European Commission

SCOEL/REC/300
2-Nitropropane

Recommendation from the
Scientific Committee on Occupational Exposure Limits

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on Occupational Exposure Limits

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EUROPEAN COMMISSION

Directorate-General for Employment, Social Affairs and Inclusion
Directorate B —Employment
Unit B.3 — Health and safety

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2017

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Contents

RECOMMENDATION FROM THE SCIENTIFIC COMMITTEE ON OCCUPATIONAL EXPOSURE LIMITS FOR 2-NITROPROPANE

8-hour TWA:	not assigned
STEL:	not assigned
BLV:	not assigned
Additional categorisation:	SCOEL carcinogen group A (DNA-reactive genotoxic carcinogen without a threshold)
Notation:	skin

The present Recommendation was adopted by SCOEL on 2017-02-08.

RECOMMENDATION EXECUTIVE SUMMARY

Outcome Considerations

2-Nitropropane (2-NP) is mainly used in chemical production as feedstock and intermediate. 2-NP is produced in low volumes and occupational exposures occur primarily in its production and its use as a solvent in inks, adhesives, paints and coatings. It is assumed that these uses have been decreasing over time as employers have eliminated 2-NP from the used solvent mixtures (UK IOM 2011).

As 2-NP is a volatile compound, the main exposure route of workers is by inhalation. However, also dermal exposure cannot be excluded.

2-NP is absorbed in the lungs, but also permeates the skin. It undergoes rapid metabolism and is eliminated primarily by exhalation as CO_2.

In a chronic rat inhalation study (Griffin et al. 1980 and 1981) a weak liver-specific carcinogenic effect of 2-NP was demonstrated. This hepatocarcinogenicity was subsequently confirmed in several rat studies (e.g. Fiala et al. 1987b, Denk et al. 1990).

Mechanistic studies have revealed that 2-NP can be metabolically activated to DNA-reactive products in several ways. A kinetic study demonstrated two metabolic processes (Denk et al. 1989), a saturable pathway at lower 2-NP concentrations related to weaker hepatocarcinogenicity and an unsaturable pathway at higher concentrations associated with stronger effects (hepatotoxicity and hepatocarcinogenicity). However, It is unclear which of the biotransformation steps in the metabolism of 2-NP are saturable and which are not.

As no evidence exists that could indicate that these modes of action are not relevant for humans, it is concluded that 2-NP is a genotoxic carcinogen, although the exact mode of action underling the carcinogenicity remains to be elucidated.

Derived Limit Values

As a genotoxic carcinogen, 2-NP acts via a non-threshold mode of action. Therefore, no limit values are recommended. A cancer risk assessment has been performed based on the chronic rat inhalation study by Griffin et al. (1981). The following risk numbers were calculated:

a tumor risk of 1 : 10 at 64.4 mg/m^3,

a tumor risk of 1 : 1000 at 0.644 mg/m^3,

a tumor risk of 1 : 10000 at 0.0644 mg/m^3,

and a tumor risk of 1 : 1000000 at 0.000644 mg/m^3.

Cancer risk assessments have previously been performed by the Dutch DECOS (NL DECOS 1999) and the German Committee on Hazardous Substances (AGS) (DE AGS 2015). Both assessments used the same critical study, but slightly different approaches, resulting in comparable risk numbers.

Skin notation

A high skin permeability of 2-NP has been demonstrated. This is supported by physico-chemical properties, in particular the high boiling point, a relatively low evaporation rate and an octanol-water partition coefficient that indates good solubility in both aqueous and hydrophobic phases. As dermal exposure is a relevant exposure route for 2-NP, a *"skin" notation* is recommended to minimise uptake of this genotoxic carcinogen.

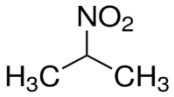
Biological Monitoring

No relevant and established biological monitoring method was identified.

RECOMMENDATION FROM THE SCIENTIFIC COMMITTEE ON OCCUPATIONAL EXPOSURE LIMITS FOR 2-NITROPROPANE

RECOMMENDATION REPORT

1. CHEMICAL AGENT IDENTIFICATION AND PHYSICO-CHEMICAL PROPERTIES

Name:	2-nitropropane	
Synonyms:	dimetylnitromethan; isonitropropan; 2-NP	
Molecular formula:	$C_3H_7NO_2$	
Structural formula:		
Index no.:	609-002-00-1	ECHA 2016a
EC No.:	201-209-1	ECHA 2016a
CAS No.:	79-46-9	ECHA 2016a
Molecular weight:	89.09 g/mol	
Octanol/water partition coefficient ($logP_{OW}$)	0.93 - 1.35	CITI 1992 ECHA 2016b
Vapour pressure:	17.32 hPa (20°C)	ECHA 2016b
Relative evaporation rate:	1.1	Riddick et al. 1985
Water solubility:	17400 mg/L (25°C, pH 7)	ECHA 2016b
Physical state:	Liquid at 20°C, 101.3 kPa	ECHA 2016b
Boiling point	120.3°C at 101.3 kPa	ECHA 2016b
Flash point:	26°C at 102.03 kPa	ECHA 2016b
Conversion:	1 ml/m^3 (ppm) = 3.7 mg/m^3 (20 °C, 101.3 kPa) 1 mg/m^3 = 0.27 ml/m^3 (ppm) (20 °C, 101.3 kPa)	DE AGS 2015

2. EU HARMONISED CLASSIFICATION AND LABELLING

Information about the EU harmonised classification and labelling for 2-nitropropane (2-NP) is provided by ECHA (2016a), as summarised in Tables 1.

Table 1: Classification according to Regulation (EC) No 1272/2008, Annex VI, Table 3.1 "List of harmonised classification and labelling of hazardous substances" (ECHA 2016a).

