also requested by the evaluating MSCA (eMSCA).

The lead registrant has submitted information allowing a higher tier assessment for exposure scenarios for which a safe use could not be demonstrated. Furthermore, the requested glove specific information has been included. Based on this new information a refined risk assessment has been carried out showing that the risk is adequately controlled. Therefore the concern has been clarified.

Based on the available new information, operational conditions and risk management measures at workplace are considered to be sufficient and therefore workers are not expected to be at risk.

## 5.2. Other actions

Not applicable.

# 6. TENTATIVE PLAN FOR FOLLOW-UP ACTIONS (IF NECESSARY)

Not applicable, see section 5.

# Part B. Substance evaluation

## 7. EVALUATION REPORT

### 7.1. Overview of the substance evaluation performed

Diallyl phthalate was originally selected for substance evaluation in order to clarify concerns about:

- CMR

- Consumer use

- Exposure/Wide dispersive use

These concerns were addressed in a decision dated 1 September 2015 requiring the Registrants to carry out a Transgenic Rodent Somatic and Germ Cell Mutation Assay (test method: EU B.58/OECD TG 488) and to provide additional information on exposure for workers and on personal protective equipment (https://echa.europa.eu/documents/10162/7f7cdb96-5fb6-4665-ba6e-a17d30965478).

**Table 3**

| EVALUATED ENDPOINTS | |
|---|---|
| **Endpoint evaluated** | **Outcome/conclusion** |
| Mutagenicity | Concern not substantiated. No further action. |
| Worker exposure assessment | Concern not substantiated. No further action. |

### 7.2. Procedure

Pursuant to Article 44(2) of the REACH Regulation, DAP was included on the Community rolling action plan (CoRAP) for evaluation in 2013. The Competent Authority of Spain was appointed to carry out the evaluation.

The evaluation was first based on the data contained in the IUCLID dataset that was compiled on 14 March 2013, including the chemical safety report. Furthermore, a literature search was also carried out by the Spanish evaluating MSCA at the beginning of the evaluation procedure in March 2013. Additional updates of the registration dossier were also taken into account by the evaluating MSCA.

The evaluation of diallyl phthalate was targeted at human health endpoints and focused on the grounds for concern that were included in the justification document for the inclusion of the substance in the CoRAP. However, all human health hazard endpoints were reviewed.

The draft decision pursuant to Article 46(1) of the REACH Regulation was submitted to ECHA on 19 March 2014.

Comments from the Registrant and several proposals for amendment to the draft decision were received from other MSCAs. The eMSCA reviewed them and amended the draft decision accordingly.

On 2 March 2015 ECHA referred the draft decision to the Member State Committee (MSC).

By 23 March 2015 the Registrant provided comments on the proposed amendments. The MSC took these comments into account.

After discussion in the Member State Committee meeting on 20 to 23 of April 2015, a unanimous agreement of the Member State Committee on the draft decision as modified at the meeting was reached on 21 April 2015. ECHA took the decision pursuant to Article 52(2) and Article 51(6) of the REACH Regulation.

On 1 September 2015, ECHA sent the final decision to the Registrant. A Transgenic Rodent Somatic and Germ Cell Mutation Assays (test method: EU B.58/OECD TG 488) was required. The test shall be conducted in mice or rats treated for 28 days, via oral route, and tissues (stomach, liver and bone marrow) shall be harvested three days after the cessation of the treatment. Mutation frequency shall be assessed in stomach, liver and bone marrow. The germ cells shall be sampled and stored for analysis if positive results are obtained in any of the somatic cells.

In addition to this, information regarding the worker exposure assessment was also required: To conduct a higher tier (Tier 2) exposure assessment, in accordance with ECHA Guidance on information requirements and chemical safety assessment, for dermal exposure to workers in exposure scenarios 1, 2 and 3; and to provide further information on personal protective equipment (e.g. gloves) regarding the type of material to be used and the breakthrough times for the gloves.

On 31 October 2017 the Registrant submitted to ECHA an update of the registration dossier containing the information required. This new information has been assessed by the eMSCA.

Finally, on 4 September 2018 the eMSCA has concluded that the new information submitted by the Registrant clarifies the concerns.

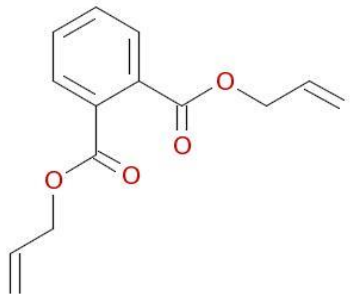
## 7.3. Identity of the substance

**Table 4**

| SUBSTANCE IDENTITY | |
|---|---|
| **Public name:** | diallyl phthalate |
| **EC number:** | 205-016-3 |
| **CAS number:** | 131-17-9 |
| **Index number in Annex VI of the CLP Regulation:** | 607-086-00-4 |
| **Molecular formula:** | $C_{14}H_{14}O_4$ |
| **Molecular weight range:** | 246.2586 |
| **Synonyms:** | 1,2-Benzenedicarboxylic acid, di-2-propenyl ester; o-phthalic acid diallyl ester; Allyl Phthalate; diallylester phthalic acid; DAP(Diallyl Phthalate); dapon 35; dapon r; diprop-2-en-1-yl benzene-1,2-dicarboxylate; 3,4-di(prop-2-en-1-yl)benzene-1,2-dicarboxylate; DAP monomer |

Type of substance ☒Mono-constituent ☐ Multi-constituent ☐ UVCB

**Structural formula:**



## 7.4. Physico-chemical properties

**Table 5**

| OVERVIEW OF PHYSICOCHEMICAL PROPERTIES | |
|---|---|
| **Property** | **Value** |
| Physical state at 20°C and 101.3 kPa | Liquid |
| Vapour pressure | 0.0213 Pa at 25 °C<br>Although different values for vapour pressure of diallyl phthalate are given ranging from 0.0049 to 0.155 Pa, the value of 0.0213 Pa is considered as most reliable. |
| Water solubility | 148 mg/L at 20 °C<br>The reported water solubility of diallyl phthalate is in the range of 45 to 182 mg/L. The key value of 148 mg/L was selected from the most reliable study. |
| Partition coefficient n-octanol/water (Log Kow) | Log Kow (Pow): 3.23 at 20 °C |
| Flammability | Not flammable.<br>Auto flammability temperature is given instead and exceeds the boiling point of diallyl phthalate: 290 °C. |
| Explosive properties | Non explosive.<br>There are no chemical groups associated with explosive properties in the molecule. |
| Oxidising properties | No oxidising properties. |
| Stability in organic solvents and identity of relevant degradation products | The substance is readily soluble in organic solvents and produced a stable solution. |
| Relative density | 1.12 at 20 °C |
| Melting / freezing point | -70 °C at 1013 hPa<br>Based on the information available, the melting point of diallylphthalate appears to be below the limit required for testing. |
| Boiling point | 290 °C at 1013 hPa |
| Flash point | 166 °C at 1013 hPa |
| Auto flammability | 435 °C at 1013 hPa |

| | |
|---|---|
| | Auto flammability temperature was reported to be equal to 385 or 435 °C. Both values are exceeding the boiling point of diallyl phthalate: 290 °C. |
| Stability: thermal, sunlight, metals | The substance should be stored at 4ºC in the dark, under nitrogen. |
| Dissociation constant | Substance does not readily dissociate in water and value will be difficult to determine accurately. |
| Viscosity | 13 mPa.s (dynamic) at 20 °C<br>Data from Hawley's Condensed Chemical dictionary. |

## 7.5. Manufacture and uses

### 7.5.1. Quantities

**Table 6**

| AGGREGATED TONNAGE (PER YEAR) | | | | |
|---|---|---|---|---|
| ☐ 1 – 10 t | ☐ 10 – 100 t | ☐ 100 – 1000 t | ☒ 1000- 10,000 t | ☐ 10,000-50,000 t |
| ☐ 50,000 – 100,000 t | ☐ 100,000 – 500,000 t | ☐ 500,000 – 1000,000 t | ☐ > 1000,000 t | ☐ Confidential |

When substance evaluation started in 2013, there was only a registration dossier for DAP in the range of 100-1,000 t/y. However, it is worth mentioning that a new joint registration dossier of DAP has been submitted to ECHA in 2018. Thus, taking into account this new information, the aggregated tonnage (per year) for DAP in November 2018 would shift from the range of 100-1,000 t/y to the range of 1,000-10,000 t/y. In addition, a new registration dossier for intermediate use of DAP has also been submitted to ECHA in 2018. Therefore, the use of DAP as an intermediate may also be considered in the overview of uses.

