BUREAU FOR CHEMICAL SUBSTANCE

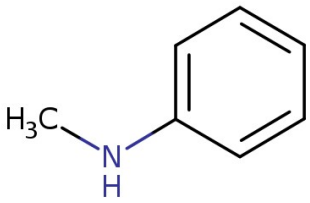
SUBSTANCE EVALUATION CONCLUSION and EVALUATION REPORT

for

N-methylaniline

EC No 202-870-9

CAS NR 100-61-8



Evaluating Member State Competent Authority: Poland

Dated: 02 July 2024

Evaluating Member State Competent Authority

MSCA name:	Bureau for Chemical Substances
Address:	Dowborczykow 30/34, 90-019 Lodz, Poland
Telephone Number:	+48 (42) 25 38 400/401
Email address:	evaluation@chemikalia.gov.pl
Web:	www.chemikalia.gov.pl

Year of evaluation in CoRAP: 2023

Further information on registered substances here:

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

Further information on the substance evaluation process here:

https://echa.europa.eu/regulations/reach/evaluation/substance-evaluation

Foreword

This Conclusion document, as required by Article 48 of the REACH Regulation, provides the outcome of the Substance Evaluation carried out by the evaluating MSCA. The document consists of two parts i.e. A) the conclusion and B) the evaluation report.

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 MSCA. In case the evaluating MSCA 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 MSCA, it does not preclude other MSCAs or the European Commission from initiating regulatory risk management measures which they deem appropriate.

Contents

List of Tables

Part A. Conclusion

1. Scope of the evaluation

N-methylaniline (NMA), 'the Substance', was originally selected for substance evaluation to clarify concerns about:

Carcinogenicity,
Mutagenicity,
Cumulative exposure,
Exposure of workers,
High RCR,
Wide dispersive use.

2. Overview of other processes / EU legislation

Table 2-1 Overview of other processes / EU legislation

No other processes	CCH	TPE	GMT	Previously on CoRAP	Annex VI (CLP)	Annex XVII (Restriction)	Candidate List/Annex XIV (Authorisation)
☐	☒	☒	☐	☐	☒	☐	☐

Three dossier evaluation decisions have been issued by ECHA:

One CCH:
https://echa.europa.eu/documents/10162/557ee45e-1e11-8ee4-d4e2-d7dd22775889

Two TPE:
https://echa.europa.eu/documents/10162/35ca95e5-e166-4186-e295-b97b5196fe9b
https://echa.europa.eu/documents/10162/30e6bebe-0903-a9fc-00a3-9052fbf1f354

Other EU legislation	Previous legislation	Stockholm convention	Other
PPP/BPR	NONS/RAR	POP	(e.g., UNEP)
☐	☐	☐	☐

3. Conclusion and regulatory follow-up action

The evaluation of the available information on the Substance has led the evaluating MSCA to the following conclusions.

Table 3-1 Conclusion and regulatory follow-up action

Initial and additional concern	Conclusion on concern	Regulatory follow-up action
Carcinogenicity	Concern confirmed Based on the limited evidence of carcinogenicity of structural analogues and metabolites of N,N-dimethylaniline, the evaluating MSCA considers that read-across approach is plausible also for this hazard property. Thus, in line with the criteria of Regulation 1272/2008, the Substance warrants classification as Carc. 2; H351 (Suspected of causing cancer).	Harmonised classification and labelling

Mutagenicity	Concern confirmed Based on the CLP Regulation guidelines on similarity to the known mutagens and structural similarity of N-methylaniline with aniline, the metabolite of the Substance, the evaluating MSCA considers that by using a read-across approach the criteria for classification in Category 2 defined in the Regulation 1272/2008 are met. Thus, the Substance warrants the classification as Muta. 2; H341 (suspected of causing genetic defects).	Harmonised classification and labelling
Cumulative exposure	Concern removed (clarification of hazard/exposure) Cumulative exposure has not been addressed by the registrant. There is only one registrant. The substance is used as an intermediate and as an additive in gasoline only.	No need for regulatory follow-up at EU level
Exposure of workers	Concern confirmed The evaluating MSCA notes that an 8-hour time-weighted average will be higher than the value estimated for one task, and it may lead to an unacceptable level of exposure. Moreover, it is unclear if contributing scenarios cover an expected exposure related to the cleaning and maintenance of equipment.	No need for regulatory follow-up at EU level
High RCR	Concern confirmed The DNEL values derived by the evaluating MSCA for workers for the dermal route are lower than DNELs derived by the registrant. As a result, the RCR values become significantly higher for some contributing scenarios. Moreover, if the carcinogenicity of the Substance is confirmed, the registrant should consider further risk management measures.	No need for regulatory follow-up at EU level
Wide dispersive use	Concern confirmed Wide dispersive use criteria included in CoRAP selection criteria document are met since the Substance is used as an additive in gasoline used by professionals and consumers (the number of sites of use is potentially high, pattern and amount of releases/exposure, the substance is incorporated into mixtures or articles used by the public (consumers), the potential size of the exposed population is high).	No need for regulatory follow-up at EU level

4. Regulatory follow-up actions at EU level

4.1 Harmonised Classification and Labelling

Based on the available information, an update of the existing harmonised classification of the substance is proposed by the evaluating MSCA as a follow-up at the EU level for the following hazard categories based on structure-activity considerations among analogue substances of the aniline (see also section 8.2 below):

- Carc. 2 with hazard statement H351: Suspected of causing cancer and
- Muta 2 with hazard statement H341: Suspected of causing genetic defects.

Harmonised classification for these hazards can have regulatory effects according to EU downstream legislation.[1] For instance, Directive 2004/37/EC includes employer obligations to prevent and reduce exposure of employees to substances or preparations that meet the criteria for classification as a carcinogen or mutagen.

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

Not applicable.

4.3 Restriction

Not applicable.

4.4 Other EU-wide regulatory risk management measures

Not applicable.

5. Currently no need for regulatory follow-up at EU level

5.1 No need for regulatory follow-up at EU level

Not applicable.

5.2. Other actions

The available use information and the exposure data provided in the registration dossier suggested risk for the workers and the consumers. Thus, the evaluating MSCA recommends a revision of the exposure assessment for workers and the consumers, as explained in Section 17.1 and Section 17. 2, respectively.

6. Tentative plan for follow-up actions

As indicated in Tables 3-1 the following regulatory action(s) at EU level are proposed.

Indication of a tentative plan is not a formal commitment by the evaluating MSCA. A commitment to prepare a REACH Annex XV dossier (SVHC, restrictions) and/or CLP Annex VI dossier should be made via the Registry of Intentions.

