ECHA Scientific report
for evaluation of limit values for Nitrosamines at the workplace

Prepared by the European Chemicals Agency

18 April 2023

Telakkakatu 6, P.O. Box 400, FI-00121 Helsinki, Finland | Tel. +358 9 686180 | Fax +358 9 68618210 | echa.europa.eu

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List of abbreviations

Abbreviation	Definition
AAG	Alkyl-adenine Glycosylase
ACGIH	American Conference of Governmental Industrial Hygienists
AGS	Ausschuss für Gefahrstoffe (German Committee on Hazardous Substances)
ANSES	Agence Nationale de SEcurité Sanitaire de l'alimentation, de l'environnement et du travail (French Agency for Food, Environmental and Occupational Health & Safety)
AP	Apurinic
ATSDR	Agency for Toxic Substances and Disease Registry (USA)
BAL	Biological Action Levels (for occupational exposure)
BAR	Biologische Arbeitsstoff-Referenzwerte (Biological reference value; corresponds to the background level present concurrently, in a reference population of persons of working age who are not occupationally exposed to this substance).
BAT	Biologische Arbeitsplatztoleranzwert (German biological tolerance value for occupational exposure)
BER	Base Excision Repair
BAuA	Bundesanstalt für Arbeitsschutz und Arbeitsmedizin (German Federal Institute for Occupational Safety and Health)
BGV	Biological Guidance Value
BLV	Biological Limit Value
BLW	Biologische Leit-Wert
BMD	Benchmark dose
BOEL(s)	Binding Occupational Exposure Limit(s)
bw	Body weight
CAD	Chemical Agents Directive 98/24/EC
CAS RN	CAS Registry Number (unique identifier providing an unambiguous means to distinguish chemical substances or molecular structures when there are many possible systematic, generic, proprietary or otherwise trivial names)
CI	Confidence Interval
CLP	Regulation EC No 1272/2008 on the Classification, Labelling and Packaging of substances and mixtures (CLP Regulation)
CMD / CMRD	Carcinogens and Mutagens Directive 2004/37/EC on the protection of workers from the risks related to exposure to carcinogens or mutagens at work. The amendment of the CMD, Directive 2022/431/EU also brought reprotoxic substances within the scope of the directive, changing the original title on the protection of workers from the risks related to exposure to carcinogens or mutagens at work to the protection of workers from the risks related to exposure to carcinogens, mutagens or reprotoxic substances at work (CMRD).
CMR	Carcinogens, Mutagens or substances toxic to Reproduction
CPDB	Carcinogenic Potency Database
DFG	Deutsche Forschungsgemeinschaft (German Research Foundation)
DIN	Deutsch Institute für Normalisierung (German Institute for Standardisation)
EC	European Commission

Abbreviation	Definition
ECHA	European Chemicals Agency
EN	Europäische Norm (European Norm)
EPA	Environmental Protection Agency
ERR	Exposure-risk relationship
EU	European Union
GESTIS Substance Database	GEfahrSToffInformationsSystem (German information system for the safe handling of hazardous substances and other chemical substances at work) Substance Database
GLP	Good Laboratory Practice
IARC	International Agency for Research on Cancer (World Health Organization)
IHD	Ischemic heart diseases
IOELV(s)	Indicative Occupational Exposure Limit Value(s)
IPM	Isopropyl myristate
ISO	International Organization for Standardization
LCDB	Lhasa Carcinogenicity Database
LOD	Limit of detection
LOQ	Limit of quantification
MGMT	O^6-methylguanine-DNA methyltransferase
MoA	Mode of action
MS	Member State
MWF	Metalworking fluids
NER	Nucleotide Excision Repair
NIOSH	National Institute for Occupational Safety and Health (USA)
NDEA	N-nitrosodiethylamine
NDELA	N-nitrosodiethanolamine
NDMA	N-nitrosodimethylamine
NDPA	N-nitrosodi-n-propylamine
OEL(s)	Occupational exposure limit(s)
OSHA	Occupational Safety and Health Administration (USA)
PPE	Personal Protective Equipment
RAC	Risk Assessment Committee
REACH	Regulation (EC) No 1907/2006 of the European Union concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals
SLA	Service Level Agreement
STEL	Short term exposure limit
TRGS	Technische Regeln für GefahrStoffe (German Technical regulations for hazardous substances)
TLS	Translesion synthesis
TWA	Time-Weighted-Average
VLB	Valeur limite biologique (Biological Limit Value)
WHO	World Health Organisation

Procedure and outcome

I. European Commission request

The European Commission is responsible for preparing the proposals for amendment of Directive 2004/37/EC on the protection of workers from the risks related to exposure to carcinogens, mutagens or reprotoxic substances at work (CMRD).
In line with the 2017 Commission Communication '*Safer and Healthier Work for All' - Modernisation of the EU Occupational Safety and Health Legislation and Policy*[1], it asked the advice of ECHA's Committee for Risk Assessment (RAC) to assess the scientific relevance of occupational exposure limits for some carcinogenic chemical substances.

Therefore, the Commission requested ECHA on 23 February Month 2022, in accordance with the Service Level Agreement (SLA) (Ares(2022)711149) to evaluate the following substances, in accordance with the CMRD:

- N-Nitrosodiethylamine (diethylnitrosamine) (EC number 200-226-1; CAS RN 55-18-5)
- N-Nitrosodimethylamine (dimethylnitrosamine) (EC number 200-549-8; CAS RN 62-75-9)
- N-Nitroso di-n-propylamine (EC number 210-698-0 ; CAS RN 621-64-7)
- N-Nitrosodiethanoamine (2,2'-(Nitrosoimino)bisethanol) (EC number 214-237-4; CAS RN 1116-54-7)

If other nitrosamines are identified as needing further attention ECHA is requested to inform the Commission but not to necessarily include this information in the scientific report.

In response to the Commission's request, ECHA has prepared a scientific report concerning occupational limit values for the nitrosamines listed above.

- ECHA launched a call for evidence between 06 June 2022 and 06 September 2022.
- ECHA launched a consultation between 18 April 2023 and 16 June 2023.

RAC has developed its opinion on occupational limit values (OELs) on the basis of ECHA's scientific report, which is attached as an Annex to the adopted RAC opinion.

All information is available on the OEL activity list (click on <Details> at the end of the row).

II. Literature search & data collection

The literature search was performed using two scientific literature databases: PubMed[2] and Web of Science by Clarivate Analytics[3] with publication data mainly searched beyond the year 2000. Search covered the years: 1980 – 2022

Search strings were developed on the basis of the four nitrosamines in the Commission's request with a focus on occupational exposure, general human exposure and occurrence data, supplemented with a general search on occupational exposure (to collect information on additional relevant nitrosamines).