### 7.5.2. Overview of uses

DAP is imported as a monomer or as a resin from outside the EU. According to literature (OECD SIDS, 2004) the manufacturing process of the substance consists in either an esterification reaction between allyl alcohol and phthalic anhydride or a condensation reaction between allyl chloride and disodium phthalate. DAP prepolymers or resins are manufactured by polymerization processes of the monomer.

According to the information from registration, uses of DAP include polymer manufacture of synthetic rubbers and polymers, manufacture of insulating varnishes, use as laboratory reagent and application of insulating varnishes.

**Table 7**

| USES | Use(s) |
|---|---|
| **Uses as intermediate** | |
| **Formulation** | |

| | |
|---|---|
| **Uses at industrial sites** | Identified uses in industrial settings include its use in the polymer manufacture of synthetic rubbers and polymers, manufacture of insulating varnishes, use as laboratory reagent and application of insulating varnishes. |
| **Uses by professional workers** | Identified uses in professional settings include the use of DAP through the service life of insulating varnishes. |
| **Consumer Uses** | Identified uses by consumers include the use of DAP through the service life of insulating varnishes. |
| **Article service life** | |

## 7.6. Classification and Labelling

### 7.6.1. Harmonised Classification (Annex VI of CLP)

**Table 8**

| HARMONISED CLASSIFICATION ACCORDING TO ANNEX VI OF CLP REGULATION (REGULATION (EC) 1272/2008) | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Index No** | **International Chemical Identification** | **EC No** | **CAS No** | **Classification** | | **Spec. Conc. Limits, M-factors** | **Notes** |
| | | | | **Hazard Class and Category Code(s)** | **Hazard statement code(s)** | | |
| 607-086-00-4 | diallyl phthalate | 205-016-3 | 131-17-9 | Acute Tox. 4*<br>Aquatic Acute 1<br>Aquatic Chronic 1 | H302<br>H400<br>H410 | - | - |

### 7.6.2. Self-classification

- In the registration(s)*:*

Acute Tox. 4 (H332: Harmful if inhaled)
Skin Sens. 1B (H317: May cause an allergic skin reaction)
Aquatic Acute 1 (H400: Very toxic to aquatic life)
Aquatic Chronic 1 (H410: Very toxic to aquatic life with long lasting effects)

- The following hazard classes are in addition notified among the aggregated self-classifications in the C&L Inventory*:*

Acute Tox. 3 (H301: Toxic if swallowed)
Acute Tox. 4 (H302: Harmful if swallowed)
Carc. 2 (H351: Suspected of causing cancer)
Aquatic Chronic 4 (H413: May cause long lasting harmful effects to aquatic life)

## 7.7. Environmental fate properties

DAP evaluation was targeted at human health and therefore, no environmental risk assessment has been carried out.

## 7.8. Environmental hazard assessment

DAP evaluation was targeted at human health and therefore, no environmental risk assessment has been carried out.

## 7.9. Human Health hazard assessment

### 7.9.1. Toxicokinetics

Toxicokinetic data of DAP were obtained from a poorly reported publication also described in the registration dossier. Excretion, distribution and toxicocokinetic studies have been performed with rats and mice using $^{14}$C-DAP (Eigenberg *et al*., 1986).

The high recovery rates of radioactivity after dosing mice and rats with $^{14}$C-DAP suggest that the substance is extensively absorbed via the oral route. DAP is cleared rapidly from the blood, with a half-life of approximately 2 minutes in both species and was not found in blood or tissues 30 minutes after i.v. administration. Therefore, DAP does not accumulate in tissues.

The metabolites monoallyl phthalate (MAP), allyl alcohol (AA), 3-hydroxypropylmercapturic acid (HPMA), and an unidentified polar metabolite (PM) were detected in the urine of rats and mice. The unidentified polar metabolite was also found in urine of rats administered with AA, indicating that this compound is a metabolite of AA. The diester of DAP is hydrolyzed to MAP and AA. The latter is oxidized in liver cytosol to acrolein which can be detoxified to acrylic acid and further metabolized to $CO_2$. AA and acrolein can also react with reduced glutathione to form HPMA. Finally, DAP is rapidly and extensively eliminated. There were two major routes of elimination of DAP, urinary and exhalation of $CO_2$.

The extent of excretion of $CO_2$ in rats were higher than in mice, indicating that rats either produced more acrolein or oxidized acrolein to acrylic acid to a greater extent. On the other hand, HPMA was detected in larger quantities in mice urine than in rat urine, which indicates that mice detoxify AA and/or acrolein by conjugation with glutathione to a greater extent than do rats. This seems to explain the greater hepatotoxicity of the substance observed in rats compared to mice.

### 7.9.2. Acute toxicity and Corrosion/Irritation

#### 7.9.2.1. Acute toxicity

Taking into account the results obtained in the reported acute toxicity studies, it can be concluded that the substance exhibits low to moderate acute oral and inhalation toxicity, with low acute dermal toxicity in rodents. Regarding this endpoint, diallyl phthalate is currently classified as Acute tox. 4 (H302: Harmful if swallowed) in table 3.1, Annex VI to CLP Regulation.

In addition, the Registrant considered the classification of DAP as Acute tox. 4 for the inhalatory route. This classification is firstly based on the 100% mortality observed in a reported study after a 4-hour exposure to an airborne concentration of 4.47 mg/L, which confirms that the LC50 for the inhalation of DAP is below 5 mg/L. Secondly, it is based on an overall LC50 of 8.3 mg/L obtained in a study after 1 hour of exposure that would correspond with a LC50 of 2.075 mg/L after 4 hours of exposure. According to the Registrant, these values indicated that the LC50 for the inhalation of DAP is between 1 and

5 mg/L, the limits established for classification as Category 4. Based on the available information, the eMSCA can support this conclusion.

#### 7.9.2.2. Irritation

Information from animal studies has shown that DAP is neither a skin nor an eye irritant. No studies in humans are available regarding the potential of DAP to cause skin, eye or respiratory tract irritation.

The outcome of the skin irritation study available (Unnamed report, 1978) is supported by the results of a corrosion study in which no irritating effects were observed with more severe conditions (Unnamed report, 1979).

Regarding eye irritation, there are two reliable studies that showed very few or no signs of eye irritation by DAP in rabbits (Unnamed reports, 1978).

The Registrant concluded that the substance is not irritating to skin nor to eye. Based on the available information, the eMSCA can support this conclusion.

#### 7.9.2.3. Corrosivity

In a non-GLP test, selected as the key study, and conducted according to the Hazardous Materials Transportation Act Regulation (49 CFR 173.1200), corrosiveness of DAP was tested on the intact skin of male albino rabbits (Unnamed report, 1979). No skin corrosion was observed throughout the study. Therefore, under these conditions, DAP was assessed as not corrosive.

Based on the available information, the eMSCA can support this conclusion.

### 7.9.3. Sensitisation

In a GLP-compliant study, the skin sensitisation potential of DAP was investigated in mice according to OECD Guideline 429 (Unnamed report, 2003). Based on the results of this test it can be concluded that DAP has sensitising properties.

The substance is also self-classified as Skin Sens. 1B. Indeed the available information shows that DAP should be classified as a moderate skin sensitiser i.e. Cat 1B according to Annex VI of Regulation (EC) 1272/2008 and the eMSCA can support this conclusion.

There is no information available on the potential of DAP to produce respiratory sensitisation.

No information on potential human sensitisation is available.

