SUBSTANCE EVALUATION CONCLUSION

as required by REACH Article 48

and

EVALUATION REPORT

for

4-Methylanisole

EC No 203-253-7

CAS No 104-93-8

Evaluating Member State(s): Ireland

Dated: 27 April 2015

Evaluating Member State Competent Authority

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Year of evaluation in CoRAP: 2012

The substance evaluation was terminated without requesting further information from the registrant under an Article 46(1) decision due to change in status of the registration dossier (cease manufacture in accordance with Article 50(3) of the REACH Regulation).

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

4-methylanisole was originally selected for substance evaluation in order to clarify suspected concerns about:

- CMR (carcinogenic, mutagenic, reproductive toxicity), specifically suspected developmental toxicity,
- wide dispersive use,
- consumer use and
- risk characterisation ratios close to 1 for human health.

During the evaluation, additional concerns were identified related to the robustness of the long term systemic DNEL for workers and consumers for all relevant routes of exposure.

2. OVERVIEW OF OTHER PROCESSES / EU LEGISLATION

Not applicable.

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

The evaluating Member State Competent Authority (MSCA) concluded that further information was required to clarify the concerns regarding developmental toxicity and to further refine the exposure assessment for the exposure scenario for “compounding" in order to conclude on whether the risk to workers was adequately controlled.

However, during the substance evaluation decision making process the only registrant ceased manufacture of the substance in accordance with Article 50(3) of the REACH Regulation and therefore the registration was revoked. As there were no other active registrations within the scope of substance evaluation, the substance evaluation was terminated.

The evaluating MSCA is of the opinion that the concern for developmental toxicity remains unverified since no additional information was requested to clarify the concern due to the termination of the substance evaluation decision making process.

4. FOLLOW-UP 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 (cease of manufacture)	X

During the substance evaluation decision making process, the only registrant of 4-methylanisole ceased manufacture of the substance in accordance with Article 50(3) of the REACH Regulation and the substance evaluation was terminated. Therefore, as there were no longer any uses within the scope of substance evaluation, the risk based concerns were removed. At the time of finalising this report, there were no other active registrations within the scope of substance evaluation.

The evaluating MSCA is of the opinion that the concern for developmental toxicity remains unverified since no additional information was requested to clarify the concern due to the termination of the substance evaluation decision making process. The evaluating MSCA recommends that further assessment of the developmental toxicity hazard be undertaken in the event of new future registrations of 4-methylanisole.

5.2. Other actions

Not applicable.

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

4-methylanisole was originally selected for substance evaluation in order to clarify suspected concerns about:

- CMR (carcinogenic, mutagenic, reproductive toxicity), specifically suspected developmental toxicity,
- wide dispersive use,
- consumer use and
- risk characterisation ratios close to 1 for human health.

During the evaluation, additional concerns were identified related to the robustness of the long term systemic DNEL for workers and consumers for all relevant routes of exposure.

Table 3

EVALUATED ENDPOINTS	
Endpoint evaluated	**Outcome / conclusion**
Developmental toxicity	The evaluating MSCA concluded that further information was required to clarify the concern regarding developmental toxicity. However due to termination of the substance evaluation process, no additional information was requested.
Worker exposure	The evaluating MSCA concluded that further refinement of the exposure assessment for the exposure scenario for “compounding" was required in order to conclude on whether the risk to workers was adequately controlled. However, due to termination of the substance evaluation process, no additional information was requested.

7.2. Procedure

Pursuant to Article 44(2) of the REACH Regulation, 4-Methylanisole was included on the Community rolling action plan (CoRAP) for evaluation in 2012. The Competent Authority of Ireland was appointed to carry out the evaluation. The substance evaluation commenced on 1 March 2012.

The evaluation was targeted to human health hazards and exposure. Although not the focus of the evaluation, a preliminary assessment of the environmental hazard and exposure data was also undertaken and no concerns were identified. The main source of information for the evaluation was the registration dossier.

