SUBSTANCE EVALUATION CONCLUSION

as required by REACH Article 48

and

EVALUATION REPORT

for

4-methylanisole

EC No 203-253-7

CAS RN 104-93-8

Evaluating Member State(s): Ireland

Final report: 8 December 2022

Evaluating Member State Competent Authority

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Year of evaluation in CoRAP: 2021

The substance evaluation was terminated without requesting further information from the registrants under an Article 46(1) decision due to a change in status of the registration dossiers (cease of manufacture or import 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

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 conducted 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

The Substance, 4-methylanisole (EC No 203-253-7), was selected for substance evaluation to clarify concerns about:

-Reproductive toxicity (developmental toxicity)

2. OVERVIEW OF OTHER PROCESSES / EU LEGISLATION

In March 2021, ECHA completed an assessment of regulatory needs (ARN) for the aromatic ethers group, which included the Substance (ECHA, 2021[2]). Based on the available hazard information, the ARN identified the potential for adverse effects on fertility and development but noted that there was a need to clarify the potential hazards through further data generation, including under substance evaluation for the Substance.

The Substance was evaluated already earlier in 2012 under substance evaluation by Irish Competent Authority, but the decision-making was terminated, and evaluation concluded without a final decision as the registrant ceased manufacture. Therefore, the concern for reproductive toxicity was unresolved. Substance evaluation conclusion and evaluation report was published in 2015 (Health and Safety Authority, 2015[3]).

3. CONCLUSION OF SUBSTANCE EVALUATION

The evaluation of the available information on the Substance has led the evaluating Member State Competent Authority (evaluating MSCA) 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

[2] https://echa.europa.eu/documents/10162/833a72fa-29f5-1c0e-1e7c-d446de1d1590

[3] https://echa.europa.eu/documents/10162/f68a1e07-d757-c192-655f-f2c0de9da66f

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 and/or import)	X

During the substance evaluation decision-making process, the registrants of the Substance ceased manufacture and/or import of the substance in accordance with Article 50(3) of the REACH Regulation and the substance evaluation process was subsequently terminated because no relevant registrant exists as addressee of the draft decision. Therefore, as there were no longer any uses within the scope of substance evaluation, the risk-based concern was removed. At the time of finalising this report, there were no active registrations for the Substance within the scope of substance evaluation.

Due to the termination of the substance evaluation decision making process, the concern for reproductive and developmental toxicity, in particular developmental immunotoxicity, remains unresolved since no additional information was requested to clarify the concern. The evaluating MSCA recommends that further assessment of the concern be undertaken in the event of new future registrations of the Substance.

If new registrations are submitted, the substance evaluation process may restart by including the Substance again on the Community rolling action plan (CoRAP).

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

The Substance was selected for substance evaluation to clarify concerns about:

- Reproductive toxicity (developmental toxicity)

Table 3

EVALUATED ENDPOINTS	
Endpoint evaluated	**Outcome/conclusion**
Reproductive toxicity	Concern unresolved. The evaluating MSCA concluded that further information was required to clarify the concern for reproductive toxicity. However, due to the termination of the substance evaluation decision making process, the concern for reproductive and developmental toxicity, in particular developmental immunotoxicity, remains unresolved since no additional information was requested to clarify the concern. At the time of finalising this report, there were no active registrations for the substance within the scope of substance evaluation.

7.2. Procedure

Due to new registrations and pursuant to Article 44(2) of the REACH Regulation, the Substance was included again on the CoRAP for evaluation in 2021. The Competent Authority of Ireland was appointed to conduct the evaluation. The substance evaluation commenced on 17 March 2021.

The evaluation was targeted to human health hazards and exposure, in particular reproductive toxicity. The main source of information for the evaluation was the registration dossier and a published study on the Substance.

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 reproductive and developmental toxicity, in particular developmental immunotoxicity. Therefore, pursuant to Article 46(1) of the REACH Regulation a draft decision to request further information was prepared. The draft decision was submitted to ECHA on 3 March 2022.