Table 6-1 Follow-up actions

Follow-up action	Date for intention	Actor
Harmonised C&L	2026	PL MSCA

Part B. Substance evaluation report

7. Overview of the Substance Evaluation Process

In accordance with Article 45(5) of the REACH Regulation, the evaluating MSCA evaluated the substance based on the information in the registration dossier(s) and on other relevant and available information.

[1]Introductory Guidance on the CLP Regulation, version 3.0, section 21, January 2019

Pursuant to Article 45(5) of REACH, the Substance was included on the Community rolling action plan (CoRAP) for evaluation in 2023. The Competent Authority of Poland was appointed to carry out the evaluation. The substance evaluation started on 18 March 2023.

The evaluation was targeted to clarify concerns on carcinogenicity, mutagenicity, cumulative exposure, exposure of workers, high RCR and wide dispersive use. Other endpoints were not evaluated.

The evaluating Member State concluded the evaluation without any further need to ask for more information from the registrants under an Article 46 decision.

8. Substance identity

The information on the Substance, including identifiers and structural formula, can be found on the cover page. For more details see ECHA CHEM: https://chem.echa.europa.eu/

Synonyms:

(Methylamino)benzene
Benzenamine,
N-methylmethylaniline-n,
Methylphenylamine,
MONOMETHYLANILINE.

8.1. Type of Substance

Mono-constituent.

8.2. Other relevant information

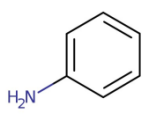
Table 8.2-1 Other information relevant to the composition of the Substance

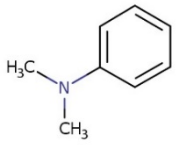
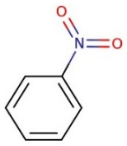
Type	Identity	Typical concentration	Concentration range	Remarks
Impurity	Confidential information	-	-	-

8.3. Analogue substance (read-across)

Three structural analogues of the Substance were used during the evaluation.
Information on these analogues is included in Table 8.3.-1.

Table 8.3-2 Relevant analogue substance(s)

EC name	EC no	CAS no	Chemical structure
Aniline	200-539-3	62-53-3	

N,N-dimethylaniline	204-493-5	121-69-7	
Nitrobenzene	202-716-0	98-95-3	

9. Physicochemical properties

Table 9-1 Overview of physicochemical properties

Property	Value
Molecular weight/weight range	107.15 g/mol
Physical state at 20°C and 101.3 kPa	liquid N-methylaniline is a colourless or slightly yellow oily liquid, which turns brown on exposure to air.
Vapour pressure	0.06 kPa at 25°C
Water solubility	5.6 g/L at 20°C
Partition coefficient n-octanol/water (Log K_{ow})	ca. 1.66 at 20°C
Density	0.9860 g/cm^3 at 20°C
Explosive properties	Non-explosive
Oxidising properties	Non-oxidising
Melting point	-57°C
Boiling point	196°C
Flash point	between 77 and 79°C

10. Manufacture and uses

10.1. Quantities

The aggregated tonnage (per year, reported as estimated tonnage on ECHA CHEM) of the Substance is 100 – 1,000 tonnes.

10.2. Overview of uses

Table 10.2-1 Overview of uses

Main uses	Key information
Formulation	Repackaging of substances and mixtures Industrial distribution of NMA or Gasoline with NMA

	Formulation and (re)packaging of substances and mixtures
Industrial	Fuel use Use as intermediate
Professional	Fuel use
Consumer	Fuel use

Used mainly in the EU as an additive in gasoline - the antiknock agent used to increase the octane number of gasoline petrol. The Substance can increase the octane rating of gasoline by slowing down the combustion process, which reduces the likelihood of engine knock. The Substance works by delaying the ignition of the air-fuel mixture in the engine cylinder.

11. Classification and labelling

Table 111-1 Classification of the Substance

Harmonised classification (Annex VI of CLP)	Self-classification in registrations	Self-classification in C&L notifications
Acute Tox. 3, H301 Acute Tox. 3, H311 Acute Tox. 3, H331 STOT RE 2, H373 Aquatic Acute 1, H400 Aquatic Chronic 1, H410	Acute Tox. 3, H301 Acute Tox. 3, H311 Acute Tox. 3, H331 Eye Irrit. 2, H319 STOT RE 2, H373 Aquatic Acute 1, H400 Aquatic Chronic 1, H410	Skin Irrit. 2, H316 Eye Irrit. 2, H320 (GHS) Muta. 2, H341 Carc. 2, H351 STOT RE 2, H373 (affected organs: target: spleen, liver and bone marrow; route of exposure: oral and Inhalation)

12. Environmental fate properties

Not in the scope of the evaluation.

13. Environmental hazard assessment

Not in the scope of the evaluation.

14. Human health hazard assessment

14.1. Toxicokinetics

Limited substance-specific data on the toxicokinetic behaviour of the Substance are available. The Substance is readily absorbed by inhalation, dermal and oral routes. It is distributed to the liver, kidney, lung, small intestine, brain and bladder tissues (HSDB, 2009). The Substance is metabolized in the liver by demethylation to aniline and/or hydroxylation of the aromatic ring to o- and p-methylaminophenols. The Substance is readily excreted in urine and thus has a low potential for bioaccumulation (SCOEL, 2012).

14.2. Acute toxicity and Corrosion/Irritation,

Not in the scope of the evaluation.

14.3. Sensitisation

Not in the scope of the evaluation.

14.4. Repeated dose toxicity

Not in the scope of the evaluation.

14.5. Mutagenicity

Mutagenicity was identified as a concern due to conflicting (negative and positive) responses in bacterial reverse mutation assays and chromosomal aberration test. In addition, aniline, a substance having high structural similarity with the Substance and present as its impurity, was clastogenic in cultured mammalian cells and in *in vivo* micronucleus assays.