[1] http://ec.europa.eu/social/main.jsp?langId=en&catId=148&newsId=2709&furtherNews=yes
[2] https://pubmed.ncbi.nlm.nih.gov/
[3] https://www.webofscience.com/wos/woscc/basic-search

Targeted grey literature searches were also performed to identify any authoritative reviews conducted by competent authorities such as EFSA, WHO and EMA. When data were available from these types of sources, they were also obtained and included in the assessment.[4]

III. ECHA evaluation and recommendation

The tables below present the outcome of the scientific evaluation to derive limit values for nitrosamines in the scope of this report.

Table 1: Outcome of the scientific evaluation

Derived Limit Values	Value
OEL as 8-hour TWA	None is proposed
STEL	None is proposed
BLV	None is proposed
BGV	None is proposed

Notations	
Skin	

Table 2: Cancer exposure-risk relationship*

NDMA Air concentration		NDEA Air concentration		Excess life-time cancer risk (cases per 100 000 exposed)
mg/m³	ppm	mg/m³	ppm	
0.000002	0.0000006	0.000007	0.000002	1
0.000008	0.000003	0.00003	0.000007	4
0.00002	0.000006	0.00007	0.00002	10
0.00008	0.00003	0.0003	0.00007	40
0.0002	0.00006	0.0007	0.0002	100
0.0008	0.0003	0.003	0.0007	400
0.002	0.0006	0.007	0.002	1000
0.008	0.003	0.03	0.007	4000

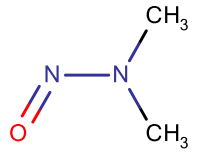
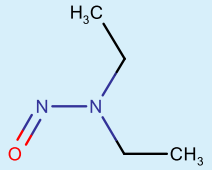
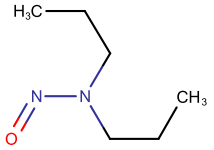
* Assuming exposure 8 hours per day and 5 days per week, over a 40-year working life period.

[4] All references are listed at the end of the report.

1. Chemical agent identification and physico-chemical properties

The chemical identifiers and main physico-chemical properties of the 4 main nitrosamines are listed in Table 3, Table 4 and Table 5.

Table 3: Substance identification

Substance name	EC No.	CAS RN	Synonyms	Molecular formula	Chemical structure	Molecular weight
Dimethylnitrosoamine (NDMA)	200-549-8	62-75-9	N-nitrosodimethylamine	C2H6N2O		74.08
Diethylnitrosoamine (NDEA)	200-226-1	55-18-5	N-nitrosodiethylamine	C4H10N2O		102.14
Nitrosodipropylamine (NDPA)	210-698-0	621-64-7	N-nitrosodi-n-propylamine	C6H14N2O		130.19

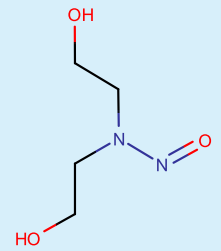
Substance name	EC No.	CAS RN	Synonyms	Molecular formula	Chemical structure	Molecular weight
2,2'-(Nitrosoimino)bisethanol (NDELA)	214-237-4	1116-54-7	N-nitrosodiethanolamine	C4H10N2O3		134.13

Table 4: Physico-chemical properties[5]

Substance name	EC/ List No.	Physical state	Density (g/cm^3 at 20°C)	Boiling point (°C)	Vapour pressure (kPa at 25°C)	Water Solubility
Dimethylnitrosoamine (NDMA)	200-549-8	Yellow liquid	1.0048	146	0.73	Very soluble
Diethylnitrosoamine (NDEA)	200-226-1	Yellow oil	0.9422	172	N/A	Soluble
Nitrosodipropylamine (NDPA)	210-698-0	Gold	0.9163	206	N/A	slightly soluble
2,2'-(Nitrosoimino)bisethanol (NDELA)	214-237-4	White – yellow oil	1.4849	N/A	N/A	N/A

Table 5: Conversion factor[6]

Substance name	EC/ List No.	Conversion factor
Dimethylnitrosoamine (NDMA)	200-549-8	1 ppm = 3.08 mg/m^3 (at 20°C) 1 mg/m^3 = 0.32 ppm (at 20°C)
Diethylnitrosoamine (NDEA)	200-226-1	1 ppm = 4.25 mg/m^3 (at 20°C) 1 mg/m^3 = 0.24 ppm (at 20°C)

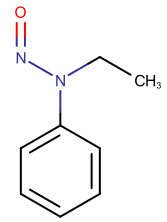
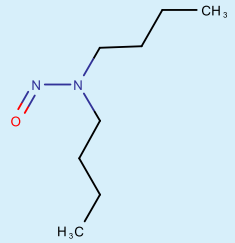
[5] from the Handbook of Chemistry and Physics (103rd Edition, 2022-2023)

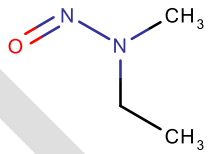
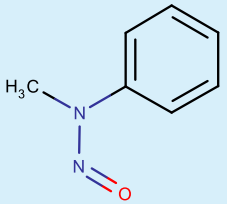
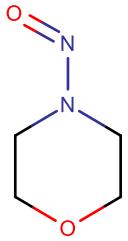
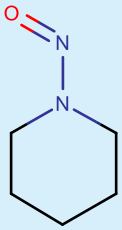
[6] $concentration\left[\frac{mg}{m^3}\right] = molecular\ weight\ \frac{g}{mol} \cdot \frac{1.013 \cdot 10^5 Pa \cdot 1m^3}{8.314 \cdot \frac{Pa \cdot m^3}{mol \cdot K} \cdot 293.15K} \cdot 10^{-3} \cdot concentration[ppm]$

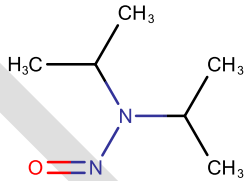
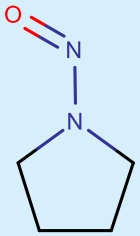
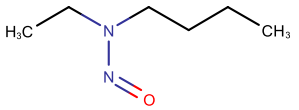
Substance name	EC/ List No.	Conversion factor
Nitrosodipropylamine (NDPA)	210-698-0	1 ppm = 5.41 mg/m^3 (at 20°C) 1 mg/m^3 = 0.18 ppm (at 20°C)
2,2'-(Nitrosoimino)bisethanol (NDELA)	214-237-4	1 ppm = 5.58 mg/m^3 (at 20°C) 1 mg/m^3 = 0.18 ppm (at 20°C)

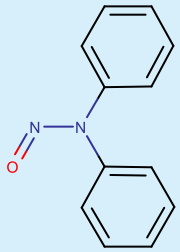
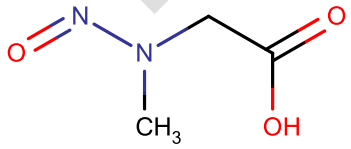
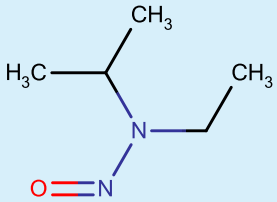
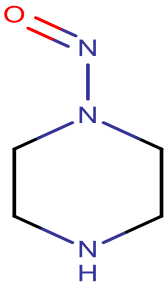
As per the Commission's request *"if other nitrosamines are identified ECHA is requested to inform the Commission"*. Consequently, additional nitrosamines are reported later and the related substance identification information is included in Table 6, Table 7 and Table 8.