Based on the evaluation of the available data, the evaluating MSCA concluded there was a need to request further information to clarify the concerns relating to developmental toxicity and worker exposure and therefore pursuant to Article 46(1) of the REACH

Regulation prepared a draft decision to request further information. The draft decision was submitted to ECHA on 7 February 2013.

On the 20 March 2013 ECHA sent the draft decision to the registrant and invited him to comment by 19 April 2013. By that date ECHA received comments from the registrant and forwarded them to the evaluating MSCA. In addition to the comments provided on the draft decision, the registrant informed the evaluating MSCA of his intention to cease manufacture of the substance in accordance with Article 50(3) of the REACH Regulation by 1 June 2013. The registration was subsequently revoked on 3 June 2013. ECHA informed the registrant and the evaluating MSCA that as the registration was revoked and as there were no other registrants of the substance at that time, the substance evaluation decision making process related to the draft decision was terminated and no further information was requested.

Therefore, the substance evaluation was terminated without a decision requesting for additional information.

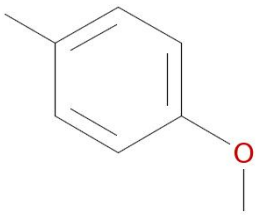
7.3. Identity of the substance

Table 4

SUBSTANCE IDENTITY	
Public name:	4-methylanisole
EC number:	203-253-7
CAS number:	104-93-8
Index number in Annex VI of the CLP Regulation:	-
Molecular formula:	$C_8H_{10}O$
Molecular weight range:	122.1644
Synonyms:	Anisole, p-methyl- Benzene, 1-methoxy-4-methyl-

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	1.01 hPa at 17.1 °C
Water solubility	0.559 g/L at 20° C
Partition coefficient n-octanol/water (Log Kow)	log Pow = 2.74 at 25 °C
Flammability	Flammable liquid
Explosive properties	Non explosive
Oxidising properties	No oxidising properties
Granulometry	Not applicable
Stability in organic solvents and identity of relevant degradation products	Not applicable
Dissociation constant	Not applicable
Flash point	42°C at 1013 mBar

7.5. Manufacture and uses

7.5.1. Quantities

At the start of the substance evaluation process, the tonnage was reported to be > 1000 tonnes per annum. However, during the substance evaluation decision making process the only registrant ceased manufacture of the substance in accordance with Article 50(3) of the REACH Regulation and therefore the registration was revoked.

At the time of finalising this report, there were no active registrations within the scope of substance evaluation.

7.5.2. Overview of uses

4-methylanisole is used in the production of fragrances and as an intermediate in chemical synthesis.

The uses below were identified in the registration dossier which was subject to substance evaluation before the revocation of the registration in 2013. At the time of finalising this report, there were no other active registrations for 4-methylanisole within the scope of substance evaluation.

Table 6

USES	Use(s)
Manufacture	Manufacture of the substance and of fine chemicals
Formulation	Compounding Formulation of preparations/mixture containing registered substance. e.g. fragrance mixture
	Formulation Formulation of final preparations or articles using a preparation/mixture containing registered substance
Uses at industrial sites	Use of Cleaning Agents – Industrial Application of cleaning agents containing registered substance at industrial sites.
Uses by professional workers	Use in Cleaning Agents – Professional Use in cleaning products for application by roller, brushing or spraying.
Consumer Uses	Use in Cleansing Agents – Consumer Use in consumer products such as polishes and waxes, washing and cleaning products.
	Use in air care User in air care products
	Use in Cosmetics Use in perfumes and fragrances and in personal care products.
	Other consumer use Use in consumer products such as biocidal products, coatings and paints, fillers and putties, plasters, modelling clay, finger paints, ink and toners.
Article service life	Other consumer use Use in scented consumer products such as clothes, erasers, toys, paper and CDs

7.6. Classification and Labelling

7.6.1. Harmonised Classification (Annex VI of CLP)

4-Methylanisole is not listed on Annex VI of CLP.

7.6.2. Self-classification

In the registration(s):

- Flam. Liquid 3; H226: Flammable liquid and vapour
- Acute Tox. 4; H302: Harmful if swallowed
- Skin Irrit. 2; H315: Causes skin irritation
- Repr. 2; H361: Suspected of damaging the unborn child
- Aquatic Chronic 3; H412: Harmful 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:

- Eye Irrit. 2; H319: Causes serious eye irritation
- Acute Tox. 3; H331: Toxic if inhaled

7.7. Environmental fate properties

Not evaluated.