The data on genotoxicity of the Substance submitted by the registrant(s) are summarised below:

Table 144.5-1 Genotoxicity in vitro

No.	Method	Results	Remarks
1	The bacterial reverse mutation assay according to guideline JAPAN: Guidelines for Screening Mutagenicity Testing Of Chemicals Test bacteria strains: S. typhimurium TA 1535, TA 1537, TA 98 and TA 100 (with and without met. act.) E. coli WP2 uvr A (with and without met. act.) Test concentrations: 0, 156.3*, 312.5, 625, 1250, 2500, 5000 ug/plate (*only without S9) Positive control substance(s): -S9 Mix, AF-2 (TA100, WP2, TA98), sodium azide (TA1535) and 9-aminoacridine (TA1537) +S9 Mix, 2-aminoanthracene (all strains)	Test results with and without metabolic activation (S9): - negative for S. typhimurium TA 1535, TA 1537, TA 98 and TA 100 - negative for E. coli WP2 uvr A cytotoxicity: at 5000 ug/plate vehicle controls valid negative controls valid positive controls valid	2 (reliable with restrictions) key study experimental study **Test material** N-methylaniline (CAS NR 100-61-8, EC No 202-870-9) Reference ECHA CHEM (2024)
2	OECD Guideline 471 (Bacterial Reverse Mutation Assay) in vitro gene mutation study in bacteria	Test results with and without metabolic activation (S9):	2 (reliable with restrictions) Data have been peer-reviewed for inclusion

	Test bacteria strains S. typhimurium TA 97 (with and without met. act.) S. typhimurium TA 1538 (with and without met. act.) S. typhimurium TA 1535, TA 1537, TA 98 and TA 100 (with and without met. act.) Test concentrations: not specified Positive control substance(s): not specified	- negative for S. typhimurium TA 97, TA 1535, TA 1537, TA 1538 TA 98 and TA 100; cytotoxicity: not specified vehicle controls valid: not specified negative controls valid: not specified positive controls valid: not specified	in the OECD-Toolbox and assumes that studies have been performed according to international guidelines or other methods scientifically accepted. weight of evidence experimental study **Test material** N-methylaniline (CAS NR 100-61-8, EC No 202-870-9) Reference ECHA CHEM (2024)
3	The bacterial reverse mutation assay – no data on guideline Test bacteria strains S. typhimurium TA 97, TA 98, TA 100 and TA 1535 (with and without met. act.) Test concentrations: 0, 10 - 10000 ug/plate No data on guideline	Test results with and without metabolic activation (S9): - negative for S. typhimurium TA 97, TA 98, TA 100 and TA 1535 cytotoxicity: not specified vehicle controls valid negative controls valid positive controls valid	Reliability 4 (not assignable as it is a review) weight of evidence experimental study **Test material** N-methylaniline Reference Zeiger et al. 1988

4	Unscheduled DNA synthesis in mammalian cells in vitro Hepatocytes: male ACI rat [primary culture] (met. act not applicable.) Test concentrations: 10.E-6, 10.E-5, 10.E-4 & 10.E-3 M Positive control substance(s): N-2-fluorenylacetamide according to guideline method of William et al. (1982); equivalent orimilar to guideline OECD Guideline 482 (Genetic Toxicology: DNA Damage and Repair, Unscheduled DNA Synthesis in Mammalian Cells In Vitro) [in vitro DNA damage and/or repair study (before 2 April 2014)]	Test results: negative for hepatocytes: male ACI rat [primary culture]; met. act.: not applicable genotoxicity: negative cytotoxicity: not specified vehicle controls valid negative controls: not specified positive controls valid	2 (reliable with restrictions) weight of evidence experimental study **Test material** N-methylaniline (CAS NR 100-61-8, EC No 202-870-9) Reference Yoshimi et al., 1988
5	***In vitro* mammalian chromosome aberration test** mammalian cell line: Chinese hamster lung (CHL/IU) Test concentrations: 0, 0.3, 0.6, 1.1 mg/ml (= 10 nM) with and without met. act. -S9 (continuous 24 and 48 hrs treatment) -S9 (short-term 6 hrs treatment) +S9 (short-term 6 hrs treatment) Positive control substance(s): -S9: Mitomycin C; +S9: Cyclophosphamide according to guideline JAPAN: Guidelines for Screening Mutagenicity Testing Of Chemicals Guideline study reported in Japanese with a summaryin English,	Test results; **All four relevant negative control groups:** no chromosomal structural aberrations were seen in any of 200 cells analysed in negative control groups **Without S9 (continuous 24 hrs treatment)** • **at 0.6 mg/ml:** 32 chromatid and/or chromosome gaps, 15 chromatid breaks, 28 chromatid exchanges, 10 multiple aberrations leading to total 85 aberrations in 200 analysed cells • **at 1.1 mg/l:** 6 chromatid and/or chromosome gaps, 16 chromatid breaks, 25 chromatid exchanges, 2 acentric fragment (chromatid type), 0 multiple aberrations leading to total 49 aberrations in 148 analysed cells **Without S9 (continuous 48 hrs treatment)** • **at 0.6 mg/ml:** 10 chromatid and/or chromosome gaps, 7 chromatid breaks, 33	2 (reliable with restrictions) key study experimental study **Test material** N-methylaniline purity 99.5%; N,N dimethylaniline (0.47%) and aniline (0.014%) were contained as impurities Reference ECHA CHEM (2024)

		chromatid exchanges, 2 acentric fragment (chromatid type), 10 multiple aberrations leading to total 63 aberrations in 200 analysed cells • **at 1.1 mg/l:** 38 chromatid and/or chromosome gaps, 37 chromatid breaks, 81 chromatid exchanges, 3 chromosome breaks, 1 chromosome exchange (dicentric and ring etc.) 2 acentric fragment (chromatid type), 60 multiple aberrations leading to total 222 aberrations in 192 analysed cells **positive control with mitomycin (MC) 0.0005 mg/ml:** relevant increase in number of chromatid and/or chromosome gaps, chromatid breaks, chromatid exchanges, chromosome breaks, chromosome exchange, acentric fragment (chromatid type), multiple aberrations leading to a total 191 aberrations after 24 hrs MC treatment and 251 aberrations after 48 hrs treatment in 200 analysed cells **Without S9 (short 6 hrs treatment)** • **at 0.6 mg/ml:** 1 chromatid and/or chromosome gap leading to total 1 aberrations in 200 analysed cells • **at 1.1 mg/l:** 3 chromatid and/or chromosome gaps, 0 chromatid breaks, 9 chromatid exchanges leading to total 12 aberrations in 200 analysed cells **With S9 (short 6 hrs treatment)** • **at 0.6 mg/ml:** 1 chromatid and/or chromosome gap, 3 chromatid breaks, 7 chromatid exchanges, 1 acentric fragment (chromatid type) leading to total 12 aberrations in 200 analysed cells • **at 1.1 mg/l:** 3 chromatid and/or	