### 7.9.4. Repeated dose toxicity

**Table 9:** Repeated-dose toxicity of diallyl phthalate in rats

| Study design | Mortality Clinical signs | Body weight Food consumption | Organ weights | Histopathology | NOAEL NOEL LOAEL (mg/kg bw/d) |
|---|---|---|---|---|---|
| 14-day gavage study<br>Fischer 344 rats<br>5 rats/sex/dose<br>0, 50, 100, 200, 400 or 600 mg/kg bw/d<br>NTP, 1985 | 600 mg/kg bw/d: all animals died<br>400 mg/kg bw/d: 3/5 males and 1/5 female | 400 mg/kg bw/d<br>Body weight gain ↓ (males/females)<br>200 mg/kg bw/d<br>Body weight gain ↓ (males) | - | ≥200 mg/kg bw/d (males/females) enlarged, darkened yellowish spots and mottled livers<br><br>50 mg/kg bw/d (males) and 100 | NOAEL: 50 mg/kg bw/d (females)<br><br>LOAEL: 50mg/kg bw/d (males) |

| | | | | | |
|---|---|---|---|---|---|
| Supporting study | | | | mg/kg bw/d (females) mottled livers | |
| 13-week gavage study Fischer 344 rats 10 animals/sex/dose 0, 25, 50, 100, 200, 400 mg/kg NTP, 1985 Key study | 400 mg/kg bw/d: 8/10 males died 200, 400 mg/kg bw/d: Diarrhoea, rough air coat, alopecia, hunched posture, general emaciation. | 400 mg/kg bw/d Body weight gain ↓ (males) Feed consumption ↓ (males/females) during the first 3 weeks | - | ≥ 200 mg/kg bw/d periportal lesions of the hepatic lobules, necrosis, fibrosis, bile duct hyperplasia and hepatocellular nodular hyperplasia<br><br>50 mg/kg bw/d (males) and 100 mg/kgbw/d (females) hepatocellular alterations | NOAEL: 50 mg/kg bw/d (females)<br><br>LOAEL: 50 mg/kg bw/d (males) |
| 2-year gavage study Fischer 344 rats 50 rats/sex/dose 0, 50, 100 mg/kg bw/d NTP, 1985 Key study | - | - | ↑ liver weight (All dose levels) | ≥50 mg/kg bw/d periportal necrosis and fibrosis, pigment accumulation in periportal histiocytes and severe bile duct hyperplasia | LOAEL: 50 mg/kg bw/d (male/female) |

**Table 10:** Repeated-dose toxicity of diallyl phthalate in mice

| **Study design** | **Mortality Clinical signs** | **Body weight Food consumption** | **Organ weights** | **Histopathology** | **NOAEL NOEL LOAEL (mg/kg bw/d)** |
|---|---|---|---|---|---|
| 14-day study B6C3F1 mice 5 mice/sex/dose 0, 50, 100, 200, 400 or 600 mg/kg bw/d NTP, 1983 Supporting study | 600 mg/kg bw/d: 2 males and 3 females died 400 mg/kg bw/d: 1 male and 2 females died | - | - | - | - |

| | | | | | |
|---|---|---|---|---|---|
| 13-week gavage study B6C3F1 mice 10 animals/sex/dose 0, 25, 50, 100, 200, 400 mg/kg bw/d NTP, 1983 Supporting study | 600 mg/kg: one male and one female died One female death at 0, 50, 100 and 200 mg/kg bw/d (no chemically-related) | 400 mg/kg bw/d Body weight gain ↓ | - | - | NOAEL: 400 mg/kg bw/d |
| 2-year gavage study B6C3F1 mice 0, 150, 300 mg/kg bw/d NTP, 1983 Supporting study | - | - | - | 300 mg/kg bw/d (males/females) 150 mg/kg bw/d (males) inflammation and hyperplasia of the forestomach | NOAEL: 150 mg/kg bw/d (females)<br><br>LOAEL: 150 mg/kg bw/d (males) |

The effects of a repeated exposure to diallyl phthalate have been obtained from subacute, subchronic and chronic repeated dose toxicity assays performed either in rats and mice.

For rats, and primarily based on the results obtained in a reported 13-week toxicity study, the liver appeared as the primary target organ, with dose-related histopathological effects at and above 50 mg/kg bw/d in males and 100 mg/kg bw/d in females. The nature of the chronic liver lesions, mostly fibrosis, was consistently found in the chronic study, appearing to be a progression of the lesions with prolonged exposure or increased susceptibility of aging animals (NTP, 1985).

A NOAEL of 50 mg/kg bw/d for females was established in the 13-week toxicity study. For males, no NOAEL was defined since no histopathological examination of the liver was performed at 25 mg/kg bw/d. A LOAEL of 50 mg/kg bw/d was determined related to the minimal hepatic changes observed in male rats.

In mice, higher tolerance to an oral exposure to the substance has been shown, compared to rats, since no liver effects were observed in any of the toxicity studies performed. Mortality was not dose-related. In the 2-year assay, a dose-dependent chronic inflammation and hyperplasia of the forestomach was noted in males and females at the highest dose and in males at the lowest dose tested (NTP, 1983Unnamed report). Based on the inflammation and hyperplasia of the forestomach observed in the 2-year toxicity study, a NOAEL/LOAEL of 150 mg/kg bw/d was established, for female and male mice, respectively.

Overall, the Registrant has selected a NOAEL of 50 mg/kg bw/d from the 13-week toxicity study in rats as a dose descriptor for DNELs derivation. The nature of the chronic liver lesions observed at this dose level, was consistently found in the 2-year study.

Based on the available information, the eMSCA can support this conclusion.

## 7.9.5. Mutagenicity

### 7.9.5.1. Non-human information

The mutagenicity of diallyl phthalate has been investigated in several *in vitro* and *in vivo* test systems.

#### 7.9.5.1.1. *In vitro* data

**Table 11:** Overview of *in vitro* genotoxicity studies for DAP

| Method/ Guideline* | Test system | Test concentrations | Results | Remarks | Reference |
|---|---|---|---|---|---|
| Bacterial reverse mutation test (Ames test) OECD 471 GLP Klimisch score 1 | *S. typh*. TA98, TA100, TA1535, TA1537 TA1538 | 25-1000 µg/plate +S9 50-6000 µg/plate -S9 | TA1535: Weakly positive –S9 | Vehicle and positive controls | Unnamed report (1986) |
| Bacterial reverse mutation test (Ames test) OECD 471 and 472 GLP Klimisch score 1 | *S. typh*. TA98, TA100, TA1535, TA1537 *E. coli* WP2uvrA/pKM101 | 1.22-5000 µg/plate ± S9 | Weakly positive in *E. coli* WP2 with metabolic activation | Vehicle and positive controls Cytotoxicity ±S9 | MOL (2000) (cited in OECD SIDS, 2004) |
| Bacterial reverse mutation test (Ames test) OECD 471 GLP Klimisch score 1 | *S. typh*. TA98, TA100, TA1535, TA1537 | 1 – 10000 µg/plate ± S9 | Negative | Concurrent solvent and positive controls | Zeiger *et al.* (1985) (cited in OECD SIDS, 2004) |
| Bacterial reverse mutation test (Ames test) OECD 471 Non-GLP Klimisch score 2 | *S. typh*. TA98, TA100, TA1535, TA1537 TA1538 | 0.01, 0.1, 1, 10, 100 µg/plate ± S9 | Negative | Concurrent solvent and positive controls | Unnamed report (1977) |
| Bacterial reverse mutation test (Ames test) OECD 471 No GLP data Klimisch score 4 | *S. typh.* TA98 | 0.25-500 µmol/plate ± S9 | Negative | No data on negative controls. Positive controls | Sato *et al.* (1994) |
| Bacterial reverse mutation test (Ames test) No OECD Guidelines Non-GLP Klimisch score 2 | *S. typh.* TA100 | No concentration information ± S9 | Negative | No data on vehicle and positive controls | Seed (1982) |