7.8. Environmental hazard assessment

Not evaluated.

7.9. Human Health hazard assessment

7.9.1. Toxicokinetics

Based on its molecular weight, log Pow and water solubility, 4-methylanisole is expected to be readily absorbed from the GI tract following oral administration, which is supported by evidence of systemic availability in the oral acute and repeated dose toxicity studies. The physicochemical properties also indicate that 4-methylanisole will demonstrate moderate dermal absorption. A brief summary (Klimisch reliability score 4) of a dermal absorption study in rats is reported in the registration data. Groups of male Sprague-Dawley rats were treated a single occlusive topical dose of ^{14}C-4-methylanisole at 100, 2320 and 1000 mg/kg bw/day for 6 hours per day. Percentage dermal absorption was estimated to be approximately 23%, 35% and 57% of the applied dose at 10, 320 and 1000 mg/kg bw/day, respectively. However, limited details are available for this study and therefore in line with ECHAs Guidance R.7[2], 100% dermal absorption is assumed. No inhalation repeat dose toxicity studies are available and no mortality was observed in the acute inhalation studies, therefore no conclusion can be drawn regarding systemic availability via this route although the low volatility of 4-methylanisole indicates a low potential for inhalation.

[2] Guidance on information requirements and chemical safety assessment. Chapter R.7: Endpoint specific guidance

7.9.2. Acute toxicity and Corrosion / Irritation

The registrant concluded that 4-Methylanisole is acutely toxic via the oral route (LD_{50} of 1920 mg/kg bw/day in rats) and irritating to skin. Based on the available information the evaluating MSCA can support this conclusion.

7.9.3. Sensitisation

Based on the results of the key study, a local lymph node assay (OECD TG 429) with the registered substance, the registrant concluded that 4-methylanisole is not a skin sensitiser. The evaluating MSCA can support this conclusion.

No information is available with respect to respiratory sensitisation.

7.9.4. Repeated dose toxicity

In a 28-day repeated dose toxicity study (OECD TG 407), 4-methylanisole was administered by oral gavage at doses of 100, 300 and 1000 mg/kg bw/day to five Wistar rats per sex per dose for 4 weeks (5 days/week). In the 1000 mg/kg bw/day group, clinical signs of toxicity included salivation following dosing, ataxia, tremor and laboured respiration. An increase in absolute and relative liver weights, together with slight hypertrophy and single cell necrosis of the hepatocytes in both sexes was also reported. At the same dose, a decrease in absolute and relative spleen weight and a decrease in relative thymus weight in males and an increase in absolute and relative kidney weight in females were observed but no histopathological correlate was reported. In the 300 mg/kg bw/day group, clinical signs were limited to salivation after dosing. A decrease in absolute spleen weights in males were reported without a histopathological correlate.

A NOEL of 100 mg/kg bw/day was identified from this study and the evaluating MSCA can support this conclusion. Based on the available data, the evaluating MSCA considers this value to be the most appropriate point of departure for the derivation of long term systemic DNELs.

7.9.5. Mutagenicity

Negative results are reported from three bacterial reverse mutation (Ames) studies with 4-methylanisole, both in the presence and absence of metabolic activation. The evaluating MSCA noted that all available Ames tests are missing an *E. coli* strain or *S. typhimurium* TA102, which are recommended under the current test guideline (OECD Guideline 471/ EC Method B13/14). Two *in vitro* unscheduled DNA synthesis studies similar to OECD TG 482 are also available; the result of the first is considered ambiguous and the second negative at non-cytotoxic concentrations. In an *in vitro* chromosomal aberration test in Chinese hamster ovary cells similar to OECD TG 473, no chromosomal aberrations were detected with or without metabolic activation following 10 hour test setup. However following 20 hour test setup, chromosomal aberrations were detected in the presence and absence of cytotoxicity.