		chromosome gaps, 11 chromatid breaks, 33 chromatid exchanges, 3 chromosome breaks, 10 multiple aberrations leading to total 57 aberrations in 177 analysed cells **Positive control with Cyclophosphamide (CPA) 0.005 mg/ml:** • **without S9 (short 6 hrs treatment):** 1 chromatid breaks, 3 chromatid exchanges leading to total 4 aberrations in 200 analysed cells • **with S9 (short 6 hrs treatment):** 8 chromatid and/or chromosome gaps, 5 chromatid breaks, 16 chromatid exchanges, 3 acentric fragment (chromatid type) leading to total 32 aberrations in 200 analysed cells **Cytotoxicity (expressed as a % of cell growth in parallel with negative control)**: • ***Continuous 48 hrs treatment with N-methylaniline without S9:*** significant cytotoxicity, 30 – 55% cell growth reduction compared to the control at conc. 0.1; 0.3; 0.6 and 1.1 mg/ml, respectively. • ***Short 6 hrs treatment with N-methylaniline without S9:*** lack of cytotoxicity: cell growth not reduced in comparison with the control. • ***Short 6 hrs treatment with N-methylaniline with S9:*** cytotoxicity, cell growth at conc. 0.3 mg/ml not reduced; at conc. 0.6 mg/ml reduced to ca. 90% of that in control, and at concentration of 1.1 mg/l to ca. 50% of that in control.	

		vehicle controls valid negative controls valid positive controls valid	
6	***In vitro* mammalian chromosome aberration test** mammalian cell line: Chinese hamster lung fibroblasts (V79) according to Guidelines for Screening Mutagenicity Testing of Chemicals (Chemical Substances Control Law of Japan)	The chromosomal aberration test with and without metabolic activation is positive for the test substance. No further details were provided.	secondary literature data based on the OECD toolbox Reliability 4 weight of evidence experimental study **Test material** N-methylaniline Reference Bogers 2010

Analysis of data

The Substance has been tested in several bacterial reverse mutagenicity assays (ECHA CHEM 2024, Zeiger et al. 1988). In each of these tests, the Substance did not increase the frequency of reverse mutations indicating that it is incapable of inducing gene mutations in bacteria. However, such a conclusion is highly uncertain because these studies are not fully reliable: full study reports are not available, it is not known whether they were performed in GLP conditions and a comparison of their methodology with relevant OECD guidelines is not possible.

No adequate *in vitro* gene mutation study in mammalian cells is available to conclude on gene mutations in mammalian cells in vitro.

The Substance does not induce unscheduled DNA synthesis (UDS) in mammalian cells *in vitro* (Yoshimi et al., 1988). However, full study report is not available, it is not known whether the study was performed in GLP conditions and a comparison of its methodology with relevant OECD guidelines is not possible. It is also noted that UDS is an indicator test that detects some DNA repair mechanisms (measured as unscheduled DNA synthesis in liver cells). However, it does not provide direct evidence of mutation. The UDS test is sensitive to some (but not all) DNA repair mechanisms and not all gene mutagens are positive in the UDS test.

The Substance, after continuous exposure of cells for 24 or 48 hours in *in vitro* conditions, without additional metabolic activation with S9 mix, at concentrations reducing the growth of cells, causes the chromosomal aberrations in mammalian cells cultivated from a cell line isolated from the lung of a female Chinese hamster (CHL/IU). At a concentration slightly reducing cell growth (by 10%) and with additional metabolic activation the Substance also induces chromosomal aberration in mammalian cells *in vitro* after 6 hours of exposure. An increase in the concentration of the Substance in cell culture induces a further increase in the frequency of chromosomal aberrations (ECHA CHEM, 2024). These data raise a concern for chromosome aberration in somatic cells *in vitro* conditions. This conclusion is supported by the results of another *in vitro* mammalian chromosome aberration test on Chinese hamster lung fibroblasts (V79) (Bogers, 2010), although a scanty description of results and lack of access to a full study report reduce the reliability of this study. However, no *in vivo* study to address the concern for chromosome aberration is available on the Substance.

Comparison with classification criteria

There is no mutagenicity test of the Substance under *in vivo* conditions, thus there is no

sufficient data for direct comparison with classification criteria for mutagenicity defined by CLP Regulation 1272/2008 since the *in vivo* assessment of mutagenicity is missing. Nevertheless, CLP Regulation notes that "*Substances which are positive in vitro mammalian mutagenicity assays, and which also show chemical structure-activity relationship to known germ cell mutagens, shall be considered for classification as Category 2 mutagens.".* Taking that statement into account the evaluating MSCA notes that the Substance is structurally related to and metabolised to aniline. Thus, hazardous properties of aniline could be used to predict the toxicity of the Substance as read-across appears to be plausible. The rationale for the choice of aniline for a read-across approach to predict the toxic properties of the Substance is based on:

- common functional group, being aniline (benzenamine)
- a fact that aniline is a metabolite of the Substance in mammalian and human tissue (Pelkonen *et al.* 1971; Stecca *et al*. 1992; ECHA CHEM, 2024; SCOEL, 2012), thus exposure to the Substance leads to occurrence of aniline in human tissues.

According to the EU RAR (2004) aniline, just like the Substance, is negative in routine bacterial mutation tests. In mammalian cell cultures, aniline caused chromosomal aberrations, sister chromatid exchanges, and possibly gene mutations. In general, stronger effects are induced in the presence of an exogenous metabolic activation system than without metabolic activation. *In vivo*, aniline is an inducer of micronuclei in mouse and rat bone marrow cells. Whereas in mice positive effects occur only at high doses in the toxic range, in rats a positive dose-related response can be seen in non-toxic doses. The mutagenicity of aniline *in vitro* and *in vivo* is supported by *in vivo* studies showing DNA strand breaks and DNA adducts in different organs. As a result of these data, aniline has harmonized classification as Muta. 2; H341. The evaluating MSCA notes that genotoxicity profiles of the Substance and aniline appears to be very similar based on the available *in vitro* data. They both are negative in bacterial mutation tests, but positive in chromosomal aberration assays in mammalian cell cultures *in vitro*.

The evaluating MSCA's conclusion

Taking into account that the Substance is clastogenic to mammalian cells in *in vitro* conditions and that aniline, a metabolite of the Substance, is clastogenic for mammalian cells under *in vivo* conditions, the evaluating MSCA considers that the criteria for classification in Category 2 defined in Regulation 1272/2008 are met, and the Substance warrants classification as Muta. 2; H341.

14.6. Carcinogenicity

There is no human data available on carcinogenicity of the Substance.

According to the review by SCOEL (2012), two old studies in which the carcinogenicity of the Substance was investigated are available.

Haemorrhagic foci in the liver, but no tumours in this or any other organ were found in 20 male and 20 female Osborne-Mendel rats after oral treatment with 0.06 % N-methylaniline-hydrochloride, i.e. hydrochloride salt of the Substance, in food for 272–758 days. No control group was described in this study (White and Mori-Chavez, 1952). Because of the short exposure period, small group size, and absence of a control group in the rat study, no definite conclusions can be drawn from these results.

