SUBSTANCE EVALUATION CONCLUSION

as required by REACH Article 48

and

EVALUATION REPORT

for

N-1-naphthylaniline

EC No 201-983-0

CAS No 90-30-2

Evaluating Member State(s): Germany

Dated: July 2022

Template Version 2.1
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Evaluating Member State Competent Authority

BAuA
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Year of evaluation in CoRAP: 2012

Before concluding the substance evaluation, two consecutive Decisions to request further information were issued on: 14 May 2014 and 14 November 2019.

Further information on registered substances here:

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

DISCLAIMER

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 registrants concerning the substance. If the evaluating Member State concludes that no further information needs to be requested, the substance evaluation is completed. If additional information is required, this is sought by the evaluating Member State. The evaluating Member State then draws conclusions on how to use the existing and obtained information for the safe use of the substance.

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

With this Conclusion document the substance evaluation process is finished and the Commission, the registrants 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

N-1-Naphthylaniline (NPNA; EC No. 201-983-0, CAS RN 90-30-2,) was originally selected for substance evaluation in order to clarify concerns about:

- Suspected PBT/vPvB properties
- Wide dispersive use

During the evaluation, additional concerns were identified:

- Carcinogenicity (External formation of a carcinogenic transformation product (corresponding N-nitrosoamine of NPNA))
- Repeated dose toxicity (neurotoxicity and haematotoxicity)
- Reproductive toxicity
- Dermal exposure of consumers.

2. OVERVIEW OF OTHER PROCESSES / EU LEGISLATION

Following the substance evaluation of NPNA, the evaluating Member State Competent Authority (eMSCA) initiated the preparation of a dossier for harmonised classification and labelling (CLH) which has been logged in May 2019 into ECHA's corresponding Registry of Intentions (RoI).[2] The proposal has been submitted to ECHA on 14 April 2022.

3. CONCLUSION OF SUBSTANCE EVALUATION

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

Table 1

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

4. FOLLOW-UP AT EU LEVEL

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

4.1.1. Harmonised Classification and Labelling

NPNA meets the criteria for classification as Acute Tox. 4, H302 (Harmful if swallowed), and Skin Sens. 1, H317 (May cause an allergic skin reaction).
Due to the severity of adverse effects that the Substance can cause, especially regarding skin sensitisation, as well as due to the noticed inconsistencies in self-classification among

[2] ECHA CLH RoI entry on NPNA: https://echa.europa.eu/de/registry-of-clh-intentions-until-outcome/-/dislist/details/0b0236e18391641f

C&L notifiers, the eMSCA considers justified and proposes an harmonised classification for NPNA, leading to a new entry in CLP-Annex VI . A respective proposal for harmonised classification of NPNA was submitted to ECHA on 14 April 2022.

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

Not applicable.

4.1.3. Restriction

Not applicable.

4.1.4. Other EU-wide regulatory risk management measures

Not applicable.

5. CURRENTLY NO FOLLOW-UP FORESEEN AT EU LEVEL

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

Not applicable.

5.2. Other actions

Not applicable.

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

Indication of a tentative plan is not a formal commitment by the eMSCA. 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 (RoI).

Table 2

FOLLOW-UP		
Follow-up action	**Date**	**Actor**
Harmonised Classification and Labelling	Dossier submitted to ECHA in April 2022.	Germany

Part B. Substance evaluation

7. EVALUATION REPORT

7.1. Overview of the substance evaluation performed

N-1-Naphthylaniline (NPNA; EC No. 201-983-0, CAS RN 90-30-2,) was originally selected for substance evaluation in order to clarify concerns about:

- Suspected PBT/vPvB properties
- Wide dispersive use.

During the evaluation, additional concerns were identified:

- Carcinogenicity (External formation of a carcinogenic transformation product (corresponding N-nitrosoamine of NPNA))
- Repeated dose toxicity (neurotoxicity and haematotoxicity)
- Reproductive toxicity
- Dermal exposure of consumers.

Table 3

EVALUATED ENDPOINTS	
Endpoint evaluated	**Outcome / conclusion**
Suspected PBT/vPvB properties	Concern refuted. Based on the available information, NPNA does not fulfil the B criterion according to Annex XIII REACH. Hence, the eMSCA does not consider the substance as PBT or vPvB.
Persistency	Concern unresolved. No up-to-date simulation test on degradation is available: NPNA is neither readily biodegradable nor highly insoluble in water to justify waiving this information requirement. Request of a simulation test on degradation in water and sediment under substance evaluation would not alter the initial PBT concern since the B criterion is not fulfilled.
Bioaccumulation potential	Concern refuted. In one available bioaccumulation study on NPNA, BCFs over 2000 were reached. However, these BCFs were measured following a decrease in bioaccumulation. These results indicate a metabolisation of NPNA. The degradation product probably is a hydroxyl derivate of NPNA which is probably more hydrophilic than the parent. Hence, the potential of bioaccumulation declines. Based on this consideration, the eMSCA does not consider the B criterion according to Annex XIII fulfilled for NPNA.
Ecotoxicity	Concern confirmed. There are additional published data concerning short term toxicity to fish and daphnia and toxicity to algae. The neglected study on toxicity to algae yielded a lower NOEC than used for the hazard assessment conducted by the registrants. The eMSCA considers the current self-classification with respect to aquatic toxicity as sufficiently protective but recommends updating of the risk assessment based on the MITI data.
Wide dispersive use	Concern refuted. The Substance is used as an antioxidant in rubber and, on itself, is used by workers. Consumers are exposed to the Substance during article service life.

EVALUATED ENDPOINTS	
Endpoint evaluated	**Outcome / conclusion**
Worker exposure	Concern resolved. The initial concern regarding worker exposure information was addressed in the first Decision: the registrants provided higher tier exposure assessments for all dermal and inhalation exposure scenarios, including scenarios at elevated temperature, with short-term exposure and the use of NPNA in metal working fluids involving moving objects. The updated CSR also included the required specifications (material, thickness, breakthrough and use time) for gloves and respiratory protection. The registrants also demonstrated that the generation of N-nitroso-NPNA is not a critical factor. On this basis, an adequate exposure assessment was possible for some scenarios.
Consumer exposure – dermal exposure	Concern resolved. Inconsistent and missing information regarding consumer products led to requests expressed in the first Decision. Exposure scenarios for rubber articles were provided by the registrants. Based on this information in the CSR, the safe use for consumers could not be demonstrated. Refinement of the exposure assessment by considering information about skin absorption clarified the concern of dermal exposure regarding the consumer articles reported in the CSR. No risks could be identified for the evaluated dermal exposure scenarios.
Carcinogenicity (External formation of nitrosamine transformation product)	Concern unresolved. Based on monitoring information provided by the registrants after the first Decision, external formation of N-nitrosamine is not considered a critical factor during the use of NPNA. However, no guideline-conform carcinogenicity study is available. Thus, if the tonnage increases, exceeding 1000 t/a, a carcinogenicity study “shall be proposed by the registrants or may be required by the Agency in accordance with Article 40 or 41 and Annex X (section 8.6.3. and/or 8.9.1)” of REACH. The eMSCA will then be ready to re-assess this endpoint based on the additional data.
Repeated dose toxicity – Neurotoxicity	Concern refuted. NPNA is not considered to be neurotoxic based on the data provided by the registrants as a result of the first Decision.
Repeated dose toxicity – haematotoxicity, liver toxicity	Concern confirmed. The Substance elicits haemolytic anaemia and liver toxicity after repeated dosing, but data is considered borderline for classification according to CLP, particularly with regards to effect severity and effective dose levels. Therefore, classification of NPNA for STOT RE is not proposed. Nevertheless, data will be included in the CLH proposal prepared by the eMSCA for transparency reasons.
Reproductive toxicity	Concern unresolved. Based on the available data, incl. data that were provided by the registrants after the first Decision, NPNA is currently not considered to be a reproductive toxicant. However it is noted that data, particularly with regards to fertility effects, are insufficient to draw a final conclusion. Thus, in case the tonnage increases, exceeding 1000 t/a, an EOGRTS “shall be proposed by the registrants or may be required by the Agency in accordance with Article 40 or 41 and Annex X (section 8.7.3.)” of REACH. In this case, the eMSCA will be ready to re-assess this endpoint based on the additional data.

EVALUATED ENDPOINTS	
Endpoint evaluated	**Outcome / conclusion**
Additional endpoints evaluated	
Acute Toxicity	Classification as Acute Tox. 4, H302 (Harmful if swallowed), according to CLP is warranted. Harmonised C&L process initiated by the eMSCA.
Skin Sensitisation	Classification as Skin Sens. 1, H317 (May cause an allergic skin reaction), according to CLP is warranted. Harmonised C&L process initiated by the eMSCA.
Mutagenicity	Based on a weight-of-evidence assessment of the available information, the eMSCA supports the conclusion of the registrants that NPNA is not mutagenic. It is noted, however, that none of the available studies were carried out in accordance with the corresponding EU/OECD TG.

7.2. Procedure

On the basis of an opinion of the ECHA Member State Committee (MSC) and due to initial grounds for concern relating to suspected PBT properties and wide dispersive use, NPNA was included in the Community rolling action plan (CoRAP) for substance evaluation to be evaluated in 2012 with Germany acting as the evaluating Member State Competent Authority (eMSCA). The updated CoRAP was published on the ECHA website on 29 February 2012 and the Substance Evaluation (SEv) started.

Additional concerns on human health, specifically the unacceptable read across approach to diphenylamine proposed by the registrants (apart from the structural similarity, the physicochemical and toxicological properties of source and target compounds are insufficiently similar to justify the proposed read-across approach). Therefore the missing information on reproductive toxicity and repeated dose toxicity (90-days) were addressed in a first Decision[3]. The registrants provided the missing information in form of original study data. In view of the eMSCA, the information provided by the registrants met the requirements of Annex IX of REACH. A thorough literature search (until January 2021) revealed an additional relevant subacute (28 days) toxicity study performed with NPNA (Tanabe et al., 2017) which was also included in the follow-up evaluation.

Based on this new data set, classification and labelling of NPNA is deemed necessary (see Section 3). Due to the severity of adverse effects caused by NPNA, especially regarding skin sensitisation, as well as due to inconsistencies in self-classifications among C&L notifiers, harmonised classification for NPNA leading to a new entry in CLP-Annex VI is proposed and considered justified.

After the evaluation of the information submitted by the registrants upon the first Decision and subsequent risk characterisation, an additional concern was identified for NPNA. Due to a lack of relevant dermal absorption data, the eMSCA calculated the dermal DNELs for NPNA based on a conservative assumption (i.e. dermal absorption was assumed to be equal to the oral absorption (~50%)). As a consequence, the risk characterisation for each considered exposure scenario with regards to systemic effects after infrequent and long-term dermal exposure of consumers and workers yielded RCR values >1. Consequently in order to refine risk characterisation, the eMSCA requested additional data on dermal absorption of NPNA in a second Decision[4], specifically asking for an *in vitro* skin absorption test (OECD TG 428) using human skin samples and several different relevant in-use formulations of NPNA alongside the neat substance.

[3] Decision on substance evaluation for NPNA dated 14 May 2014 ("first Decision"): https://echa.europa.eu/documents/10162/302da1e8-d3c8-bf3f-a9b5-fdf01842aa67

[4] Decision on substance evaluation for NPNA dated 14 November 2019 ("second Decision"): https://echa.europa.eu/documents/10162/6ef868c3-c9af-3066-ebd8-c88d11104d51

After receiving this additional data (including the original study report), a detailed evaluation revealed shortcomings in the execution of the dermal absorption test (exposure duration of 8 h instead of 24 h, as requested in the second Decision). The eMSCA, thus, considers the provided study as incompliant with the study request as expressed in the Decision. Nevertheless, the new data may be used for DNEL derivation and subsequent risk characterisation when applying a conservative approach (see Section 227.9.1). By implementing this approach, no risks were identified for any of the calculated dermal exposure scenarios for consumers (see Section 7.13.1.2). Only for one combined scenario (i.e. inhalation and dermal exposure combined), an RCR value slightly above 1 was derived.

The eMSCA highlights that in case the annual tonnage of NPNA will exceed 1000 t/a in the future, the endpoints reproductive toxicity and carcinogenicity must be re-examined. In that case, an EOGRTS and a carcinogenicity study, respectively, shall be proposed by the registrants or may be required by the Agency in accordance with Article 40 or 41 and Annex X of the REACH Regulation (see Section 3). In that case, the eMSCA will be ready to re-assess these endpoints based on such additional data.

The initial concerns regarding worker exposure information were addressed in the first Decision and the registrants provided higher tier exposure assessments for all dermal and inhalation exposure scenarios, including scenarios at elevated temperature, with short term exposure and the use of NPNA in metal working fluids involving moving objects. The updated CSR also included the required specifications (material, thickness, breakthrough and use time) for gloves and respiratory protection. The registrants also demonstrated that the generation of N-nitroso-NPNA is not a critical factor. On this basis, an adequate exposure assessment was possible for some scenarios.

Inconsistencies and data gaps in the CSR regarding consumer exposure led the eMSCA to consider that risks could be expected, and further information was requested in a first Decision. Although no consumer uses were identified, NPNA was addressed in the CSR and in its Technical Data Sheet as ingredient in products (PC24: Lubricants, greases, release products; AC10: rubber products) which might be used by consumers.

After the first SEv decision on NPNA (issued on 14 May 2014), the registrants removed the information regarding PC24 from their updated CSR and provided in July 2017 (for the first time) exposure scenarios for rubber articles (AC10). After the evaluation of these scenarios, the eMSCA concluded that the calculated RCRs were above 1. For further refinement of exposure, additional information was necessary.