In an unscheduled DNA synthesis assay (OECD TG 486) in male Wistar rats, 4-Methylanisole was administered orally at doses of 1000 and 2000 mg/kg bw and hepatocytes were harvested at 3 and 14 hours after administration. No biologically relevant increase in the mean net nuclear grain counts was noted at any dose level at either sacrifice interval. Under the experimental conditions of this study, it can be concluded that 4-methylanisole did not induce DNA-damage leading to increased unscheduled DNA synthesis in hepatocytes of male Wistar rats *in vivo*. In a micronucleus

study (OECD TG 474) in male NMRI mice, 4-Methylanisole was administered orally at doses of 500, 1000 and 2000 mg/kg bw (24 hour preparation interval) or 2000 mg/kg bw (48 hour preparation interval). No cytotoxic effects in the bone marrow were reported and there was no biologically relevant or statistically significant increase in the frequency of the detected micronuclei at any preparation interval and dose level tested.

Based on the available data the evaluating MSCA concludes that 4-methylanisole is not genotoxic.

7.9.6. Carcinogenicity

No information available.

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

Two reproduction/developmental toxicity screening studies (OECD TG 421) with 4-methylanisole are available.

4-methylanisole was administered by gavage at doses of 0, 100, 300 and 1000 mg/kg bw/day to groups of 10 male and 10 female Wistar rats for a premating period of 2 weeks and a mating period of 2 weeks in both sexes, and in females for the entire gestation period as well as 4 days of lactation and approximately 1 week thereafter. At 1000 mg/kg bw/day, food consumption was increased in females during GD 0-14 and decreased during lactation. A decrease in body weight gain was observed in males (-39%) and in females during gestation (-36%) and lactation (-70%). This correlated with a decrease in terminal body weight in both sexes. At 300 mg/kg bw/day, decreased food consumption was observed in females during lactation only. A dose dependent enlargement of the liver, characterised by centrilobular hypertrophy was observed at 300 and 1000 mg/kg bw/day in both sexes.

No treatment related adverse effects on fertility parameters (mating and fertility indices, time to successful copulation, duration of pregnancy and mean number of implantations) or reproductive organs were observed in the parental animals at any dose levels.

A dose dependent adverse effect on pre- and post-natal development was observed at 300 and 1000 mg/kg bw/day. At 1000 mg/kg bw/day, a decrease in live birth index (84% vs. 100% in control), an increase in post implantation loss (17% vs. 6.3% in control), and an increase in the number of stillborn pups (16% vs. 0% in control) was observed. There was total litter loss by PND 4, and thus the viability index was 0% and mean pup body weight could not be calculated since no pups survived. One female pup alive on PND 1 weighed 29% less than the control. At 300 mg/kg bw/day, the similar effects were noted but at a lower incidence; a decrease in live birth index (90% vs. 100% in control), an increase in the number of stillborn pups (9.6% vs. 0% in control) and a decrease in viability index (58% vs. 100% in control) were observed. The mean pup weight at PND 1 and 4 was -16% and -17% of that of the control pups. There was also an increase in the number of runts (10 vs. 1 in control). No effects on offspring were observed at 100 mg/kg bw/day. At necropsy, empty stomachs were observed in 15% and 20% of the pups at 1000 and 300 mg/kg bw/day respectively, which is considered to be a treatment related effect. While the reduced pup survival could be influenced by a disturbance in maternal care, as demonstrated by empty stomachs in pups, the evaluating MSCA considers that the increase in post implantation loss and increase in the number of stillborn pups on PND 0 at 300 and 1000 mg/kg bw/day, and the severity of the effect on pups (e.g. total litter loss by PND 4) observed at 1000 mg/kg bw/day, cannot be completely explained by decreased maternal care. In addition, the effects observed in parental females at 300 mg/kg bw/day were limited to alterations in food

consumption and liver enlargement, and at the same dose a significant effect on pup survival was observed. Based on the results of the study, the evaluating MSCA considers that the NOAEL for developmental toxicity to be 100 mg/kg bw/day based on pre- and post-natal pup mortality and the NOAEL for parental systemic toxicity to be 100 mg/kg bw/day, based on effects on body weight, food consumption and liver enlargement at 300 and 1000 mg/kg bw/day.