Classification		**Labelling**			**Spec. Conc. Limits, M-factors**
Hazard Class & Category Code(s)	**Hazard statement code(s)***	**Hazard statement code(s)***	**Suppl. Hazard statement code(s)**	**Pictograms, Signal Word Code(s)**	
Flam. Liq. 3	H226	H226	-	GHS07 GHS02 GHS08 Dgr**	-
Acute Tox.4	H302	H302			
Acute Tox.4	H332	H332			
Carc. 1B	H350	H350			

* *Flam. Liq. 3, H226 Flammable liquid and vapour*
Acute Tox.4, H302 Harmful if swallowed
Acute Tox.4, H332 Harmful if inhaled
Carc. 1B, H350 May cause cancer

** *Signal word code 'Dgr' for 'Danger*

3. CHEMICAL AGENT AND SCOPE OF LEGISLATION

2-Nitropropane is a hazardous chemical agent in accordance with Article 2 (b) of Directive 98/24/EC and falls within the scope of this legislation.

2-Nitropropane is also a carcinogen or mutagen for humans in accordance with Article 2(a) and (b) of Directive 2004/37/EC and falls within the scope of this legislation.

4. EXISTING OCCUPATIONAL EXPOSURE LIMITS

An OEL for 2-NP at EU level has not been adopted yet, nor is there any known BLV (Biological Limit Value); however, OEL's and risk-based values exist in various Member States as well as outside the EU. These OEL's and risk-based values are presented in Table 2 as examples, but the list should not be considered as exhaustive.

Overall, the 8 hrs TWA values adopted in EU Member States and in other countries overseas can be grouped into 5 clusters:

- risk-based values
- OEL < 18 mg/m³ (<5 ppm)
- OEL of 18-19 mg/m³ (5 ppm)
- OEL of 35-36 mg/m³ (10 ppm)
- OEL of 90 mg/m³ (25 ppm)

Most EU Member States use 18 mg/m^3 (5 ppm) and most non-EU Member States use 36 mg/m^3 (10 ppm). Potential reasons for value differences are manifold, e.g. selection of a different key study and/or point of departure (POD) and the application of different uncertainty factors. However, the differences were not evaluated in detail.

The current OEL (OSHA permissible exposure limits (PEL)) in the USA is 90 mg/m³ or 25 ppm (US OSHA 2016), although the ACGIH threshold limit values (TLV) is 36 mg/m^3 (10 ppm). NIOSH did not establish a numeric REL-value (recommended exposure limit), but recommends to control and handle 2-NP as a potential human carcinogen, i.e. to keep exposure to the lowest feasible level (US NIOSH 1988; US NIOSH 2016).

The lowest OEL, established in Sweden, and the risk-based values from the Netherlands and Germany are considered in some detail:

- Sweden lowered the TWA from 18 to 7 mg/m^3 as the MOS (Margin of Safety or Safety Margin) had to be increased because of the seriousness of the critical effect (liver toxicity), the short exposure required to induce effects in humans (supported by animal data) and genotoxic carcinogenicity observed in animal that was considererd relevant for humans. An impact assessment indicated no extra cost at a lowering of the OEL to 7 mg/m^3. As such, the lowering of the OEL was a precautionary measure with no socio-economic costs foreseen (Jarnberg, personal communications 2016.01.15 and 2016.01.18). The present Swedish OEL for 2-NP is from 1996 (SE SWEA (2011) and is based on a consensus report from the Swedish Criteria Group for Occupational Standards (SE SCG 1995).
- The Netherlands considered 2-NP as a genotoxic carcinogen and estimated that an "additional lifetime cancer risk" (ALCR) of 4x10^{-3} was associated with an 8h/d, 40 years occupational exposure level of 3.6 mg/m^3 (1 ppm) and that an ALCR of 4x10^{-5} was associated with 0.036 mg/m^3 (0.01 ppm) under the same occupational exposure conditions (DECOS 1999). The latter was enforced as of 2007 (NL STCRT 2006).
- Also Germany concluded that 2-NP is a genotoxic carcinogen (DE AGS 2015) and considered a worklife exposure of 1.78 mg/m^3 to be associated with a "tolerable risk" of 4:10^3 and a worklife exposure of 0.178 mg/m^3 (0.048 ppm) with the "acceptable risk" of 4:10^4.

Sweden, the Netherlands and Germany had based their concentrations on animal health effects data from two publications by Griffin et al. (1980 and 1981).

Table 2: Overview of existing OELs and risk numbers for 2-NP (adapted from the GESTIS database)

EU	TWA* (8 hrs)		STEL# (15 min)		Remarks	References
	ppm	mg/m³	ppm	mg/m³		
Austria	5	18	20	72	TRK@	AT GKV (2011)
Belgium	10	37	-	-	-	BE KB (2014)
Denmark	5	18	-	-	-	DK DWEA (2016)
Finland	5	18	40	150	-	FI MSAH (2012)
Germany	0.48	1.78	-	-	$4:10^3$ ("Toleranzrisiko")	DE AGS (2015)
Germany	0.048	0.178	-	-	$4:10^4$ ("Akzeptanzrisiko")	DE AGS (2015)
Hungary	-	-	-	18	-	HU MHSFA (2000)
Ireland	5	18	-	-	-	IE HSA (2011)
Netherlands	-	3.6	-	-	$4x10^{-3}$ ("ALCR")&	NL DECOS (1999)
Netherlands	-	0.036	-	-	$4x10^{-5}$ ("ALCR")	NL STCRT (2006)
Spain	5	19	-	-	-	ES INSHT (2011)
Sweden	2	7	6	20	-	SE SWEA (2011)
United Kingdom	5	19	-	-	-	UK HSE (2011)
Non-EU						
Australia	10	36	-	-	-	AU SWA (2011)
Canada (Ontario)	10	-	-	-	-	CA OML (2013)
Canada (Québec)	10	36	-	-	-	CA IRSST (2010)
China	-	30	-	-	-	GESTIS (2015)
New Zealand	5	19	-	-	-	NZ HS (2013)
Norway	10	35	-	-	-	NO NLIA (2011)
Singapore	10	36	-	-	-	GESTIS (2015)
South Korea	10	35	-	-	-	GESTIS (2015)
Switzerland	5	18	-	-	-	CH SUVA (2015)
USA (OSHA)	25	90	-	-	Current OSHA PEL - TWA	US OSHA (2016)
USA (NIOSH)	-	-	-	-	REL$	US OSHA (2016)