Table 6: Substance identification of additional nitrosamines

Substance name	EC/List Number	CAS RN	Molecular formula	Chemical structure	Molecular weight
N-Nitrosoethylphenylamine (aka N-nitrosoethylaniline) (NEPA or NEA)	866-116-6	612-64-6	C8H10N2O		150.18
N-Nitrosodibutylamine (NDBA)	213-101-1	924-16-3	C8H18N2O		158.24

Substance name	EC/List Number	CAS RN	Molecular formula	Chemical structure	Molecular weight
N-Nitrosomethylethylamine (NMEA)	621-991-1	10595-95-6	C3H8N2O		88.11
N-Methyl-N-nitrosoaniline N-Nitrosomethylphenylamine (aka N-nitrosomethylaniline) (NMPA)	210-366-5	614-00-6	C7H8N2O		136.15
N-Nitrosomorpholine (NMor)	627-564-6	59-89-2	C4H8N2O2		116.12
N-Nitrosopiperidine (NPip)	202-886-6	100-75-4	114.1457		114.15

Substance name	EC/List Number	CAS RN	Molecular formula	Chemical structure	Molecular weight
N-Nitrosodi-i-propylamine (NDiPA)	690-128-9	601-77-4	C6H14N2O		130.19
N-Nitrosopyrolidine (NPyr)	213-218-8	930-55-2	C4H8N2O		100.12
N-Nitroso-N-ethylbutylamine (NEBA)	627-593-4	4549-44-4	C6H14N2O		130.19

Substance name	EC/List Number	CAS RN	Molecular formula	Chemical structure	Molecular weight
N-Nitrosodiphenylamine (NDPhA)	201-663-0	86-30-6	C12H10N2O		198.22
[methyl(nitroso)amino]acetic acid N-Nitrososarcosine (NSAR)	877-093-7	13256-22-9	C3H6N2O3		118.09
N-Ethyl-N-isopropylnitrous amide NEiPA	835-435-2	16339-04-1	C5H12N2O		116.16
1-Nitrosopiperazine (MNPiz)	803-995-7	5632-47-3	C4H9N3O		115.13

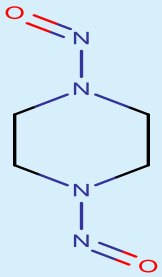
Substance name	EC/List Number	CAS RN	Molecular formula	Chemical structure	Molecular weight
1,4-Dinitrosopiperazine (DNPiz)	205-434-6	140-79-4	C4H8N4O2		144.13

Table 7: Physico-chemical properties of additional nitrosamines[7]

Substance name	EC/ List No.	Physical state	Density (g/cm^3 at 20°C)	Boiling point (°C)	Melting point (°C)	Vapour pressure (kPa at 25°C)	Water Solubility
NEPA	866-116-6	N/A	N/A	N/A	N/A	N/A	N/A
NDBA	213-101-1	N/A	N/A	N/A	N/A	N/A	N/A
NMEA	621-991-1	Yellow liquid	N/A	67	N/A	N/A	N/A
NMPA	210-366-5	Yellow crystals	1.1240	225 (decomposes)	14.7	N/A	insoluble
NMor	627-564-6	N/A	N/A	225	29	N/A	soluble
NPip	202-886-6	Pale yellow	1.0631	211	N/A	N/A	soluble
NDiPA	690-128-9	Crystals (diethyl ether, water)	0.9422	194.5	48		slightly soluble
NPyr	213-218-8	N/A	1.085	214	N/A	N/A	N/A
NEBA	627-593-4	N/A	N/A	N/A	N/A	N/A	N/A
NDPhA	201-663-0	solid[8]	0.666[8]	101[8]	66.7[8]	9×10^{-5} [8]	insoluble
NSAR	877-093-7	N/A	N/A	N/A	N/A	N/A	N/A

[7] from the Handbook of Chemistry and Physics (103rd Edition, 2022-2023) – unless otherwise stated – N/A means data is "not available" in the Handbook
[8] From ECHA registration dossiers available at https://echa.europa.eu/

Substance name	EC/ List No.	Physical state	Density (g/cm^3 at 20°C)	Boiling point (°C)	Melting point (°C)	Vapour pressure (kPa at 25°C)	Water Solubility
NEiPA	835-435-2	N/A	N/A	N/A	N/A	N/A	N/A
MNPiz	803-995-7	N/A	N/A	N/A	N/A	N/A	N/A
DNPiz	205-434-6	Pale yellow plates	N/A	N/A	155.9	N/A	N/A

Table 8: List of substance acronyms

Acronyms	Substance names	EC/List Number	CAS RN
NDMA	**Dimethylnitrosoamine** N-nitrosodimethylamine	200-549-8	62-75-9
NDEA	**Diethylnitrosoamine** N-nitrosodiethylamine	200-226-1	55-18-5
NDPA	**Nitrosodipropylamine** N-nitrosodi-n-propylamine	210-698-0	621-64-7
NDELA	**2,2'-(nitrosoimino)bisethanol** N-nitrosodiethanolamine	214-237-4	1116-54-7
NEPA or NEA	**N-ethyl-N-phenylnitrous amide** N-nitrosoethylphenylamine (aka N-nitrosoethylaniline)	866-116-6	612-64-6
NDBA	**N-nitrosodibutylamine**	213-101-1	924-16-3
NMEA	**N-ethyl-N-methylnitrous amide** N-nitrosomethylethylamine	621-991-1	10595-95-6
NMPA	**N-methyl-N-nitrosoaniline** N-nitrosomethylphenylamine; N-nitrosomethylaniline) N-nitrosomethylphenylamine (aka N-nitrosomethylaniline)	210-366-5	614-00-6
NMor	**4-nitrosomorpholine** N-nitrosomorpholine	627-564-6	59-89-2
NPip	**1-nitrosopiperidine** N-nitrosopiperidine	202-886-6	100-75-4
NDiPA	**N,N-diisopropylnitrous amide** N-nitrosodi-i-propylamine	690-128-9	601-77-4
NPyr	**1-nitrosopyrrolidine**	213-218-8	930-55-2
NEBA	**N-butyl-N-ethylnitrous amide** N-nitroso-N-ethylbutylamine	627-593-4	4549-44-4
NDPhA or NDPheA	**Nitrosodiphenylamine**	201-663-0	86-30-6
NSAR	**[methyl(nitroso)amino]acetic acid**	877-093-7	13256-22-9

