SUBSTANCE EVALUATION CONCLUSION

as required by REACH Article 48

and

EVALUATION REPORT

for

Dimethyl phosphonate

EC No 212-783-8

CAS No 868-85-9

Evaluating Member State: the Netherlands

Dated: 10 February 2017

Evaluating Member State Competent Authority

Bureau REACH on behalf of the Ministry of Infrastructure and the National Institute for Public Health and the Environment
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Year of evaluation in CoRAP: 2012

Member State concluded the evaluation without any further need to ask more information from the registrants under Article 46(1) decision.

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

Dimethyl phosphonate (DMP) was originally selected for substance evaluation in order to clarify concerns about:

- Carcinogenicity, mutagenicity and reproduction toxicity (CMR)
- Wide dispersive use
- Consumer use
- High (aggregated) tonnage
- High risk characterisation risk (RCR)

2. OVERVIEW OF OTHER PROCESSES / EU LEGISLATION

The substance evaluation started in 2012 based on a full registration dossier of one registrant. Based on the available information in the dossier, a Draft Decision was prepared by the eMSCA and send to the Registrants for comments.

Via informal contact and in their comments to the Draft Decision, the lead Registrant indicated a change of the dossier to intermediate use only, according to Article 17 and 18 of the REACH legislation. Sufficient information on the intermediate use and relating measures is needed to ensure safe use of intermediates. A registrant shall submit all available information upon request according to Article 36 of the REACH legislation. Therefore, Germany (the member state in which the lead registrant is established) was asked by the eMSCA to request further information on the use of dimethyl phosphonate by downstream users and the fields of application. The available information indicates the uses and the implementation of risk management measures, also by downstream users. The Registrants confirmed that the substance is only manufactured and used under strictly controlled conditions, according to Article 17 and/or Article 18 under the REACH legislation.

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 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

4. FOLLOW-UP AT EU LEVEL

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

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 The concern could be removed because	Tick box
Clarification of hazard properties/exposure	
Actions by the registrants to ensure safety, as reflected in the registration dossiers (change in supported uses, applied risk management measures)	X

A joint registration of three Registrants and one registration from one Registrant are available. The joint registration was initially provided as a full registration. The eMSCA prepared a Draft Decision and sent this to ECHA for commenting by the Registrants. In their comments, the Registrants indicated that the substance is used only as intermediate under Article 17 and 18 of REACH, with implementation of strictly controlled conditions, and adapted their registration dossier accordingly.

The initial concerns were related to the CMR properties, wide dispersive use, consumer use and high (aggregated) tonnage and RCR of dimethyl phosphonate. However, when all strictly controlled conditions are in place, there is no exposure to workers or consumers and therefore no risk. The initial concerns are therefore withdrawn.

The eMSCA recommends that a new assessment of the initial concerns should be undertaken in the event of emerging new uses of dimethyl phosphonate substantiated by dossier submission.

5.2. Other actions

The joint registration of three Registrants was a full registration at the start of the substance evaluation process. During the process, this registration was changed to intermediate use only according to Article 17 and 18 under REACH, with confirmation that strictly controlled conditions are into place. The strictly controlled conditions are essential for the risk assessment of intermediates for human health. When these conditions are implemented, there will be no expected exposure of humans to the substance and hence no risk for humans. However, based on the available information it cannot be confirmed or disproved that these conditions are into place. Further evaluation of the implementation of the strictly controlled conditions is not directly in the scope of substance evaluation. Therefore, further action by enforcement may be considered to ensure that all appropriate risk management measures are in place in the future too.

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

Not applicable.

Part B. Substance evaluation

7. EVALUATION REPORT

7.1. Overview of the substance evaluation performed

Dimethyl phosphonate (DMP) was originally selected for substance evaluation in order to clarify concerns about:

- Carcinogenicity, mutagenicity and reproduction toxicity (CMR)
- Wide dispersive use
- Consumer use
- High (aggregated) tonnage
- High risk characterisation risk (RCR)

Table 4

EVALUATED ENDPOINTS	
Endpoint evaluated	**Outcome/conclusion**
CMR	Change of dossier to intermediate use only; no concern.
Wide dispersive use	Change of dossier to intermediate use only; no concern.
Consumer use	Change of dossier to intermediate use only; no concern.
High (aggregated) tonnage	Change of dossier to intermediate use only; no concern.
High RCR	Change of dossier to intermediate use only; no concern.