The initial concern for suspected PBT properties was based on a PBT screening of substances registered in 2010. NPNA fulfills the screening PBT criteria. Accordingly, the evaluation was targeted to the persistency (P criterion), the bioaccumulation potential (B criterion) and toxicity (T criterion) of NPNA. As the T criterion with regards to ecotoxicity is based on an aquatic NOEC for pelagic organisms, the terrestrial compartment and terrestrial toxicity was not subject of this substance evaluation. Additionally, endpoints referring to ecotoxicity data (PNEC and PEC/PNEC-ratio) were checked but not evaluated in detail.

The eMSCA concluded its evaluation in 2022 based on the new information provided by the registrants.

7.3. Identity of the substance

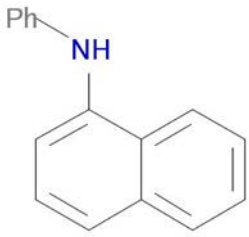
Table 4

SUBSTANCE IDENTITY	
Public name:	N-1-naphthylaniline
EC number:	201-983-0
CAS number:	90-30-2
Index number in Annex VI of the CLP Regulation:	-

Molecular formula:	$C_{16}H_{13}N$
Molecular weight range:	219.28 g/mol
Synonyms:	1-Naphthyl(phenyl)amin, *N*-Phenyl-α-naphthylamin, *N*-(1-Naphthyl)anilin, 1-(Phenylamino)naphthalin, 1-Anilinonaphthalin, PANA, PAN, NPNA

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

Structural formula:



7.4. Physico-chemical properties

Table 5

OVERVIEW OF PHYSICOCHEMICAL PROPERTIES	
Property	**Value**
Physical state at 20°C and 101.3 kPa	crystalline flakes or pellets; lemon to tan, discolours to dark brown or purple in air; pungent odour
Vapour pressure	0.0011 Pa at 20°C
Water solubility	3 mg/L at 20°C
Partition coefficient n-octanol/water (Log K_{ow})	4.28
Granulometry	D50: 73.49 µm (laser diffractometry) Maximum at 100 µm, mostly accompanied by a co-maximum at 1000 µm (agglomeration).
Stability in organic solvents and identity of relevant degradation products	Good solubility in most organic solvents (e.g. benzene, methylene chloride, acetone and ethanol), soluble in petrol.
Dissociation constant	4.93 at 25°C
Melting/freezing point	62°C
Boiling point	335°C at 558 mm Hg (equivalent to 744 hPa)

7.5. Manufacture and uses

7.5.1. Quantities

Table 6

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

In addition, NPNA was separately registered as an intermediate.
However, this registration is no longer valid as the sole registrant ceased manufacture in July 2018 after receipt of a draft evaluation decision.

7.5.2. Overview of uses

The registered substance is not manufactured in the EU and no details on the manufacturing process are presented here. According to RÖMPP-Online (Roempp online, 2007) NPNA can be manufactured from 1-naphthol and aniline or 1-naphthylamine and aniline at 300 °C on an aluminium-oxide catalyst.

NPNA is used as an antioxidant in hydraulic, lubrication, gearbox- and bearing oils and as antioxidant or protective agent/stabiliser in rubber (Roempp online, 2007; WHO, 1998). It is mainly used in stressed rubber articles like rolls/drums, conveyor belts, rubber seals, shoe parts (Roempp online, 2007) and several other rubber products (INFU, 2012). It is also used in synthetic oils for jet engines (Winder, 2006).

Information on identified uses was provided by the registrants using a general description of the use (*e.g.* industrial formulation) and the descriptor system described in REACH Guidance chapter R.12 (ECHA, 2010a). According to the disseminated information on ECHA's database on NPNA (last accessed 19 January 2022), the Substance is not registered for consumer use. However there is evidence indicating relevance of article service life for NPNA.

According to the Technical Data Sheet of Rhenofit PAN (TDS Rhenofit PAN, 2012[5]) the chemical is effective against oxidation and heat. It affords excellent protection from rubber poisons and is very suitable for vulcanisates based on polychloroprene that are exposed to heat. Rhenofit PAN can be used "*for articles subjected to heavy dynamic stressing, e.g. tires, conveyor belts, transmission belts and buffers and also for soles, heels, boots, hoses, extrudates, rollers, roller covers, etc.*"

The recommended dosage based on 100 parts per hundred rubber (phr) is
- as antioxidant: 0.75-1.75 phr Rhenofit PAN
- as antioxidant (particularly for CR vulcanisates): 1.0-2.0 phr Rhenofit PAN
- as anti-flexcracking agent: 1.0-3.0 phr Rhenofit PAN
- or 1.0-3.5 phr Rhenofit PAN and Vulkanox 4010 NA (1:1)

"The chemical may also migrate into materials the article is in contact (e.g. into plastics, paintwork or other rubber goods). These materials may be discoloured through mere contact or - after contact - through exposure to light."

According the Technical Data Sheet of Additin RC 7130 (TDS Additin RC 7130, 2012[6]), it is used as an "antioxidant with a broad field of application", e.g. "*hydraulic fluids, turbine- and compressor oils, gear oils, greases, and jet turbine oils (synthetic ester) […]. This*

[5] https://rch.lanxess.com/product/rhenofit-pan-5?lang=en (accessed in February 2022)
[6] https://petrico.com/wp-content/uploads/2019/03/RC7130.pdf (accessed in February 2022)

product is acceptable as an ingredient for use in lubricants with incidental food contact (HX-1) for use in and around food processing areas."

Only limited further information on consumer uses is available. The Hazard Substance Data Bank (HSDB 2012) also indicates the use of NPNA as an antioxidant in gear, hydraulic, lubrication, and bearing oils and as a protective agent and antioxidant in rubbers and rubber mixtures, including tires and as a thermostabiliser for vulcanisates and polyethylene.

The SPIN database (2012) recorded "one or several uses indicate a probable exposure" with an "intermediate range of applications". It is mainly listed as "hydraulic fluids and additives" and "lubricants and additives". Entries from 2008 listed furthermore the use as "cutting fluids" and "paints, lacquers and varnishes". NPNA was measured in artificial turf which was manufactured using recycled car tyres (Nilsson et al., 2008).
The application in consumer articles is foreseen according the Technical Data Sheet. In conclusion, it can be assumed that consumer articles contain NPNA.
In line with this information the registrants provided consumer exposure scenarios for rubber articles in July 2017.
The following information from the registration dossier(s) on uses in industrial settings has been disseminated on ECHA's website (last accessed 21 September 2021).

Table 7

USES OF NPNA	
	Use(s)
Formulation	General Rubber Goods Manufacturing Process – Mixing (PROC 5, PROC 8b, PROC 9) Industrial formulation (PROC1, PROC 2, PROC 3, PROC 4, PROC 5, PROC 8a, PROC 8b, PROC 9, PROC 15) Handling and dilution of metalworking fluid concentrates (PROC 1, PROC 2, PROC 5, PROC 8b) General Rubber Goods Manufacturing Process – Strorage (PROCX 8b, PROC 9) Industrial formulation of lubricant additives, lubricants and greases. Includes material transfers, mixing, large and small scale packing, sampling, maintenance and associated laboratory activities. (PROC 1, PROC 2, PROC 3, PROC 4, PROC 5, PROC 8a, PROC 8b, PROC 9, PROC 15) General Rubber Goods Manufacturing Process – Curing (PROC 14) General Rubber Goods Manufacturing Process – Shaping (PROC 21) ATIEL-ATC Group A [i]: Industrial formulation of lubricant additives, lubricants and greases. Includes material transfers, mixing, large and small scale packing, sampling, maintenance and associated laboratory activities. (PROC 1, PROC 2, PROC 3, PROC 5, PROC 8a, PROP 8b, PROC 9, PROC 15) ETRMA 1: Formulation - General rubber goods (PROC 5, PROC 8a, PROC 8b, PROC 9, PROC 14, PROC 21) General Rubber Goods Manufacturing Process - Filling/Weighing (PROC 9) ATIEL-ATC Group E [i]: (Industrial) Handling and dilution of metalworking fluid concentrates (PROC 1, PROC 2, PROC 5, PROC 8b)
Uses at industrial sites	(Industrial) Use in high energy open processes (PROC 1, PROC 2, PROC 8b, PROC 17) General industrial use of lubricants and greases in vehicles or machinery. Includes filling and draining of containers and enclosed machinery (including engines) (PROC 1, PROC 2, PROC 8b, PROC 9) ATIEL-ATC Group D [i]: (Industrial) Use of lubricants in open high temperature processes, e.g. quenching fluids, glass release agents (PROC 1, PROC 2, PROC 8b, PROC 13) General Rubber Goods Manufacturing Process – Curing (PROC 14) General Rubber Goods Manufacturing Process – Shaping (PROC 21) General industrial use (PROC 1, PROC 2, PROC 8a, PROC 8b, PROC 9) General Rubber Goods Manufacturing Process - Filling/Weighing (PROC 9) ETRMA 2: Manufacture - General rubber goods (PROC 1, PROC 2, PROC 8b, PROC 9, PROC 14, PROC 21) Use in open high temperature processes (PROC 1, PROC 2, PROC 8b, PROC 13)

USES OF NPNA	
	Use(s)
	(Industrial) Use in open system (PROC 1, PROC 2, PRODC 8b, PROC 9, PROC 10, PROC 13) ATIEL-ATC Group C [i]: (Industrial) Use in open system. Application of lubricant to work pieces or equipment by dipping, brushing or spraying (without exposure to heat), e.g. mould releases, corrosion protection, slideways (PROC 1, PROC 2, PROD 8b, PROC 9, PROC 10, PROC 13) General Rubber Goods Manufacturing Process – Strorage (PROC 8a, PROC 8b, PROC 9) ATIEL-ATC Group B [i]: General industrial use of lubricants and greases in vehicles or machinery. Includes filling and draining of containers and enclosed machinery (including engines) (PROC 1, PROC 2, PROC 8b, PROC 9) ATIEL-ATC Group F [i]: (Industrial) Use of lubricants in high energy open processes, e.g. in high speed machinery such as metal rolling / forming or metalworking fluids for machining and grinding (PROC 1, PROC 2, PROC 8b, PROC 17, PROC 18) General Rubber Goods Manufacturing Process – Mixing (PROC 5, PROC 8b, PROC 9)
Uses by professional workers	General professional use (PROC 1, PROC 2, PROC 8a, PROC 8b, PROC 20) ATIEL-ATC Group B [p] indoor: General professional use of lubricants and greases in vehicles or machinery. Includes filling and draining of containers and enclosed machinery (including engines), indoor (PROC 1, PROC 2, PROC 8a, PROC 8b, PROC 20) ATIEL-ATC Group F [p]: (Professional) Use of lubricants in high energy open processes, e.g. in high speed machinery such as metal rolling / forming or metalworking fluids for machining and grinding (PROC 1, PROC 2, PROC 8a, PROC 17, PROC 18) ATIEL-ATC Group B [p] outdoor: General professional use of lubricants and greases in vehicles or machinery. Includes filling and draining of containers and enclosed machinery (including engines), outdoor (PROC 1, PROC 2, PROC 8a, PROC 8b, PROC 20) ATIEL-ATC Group C [p] indoor: (Professional) Use in open system. Application of lubricant to work pieces or equipment by dipping, brushing or spraying (without exposure to heat), e.g. mould releases, corrosion protection, slideways, indoor (PROC 1, PROC 2, PROC 8a, PROC 10, PROC 13) General professional use of lubricants and greases in vehicles or machinery. Includes filling and draining of containers and enclosed machinery (including engines), outdoor (PROC 1, PROC 2, PROC 8a, PROC 8b, PROC 20) (Professional) Use in open system (PROC 1, PROC 2, PROC 8a, PROC 10) General professional use of lubricants and greases in vehicles or machinery. Includes filling and draining of containers and enclosed machinery (including engines), indoor (PROC 1, PROC 2, PROC 8a, PROC 8b, PROC 20) (Professional) Use in high energy open processes (PROC 1, PROC 2, PROC 8a, PROC 17) ATIEL-ATC Group C [p] outdoor: (Professional) Use in open system. Application of lubricant to work pieces or equipment by dipping, brushing or spraying (without exposure to heat), e.g. mould releases, corrosion protection, slideways, outdoor (PROC 1, PROC 2, PROC 10)
Consumer Uses	AC 10: Rubber articles (see article service life)
Article service life	ETRMA 3: Article Service Life - ERC10b - Brake pads in automotive industry (PROC 21) ETRMA 5: Article Service Life - ERC10b - General rubber goods (PROC 21) ETRMA 4: Article Service Life - ERC11a - Tyre mounting and dismounting and handling of technical rubber goods (PROC 21) Use of tyres and general rubber goods (Consumer, indoor/outdoor) Rubber products: Oil-resistant hoses, tyres - side walls, belts (fan belts, cam belts)

7.6. Classification and Labelling

7.6.1. Harmonised Classification (Annex VI of CLP)

NPNA is currently not listed in Annex VI of Regulation (EC) No 1272/2008. The eMSCA has submitted a CLH dossier to ECHA for accordance check in November 2021.[7]

7.6.2. Self-classification

In the registration, NPNA is classified as:

Acute Tox. 4	H302
Skin Sens. 1B	H317
STOT RE 2 (blood, kidney)	H373
Aquatic Acute 1	H400 (M=1)
Aquatic Chronic 1	H410 (M=1)

In addition, NPNA is self-classified by numerous notifiers. As reported on the ECHA dissemination website, there are in total a number of 1628 notifiers (42 aggregated notifications) listed in the C&L inventory (as of July 8, 2021). Notifications of the 1628 notifiers for classification and labelling concerning human health hazards are inconsistent and contradictory as shown below:

Acute Tox. 4	H302	1406/1628
Skin Sens 1	H317	1434/1628
Skin Sens 1A	H317	1/1628
Skin Sens 1B	H317	114/1628
Skin Irrit. 2	H315	8/1628
Eye Irrit. 2	H319	8/11628
STOT SE 1 (no data/unknown, dermal)		
	H370	92/1628
STOT SE 2 (blood system)	H371	1/1628
STOT SE 3 (respiratory tract)	H335	7/1628
STOT RE 2 (blood system/kidney and cardiovascular, respectively)		
	H373	1145/1628
Not classified		69/1628

7.7. Environmental fate properties

The assessment of the environmental properties and clarification of the PBT/vPvB concern was concluded after the initial assessment period in 2012 based on the information available at that time. Data after this initial assessment period has not been taken into account.