Acronyms	Substance names	EC/List Number	CAS RN
	N-Nitrososarcosine		
NEiPA	**N-Ethyl-N-isopropylnitrous amide**	835-435-2	16339-04-1
MNPiz	**1-Nitrosopiperazine**	803-995-7	5632-47-3
DNPiz	**1,4-Dinitrosopiperazine**	205-434-6	140-79-4
NHPPNA	**N-(2-hydroxypropyl)-N-propylnitrous amide** B-hydroxypropyl-n-propylnitrosamine ; N-nitroso-2-hydroxy-n-propyl-n-propylamine	N/A	39603-53-7

2. EU harmonised classification and labelling- CLP (EC) 1272/2008

The harmonised classification for three (NDMA, NDPA, NDELA) of the four main nitrosamines is presented in Table 9. The fourth main nitrosamine (NDEA) does not have a harmonised classification under CLP, but was notified (i.e. reflects self-classification by EU operators).

Table 9: Summary of existing EU classifications for the four main nitrosamines

Index No	Acronyms	EC number	CAS RN	CLP hazard class and category	Hazard statement code
612-077-00-3	NDMA	200-549-8	62-75-9	Acute Tox. 3 Acute Tox. 2 Carc. 1B STOT RE 1 Aq. Chronic 2	H301 H330 H350 H372 H411
Not available/ only notified under CLP	NDEA	200-226-1	55-18-5	Acute Tox. 3 Carc. 1A, 1B Muta. 1B, 2 Aq. Chronic 3 Flam. Liq. 4 Aq. Acute 3	H301 H350 H340, H341 H412 H227 H402
612-098-00-8	NDPA	210-698-0	621-64-7	Acute Tox. 4 Carc. 1B Aq. Chronic 2	H302 H350 H411
612-090-00-4	NDELA	214-237-4	1116-54-7	Carc. 1B	H350

The existing notifications and associated hazard classes of additional nitrosamines, including those thought to be relevant to occupational health (see section 5.5) are listed in Table 10.

Table 10: Summary of existing notifications for the additional nitrosamines

Acronyms	EC number	CAS RN	CLP hazard class and category	Hazard statement code
NEPA	866-116-6	612-64-6	Acute Tox. 3 Carc. 1B	H301 H350
NDBA	213-101-1	924-16-3	Acute Tox. 4 Carc. 2	H302 H351
NMEA	621-991-1	10595-95-6	Acute Tox. 3 Skin Irrit. 2 Eye Irrit. 2 STOT SE 3 Carc. 2 Repr. 2 Flam. Liq. 3	H301 H315 H319 H335 H351 H361 H226
NMPA	210-366-5	614-00-6	Acute Tox. 3 Eye Irrit. 2A Carc. 2	H301, H311 H319 H351
NMor	627-564-6	59-89-2	Acute Tox. 3 Carc. 2 Muta. 2	H301 H351 H341
NPip	202-886-6	100-75-4	Acute Tox. 3 Carc. 2 Skin Irrit. 2 Eye Irrit. 2	H301 H351 H315 H319
NDiPA	690-128-9	601-77-4	Acute Tox. 3 Muta. 1B Carc. 1B	H301 H340 H350

Acronyms	EC number	CAS RN	CLP hazard class and category	Hazard statement code
			Acute Tox. 4	H302
NPyr	213-218-8	930-55-2	Acute Tox. 4 Carc. 2 Carc. 1A	H302 H351 H350
NEBA	627-593-4	4549-44-4	Acute Tox. 4, 3 Skin Irrit. 2 Eye Irrit. 2A STOT SE 3 Carc. 1B	H302, H301 H3015 H319 H335 H350
NDPhA	201-663-0	86-30-6	Skin Sens. 1A Carc. 2 Repr. 2 Muta. 2 STOT RE 2 STOT SE 2 Acute Tox. 4 Skin Irrit. 2 Eye Irrit. 2, 2A Resp. Sens. 1 Aq. Chronic 2, 1, 3	H317 H351 H361 H341 H373 H371 H302 H315 H319 H334 H411, H410, H412
NSAR	877-093-7	13256-22-9	Acute Tox. 4 Skin Irrit. 2 Eye Dam. 1 STOT SE 3 Carc 2 Repr. 2	H302 H315 H318 H335 H351 H361
NEiPA	835-435-2	16339-04-1	Flam Liq. 4 Actue Tox. 4 Carc. 1B Aquatic Chronic 3	H227 H301 H350 H412
MNPiz	803-995-7	5632-47-3	Skin Corr. 1B Skin Sens.1 Resp. Sens. 1 Carc. 2 Repr. 2	H314 H317 H334 H351 H361
DNPiz	205-434-6	140-79-4	Acute Tox. 3 Skin Irrit. 2 Eye Irrit. 2A STOT SE 3 Carc 1B	H301 H315 H319 H335 H350

3. Chemical Agent and Scope of Legislation – Regulated uses in the EU

Table 11: Scope of legislation for main four (NDMA, NDEA, NDPA, NDELA) and additional nitrosamines

Legislation	Applicable	Comment
Directive 98/24/EC (CAD)	Not listed	/
Directive 2004/37/EU (CMRD)	Not listed	/
Regulation (EC) No 1907/2006 (REACH) – Annex XIV (Authorisation)	Not listed	/
Regulation (EC) No 1907/2006 (REACH) – Annex XVII (Restriction)	Not listed	/
Regulation (EU) 528/2012 – Biocidal Products	Not listed	Nitrosamines are not registered as biocides and no impurity limits for nitrosamines accompany any biocidal active substances
Regulation (EC) 1107/2009 - Plant Protection Product	Not authorised	Contains nitrosamine impurity limits for 4 active ingredients: (1) Daminozide: max. 2.0 mg/kg NDMA; (2) Benfluralin: max. 0.1 mg/kg of NEBA); (3) Triallate: max. 0.02 mg/kg of NDiPA; (4) Oryzalin: max. 0.1 mg/kg of NDPA
Directives 2001/83/EC – Human Medicinal Products	Not listed	The acceptable intake limit for nitrosamines in human medicinal products is considered to be a theoretical excess cancer risk of <1 in a 100,000, based on lifetime daily exposure, pursuant to Article 5(3) of Regulation (EC) No 726/2004
Directives 2004/28/EC – Veterinary Medicinal Products (VMPs)	Not listed	EMA guidance on the assessment and control of DNA reactive (mutagenic) impurities in VMPs, includes N-nitroso compounds: no impurities of this nature are allowed in veterinary active ingredients or products. However, a case-by-case approach is taken to justify acceptable intakes for authorised VMPs.