* Occupational Exposure Limit (e.g. MAK, TRK, TLV, PEL, REL)
\# Short Term OEL (e.g. STEL)
& Additional Lifetime Cancer Risk
$ Recommended Exposure Level: Exposure to be minimized to the lowest feasible level

5. OCCURRENCE, USE AND OCCUPATIONAL EXPOSURE

5.1. Occurrence

There is no clear evidence about the occurrence of 2-NP in nature. Therefore, it appears that synthetically produced 2-NP enters the environment mainly as a result of anthropogenic activities. 2-NP substance may be formed during the combustion of nitrogen-rich organic material, as is the case with cigarette smoking (CASA 2010), but probably also on a minor scale by natural fires. 2-NP enters the atmosphere during its manufacture (although it is generally used in closed system since the 1980s) and enters the environment also as a result of its use as a solvent (IARC 1999) in printing ink and in surface coatings (IPCS 1992). It appears that there are no reports of occurrence of 2-NP in outdoor air or water distinct from areas of manufacture and use (IPCS 1992).

Since it is slightly water soluble, adsorbed by sediment, not strongly bio-accumulating and volatile so that it evaporates readily into the atmosphere, it will be distributed in both air and water and is unlikely to accumulate in any individual environmental compartment (IPCS 1992). Ultraviolet photo-absorption by 2-NP is within the range of wavelengths occurring naturally in the environment, and it is thus likely that 2-NP undergoes slow photolysis in the atmosphere. Slow biological conversion of 2-NP to less toxic compounds also appears likely in both aquatic and terrestrial environments (IPCS 1992).

5.2. Production and use information

Production of 2-NP in the EU and import into the EU is in the tonnage range of less than 10 tonnes per annum (ECHA 2016a). Currently there is probably only one major EU manufacturer (IPCS 1992), being the only registrant under REACH (ECHA 2016b). No indications were found for a recent shift in production sites or countries. In Europe, 2-NP is produced by reacting propane with nitrogen peroxide (N_2O_4) and excess O_2 at 150-330°C and 0.9-1.2 MPa (9-12 atm). Reaction products are condensed, washed, and separated by fractional distillation (IPCS 1992; TOXNET 2016). Information about the main uses of 2-NP is summarised in Table 3, demonstrating that 2-NP is almost exclusively used in chemical production as feedstock and intermediate.

Table 3: Main uses of 2-NP and 2-NP containing products. Based on CASA 2010, UK IOM 2011 and NTP 2014.

Industry	Application	Importance
Chemical production	Feedstock and intermediate for producing amino-alcohols	>99% of use
Printing inks production (non-intermediate manufacture)	Solvent in printing inks	Included on the 'Eu Print Industry Association (EuPIA; 85% of EU Manufacturers and Importers of paints, printing inks and artists' colours) Exclusion List' since 1996, therefore very limited.
Coatings production (non-intermediate manufacture)	Solvent in surface coatings, e.g. for beverage cans	Unknown
Explosives	Explosive taggant in C4 explosives	Minor and reduced since 1991
Research	R&D Laboratory applications	Assumed limited
Adhesives and epoxy resins	Manufacture and use	Relatively minor
Aerospace	Solvent in specific coatings	Limited
Fuel	Rocket propellant	Limited
Food industry	Fractionating solvent in production of fats and oils	Abandoned in the early 1990s
Consumer applications	None	No

5.3. Occupational exposure

Number of sites

In 1977, production of 2-NP in the United States was estimated to be 13 600 tonnes. Later, 2-NP was reported to be produced by two companies in the United States and one company in France (IPCS 1992 and as cited by IARC 1999). More recently, it was stated that the number of sites at which workers are exposed during production of 2-NP is very limited. In 2009 there was only one producer of 2-NP in the EU (NTP 2014). This is in line with information on the REACH-registered substance (see above).

2-NP is produced in relatively low volumes and occupational exposures occur primarily in its production and use as a solvent in inks, adhesives, paints and coatings. It is assumed that these uses have been decreasing over time as employers have eliminated 2-NP from the used solvent mixtures (UK IOM 2011).

NTP 2014 reported a total number of 16 suppliers, eight of which were located in the USA.

Number of people exposed

Since decades, 2-NP is manufactured largely in closed processes. In 1979, 21 tonnes, i.e. 0.3%, of the produced amount was released into the environment (IPCS 1992).

Industrial exposure worldwide is unknown, but in the USA appears to be limited to 0.02-0.19% of the workforce. Significant exposure (exposure to 9.1 mg/m^3 = 2.5 ppm or more) in the USA may be limited to about 4000 workers (approximately 0.005% of the workforce) according to IPCS 1992.

According to a US National Occupational Exposure Survey in the early 1980s, about 10 000 workers in the US were potentially exposed during production of 2-NP and its use as a solvent (IARC 1999).

A UK IOM 2011 report estimated that currently less than 50 000 individuals are exposed, and acknowledged that in the past more than ten times this number could have been exposed.

Levels of exposure

Although 2-NP process area time-weighted concentrations exceeded the TLV of 90 mg/m^3 (25 ppm), with some exceptions, the personal exposure remained below the TLV during industrial solvent extraction between 1981-1983 (Crawford et al. 1985).

2-NP is manufactured in a closed process minimising occupational exposure. However, in the past some workers in several industries such as painting, printing, and solvent extraction have been exposed to levels beyond the highest occupational exposure limit of Table 3. Several industrial fatalities have been attributed to occupational exposure to an estimated concentration of 2180 mg/m^3 (600 ppm) airborne 2-NP (Harrison et al. 1987 and as cited by IPCS 1992). Concentrations of 2-NP as high as 6000 mg/m^3 (1640 ppm) in air were recorded in a drum-filling operation (IPCS 1992).