7.7.1. Degradation

7.7.1.1. Abiotic degradation

7.7.1.1.1. Hydrolysis

The eMSCA disagrees with the registrants' assessment of this endpoint. In the available hydrolysis study, an aqueous solution of NPNA was analysed periodically by HPLC. To avoid photolytic effects the test was conducted in the dark. Total recovery of the test substance was 45-52% after 34 days. No degradation products could be detected. The results suggest that NPNA is removed from the solution, but this removal levels off with time. Behaviour of this type is inconsistent with either oxidative or hydrolytic processes, particularly since no degradation products could be detected. The authors conclude that adsorption to the glass surface could account for the observed concentration. The test was repeated with radiolabeled ^{14}C-NPNA. Any disappearance of radioactivity from the solution was caused by adsorption (Syracuse, 1981). Hence, the eMSCA concludes that NPNA does not undergo hydrolytic breakdown.

[7] ECHA website CLH section on NPNA: https://echa.europa.eu/de/registry-of-clh-intentions-until-outcome/-/dislist/details/0b0236e18391641f

7.7.1.1.2. **Phototransformation / photolysis**

7.7.1.1.2.1. Phototransformation in air

Not assessed.

7.7.1.1.2.2. Phototransformation in water

Phototransformation in water is expected to be quick with a half-life of 5 to 8 minutes. However, under environmentally realistic conditions, where only part of the substance is exposed to sunlight because, for example, suspended matter reduces the penetration of light into deeper layers of water, this half-life is not expected to be realistic. Photodegradation is therefore not considered in the environmental assessment according to the REACH guidance document.

7.7.1.1.2.3. Phototransformation in soil

Not assessed.

7.7.1.2. Biodegradation

7.7.1.2.1. **Biodegradation in water**

7.7.1.2.1.1. Estimated data

Not assessed.

7.7.1.2.1.2. Screening tests

As stated by the registrants, the key study was a GLP study according to OECD TG 301C. The test duration was 28 d with an initial concentration of 100 mg/L activated sludge. 0% degradation was observed. Hence the test material is considered as not readily biodegradable under the test conditions (IFUB, 1990). This finding is supported by a study conducted by the Japanese National Institute of Technology and Evaluation, also reporting 0% degradation after 14 d in a test according to OECD TG 301C (MITI-List, 2002).

The results of a third screening test were not correctly summarised by the registrants. In a non-standard study primary degradation of NPNA was measured (Syracuse, 1981; Rosenberg 1983). Surface water and an effluent of a municipal WWTP were used as inoculum. A half-life of 4.2 d was reported for the primary degradation of NPNA in effluent waste water. In the control, incubated with sterilised effluent water of the WWTP, 80% of the test material was analysed after 18 days. The addition of nutrients or yeast extract resulted in an enhanced degradation. After 2 days > 75% of the substance disappeared and no NPNA could be detected after 18 days. In lake water the degradation started after a lag phase of 5 d on a slower rate compared to the wastewater inoculums. The reported half-life of primary degradation was 10 d. Again, the addition of an external carbon source enhances the rate of degradation.

In analogue studies the mineralisation of radiolabeled ^{14}C-NPNA was analysed by CO_2 evolution. In samples containing effluent wastewater, 13% of the initial ^{14}C-NPNA concentration was mineralised to $^{14}CO_2$ after 15 days. After 35 days, 21% of the initial ^{14}C-NPNA concentration was mineralised to $^{14}CO_2$. The addition of nutrients enhanced the degradation marginally (27% $^{14}CO_2$ after 13 days). In this study, the presence of major metabolites was detected (95% of extractable radioactivity after 10 d), tentatively identified by GC-MS as a dihydroxylated derivative of NPNA (m/e 252) and N-acetyl-NPNA (m/e 262) (Syracuse, 1981). However, the position of the radioactive labelling is not known. Therefore, the degradation products cannot be explicitly identified. The stability of the degradation products has not been assessed.

7.7.1.2.1.3. Simulation tests (water and sediments)

The data waiving by the registrants is not considered justified. The substance is not readily biodegradable and the production volume per year exceeds the 100 tons level. According to Annex IX of the REACH regulation, a simulation test on degradation in water and sediment is necessary to clarify if the persistence criterion is fulfilled.

7.7.1.2.2. Biodegradation in soil

Rosenberg (1983) investigated the degradation of ^{14}C-labelled NPNA for 11 days at 26 °C in the dark under aerobic conditions in soil and soil suspension (100g soil and 125 ml solution of inorganic salts). Initial concentration of the test substance was 1.54 µg/g soil and 0.77 mg/L (20 nCi) of ^{14}C-NPNA/mL in suspension. Possible non-biological transformation of ^{14}C-NPNA was assessed using soil previously sterilised for three successive days for 1 h at 121 °C.

Two sets of flasks were prepared either adding nutrient broth to the soil or soil suspension or not. Temperate soil with no nutrient broth evolved more ^{14}C-CO_2 than the nutrient broth-supplemented soil. After 2 days, 7% of the initial radioactivity was recovered as $^{14}CO_2$ and nearly 17% after 11 days. From the carbon-supplemented soil, 3.5% and 12.5% of the initial radioactivity were evolved as $^{14}CO_2$ after 2 and 11 days, respectively.

Similarly, $^{14}CO_2$ evolution was higher in the soil suspension with no nutrient broth than in the carbon-supplemented system. After 2 days, 17% of the initial radioactivity had been evolved as $^{14}CO_2$ while 35% was evolved after 11 days. After 2 days only 6% of radioactivity was recovered as $^{14}CO_2$ while 22% was recovered as $^{14}CO_2$ after 11 days from the nutrient broth-supplemented soil suspension. The author describes the degradation of the substance to two products: the dihydroxy and N-acetyl derivatives (Rosenberg, 1983).

Less than 2% of the ^{14}C was released as $^{14}CO_2$ in autoclaved soil and soil suspension indicating that degradation of ^{14}C-NPNA was attributed to the action of microorganisms in the respective ecosystems investigated.

The study authors attribute the higher degree of disappearance of ^{14}C-NPNA in soil and soil suspensions in the absence of nutrient broth to higher adsorption of NPNA to soil or suspended soil particles. However, the data can be interpreted in the way that microorganisms only degrade NPNA in those cases where no other carbon source is available.

It has to be noted that the position for the radioactive labeling is not documented. Therefore, the degradation products cannot be explicitly identified. Moreover, the maximum water retention capacity of the soil used in the study is 75%. In the guidelines, soils with a water retention capacity of 40% are recommended.

7.7.1.3. Summary and discussion on degradation

NPNA does not undergo hydrolytic breakdown.

Photodegradation of NPNA in aqueous solutions by sunlight is rapid and proceeds with a half-life of 5 to 8 min. Consequently, it is not expected to be present in surface waters in significant concentrations. However, this degradation rate may not necessarily be representative of an entire natural aquatic system. In most cases, depth, degree of mixing and season would be critical factors in determining the rate at which NPNA is degraded by sunlight. One primary photoproduct was identified which is relatively photostable, probably the aniline adduct of 1,3-naphthoquinone.

NPNA has shown to be not readily biodegradable in two biodegradation studies according to OECD TG 301C, yielding 0% degradation in both studies after 14 and 28 days, respectively. The results of a third screening test were not correctly summarised by the registrants. In this non-standard study, primary degradation of NPNA was measured in surface water and in an effluent of a municipal WWTP. Half-lives in the range of 4.2 d to 10 d were reported for the primary degradation of NPNA. The addition of nutrients or yeast extract resulted in an enhanced degradation. In analogue studies, the mineralisation of radiolabeled ^{14}C-NPNA was analysed by CO_2 evolution and reached not more than 27% after 13 days. In this study, the presence of major metabolites was shown (95% of extractable radioactivity after 10 d) and tentatively identified by GC-MS as dihydroxy derivative of NPNA (m/e 252) and N-acetyl-NPNA (m/e 262) (Syracuse, 1981). However, the position of the radioactive labelling is not known. Therefore, the degradation products

cannot be explicitly identified. The stability of the degradation products has not been assessed.

In summary, all three screening tests showed that NPNA is not readily biodegradable, and it is not possible to conclusively assess whether the substance is persistent in the environment or not.
The biodegradation of ^{14}C-labelled NPNA in soil was investigated in a non-guideline study. Biodegradation of ^{14}C-labelled NPNA in carbon-supplemented soil resulted in 3.5% and 12.5% degradation after 2 and 11 days, respectively (unsupplemented soil suspensions: 6% and 22% after 2 and 11 days, respectively).

The waiving of a water sediment simulation study is not justified. The substance is not readily biodegradable and the production volume per year exceeds the 100 tpa-level. Consequently, according to Annex IX of the REACH regulation simulation tests on degradation in the different media are necessary. Until now, only a soil simulation test (Rosenberg, 1983) is available which was not standard.
Simulation tests on degradation in water and sediment are missing in the registration dossier and would be needed at Annex IX and to clarify if the persistence criterion is fulfilled.

7.7.2. Environmental distribution

7.7.3. Bioaccumulation

7.7.3.1. Aquatic bioaccumulation

In total, four studies are available. Three of these studies investigated the uptake in fish. One study investigated the uptake in *Daphnia magna*.

In the first study, the bioconcentration of NPNA in *Cyprinus carpio* was examined according to OECD TG 305C in a flow-through system for 56 days (MITI Database, 2002). As a result, bioconcentration was observed with BCF values of 427 to 2730 (0.1 mg/L) and 889 to 2490 (0.01 mg/L) referred to a lipid content of 5.4% of *Cyprinus carpio*. Normalisation to a lipid content of 5% yields BCFs of 395-2527 (0.1 mg/L) and 823-2305 (0.01 mg/l). BCFs were measured the first and the second week as well as the 4th, 6th and 8th week. The highest BCF values were observed in the second week. BCFs were 2730 (0.1 mg/L) and 2490 (0.01 mg/L). Afterwards the BCFs decreased and were smaller than 2000. This indicates that NPNA may be metabolised. The delay in metabolisation and thus a peak bioaccumulation in the second week may be explained by a delayed formation of metabolizing enzymes. A BCF of 874 mg/L (lipid normalised) is considered as steady-state BCF.

The second study investigated uptake and elimination of ^{14}C-NPNA by bluegill sunfish in a flow-through system following recommendations of US EPA (Syracuse, 1981). NPNA was readily taken up, equilibrium was reached apparently between 8 and 10 days. At this time, BCFs were 600 for whole fish, 339 for edible flesh and 2063 for viscera. The uptake and depuration rate constants (whole fish) were 14.7/h and 0.14/h, respectively. Half of the ^{14}C-NPNA-derived radioactivity in the fish was eliminated in about 2 days after transfer to clean flowing water. HPLC analysis of fish exposed to ^{14}C-NPNA for 10 days indicated that about 50% of the radioactivity was present as NPNA metabolite(s). A major metabolite in the fish extract was identified as a dihydroxylated derivative of NPNA.
Uptake and elimination of ^{14}C-N-1-naphthylaniline was also studied in two static tests with *Lepomis macrochirus* and *Daphnia magna*, respectively (Syracuse, 1981). These tests are considered as not reliable because of the static test conditions.

In summary, two reliable (Klimisch 2) bioaccumulation studies for NPNA are available which show that the substance has a moderate bioaccumulation potential.

7.7.3.2. Terrestrial bioaccumulation

Not assessed.

7.7.3.3. Summary and discussion of bioaccumulation

In a MITI study, BCF over 2000 were reached. However, these BCFs were measured after two weeks following a decrease in bioaccumulation. These results indicate metabolism of NPNA. This is also confirmed by the results from another study (Syracuse, 1981). The degradation product might be a hydroxyl derivate of NPNA. The bioaccumulation potential of this compound has not been assessed. As the degradation product is probably more hydrophilic than NPNA, the potential for bioaccumulation might be lower than that of the parent compound. Hence, NPNA does not fulfil the B criterion.

7.8. Environmental hazard assessment

7.8.1. Aquatic compartment (including sediment)

7.8.1.1. Fish

7.8.1.1.1. Short-term toxicity to fish.

Acute toxicity was investigated in two fish species following US EPA recommendations (Syracuse, 1981). *Oncorhynchus mykiss* was tested in a semi-static system and flow-through system similar to the OECD TG 203. The semi static study yielded an LC_{50} value (96 h) of 0.44 mg/L based on the nominal concentration. The LC_{50} (96 h) value resulting from the flow-through test was 0.74 mg/L based on the nominal concentration.