3.1 REACH Registrations

None of the four main nitrosamines (NDMA, NDEA, NDPA and NDELA) or other nitrosamines in general are registered under REACH, except NDPhA (1 registrant).

Table 12: REACH Registrations and tonnage

Substance(s)		Tonnage (tonnes/annum)	
Name	EC number	Full registration	Intermediate uses
NDPhA	201-663-0	10-100	Polymer preparations and compounds (manufacture of rubber products)

3.2 Other legislations

3.2.1 Cosmetics Regulation (EC) 1223/2009

Nitrosamines in general (e.g. NDMA, NDEA, NDPA and NDELA) are listed in Annex II as substances prohibited in cosmetic products.

There are restrictions on nitrosamines' impurities and precursors for a number of other cosmetic ingredients, e.g. sodium nitrite is not to be used with secondary and/or tertiary amines or other substances forming nitrosamines. Maximum secondary amine concentrations are set at 0.5% in the formulation and raw material for monoalkylamines, monoalkanolamines and their salts; 0.5% in the formulation and 5% in the raw material for fatty acid dialkylamides and dialkanolamides; and 0.5% in the raw material for trialkylamines, trialkanolamines and their salts.

Conditions for the use of bronopol and 5-bromo-5-nitro-1,3-dioxane as preservatives require to avoid the formation of nitrosamines. Forty-six other cosmetic ingredients have the following use conditions attached: "maximum nitrosamine content: 50 µg/kg" (as a by-product), "do not use with nitrosating agents", and "keep in nitrate-free containers."

3.2.2 Food and drinking water

Regulation (EU) 1129/2011 notes the potential formation of nitrosamines from nitrites used as preservatives in meat products. Nitrites (sodium nitrite [E250] and potassium nitrite [E249]) and nitrates (sodium nitrate [E251] and potassium nitrate [E252]) are authorised as food additives for the preservation of certain meat, fish and cheese products, with maximum allowable levels ranging from 50 to 180 mg/kg for nitrites and 10 to 500 mg/kg for nitrates.

There are no provisions on nitrosamines in drinking water under Directive (EU) 2020/2184.

3.2.3 Other regulations

The release of nitrosamines and N-nitrosatable substances from rubber teats and soothers is managed under Directive 93/11/EEC. The Toy Safety Directive 2009/48/EC sets migration limits of 0.05 mg/kg for nitrosamines and 1 mg/kg for nitrosatable substances in toys intended for use by children under 36 months or in other toys intended to be placed in the mouth.

4. Existing Occupational Exposure Limit values

4.1 Occupational Exposure Limits (OEL)

Several EU Member States have established OEL and short-term limit values (STEL) values for nitrosamines. The list should not be considered as exhaustive.

Table 13: Existing Occupational Exposure Limits (OELs)

Country	TWA (8 hrs)		STEL (15 min)		Remarks / Notations
	ppm	mg/m³	ppm	mg/m³	
Austria		2 (1) (2)		10 (1) (2) (3)	(1) Total nitrosamines (NDBA, NDEA, NDMA, NDiPA, NEPA, NMEA, NMPA, NMor, NPip, NPyr; (2) TRK based on technical feasibility; (3) 30 minutes average value
Belgium					Skin notation
Germany		0.75 (1) (2) 0.075 (3)(4)		6(1)	(1) NDMA; (2) Workplace exposure concentration corresponding to the proposed tolerable cancer risk; (3) Total nitrosamines; (4) Workplace exposure concentration corresponding to the proposed acceptable cancer risk
Netherlands		0.2 (1)			(1) NDMA
Slovenia		2.5 (1)			(1) NDMA

Switzerland		1 (1)			(1) Total nitrosamines (NDBA, NDEA, NDMA, NDELA, NMEA, NMor, NPip, NDPA)

Notes: TWA: Time-Weighted-Average; STEL: Short term exposure limit; TRK: Technical Guidance Concentrations
Source: GESTIS Substance Database; last accessed November 2022

4.2 Biological Limit Values (BLV) and Biological Guidance Values (BGV)

No Biological Limit Values (BLV) or Biological Guidance Values (BGV) were identified for nitrosamines.

5. Occurrence, uses and occupational exposure

5.1 Occurrence

Nitrosamines are formed by the reaction of nitrosamine precursors (generally secondary amines) with nitrosating agents such as nitrogen oxides (

Figure **1**).

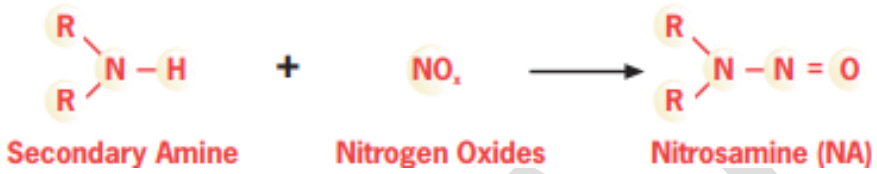


Figure 1: Example of nitrosation reaction

Precursors to N-nitroso compounds are mainly secondary amines (i.e. there are two carbons bonded to the nitrogen). Primary amines (with only one carbon bonded to the nitrogen) may form unstable nitrosamines that decompose quickly, whereas nitrosamines are not typically formed from tertiary amines, although this may occur under certain circumstances (Keen et al., 2000).

Nitrosating agents or their precursors include nitrogen oxides (which may be formed by heating any nitrogen-containing compound), nitrites (including those produced by chemical or bacterial reduction of nitrates) and organic nitro and nitroso compounds (BAuA, 2018). The formation of nitrosamines in air requires the presence of water (Spiegelhalder and Preussmann, 1983). There is negligible nitrosamine formation in dry air, whereas secondary and tertiary amines can react rapidly in the dark to yield up to 3% nitrosamines at 20 to 50% relative humidity. Nitrosamines are degraded in sunlight.

Nitrosamines have been detected in drinking water, food stuffs, personal care products, tobacco smoke, medicines and diesel exhausts (ATSDR, 2022; WHO, 2002; EC, 2013).

N-nitroso compounds occur in foods that utilise nitrite salts either for preservation, colouring and / or combustion gases for drying or other related processes (PAS, 2017) as well as being formed endogenously upon digestion of nitrate and nitrite (RIVM, 2020). They have also been identified as occurring in malt beverages and alcohol (ATSDR, 2019; PAS, 2017).