7.2. Procedure

The evaluation was targeted to a concern on CMR, wide dispersive use, consumer use, high tonnage and high RCR. Other endpoints were not evaluated.

The registration dossier as available was used to evaluate DMP, starting in March 2012. During the process of evaluation, an informal meeting (August 2012) with representatives of the concerned registrant was held and parts of the registration dossier were discussed. The representatives of the registrant provided information about the intermediate use of DMP, however, the information was not available in the registration dossier yet. Based on the registration dossier, the evaluating MSCA considered that further information was required to clarify the above mentioned concerns. Therefore, it prepared a draft decision to request further information. It submitted the draft decision to ECHA in February 2013.

During and after the one-year evaluation period, the registration dossier became a joint registration with two additional registrants and another registration dossier with one registrant became available. This latter dossier was the registration of intermediate use only.

In their comments, the Registrants of the joint registration indicated that the registration dossier will be changed to full intermediate use only. Based on this change, the initial concerns are pointless and the requested information is not applicable anymore. As a consequence, the substance evaluation was terminated. Therefore, as there were no longer any uses within the scope of substance evaluation, the risk-based concerns do not longer exist. At the time of finalising this report, there were no other than intermediate uses.

The eMSCA is of the opinion that the initial concerns related to potential hazards of the substance remain unclarified. The eMSCA recommends that a new assessment of the initial concerns should be undertaken in the event of emerging new uses of dimethyl phosphonate substantiated by dossier submission.

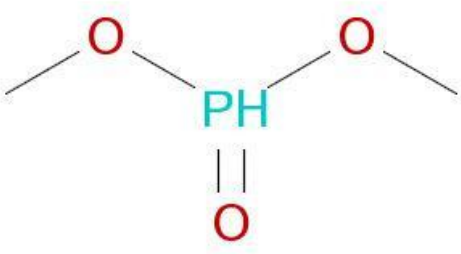
7.3. Identity of the substance

Table 5

SUBSTANCE IDENTITY	
Public name:	Dimethyl phosphonate
EC number:	212-783-8
CAS number:	868-85-9
Index number in Annex VI of the CLP Regulation:	-
Molecular formula:	C2H7O3P
Molecular weight range:	110.049
Synonyms:	DMP Dimethyl phosphite Phosphonic acid, dimethyl ester

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

Structural formula:



7.4. Physico-chemical properties

Table 7

OVERVIEW OF PHYSICOCHEMICAL PROPERTIES	
Property	**Value**
Physical state at 20°C and 101.3 kPa	Liquid, colourless
Vapour pressure	1.35 hPa at 20°C
Water solubility	> 100 g/L at 20°C, hydrolysis in water
Partition coefficient n-octanol/water (Log Kow)	-1.13 (calculated with EPI Suite (v3.20))
Flammability	Data waiving, study scientifically unjustified
Explosive properties	Data waiving, other justification
Oxidising properties	No oxidizing properties
Granulometry	Data waiving, other justification
Stability in organic solvents and identity of relevant degradation products	-
Dissociation constant	-

7.5. Manufacture and uses

7.5.1. Quantities

0 - 10 tonnes per annum

Table 8

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

* intermediate use only

7.5.2. Overview of uses

Table 9

USES	Use(s)
Uses as intermediate	Use as intermediate in chemical synthesis under strictly controlled conditions (manufacture of chemicals, including petroleum products)
Formulation	
Uses at industrial sites	
Uses by professional workers	
Consumer Uses	
Article service life	

7.6. Classification and Labelling

7.6.1. Harmonised Classification (Annex VI of CLP)

No harmonised classification of dimethyl phosphonate.