For *Lepomis macrochirus*, an LC_{50} value (96 h) of 0.82 mg/L was obtained both in a semi-static and flow-through test system.

These fish studies are reliable with restriction. The studies are acceptable, based on a well-documented publication, which meet basic scientific principles.

7.8.1.1.2. Long-term toxicity to fish

There are no data available.

7.8.1.2. Aquatic invertebrates

7.8.1.2.1. Short-term toxicity to aquatic invertebrates

The eMSCA agrees with the summaries of the studies taken into account by the registrants, but disagrees with the registrants' assessment. There is an additional study, which was not taken into account.

This GLP study was conducted in accordance with the OECD TG 202 with *Daphnia magna* and yielded a EC_{50}(48 h) of 0.26 mg/L MITI, 2005. This study is reliable with restriction as a full report with details about the test is not available.

The following summarises the results of the studies taken into account by the registrants. Additionally acute toxicity to *Daphnia magna* was investigated either as neonates or adult daphnia following US EPA recommendations (Syracuse 1981). This study yielded an EC_{50}value (48h) of 0.3 mg/L based on the nominal concentration.
For adult daphnia, an EC_{50} value (48 h) of 0.68 mg/L based on the nominal concentration was obtained in the same static test system with soft water.

Additionally for first-instar daphnia, EC_{50} values (48 h) were obtained in a semi-static test system with either soft or hard water EC_{50} values (48 h) of 0.68 mg/L and 0.67 mg/L resulted from exposure with hard water and soft water, respectively.
The daphnia studies are reliable with restriction. The studies are acceptable, well documented publication, which meet basic scientific principles.

7.8.1.2.2. Long-term toxicity to aquatic invertebrates

The eMSCA agrees with the registrants' assessment of this endpoint. Two long-term toxicity tests are available for NPNA to *Daphnia magna*.

In the first study, effects of NPNA on daphnia reproduction were investigated in a GLP study according to OECD TG 202 part II (IFU 1996). This study yielded a 21-d NOEC for reproduction of 0.032 mg/L.

The second study was conducted in accordance with the US EPA recommendations (Syracuse, 1981). As a result, a 21-d NOEC of 0.02 mg/L was obtained for mortality. However, mortality is an endpoint of minor relevance for chronic toxicity tests. The study is reliable with restriction.

7.8.1.3. Algae and aquatic plants

The eMSCA agrees with the summaries of the study taken into account by the registrants, but disagrees with the registrants' assessment. There is an additional study which was not taken into account. Therefore there are two studies on growth rate and biomass production of *Scenedesmus subspicatus* for NPNA.

The study not taken into account by the registrants was conducted on *Pseudokirchneriella subcapitata* in accordance with the OECD TG 201 (growth inhibition) and yielded a NOEC (72 h) of 0.0036 mg/L (MITI, 2005). This study is reliable with restriction as a full report with details about the test is not available.

The following summarises the results of the studies taken into account by the registrants.

In the second study NPNA was investigated in a GLP study according to EU method C.3 on *Scenedesmus subspicatus* and yielded an EC_{50} for growth rate inhibition of ≥ 0.25 mg/L (IFU 1996). However, in agreement with the registrants' assessment the study suffers from several methodological deficiencies and therefore is not reliable.

7.8.2. Terrestrial compartment

Not part of this substance evaluation.

7.8.3. Microbiological activity in sewage treatment systems

Not part of this substance evaluation.

7.8.4. PNEC derivation and other hazard conclusions

Not part of this substance evaluation.

7.8.5. Conclusions for classification and labelling

Not part of this substance evaluation.

7.9. Human Health hazard assessment

7.9.1. Toxicokinetics

Syracuse (1981) examined absorption, metabolism, distribution and elimination of ^{14}C-NPNA in rats after oral gavage of 160 mg/kg bw. The test substance was readily absorbed, almost completely metabolised, and excreted via faeces and urine. The maximum radioactivity was measured in plasma after 4 hours. After 24 hours, 20% of the radioactivity was found in the gastrointestinal tract, 2.4% in fat tissue, and 0.4% in the liver and 0.1% in the kidneys. More than 90% of the administered radioactive labelled carbon has been excreted within 48 hours after administration via faeces (60%) and via urine (32%). In the ether extract of the urine, using HPLC analysis, five ^{14}C-metabolites were determined but parent NPNA was not detected. The elimination half-lives were reported as 1.68 hours for the fast elimination phase and 33 hours for the slow elimination phase. The following metabolites were identified in two additional *in vitro* metabolic studies (Syracuse, 1981; Xuanxian and Wolff, 1992): mono- and di-hydroxylated derivatives of NPNA. Syracuse (1981) suggested that the metabolism of NPNA is primarily via hydroxylation and subsequent O-glucoronidation or O-sulfation. Pre-treatment of male rats

with phenobarbital or 3-methylcholanthrene increased the rate of microsomal metabolism of NPNA, indicating that more than one P-450 monooxygenase mediates the reaction (Xuanxian and Wolff, 1992).
A dermal absorption study according to OECD TG 428, which was requested in the second Decision, was submitted by the registrants in March 2021.

The registrants indicated that exposure to the test item mainly occurs "during handling of the pure compound and during processing, for example, after dilution in a base oil for lubricants or after incorporation into a rubber matrix". Hence, concentrations of NPNA tested within the scope of the study represented i) the neat product (ca. 100% (w/w) moistened with water), ii) relevant in-use concentrations diluted in base oil for lubricants (ca. 5% (w/v) and ca. 1% (w/v)), as well as iii) test item in a rubber matrix (i.e. a 3.5% (w/w) and ca 0.5% (w/w) in a rubber disc). The latter was used by the study authors to generate a relevant and technically feasible test sample representing a worst case example based on the actual industrial processing.

The rubber discs and test preparations, respectively, were applied to human split-thickness skin membranes from four to six different donors and the diffusion cells were left open to the atmosphere. Percutaneous absorption was assessed by collecting receptor fluid at 1, 2, 4, 8 and 12 h post-dosing. At 8 h post-dosing, the exposure period was terminated by removing the test preparation/rubber disc (and washing). At 24 h post-dosing, the skin was removed from the static cells, the stratum corneum tape stripped and the skin divided into exposed and unexposed skin (i.e. dermis and epidermis), and receptor fluid was collected. Analysis was performed by liquid scintillation counting.
It is noted that an exposure duration of 24 h was requested in the second SEv Decision, while the human skin samples were in fact exposed to NPNA for only 8 h (plus an additional 16 h post-exposure observation period). The eMSCA, thus, considers the provided study as incompliant with the study requested in the second Decision.

Nevertheless, although the study design did not concur with the original request, the eMSCA is of the opinion that the new data may be used for DNEL derivation and subsequent risk characterisation, when applying a conservative (worst case) approach in study interpretation. Applying such a conservative approach is considered necessary by the eMSCA, as the available data indicate that dermal absorption of NPNA occurs continuously over the exposure and the subsequent observation period, and particularly increases after the initial direct 8 h skin contact independent of the type of tested formulation/matrix.
To address the amount of NPNA which may migrate from the stratum corneum into deeper skin layers and the receptor fluid, respectively, after the end of the direct exposure, the eMSCA added the amounts of NPNA that were present in stratum corneum (without the first two "tape-strips") when calculating the dermally absorbed fraction of NPNA. This was also considered by the registrants/study authors when determining the dermal absorption for the various types of sample preparations. In order to account for additional uncertainties, the eMSCA also added one standard deviation (SD) to the mean value of the relevant measurements, as proposed by the Scientific Committee on Consumer Safety (SCCS) in its document "Basic criteria for the in vitro assessment of dermal absorption of cosmetic ingredients" (SCCS, 2010). The registrants, on the other hand, used a method based on the EFSA Guidance on Dermal Absorption (2017[8]). Consequently, the eMSCA calculated values for dermal absorption which were slightly higher than those calculated by the registrants/study authors.

Considering a worst-case scenario, the highest value for dermal absorption among the test preparations was selected as the dermal absorption percentage and this value was subsequently used (for route-to-route extrapolation) when deriving the dermal DNELs and performing the risk characterisation for dermal exposure scenarios.

Based on the approach described above, the following potentially absorbable doses (=cumulative receptor fluid + chamber wash +exposed skin + tape strips 3-20) and dermal

[8] https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2017.4873

absorption estimates (=cumulative receptor fluid + chamber wash +exposed skin + tape strips 3-20 + 1SD), respectively, were calculated by the eMSCA:

a) Neat NPNA (moistened with water): 0.47% (23.7 µg equiv./cm²) and 0.71% (36.5 µg equiv./cm²);
b) Rubber discs containing 0.5% NPNA (w/w): 0.31% (1.7 µg quiv./cm²) and 0.36% (2.0 µg equiv./cm²);
c) Rubber discs containing 3.5% NPNA (w/w): 0.32% (14.7 µg equiv./cm²) and 0.39% (17.9 µg equiv./cm²);
d) Base oil containing 1% NPNA (w/v): 4.57% (4.8 µg equiv./cm²) and 6.1% (6.4 µg equiv./cm²);
e) Base oil containing 5% NPNA (w/v): 4.84% (25.9 µg equiv./cm²) and 7.10% (37.9 µg equiv./cm²).

The scenario leading to the highest **dermal absorption estimate (7%)** obtained from the formulation of 5% NPNA in base oil (w/v) was used for dermal DNEL derivation for consumers and workers (worst case; see Section 7.9.9.1).

7.9.2. Acute toxicity and Corrosion / Irritation

7.9.2.1 Acute Toxicity

The registrants concluded that the substance warrants classification as Acute Tox. 4, H302, and based on the available information, the eMSCA can support this conclusion. Based on the lowest oral LD_{50} of 1231 mg/kg bw and 1625 mg/kg bw established in a study in mice and rats, respectively (AMR, 1974), NPNA has to be classified as **Acute Tox. 4, H302 (Harmful if swallowed)**, according to CLP (Regulation (EC) 1272/2008). This endpoint is included in the CLH proposal that has been prepared by the eMSCA and submitted to ECHA for accordance check.
The available data further indicate that classification of NPNA for the hazard class acute dermal toxicity is not warranted. Information on acute inhalation toxicity is not available.

7.9.2.2 Skin Irritation / Corrosion

The registrants concluded the substance is not irritating/corrosive to the skin, and based on the available information, specifically a negative guideline-conform ‘Acute Dermal Irritation/Corrosion Study’ according to OECD TG 404 and several supporting studies, the eMSCA can support this conclusion. **Classification of NPNA is not warranted for this endpoint and hazard class**, respectively.

7.9.2.3 Eye Irritation / Damage

The registrants concluded that the substance is not irritating/corrosive to the eyes. Based on the available information, i.e. a negative guideline-conform ‘Acute Eye Irritation/Corrosion Study’ according to OECD TG 405 and an additional negative supporting study, the eMSCA agrees with this conclusion. Classification of NPNA for the hazard class eye irritation/damage is not warranted.

7.9.2.4 Sensitisation

NPNA was tested in three Guinea Pig Maximisation Tests with positive results in all of the tests. In all studies, concentrations of > 1% were used for intradermal induction. In addition, there are several case reports indicating that NPNA may cause allergic skin reactions as seen in various positive patch tests performed with patients possibly or confirmedly suffering from contact dermatitis.

The registrants concluded the substance is a skin sensitiser, and based on the available information, the eMSCA supports this conclusion. Due to the high sensitisation rate of 90% at an intradermal induction concentration of 10% (and a challenge concentration of 3%) in the key study contained in the registration and further taking into account the available supporting information, NPNA is considered a moderate skin sensitiser, that - according to Regulation (EC) 1272/2008 - has to be classified as **Skin Sens. 1, H317 (May cause an allergic skin reaction)**. As in none of the available studies, a concentration of < 1% for

intradermal induction was tested, sub-categorisation (i.e. Skin Sens. 1A or 1B) is not possible.
This endpoint is included in the CLH proposal, which has been prepared by the eMSCA and submitted to ECHA for accordance check.
Information on respiratory sensitisation is not available.

7.9.3. Repeated dose toxicity

As detailed in the first Decision[9], the initial human health hazard assessment raised a concern for neurotoxicity: an available subacute guideline study (OECD TG 407) indicated neurotoxicity in the functional observational battery (FOB) (Bayer, 2002), as gait abnormalities were observed in some female rats in a dose dependent manner on day 25 of the administration period. In a pilot dose-range-finding study (7 days) from the same laboratory (Bayer, 2000), similar dose-dependent increases in gait abnormalities were noted in the FOB at high doses (i.e. ≥ 250 mg/kg bw). In addition to neurotoxicity, haematotoxicity was observed in this subacute study raising an additional concern, especially with regards to NPNA eliciting methaemoglobinaemia. Methaemoglobin formation was not examined in this study, although prior data using the intraperitoneal application of NPNA indicated that methaemoglobin is formed upon exposure in the mouse (Nomura, 1977).

Furthermore, no subchronic toxicity study with NPNA was available, as the read across approach to the source substance diphenylamine (CAS No. 122-39-4) applied by the registrants was considered inappropriate by the eMSCA. In particular, the registrants failed to demonstrate that apart from structural similarity, the physicochemical and toxicological properties of source and target compound are sufficiently similar to justify the proposed read-across approach.