Nitrosamines, and in particular NDMA, occur at low levels as a by-product of disinfection in water-treatment plants during the chlorination or chloramination of drinking water and wastewater (ATSDR, 2022). NDMA may also be released into the environment as the result of application of sewage sludge, as NDMA can be formed in sewage treatment, to soils rich in nitrate or nitrite (WHO, 2002).

Certain nitrosamines, such as NDMA, can be formed as a result of biological, chemical, or photochemical processes and have been identified in the environment; this is due to its ready

formation from commonly found precursors (typically secondary amines) that may be present in water, air, and soil and chemical reaction with nitrosating agents (typically nitrites) (WHO, 2002; ATSDR, 2022).

Examples of these natural formation processes include the formation of NDMA in air at night due to atmospheric reactions of dimethylamine (DMA) with nitrogen oxides and the synthesis of NDMA from nitrate, nitrite, and amine compounds by soil bacteria (WHO, 2002). Atmospheric nitrosamine concentrations are a steady-state balance of the rate of formation from ongoing emissions of amines and the rapid rate of removal for example by photolysis and wash out as most nitrosamines are water soluble (EA, 2022).

Certain nitrosamines such as NDELA are not known to occur naturally (IARC, 2000). The rate of formation of NDELA in aqueous solutions of ethanolamines is pH-, temperature- and time-dependent, with low pH values promoting the formation of nitrosamines (IARC, 2000, BAuA, 2007). The optimal pH range for the formation of nitrosamines is mostly between 2 and 5; nevertheless, under certain reaction conditions, nitrosamines can also be formed during the use of water-mixed cooling lubricants in alkaline media up to a pH of approx. 9.5, albeit with a lower yield (BAuA, 2007). Nitrosation of secondary amines in metal-working fluids (MWFs) also occurs at near-neutral pH by the action of bacteria and at basic pH with appropriate catalysts (IARC, 2000).

Nitrosamines may inadvertently be formed during the manufacture of commercial preparations, often during formulation through the action of unsuspected added ingredients or environmental conditions, and have been identified in cosmetic products, balloons and pesticides used by the general population as well as cigarette smoke (EC, 2013; WHO, 2002).

In medicines, nitrosamine impurities could be linked directly to the simultaneous presence of the reagent sodium nitrite ($NaNO_2$) and secondary and tertiary amines in the form of solvents, reagents and catalysts (EMA, 2020). Additionally, formation in and contamination of finished products during primary packaging has been identified with nitrocellulose in the foil lids as the responsible nitrosating agent (EMA, 2020).
Occurrence during industrial processes, for example in the rubber industry, are described in detail in sections 5.2 and 5.3.

5.2 Production and uses

In the past, nitrosamines were directly used in certain industries (e.g. NDPhA, was used as a retarder in the rubber industry until the early 1980s) but this practice has now largely ceased, and nitrosamines now only occur in industrial situations where they are formed unintentionally due to the coexistence of precursors (generally secondary amines and nitrosating agents) under favourable conditions (ECETOC, 1990; Keen et al, 2000). However, one registrant remains in the EU that manufactures NDPhA, for use in polymer preparations to manufacture rubber.

BAuA (2018) has investigated the work areas in which carcinogenic nitrosamines can occur (Table 14).

Table 14: Industrial sectors and activities with known exposure to nitrosamines (Table 1 in BAuA 2018, TRGS 552)

Industry	Workspace/production area	Critical work areas and conditions
Rubber industry	Weighing, mixing, semi-finished pre-vulcanisation processing, vulcanisation, post-vulcanisation processing, storage	Calenders, extrusion lines, salt baths, vulcanisation, moulding, control, storage of technical rubber items and tyres Processing of emulsion polymers
Metal industry and other industries with material processing	Use of water-mixed cooling lubricants	Use of water-mixed coolants that do not comply with TRGS 611 and may contain secondary amines (see TRGS 611) Activities with anti-corrosion agents and

Industry	Workspace/production area	Critical work areas and conditions
	Manufacture and use of anti-corrosion agents including VCI ("volatile corrosion inhibitors") materials	handling of corrosion-protected metal parts including VCI materials that contain secondary amines or nitrite (see TRGS 615)
Chemical industry	Manufacture and use of amines, filling, decanting and filling work of amines, production of polyacrylonitrile fibers, coatings using the coagulation process	Production and use of secondary amines and solvents such as dimethylformamide/ dimethylacetamide
Leather industry	Water workshop	Processing of skins
Foundries	Use of cores made with aminic catalysts.	Pouring, cooling as well as the subsequent removal of moulding sand and residues, especially from the cores
Other industrial areas	Activities with rubber articles	Processing and storage of technical rubber articles

The EU-OSHA (2007) survey of OELs includes listings for nitrosamines with comments that these values are of most relevance for the rubber industry ('vulcanisation and following processes including storage of rubber products, storage places for tyres'), textiles ('manufacture of polyacrylonitrile dry spinning process using dimethylformamide'), and chemical industry ('filling of vessels and reactors with amine').

ECHA (2014) lists the following sectors, aligning with TRGS 552 (BAuA, 2018), in which activities (even using state of the art technology) are anticipated to lead to the formation and potential release of carcinogenic nitrosamines of Category 1A or 1B:

- Rubber industry
- Metal industry and metal processing industry
- Chemical industry manufacturing/using secondary amines
- Leather industry
- Foundries and others

These industries are considered in more detail in the sections below with a specific focus on the rubber industry as the highest levels of nitrosamine exposure have been determined in this sector (Iavicolo and Carelli, 2006). The most prominent nitrosamines that occur in these industrial sectors are described in the section texts, noting that different studies identify different nitrosamines although some, such as NDMA and NDEA, are consistently present. Usually there is a mixture of nitrosamines, based on the raw materials present, and a more exhaustive list identifying also those nitrosamines that are less prominent but are generated in the different industrial sectors is provided in the table in Section 5.5.

5.2.1 Rubber industry

The production of natural and synthetic rubber products typically consists of four steps (Groover, 2021):

1. Compounding: Natural or synthetic rubber is combined with fillers (e.g. carbon black, clay, limestone, chalk, synthetic polymers) and other rubber additives (e.g. antioxidants, pigments, plasticisers, process aids) for its intended end-use. Rubber formulations can typically comprise of 100 to 200 components.
2. Mixing: The rubber formulation is homogenised by internal mixing (e.g. Banbury or Intermix mixers) or by external/open mill mixing (e.g. horizontal two-roll mills).
3. Shaping: The homogenised rubber mixture is shaped into its intended form under pressure. Shaping processes include extrusion, calendering, coating, moulding and casting.
4. Vulcanisation (curing): Heat is applied to the rubber article to create polymer linkages. Hard rubbers have more polymer linkages than soft rubbers.