| Method/ Guideline* | Test system | Test concentrations | Results | Remarks | Reference |
|---|---|---|---|---|---|
| *In vitro* mammalian micronucleus test<br>OECD 487<br>GLP<br>Klimisch score 1 | Chinese hamster lung cells (CHL/IU) | 1.3-40 μg/mL +S9<br>20-120 μg/mL –S9 | Positive at 11 μg/mL and higher +S9 | Negative and positive control groups<br><br>Cytotoxicity +S9 (78 μg/mL) | MOL (2002) (cited in OECD SIDS, 2004) |
| Chromosomal aberration test<br>OECD 473<br>No GLP data<br>Klimisch score 1 | Cultured Chinese hamster ovary cells (CHO) | 50-300 μg/mL +S9<br>100-500 μg/mL –S9 | Positive for chromosomal aberrations at 200-300 μg/mL +S9 | Negative and positive control groups<br><br>Cytotoxicity +S9 (200-300 μg/mL) | Gulati *et al*. (1989) |
| Mammalian cell mutation test<br>OECD 476<br>No GLP data<br>Klimisch score 1 | Mouse lymphoma L5178Y cells | 12.5-200 nL/mL +S9<br>30-120 nL/mL –S9 | Equivocal mutagenic response –S9<br><br>Clear mutagenic response +S9 | Negative and positive control groups<br><br>Cytotoxicity ±S9 | Myhr and Caspary (1991) |
| Sister chromatid exchange assay (SCE)<br>OECD 479<br>No GLP data<br>Klimisch score 1 | Cultured Chinese hamster ovary cells (CHO) | 5-250 μg/mL +S9<br>1.6-125 μg/mL –S9 | Positive for chromosomal aberrations +S9 | Negative and positive control groups | Gulati *et al*. (1989) |

*Klimisch score as provided by the Registrant or as reported in the literature

### 7.9.5.1.2. *In vivo* data

**Table 12:** Overview of *in vivo* genotoxicity studies for DAP

| Method/ Guideline* | Species/ Strain | Dose levels, Duration of exposure | Results | Remarks | Reference |
|---|---|---|---|---|---|
| Mammalian erythrocyte micronucleus test<br>Similar to OECD 474<br>GLP: No data<br>Klimisch score 2 | Mouse, B6C3F1 Bone marrow cells | 0-175 mg/kg bw/d<br><br>Single i.p. injection, 3 day exposure | Negative | No citotoxicity | Shelby *et al*., (1993) |
| Mammalian chromosome aberration test<br>OECD 475<br>GLP: No data<br>Klimisch score 2 | Mouse, B6C3F1 Bone marrow cells | 0-300 mg/kg bw<br><br>Single i.p. injection, 17 h exposure | Positive in one of two trials | Equivocal clastogenicity | Shelby and Witt (1995) |

| Method/ Guideline* | Species/ Strain | Dose levels, Duration of exposure | Results | Remarks | Reference |
|---|---|---|---|---|---|
| Transgenic rodent somatic and germ cell gene mutation assay (TGR)<br>OECD guideline 488<br>and<br>Micronucleus (MN) assay<br>OECD guideline 474<br>GLP: Yes | Mouse (Muta™Mouse)<br>$CD_2$-LacZ80/HazfBR | 100, 200 and 400 mg/kg bw/d<br><br>Oral: Gavage, 28 days | Negative | TGR assay: MF was measured in liver, bone marrow and forestomach.<br><br>MN assay: MNRET incidence was measured in peripheral blood. | Unnamed report, 2016 |

*Klimisch score as provided by the Registrant

**New information after ECHA decision on substance evaluation**

*Transgenic rodent somatic and germ cell gene mutation assay (TGR) and micronucleus (MN) assay*

A GLP transgenic rodent somatic and germ cell gene mutation assay (TGR) according to OECD guideline 488, where mutation frequency was assessed in liver, bone marrow and forestomach, was conducted in mice with DAP following the information requirement included in the ECHA final decision on substance evaluation. In the decision, the inclusion of a micronucleus (MN) assay (OECD guideline 474) in combination with the TGR was left to the consideration of the Registrant, who finally decided to perform the combination of both studies (Unnamed report, 2016).

In this combined study, DAP in corn oil at doses of 100, 200 and 400 mg/kg bw/d and the negative control substance (vehicle) were administered orally by gavage to 6 transgenic CD2-LacZ80/HazfBR male mice per group (except for the 400 mg/kg bw/d group, where 8 animals were used) once daily for 28 consecutive days. Doses were established based on a dose range-finding study performed in non-transgenic CD2F1/Slc mice (wild type of Muta™Mouse) and taking into account information derived from repeated dose toxicity studies.

For the TGR assay, 100 mg/kg bw/d of N-ethyl-nitrosourea (ENU), used as positive control, were administered intraperitoneally to 6 animals, once daily for 2 consecutive days (Days 2 and 3). For the MN assay, 0.5 mg/kg bw of Mitomycin C (MMC) as positive control, were administered by the same route of exposure, once (Day 27) to 6 animals.

In the TGR assay, a statistically significant increase ($p \leq 0.05$) in the mutant frequency (MF) was observed in the liver at the mid dose of 200 mg/kg bw/d, compared with the negative control group ($55.4 \pm 13.6 \times 10^{-6}$ *vs* $37.6 \pm 8.3 \times 10^{-6}$, respectively). Nevertheless, this difference was within the acceptable range calculated from historical data for the negative control group ($50.1 \pm 16.5 \times 10^{-6}$) and did not show dose-dependency. Therefore, authors considered this increase not-treatment related and not biologically relevant.

The mutant frequency in the forestomach and bone marrow did not show any differences, compared with the negative control group. On the other hand, as it was expected, the positive control substance (ENU) produced a clear statistically significant increase in the mutant frequency for all tissues evaluated.

On the other hand, no positive results were observed in the MN assay.

To sum up, results obtained indicated that, under these test conditions, DAP did not induce gene mutations or micronucleus formation in the combined TGR-micronucleus assay.

A more detailed description of the assay is included in the confidential annex.

### 7.9.5.2. Human information

No information available.

### 7.9.5.3. Summary and discussion of mutagenicity

The mutagenicity of diallyl phthalate has been investigated in several *in vitro* and *in vivo* test systems reported in the IUCLID file and in the literature.

There were some positive results obtained in two bacterial reverse mutation assays in *Salmonella typhimurium* strain TA1535 in the absence of metabolic activation (Unnamed report, 1986) and in *Escherichia coli* strain WP2 in the presence of metabolic activation. However, other bacterial mutagenicity assays reported in the dataset showed clear negative responses, with and without metabolic activation (MOL, 2000, quoted in OECD SIDS, 2004).

Clastogenic effects were observed in an *in vitro* chromosome aberration test. In the presence of metabolic activation system, DAP was able to induce chromosomal aberrations in CHO cells. Similar pattern of results was obtained in a sister chromatid exchange assay in CHO cells (Gulati *et al*., 1989).

In addition, a positive response was reported in a mammalian cell gene mutation assay where increases in mutations were clearly observed in the presence of metabolic activation and equivocal mutagenic responses were obtained in the absence of metabolic activation (Myhr and Caspary, 1991).

Discrepant results were obtained in two poor-quality *in vivo* assays for the induction of chromosomal aberrations in somatic cells. DAP did not induce micronuclei formation in a mouse micronucleus test (Shelby *et al.,* 1993) but gave equivocal results in a bone marrow cell chromosomal aberration test (Shelby and Witt, 1995).

The potential of DAP to cause gene mutations, taking into account the results obtained *in vitro*, was clarified by conducting a TGR assay (OECD TG 488) in mice, as required via SEV decision. In combination with this assay, the Registrant decided to perform an *in vivo* micronucleus assay (OECD TG 474) on peripheral blood in order to clarify the uncertainty concerning chromosome aberration.

The results obtained showed that DAP did not induce gene mutations or micronucleus in male transgenic mice under the experimental conditions.

Considering the dossier update, the eMSCA concluded that the mutagenicity concern has been removed and neither further information nor additional classification is required under this substance evaluation.