On 16 March 2022, ECHA sent the draft decision to the registrants and invited them to comment by 22 April 2022. By that date, ECHA received comments from the registrants and forwarded them to the evaluating MSCA. On 1 July 2022, the registrants notified ECHA of their intention to cease manufacture and/or import of the Substance in accordance with Article 50(3) of the REACH Regulation. The registrations were subsequently invalidated by ECHA. As there were no other active registrations of the substance within the scope of substance evaluation, the substance evaluation decision making process was terminated and no further information was requested.

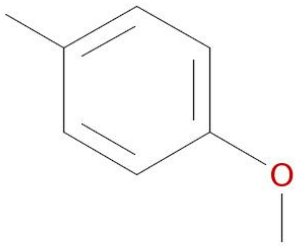
7.3. Identity of the substance

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:	122.164
Synonyms:	Anisole, p-methyl- Benzene, 1-methoxy-4-methyl- 1-methoxy-4-methylbenzene

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

Structural formula:



7.4. Physico-chemical properties

The physicochemical data reported in the registration data for the Substance is reported in table 5 below.

Table 5

OVERVIEW OF PHYSICOCHEMICAL PROPERTIES	
Property	**Value**
Physical state at 20°C and 101.3 kPa	Liquid
Vapour pressure	79 Pa at 20 °C
Water solubility	0.559 g/L at 20 °C
Partition coefficient n-octanol/water (Log K_{ow})	2.8 at 35 °C
Flammability	Not flammable
Explosive properties	Not explosive
Oxidising properties	Not oxidising
Granulometry	Not applicable
Stability in organic solvents and identity of relevant degradation products	-
Dissociation constant	-
Flash point	62 °C at 1013 mBar

7.5. Manufacture and uses

7.5.1. Quantities

At the start of the substance evaluation process, the aggregated tonnage was reported to be 10 to 100 tonnes per year. However, during the substance evaluation decision making process the registrants ceased manufacture and/or import of the substance in accordance with Article 50(3) of the REACH Regulation and therefore the registrations were invalidated.

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

7.5.2. Overview of uses

The Substance is primarily used as a fragrance ingredient, which is formulated into fragrance products and fragranced end-products for industrial, professional and consumer use.

Table 6 summarises the main uses reported in the registration dossiers that were subject to substance evaluation before the registrations were invalidated in accordance with Article 50(3) of REACH. At the time of finalising this report, there were no active registrations for the substance within the scope of substance evaluation.

Table 6

USES	Use(s)
Uses as intermediate	-
Formulation	Formulation of fragrance products Formulation of fragranced end products
Uses at industrial sites	Use of washing and cleaning products Use of metal surface treatment products Use of disinfectants
Uses by professional workers	Use of washing and cleaning products Use of polishes and waxes Use of disinfectants Use of cosmetics Use in hairdressing services
Consumer Uses	Use of washing and cleaning products Use of polishes and waxes Use of air care products Use of cosmetics Use of biocides Use of tobacco products
Article service life	-

The Substance is also registered as an intermediate. This use is outside the scope of substance evaluation.

7.6. Classification and Labelling

7.6.1. Harmonised Classification (Annex VI of CLP)

The Substance is not listed on Annex VI of CLP.

7.6.2. Self-classification

In the registrations:

- Acute toxicity category 4 (H302: Harmful if swallowed)
- Skin irritation category 2 (H315: Causes skin irritation)
- Reproductive toxicity category 2 (H361: Suspected of damaging fertility or the unborn child).

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

- Flammable liquid category 3 (H226: Flammable liquid and vapour)
- Aquatic chronic category 3 (H412: Harmful to aquatic life with long lasting effects)
- Eye irritation category 2 (H319: Causes serious eye irritation).

7.7. Environmental fate properties

Not evaluated.

7.8. Environmental hazard assessment

Not evaluated.

7.9. Human Health hazard assessment

7.9.1. Toxicokinetics

No information available.