The cured rubber product then proceeds to finishing and assembly, where it may undergo further shaping (e.g. cutting), be combined with other components and materials, undergo additional treatment (e.g. conditioning) or quality control, followed by packaging, storage and transport (INRS, 2019; Oury et al., 1997).

The US National Institute for Occupational Health (NIOSH) has reported nitrosamine exposures for workers involved at all stages of rubber processing: compounding (e.g. mill operator, tray compounder), mixing (e.g. Banbury operator), shaping (e.g. extruder operator, mould press operator, press operator, calendar machine operator, laminator) and vulcanisation (e.g. cure heater operator) (OSHA, 1989). Nitrosamine exposure in rubber processing has previously been categorised in three levels, based on a survey of male German rubber workers between 1950 and 1991 (Straif et al. 2000a,b):

- High exposure: Salt bath curing, vulcanisation and post-vulcanisation
- Medium exposure: Post-vulcanisation processes
- Low exposure: All other work areas pre-vulcanisation (e.g. raw material handling, weighing, mixing, milling, extruding, calendaring, assembly, building)

The main process where nitrosamines are formed in rubber production is during the last step, i.e. during vulcanisation (Breuer and van Gelder, 2001; INRS, 2019).

Based on process workflow and potential for nitrosamine exposure, "pre-vulcanisation" (e.g. compounding, mixing and shaping processes), "vulcanisation" and "post-vulcanisation" (e.g. finishing, storage, transport, use) activities are respectively grouped and discussed below (see sections 0 to 5.2.1.3).

Sources of nitrosating agents in rubber processing include nitrogen oxides adsorbed to inorganic additives (e.g. carbon black, zinc oxide), additives containing nitro- or nitroso- groups, atmospheric nitrogen oxides, some blowing agents, and nitrite and nitrate ions in molten salt baths used in vulcanisation (Spiegelhalder, 1983; Spiegelhalder and Wacker, 1994; INERIS, 2014; Iavicoli and Carelli, 2006; Fishbein, 1983).

N-nitrosodiphenylamine (NDPhA) is also a nitrosating agent and was historically used as a vulcanisation retarder but this practice is considered to have largely been eliminated (Monarca et al., 2001; Keen et al., 2000), although one registrant remains in the EU who manufactures NDPhA for use in rubber manufacture.

Vulcanisation accelerators are the main sources of nitrosamine precursors. Secondary amines may be generated from the degradation of thiurams (e.g. tetramethylthiuram disulphide), dithiocarbamates (e.g. zinc diethyldithiocarbamate), sulphenamides and dithiomorpholines (e.g. morpholinomercaptobenzothiazole) (Oury et al., 1997; Sheth and Desat, 2013) at high temperatures. Various nitrosamine compounds are formed depending on the specific vulcanisation accelerators used to achieve a particular technical quality and the specific manufacturing process (Monarca et al., 2001; Breuer and van Gelder, 2001; Spiegelhalder and Preussmann, 1983; Fishbein, 1983).

NDMA and NMor are the most commonly formed nitrosamines in rubber processing (Monarca et al., 2001; Breuer and van Gelder, 2001; Hidajat et al., 2019).

NDEA, NPip, NDBA, NPyr, NEPA and NMPA have also been reported in the rubber industry (Jonsson et al., 2006; Oury et al., 1997; INERIS, 2014; Reh and Fajen, 2010; Breuer and van Gelder, 2001). The highest nitrosamine concentrations have been observed in styrene-butadiene rubber manufacturing (the most prevalent synthetic rubber), followed by acrylonitrile-butadiene rubber manufacturing and ethylene-propylene rubber manufacturing, although only these rubber types were assessed (Monarca et al., 2001).

5.2.1.1 Pre-vulcanisation

There is some potential for nitrosamine formation before curing due to the presence of nitrosamine precursors and nitrosating agents in the raw rubber mixture (Fishbein, 1983). Vulcanisation accelerators (nitrosamine precursors) and additives (sources of nitrosating agents)

are added to the rubber formulation during compounding. Mixing of the rubber formulation is typically performed at 160°C (Rodgers and Waddell, 2013). Vulcanisation agents (e.g. sulphur, peroxides) are usually added after mixing and cooling the rubber formulation to avoid premature vulcanisation (Groover, 2021). A second mixing step is performed after the addition of vulcanisation agents at temperatures not exceeding 115°C.

There are four general shaping processes for rubber, all with varying process conditions for production of the intended rubber article (Groover, 2021; HSE[9]):

1. Extrusion: Screw extruders are used to force cold, warm or hot rubber mixtures through a die to produce a sheet or profile. It may be combined with calendering processes.
2. Calendering: Rubber mixtures are fed through a series of heated or unheated horizontal rolls of decreasing thickness to create a rubber sheet or to apply a thin layer of rubber on another material.
3. Coating: In addition to calendering, rubber can be coated onto other materials by skimming, dipping and spraying. For the skimming process, a solution of the rubber mixture is prepared in an organic solvent (commonly toluene, xylene, acetone, methyl ethyl ketone or n-hexane based petroleum naptha blends) and coated onto material. The solvent is evaporated by heat prior to vulcanisation. Dipping involves immersion of the material into a highly fluid solution of the rubber mixture (e.g. latex). Spraying uses a spray gun to apply a solution of the rubber mixture onto the material.
4. Moulding and casting: There are three principal moulding techniques, all of which may be combined with vulcanisation in a continuous process. Compression moulding is the most common moulding technique in the rubber industry, which involves forcing the rubber mixture into the cavity of a heated mould. Transfer moulding involves loading an unformed piece of rubber into the cavity of a mould and closing the mould, forcing the rubber to fill the cavity. Injection moulding involves feeding the pre-heated rubber mixture into a mould cavity. One approach to casting involves dipping a form into a solution of the rubber mixture and stripping the rubber coating from the form. A separate vulcanisation step is required for casting.

The use of nitrosation inhibitors, such as primary amines, α-tocopherol, urea and amidosulfonic acid, to react with nitrosating agents can be considered at the compounding stage to reduce the potential for nitrosamine formation (INERIS, 2014; Spiegelhalder and Wacker, 1994). The potential for nitrosamine formation can also be reduced by the elimination of nitrosating agents, such as combustion sources (e.g. heat engines) (INERIS, 2014; Spiegelhalder, 1983).