In a dermal reproductive / developmental screening study, conducted in accordance with OECD TG 421, 4-methylanisole was applied dermally (6 hours/day; 7 days/week) to groups of 10 male and 10 female Wistar rats at dose levels of 0 (corn oil served as vehicle control), 100, 300 and 1000 mg/kg bw/day. The test area was reported to be at least 10% of the body surface, with the test material held in place with semi-occlusive dressing and the skin washed after exposure. The duration of treatment covered a premating period of 2 weeks and a mating period of 2 weeks in both sexes, and approximately 1 week post-mating in males, and the entire gestation period until gestation day (GD) 19 in females. The females were not treated at the end of gestation or during lactation.

4/10 males and 1/10 males at 100 and 300 mg/kg bw/day, respectively, did not generate pups. No histopathological effects were reported which would explain these apparent infertilities and in the absence of a dose response, the toxicological significance of the effect is unclear. In females, there was a slight increase in the mean duration until sperm detection (GD 0): 2.6, 2.5, 3.0 and 3.4 days (0, 100, 300 and 1000 mg/kg bw/day, respectively).

No adverse effects were observed on pup numbers, status at delivery, pup viability, sex ratio, pup clinical observations or pup body weights. A significant increase in post-implantation loss was observed at 100 mg/kg bw/day (18%); however there was no dose-response relationship and no abnormal findings were observed during pup necropsy. Based on the results of the study, a NOAEL for both parental systemic toxicity and developmental toxicity of 1000 mg/kg bw/day was identified.

The evaluating MSCA noted that while the dermal reproduction/developmental screening study may represent a relevant route of human exposure, the study design has a number of limitations which indicate that the NOAEL may not be sufficiently robust. In particular, OECD TG 421 assumes an oral route of exposure and does not include any specifications for dermal administration. Also, the rate of dermal penetration of 4-methylanisole has not been quantified, and it is therefore not clear what proportion of the dose is systemically available in this study. Therefore, the evaluating MSCA considers that the dermal reproduction/developmental screening study is not the most appropriate study to derive a dose descriptor for developmental toxicity, in particular since the results of the oral reproduction/developmental screening study indicate that developmental toxicity is a critical effect. In addition, the evaluating MSCA is of the opinion that the NOAEL is not sufficiently robust to be used as the point of departure in the derivation of a long term systemic DNEL for the dermal route.

A concern for developmental toxicity was identified from the oral reproduction/ developmental screening study. However, as this is a screening study, it provides limited information with respect to developmental toxicity and given the wide dispersive and consumer uses of the substance which were reported in the registration dossier, the evaluating MSCA concluded that further information was required in order to clarify the concern regarding developmental toxicity, the adequacy of the existing risk management measures, and the need for a higher hazard classification, i.e. reproductive toxicity category 1B H360 (may damage the unborn child). The evaluating MSCA was of the opinion that an oral pre-natal developmental toxicity study (OECD TG 414/EU B.31) in rat was the appropriate study to request to clarify the concern. However, as outlined in section 7.2, during the substance evaluation decision making process, the only registrant of 4-methylanisole ceased manufacture of the substance in accordance with Article 50(3) of the REACH Regulation and the process was terminated.

The evaluating MSCA is of the opinion that the concern for developmental toxicity remains unverified since no additional information was requested to clarify the concern due to the termination of the substance evaluation decision making process.

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

No DNELs were derived for systemic effects after short term dermal or inhalation exposure for workers or the general population since 4-methylanisole is not classified for these endpoints and thus the respective long-term DNELs are considered to be protective.

No DNELs were derived for local effects after short or long term dermal exposure since no quantitative hazard data is available for these endpoints, and therefore a qualitative risk characterisation was performed by the registrant. In the absence of quantitative hazard data, the evaluating MSCA can support this approach.

Based on the data available at the time of finalising this report, the evaluating MSCA identified long term systemic DNELs for workers and the general population, which are summarised in tables 7 and 8 below.