There are very little data on the level of exposure to 2-NP in industry. However, based on the available data, the UK IOM 2011 report considered it likely that currently no workers would be exposed in excess of the typical OEL of 19 mg/m^3 in manufacturing. Their worst-case estimates suggest levels below 6 mg/m^3. Exposures are assumed to have been decreasing over recent years by about 7% per annum (UK IOM 2011).

5.4. Routes of exposure and uptake

The routes of potential human exposure to 2-NP are inhalation, ingestion, and dermal contact (IPCS, 1992). For the general population, daily intake of 2-NP has been estimated at 50 to 100 mg[1], which includes exposure due to its use as a solvent for beverage-can coatings, film-laminating adhesives, and printing inks for food packaging (3 ng) and from vegetable oils (30 ng). Cigarette smokers receive an additional exposure of 1.2 µg per cigarette. 2-NP was measured in mainstream smoke at concentrations ranging 7.4 – 19.1 ng per cigarette (NTP, 2014). 2-NP was measured in the exhaled breath of healthy non-smoking urban dwellers at an average concentration of 0.406 ng/L among individuals who had avoided known sources of 2-NP (e.g., medication, perfume, paint, glue, aerosols, dust, tobacco smoke, and areas with polluted air from industrial wastes) for the week prior to sampling and for the duration of sampling (IPCS 1992).

As 2-NP is a volatile compound, the main exposure route of workers is by inhalation. However, also dermal exposure, e.g. by spills, cannot be excluded. It is noted that smokers are confronted with a significant exposure to 2-NP that is not due to occupational exposure but to the formation of 2-NP during combustion of nitrogen-rich organic material while smoking. For reasons of comparison, the IRIS reference concentration for lifelong inhalation is 0.020 mg/m^3 (IRIS 2016). This is approximately 0.400 mg/d assuming an inhalation rate of maximum 20 m^3/d as taken as reasonable worst case from the US EPA Exposure Factors Handbook (US EPA 2011).

[1] Comparing this range to the levels of exposure from specific sources, this seems to be a gross overestimation (0.342 mg/d for a 60 kg person) or an error of a factor of 1000. The individual sources are mostly in the ng/d range, except from smoking that would count at maximum 60 µg/d assuming 50 cigarettes per day. Altogether, this would sum up to 50-100 µg/d, a factor of 1000 lower than 50-100 mg/d.

6. MONITORING EXPOSURE

2-NP can be monitored in workplace air by applying the following fully evaluated methods (US NIOSH 2011):

- US OSHA 1980. Method ORG-15
- US OSHA 1984. Method ORG-46
- US NIOSH 1994. Method 2528

In all three methods 2-NP is sampled from the air in the workplace by adsorption onto a solid sorbent or absorption into solution, followed by extraction of 2-NP with an organic solvent. The 2-NP-containing extract can then be analysed by gas chromatography (GC), using flame ionisation detection (FID), as shown in Table 4.

Table 4 Overview of sampling and analytical methods for monitoring 2-NP in the workplace.

Method	Sorbent	Desorp-tion	Analysis	Recov. (%)	Limits of determination /detection	Concentration range	Reference
Method ORG-15	Chromosorb 106	Ethyl acetate	GC-FID	> 78.8 #	0.98 mg/m^3 (0.27 ppm)[1]	2-200 mg/m^3 (0.54-54 ppm))	US OSHA 1980
Method ORG-46	XAD-4	Carbon disulfide	GC-FID	96.4	0.091 mg/m^3 (0.025 ppm)[2]	n.d.	US OSHA 1984
Method 2528	Chromosorb 106	Ethyl acetate	GC-FID	not mentioned	1 µg per sample	3.1 to 28.3 mg/m^3 (3-L samples)	US NIOSH 1994

[#] When storage is maximum 14 days.

[1] Detection limit

[2] Reliable quantitation limit

7. HEALTH EFFECTS

7.1. Toxicokinetics (absorption, distribution, metabolism, excretion)

A systematic literature search of PubMed (conducted on June 25, 2015) using the search terms '2-nitropropane' alone and in combination with 23 ADME-specific terms, such as 'toxicokinetics' and 'pharmacokinetics', identified 63 relevant publications. In addition, other sources, primarily documents issued by regulatory bodies, were consulted.

It needs to be noted that 2-NP exist at pH 5-7 in equilibrium with the tautomers propane-2-nitronic acid and its anionic form propane-2-nitronate (Fig. 1).

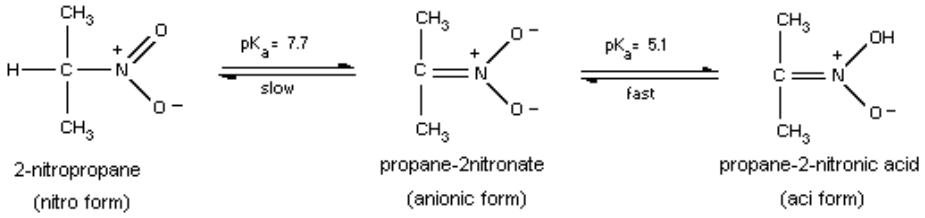


Figure 1: Tautomerism of 2-NP with P2N (anionic form) and the acid form P2NA (adapted from Porter and Bright, 1983)

7.1.1. Human data

No human toxicokinetic data were identified.

7.1.2. Animal data

Smith and Anderson (2013) and the German AGS (DE AGS 2015) reviewed the toxicokinetic of 2-NP in detail. Most kinetic research has focused on understanding the genotoxic mechanism of 2-NP.