In another study, 20 male and 20 female Swiss mice received the Substance in food (1 950 mg/kg food) for 28 weeks followed by a post-treatment period of 12 weeks. Results showed no significant difference in lung adenoma incidence between the treated and control groups. No other tumours were observed (Greenblatt et al 1971). However, the incidence of lung adenomas was increased significantly when the Substance-treated animals also received sodium nitrite ($NaNO_2$) at 0.1 % in drinking water 5 times/week (Greenblatt et al. 1971). It was determined that the Substance, as a secondary amine,

could be converted to corresponding N-nitroso compounds in certain conditions, leading to the formation of carcinogenic nitrosamines *in vivo*.

According to Material Safety Data Sheet (https://pubchem.ncbi.nlm.nih.gov/compound/N-Methyl-N-nitrosoaniline), N-Nitroso-N-methylaniline is an esophageal carcinogen in F344 rats. Attempts to detect the binding of N-nitroso-N-methylaniline to DNA or RNA have not been successful. N-nitroso-N-methylaniline is not mutagenic in the standard Ames bacterial assay, and it did not induce sister chromatid exchanges in mammalian cells. N-nitroso-N-methyl aniline forms the benzenediazonium ion (BDI) during metabolism. This ion has been known to react with aromatic amines, such as adenine, to form coupling products (https://pubchem.ncbi.nlm.nih.gov/compound/N-Methyl-N-nitrosoaniline).

The evaluating MSCA considers that the available data (White and Mori-Chavez, 1952; Greenblatt et al. 1971) are considered as not conclusive for assessment of carcinogenicity of the Substance.

The study of White and Mori-Chavez (1952) was performed without OECD guidelines, with one dose level (42 - 46 mg/kg bw/d) only, used without any justification, which most probably was inadequate to identify the principal target organs and toxic effects, with too small (20 instead of 50) number of animals, without positive or negative control. Thus, the study is considered unreliable for the assessment of carcinogenicity of N-methylaniline-hydrochloride.

The study of Greenblatt et al. (1971) is unreliable and not conclusive for the assessment of carcinogenicity of the Substance alone, because of the use of only one dose level (1950 mg/kg food), a small number of animals (20 instead of 50), short duration of the study (28 weeks instead of 18-24 months). On the other hand, this study reveals that dietary exposure of mice to the Substance in combination with their exposure to sodium nitrite (NaNO2) at 0.1 % in drinking water may cause an increase in the incidence of lung adenoma, most probably due to the formation of N-nitroso-N-methyl aniline.

Comparison with classification criteria

The analysis of existing studies allows for concluding that the Substance has not been adequately tested to reveal the potential carcinogenicity of that substance. However, two structural analogues of the Substance, namely aniline and dimethylaniline, have harmonised classification as Carc. 2, H351, according to Annex VI of Regulation 1272/2008. In addition, nitrobenzene, a metabolite of the Substance in dogs is also classified in Annex VI of Regulation 1272/2008 as Carc. 2, H351. Further, the evaluating MSCA notes that in line with point 3.6.2.2.7. of Regulation 1272/2008: *"A substance that has not been tested for carcinogenicity may in certain instances be classified in Category 1A, Category 1B or Category 2 based on tumour data from a structural analogue together with substantial support from consideration of other important factors such as formation of common significant metabolites."*

The evaluating MSCA considers that read-across from aniline, dimethylaniline and nitrobenzene is plausible to predict carcinogenic properties of the Substance based on the following rationale:

- N,N-dimethylaniline, aniline and nitrobenzene are structural analogues of the Substance;
- aniline is a metabolite of the Substance in mammalian and human tissue (Pelkonen *et al.*1971; Stecca *et al.* 1992; ECHA CHEM (2024), SCOEL, 2012);
- N,N-dimethylaniline is metabolized to the Substance by mammalian microsomes (Heimbrook et al. 1984, Pandey et al. 1989);
- nitrobenzene is a metabolite of the Substance in dogs (SCOEL, 2012).

According to the EU RAR Aniline (2004), aniline produced dose-dependently higher incidences of spleen sarcomas in males in two carcinogenicity studies in F344 rats. A few splenic tumours observed in female rats were also considered to be related to aniline

treatment. Aniline is genotoxic *in vivo* in rats and mice. However, other mechanisms are also possible to be involved in tumour development. It has not been possible to demonstrate a plausible mode of action indicating the existence of a threshold mechanism for the carcinogenicity of aniline (the EU RAR Aniline, 2004).

N,N- Dimethylaniline was tested for carcinogenicity when administered orally via gavage to mice (0, 15 and 30 mg/kg bw/day) and rats (0, 3 and 30 mg/kg bw/day) in separate carcinogenicity studies. Under the conditions of these 2-year gavage studies, there was some evidence of carcinogenic activity of N,N-dimethylaniline in male F344/N rats, as indicated by the increased incidences of sarcomas or osteosarcomas (combined) of the spleen. There was no evidence of carcinogenic activity of N, N-dimethylaniline in female F344/N rats given 3 or 30 mg/kg body weight/day by gavage for 2 years. There was no evidence of carcinogenic activity of N,N-dimethylaniline in male B6C3F1 mice given 15 or 30 mg/kg body weight by gavage for 2 years. There was equivocal evidence of carcinogenic activity of N,N-dimethylaniline in female B6C3F1 mice, as indicated by an increased incidence of squamous cell papillomas of the forestomach. Both rats and mice could have tolerated doses higher than those used in these studies (NTP, 1989; IARC, Vol. 57, 1993).

Nitrobenzene has not been studied for its carcinogenic effects in animals after oral or dermal exposure. The potential carcinogenicity of inhaled nitrobenzene has been evaluated following a 2-year exposure period in B6C3F1 mice, Fischer-344 rats and Sprague-Dawley rats. The mice were exposed to nitrobenzene vapour at concentrations 0, 0.005, 0.025, 0.13 and 0.26 mg/L (0, 1, 5, 25 and 50 ppm) for 6h/d, 5d/w for 107 weeks and the rats were exposed to nitrobenzene vapour at concentrations 0, 0.005, 0.025, 0.13 mg/L (0, 1, 5, 25 ppm) for 6h/d, 5d/w for 107 weeks. According to the RAC opinion (https://echa.europa.eu/documents/10162/193e8638-de87-1bf9-7452-64f6172aa433) adopted on 3 February 2012, the evidence of nitrobenzene carcinogenicity should be interpreted as limited because there was a significant increase in the frequency of benign neoplastic changes such as adenoma in lung and thyroid only in male mice, but not in female mice. The increase in mammary gland carcinoma in the highest group of female mice could not be supported by the results in the low-exposed group because they were not microscopically examined. The location of benign tumours in rats was different than in mice. They were located only in the liver of male F344 and CD rats, and in the kidneys of F344 rats, but not in female F344 rats. Hence, there is inconsistency in neoplastic responses between mice and rats and between females and males, which lowers the strength of evidence. Based on this limited evidence RAC concluded that nitrobenzene should be classified as Carc. 2; H351 Suspected of causing cancer.