Consequently, a 'Repeated Dose 90-Day Oral Toxicity Study in Rodents' (OECD TG 408) combined with a 'Neurotoxicity Study in Rodents' (OECD TG 424) (registered substance, rats, oral route) with some additional specific analyses (e.g. methaemoglobin formation) was requested in the first Decision, which was issued to the registrants in May, 2014.
The registrants provided the requested repeated dose data (BASF, 2016b), which was considered adequate to meet the requirements of Annex IX of the REACH Regulation. The PNDT study (BASF, 2016a) which also was requested in the first Decision was included in the weight of evidence assessment for concluding on repeated dose toxicity. An additional literature search (until January 2021) revealed a further subacute (28 days) toxicity study (Tanabe et al., 2017) which was also included in the evaluation.

7.9.3.1. Hematotoxicity

Methaemoglobin levels were not measured in the subacute and subchronic oral toxicity studies (although specifically requested in the latter study), but increases in methaemoglobin levels after repeated intraperitoneal application of NPNA were previously demonstrated in mice (Nomura, 1977), suggesting slight to moderate methaemoglobinaemia. Key effects after repeated oral application in rats further included reductions in red blood cell (RBC) counts, haemoglobin (Hb) concentrations and haematocrit (HCT). The measured reductions in RBC counts and Hb concentration did not exceed a mean value of 10%, but numerous treated individuals showed a more severe reduction in both parameters of up to 16%. Furthermore, it has to be considered that blood analysis only took place once, at the end of each respective exposure period, when the adaptive response already kicked in. Thus, a more frequent sampling also at earlier time points likely would have resulted in a more drastic reduction of those two parameters, RBC counts and Hb concentration.

Additional effects of repeated oral dosing were increases in mean corpuscular volume (MCV) and mean corpuscular haemoglobin content (MCH), indicating erythrocyte deformation e.g. due to increased (secondary) reticulocytosis. Correspondingly, as an adaptive response to the systemic haemolysis an increase in extramedullary

[9] https://echa.europa.eu/documents/10162/302da1e8-d3c8-bf3f-a9b5-fdf01842aa67

haematopoiesis in spleen and an increased percentage of reticulocytes in the blood were noted. Moreover, increased organ weights (spleen, liver and kidney) were consistently recorded in the available studies. The weight increase in spleen was generally associated with extramedullary haematopoiesis and haemosiderosis. In the subacute study, an increased haemosiderin (iron) deposition in liver (Kupffer cells) was noted as well. Dose-dependent kidney degeneration and regeneration of the proximal tubules were reported in male rats of the subchronic study. Although this tubular cell loss can be partially or fully reversed via cell regeneration, haemosiderin-related tubular cell death is considered adverse, and in severe cases can result in secondary nephrotoxic effects (Muller et al., 2006). Consistently, significant increases in plasma creatinine and/or urea levels were reported in treated animals of the requested subchronic (BASF, 2016b) and the PNDT (BASF, 2016a) study. Together with the increases in (absolute and relative) kidney weight, these effects are indicative of renal dysfunction. Furthermore, elevated bilirubin, and urobilinogen as well as blood cell excretion via urine were observed, alongside highly elevated bilirubin plasma levels, which were consistently reported in all of the studies. These effects are additional indicators for severe chronic haemolytic anaemia (Muller et al., 2006). Hence and corresponding to the results of the initially available subacute *in vivo* studies, the results of the 90-day and PNDT study, respectively, are indicative of severe haematotoxicity as well, yielding organ dysfunction (i.e. kidney) as a secondary effect to the haemolytic anaemia.

Nevertheless, although data clearly indicate that NPNA causes significant and extensive haemolytic anaemia, affecting multiple organs and general health of rats and mice, although data for the latter species is limited, it is noted that the effects on blood parameters may have to be seen as borderline with respect to the criteria as laid down in Muller et al. (2006) and the ECHA Guidance on the Application of the CLP Criteria (ECHA, 2017) (e.g. regarding Hb reduction of ≥ 10%). In addition, it is noted that several haematotoxic effects were only observed at a dose slightly above the upper limit value for STOT RE 2 classification (i.e. 100 mg/kg bw/d). Nevertheless, it is emphasised that in several studies these limit values of relevant blood parameters were exceeded in numerous individual test animals, while the mean values may be below 10%, demonstrating high individual variability in the strength of effect that should be considered as relevant for humans. Hence, it is concluded that **classification of NPNA for STOT RE 2, H373 (blood system) may be considered (as done by the registrants by applying a respective self-classification).** Nevertheless, effects are borderline for classification with respect to severity of effects and effective dose levels. Thus, in light of these uncertainties, **classification of NPNA for the hazard class STOT RE is not proposed in the CLH proposal**, which has been prepared by the eMSCA and submitted to ECHA for accordance check. However, all data will be presented in detail in the dossier anyway, in order to transparently provide all relevant data for RAC to conclude on this borderline endpoint.

7.9.3.2. Liver toxicity

In addition to haemolytic anaemia, severe increases in relative and/or absolute liver weights were frequently observed in the available repeated dose studies, which cannot be explained as secondary to haemolytic anaemia. Absolute and relative liver weight was reported to be increased around/above 10% in both sexes after subacute exposure to NPNA at 80 mg/kg bw/d (not fully reversible during recovery) (Bayer, 2002). Increases were more marked after subacute exposure at ≥ 100 mg/kg bw/d (around/above +20% in both sexes) and exceeded +70% when compared to controls at a dose of 500 mg/kg bw/d (Tanabe et al., 2017). In the subchronic study (BASF, 2016b), NPNA doses of ≥ 25 mg/kg bw/d similarly yielded dose-dependent increases in liver weight, reaching approximately +30% at the high dose of 125 mg/kg bw/d. Although these weight increases were not corroborated by histopathological findings that might explain these effects, and no metabolic enzyme activities were measured to reveal a potential mode of action, such massive increases in organ weight are considered as a pathological effect elicited by NPNA. The lack of other relevant histopathological findings accompanying these weight increases is noteworthy, as one would assume that microscopic effects are generally observable in cases of increases in organ weight of ≥ 20% (Hall et al., 2012). Nevertheless and due to the severity of these marked and dose-dependent effects, the increases in absolute and relative liver weight, which were consistently noticed in all available repeated dose toxicity

studies, are judged as adverse per se. Hence, **the liver is considered an additional target organ of NPNA toxicity**.
Data on liver toxicity is also included in the CLH proposal that has been prepared by the eMSCA and submitted to ECHA for accordance check. **However**, **classification is not proposed**.

7.9.3.3. Neurotoxicity

The concern regarding neurotoxicity could not be verified based on the subchronic *in vivo* study provided by the registrants subsequent to the first Decision. The neurological effects that were seen after subacute exposure to NPNA (up to 80 mg/kg bw/d; Bayer (2002)), i.e. gait abnormalities observed in the FOB (females only), were not observed during 90 days of oral administration of the test substance at doses up to 125 mg/kg bw/d (BASF, 2016b). Furthermore, no test substance related effects were observed at any dose level during the respective neurohistopathologic investigations. In addition, signs of neurotoxicity were neither observed in the concomitantly requested oral PNDT study with NPNA doses up to 150 mg/kg bw/d (BASF, 2016a), nor in the FOB of an additional 28-day study administering up to 500 mg/kg bw/d (Tanabe et al., 2017) retrieved during a literature search. Moreover, neither the recovery male nor recovery female animals of the initially available 28-day guideline study, in which the adverse effects on gait of females of the main group(s) were noted (i.e. Bayer (2002)), exhibited any gait abnormalities at any of the observation time points at the high dose of 80 mg/kg bw/d. It was noted that in this study adverse effects linked to haemolytic anaemia were seen in some control animals as well, which may limit the validity of this study.

Overall, the registrants concluded that NPNA is not neurotoxic, and in weight of evidence of the available information, the eMSCA supports this conclusion.

The registrants used the LOAEL of 5 mg/kg bw/d from the subchronic study (BASF, 2016b) as point of departure (PoD) for DNEL derivation, and on the basis of the available data, the eMSCA agrees with this choice (see Section 7.9.9.1).

7.9.4. Mutagenicity

NPNA neither induced gene mutations in several bacterial gene mutation tests nor in a mitotic recombination test with the yeast Saccharomyces cerevisiae strain D4. Furthermore, no induction of mutagenic effects was observed *in vitro* in mammalian cells. The negative result with and without S9-mix in a mouse lymphoma test indicates that NPNA neither induces gene mutations nor chromosomal aberration in L5178Y cells. Several chromosome aberration tests, two tests with CHO cells and one test with CHL cells, demonstrated negative results with and without S9-mix. The result of an in vitro UDS test with WI-38 embryonic lung cells was equivocal with and without S9-mix and a SCE test with CHO cells was marginally positive with S9-mix. However, the results of the latter in vitro genotoxicity tests need to be put into perspective considering the observed lack of a dose-response and the negative results of the mouse lymphoma and the chromosome aberration tests, respectively. An *in vivo* dominant lethal assay with male mice further demonstrated a negative result after intraperitoneal injection of NPNA.

None of the tests was carried out in accordance with the corresponding EU/OECD TG. Nevertheless, by means of a weight of evidence approach, the existing information for the toxicological endpoint mutagenicity was regarded as sufficient by the registrants for concluding that NPNA is not mutagenic. Based on the available information, the eMSCA supports this conclusion.

Classification for mutagenicity according to Regulation (EC) 1272/2008 is currently not warranted.

7.9.5. Carcinogenicity

Several older carcinogenicity studies performed with NPNA are available, which are neither in compliance with relevant guidelines nor with GLP, and therefore considered “not reliable” according to the Klimisch score method (i.e. Klimisch 3).

In an oral carcinogenicity study in three dogs (exposure via feed for 3 years; 5 days/week; no mentioning of any control groups), there was no indication of bladder tumour development. However, no additional information on any toxic effects or other tumour types is given and the number of tested animals is very low (Gehrmann et al., 1948; Haskell, 1945; McCormick, 1972).

In a dermal carcinogenicity study in mice (80 weeks; application twice per week; n = 50; only study summary available; no information on the purity of the test substance; no mentioning of any control groups), no skin tumours or adverse effects on survival were reported. However, pigmentation, fibrosis, scar formation, acanthosis, and hyperkeratosis of the skin were noted. Histopathological examinations of organs other than the skin were not performed and no additional information was given on other adverse effects, such as haematotoxicity (Kettering, 1985).

Some indications for possible carcinogenic effects of NPNA arise from a study in which NPNA ("technical grade" or "pure") was repeatedly applied subcutaneously to mice (Wang et al., 1984). The test substance caused malignant tumours in treated mice (Table 8): lung tumours and haemangiosarcomas predominantly in the kidney. Unfortunately, documentation of the study is very poor (2-page publication), only a limited number of animals was tested, and group designations differ in several cases between the publication text and the corresponding tables, leading to the conclusion that this study is of limited reliability.

Table 8

Tumour incidences after s.c. application of NPNA to male mice according to Wang et al. (1984)

Strain	(n)	Purity	Total dose (mg)	Malignant tumours (no/%)	Lung carcinoma (no/%)	Kidney carcinoma (no/%)	Haemangio-sarcoma in lung, kidney and liver (no/%)	Lymphoma (no/%)
Exposure duration: 290 – 296 days, 3 injections per week for 9 weeks								
							total	
ICR	30	techn.	432	**14**/ 46.6**	**5*/16.6**	1/3.3	**5*/16.6**	1/3.3
ICR	23[e]	pure	432	**12**/ 52.2**	3/13	3/13	**4*/17.4**	2/8.6
ICR	25	pure	135	**11**/44**	**6*/24**	1/4	**4*/16**	0
ICR[a]	24	--[a]	0	0	0	0	0	0
Exposure duration: 262 – 273 days. 2 injections per week, no information on exposure duration or total no. of injections; only information on total dose given (--> 23.5 injections?)								
							of kidney only	
TA-1[b, c]	16	pure	328	**12**/75**	1/6.3	0	**12**/75**	--
TA-1[b,d]	13	techn.	328	**13**/100**	1/7.6	1/7.6	**13**/100**	--[f]
TA-1	19	techn.	328	**7*/36.8**	0	0	**7*/36.8**	--[f]
TA-1[a]	18	--[a]	0	0	0	0	0	--[f]

[a] control (0.1 ml DMSO)
[b] unilateral nephrectomy (left kidney)
[c] **used substance may as well be N-phenyl-2-naphtylamine, equivocal documentation**
[d] exposure duration only 262 days instead of 273 days
[e] **number of animals quoted in the table dissent from the number of animals quoted in the methods section of the publication**
[f] not reported
** p = 0.01; * p = 0.05

Furthermore, an occupational cohort study on different types of cancers among workers exposed to antirust oil indicates that NPNA may cause an increased incidence of tumours in various organs of female (12/78 versus 3.9 expected cases) but not male (0/20) staff (Järvholm and Lavenius, 1981). Affected organs were mainly the uterus and ovaries. It is noted that these organs were not identified as target organs in any of the available repeated dose studies in rats. In addition, the antirust oil tested in that study was comprised of 50% White spirit, 16.5% mineral oil, 16.5% lanolin, 16.5% zinc naphthenate, 0.5% NPNA. It is highlighted that the main ingredient, i.e. White Spirit, is listed in Annex VI of the CLP Regulation as Carc. 1B and Muta. 1B. The authors admittedly stated that the carcinogenic White spirit was evaporated 1 day before workers were exposed to antirust

oil covered products, but analytical evidence of a complete evaporation was not provided, precluding any inferences on a possible association between NPNA exposure and increased cancer incidences. It was, moreover, speculated that the increased cancer incidences may as well be caused by the formation of an N-nitroso compound from NPNA in the antirust oil and sodium nitrite in the packaging paper. It is noted, however, that the eMSCA asked the registrants in the first Decision to prove that the corresponding N-nitrosamine to NPNA is not formed externally above a concentration of 0.001% (w/w) in mixtures or 0.075 µg/m³ in the air during the use of NPNA. Based on the data provided subsequently by the registrants, the eMSCA came to the conclusion that the external formation of nitrosamines is not regarded as a critical factor in the use of NPNA, contradicting the above mentioned speculation by Järvholm and Lavenius (1981) on N-nitroso formation potentially being the cause of the observed increases in cancer incidences. Another explanation of the study authors was that the increased cancer incidences may be “caused by chance”. This could not be excluded due to the low number of subjects in the reference groups (25 women and 8 men; no distinct reporting of cancer incidences for the different sexes: 4/33 versus 2 expected cases). Moreover, other confounding factors, i.e. the undeniably low statistical power, potential random clustering, other exposure sources and/or population characteristics including individual genetic make-up, susceptibility to cancer, lifestyle factors, and personal habits (e.g. smoking and drinking) were not addressed in the publication. Likewise, potential biases (e.g. in the method of selection of exposed and unexposed workers) were not considered in the publication and uncertainties regarding the actual doses received by the different study populations remained. All in all, these shortcomings in study design and reporting/analysing markedly increase the uncertainties associated with the reported study results.