The two animal studies from Nolan et al. (1982) and Muller et al. (1983) used radiolabelled 2-NP providing evidence of absorption, metabolism, distribution and excretion. Nolan et al. exposed rats to doses of 74 and 570 mg/m^3 for 6 hours by inhalation and measured elimination for 48h before investigating the body distribution. Müller et al. (1983) let rats inhale 740 mg/m^3 for 3 hours. In addition, they applied single doses of 2-NP intraperitoneally to rats (25 and 50 mg/kg bw) and chimpanzees (10 mg/kg bw). In both studies, more than 50% of radioactivity was exhaled as metabolites, mainly CO_2. Nolan et al. (1982) suggested that more than 40% of inhaled 2-NP was absorbed. Only a minor proportion of radioactivity was excreted in urine and feces, regardless of administration route. Absorbed 2-NP was distributed to all tissues. Nolan et al. (1982) found most radioactivity in lungs, kidney and liver, while a MAK commission document reported similar 2-NP amounts in liver and bone marrow (MAK Value Documentation 1989), probably refering to a dissertation from 1988 by M. Hass-Jobelius (in German, not available).

Based on these studies, denitrification of 2-NP to acetone and isopropanol, which are likely oxidised to CO_2, has been proposed as main metabolic pathway (Smith and Anderson, 2013). With the aim to elucidate metabolic intermediates responsible for the carcinogenicity of 2-NP, research has focused on generating and confirming hypotheses on the metabolic activation of 2-NP to toxic substrates. Therefore, this research is closely

linked to the investigation of the genotoxicity of 2-NP. This aspect was mainly studied in vitro and is addressed under 7.1.3.

Kinetics of 2-NP metabolism have been investigated by Denk et al. (1989). Rats (Sprague-Dawley) were exposed to atmospheric concentrations of 2-NP ranging from 3.7 to at least 925 mg/m^3 to obtain rates of inhaled 2-NP metabolism (steady state). Two metabolic processes were proposed: a saturable pathway that could be modelled by Michaelis-Menten kinetics and an unsaturable pathway. In male rats, saturation of metabolism was evident at 110 mg/m^3 (30 ppm). The non-saturable pathway dominated the metabolism above 220 mg/m^3 (60 ppm). In females the respective concentrations were 260 mg/m^3 (70 ppm) and 660 mg/m^3 (180 ppm).

7.1.3. In vitro data

Metabolism

The hepatocarcinogenicity of 2-NP in animal studies had triggered considerable in vitro research to elucidate the underlying mechanism, with a strong focus on the identification of the toxic metabolic intermediates.

Basically three hypotheses, all assuming (DNA-)reactivity as the fundamental mechanism, have been explored and substantiated by direct or indirect experimental data:

a) enzymatic activation of 2-NP (Marker et al. 1985 and 1986, Roscher et al., 1990, Robbiano et al 1991), potentially producing propane 2-nitronate (P2N) (Kohl et al. 1994)

b) conversion of 2-NP to P2N that is activated to a DNA damaging product by sulfotransferases (Kohl & Gescher, 1997, Andrae et al., 1999, Kreis et al., 2000). Bors et al. (1993) suggested a nonenzymatic formation of NO2.radicals after enzymatic oxidation of propane-2-nitronate to the corresponding secondary alkyl radical, whereas Kohl et al. (1995) proposed involvement of a NO species.

c) 2-NP metabolism to oxime- and hydroxylamine-O-sulfonates (Sodum et al. 1993, 1994, 1997 and 1998)

Supported by the two metabolic processes proposed by Denk et al. (1989), 2-NP is most likely metabolised in at least two different ways. However, it remains unknown how metabolites and the pathway relate to each other (DE AGS 2015).

Reductive metabolism, although no corresponding metabolites were found in animal studies, was demonstrated in one in study using primary rat hepatocytes and V79 cells (Haas-Jobelius et al., 1991).

Skin Absorption

An in vitro skin absorption study using human skin was conducted with radiolabeled 2-NP. Pure 2-NP was applied to human cadaver skin samples in an amount of 1200µL/cm^2 for up to eight hours to determine the permeability coefficient (kp) and in an amount of 10µL/cm^2 to determine the short-term absorption rate after 10 and 60 minutes. A kp of 0.000119 cm/h was calculated. For the short-term exposure of 10 and 60 minutes, a short-term penetration rate of 268 and 67 µg equiv/cm^2/h was determined, respectively (ECHA, 2016b). The skin permeability of 2-NP is supported by the kp of 0.00206 cm/h as estimated with the EPI Suite™ tool (US EPA 2012).

No information on skin metabolism is available, but extensive metabolism in skin is considered unlikely.

7.1.4. Toxicokinetic modelling

No studies modelling the toxicokinetics of 2-NP were identified.

7.1.5. Biological monitoring

The only study with potential relevance for biomonitoring is that by Derks et al. (1988) who established an HPLC method with UV detection for 2-NP in fresh rat blood samples. For promptly analysed blood samples collected in chilled heparinised vials, the detector response was linear up to 0.8 ug/ml. According to the authors, 2-NP is unstable in blood, therefore the samples require immediate processing. This instability makes measurement of 2-NP in blood of limited use for biological monitoring.

7.2. Acute toxicity

7.2.1. Human data

Three reports are available that document acute inhalation toxicity likely related to exposure to 2-NP (Gaultier et al., 1964; Hine et al., 1978; Harrison et al., 1987), being in many cases lethal for exposed workers. While the first two studies suffer from unknown 2-NP exposure conditions and co-exposures, Harrison et al. (1987) measured 2-NP serum concentration for the two exposed workers (8.5 mg/L and 13.0 mg/L, the latter being lethal). No data on acute human oral and dermal toxicity are available.

7.2.2. Animal data

Inhalation

LC50 value of 1480 mg/m^3 (400 ppm) and 2670 mg/m^3 (720 ppm) have been reported for male and female rats, respectively, which are supported by other rodent studies (IPCS 1992, ECHA 2016b).

Oral exposure

Several oral toxicity studies conducted with rats, mice or rabbits have been reported (ECHA 2016b). Across species, acute oral toxicity LD50 ranged from approx. 200 to 900 mg/kg bw.

Dermal exposure

2-NP has been found to be not acute dermally toxic to rabbits (ECHA 2016b).

7.2.3. In vitro data

No in vitro data relevant for the acute toxicity of 2-NP have been identified.