The available data indicate that aniline which is a metabolite of the Substance, and N,N-dimethylaniline have a similar carcinogenicity profile. Both these substances induce sarcomas in the spleen of male rats after oral exposure, but in female rats to a much lesser degree (aniline) or not at all (N,N-dimethylaniline)

Nitrobenzene, a metabolite of the substance in dogs, has been demonstrated to induce adenomas in the lungs and thyroid of male mice, and benign tumours in the liver and kidney of male rats. Thus, the type and location of neoplasms are different than those induced by aniline and N,N-dimethylaniline.

The evaluating MSCA's conclusion

Based on the limited evidence of carcinogenicity of structural analogues and metabolites of the Substance, it can be inferred by read-across approach that N-methylaniline may also possess this property. Therefore, the evaluating MSCA considers that according to the criteria of Regulation 1272/2008 the Substance should be classified as Carc. 2; H351 Suspected of causing cancer.

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

Not in the scope of the evaluation.

14.8. Hazard assessment of physicochemical properties

Not in the scope of the evaluation.

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

Table 14.9-2 Overview of dose descriptors as result of hazard assessment

OVERVIEW OF DOSE DESCRIPTORS AS RESULT OF HAZARD ASSESSMENT				
Endpoint of concern	**Type of effect**	**Critical study(ies)**	**Corrected dose descriptor(s) (e.g. NOAEL, NOAEC)**	**Justification/ Remarks**
Repeated dose toxicity	Blood (adverse effects on hemoglobin and PCV with a treatment related increase of reticulocytes and bilirubin concentration) Spleen (histopathological changes in the spleens of rats exposed to the lowest concentration)	30 days inhalation study in rats (ECHA CHEM (2024)	LOAEC worker inhalation 6.68 mg/m^3	Study reliable without restrictions
			LOAEC general population inhalation 2.37 mg/m^3	Study reliable without restrictions
Repeated dose toxicity	Heamatology, organ weights (spleen, liver) and appearance (liver, kidneys), histopathology	28 days oral (gavage) study in rats (ECHA CHEM (2024)	NOAEL worker dermal 7 mg/kg bw	Study reliable with restrictions
			NOAEL general population dermal 5 mg/kg bw	

The evaluating MSCA has performed DNELs derivation for systemic effects, following the method proposed in the ECHA Guidance on information requirements and chemical safety assessment, Chapter R.8.

DNEL worker inhalation

The eMSCA has used LOAEC of 13.3 mg/m^3 from the 30-day inhalation rat study as a starting point.

The eMSCA has applied the correction of respiratory volume considering light activity and 8h exposure for a worker.

LOAECworker = 13.3 mg/m^3 x (6.7/10) x (6/8) = 6.68 mg/m^3

Overall Assessment Factor:450

AF for dose-response relationship: 3 (starting point is a LOAEL)

AF for the difference in duration of exposure: 6 (sub-acute study)

AF for interspecies differences (allometric scaling): 1 (allometric scaling)

AF for other interspecies differences: 2.5 (for remaining interspecies difference)

AF for intraspecies differences: 5 (worker DNEL)

AF for the quality of the whole database: 2 (taking into account completeness of the database - the assessment of mutagenicity and carcinogenicity has been completed by eMSCA based on read-across)

DNELworker for inhalation route derived by the eMSCA is 14.84 µg/m³ and is about 2 times higher than DNEL derived by the registrant.

DNEL worker dermal

The eMSCA has used NOAEL of 5 mg/kg bw from the 28-day oral rat study as a starting point.

The eMSCA corrected the starting point to adjust different exposure conditions of the animal experiment to the workplace of humans (7 days of exposure in the animal study vs. 5 days at the workplace). Dermal adsorption was considered by default equal to oral adsorption as a worst-case approach.

NOAELworker = 5 mg/kg bw x 1.4 = 7 mg/kg bw

Overall Assessment Factor: 600

AF for dose-response relationship: 1 (starting point is a NOAEL)

AF for the difference in duration of exposure: 6 (sub-acute study)

AF for interspecies differences (allometric scaling): 4 (from rats to humans)

AF for other interspecies differences: 2.5 (for remaining interspecies differences)

AF for intraspecies differences: 5 (worker DNEL)

AF for the quality of the whole database: 2 (taking into account completeness of the database - the assessment of mutagenicity and carcinogenicity has been completed by eMSCA based on read-across)

DNELworker for the dermal route derived by the eMSCA is 11.67 µg/kg bw/day and is about 5 times lower than DNEL derived by the registrant.

DNEL general population inhalation

The eMSCA has used LOAEC of 13.3 mg/m³ from the 30-day inhalation rat study as a starting point.

The eMSCA corrected the starting point to adjust the different days of exposure (5 days exposure in the animal study and 7 days exposure of consumers) and different hours of exposure (6 h rats vs. 24 h consumers).

LOAECcorrected = 13.3 mg/m^3 x (6/24) x (5/7) = 2.37 mg/m^3

Overall Assessment Factor: 900

AF for dose-response relationship: 3 (starting point is a LOAEL)

AF for the difference in duration of exposure: 6 (sub-acute study)

AF for interspecies differences (allometric scaling): 1 (allometric scaling)

AF for other interspecies differences: 2.5 (for remaining interspecies differences)

AF for intraspecies differences: 10 (general population DNEL)

AF for the quality of the whole database: 2 (taking into account completeness of the database - the assessment of mutagenicity and carcinogenicity has been completed by eMSCA based on read-across)

DNELgeneral population for the inhalation route derived by the eMSCA is 2.63 µg/m³ and is about 2 times higher than DNEL derived by the registrant.

DNEL general population dermal

The eMSCA has used NOAEL of 5 mg/kg bw from the 28-day oral rat study as a starting point. No correction factors was applied by the eMSCA.

Dermal adsorption was considered by default equal to oral adsorption as a worst-case approach.