7.6.2. Self-classification

- In the registration(s)*:*
  - Skin Sens. 1
  - Muta. 2
  - Carc. 2
  - Aquatic Chronic 3
- The following hazard classes are in addition notified among the aggregated self-classifications in the C&L Inventory*:*
  - Skin Irrit. 2
  - Eye Irrit. 2
  - Acute Tox. 3
  - Acute Tox. 4
  - Skin Sens. 1B
  - Flam. Liq. 3

7.7. Environmental fate properties

Not evaluated.

7.8. Environmental hazard assessment

Not evaluated.

7.9. Human Health hazard assessment

7.9.1. Toxicokinetics

Not evaluated.

7.9.2. Acute toxicity and Corrosion/Irritation

Not evaluated.

7.9.3. Sensitisation

Not evaluated.

7.9.4. Repeated dose toxicity

This endpoint was evaluated in relation to the possible carcinogenicity of dimethyl phosphonate.

Oral studies

Two sub-acute, two sub-chronic and two chronic oral investigations studying the repeated dose toxicity of dimethyl phosphonate were performed in rats and mice. In one good quality sub-chronic investigation male and female Fischer 344 rats were administered 25, 50, 100, 200, 400 mg/kg bw/day dimethyl phosphonate on 5 days/week for 13 weeks via gavage (NTP, 1985). A decreased body weight gain was observed in female rats at 200 mg/kg bw/day and above and for male rats at 400 mg/kg bw/day. Mortality was increased at 400 mg/kg bw/day for both sexes. Eye changes (degeneration of the lens, acute diffuse inflammation of the cornea) and increased lung lesions (inflammation, congestion, histiocytosis) were found in male and female rats at 400 mg/kg bw/day. In male rats increased urinary bladder calculi were observed at 400 mg/kg bw/d. The NOAEL is 100 mg/kg bw/day for female and 200 mg/kg bw/day for male rats.

In a well conducted chronic study male Fischer 344 rats were administered 100, 200 mg/kg bw/day dimethyl phosphonate and female rats 50, 100 mg/kg bw/day, respectively, on 5 days/week for two years. At doses > or = 100 mg/kg bw/day male rats showed dose-related lung effects (interstitial pneumonia, alveolar/bronchiolar adenoma or carcinoma) and at 200 mg/kg bw/day increased cataract formation, and squamous cell carcinoma. Focal mineralization in the cerebellum was observed in males at 200 mg/kg bw/day (NTP, 1985). Female rats showed forestomach hyperplasia and a statistically not significant, but doserelated increase in lung alveolar/bronchiolar carcinoma at doses > or = 100 mg/kg bw/day. The LOAEL for male rats is 100 mg/kg bw/d and the NOAEL for female rats is 50 mg dimethyl phosphonate/kg bw/day.

In a sub-acute study B6C3F1 mice were treated with 250, 500, 1000, 2000, or 3000 mg/kg bw/day dimethyl phosphonate for 15 days. A NOAEL could not be derived from this study due to stomach lesions down to the lowest test concentration (epithelial ulcerations, glandular stomach ulcerations, acute/chronic gastritis, squamous atrophy, hyperplastic gastropathy, hyperkeratosis, submucosal and intra-epithelial abscesses, massive necrosis) (NTP, 1985).

In a sub-chronic investigation B6C3F1 mice were treated with 95, 190, 375, 750, 1500 mg bw/kg bw/day dimethyl phosphonate. At 190 mg/kg bw/day and above cardiac mineralization was seen in male mice and hepatocellular vacuolization in female mice (NTP, 1985). At 375 mg/kg bw/day the liver changes were also seen in male mice. Lung congestions were observed with higher incidence at 375 mg/kg bw/day in both sexes, and mortality was increased at this dose. Testicular atrophy was observed at 375 mg/kg bw/day. 750 mg/kg bw/day was lethal for all animals within 4 weeks. The NOAEL is therefore 95 mg/kg bw/day for male and female mice.

In a chronic investigation male B6C3F1 mice (males and females were administered 100, 200 mg/kg bw/day for two years) showed calcification of testis at concentrations of > or = 100 mg/kg bw/day. At 200 mg/kg bw/day lower body weights and increased mortality was observed in males only (NTP, 1985). LOAEL for male and female mice was 100 mg/kg bw/day.