7.3. Specific Target Organ Toxicity/Repeated Exposure

7.3.1. Human data

Human data on repeated exposure to 2-NP are scarce. Effects such as anorexia, nausea, diarrhea, vomiting and headache have been reported after prolonged inhalation to 20 to 45 mg/m^3 (Skinner, 1947). Williams et al. (1974) associated toxic hepatitis with inhalative and potentially dermal exposure to 2-NP.

7.3.2. Animal data

7.3.2.1. Inhalation

Three published studies investigated the (sub-)chronic inhalation toxicity of 2-NP.

Treon and Dutra (1952) exposed rats, rabbits, guinea pigs to doses of 300 and 1200 mg/m^3 (83 and 328 ppm) and rhesus-monkey to 300 mg/m^3 (83 ppm) for approximately six months. The poorly reported study suggests that no effects were observed in any of the examined tissues of these species. Similar results were also obtained for rhesus-monkey exposed to 1200 mg/m^3 (328 ppm) for approximately three months. In contrast, cats died after 3-4 weeks exposure to 1200 mg/m^3 (328 ppm) showing severe degeneration of the liver parenchym and liver necrosis, slight degeneration of the heart and kidney and liver necrosis, but survived approx. six months exposure to 300 mg/m^3 (83 ppm).

Lewis et al. (1979) exposed rats and rabbits to 2-NP at concentrations of approx. 100 mg/m^3 (27 ppm) and 766 mg/m^3 (207 ppm) for up to six months. In rats increased liver and lung weights and liver toxicity, such as pale appearances, necrosis and surface lesions, were observed in the high dose group after three months. Also after three months, hematologic changes of unclear relevance were present in both dose groups. After six months, hepatocellular carcinomas were present in rat livers. In rabbits, no treatment related effects were observed for both dose groups.

Griffin et al. (1980) exposed rats to 78 mg/m^3 2-NP for up to 22 months (7 hours /day and 5 days/week). At the end of the study, slightly increased liver weights (both sexes) and changes in liver morphology, such as focal vacuolization (males only), hepatocellular nodules (males only) and liver congestion (both sexes), were observed.

7.3.2.2. Oral exposure

In a study by Fiala et al. (1987b) assessing the carcinogenicity of 2-NP, rats (Sprague-Dawley) received 90 mg/kg bw three times per week over a period of sixteen weeks by gavage. Benign and malignant liver tumors were found in all animals surviving the treatment period. In addition, besides mortality, an unspecified decrease in body weight was observed.

7.3.2.3. Dermal exposure

No in vivo data relevant for the dermal repeated toxicity of 2-NP have been identified.

7.3.3. In vitro data

No in vitro data relevant for the repeated toxicity of 2-NP have been identified.

7.4. Irritancy and corrosivity

7.4.1. Human data

No human data relevant for the irritancy and corrosivity of 2-NP have been identified.

7.4.2. Animal data

7.4.2.1. Skin

Rabbit studies demonstrated that 2-NP is not a skin irritant (ECHA 2016b).

7.4.2.2. Eyes

Rabbit studies demonstrated that 2-NP is a slight eye irritant (ECHA 2016b).

7.4.3. In vitro data

No in vitro data relevant for the irritancy and corrosivity of 2-NP have been identified.

7.5. Sensitisation

7.5.1. Human data

No human data relevant for the skin and respiratory sensitisation of 2-NP have been identified.

7.5.2. Animal data

In a guinea pig study, following a protocol similar to the respective OECD test guideline 406, 2-NP did not induce skin sensitisation (ECHA 2016b).

No in vivo data relevant for the respiratory sensitisation of 2-NP have been identified.

7.5.3. In vitro data

No in vitro data relevant for the skin and respiratory sensitisation of 2-NP have been identified.

7.6. Genotoxicity

7.6.1. Human data

No human data relevant for the genotoxicty of 2-NP have been identified.

7.6.2. Animal data

There is considerable evidence demonstrating the hepatogenotoxic effect of 2-NP in animal studies. Several in vivo micronucleus studies have been conducted. George et al. (1989) and more recently Kawakami et al. (2015) demostrated that 2-NP clearly increased the micronuclei frequency in rat liver. In contrast, 2-NP was repeatedly negative in mouse and rat bone marrow micronucleus tests (Hite and Skeggs, 1979; Kliesch and Adler, 1987; George et al., 1989; Kawakami et al., 2015).

Most in vivo genotoxicity studies, almost exclusively in rats, have been carried out to support elucidation of the genotoxic mechanism of 2-NP. In these studies modified nucleosides potentially miscoding DNA, such as 8-aminodeoxyguanosine, 8-hydroxydeoxyguanosine, 8-oxoguanine, 8-aminoguanosine, 8-hydroxy-guanine and 8-hydroxyguanosine, were observed in liver DNA or RNA (Fiala et al., 1989 and 1997; Guo et al., 1990; Hussain et al., 1990; Conaway et al., 1991; Dahlhaus et al. 1993; Sodum et al., 1993 and 1994). Guo et al. (1990) did not see this effects in rat kidneys, whereas Fiala et al. (1993) saw less pronounced increases in 8-oxoguanine and the formation of 8-aminoguanine in rabbit liver.

Andrae et al. (1988) observed, both in vivo and in vitro, that 2-NP more strongly induced DNA repair synthesis in male rat hepatocytes than in female hepatocytes.

7.6.3. In vitro

2-NP was mutagenic to various Salmonella typhimurium strains (TA92, TA98, TA100, TA102) with and without metabolic activation. Seven studies have been summarised in IARC Volume 71 from 1999 (Hite and Skeggs, 1979; Speck et al., 1982; Haworth et al., 1983; Fiala et al., 1987a; Göggelmann et al., 1988; Conaway et al., 1991; Kohl et al., 1994). In addition, Kawai et al. (1987) reported weakpositive results for 2-NP in the strain TA98 and TA 100. No more recent studies were identified.