Overall, it is difficult to assess the robustness and biological significance of the available older data mentioned above. The malignant tumours in rats observed in the study by Wang et al. (1984), for instance, may have been a ‘side-effect’ from the unphysiological subcutaneous application route. However, it cannot be ruled out that the occurrence of haemangiosarcomas in the (target organs) liver and kidney could be the result of substance-induced chronic haematotoxicity (as this mode of action is known for other substances that induce haemolytic anaemia). However, various methodological deficiencies in addition to the very poor reporting have been detected when reviewing this study, including varying statements on the (generally rather low) number of test animals and group designations, exposure duration and test substance used (i.e. NPNA or N-2-naphtylaniline). Hence, this study is considered to be of very limited reliability. Similarly, limited reliability had to be assigned to the available occupational cohort study on cancers among workers exposed to antirust oil, as a clear assignment of the observed effects to NPNA exposure is considered impossible.

The registrants concluded that **classification for carcinogenicity is - according to Regulation (EC) 1272/2008 - currently not warranted**. Based on the limited validity and reliability of the available information and due to the lack of guideline-conform cancer studies with NPNA, the eMSCA is of the opinion that **no final conclusion can be drawn on the carcinogenic potential of NPNA.** As proportionality is to be considered when requesting new data in a SEv process, no carcinogenicity study with NPNA was requested in the two Decisions, because the substance is registered for 100 – 1000 t/a (Annex IX) only. Thus, if/when the annual tonnage of NPNA will exceed 1000 t, the carcinogenic potential of NPNA shall be re-examined. This is of particular importance, as the identified carcinogenicity concern could not be clarified based on the available inconsistent and unreliable data and further considering the fact that the structurally similar substance N-2-naphtylaniline (CAS 135-88-6, EC 205-223-9) is suspected of being a carcinogen as well (i.e. listed in Annex VI of CLP as Carc. 2, H351). Hence, in case the annual tonnage of NPNA will exceed 1000 t in the future, a carcinogenicity study shall be proposed by the registrants or may be required by the Agency in accordance with Article 40 or 41 and Annex X (section 8.6.3. and 8.9.1.) of the REACH Regulation. The eMSCA will be ready to assess such new data upon submission to be able to eventually conclude on the carcinogenic potential of NPNA and to initiate possible risk management measures.

7.9.6. Toxicity to reproduction (effects on fertility, developmental toxicity and toxicity on or via lactation)

Specific information on potential effects of NPNA on fertility is not available (e.g. a Reproduction/Developmental Toxicity Screening Test (OECD TG 421) or an EOGRTS (OECD TG 443)). As the substance is an Annex IX substance and as a PNDT study (OECD TG 414) is available as a result of the first Decision, waiving of an OECD TG 421/422 study is considered appropriate according to REACH Annex IX, section 8.7.1, column 2.

The only relevant information regarding the endpoint fertility, thus, comes from the recently conducted oral repeated dose study combining OECD TGs 424 and 408 (BASF, 2016b), and the PNDT study (OECD TG 414 BASF (2016a)), both performed in rats.

The (histo)pathological results of the 90-day study did not reveal any effects of NPNA on reproductive organs. Further, no effects on behavioural parameters and motor activity were detected, that might indicate or could yield a reduction in fertility of exposed animals. Likewise, no adverse effects on any reproductive parameters, such as conception rate, mean number of corpora lutea, mean number of implantations, as well as pre- and post-implantation losses were noted in the PNDT study (BASF, 2016a). Thus, these studies did not reveal any concern regarding fertility, which would warrant classification. Nevertheless, the eMSCA considers the limited data available insufficient to eventually conclude on this endpoint, as no study is available particularly focussing on fertility effects (i.e. OECD TG 421/422 or 443).

The registrants provided results of the recently conducted PNDT study in rats applying OECD TG 414 (BASF, 2016a) in compliance with GLP. A statistically significant increased incidence of minor skeletal variations, such as incomplete ossification of the cervical arch (at ≥ 50 mg/kg bw/d) and wavy ribs (at the high dose of 150 mg/kg bw/d) were reported in pups of treated dams. Effects were suggested by study authors to represent either minor deviations from normal morphology (variations) or slight delays of ossification irrelevant for classification. The eMSCA agrees that the observed effects depict slight variations according to Solecki et al. (2001). Moreover, maternal toxicity (i.e. increased water consumption, reduced food consumption, decreased body weight gain and (regenerative) haemolytic anaemia) was observed especially at the highest dose of 150 mg/kg bw/d NPNA; initial effects pointing towards haematotoxicity in dams were already seen at ≥ 15 mg/kg bw/d. Overall, the incidence of (total) foetal variations in the test groups was comparable to the control group. Based on the available data, classification of NPNA for developmental toxicity is considered unjustified.

No information is available regarding effects of NPNA on or via lactation.

The registrants concluded that classification of NPNA for reproductive toxicity **(fertility, developmental toxicity and effects on or via lactation) is currently not warranted** according to Regulation (EC) 1272/2008. Based on the available information, the eMSCA supports this conclusion but highlights that **data are insufficient for drawing a final conclusion, particularly on fertility effects after exposure to NPNA**.
Hence, in case the annual tonnage of NPNA exceeds 1000 tpa, reproductive toxicity of the substance shall be re-examined. In that case, an EOGRTS shall be proposed by the registrants or may be required by the Agency in accordance with Article 40 or 41 and Annex X (Section 8.7.3.) of REACH. The eMSCA will be ready to assess such new data upon submission in order to be able to eventually conclude on the reproductive toxicity of NPNA and to initiate possible risk management measures.

7.9.7. Hazard assessment of physico-chemical properties

Not part of this substance evaluation.

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

7.9.8.1 Derivation of DNEL(s)

According to Section R.8.4 of the REACH Guidance on Information Requirements and Chemical Safety Assessment (ECHA, 2012), a DNEL for the leading health effect needs to be derived for workers and every relevant human population, as well as every relevant route, duration and frequency of exposure if feasible. The registrants have calculated DNELs which are intended to protect both, workers and consumers, from acute and long-term systemic effects caused by inhalation, oral and dermal exposure to NPNA.

7.9.8.1.1 Workers

The routes of exposure to NPNA for workers are inhalation and dermal contact. Due to its very low vapour pressure inhalation exposure may occur in processes where aerosols are formed. Currently, there is no occupational exposure limit (OEL) of NPNA.

The eMSCA as well as the registrants concluded that NPNA has the potential to be harmful to human health following repeated exposure. Effects on the blood system and the liver occur at very low doses in different *in vivo* repeated dose toxicity studies. The lowest value which is associated with changes of different clinic parameters results from the 90-day study in rats conducted in 2016 (key study, for more detailed description see chapter 7.9.4). These changes represent the first signs of haemolytic anaemia and were considered as LOAEL and used as point of departure (PoD) for DNEL derivation by the eMSCA.

The following table summarises the study which was used for derivation of the long-term systemic DNELs for workers.

Table 9

DOSE DESCRIPTORS PER ENDPOINT				
Endpoint of concern	**Type of effect**	**Critical studies**	**Dose descriptor (LOAEL)**	**Justification/Remarks**
Repeated dose toxicity	Haemolytic anaemia	Repeated dose (90 days) oral toxicity study (OECD TG 424 combined with OECD TG 408) in rats exposed to NPNA (BASF 2016b).	Lowest observed adverse effect level (**LOAEL**) of **5 mg/kg bw per day.**	The LOAEL results from a subchronic oral repeated dose toxicity study (90 days) in rats (BASF, 2016b) is used as PoD.

The following two tables (10 and 11) show the detailed steps which were applied to get the worker DNELs for inhalation and dermal route.

Table 10

DETAILED OVERVIEW OF THE DNEL DERIVATION FOR INHALATION ROUTE ($DNEL_{WORKERS, INHALATION, LONG-TERMN, SYSTEMIC}$) CONDUCTED BY THE EVALUATING MSCA.		
Descriptor	**Value**	**Remarks**
Relevant dose descriptor	LOAEL: 5 mg /kg bw per d	The LOAEL is based on the sub-chronic oral toxicity study in rats. The critical systemic effect is haemolytic anaemia.
Modification of the relevant dose descriptor	70 kg bw 10 m^3/d respiratory volume 2 default absorption	Route-to-route extrapolation is needed from the oral to the inhalation route. For this purpose a default body weight of 70 kg and a respiratory volume of 10 m^3 per person and day are applied for workers according to the REACH Guidance R.8. In the absence of route-specific information an additional assessment factor of 2 was used to consider the different absorption properties of the respiratory tract and after oral intake. In addition, a factor of 7/5 is applied due to differences

	7/5 days/week	in experimental and worker exposure conditions (7 days/week → 5 days/week).
Corrected dose descriptor	5 mg/kg bw/d x 70 kg / 10 m^3/d / 2 x 7/5= 24.5 mg/m^3	
Assessment factor (AF)	**AF Value**	**Remarks**
Interspecies	4 x 2.5	The default factors for allometric scaling rat (4) and remaining differences (2.5) are applied according to the REACH Guidance R.8.
Intraspecies	5	The default factor for workers is applied according to the REACH Guidance R.8.
Exposure duration	2	The default factor for differences in exposure duration (sub-chronic → chronic) is applied according to the REACH Guidance R.8.
AF related to Dose-response-relationship	3	A default AF of 3 is applied according to the REACH Guidance R.8, as the as a starting point for the DNEL derivation is a LOAEL.
Quality of database	-	Not applicable.
$DNEL_{workers,}$ inhalation, long-term, systemic	24.5 mg/m^3 / (4 x 2.5 x 5 x 2 x 3) = **0.08 mg/m^3**	

Table 11

DETAILED OVERVIEW OF THE DNEL DERIVATION FOR DERMAL ROUTE ($DNEL_{WORKERS.\ DERMAL,\ LONG-TERMN,\ SYSTEMIC}$) CONDUCTED BY THE EVALUATING MSCA.		
Descriptor	**Value**	**Remarks**
Relevant dose descriptor	LOAEL: 5 mg /kg bw per d	The LOAEL is based on the sub-chronic oral toxicity study in rats. The critical systemic effect is haemolytic anaemia.
Modification of the relevant dose descriptor	7/5 days/week	Route-to-route extrapolation is needed from the oral to the dermal route. A factor of 7/5 is applied due to differences in experimental and worker exposure conditions (7 days/week → 5 days/week).
route-to-route extrapolation	7% dermal absorption	Route-to-route extrapolation is needed from the oral to the dermal route. Oral absorption was assumed to be ca. 50%, while dermal absorption is considered to be 7% (see 7.9.1; Charles River Laboratories (2021)). Thus, an additional modification factor of 7 (= 50%/7%) was used according to the REACH Guidance R.8 in order to consider different absorption values for the different uptake routes.
Corrected dose descriptor	5 mg/kg bw per d x 7/5 x 7 = 49 mg/kg bw per d	
Assessment factor (AF)	**AF Value**	**Remarks**
Interspecies	4 x 2.5	The default factors for allometric scaling rat (4) and remaining differences (2.5) are applied according to the REACH Guidance R.8.
Intraspecies	5	The default factor for workers is applied according to the REACH Guidance R.8.

DETAILED OVERVIEW OF THE DNEL DERIVATION FOR DERMAL ROUTE ($DNEL_{WORKERS, DERMAL, LONG-TERMN, SYSTEMIC}$) CONDUCTED BY THE EVALUATING MSCA.		
Descriptor	**Value**	**Remarks**
Exposure duration	2	The default factor for differences in exposure duration (sub-chronic → chronic) is applied according to the REACH Guidance R.8.
AF related to Dose-response-relationship	3	A default AF of 3 is applied according to the REACH Guidance R.8, as the as a starting point for the DNEL derivation is a LOAEL.
Quality of database	-	Not applicable.
$DNEL_{workers,}$ dermal, long-term, systemic	49 mg/kg bw/d / (4 x 2.5 x 5 x 2 x 3) = **0.16 mg/kg bw per d**	

An overview of the hazard conclusion by the eMSCA can be found in 3. A long-term systemic DNEL of 0.08 mg/m^3 for inhalation route as well as a long-term systemic DNEL of 0.16 mg/kg bw per d for dermal route was calculated (Table 12).