## 7.9.6. Carcinogenicity

**Table 13:** Overview of available carcinogenicity data for diallyl phthalate

| Method/ Guideline | Route | Species, Strain, Sex, No/group | Dose levels, Duration of exposure | Results | Reference |
|---|---|---|---|---|---|
| Carcinogenicity study, comparable to OECD 451<br>No data on GLP | Oral (gavage) | Mice B6C3F1<br>Males/ Females<br>50 | DAP: 0, 150, 300 mg/kg bw/d<br>5 d/wk, for 103 wk | Increase in the incidence of males with lymphomas and in the incidence with either lymphomas or leukemia. This increase was not significantly greater than typical historical controls. No increases were observed by pairwise comparisons.<br>The incidences of female mice with hematopoietic system | NTP (1983) |

| Method/ Guideline | Route | Species, Strain, Sex, No/group | Dose levels, Duration of exposure | Results | Reference |
|---|---|---|---|---|---|
| | | | | tumors were not statistically significant. | |
| Carcinogenicity study, comparable to OECD 451<br>No data on GLP | Oral (gavage) | Rat F344<br>Males/ females<br>50 | DAP: 0, 50, 100 mg/kg bw/d<br><br>5 d/wk, for 103 wk | Mononuclear cell leukemia (MNCL) significantly increased in female rats at the high dose by pairwise comparisons. No hematopoietic system tumors were observed for male mice.<br>Because of the variability in incidence of this neoplasm in aged Fischer 344 rats and the difficulty to definitively diagnose this lesion, the authors considered the results to be equivocal evidence of carcinogenicity in female rats. | NTP (1985) |

The data for the carcinogenicity of diallyl phthalate were obtained from reliable carcinogenicity studies performed in mice and rats (NTP, 1983; 1985).

In mice, trend tests showed an increase in the incidence of males with lymphomas and in the incidence with either lymphomas or leukemia that was not significantly greater than typical historical controls. No increases were observed by pairwise comparisons between DAP-administered and control groups. The incidence of female mice with hematopoietic system tumours was not statistically significant.

The administration of DAP increased the incidence of male mice with hepatocellular adenomas but it was considered of little or no toxicological significance due to the abnormally low incidence of this effect in control animals and because the combined incidences of hepatocellular carcinomas or adenomas were not increased.

In addition, there was a dose-related fashion increase in the incidences of hyperplasia and inflammatory lesions of the forestomach in both sexes and non-statistically significant increases in the incidence of uncommon forestomach papillomas in males and females. These proliferative lesions were related to DAP administration even though the available data were insufficient to establish a clear cause-effect relationship.

Overall, results obtained in this study in mice did not provide evidence that DAP has a carcinogenic effect in this species.

In Fischer 344 rats, mononuclear cell leukemia (MNCL) was the only tumour that occurred with significant incidence. Its increase was observed in female rats at the high dose by pairwise comparisons, while no hematopoietic system tumours were observed for male mice.

Significant increases in the incidence of liver tumours were not observed in rats despite the occurrence of chronic liver injury reported in a 13-week repeated dose toxicity study. Only a few carcinomas and neoplastic nodules were observed with almost the same frequency in treated and control groups.

Overall, it is difficult to judge the biological significance of the findings related to carcinogenicity in rats, based on the next considerations:

1. MNCL seems to be a common neoplasm only in Fischer-344 female rats.
2. The increased tumour occurrence is generally restricted to one sex and specie.
3. Its relevance is questionable since MNCL occurs in aged animals at a high and variable rate.

4. No other significant neoplastic effects are observed.

In summary, it can be concluded that equivocal evidence of carcinogenicity of DAP was observed in female rats but no evidence of carcinogenic effect was noted in male rats.

Finally, taking into account collectively the data from mouse and rat studies, authors considered that results obtained did not provide evidence that DAP had a carcinogenic effect in rodents.

Based on the available information, the eMSCA supports this conclusion.

## 7.9.7. Toxicity to reproduction (effects on fertility and developmental toxicity)

With respect to fertility, the only information available is from a well reported reproduction/developmental toxicity screening test in Sprague-Dawley rats in accordance with OECD Guideline 421 (Unnamed report, 2004). Exposure to DAP was associated with histopathological changes in the liver at concentrations of 150 mg/kg bw/d in parental animals, and with no effects on offspring viability, growth and development. At the same dose level there were three mortalities, associated with possible dystocia. This effect may be secondary to the parental toxicity of DAP. The NOAELs derived from this study were 50 mg/kg/d for parental animals and greater than 150 mg/kg bw/d for offspring.

With regard to developmental toxicity, the Registrant included a study in rats according to OECD Guideline 414 (Saillenfait *et al.*, 2008). The results showed that oral administration of DAP to pregnant rats from implantation up to the term of pregnancy produced fetal toxicity at doses of 200 mg/kg/d or higher, which were also maternally toxic. The maternal liver macroscopic findings in this study were consistent with those observed in the reproduction/developmental toxicity screening test and in the repeated dose toxicity studies. From these results, a NOEL for developmental toxicity was established by the Registrant at 150 mg/kg bw/day, based on reduced fetal body weights and an increase incidence of skeletal variations. A maternal NOEL was established at 100 mg/kg bw/d based on the liver lesions observed.

The eMSCA concluded that the substance does not show concern regarding reproduction and based on the available information no further information is required under this substance evaluation.

## 7.9.8. Hazard assessment of physico-chemical properties

There are no indications for classification of DAP with regard to physico-chemical properties. The substance is considered of no concern for human health concerning physico-chemical properties.

## 7.9.9. Selection of the critical DNEL(s)/DMEL(s) and/or qualitative/semi-quantitative descriptors for critical health effects

The eMSCA revised the Derived No Effect Level (DNEL) for workers and general population. The revised DNELs values are summarized below.

An overall NOAEL of 50 mg/kg bw/d form the oral subchronic repeated dose toxicity study is selected for the derivation of long-term, systemic effects DNELs. An LC1 of 580 mg/m3 was calculated by the Registrant since it was considered the most sensitive starting point for deriving the short-term DNEL value for the inhalation route. In addition a LOAEL (EC3) of 4% obtained from a local lymph node skin sensitisation study was used to derive the long-term, local effects DNEL value.

**Workers**

***Long-term, systemic effects***

Occupational exposure to diallyl phthalate may occur via inhalation and dermal routes. Under normal working practices the oral route would not be considered as a significant

route of exposure, therefore, only DNELs for dermal and inhalation routes have been derived.

| CRITICAL DNELS/DMELS – WORKERS | | | | | |
|---|---|---|---|---|---|
| **Endpoint of concern** | **Type of effect** | **Critical study(ies)** | **Corrected dose descriptor(s) (e.g. NOAEL, NOAEC)** | **DNEL/ DMEL** | **Justification/ Remarks** |
| *Repeated dose toxicity* | Systemic effects, long-term, dermal | Oral subchronic toxicity study | NOAEL of 50 mg/kg bw/d | DNEL of 0.5 mg/kg bw/d | AF of 100 (interspecies: 4; differences in the exposure duration: 2; intraspecies: 5; dose-reponse: 1; other interspecies: 2.5; quality of whole database: 1) |
| *Repeated dose toxicity* | Systemic effects, long-term, inhalation | Oral subchronic toxicity study | NOAEC of 88 $mg/m^3$ | DNEL of 3.52 $mg/m^3$ | AF of 25 (intraspecies: 5; differences in the exposure duration: 2; dose-reponse: 1; other interspecies: 2.5; quality of whole database: 1) |

***Acute/short-term, systemic effects***

Based on the toxicological profile of diallyl phthalate, an acute DNEL for the inhalation route needs to be established.

| CRITICAL DNELS/DMELS – WORKERS | | | | | |
|---|---|---|---|---|---|
| **Endpoint of concern** | **Type of effect** | **Critical study(ies)** | **Corrected dose descriptor(s)** | **DNEL/ DMEL** | **Justification/ Remarks** |
| *Acute toxicity (inhalation)* | Systemic effects, acute/short-term, inhalation | Acute toxicity study (inhalation) | $LC_1$ = 580 $mg/m^3$ | DNEL of 6.22 $mg/m^3$ | AF of 6.25 (dose-response: 5: ; intraspecies: 5; other interspecies: 2.5; quality of whole database: 1) |

***Long-term, local effects***

Although diallyl phthalate is not classified as skin irritant, it has been self-classified by the Registrant as a moderate skin sensitizer (Skin Sens. 1B) from reliable data obtained in a local lymph node skin sensitisation (LLNA) study. Therefore, a quantitative risk characterisation for long-term, dermal, local effect is proposed. A dose-response correlation was observed in this study, which allows the calculation of an EC3 value for the derivation of DNEL.