In several studies, using primary rat and mouse hepatocytes without metabolic activation, 2-NP induced unscheduled DNA synthesis (Davies et al., 1993; Kohl et al., 1994; Fiala et al., 1995; Andrae at al., 1999).

Roscher et al. (1990) investigated the genotoxicity of 2-NP by DNA repair synthesis, micronuclei formation and induction of 6-thioguanine mutations using the rat hepatoma cell lines 2sFou, H4IIEC3/G- and C2Rev7, and V79 Chinese hamster cells. Cells pretreated with a cytochrome P450 inducer, were, when treated with 2-NP, positive for all endpoint. Non-induced cells, however, showed only weak or no genotoxicity. Two later studies using V79-derived cell lines engineered for expression of individual forms of rat or human sulfotransferases demonstrated induction of DNA repair synthesis by 2-NP and P2N, but not in parental V79-MZ cells (Andrea et al., 1999; Kreis et al., 2000).

Chromosomal effects, i.e. clastogenicity and sister chromatid exchanges, induced by 2-NP were observed in human lyphocytes with metabolic activation only (Bauchinger et

al., 1987; Göggelmann et al., 1988), but not at all in Chinese hamster ovary cells (Galloway et al., 1987).

8-Amino-2'-deoxyguanosine (8-amino-dG), which has been identified in the liver of 2-NP treated rats and suspected as a cause of 2-NP carcinogenicity, has been shown to be a weak pro-mutagenic lesion using transfected simian kidney cells and Escherischia coli (Tan et al., 1999; Venkatarangan et al., 2001).

7.7. Carcinogenicity

7.7.1. Human data

No reliable epidemiological information on the carcinogenicity of 2-NP in human was identified

7.7.2. Animal data

Several animal studies investigating the carcinogenicity of 2-NP were identified. In 1979, Lewis et al. investigated the subchronic inhalation toxicity as described in section 7.3.2.1. Upon sacrifice, mutiple hepatocellular carcinomas were found in all ten rats that were treated for six months with 766 mg 2-NP/m^3, but not in the low dose group of 100 mg 2-NP/m^3.

Griffin et al. published the results of a chronic inhalation study in two papers (Griffin et al., 1980 and 1981). Sprague-Dawley rats were exposed to 78 mg/m^3 (25 ppm; conversion of 3.12 adjusted to temperature of 25°C and a pressure at 1350 m above standard elevation zero) 2-NP for up to 22 months (7 hours /day and 5 days/week). While the earlier publication presented the overall results (see 7.3.2.1), the second paper from 1981 focused on the histologic examination of the major organs. An increased number of focal areas of hepatocellular nodules as compared to control was observed. Incidences of 3/250 (two males and one female) in the control and 13/250 (10 males and 3 females) in the treated group are reported. However, animal number at the end of the study were substantially lower in the treated group than in the control group (control: 111; treated: 56). In contrast to the authors, this difference has been interpreted by others as a weak carcinogenic effect (DE AGS, NL DECOS 1999).

In a tumor promotion study, Denk et al. (1990) demonstrated a linear dose-dependent increase in the number of preneoplatic liver foci in rats that inhaled 2-NP in concentration from 92.5 to 462.5 mg/m^3 for three weeks with higher female sensitivity.

Carcinogenicity of 2-NP was also observed in an oral repeated dose study (Fiala et al., 1987b), in which rats (Sprague-Dawley) received 90 mg/kg bw three times per week over a period of sixteen weeks by gavage. Benign and malignant liver tumors were found in all exposed animals surviving the treatment period.

Two further studies applied 2-NP intraperitoneally to rats (Astorg et al. 1994, Doi et al. 2011). Astorg et al. (1994), who tested N2P in parallel, observed comparable increases in the amount of preneoplastic foci in the liver induced by six treatments with concentrations ranging from 92.5 to 370 mg/m^3. Also Doi et al. (2011) observed a positive response (significantly increased number and areas of foci) in a rat medium-term liver carcinogenesis bioassay after single injections 0.8, 4 or 20 mg/kg/day.

7.8. Reproductive toxicity

7.8.1. Human data

No human data relevant for the reproductive toxicity of 2-NP have been identified.

7.8.2. Animal data

7.7.2.1. Fertility

No relevant data for the effects of 2-NP on animal fertility have been identified. A mice sperm abnormality test, in which the positive control failed to induce effects, was considered unreliable and disregarded (ECHA 2016b).

7.7.2.2. Developmental toxicity

(a) Inhalation

No animal data relevant for the developmental toxicity of inhaled 2-NP have been identified.

(b) Oral

No animal data relevant for the developmental toxicity of orally administered 2-NP have been identified.

(c) Dermal

No animal data relevant for the developmental toxicity of dermally administered 2-NP have been identified.

(d) Other routes

One study investigating the developmental toxicity of 2-NP by exposing rats intraperitoneally to 170 mg/kg bw daily for 15 days (day 1-15 of gestation) was available (Hardin et al., 1981). In the absence of maternal effects, delayed fetal development was observed, but no teratogenic effects, i.e. grossly visible external or internal (visceral or skeletal) malformations.

7.8.3. In vitro data

No in vitro data relevant for the reproductive toxicity of 2-NP have been identified.

7.9. Mode of action and adverse outcome pathway considerations

2-NP has been show to be a weak carcinogen in the animal inhalation studies by Griffin et al. (1981), which has triggered considerable research to elucidate the carcinogenic mode of action. The following aspects are considered most pertinent to this mode of action:

1) 2-NP exist in equilibrium with the tautomers propane-2-nitonic acid and its anionic form propane-2-nitronate (P2N) (Porter and Bright 1983).