Table 7

CRITICAL DNELS/DMELS - WORKERS					
Route	**Type of effect**	**DNEL**	**Corrected dose descriptor**	**Most sensitive endpoint**	**Critical study**
Inhalation	Systemic effects - Long-term	DNEL: 1.17 mg/m³	NOAEC: 88 mg/m^3 (applying AF of 75)	Systemic toxicity Repeated dose toxicity (oral)	28-day oral repeated dose toxicity study
Dermal	Systemic effects - Long-term	DNEL: 0.33 mg/kg bw/day	NOEL: 100 mg/kg bw/day (applying AF of 300)	Systemic toxicity Repeated dose toxicity (oral)	28-day oral repeated dose toxicity study

Table 8

CRITICAL DNELS/DMELS – GENERAL POPULATION					
Route	**Type of effect**	**DNEL**	**Corrected dose descriptor**	**Most sensitive endpoint**	**Critical study**
Inhalation	Systemic effects - Long-term	DNEL: 0.29 mg/m³	NOAEC: 43 mg/m^3 (applying AF of 150)	Systemic toxicity Repeated dose toxicity (oral)	28-day oral repeated dose toxicity study
Dermal	Systemic effects - Long-term	DNEL: 0.17 mg/kg bw/day	NOEL: 100 mg/kg bw/day (applying AF of 600)	Systemic toxicity Repeated dose toxicity (oral)	28-day oral repeated dose toxicity study

CRITICAL DNELS/DMELS – GENERAL POPULATION					
Route	**Type of effect**	**DNEL**	**Corrected dose descriptor**	**Most sensitive endpoint**	**Critical study**
Oral	Systemic effects - Long-term	DNEL: 0.17 mg/kg bw/day	NOEL: 100 mg/kg bw/day (applying AF of 600)	Systemic toxicity Repeated dose toxicity (oral)	28-day oral repeated dose toxicity study

The evaluating MSCA was not in agreement with the registrant regarding the choice of the point of departure for the derivation of the long term systemic dermal DNELs for workers and the general population. As discussed in section 7.9.7, the evaluating MSCA considered that there are some limitations in the design of the dermal reproduction/developmental toxicity screening study which may indicate that the NOAEL may not be sufficiently robust. As no other dermal repeated dose toxicity study was available, the evaluating MSCA considers that the NOEL from the oral 28-day repeated dose toxicity study should be used for the derivation of the dermal DNELs, applying route to route extrapolation.

The evaluating MSCA was also not in agreement with the registrant regarding the choice of assessment factors used in the derivation the long term systemic inhalation and dermal DNELs.

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

4-Methylanisole was self-classified as:

- Acute Tox. 4; H302: Harmful if swallowed
- Skin Irrit. 2; H315: Causes skin irritation
- Repr. 2; H361: Suspected of damaging the unborn child

Based on the available information the evaluating MSCA can support this conclusion.

As discussed in section 7.9.7, the evaluating MSCA considered that further information was required to clarify the developmental toxicity hazard identified in the oral reproduction/developmental toxicity screening study and to determine the need for a higher hazard classification, i.e. reproductive toxicity category 1B H360 (may damage the unborn child). However, due to the termination of the substance evaluation procedure, no further information was requested.

7.10. Assessment of endocrine disrupting (ED) properties

Not evaluated.

7.11. PBT and VPVB assessment

Not evaluated.

7.12. Exposure assessment

7.12.1. Human health

7.12.1.1. Worker

The exposure scenarios identified in the registration dossier as relevant for worker exposure were:

- Manufacturing
- Compounding
- Formulation
- Use of cleaning agents – Industrial
- Use in cleaning agents – Professional

The exposure assessment for workers covered both dermal and inhalation exposure. For all scenarios, exposure was considered to be direct exposure to the registered substance. Based on the available information, the evaluating MSCA could support the conclusion of the registrant regarding worker exposure for the exposure scenarios for manufacturing, formulation, use of cleaning agents (industrial) and use in cleaning agents (professional).