The acute, local DNEL for the dermal route is not derived since the short-term conditions are controlled by the long-term ones.

| CRITICAL DNELS/DMELS – WORKERS | | | | | |
|---|---|---|---|---|---|
| **Endpoint of concern** | **Type of effect** | **Critical study(ies)** | **Corrected dose descriptor(s)** | **DNEL/ DMEL** | **Justification/ Remarks** |
| *Skin sensitisation* | Local effects/long-term | Local Lymph node skin sensitisation (LLNA) study | EC3/LOAEL of 1000 µg/cm$^2$ | DNEL of 20 µg/cm$^2$ | AF of 50 (dose-response: 4; duration of exposure: 1; intraspecies: 5; other interspecies: 2.5; quality of whole database: 1) |

**General population**

***Long-term, systemic effects***

Even though consumer exposure and exposure of humans via the environment are expected to be negligible, DNELs for the three routes of exposure have been estimated for the general population. A NOAEL of 50 mg/kg/day from the oral subchronic toxicity study has been selected as the relevant dose-descriptor.

| CRITICAL DNELS/DMELS – GENERAL POPULATION | | | | | |
|---|---|---|---|---|---|
| **Endpoint of concern** | **Type of effect** | **Critical study(ies)** | **Corrected dose descriptor(s) (e.g. NOAEL, NOAEC)** | **DNEL/ DMEL** | **Justification/ Remarks** |
| *Repeated dose toxicity* | Systemic effects, long-term, dermal | Oral subchronic toxicity study | NOAEL of 50 mg/kg bw/d | DNEL of 0.12 mg/kg bw/d | AF of 400 (interspecies: 4; intraspecies: 10; dose-reponse: 1; quality of whole database: 2; other interspecies: 2.5; differences in the duration of exposure: 2) |
| *Repeated dose toxicity* | Systemic effects, long-term, inhalation | Oral subchronic toxicity study | NOAEC of 43.5 mg/m$^3$ | DNEL of 0.43 mg/m$^3$ | AF of 100 (intraspecies: 10; dose-reponse: 1; quality of whole database: 2; other interspecies: 2.5; differences in the duration of exposure: 2) |
| *Repeated dose toxicity* | Systemic effects, long-term, oral | Oral subchronic toxicity study | NOAEL of 50 mg/kg bw/d | DNEL of 0.12 mg/kg bw/d | AF of 400 (interspecies: 4; intraspecies: 10; dose-reponse: 1; |

| | | | | | |
|---|---|---|---|---|---|
| | | | | | quality of whole database: 2; other interspecies: 2.5; differences in the duration of exposure: 2) |

***Long-term, local effects***

Although diallyl phthalate is not classified as skin irritant it has been self-classified by the Registrant as a moderate skin sensitizer (Skin Sens. 1B) from reliable data obtained in a local lymph node skin sensitisation study. Therefore, a quantitative risk characterisation for long-term, dermal, local effects is proposed. A dose-response correlation was observed in this study, which allows the calculation of an EC3 value for the derivation of DNEL.

The acute, local DNEL for dermal route is not derived since the short-term conditions are controlled by the long-term ones.

| **CRITICAL DNELS/DMELS – GENERAL POPULATION** | | | | | |
|---|---|---|---|---|---|
| **Endpoint of concern** | **Type of effect** | **Critical study(ies)** | **Corrected dose descriptor(s)** | **DNEL/ DMEL** | **Justification/ Remarks** |
| *Skin sensitisation* | Local effects/long-term | Local Lymph node skin sensitisation (LLNA) study | EC3/LOAEL of 1000 µg/cm$^2$ | DNEL of 10 µg/cm$^2$ | AF of 100 (dose-response: 4; differences in the duration of exposure: 1; intraspecies: 10; other interspecies:2.5; quality of whole database: 1) |

## 7.9.10. Conclusions of the human health hazard assessment and related classification and labelling

After the evaluation of the information available on DAP, it is concluded that there are no grounds for concern for any human health endpoint. Taking into account the results obtained from both gene mutation and micronucleus assays, it seems to be enough evidence to consider that initial classification of DAP regarding mutagenicity is not justified.

Diallyl phthalate is currently classified as Acute tox. 4 (H302: Harmful if swallowed) in Annex VI to CLP Regulation.

In addition, the Registrant has self-classified the substance as Acute Tox. 4 (H332: Harmful if inhaled) and Skin Sens. 1B (H317: May cause an allergic skin reaction). Taking into account the information available, the eMSCA supports this self-classifications.

According to CLP Regulation, harmonized classification and labelling for hazard classes/differentiations other than CMR and respiratory sensitization can be proposed if a justification demonstrating the need for action at EU level is provided. In this particular case, effects on human health are correctly identified in the registration dossier through the self-classification, and operational conditions and risk management measures at the workplace are considered to be sufficient to control the risks derived from dermal exposure to DAP. Therefore, the eMSCA does not consider a proposal for harmonized classification as a priority.

## 7.10. Assessment of endocrine disrupting (ED) properties

No information is available.

## 7.11. PBT and VPVB assessment

DAP evaluation was targeted at human health and therefore no PBT/vPvB assessment has been carried out.

## 7.12. Exposure assessment

This is a non-confidential summary of the exposure assessment section. The complete section is included in the confidential annex.

This substance evaluation report is based on the updated registration dossier (October 2017). Additional information from literature has also been taken into account. In contrast with the previous registration dossier (December 2013), the new information provided by the Registrant indicates that the risks are adequately controlled for the use of the registered substance in all the exposure scenarios described for workers.

In the substance evaluation decision notified to the Registrant, a higher tier (Tier 2) exposure assessment for workers was requested, since the Registrant were not able to prove that dermal exposure to DAP was adequately controlled in exposure scenarios 1-3. In addition, glove specific information was also requested by the eMSCA.

Contributing scenarios and conditions of use are now better described in these exposure scenarios. Requested glove specific information has been included. Higher tier models (Advanced REACH Tool (ART) v1.5 for inhalation exposure and Riskofderm v2.1 for dermal exposure) have been used for exposure refinement in some worker contributing activities. Furthermore, measurement data have been included in exposure scenarios 1-3 to demonstrate safe use of the substance in those tasks with higher potential for dermal contact.

The evaluating MSCA has evaluated these additional data and found that the uses described in the updated CSR and the additional data regarding gloves can be considered as sufficiently specified.

Based on the available new information, OCs and RMMs at workplace are considered to be sufficient and therefore workers are not expected to be at risk.

### 7.12.1. Human health

Considering the registration dossier, human exposure to this substance occurs primarily through occupational sources involving formulation and use of polymers, specifically coating electronic/mechanical objects with insulating varnish containing DAP. Diallyl phthalate added to such polymers is incorporated via covalent bonds into the polymer matrix of the finished consumer products. Diallyl phthalate is expected to be consumed during the process. Articles that contain insulating varnishes include electronic chips and motor coils. These articles will have low or unintended release of the substance. Consumer exposure will not be expected due to the unlikely occurrence of accessing the components of household appliances (cleaners and washing machines).

The substance is readily biodegradable and not bioaccumulative (OECD SIDS, 2004). Therefore, indirect exposure through the environment is considered negligible.

The information presented in this chapter was taken mainly from the updated registration dossier (2017) and from literature sources.

### 7.12.1.1. Worker

DAP is imported into the EU. Therefore, occupational exposure to DAP may occur through inhalation and dermal contact in industries where it is formulated or used. According to the very low vapour pressure of DAP, dermal exposure may contribute significantly to overall exposure. Oral exposure is assumed to be prevented by good hygiene practices.