2) Both 2-NP and P2N are metabolically activated. Various activation pathways have been proposed, including

- enzymatic activation of 2-NP (Marker et al 1985 and 1986, Roscher et al., 1990, Robbiano et al 1991), potentially to or via P2N (Kohl et al. 1994)
- activation of P2N to a DNA damaging product by sulfotransferases (Kohl & Gescher 1997, Andrae et al. 1999, Kreis et al. 2000).
- Bors et al. (1993) suggested a nonenzymatic formation of NO2.radicals after enzymatic oxidation of P2N to the corresponding secondary alkyl radical, whereas Kohl et al. (1995) proposed involvement of an NO species.
- metabolism of 2-NP to oxime- and hydroxylamine-O-sulfonates (Sodum et al. 1993, 1994, 1997 and 1998)

3) The increase in the promutagenic lesion such as 8-amine-2'-deoxyguanosine either implies increased oxidative stress or higher sensitivity for oxidative stress after treatment with 2-NP.

4) At least two metabolic pathways, one saturable being likely responsible for weaker carcinogenicity for concentrations of 2-NP up to approx. 100 mg/m^3 and one unsaturable inducing much stronger effects (hepatotoxicity and hepatocarcinogenicity) at higher concentrations. It is unclear which of the biotransformation steps in the metabolism of 2-NP are saturable and which are not. Theoretically, oxidative metabolism to acetone, nitrite and CO_2 should be saturable, while the structural rearrangement of 2-NP to P2N should not. In addition, sex specific differences in 2-NP metabolism (males more sensitive than females) have been observed (Andrae et al. 1988, Guo et al. 1990) and are also reflected in different toxicokinetic parameters (Denk et al. 1989). However, as Denk et al. (1990) observed a higher sensitivity of females, the available evidence is inconsistent and does not allow to draw sound conclusions on sex differences.

5) In addition, the stimulatory effect of 2-NP on the cellular proliferation observed in rat liver has been suggested as one of the mechanisms contributing to the carcinogenicity (Cunningham et al. (1991), El-Sokkary et al. (2002)).

6) 2-NP is specifically hepatotoxic/-carcinogenic (e.g. negative in in vivo micronucleus studies investigating bone marrow), leading for example to its use as a modelling compound for liver toxicity and/or carcinogenicity.

7) No evidence exists that could indicate that these modes of action are not relevant for humans. An in vitro study using V79-derived cell lines engineered for expression of individual forms of human sulfotransferases demonstrated induction of DNA repair synthesis by 2-NP and P2N, but not in parental V79-MZ cells (Kreis et al. 2000).

Overall, there is convincing evidence that 2-NP is a genotoxic carcinogen (assigned to SCOEL carcinogen group A: DNA-reactive genotoxic carcinogen without a threshold), although the exact mode of action underling the carcinogenicity remains to be elucidated. This implies that a health based recommended occupational exposure limit (HBR-OEL) cannot be defined.

7.10. Lack of specific scientific information

No information is lacking in order to derive a SCOEL conclusion.

8. CANCER RISK ASSESSMENT

As 2-NP is a genotoxic carcinogen, a cancer risk assessment has been performed based on the study by Griffin et al. (1980 and 1981). In this study a single dose was tested, so that a BMD could not be applied. Instead, a T25 approach with linear extrapolation was used. The rat T25, i.e. the dose that would have caused tumors in 25% of the rats, was calculated using the applied dose (78 mg/m^3), the tumor incidences in treated and control group based on the number of surviving rats at the end of the Griffin et al. (1981) study and adjusting for a lifetime exposure of 104 weeks:

$T25 = D \times 0.25/(I_t-I_c) \times (1- I_c) \times X_{po}/L \times X_{pe}/L =$

$= 78.0 \text{ mg/m}^3 \times 0.25/(13/56 - 3/110) \times (1 - 3/110) \times 96/104 \times 96/104$

$= 78.8 \text{ mg/m}^3$ (25.3 ppm)

with I_t (13/56) and I_c (3/110) being the incidences of tumor observed at the end of the study in the treated and control group divided by the animals in the treated and control group still alive at the end of the study, respectively, D the dose of 25 ppm (taken as equal to 78 mg/m^3 using a conversion factor of 3.12 mg/m^3 per ppm) , X_{po} the exposure period of 22 months (converted to 96 weeks), X_{pe} the experimental period of 22 months (converted to 96 weeks) and L the rat lifetime of 104 weeks. The exposure of seven hours for five days per week was considered as sufficiently covering the real exposure duration at the workplace, so that no adjustment was applied. In a second step, this value was converted to a human T25 (hT25), i.e. the concentration that leads to an additional lifetime cancer risk of 25%, applying an interspecies assessment factor of 1 assuming that concentrations are appropriately scaled because the ventilation rate directly depends on the metabolic rate. and adjusted to workplace exposure, assuming a working exposure of 40 years with an expected lifetime of 75 year and 48 working weeks per working year and, according to the current SCOEL methodology, without adjusting for ventilation rate:

$hT25 = T25 \times 75y/40y \times 52w/48w = 78.8 \text{ mg/m}^3 \times 75/40 \times 52/48$

$= 160.1 \text{ mg/m}^3$ (51.3 ppm)

From the hT25 risk numbers can be calculated for a risk R by linear extrapolation as 4*hT25*R.

This approach resulted in the following risk numbers:

a tumor risk of 1 : 10 at 64.4 mg/m^3,

a tumor risk of 1 : 1000 at 0.644 mg/m^3,

a tumor risk of 1 : 10000 at 0.0644 mg/m^3,

and a tumor risk of 1 : 1000000 at 0.000644 mg/m^3.

Also the Dutch Expert Committee on Occupational Standards (DECOS) and the German Federal Institute for Occupational Safety and Health conducted cancer risk assessments based on the same study of Griffin et al. (1981) (NL DECOS 1999; DE AGS 2015). DECOS derived health-based calculated occupational cancer risk values (HBC-OCRV), while AGS applied a comparable T25 approach. Both approaches resulted in similar risk numbers (DECOS: tumor risk of 1:10 at 90 mg/m^3; AGS: tumor risk of 1:10 at 44.4 mg/m^3), which also demonstrated the marginal impact of some adjustments that indicate an exaggerated level of precision.

9. GROUPS AT EXTRA RISK

No groups being at extra risk have been identified.

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