Inhalation studies

One subacute inhalation study (4-week exposure) was also conducted (unnamed report, 1982). However the test is not reliable because several relevant methodological deficiencies: at the commencement of the study the weights variation of animals used exceeded ± 20% of the mean weight (21% in males and 33% in females); only vehicle control used; the lowest concentration showed evidence of toxicity; analytical purity was not reported; test material administration was conducted in different ways in different test groups; exposure atmospheric sampling was not conducted properly; temperature at which the test was performed was between 24-27 °C; on test day 16 four male rats of group treated with 483.1 mg/m³ were not loaded into the chamber and did not receive exposure to the test material, due to a technician error. Therefore, this data source is not acceptable for assessment.

Male and female Sprague-Dawley rats (20/sex per group) inhaled 48.7, 142.1, 483.1, and 803.9 mg/m³ (12, 35, 119, and 198 ppm) dimethyl phosphonate vapour for 6 hours/day on 5 days/week (unnamed report, 1982). At all concentrations increased kidney weights were observed in male and female rats. Irritation of superficial ocular structures, mucosal irritation and keratitis were shown in all dose groups and in both sexes. The eye changes progressed to cataracts in dose groups of > or = 142.1 mg/m³. At doses > or = 142.1 mg/m³ cutaneous irritation was observed, the skin effects progressed to dermatitis at 483.1 mg/m³, and at 803.9 mg/m³ necrosis and acute purulent inflammation of the skin were main causes of deaths. At 142.1 mg/m³ inflammation of the anterior nares was visible in male and female rats. At 483.1 mg/m³ the external nares were affected, and at 803.9 mg/m³ red discoloration of the lungs and the nasal turbinates were observed in both sexes. In male rats reduced body weight gains were observed at doses > or = 142.1 mg/m³. In the next higher dosage (483.1 mg/m³) body weight losses and increased mortality was shown in male and female rats. Time to death varied between 7 and 26 days at 483.1 and 803.9 mg/m³. Hypospermatogenesis was observed in male rats at lethal doses of > or = 483.1 mg/m³. Hematopoiesis in the spleen occurred in 4/18 female rats at 803.9 mg/m³ only and was not observed in the controls or the lower doses. No historical control data were provided. The LOAEL derived for this study is 48.7 mg/m³ (12 ppm; corresponds to about 10 mg/kg bw/day). No NOAEL was achieved in this study.

7.9.5. Mutagenicity

Bacterial tests

Ames tests performed with dimethyl phosphonate were primarily negative.

In one NTP assay the results of the Salmonella typhimurium strains TA 98, 100, 1535, 1537 in concentrations up to 10000 µg /plate were judged negative with and without metabolic activation. Cytotoxicity was reached at 10000 µg dimethyl phosphonate/plate (NTP, 1985).

A further assay equivalent to OECD TG 471 and conducted with GLP conditions was judged negative: 775 to 12400 µg dimethyl phosphonate /plate were tested with the Salmonella typhimurium strains TA 98, 100, 1535 and 1537 in duplicates (unnamed report, 1988). In the first experiment the mutant counts of the Salmonella typhimurium strain TA 100 with S-9 mix were significantly increased. This result could not be reproduced in the replicate. At 6200 µg/plate bacteriotoxic effects were observed but the test could be evaluated (unnamed report, 1988).

Tests performed according to a NTP standard protocol gave positive results with strain TA 100 at aconcentration of 10 000 µg/plate in the presence of S-9 mix. The other standard tester strains TA 98, 1535, 1537 were negative (Mortelmans et al., 1986; Zeiger, 1987; Tennant et al., 1987a). The data from the study by Tennant et al. (1987a) were re-evaluated by Prival and Dunkel (1989) using more stringent criteria for a positive result. The positive results with Salmonella typhimurium strain TA100 were made negative by disregarding the positive results at a dose of 10000 µg /plate (Prival and Dunkel, 1989). It is noted that this concentration also exceeds the limit dose of 5000 µg/plate which is recommended in current guidelines.