Table 12

HAZARD CONCLUSIONS FOR WORKERS MADE BY THE EVALUATING MSCA FOR NPNA.		
Route	**Hazard conclusion**	**Type of effect**
Inhalation	$DNEL_{systemic, long-term}$ = 0.08 mg/m^3	Haemolytic anaemia
Dermal	$DNEL_{systemic, long-term}$ = 0.16 mg/kg bw per d	Haemolytic anaemia

Acute DNELs

The registrants identified an acute hazard for NPNA and classified the substance as Acute Tox. 4 (H302). DNELs covering effects after acute inhalation and dermal exposure were derived by the registrants by using LD50 values from acute oral and dermal studies as PoD. In the opinion of the eMSCA a derivation of acute DNELs based on data resulting on lethality entail too many uncertainties and the eMSCA does not support the acute DNELs derived by the registrants. According to REACH Guidance on information requirements and chemical safety assessment, Chapters R.8 and R.14 and Part E the preferred approach is to set acute DNELs for a reference period of 15 min at 1-5 times the value of the long-term DNEL (default 3).

7.9.8.1.2 Consumers

Based on the types of rubber articles described in the CSR (ASL), the relevant route of exposure to NPNA for consumers is dermal contact.
As detailed in section 7.9.4, the LOAEL of 5 mg/kg bw/d (lowest tested dose in an oral subchronic guideline study (BASF, 2016b)) is used as PoD for long-term DNEL derivation. Respective data indicate that repeated oral exposure to the substance elicits adverse systemic effects in rats, i.e. haemolytic anaemia and liver toxicity. Both are considered relevant for human health. Local effects were not observed, except for the moderate skin sensitising potential of NPNA. Overall, the haematotoxic effects after repeated dosing by the oral route are considered most relevant for determining the PoD for the derivation of relevant DNELs for NPNA. For DNEL derivation, oral absorption is considered to be approximately 50%, while dermal absorption is considered to be 7% (worst case assumption; see 7.9.1).
A detailed overview of the derivation of the infrequent and long-term dermal DNELs as conducted by the eMSCA is presented in the following tables.

Long-term and infrequent DNELs - Dermal

Table 13

DETAILED OVERVIEW OF THE DERIVATION OF THE DNEL$_{CONSUMERS, LONG-TERM, DERMAL, SYSTEMIC EFFECTS}$ FOR NPNA CONDUCTED BY THE EMSCA		
Description (AF=Assessment factor)	**Value**	**Remark**
Relevant dose descriptor	5.0 mg/kg bw/day = LOAEL	This LOAEL resulting from a subchronic oral repeated dose toxicity study (90 days) in rats (BASF, 2016b) is used as PoD.
Modification of relevant dose descriptor (route-to-route extrapolation)	5.0 mg/kg bw/day * 7 = $LOAEL_{corr.}$	Route-to-route extrapolation is needed from the oral to the dermal route. Oral absorption was assumed to be ca. 50%, while dermal absorption is considered to be 7% (see 7.9.1; Charles River Laboratories (2021)). Thus, an additional modification factor of 7 (= 50%/7%) was used according to the REACH Guidance R.8 in order to consider different absorption values for the different uptake routes.
Corrected dose-descriptor	**35 mg/kg bw/day**	
Overall AFs	**600**	
AF for interspecies differences	4*2.5	The default factors for allometric scaling rat (4) and remaining differences (2.5) are applied according to the REACH Guidance R.8.
AF for intraspecies differences	10	The default factor is applied according to the REACH Guidance R.8 because no substance-specific information is available for an adjustment.
AF for differences in exposure duration	2	This AF was applied according to the REACH Guidance R.8 to extrapolate the duration from sub-chronic to chronic.
AF related to dose response relationship	3	A default AF of 3 is applied according to the REACH Guidance R.8, as the as a starting point for the DNEL derivation is a LOAEL.
AF related to quality of database	1	Default value.
$DNEL_{consumers, dermal, long-term, 24 h/day, systemic effects}$	**0.06 mg/kg bw/day**	

Table 14

DETAILED OVERVIEW OF THE DERIVATION OF THE DNEL$_{CONSUMERS, INFREQUENT USE, DERMAL, SYSTEMIC EFFECTS}$ FOR NPNA CONDUCTED BY THE EMSCA		
Description (AF=Assessment factor)	**Value**	**Remark**
Relevant dose descriptor	5.0 mg/kg bw/day = NOAEL	This NOAEL results from a subacute oral repeated dose toxicity study in rats (Bayer, 2002). The NOAEL is based on significantly affected blood parameters at the next higher dose tested (20 mg/kg bw/day). According to REACH Guidance R.15 (section R.15.2.3., step 4) a DNEL adjusted to infrequent use (< 15 d/a) can be based on the results of short-term repeated-dose toxicity studies. The NOAEL observed in the 28-day study was based on similar effects compared to the 90-day study. Thus, the 28-day

DETAILED OVERVIEW OF THE DERIVATION OF THE DNEL$_{CONSUMERS, INFREQUENT USE, DERMAL, SYSTEMIC EFFECTS}$ FOR NPNA CONDUCTED BY THE EMSCA		
Description (AF=Assessment factor)	**Value**	**Remark**
		study is considered appropriate for derivation of the DNEL for infrequence exposure. By default, this DNEL should be derived for 24 h exposure/d.
Modification of relevant dose descriptor (route-to-route extrapolation)	5.0 mg/kg bw/day *7 = $LOAEL_{corr}$	Route-to-route extrapolation is needed from the oral to the dermal route. Oral absorption was assumed to be ca. 50%, while dermal absorption is considered 7% (7.9.1; Charles River Laboratories (2021)). Thus, an additional modification factor of 7 (= 50%/7%) was used according to REACH Guidance R.8 in order to consider the different absorption values for the different uptake routes.
Corrected dose-descriptor	**35 mg/kg bw/day**	
Overall AFs	**100**	
AF for interspecies differences	4*2.5	The default factors for allometric scaling rat (4) and remaining differences (2.5) are applied according to the REACH Guidance R.8.
AF for intraspecies differences	10	The default factor is applied according to the REACH Guidance R.8 because no substance-specific information is available for an adjustment.
AF for differences in exposure duration	1	According to REACH Guidance R.8, the AF for extrapolation from a subacute study to the long-term consumer DNEL can be omitted in case of DNEL for infrequent use.
AF related to dose response relationship	1	As the dose descriptor is a NOAEL already, no AF has to be applied.
AF related to quality of database	1	Default value.
$DNEL_{consumers, dermal, infrequent use, 24 h/day, systemic effects}$	**0.35 mg/kg bw/day**	

It is noted that the long-term dermal DNEL derived by the Lead Registrant (reference to the dossier update of March 2021) did not consider the considerably lower absorption after dermal exposure compared to oral exposure (i.e. 7% versus 50%), although this fact was mentioned by the registrants in this context. Thus, the dermal long-term DNEL derived by the registrants is considerably lower than the one calculated by the eMSCA shown above. No infrequent DNELs were derived by the registrants.

No adjustment of the dermal (long-term and infrequent) DNELs for shorter daily exposure duration was performed, as in case of dermal exposure it has to be assumed (and the available dermal absorption data suggests) that the test substance may accumulate in the stratum corneum enabling dermal penetration of NPNA even after the direct dermal exposure had ceased.

The qualitative assessment revealed that the test substance is a moderate skin sensitiser according to the potency categorisation suggested in REACH Guidance R.8 (ECHA, 2012), that according to Regulation (EC) 1272/2008 has to be classified as Skin Sens. 1, H317 (May cause an allergic skin reaction). No quantitative data suitable for deriving a DNEL/DMEL for the dermal route for sensitising effects were available.

Table 15

HAZARD CONCLUSIONS		
Route	**Type of effect**	**Hazard conclusion**
Dermal	Systemic effects, infrequent use, 24 h/day Haemolytic anaemia	**$DNEL_{consumers, dermal, infrequent use, 24 h/day, systemic effects}$ = 0.35 mg/kg bw/day**
Dermal	Systemic effects, long-term, 24 h/day Haemolytic anaemia	**$DNEL_{consumers, dermal, long-term, 24 h/day, systemic effects}$ = 0.06 mg/kg bw/day**
Dermal	Local effects, long-term and infrequent use	The qualitative assessment revealed that the test substance is a moderate sensitiser. Quantitative data suitable to derive a DNEL/DMEL are not available. The registrants concluded that the consumer does not come into contact with the test substance itself. The exposure is limited to rubber articles that contain the test article at very low concentration and with low release, wherefore, the risk is considered to be rather low.

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

Classification of NPNA as Acute Tox. 4, H302 (Harmful if swallowed) and Skin Sens. 1, H317 (May cause an allergic skin reaction) is warranted. Furthermore, various *in vivo* repeated dose toxicity studies are available, indicating that CLP classification of NPNA regarding STOT RE may be warranted. These studies indicate that NPNA causes haemolytic anaemia and liver toxicity in rats; however, effects are considered borderline with respect to severity and effect levels. Thus, classification of NPNA as STOT RE 2 is currently not proposed by the eMSCA.

Due to the severity of adverse effects that NPNA can cause, especially regarding skin sensitisation, as well as due to the inconsistency in self-classification among C&L notifiers, harmonised classification for NPNA leading to a new entry in CLP-Annex VI is proposed and considered justified. A respective CLH proposal has been prepared by the eMSCA and submitted to ECHA for accordance check. For transparency reasons, the relevant data with respect to specific target organ toxicity after repeated exposure (haematotoxicity and liver toxicity) will be included in the CLH proposal, as well.

7.10. Assessment of endocrine disrupting (ED) properties

Not part of this substance evaluation.

7.11. PBT and VPVB assessment

The PBT/vPvB concern leading to the evaluation of the substance has been removed during the initial assessment. Based on the available information on bioaccumulation for the substance, the eMSCA does not consider the B criterion according to REACH Annex XIII fulfilled for NPNA. Consequently, despite potential persistence of NPNA and its (eco)toxic properties leading to the fulfilment of the P and T criterion, the eMSCA concludes that NPNA is neither a PBT nor a vPvB substance. See section 7.8 for a more detailed assessment of the available data on the persistence, bioaccumulation and ecotoxicity of the substance.

7.12. Exposure assessment

7.12.1. Human health

7.12.1.1. Workers

7.12.1.1.1. Overview of uses and exposure scenarios

The eMSCA assessed the exposure scenarios contained in the registration in a separate confidential annex to this report.

7.12.1.1.2. Scope and type of exposure

In the initial registration dossiers the registrants provided a worker exposure assessment based on modelled data. No measured data were submitted. Exposure related issues identified by the eMSCA in the initial SEv procedure were addressed adequately by the registrants in an updated registration dossier. This section of the substance evaluation report is mainly based on the exposure assessment and exposure scenarios from the updated registration dossier.
A summary of general remarks and assumptions is given in Table 16.

Table 16

DETAILS OF THE EXPOSURE ESTIMATION IN THE UPDATED CSR		
Exposure route	**Assessment method**	**Remarks and modifications**
Inhalation	Modelled: EasyTRA 4.1.0 In some instances, the exposure values have been calculated with the Advanced Reach Tool (ART v1.5)	For inhalation exposure, the banded approach specified by ECETOC was applied.
Dermal	Modelled: EasyTRA 4.1.0 In some instances, the exposure values have been calculated with the RiskofDerm v2.1 model .	Concentrations: For dermal exposure, the substance concentrations in preparations have been modified using a linear approach. Duration: The duration of activity was considered based on the banded approach (ECETOC).
Oral	N.A.	N.A.

For the inhalation and dermal exposure estimation the registrants used the EasyTRA 4.1.0. Technical measures are merely represented by the corresponding PROCs in the respective setting (industrial, professional) with some additional information on the work practice and operational conditions. For dermal exposure, the substance concentrations in preparations have been modified using a linear approach. Under the assumption that EasyTRA estimates reflect reasonable worst case situations, this approach was accepted by the eMSCA.

In some of the exposure scenarios additional risk management measures are necessary to control the risk resulting from occupational exposure: Local exhaust ventilation, a respirator (Dust: half or full mask with P2 or P3 filter; Fumes: full mask with ABEK P3 filter) or gloves (the registrants have specified the thickness and breakthrough time for natural latex, polychloroprene and nitrile). For gloves implemented as an additional risk management measure (RMM) the following effectiveness values are assumed: Use of suitable gloves: 80%; Use of suitable gloves in combination with basic employee training: 90%; Use of suitable gloves in combination with specific activity training: 95%; Use of suitable gloves in combination with intensive management supervision controls: 98%. The registrants also specified the use time of gloves and addressed exposure scenarios where moving objects prevent the use of gloves because gloves can be caught into the machinery leading to serious injuries of workers. The registrants stated that machinery with moving parts is always encapsulated preventing a caught up of gloves. Acute exposure or peak

exposure has been assessed for all scenarios. In the sections below the exposure estimation is summarised.

7.12.1.1.3. Monitoring data

No monitoring data available.

7.12.1.1.4. **Modelled data**

Each contributing scenario in the CSR of NPNA is described by the corresponding process category (PROC), only. In some instances, the model parameters of the Advanced Reach Tool (ART v1.5) and RiskofDerm v 2.1 are also described. The registration dossier contains several overviews over the exposure scenarios and settings applied for the exposure estimation. All scenarios assume the implementation of a good basic standard of occupational hygiene.

7.12.1.1.5. Comparison of monitoring and modelled data

Not relevant.