The exposure scenario "compounding" covered the industrial use of 4-methylanisole and contained seven contributing exposure scenarios, in which inhalation and dermal exposure to workers was estimated. The evaluating MSCA noted that when the inhalation exposure estimates were compared with the long term systemic DNEL of 1.17 mg/m^3, there was some uncertainty regarding whether the risk to workers was adequately controlled for a number of contributing scenarios (PROCs 2, 2, 5, 8b and 15).

It was noted that in the registration dossier the inhalation exposure estimates for this exposure scenario were generated using a tier 1 exposure model. Tier 1 exposure models are inherently conservative and thus may overestimate the actual exposure levels. ECHAs Guidance R.14[3] states *"when according to Tier 1 assessment the level of protection is not adequate, a Tier 2 assessment is necessary".* The evaluating MSCA concluded that further refinement of the inhalation exposure estimates using a higher tier (Tier 2) exposure assessment was required in order to clarify whether the exposure to workers was adequately controlled for the compounding exposure scenario.

As outlined in section 7.2, during the substance evaluation process the status of the registration for 4-methylanisole was changed such that the registration was revoked. As there were no other registrants of the substance at that time, there was subsequently no valid registration. Therefore, the substance evaluation decision making process was terminated and no further information was requested.

7.12.1.2. Consumer

Based on the available information, the evaluating MSCA concluded that there was no concern for consumer exposure.

7.12.2. Environment

Not evaluated.

[3] Guidance on information requirements and chemical safety assessment. Chapter R.14: Occupational exposure estimation

7.12.3. Combined exposure assessment

Not evaluated.

7.13. Risk characterisation

7.13.1. Human Health

A concern for developmental toxicity was also identified and the evaluating MSCA concluded that further information was required in order to clarify the concern regarding developmental toxicity, the adequacy of the existing risk management measures, and the need for a higher hazard classification, i.e. reproductive toxicity category 1B H360 (may damage the unborn child).

The evaluating MSCA is of the opinion that the concern for developmental toxicity remains unverified since no additional information was requested to clarify the concern due to the termination of the substance evaluation decision making process.

7.13.1.1. Workers

The evaluating MSCA identified a concern for the exposure scenario for the industrial use of “compounding” and concluded that further information was required in order to clarify whether the exposure to workers was adequately controlled. For the remaining exposure scenarios, the evaluating MSCA concluded that the RCR values for both inhalation and dermal exposures were below 1.

As discussed in section 7.2, during the substance evaluation decision making process the only registrant ceased manufacture of the substance in accordance with Article 50(3) of the REACH Regulation and therefore the registration was revoked. As there were no other active registrations within the scope of substance evaluation, the substance evaluation was terminated and no further information was requested. Therefore, it was not possible for the evaluating MSCA to conclude on whether the risk to workers in the exposure scenario for compounding was adequately controlled. At the time of finalising this report, the evaluating MSCA concluded that since there were no registered uses of 4-methylanisole within the scope of substance evaluation, there is currently no concern for worker inhalation exposure.

7.13.1.2. Consumers

At the time of finalising this report, there were no registered consumer uses of 4-methylanisole.

7.13.2. Environment

Not evaluated.

7.14. References

Registration dossier for 4-methylanisole, European Chemicals Agency, http://echa.europa.eu/

7.15. Abbreviations

AF	Assessment factor
Bw	Body weight
CAS	Chemical abstracts service
C&L	Classification and labelling
CLP	Classification, labelling and packaging (Regulation (EC) No 1272/2008)
CMR	Carcinogenicity, mutagenicity and toxicity to reproduction
DNEL	Derived no effect level
GD	Gestation day
GI	Gastro Intestinal
LD50	Median lethal dose. The dose causing 50 % lethality
MSCA	Member state competent authority
NOAEC	No observed adverse effect concentration
NOAEL	No observed adverse effect level
NOEL	No observed effect level
OECD	Organisation for Economic Co-operation and Development
PBT	Persistent, Bioaccumulative, Toxic
PND	Post natal day
PROC	Process category
RCR	Risk characterization ratio
TG	Test guideline
TPA	Tonnes per annum
vPvB	Very Persistent and very Bioaccumulative