According to the registration dossier, DAP is mainly used by workers for polymer manufacture, including synthetic rubbers, polymers and insulating varnishes. All uses are restricted to industrial sites. These processes are described to take place generally in closed or semi-closed systems.

It is estimated that half of the DAP production is used as a monomer for the preparation of DAP-prepolymers. Such semi-polymerised resins are further used, in the same way that the monomer added to other polymers, as a reactive plasticizer for the manufacture of finished consumer products. DAP monomer or residual DAP in the prepolymer (<2% w/w) reacts to be incorporated via covalent bonds into the polymer matrix during completion of the polymerisation to produce finished products. Therefore, complete reaction of the substance during the process is expected.

DAP is also used as a crosslinking agent. It is added to polymer systems in order to produce finished products. During the curing process, it binds covalently into the polymer matrix. Therefore, low potential if any for the substance to be released from the finished products is expected.

#### 7.12.1.1.1. Overview of uses and exposure scenarios

The exposure assessment has been improved in the updated CSR. In contrast with previous dossier (2013) where ECETOC TRAv3 was used for exposure estimation in all activities, estimates from higher tier models (Advanced REACH Tool (ART) v1.5 and Riskofderm v2.1) and measurements data have been also reported for some activities in exposure scenarios 1-3 of the updated dossier (2017).

Five exposure scenarios for workers are described in the registration dossier; two of them are related to formulation, two correspond to end-use in industrial settings and the last one to service life of articles containing insulating varnishes.

ES 1: Formulation of polymers and synthetic rubber

ES 2: Formulation of coatings

ES 3: Industrial application of coatings

ES 4: Use as laboratory reagent

ES 5: Service life of coatings

The use areas described in the dossier through the five exposure scenarios are consistent with the ones identified during the literature search performed by the MSCA. Because this compound has a very low vapour pressure, dermal exposure may contribute significantly to overall exposure.

External exposure by inhalation and dermal routes has been reassessed in all scenarios by the Spanish evaluating MSCA.

#### 7.12.1.1.2. Scope and type of exposure

##### 7.12.1.1.2.1. Monitoring data

A dermal monitoring study, contracted by the Registrant, measured dermal exposure of DAP monomer during its use in formulations of polymers and synthetic rubbers at an industrial site. This study was designed for the evaluation of some transfer activities where models predicted potentially high levels of dermal exposure. Results from the monitoring program have been included by the Registrant in the exposure assessment part of the updated CSR.

Regarding inhalation exposure of DAP, measured data can be found in the bibliography. SIDS Initial Assessment on DAP (OECD SIDS, 2004) reported measurements of DAP conducted at a factory manufacturing DAP and poly-DAP in Japan. This survey was conducted by the Japanese Industrial Safety and Health Association (JISHA, 2004).

#### 7.12.1.1.2.2. Modelled data

In the previous registration dossier (December 2013), ECETOC TRA v3.1 model tool was applied by the Registrant for worker exposure estimation in all contributing scenarios of ES 1-4. After the substance evaluation decision, the Registrant has updated the exposure part using higher tier modelling tools, and measured data for some transfer activities where models predicted potentially high levels of dermal exposure.

In the updated registration dossier, ECETOC TRA v3.1 has been applied by the Registrant in order to assess external exposure for workers in fully enclosed transfer processes, for some closed mixing processes and use as laboratory reagent in ES 1-4. In addition, higher tier modelling tools (Advanced REACH Tool (ART) v1.5 for inhalation exposure and Riskofderm v2.1 for dermal exposure) have been used in other less controlled processes, including transfer, mixing, application or sampling in ES 1-3.

Each activity within its exposure scenario has been reassessed by the Spanish evaluating MSCA applying the modelling tool selected by the Registrant and the information provided in the registration dossier. The description of activities covered by each exposure scenario, selection of model input parameters and any modifications made outside the model has also been assessed. Exposure estimates are calculated for systemic effects following acute and long-term inhalation exposure and long-term dermal exposure.

#### 7.12.1.1.2.3. Comparison of monitoring and modelled data

In the registration dossier, monitoring and modelled data have been reported by the Registrant. In the case of fully enclosed transfer processes and for some closed mixing processes, exposure has been estimated using ECETOC TRA v3.1 model. In other less controlled processes, including transfer, mixing, application or sampling, higher tier modelling tools (Advanced REACH Tool (ART) v1.5 for inhalation exposure and Riskofderm v2.1 for dermal exposure) have been used by the Registrant to demonstrate safe use. On the other hand, for transfer activities with higher dermal contact and where exposure modelling was unable to show safe use, monitoring data have been documented by the Registrant to demonstrate that risks are adequately controlled.

In the reported dermal monitoring study, low exposure values are documented for the transfer activities selected. These tasks are assumed to represent the highest manual interaction between workers and DAP in an industrial site where formulation of polyester and synthetic rubbers takes place. The highest dermal exposure value measured corresponds to unloading road tankers of DAP to IBCs (Intermediate Bulk Containers).

Although limited number of dermal exposure samples is reported in the monitoring study, their values are two orders of magnitude lower than the corresponding DNEL for long-term dermal exposure of workers. Therefore, data collected from the reported monitoring study may be seen as sufficient for demonstrating safe use of the substance in the mentioned transfer activities.

Worst case modelled dermal exposure values are well above the dermal exposure values measured (1-2 orders of magnitude higher). Additionally, these measured values have been collected from activities where more interaction between workers and DAP is expected in comparison with the modelled activities.

This difference can be explained by the high degree of conservatism followed in the modelled exposure estimation. Apart from the inherent conservatism of the models, worst-case situations and not fully realistic conditions of use have been selected as input parameters for some activities.

Regarding inhalation exposure, no monitoring data has been provided by the Registrant. However, quality data has been reported in SIDS Initial Assessment on DAP (OECD SIDS,

2004), both for manufacture of monomer and production of polymers. The highest worker exposure level was ≤0.11 mg/m$^3$ during manufacture of DAP (maximum exposure occurred at sampling of the chemical for analysis). During manufacture, workers were exposed to DAP at concentrations of 0.02-0.96 mg/m$^3$ (maximum exposure occurred during cleaning operations). These values were collected in the absence of LEV.

The maximum exposure level obtained in this survey is half of the calculated SVC (Saturated Vapour Concentration) and seems more realistic than the higher worst case modelled inhalation exposure values for ES 1- 4.

OECD SIDS (2004) provides also information about exposure through emission from articles. Although these data refers to other kind of articles than those identified by the Registrant, they could support the initially assessed low exposures to residual monomer during the use of polymers.

Due to the reasons explained above, the eMSCA has no remaining concern for worker exposure.

#### 7.12.1.2. Consumer

Consumer exposure to DAP within the EU may occur through inhalation, dermal and oral contact with mixtures or articles containing the substance used by the general population.

According to the registration dossier, household appliances (cleaners and washing machines) enclosing articles coated with insulating varnishes containing DAP are used by consumers.

Articles that contain insulating varnishes include electronic chips and motor coils. DAP is expected to be consumed during the previous application process. These articles will have low or unintended release of the substance. Furthermore, unlikely occurrence of accessing the components of household appliances (cleaners and washing machines) is expected. Therefore, consumer exposure to DAP is anticipated to be negligible.

The Registrant has considered only one scenario: ES 5 "Service life of coatings". This exposure scenario covers the service life stage of electronical/mechanical devices that have been coated with insulating varnishes containing DAP during formulation stage (ES 3).

The Registrant considers that both workers and consumers could be exposed to DAP during the service life of articles with coatings containing DAP. In this context, the Registrant includes both the use of articles by consumers and by professionals in this scenario.

According to the Registrant, only dermal contact of adults could be expected since the relevant articles are electronic and mechanical components.

In the registration dossier, the consumer exposure assessment has been based on modelled data. ConsExpo v4.1 model (50$^{th}$ percentile of point values) has been applied for the consumer exposure assessment of DAP through the inhalation and dermal routes. The Registrant concluded that there is no unacceptable risk identified.

No monitoring data have been reported by the Registrant in the dossier.