NOAELgeneral population = 5 mg/kg bw

Overall Assessment Factor: 1200

AF for dose-response relationship: 1 (starting point is a NOAEL)

AF for the difference in duration of exposure: 6 (sub-acute study)

AF for interspecies differences (allometric scaling): 4 (from rats to humans)

AF for other interspecies differences: 2.5 (for remaining interspecies differences)

AF for intraspecies differences: 10 (general population DNEL)

AF for the quality of the whole database: 2 (taking into account completeness of the database - the assessment of mutagenicity and carcinogenicity has been completed by eMSCA based on read-across)

DNELgeneral population for the dermal route derived by the eMSCA is 4.17 µg/kg bw/day and is about 2 times lower than DNEL derived by the registrant.

DNEL general population oral

The eMSCA has used NOAEL of 5 mg/kg bw from the 28-day oral rat study as a starting point.

No correction factors were applied by the eMSCA.

Overall Assessment Factor: 1200

AF for dose-response relationship: 1 (starting point is a NOAEL)

AF for the difference in duration of exposure: 6 (sub-acute study)

AF for interspecies differences (allometric scaling): 4 (from rats to humans)

AF for other interspecies differences: 2.5 (for remaining interspecies differences)

AF for intraspecies differences: 10 (general population DNEL)

AF for the quality of the whole database: 2 (taking into account completeness of the database - the assessment of mutagenicity and carcinogenicity has been completed by eMSCA based on read-across)

DNELgeneral population for the oral route derived by the eMSCA is 4.17 µg/kg bw/day and is about 2 times lower than DNEL derived by the registrant.

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

The Substance was selected for substance evaluation due to concerns about carcinogenicity and mutagenicity.

During the evaluation the Member State has come to the following conclusions based on the available data:

Mutagenicity
Several *in vitro* studies were conducted on the Substance. There are no mutagenicity tests of the Substance in *in vivo* conditions available. Based on the CLP Regulation guidelines on similarity to the known mutagens and structural similarity of the Substance with aniline, the metabolite of N-methylaniline, the evaluating MSCA considers that by using a read-across approach the criteria for classification in Category 2 defined in the Regulation 1272/2008 are met. Thus, the Substance warrants the classification as Muta. 2; H341 (suspected of causing genetic defects).

Carcinogenicity
There is no human data available on the carcinogenicity of the Substance, and animal studies do not provide clear conclusions regarding the carcinogenicity. However, two structural analogues of the Substance, aniline and dimethylaniline, and nitrobenzene detected following i.v. administration of the Substance in dogs – have harmonized classification as Carc. 2, H351 according to Annex VI of the Regulation 1272/2008. Aniline, a metabolite of the Substance, and N,N-dimethylaniline, a structural analogue of the Substance, have a similar carcinogenicity profile. Both these substances induce sarcomas in the spleen of male rats after oral exposure, but in female rats to a much lesser degree (aniline) or not at all (N,N-dimethylaniline). Nitrobenzene has been demonstrated to induce adenomas in the lungs and thyroid of male mice, and benign tumours in the liver and kidney of male rats.

Based on the limited evidence of carcinogenicity of structural analogues and metabolites of N,N-dimethylaniline, the evaluating MSCA considers that read-across approach is plausible also for this hazard property. Thus, in line with the criteria of Regulation 1272/2008, the Substance warrants classification as Carc. 2; H351 (Suspected of causing cancer).

15. Endocrine disrupting (ED) properties assessment

Not in the scope of the evaluation.

16. PBT/vPvB and PMT/vPvM assessment

Not in the scope of the evaluation.

17. Exposure assessment

17.1. Human health

17.1.1. Worker

The evaluating MSCA expresses multiple concerns regarding the quantitative assessment of inhalation and dermal exposure for workers provided by the registrants. In most exposure scenarios provided by the registrant, there are no estimations for a full work shift. The evaluating MSCA doubts that every task is performed by different workers.

The evaluating MSCA notes that an 8-hour time-weighted average will be higher than the value estimated for one task, and it may lead to an unacceptable level of exposure. Therefore, the evaluating MSCA recommends the registrant revise its exposure assessment. Moreover, it is unclear if contributing scenarios cover an expected exposure related to the cleaning and maintenance of equipment.

Given the above, the evaluating MSCA recommends correction to include consideration of equipment cleaning and maintenance scenarios, if applicable, and estimation of combined exposure for the full work shift. The evaluating MSCA notes that revised exposure assessment may result in higher estimated values leading, in consequence, to an unacceptable level of exposure that requires further risk management measures to be considered by the registrant.

17.1.2. Consumer

The evaluating MSCA has recalculated the exposure and risk assessment provided by the registrant by using the model Consumer ECETOC TRA v3.1 for inhalation and dermal exposure.

The following input parameters were used for the ECETOC TRA assessment CONCAWE_SCED_13_1_a_v2: Fuels, Liquid, Automotive Refuelling:

- amount of product used per application (g/event): 37500 (based on 50 L fuel dispensed and density of 750 g/L. Value is consistent with reported refuelling amounts: 90th percentile of 53 L and the average of 30 L)[2]
- inhalation and dermal transfer factor: 0.002
- skin contact area (cm2): 210
- exposure time per event (hr): 0.05
- frequency of use over a year (times/year): 52
- frequency of use over a day: 1
- place of use: outdoor
- product ingredient fraction (by weight): 0.001 (based on data provided by the registrant).

Inhalation exposure calculated by the evaluating MSCA is more than 100 times higher than the exposure estimation provided by the registrant. Therefore, the evaluating MSCA recommends that the registrant should revise its exposure assessment.

17.2. Environment

Not in the scope of the evaluation.

17.3. Combined exposure assessment

Exposure via environment was not in the scope of the evaluation thus combined exposure has not been evaluated.

[2] https://echa.europa.eu/documents/10162/2777298/concawe_sceds_v2-1_2017_en.pdf/c48af5f9-d5b3-fe06-6ad9-e221ef0d9574?t=1599670375593

18. Risk characterisation

Workers

The evaluating MSCA considers that the quantitative risk characterisation needs to be revised by the registrants in the CSRs as a consequence of the recommended revision of the exposure assessment (see section 17.1.1).

Additionally, the DNEL values derived by the evaluating MSCA for workers for the dermal route are lower than DNELs derived by the registrant. If these DNEL values are used in the risk assessment, the RCR values become significantly high (above 2) for some contributing scenarios.

Moreover, the evaluating MSCA's identification of the need to classify the Substance as carcinogenic (Carc. 2, H351) and mutagenic (Muta. 2; H341) may be the most critical, leading to the lowest hazard reference levels for risk characterisation, which should be considered. However, DMELs (non-threshold carcinogen) or DNELs (threshold carcinogen) to describe the likelihood of risks to workers concerning the carcinogenic potential of the Substance were not derived.