In vitro data

In a cytogenetic assay, performed according to NTP standard protocol, with L5178Y mouse lymphoma cells, dimethyl phosphonate showed positive results with metabolic activation at concentrations of > or = 1700 µg/mL (Tennant et al., 1987a). A further mouse lymphoma assay showed also mutagenic activity of dimethyl phosphonate in concentrations of > or = 2100 µg/mL in the presence of S-9 mix (McGregor et al., 1988). Concentrations > 2200 µg/mL (without S-9 mix) and > 2500 µg/mL (with S-9 mix) resulted to be cytotoxic in this assay.

In chromosomal aberration tests with Chinese hamster ovary cells performed after NTP standard protocol dimethyl phosphonate clearly induced chromosomal aberrations in the presence of S-9 mix and was weakly positive in the absence of S-9 mix at concentrations of > or = 1600 µg/mL each (Gulati et al. 1989).

Dimethyl phosphonate was positive in a DNA damage and repair assay with primary rat hepatocytes pretreated with Aroclor-1254 (Aro) and 3-methylcholanthrene (3-MC). The netto nuclear grains (NNG) and the percentage of cells with three NNGs above the solvent control (% IR) respectively were evaluated. The % IR was clearly elevated in the rat hepatocytes pretreated with Aro (in concentrations of > or = 0.01 µg/mL) and 3-MC (in concentrations of > or = 0.025 µg/mL) representing unscheduled DNA synthesis and indicating DNA mutations of dimethyl phosphonate (Shaddock et al., 1990). Dimethyl phosphonate was negative in untreated primary rat hepatocytes (Shaddock et al. 1990). A further negative result was obtained in an unscheduled DNA synthesis assay with primary rat hepatocytes and limited documentation (Tennant et al., 1987b).

In a sister chromatid exchange (SCE) assay with Chinese hamster ovary cells dimethyl phosphonate caused increased total SCE numbers in cells and increased numbers of SCE/cell with and without metabolic activation at concentrations of > or = 250 µg/mL. The concentration range tested was 5 - 1600 µg/mL without S-9 mix and 16 - 4000 µg/mL with S-9 mix and fifty second-division metaphase cells were scored per dose (Gulati et al., 1989).

In vivo data

In a micronucleus assay in bone marrow cells of B6C3F1 mice, which received daily i.p. injections of 250 and 500 mg/kg bw/day dimethyl phosphonate for three days, the number of micro-nucleated polychromatic erythrocytes (PCEs) per 1000 PCEs scored was significantly elevated in the first trial at 500 mg/kg bw/day. This result could not be clearly reproduced in the second trial.

The trend analysis of the repeat test gave P=0.078. The authors judged the data as "adequate evidence of an effect", though not conclusive: "... additional tests would be needed to provide conclusive evidence of MN-inducing ability"of dimethyl phosphonate (Shelby et al., 1993).

In a separate micronucleus assay with NMRI mice, no clastogenic effect was observed according to the study authors after a single i.p. administration of 2000 mg/kg bw dimethyl phosphonate (unnamed report, 1994). The incidences of micro-nucleated polychromatic erythrocytes (PCEs) per 1000 PCEs scored were measured 16, 24 and 48 hours after i. p. injection of dimethyl phosphonate. There was a statistically non-significant doubling of micro-nucleated PCEs after 48 hours (negative controls 1.3 ± 1.1, 16h 0.8 ± 1.1, 24h 1.8 ± 1.5, 48 h 2.7 ± 3.1). Although statistically significant, the values for the positive control group (cyclophosphamide, 20 mg/kg bw i. p.) were unusually low (7.3 ± 5.5 as compared to the laboratory`s historical positive control range of 10.2 – 25.1). It is therefore not certain, whether this test was sufficiently sensitive.

Summary and conclusions

Based on the provided data in the registration dossier there was a concern related to the potential for somatic cell and germ cell mutagenicity. The proposed classification from the registrant is Muta. 2 according to CLP/GHS. However, based on the information in the registration dossier it cannot be determined if dimethyl phosphonate can be regarded as an inducer of heritable mutations in the germ cells, resulting in classification Muta. 1B. Subsequently, the probability of dimethyl phosphonate to induce mutagenicity in specific tissues may affect its probability of inducing carcinogenicity.