SIDS Initial Assessment on DAP (OECD SIDS, 2004) reported measurements of DAP in residential indoor air environment in four studies. Every study focused on the growing concern for sick building syndrome and the indoor air for many phthalates including DAP and other air pollutants. Matsumura *et al.* (2000) reported the concentrations of the DAP in indoor air of three houses in Japan were 79.3 (before repair of existing house), 25.8 (after repair of existing house), 7.1 (new house) and 134.5 (new house) ng/m$^3$. Matsumura *et al.* (2004) also reported that the concentration of DAP in the air of four houses in Japan were 0 (existing house), 6.2 (existing house), 17.1 (new house), and 12.3 (existing house) ng/m$^3$. These monitoring studies demonstrated that indoor DAP levels and levels of other phthalate esters were more or less comparable. In contrast, no DAP was detected by the survey conducted by Saito *et al.* (2001, 2002) for 45 rooms (23 houses) and 12 offices (12 office building) in different points in Tokyo between 1999 and 2001.

In addition, SIDS Initial Assessment on DAP (OECD SIDS, 2004) provides also information about exposure through emission from articles. These data involves the use of DAP pre-

polymer in the manufacturing of pre-impregnated paper. The paper contains less than 0.1-0.5% DAP monomer. Measurements of DAP emission rate from decorative laminate boards were in the order of 0.011 µg/$m^3$.

Although these data refer to other kind of articles than those identified by the Registrant (use of household appliances), they could support the initially assessed low exposures to residual monomer during the use of polymers.

Due to the reasons explained above, the eMSCA considers that there is no concern for consumer exposure.

### 7.12.2. Environment

Not evaluated.

### 7.12.3. Combined exposure assessment

Not evaluated.

## 7.13. Risk characterisation

This is a non-confidential summary of the risk characterization section performed by the Spanish evaluating MSCA. The complete section is included in the confidential annex.

### 7.13.1. Human Health

Workers are primarily assumed to be exposed to DAP. Consumer exposure is not expected to be significant due to the unlikely occurrence of accessing the articles containing DAP. After the exposure assessment, dermal route is assessed as the most relevant one.

#### 7.13.1.1. Workers

The lead registrant has submitted information allowing a higher tier assessment for exposure scenarios for which a safe use could not be demonstrated. Furthermore, the requested glove specific information has been provided. Based on this new information a refined risk assessment has been carried out showing that the risk is adequately controlled.

Modelled results for inhalation and dermal exposure have been used for risk characterization purposes. RCR values have been obtained for each activity as a result of calculating the quotient between external exposure values and the corresponding derived DNELs for the inhalation and dermal routes. In this context, the derived DNELs in section 7.9.9 have been used:

- DNEL $_{\text{long-term, inhalation, systemic}}$ = 3.52 mg/$m^3$
- DNEL $_{\text{acute/short-term, inhalation, systemic}}$ = 6.22 mg/$m^3$
- DNEL $_{\text{long-term, dermal, systemic}}$ = 0.5 mg/kg bw/day
- DNEL $_{\text{long-term, dermal, local}}$ = 20 µg/$cm^2$

Systemic long term and acute exposure via inhalation is estimated to be lower than the respective DNELs under the described conditions of use.

Systemic and local exposure via the dermal route are estimated to be lower than the calculated DNELs under the described conditions of use.

#### 7.13.1.2. Consumers

ConsExpo v4.1 model has been used for exposure assessment. For RCR calculation, each external exposure estimate has been divided by the corresponding derived DNELs for the

inhalation and dermal routes. In this context, the derived DNELs in section 7.9.9 have been used:

- DNEL $_{\text{long-term, inhalation, systemic}}$ = 0.43 mg/m$^3$
- DNEL $_{\text{long-term, dermal, systemic}}$ = 0.12 mg/kg bw/day
- DNEL $_{\text{long-term, dermal, local}}$ = 10 µg/cm$^2$

Regarding local inhalation hazards, the eMSCA considers that DNEL are not required as no hazard has been identified via the inhalation route for local effects. The DNEL derived for long-term systemic effects is likely to be protective of potential local effects via the inhalation route. It is assumed that under typical conditions of use of the substance, no local dermal effect is to be expected.

Estimated RCR values are well below 1. The risk for human health is considered controlled for each route of exposure in consumers.

Systemic long-term exposure is estimated to be lower than the respective DNELs. It is expected that as no unacceptable level of risk has been identified for systemic long-term exposure there will also be no unacceptable level of risk associated with systemic acute exposure.

#### 7.13.1.3. Indirect exposure of humans via the environment

Indirect exposure through the environment is considered negligible.

### 7.13.2. Environment

Not evaluated.

### 7.13.3. Overall risk characterization

#### 7.13.3.1. Human health (combined for all exposure routes)

The combined values of inhalation and dermal routes have been considered for characterization of overall systemic health risks of DAP in workers. Oral exposure is assumed to be prevented by good hygiene practices. As occupational exposure greatly exceeds consumer exposure or indirect exposure via the environment, contribution from sources other than workers has not been added for the assessment of combined exposure.

The combined RCR values of inhalation and dermal routes are below 1. Therefore, overall systemic health risks of DAP in workers may be considered adequately controlled.

#### 7.13.3.2. Environment (combined for all exposure routes)

Not evaluated.

## 7.14. References

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## 7.15. Abbreviations

| | |
|---|---|
| AA | Allyl alcohol |
| AF | Assessment Factor |
| bw | body weight / Bw, b.w. |
| CAS | Chemical Abstracts Service |
| CLP | Classification, Labelling and Packaging |
| CoRAP | Community Rolling Action Plan |
| CSR | Chemical Safety Report |
| DAP | Diallyl phthalate |
| DMEL | Derived Minimal Effect Level |
| DNEL | Derived No Effect Level |
| EC | European Communities |
| EC3 | Effect concentration 3 |
| ECETOC | European Centre for Ecotoxicology and Toxicology of Chemicals |
| ECHA | European Chemicals Agency |
| ENU | N-ethyl-nitrosourea |
| ES | Exposure Scenario |
| EU | European Union |
| GLP | Good Laboratory Practice |
| HPMA | 3-Hydroxypropylmercapturic acid |
| IBC | Intermediate bulk container |
| IUCLID | International Uniform Chemical Information Database |
| IUPAC | International Union for Pure and Applied Chemistry |
| i.v. | intravenous |
| LC | Lethal Concentration |
| LC50 | median Lethal Concentration |

| | |
|---|---|
| LD50 | median Lethal Dose |
| LEV | Local Exhaust Ventilation |
| LLNA | Local lymph node assay |
| LOAEL | Lowest Observed Adverse Effect Level |
| MAP | Monoallyl phthalate |
| MF | Mutant frequency |
| MMC | Mitomycin C |
| MN | Micronucleus assay |
| MNCL | Mononuclear cell leukemia |
| MNRET | Micronucleated reticulocytes |
| MSC | Member State Committee |
| MSCA | Member State Competent Authority |
| MTD | Maximum tolerated dose |
| NOAEC | No Observed Adverse Effect Concentration |
| NOAEL | No Observed Adverse Effect Level |
| NOEL | No Observed Effect Level |
| OC | Operational conditions |
| OECD | Organisation for Economic Cooperation and Development |
| PBT | Persistent, Bioaccumulative and Toxic |
| PM | Polar metabolite |
| PNEC | Predicted No Effect Concentration |
| PPE | Personal Protective Equipment |
| RCR | Risk Characterisation Ratio |
| REACH | Registration, Evaluation, Authorisation and Restriction of Chemicals |
| RET | Reticulocytes |
| RMM | Risk Management Measure |
| SEV | Substance evaluation |
| SVC | Saturated Vapour Concentration |
| SVHC | Substances of very high concern |
| TG | Technical Guidance |
| TGR | Transgenic Rodent Somatic and Germ Cell Mutation Assay |
| UVCB | Unknown or variable composition, complex reaction products or of biological materials |
| vPvB | very Persistent and very Bioaccumulative |
| w/w | weight per weight ratio |
| wRV | worker Respiratory Volume |