7.9.2. Acute toxicity and Corrosion/Irritation

The registration data for the Substance identified an LD_{50} (oral) of 1920 mg/kg bw in rats, an LC_{50} (inhalation, vapour, 4 hours) of 6.1 mg/l (highest technically achievable concentration) and an LD_{50} (dermal) of 4850 mg/kg bw. The registration data applies a classification of acute toxicity category 4 for the oral route.

Based on the available irritation data, the registration data applies a classification of skin irritation category 2. No classification for eye irritation is warranted.

Based on the available information, the evaluating MSCA can support these conclusions.

7.9.3. Sensitisation

A local lymph node assay (LLNA), conducted in accordance with OECD TG 429, is reported in the registration data. The Substance in a methyl ethyl ketone vehicle was applied topically to the dorsal surface of the ears of groups of four female CBA:Ca mice at 10%, 25% and 50% w/v for three consecutive days. The positive control was reported to be hexyl cinnamic aldehyde, although no results from the positive control are reported in the study summary. The stimulation index (S.I.) for the 10%, 25% and 50% w/v groups were reported as 1.56, 2.08 and 2.39, respectively. The EC3 value was not estimated. Under the conditions of the study, the Substance was not sensitising to skin.

Based on the results of LLNA, the evaluating MSCA can support the conclusion that the Substance is not a skin sensitiser.

No information is available with respect to respiratory sensitisation.

7.9.4. Repeated dose toxicity

An oral 28-day repeated dose toxicity study, conducted in accordance with OECD TG 407, is reported in the registration data. The Substance was administered by oral gavage to five Wistar rats per sex per dose for 4 weeks (5 days/week) at 100, 300 and 1000 mg/kg bw/day. At 1000 mg/kg bw/day, clinical signs of toxicity included salivation, ataxia, tremor, and laboured respiration. Salivation was also reported at 300 mg/kg bw/day. An increase in body weight was observed in females on days 21 and 28 at 1000 mg/kg bw/day, which corresponded with an increase in food consumption in this group.

At 1000 mg/kg bw/day, an increase in absolute and relative liver weights, along with slight diffuse hypertrophy and single cell necrosis of the hepatocytes, was observed in both sexes. At the same dose, a decrease in absolute spleen weight and a decrease in absolute

and relative thymus weight was reported in males and an increase in absolute and relative kidney weight was reported in females. At 300 mg/kg bw/day, a decrease in absolute spleen weights was observed in males. The registration data identifies a NOAEL of 100 mg/kg bw/day, which is supported by the evaluating MSCA.

7.9.5. Mutagenicity

Three bacterial reverse mutation tests (OECD TG 471) with the Substance are reported in the registration data, all of which are negative in the presence and absence of metabolic activation. The evaluating MSCA notes that all the tests are missing the fifth strain of *E. coli* WP2 uvrA, *E. coli* WP2 uvrA (pKM101) or *S. typhimurium* TA102, which is required under the current version of OECD TG 471 (June 2020).

An *in vitro* chromosomal aberration test (similar to OECD TG 473) in Chinese hamster ovary cells is reported in the intermediate registration dossier for the Substance. In this study, an increase in chromosome aberrations was observed in the presence of metabolic activation following a 20-hour incubation period with the Substance. Two *in vitro* unscheduled DNA synthesis studies (similar to OECD TG 482) with the Substance are also reported in the registration data, one with a positive result and the other a negative result. The evaluating MSCA notes that OECD TG 482 was deleted in April 2014 and is no longer considered a valid OECD test guideline.

In a mammalian erythrocyte micronucleus study (OECD TG 474), male NMRI mice were administered a single dose of the Substance via oral gavage at 0, 500, 1000 and 2000 mg/kg bw. Bone marrow was sampled at 24 hours (all dose groups) and at 48 hours (2000 mg/kg bw) post-dosing. No cytotoxic effects in the bone marrow were reported and there was no biologically relevant or statistically significant increase in the frequency of micronuclei at any dose. Based on the information reported in the registration data, the evaluating MSCA considers that there may be some uncertainty regarding whether the test material reached the bone marrow, since no evidence of cytotoxicity in bone marrow cells was observed at any dose. In addition, the study deviated from the current version of OECD TG 474 (July 2016) in that 2000 polychromatic erythrocytes were scored instead of the current requirement of at least 4000.