7.12.1.1.6. **Discussion**

Exposure Estimates

A sample of recalculated exposure estimates has shown no significant deviations between the values obtained by the eMSCA and the estimates provided in the updated CSR. For the estimation of dermal exposure the registrants have used modifying factors accounting for the reduction of exposure due to lower concentration of the substance in preparations and due to dermal absorption. Under the assumption that EasyTRA estimates reflect reasonable worst case situations, this approach was accepted by the eMSCA. For all other scenarios the registrants generally used the banded approach of EasyTRA. Additionally, the process temperature was taken into in the updated version of the CSR. At least in exposure scenario ES 8 ('Use of lubricants in open high temperature processes, e.g. quenching fluids, glass release agents') a higher volatility for NPNA was considered due to a higher process temperature.

Peak exposure

According to REACH Annex I, an exposure scenario is 'the set of conditions that describe how the substance is manufactured or used during its life-cycle and how the manufacturer or importer controls, or recommends downstream users to control, exposures of humans and the environment' (EC, 2012b). These conditions should therefore also cover the control of peak exposures where these could occur and where they might lead to a risk. Although relevant information from the CSR indicated peak exposure during the use of the substance, the initial CSR did not assess peak exposure at all. According to REACH Guidance chapters R.8 and R. 14 (ECHA, 2010b; ECHA, 2010c), if such peak exposure is expected and the substance is classified for acute effects, generally an acute DNEL has to be derived and the acute exposure has to be assessed. In the updated CSR an acute DNEL has been derived. The updated CSR also now contains exposure estimations using modelled data for acute (peak) exposures for all scenarios.

Personal Protective Equipment

Dermal protection

In all exposure scenarios the use of suitable gloves is recommended. While suitable gloves were not specified in the initial CSR the registrants) have specified the glove material (natural latex, polychloroprene and nitrile), the thickness and breakthrough time in the updated CSR. For gloves implemented as an additional RMM the following effectiveness values are assumed: Use of suitable gloves: 80%; Use of suitable gloves in combination with basic employee training: 90%; Use of suitable gloves in combination with specific activity training: 95%; these values are supported by the ECETOC documentation, for industrial, and for professional settings. The use of suitable gloves in combination with intensive management supervision controls may also justify a glove efficacy of 98%.

Respiratory protection

In exposure scenarios ES 1, 3, 10, 11, for some contributing scenarios a respirator is either required or an option to control exposure. While the equipment to be used is not described in the initial CSR the registrants recommend the following respiratory protection in the updated CSR: Dust: half or full mask with P" or P3 filter, fumes: full mask with ABEK P3 filter.

Duration of use of personal protective equipment

According to Article 4, Directive 89/656/EEC (EC, 1989) (on the minimum health and safety requirements for the use by workers of personal protective equipment at the workplace) the PPE used must be appropriate for the risk involved, without itself leading to any increased risk.

It has been demonstrated that exceedance of a certain duration of use comprises a burden to the worker and increases the risk (AGS, 2011). It should be noted that extended use of occlusive gloves can be considered a wet work exposure, if the hands become moist due to sweat (AGS, 2011). Wet work includes activities where the workers wear protective gloves with occlusion effects (accumulation of heat and moisture) for a corresponding period. The specified maximum duration of use of PPE shall be taken into account in the exposure scenario. The registrants specified the use time of gloves for all scenarios and indicated in the updated CSR that workers are advised to change gloves, if exposure to the substance has occurred.

7.12.1.2. Consumers

No consumer uses were identified by the registrants during the first year of substance evaluation and therefore exposure assessment and risk characterisation for consumers were missing in the CSR. However, publicly available data of the registrants indicated that consumer exposure to NPNA was likely and further information was requested in the first Decision.

In July 2017, the registrants provided first consumer exposure scenarios about rubber products for oil-resistant hoses, tyres - side walls, and belts (fan belts, cam belts). In their exposure estimates, only chronic effects have been assessed by averaging the event exposure over time. An exposure assessment for acute effects is missing for all contributing consumer exposure scenarios. The consumer exposure assessment of the eMSCA based on the identified uses of the registrants' recalculations according to the REACH Guidance chapters R.8 and R.15 and without averaging over the year led to higher exposure estimates, even when considering less conservative exposure parameters in terms of room volume, ventilation rate and exposure duration. In particular for the dermal route, the concern could not be clarified without additional data.

In March 2021, the registrants updated the exposure scenarios of consumer ASL of rubber products and considered the results of the requested dermal absorption study. The scope of this evaluation was, thus, focussed on dermal exposure only, as risks regarding dermal exposure of consumers were identified upon the first Decision.

Table 17

DETAILS OF THE EXPOSURE ESTIMATION IN THE UPDATED CSR		
Exposure route	**Assessment method**	**Remarks and modifications**
Inhalation	Modelled: ConsExpo web v1.0.7	Evaporation model
Dermal	Modelled: ECETOC TRA	Thickness model, algorithm: PI x CA x FQ x TL x D x 1000/BW)
Oral	N.A.	N.A.

Further details about the exposure assessment are recorded in a confidential annex to this report.

7.12.2. Environment

Environmental exposure assessment was not part of the substance evaluation.

7.13. Risk characterisation

7.13.1. Human Health

7.13.1.1. Workers

For the calculation of the RCRs, the DNELs derived from the LOAEL obtained in an oral 90-day study with NPNA were used. The DNEL derivation is based on haemolytic anaemia in rats as the most critical systemic effect. For detailed description of the DNEL derivation refer to chapter 7.9.9. The predicted exposure levels according to the registration update are compared to the long-term systemic DNEL of 0.08 mg/m3 for the inhalation route and the long-term systemic DNEL of 0.16 mg/kg bw per day for the dermal route.

During the SEv the registrants implemented a quantitative risk assessment addressing potential acute effects resulting from peak exposure. The eMSCA does not support the acute DNELs used by the registrants. According to REACH Guidance R.8, the preferred approach by eMSCA is to set acute DNELs for a reference period of 15 min at 1-5 times the value of the long-term DNEL (default value of 3). These derived values were compared to the short-term exposure levels predicted by the Lead Registrant according to the CSR (Update 03/2021).

7.13.1.1.1. Inhalation route

The risk assessment for each scenario regarding systemic effects after long-term inhalation yielded risk characterisation ratios (RCRs) of less than 1 (highest numeric value was 0.44), when RMM described in chapter 2.1.1 (confidential part) are implemented.

Regarding occupational risks associated with peak exposure for the inhalation route, there are two scenarios (ES 12.2, ES 13.2) with RCRs above 1 (10) using three times the value of the long-term DNEL (i.e. 0.24 mg/m³). However, the implementation of LEV or RPE respectively as additional RMM would result in RCRs less than 1.

7.13.1.1.2. Dermal route

The risk assessment for each scenario regarding systemic effects after long-term dermal exposure yielded RCRs of less than 1 (highest numeric value of 0.34) when risk reduction measures described in chapter 2.1.1 (confidential part) are implemented.

Regarding occupational risks associated with peak exposure for the dermal route, there are no scenarios RCRs above 1 using 3-times the value of the long-term DNEL (i.e. 0.48 mg/kg bw/d).

7.13.1.1.3. Combined routes (inhalation and dermal)

Combined risk characterisation via the inhalation and dermal route is performed by summation of the respective RCRs and resulted in RCRs less than 1.

7.13.1.1.4. N-nitrosamine formation

It is well known that secondary amines and nitrosating agents can form N-nitrosamines. About 90% of the tested N-nitrosamines have been shown to be carcinogenic in animal studies (Wolf, 1989).
The reaction of secondary amines and nitrosating agents depends on a variety of different factors (e.g. the concentration and properties of the precursors, process parameters and external influences) (Brown, 1999; Issenberg, 1976). Therefore it is difficult to predict, if external N-nitrosamine will be generated from its secondary amine and at that time it was not possible to estimate the amount formed (Wolf, 1989).

As N-nitrosamines are not manufactured in the sense of the REACH definition but are inadvertently formed, there exist no toxicological assessment for the corresponding N-

nitrosamine (N-nitroso-NPNA). NPNA is a secondary amine, meaning that it can, in principle, generate the corresponding N-nitrosamine. The possibility of N-nitrosamine formation was not mentioned and assessed in the initial registration dossier(s). A literature search did not reveal information, based on which the risk could be excluded.

The eMSCA therefore requested the registrants in the draft decision to prove that the corresponding N-nitrosamine to NPNA is not formed above a concentration of 0.001% (w/w) in mixtures or 0.075 µg/m³ in the air during the use of NPNA.
In their response to the Decision the registrants described the assay of N-nitroso-NPNA in mixtures and in the air during handling of NPNA.

According to the registrants, lubricants represent the most likely use in which nitrosamines are formed externally, since the lubricant is exposed to air over a prolonged period of time, and the quenching object generates a localised heat and mixing with air. Rubber products do not differ significantly in the way they are manufactured, the critical step concerning the nitroso formation is the vulcanisation. Therefore, this step can be easily simulated in the Rubber Application Laboratory in a controlled way. A worst-case rubber mixture with a high amount of NPNA was prepared and the off-gassing of the vulcanisation was monitored. In the neat substance and in the lubricant mixtures no N-nitroso compound was detected. In the vulcanisation experiment, a small amount of the N-nitroso compound could be detected in the off-gas of the vulcanisation oven. The amount was below the given limit of 75 µg/m3, representing a worst-case scenario, which is not representative for the air that workers are exposed to, because the concentration of NPNA was higher than normal and the off-gas was further diluted in the room air. The external formation of nitrosamines is therefore not regarded as a critical factor in the use of NPNA.

7.13.1.2. Consumers

For the calculation of the RCRs, the DNELs derived from the LOAEL obtained in an oral 90-day study with NPNA (i.e. 5 mg/kg bw/d; (BASF, 2016b)) were used. For a detailed description of the DNEL derivation refer to chapter 7.9.9.1.The exposure levels predicted by the registrants in the registration update from July 2017 were compared to the corrected systemic DNELs for long-term and infrequent use.
As indicated in the preceding paragraph, external nitrosamine-formation is not considered a critical factor in the use of NPNA.

The risk assessment for each scenario regarding systemic effects after infrequent and long-term dermal exposure yielded RCRs below 1 (highest numeric value: 0.88). Hence, no risks were identified for consumers with regards to dermal exposure to NPNA. Further details on RCR calculation can be found in the confidential Annex, section 3.
It is highlighted that NPNA is a moderate skin sensitiser. However, no DNELs/DMELs for local effects (i.e. skin sensitisation) could be derived, as no suitable quantitative data were available. According to REACH Guidance Part E and R.8, for these types of effects, the registrants need to develop a qualitative argumentation to demonstrate under which conditions of use the risk is adequately controlled and to provide arguments that the conditions of use as described in the exposure scenario will make it unlikely that adverse effects occur. The registrants stated in the dossier: “However, the general population does not come into contact with the test article itself. The exposure is limited to rubber articles that contain the test article at very low concentration and with low release. Therefore, the risk is considered to be negligible.” The eMSCA partly agrees with this statement, as dermal absorption data indicates that < 10% NPNA is absorbed through the skin from a formulation using base oil containing 5% NPNA (worst-case assumption by the registrants). < 1% NPNA was absorbed when pure NPNA or NPNA incorporated in a rubber matrix (disc) containing up to 3.5% NPNA was tested. These rubber discs were chosen as they were reported to represent relevant worst-case samples (“Due to the use pattern of the test item, a rubber matrix was selected to generate a relevant and technically feasible test sample representing a worst-case sample of the test item using a simplified manufacturing method based on the actual industrial processing (ca 3.5% (w/w) and ca 0.5% (w/w) in a rubber disc)”). Homogeneity and concentration of NPNA in the rubber discs were ensured by respective analyses. Nevertheless, the eMSCA highlights that skin sensitisation due to dermal exposure of consumers to (rubber articles containing) NPNA cannot be entirely excluded, although dermal absorption is considered to be low. This is of particular interest,

as not only the direct contact is of relevance when assessing the dermal route of exposure, but data further indicate that absorption (and hence potentially also toxicity) may occur after the direct dermal exposure ceased, e.g. due to remaining substance in the stratum corneum (for details refer to section 7.9.1).

According to Regulation (EC) 1272/2008, NPNA has to be classified as Skin Sens. 1, H317 (May cause an allergic skin reaction). A respective CLH proposal has been prepared by the eMSCA and submitted to ECHA for accordance check.

7.14. References

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7.15. Abbreviations

ALT	Alanine aminotransferase
Bw	Body weight
CHL	Chinese hamster lung
CHO	Chinese hamster ovary
C&L	Classification and labelling
CLP	Classification, Labelling and Packaging
CoRAP	Community Rolling Action Plan
d	day
DIT	Developmental immunotoxicity
DMSO	Dimethyl sulfoxide
DNEL	Derived no effect level
DNT	Developmental neurotoxicity
(e)MSCA	(evaluating) Member State Competent Authority
EOGRTS	Extended One-Generation Reproductive Toxicity Study
EU	European Union
GD	Gestation day
Hb	Haemoglobin
HCT	Haematocrit
HPLC	High performance liquid chromatography
L	Liter
LD50	Lethal dose 50%
LEV	Local exhaust ventilation
LOAEL	Lowest observed adverse effect level
MCH(C)	Mean corpuscular haemoglobin (concentration)
MCV	Mean corpuscular volume
Na	sodium
NOAEL	No observed adverse effect level
NPNA	N-1-naphtylaniline
OECD	Organisation for Economic Co-operation and Development
Pa	Pascal
P(N)EC	Predicted (no) effect concentration
RBC	Red blood cell
RCR	Risk characterisation ratios
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals
RET	reticulocytes
RPE	Respiratory protective equipment
TG	Test guideline