The registration dossier includes positive bacterial tests (Ames test), and positive in vitro tests in mammalian cells for mutagenicity (mouse lymphoma assay and unscheduled DNA synthesis test) and clastogenicity (chromosome aberration test and sister chromatid exchange assay). Two in vivo clastogenicity tests (micronucleus assay) were provided, with conflicting results (one positive result and one negative result).

The available in vitro information shows that dimethyl phosphonate is mutagenic (inducing gene mutations) and clastogenic in vitro. This was followed up by in vivo micronucleus studies, that cover only the potential clastogenic effects. These in vivo results are equivocal. Moreover, no in vivo information regarding the mutagenic effect observed in vitro is available.

The available carcinogenicity assays indicate carcinogenicity in the lung. It is unclear whether this is caused by the toxicity in the lung, whether this is due to the potential mutagenicity or both.

For substances that are mutagenic in somatic cells, information on the potential for mutagenicity in germ cells is required to justify the correct classification and thereby to determine if special action is required to control the risks during production and use of the substance. No such information is available.

Based on the lack of information, a Transgenic Rodent Somatic and Germ Cell Gene Mutation Assay (TGR) and the Comet assay were initially requested in the draft decision. The TGR detects mainly gene mutations whereas the Comet assay is an indicator test (genotoxicity) for gene mutations and chromosome mutations (clastogenicity). Moreover, the TGR can be used as a stand-alone test for classification and labelling of substances. Therefore, this conclusive test was required first in the draft decision. In case of negative results in the TGR, the Comet assay can be used to determine whether there is an in vivo potential to induce clastogenicity in somatic cells and germ cells. The results would have been used to determine the best approach for risk assessment (DNEL or DMEL) and for classification and labelling.

However, the registration dossier was amended by the registrants as a response to the first Draft Decision and it was indicated that all uses are intermediate use. As a consequence, taking into account that strictly controlled conditions are implemented, no exposure of workers or consumers to dimethyl phosphonate is expected and therefore, based on a lack of concern, the initial requests were withdrawn.

7.9.6. Carcinogenicity

The information from the carcinogenicity studies is included because of the relation with mutagenicity. The initially requested mutagenicity tests may have provided information about the mode of action of tumor induction by dimethyl phosphonate, thereby affecting the classification for carcinogenicity. The carcinogenicity studies were therefore not evaluated in great detail.

Dimethyl phosphonate was tested for carcinogenicity (method equivalent to OECD guideline 451) in doses of 100 and 200 mg/kg bw/day in male F344 rats and 50 and 100 mg/kg bw/day in female F344 rats respectively. The doses were administered orally via gavage on 5 days/week for 103 weeks. A clear evidence of carcinogenicity was found for male rats and an equivocal evidence for female rats. In gross pathology and histopathology statistically significant squamous cell carcinoma in lung and alveolar/bronchial cell adenoma or carcinoma in male rats were found to be treatment related. In male rats in the highest dose group the incidence of alveolar/bronchiolar adenoma is 5/50 and the incidence of the alveolar/bronchiolar carcinoma is 20/50. In female rats a marginally increase in alveolar/ bronchial cell adenoma or carcinoma was assessed as to be dose-related (0/50, 1/49, 3/50), but was not statistically significant (NTP, 1985). Regarding the forestomach carcinogenicity, statistically significant hyperplasia, hyperkeratosis, and squamous cell carcinoma or adenoma (6/50) were observed in male rats in the highest dose group. In the forestomach of female rats hyperplasia was found in the 100 mg/kg bw/day dose group. The incidence of forestomach neoplasms was only slightly and not statistically significantly increased. Statistically significant mononuclear cell leukemia was observed with higher incidences in male rats of the 100 mg/kg bw/d dose group. In the high dose group a slightly lower incidence was observed. The incidence of mononuclear cell leukemia in low dose male rats was significantly greater than that in the vehicle controls (vehicle control, 9/50; low dose, 15/50; high dose, 13/50). The incidence was at the upper limit of the historical control and confined to male animals (NTP, 1985).