Therefore, if the carcinogenicity of the Substance is confirmed, the registrant should consider further risk management measures.

Consumers

DNELs for the general population for oral and dermal routes derived by the evaluating MSCA are lower than DNELs derived by the registrant.

The evaluating MSCA has recalculated the exposure and risk assessment provided by the registrant by using the model Consumer ECETOC TRA v3.1. Inhalation exposure calculated by the evaluating MSCA is more than 100 times higher than the exposure estimation provided by the registrant (see section 17.1.2).

As a consequence, the RCR for inhalation exposure calculated by the evaluating MSCA is more than 100 times higher than the RCR provided by the registrant. The risk characterisation performed by evaluating MSCA shows that risk for consumers arising from the use of products containing the Substance is not adequately controlled.

Moreover, the evaluating MSCA's identification of the need to classify the Substance as carcinogenic (Carc. 2, H351) and mutagenic (Muta. 2; H341) may be the most critical, leading to the lowest hazard reference levels for risk characterisation, which should be considered. However, DMELs (non-threshold carcinogen) or DNELs (threshold carcinogen) to describe the likelihood of risks to the general population concerning the carcinogenic potential of the Substance were not derived.

Therefore, if the carcinogenicity of the Substance is confirmed, the registrant should consider further risk management measures.

The evaluating MSCA considers that the quantitative risk characterisation needs to be revised by the registrants in the CSRs.

19. References

Armstrong P, Hollenberg P (1989). Oxidative N-demethylation of N,N-dimethylaniline by purified isozymes of cytochrome P-450. Biochemical Pharmacology, Volume 38, Issue 13: 2181-2185.

ECHA CHEM (2024): https://chem.echa.europa.eu/100.002.610/overview

Greenblatt M, Mirvish S (1971). Nitrosamine studies: induction of lung adenomas by concurrent administration of sodium nitrite and secondary amines in Swiss mice. J Natl Cancer Inst. May;46(5):1029-34.

Handbook of Intermediary Metabolism of Aromatic Compounds Recommendation from the Scientific Committe / Scientific Committee on Occupational Exposure Limits/review article or handbook, 2012.

Heimbrook D.C., MurrayR.I., Egeberg K.D., Sliga S.G., Nee M.W., and Bruice T.C.. (1984). Demethylation of N,N-dimethylaniline and p-cyano-N,N-dimethylaniline and their N-oxides by cytochromes P450LM2 and P450CAM. J. Am. Chem. Soc., 106, 5, 1514–1515.

IARC Monographs on the evaluation of carcinogenic risks to humans (1993), World Health Organization, vol. 3.

Miller et al (2001), Estrogenic Activity of Phenolic Additives Determined by an In Vitro Yeast Bioassay. Environ Health Perspect 109(2), pp. 133-137.

National Library of Medicine HSDB Database (2009). N-METHYLANILINE. http: //toxnet. nlm. nih. gov/cgi-bin/sis/search/a?dbs+hsdb: @term+@DOCNO+1654.

NTP Technical Report on the Toxicology and Carcinogenesis Studies of N,N-Dimethylaniline (CAS NO. 121-69-7) in F344/N rats and B6C3F1 mice (gavage studies), NTP TR 360 (1989), NIH Publication No.90-2815.

OECD-Toolbox (2009). AMES mutagenity testing with N-Methylaniline. Danish EPA; Japan EXCHEM; OASIS Genotox.

Pandey, RN., Armstrong, AP. & Hollenberg, P.F. (1989) Oxdative N-demethylation of N,N-dimethylanilne by purified isozymes of cytochrome P-450. Biochem. Phannacol., 38, 2181-2185.

Pelkonen O, Arvela P and Karki NT (1971). 3,Q-Benzpyrene and N-Methylaniline Metabolizing Enzymes in the Immature Human Foetus and Placenta. Acta Pharmacol. et Toxicol., 30, 385-395.

Recommendation from the Scientific Committee on Occupational Exposure Limits for N-Methylaniline, SCOEL/SUM/178 December 2012.

Stecca C, Cumps J and Duverger-Van Bogaert M (1992). Enzymic N-Demethylation Reaction Catalysed By Red Blood Cell Cytosol. Biochemical Pharmacology. Vol. 43. No. 2, pp. 207 - 211.White J, Mori-Chavez P (1952). Acute necrotizing renal papillitis experimentally produced in rats fed mono-N-methylaniline. J Natl Cancer Inst. 12(4):777-87.

Yoshimi Naoki, Shigeyuki Sugie, Hitoshi Iwata, Kenji Niwa, Hideki Mori, Chise Hashida and Hidesuke Shimizu (1988). The genotoxicity of a variety of aniline derivatives in a DNA repair test with primary culture rat hepatocytes. Mutation Research, 206 (1988) 183-191.

Zeiger E., Anderson B., Haworth S., Lawlor T., Mortelmans K. (1988). Salmonella mutagenicity tests: iv. results from the testing of 300 chemicals, Environ. Mol. Mutagen.

11(SUPPL.12):1-158.

20. Abbreviations

BPR	Biocidal products regulation (EU) 528/2012
CAS RN	CAS registry number
CCH	Compliance check
CLP	Classification, labelling and packaging
CoRAP	Community rolling action plan
DMEL	Derived minimal effect level
DNEL	Derived no-effect level
EC	European community
ECHA	European chemicals agency
ED	Endocrine disruption
EU	European union
MSCA	Member state competent authority
NOAEC	No observed adverse effect concentration
NOAEL	No observed adverse effect level
NONs	Notification of new substances
OECD	Organisation for economic co-operation and development
PBT	Persistent, bioaccumulative and toxic
PMT	Persistent, mobile, and toxic
PNEC	Predicted no-effect concentration
POP	Persistent organic pollutants
PPP	Plant protection products regulation EC 1107/2009
QSAR	Quantitative structure-activity relationship
RAR	Risk assessment report
REACH	Regulation No 1907/2006 concerning registration, evaluation, authorisation, and restriction of chemicals
STOT RE	Specific target organ toxicity – repeated exposure
STOT SE	Specific target organ toxicity – single exposure
SVHC	Substances of very high concern
TG	Test guideline
TGD	Technical guidance document
TPE	Testing proposal examination
UNEP	United nations environment program
UVCB	Unknown or variable composition, complex reaction products or of biological materials.
vPvB	Very persistent and very bioaccumulative
vPvM	Very persistent and very mobile