In an unscheduled DNA synthesis (UDS) test with mammalian liver cells *in vivo* (OECD TG 486), male Wistar rats were administered a single dose of the Substance via oral gavage at 0, 1000 and 2000 mg/kg bw. 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. The study summary notes that there was no decrease in primary hepatocytes or changes in liver cell morphology, indicating no cytotoxicity in the liver. Based on the reported information, the evaluating MSCA considers that there is some uncertainty regarding whether the test material reached the liver since no evidence of cytotoxicity in hepatocytes was reported at any dose. OECD TG 486 states it is not appropriate to use the UDS test if there is evidence that the test substance will not reach the target tissue (liver). However, it is noted that the liver was identified as a target organ in the 28-day repeated dose toxicity study (reported in section 7.9.4). The evaluating MSCA notes that the UDS test is an indicator test measuring DNA repair of liver cells, which can detect substances that induce *in vivo* gene mutation (rather than chromosome aberrations). However, ECHA guidance[4] (ECHA, 2017) states "a negative result in an UDS assay alone is not proof that a substance does not induce gene mutation".

Based on the available data, the registration data concludes that the Substance is not genotoxic. As discussed above, the evaluating MSCA notes there are some limitations in the available studies and considers these could be addressed under the compliance check

[4] ECHA Guidance R.7a section 7.7.6.3

process of REACH. However, at the time of finalising this report, there were no active registrations for the Substance within the scope of dossier evaluation.

7.9.6. Carcinogenicity

No information available.

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

A reproduction/developmental toxicity screening test conducted in accordance with OECD TG 421 is reported in the registration data. The Substance was administered by oral gavage to ten Wistar rats per sex per dose at 0, 100, 300 and 1000 mg/kg bw/day. Animals were treated during pre-mating (2 weeks) and mating (2 weeks). Females were then treated during gestation, 4 days of lactation, until 13 days post-partum. Parental males were treated for 29 days. Pups were sacrificed on post-natal day (PND) four.

Clinical signs of toxicity observed in males and females at 1000 mg/kg bw/day included abdominal position, apathy, and ataxia. Unsteady gait was also observed in females at this dose. At 1000 mg/kg bw/day, a significant decrease in maternal body weight was observed at gestation day (GD) twenty and lactation day (LD) 4 (90 % of control values at both time points). This corresponded with a decrease in the mean maternal body weight change at this dose at GD 0-20 and LD 0-4. Body weights were also decreased in males at 1000 mg/kg bw/day during weeks 3 and 4. Food consumption was increased in females at 1000 mg/kg bw/day during GD 0-14 and decreased during LD 0-4.

A dose dependent enlargement of the liver, characterised by centrilobular hypertrophy and lymphoid infiltration, was observed at ≥ 300 mg/kg bw/day in both sexes. The incidence of centrilobular hypertrophy was 0/10, 0/10, 1/10 and 10/10 in males and 0/10, 0/10, 1/10 and 10/10 in females at 0, 100, 300 and 1000 mg/kg bw/day, respectively. A decrease in absolute epididymis weight was observed in males at 1000 mg/kg bw/day. No effect on testes or ovary weight was observed.

A biologically significant increase in post-implantation loss was observed at 1000 mg/kg bw/day. The percentage post-implantation loss was 6.3%, 3.7%, 1.7% and 17.4% at 0, 100, 300 and 1000 mg/kg bw/day, respectively. The study authors noted that the post-implantation loss at 1000 mg/kg bw/day (17.4%) was outside the historical control range of the test laboratory (2.5% – 12.9%) and was therefore considered to be treatment related.