B6C3F1 mice were treated with 100 and 200 mg/kg bw/day in the same way as described above. Statistically significant increased numbers of hepatocellular adenomas were observed in the 100 mg/kg bw/day female group only. No evidence of carcinogenicity was concluded for B6C3F1 mice (NTP, 1985). The International Agency for Research on Cancer concluded in 1990 and 1999 that there is limited evidence for the carcinogenicity of dimethyl phosphonate in experimental animals. Therefore dimethylphosphonate is 'not classifiable as to its carcinogenicity to humans (Group 3)' (OECD SIDS, 2004; IARC, 1990; IARC, 1999).

Summary and conclusions

The carcinogenicity study in the rats shows clear evidence of carcinogenicity in males and equivocal evidence in females. Different dose levels were used for males and females (100 and 200 mg/kg bw/day in male F344 rats and 50 and 100 mg/kg bw/day in female rats). These dose levels were determined based on the decreased body weight gain as observed in a 13-week exposure study. However, in this 13-week study lung lesions were found in both males and females at 400 mg/kg bw/day. This indicates that the dose levels for females may not have been high enough to induce carcinomas and adenomas in the lung.

No carcinogenicity was observed in the carcinogenicity study in mice. However, lung lesions were observed in a 13-week exposure study in both males and females. These lung lesions (lung congestion) were also observed in the 13-week study in rats.

DMP is considered carcinogenic in the lung of male rats. However, the mode of action remains unknown and it is not clear whether tumours are formed via a genotoxic mechanism.

In the initial draft decision, genotoxicity tests were requested. The outcome of these tests may affect the evidence for the carcinogenicity and any possible classification of dimethyl phosphonate. However, the registration dossier was amended by the registrants as a response to the first draft decision and it was indicated that all uses are intermediate use. As a consequence, taking into account that strictly controlled conditions are implemented, no exposure of workers or consumers to dimethyl phosphonate is expected and therefore, based on a lack of concern, the initial requests were withdrawn.

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

Not evaluated.

7.9.8. Hazard assessment of physico-chemical properties

Not evaluated.

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

Not evaluated.

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

Based on the provided data in the registration dossier there is a concern related to the potential for somatic cell and germ cell mutagenicity. The proposed classification from the registrant is Muta. 2 according to CLP/GHS. However, based on the information in the registration dossier it cannot be determined if dimethyl phosphonate can be regarded as an inducer of heritable mutations in the germ cells, resulting in classification Muta. 1B. Subsequently, the probability of dimethyl phosphonate to induce mutagenicity in specific tissues may affect its probability of inducing carcinogenicity.

Further refinement would be needed to come to conclusions on the hazard of dimethyl phosphonate. However, as the registration dossier was amended by the registrants to intermediate use only, there is no concern for a risk and this substance evaluation is concluded without requesting further information.

7.10. Assessment of endocrine disrupting (ED) properties

Not evaluated.

7.11. PBT and VPVB assessment

Not evaluated.

7.12. Exposure assessment

Based on the initial registration dossier, there was a concern on the exposure assessment of dimethyl phosphonate for workers and consumers. Further information on specifications on risk management measures and on estimations of exposure concentrations was requested as included in the Draft Decision.

However, the registration dossier was adapted and the substance is used as intermediate only, according to Article 17 and 18 under REACH. As a result, and taking into account that strictly controlled conditions are implemented, there is no exposure to workers or consumers expected. Therefore, there is at present no concern anymore for a risk on human health for workers and consumers.

7.13. Risk characterisation

Not applicable in view of the change to intermediate use.

7.14. References

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7.15. Abbreviations

CMR	carcinogenicity, mutagenicity and reproduction toxicity
CoRAP	community rolling action plan
DMP	dimethyl phosphonate
eMSCA	evaluating member state competent authority
LOAEL	lowest observed adverse effect level
NNG	netto nuclear grains
NOAEL	no observed adverse effect level
PCE	polychromatic erythrocyte
RCR	risk characterisation risk
SCE	sister chromatid exchange
SVHC	substance of very high concern
TGR	transgenic rodent somatic and germ cell gene mutation assay