An increase in the number of females with stillborn pups was observed at ≥ 300 mg/kg bw/day. The incidence was 0/10, 0/10, 4/10 and 9/10 at 0, 100, 300 and 1000 mg/kg bw/day, respectively. There was also an increase in the number of stillborn pups at ≥ 300 mg/kg bw/day. The incidence was 0%, 0%, 9.6% and 16% at 0, 100, 300 and 1000 mg/kg bw/day, respectively.

At ≥ 300 mg/kg bw/day, there was an increase in the number of pups that died after birth (0%, 0%, 25% and 21% at 0, 100, 300 and 1000 mg/kg bw/day, respectively) or were cannibalized (0%, 0%, 14% and 63% at 0, 100, 300 and 1000 mg/kg bw/day, respectively). At 1000 mg/kg bw/day, there was total litter loss by PND 4, and thus the viability index was 0% and the mean pup body weight could not be calculated since no pups survived. At this dose, only one female pup was alive at PND 1, and the pup weighed 29% less than control pups. At 300 mg/kg bw/day, there was a decrease in pup survival during PND 0-4. The number of surviving pups was 121/121, 98/98 and 65/125 at 0, 100 and 300 mg/kg bw/day, respectively, resulting in a decrease in pup viability index at ≥ 300 mg/kg bw/day (100%, 100% and 58% and 0% at 0, 100, 300 and 1000 mg/kg bw/day, respectively). At 300 mg/kg bw/day, there was a decrease in pup body weight at PND 1 and 4 and an increased incidence of runts (10 compared to 1 in the control). At

necropsy, there was an increased incidence of pups with empty stomachs at ≥ 300 mg/kg bw/day. No effects on offspring were observed at 100 mg/kg bw/day.

The registrants identify NOAELs of 100 mg/kg bw/day for parental toxicity and effects on development and a NOAEL of 1000 mg/kg bw/day for effects on fertility. Based on the results of this study, the registrants conclude that the Substance meets the criteria for classification for reproductive toxicity category 2.

The evaluating MSCA notes that at 1000 mg/kg bw/day there was a significant decrease in maternal body weight and therefore, it cannot be excluded that the effects on post-implantation loss, pup development, pup viability and the reduced maternal care observed at this dose may have been secondary to maternal toxicity. However, the evaluating MSCA notes that post-natal effects were also observed at 300 mg/kg bw/day, which did not have any effect on maternal body weight or cause other signs of maternal toxicity.

In a non-guideline study in rats, a number of pup immune parameters were assessed following pre- and/or post-natal exposure to the Substance at 0, 8, 16, 32, 64, 125 and 250 mg/kg bw/day (Tonk *et al*., 2015). Four different study designs were used with different combinations of maternal exposures (from pre-mating to PND 10-21) and/or direct exposure to offspring (from PND 10-50). Pups were sacrificed on PND 50, and organ weights were measured, and haematological and immunological assessments conducted on six male pups per dose group. Separate groups of six male pups per dose group were immunised with keyhole limpet hemocyanin (KLH) on PND 21 and PND 35 and primary IgM and IgG and secondary IgM and IgG responses were assessed. A delayed hypersensitivity response was assessed following a challenge with KLH on PND 45. The study authors calculated benchmark doses (BMD) instead of presenting the data per dose group.

A decrease in litter size was reported at 250 mg/kg bw/day (reported to be 24% less than control values). In pups, absolute and relative liver and kidney weights were increased and absolute and relative spleen and thymus weights were decreased. The BMD for changes in absolute spleen and thymus weights were 114 and 154 mg/kg bw/day, respectively, with maximum responses reported to be 11% and 8% less than control values, respectively. A dose dependent decrease in the number of cells per spleen at PND 50 was also observed; the BMD was reported to be 115 mg/kg bw/day, with a maximum response of 10% less than control values. The T/B cell ratio in the spleen was increased in groups where there was no maternal exposure and only direct exposure to pups during PND 10-50. The BMD were reported to be 54 mg/kg bw/day for groups exposed during PND 21–50 and 123 mg/kg bw/day for groups exposed during PND 10–50, with maximum responses of 27% and 11% greater than control values, respectively. No other effects on the splenic lymphocyte population were observed.

A decrease in the number of eosinophils was reported, with a BMD for this effect of 26 mg/kg bw/day and a maximum response of 36% less than control values.

With respect to the assessment of functional immune parameters, a dose dependent increase in tumour necrosis factor alpha (TNF-α) production by adherent splenocytes was observed at PND 50 in groups where there was no maternal exposure and only direct exposure to pups during PND 10-50, with the BMD reported to be 53 mg/kg bw/day and the maximum response to be 27% greater than control values. An increase in interleukin-13 (IL-13) and TNF-α following immunisation with KLH on PND 21 and 35 and subsequent challenge with KLH on PND 45 was observed in all study designs (reported to be 46% and 25% greater than control values, respectively). The effect on the secondary immunoglobulin G (IgG) response was considered by the study authors to be ambiguous. No effects on other functional immune parameters were reported.

The evaluating MSCA notes there are a number of limitations with the study, including no information on the number of parental animals in each cohort, the low number of pups assessed per group and the limited reporting of the results. However, the significant effect on spleen and thymus weights, in addition to alterations in cells associated with both innate

and acquired immunity immune parameters seen in the small number of pups assessed for each parameter indicates a potential effect on the developing immune system. In addition, although the study only reports BMDs, the effects observed on immune parameters occurred at doses lower than those which resulted in a decrease in litter size, indicating that effects on the developing immune system may be a more sensitive indicator of developmental toxicity.

A dermal reproduction/developmental screening study, conducted in accordance with OECD TG 421, is reported in the intermediate registration dossier for the Substance. In this study, the Substance was applied dermally (6 hours/day; 7 days/week) to groups of ten male and ten female Wistar rats at dose levels of 0, 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 2-week premating period and a two-week mating period in both sexes, and 1-week post-mating in males and until GD 19 in females. The females were not treated at the end of gestation or during lactation.

All females were sperm positive after the mating period, with the mating index 100% in all groups. 4/10 males and 1/10 males at 100 and 300 mg/kg bw/day, respectively, did not produce pups. There were no histopathological findings in the epididymides or testes and therefore, in the absence of a dose response, the toxicological significance of the effect is unclear.

No effect on the number implantation sites was reported. A statistically significant increase in post-implantation loss was observed at 100 mg/kg bw/day. However, in the absence of a dose response this effect is not considered to be treatment related. There was no effect on the number of live births, stillborn pups, or runts, or on pup viability, pup body weights or sex ratio of pups. The registrants identify a NOAEL of 1000 mg/kg bw/day for parental toxicity, effects on fertility and effects on development.

The evaluating MSCA notes that while in general the dermal route of administration may be a relevant route of human exposure, OECD TG 421 recommends the oral route of exposure and does not include any specifications for dermal administration. Furthermore, according to ECHA Guidance R.7a[5], the oral route is the default route (except for gases) to investigate reproductive toxicity. It is also noted that the dermal absorption potential of the Substance 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 sufficiently reliable to conclude on the potential reproductive toxicity of the Substance.

Overall, based on the available information a concern for reproductive and developmental toxicity, in particular developmental immunotoxicity was identified. However, the evaluating MSCA considered that the available data was not sufficient to conclude on the potential hazard. As there were uses reported in the registration data which indicated the potential for exposure to workers and consumers, the evaluating MSCA concluded that further information was required to clarify the potential risk related to reproductive and pre- and post-natal developmental toxicity, in particular developmental immunotoxicity.

The evaluating MSCA was of the opinion that an Extended One Generation Reproductive Toxicity Study (OECD TG 443) with the inclusion of cohort 3 (Developmental Immunotoxicity) was the appropriate study to request to clarify the potential risk. This study would allow a conclusion on whether the Substance should be classified more stringently for reproductive toxicity (i.e., reproductive category 1B) under the CLP Regulation, as well as supporting the identification of appropriate risk management measures in the chemical safety assessment. However, as outlined in section 7.2, during

[5] Guidance on information requirements and chemical safety assessment. Chapter R.7a: Endpoint specific guidance. Version 6.0, July 2017.

the substance evaluation decision-making process the registrants of the Substance ceased manufacture and/or import of the substance in accordance with Article 50(3) of the REACH Regulation and the substance evaluation process was terminated.

Due to the termination of the substance evaluation decision making process, the concern for reproductive and developmental toxicity, in particular developmental immunotoxicity, remains unresolved since no additional information was requested to clarify the concern.

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 derived.

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

The Substance is self-classified as:

- Acute toxicity category 4 (H302: Harmful if swallowed)
- Skin irritation category2 (H315: Causes skin irritation)
- Reproductive toxicity category 2 (H361: Suspected of damaging fertility or the unborn child).

Based on the available information, the evaluating MSCA can support these conclusions.

As discussed in section 7.9.7, the evaluating MSCA concluded that further information was required to clarify the potential risk related to reproductive and pre- and post-natal developmental toxicity, in particular developmental immunotoxicity. However, due to the termination of the substance evaluation decision making process, this concern remains unresolved since no additional information was requested to clarify the concern.

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

A detailed exposure assessment was not performed.

7.12.1.1. Worker

The potential for dermal and inhalation exposure to industrial and professional workers was identified based on the following uses reported in the registration dossiers:

<u>Industrial workers:</u>

- Formulation of fragrance products
- Formulation of fragranced end products
- Use of washing and cleaning products
- Use of metal surface treatment products
- Use of disinfectants

Professional workers:

- Use of washing and cleaning products
- Use of polishes and waxes
- Use of disinfectants
- Use of cosmetics
- Use in hairdressing services

7.12.1.2. Consumer

The potential for dermal and inhalation exposure to consumers was identified based on the following uses reported in the registration dossiers:

- Use of washing and cleaning products
- Use of polishes and waxes
- Use of air care products
- Use of cosmetics
- Use of biocides
- Use of tobacco products

As discussed in section 7.2, during the substance evaluation decision-making process the registrants of the Substance ceased manufacture and/or import of the substance in accordance with Article 50(3) of the REACH Regulation and the substance evaluation process was terminated.

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

7.12.2. Environment

Not evaluated.

7.12.3. Combined exposure assessment

Not evaluated.

7.13. Risk characterisation

The evaluating MSCA concluded that further information was required to clarify the concern regarding reproductive and developmental toxicity, in particular developmental immunotoxicity. However, during the substance evaluation decision-making process, the registrants ceased manufacture and/or import of the Substance in accordance with Article 50(3) of the REACH Regulation. As there were no other active registrations of the Substance within the scope of substance evaluation, the substance evaluation decision making process was terminated and no further information was requested.

Due to the termination of the substance evaluation decision making process, the concern for reproductive and developmental toxicity, in particular developmental immunotoxicity, remains unresolved since no additional information was requested to clarify the concern.

7.14. References

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ECHA (2022). IUCLID dossier, 4-methylanisole, EC No 203-253-7. European Chemicals Agency, http://echa.europa.eu/

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7.15. Abbreviations

BMD	Benchmark dose
Bw	Body weight
CAS	Chemical abstracts service
C&L	Classification and labelling
CLP	Classification, labelling and packaging (Regulation (EC) No 1272/2008)
CoRAP	Community rolling action plan
DNEL	Derived no effect level
GD	Gestation day
GLP	Good laboratory practice
Ig	Immunoglobulin
KLH	Keyhole limpet hemocyanin
LC	Median lethal concentration
LD	Lactation day
LLNA	Local lymph node assay
LD50	Median lethal dose
MSCA	Member state competent authority
NOAEL	No observed adverse effect level
OECD	Organisation for Economic Co-operation and Development
PBT	Persistent, Bioaccumulative, Toxic
PND	Post-natal day
TPA	Tonnes per annum
vPvB	Very Persistent and very Bioaccumulative
Wk	Week