5.2.1.2 Vulcanisation

There are various methods available for the vulcanisation of rubber, a number of these generate significant amounts of nitrosamines due to the use of accelerators that contain or form secondary amines, but methods are also available which do not employ nitrosamine-generating precursors. Process temperatures of 140°C to 180°C are typically used for sulphur vulcanisation with the use of accelerators[10,11], with process times ranging from 20 minutes to one hour (Coran, 2013). Vulcanisation using the salt bath method (with alkali metal nitrates and nitrites) produces the highest levels of nitrosamines, since nitrites and nitrates are nitrosating agents. Comparing different methods, nitrosamine levels are three times less for vulcanisation by hot air/ microwave/ fluid-bed method and almost twenty times less for vulcanisation by compression and injection method (Jonsson et al., 2006; Oury et al., 1997). All of these processes are

[9] https://www.hse.gov.uk/rubber/introduction-to-rubber-processing.pdf (accessed 25/08/2022)
[10] https://www.nocil.com/Downloadfile/DTechnicalNote-Vulcanization-Dec10.pdf (accessed 12/09/2022)
[11] https://monroeengineering.com/blog/how-vulcanization-improves-the-properties-of-rubber/ (accessed 12/09/2022)

performed in closed production lines[12,13,14], although some particular processes require open production lines (e.g. sealing and joining rubber components[15]). In a small survey of four rubber curing factories in the UK, salt bath curing was used for the production of general rubber goods by all factories between 1998 and 2001, whereas only one factory was still using salt bath curing by 2007 (HSE, 2010). There is no information on the current extent of salt bath curing processes in the EU, but it is considered to still be a commonly used vulcanisation technique[16]. Nitrite-containing vulcanisation salts are still available on the market[17,18], although nitrate-free vulcanising salts are also available[19,20].

Salt bath vulcanisation is best suited for manufacturing rubber tubing, hoses and weather stripping[21]. In particular, nitrited molten salt baths have been considered to produce the best surface finish for vehicle sealing strips compared to other vulcanisation methods (Oury et al., 1997). These articles are often based on ethylene propylene diene monomer, which require thiuram and carbamate accelerators that are easily nitrosated in nitrite salt baths.

Nitrosamine emissions for this process have been observed to be 3 to 10 times higher than the German acceptable and tolerable concentrations[22] for total nitrosamines, whereas for other vulcanisation methods (not employing salt baths), only 6% of cases have exceeded this limit.

High accelerator loadings (for rapid curing) and the manufacture of articles with high specific surface area have been identified as key process factors contributing to exceedance of the German acceptable and tolerable concentrations[22] for total nitrosamines.

Alternative vulcanisation accelerators, such as tetrabenzylthiuram disulphide, zinc dibenzyldithiocarbamate, N,N'-diphenyl guanidine, 2-mercaptobenzothiazole and polymerisation terminators (e.g. diethylhydroxylamine) have been successful in reducing nitrosamine formation (Oury et al. 1997; INERIS 2014).

Other methods of vulcanisation, such as hot air oven or ultra-high frequency techniques, can be used to replace salt baths (INERIS 2014). The article itself and the required specifications are likely to be key factors in application of alternative vulcanisation methods to replace salt baths and nitrosamine-generating vulcanisation accelerators. Around the workplace, good ventilation of vulcanisation activities and the physical separation of salt bath processes from other processing activities can be implemented to reduce nitrosamine exposure to workers (Oury et al. 1997).

5.2.1.3 Post-vulcanisation

Nitrosamines can naturally migrate to the surface of finished rubber articles after curing, resulting in nitrosamine exposure during product finishing, storage, transport and use (INRS,

[12] Rubicon Gummitechnik und Maschenenbau GmbH, Germany. https://www.rubicon-halle.de/en/products/vulcanization-lines/rubber (accessed 28/10/2022)

[13] MDC Engineering GmbH, Germany. https://mdc-engineering.net/?-Vulcanoclean-12-&lang=en (accessed 28/10/2022)

[14] Zhejiang Baina Rubber & Plastic Equipment Co., Ltd., China. https://www.zjbaina.com/product/rubber-salt-bath-curing-production-line-lcm/rubber-salt-bath-curing-production-line-lcm.html (accessed 28/10/2022)

[15] EMKA Beschlagteile GmbH & Co. KG, Germany. https://www.emka-profile.com/de_en/company/ (accessed 28/10/2022)

[16] MDC Engineering GmbH, Germany. https://mdc-engineering.net/?-Vulcanoclean-12-&lang=en (accessed 28/10/2022)

[17] Petrofer, Turkey. https://petrofer.com.tr/index.php?option=com_content&view=article&id=49&Itemid=71&lang=en (accessed 28/10/2022)

[18] Kolene Corporation, USA. https://www.kolene.com/files/3316/2611/4258/Kolene_HeatTreating_Chemicals.pdf (accessed 28/10/2022)

[19] HEF Durferrit, Germany. https://www.nitriersalze.com/en/salt-bath-heat-treatment/heat-treatment-salts/vulcanizing.html (accessed 28/10/2022)

[20] DuBois Chemicals, USA. https://www.duboischemicals.com/manufacturing/products/heat-treatment/rubber-curing-salts/ (accessed 28/10/2022)

[21] https://elbex-us.com/news/vulcanized-rubber-salt-bath-cure (accessed 24/08/2022)

[22] BAuA does not recommend conventional OELs for nitrosamines as they are non-threshold carcinogens. Instead BAuA has derived acceptable and tolerable concentrations of nitrosamines (see Section 4).

2019). NDMA comprised 80% of total nitrosamines detected in a warehouse of finished rubber products in Canada between 2005 and 2008 (Québec Public Health Institute, 2011). Despite recent reductions in nitrosamine exposure reported for the rubber industry as a whole, NDMA exposures in the UK and Germany were slightly higher for finishing, assembly and miscellaneous processes for both tyres and general rubber goods in 2002 compared to 1985 (Hidajat et al., 2019). NDMA exposures were also reported to have increased between 1980 and 2000 for tyre maintenance and engineering (de Vocht et al., 2007).

The handling and storage of newly vulcanised rubber articles in poorly ventilated areas and the storage of large quantities of vulcanised articles in confined spaces have been identified as key factors for exceeding the German acceptable and tolerable concentrations[22]. for total nitrosamines (Oury et al., 1997; Spiegelhalder, 1983). To mitigate this problem, ventilation has been installed in some tyre storage facilities to reduce nitrosamine exposures.

Nitrosamines have been detected in other rubber articles including shoe soles, baby nursing items, pharmaceutical packaging components, condoms, gloves and automotive and household tubing and sealing systems (Sheth and Desat, 2013). Several nitrosamines, including NDMA and NDEA, have been detected during the installation of rubber sealing in vehicles (Reh and Fajen, 1996) as well as in new cars (Oury et al., 1997).

5.2.1.4 Summary of nitrosamine exposure control and reduction in the rubber industry

Over the past few decades, the rubber industry has reduced the potential for nitrosamine formation through the replacement of nitrosamine precursors and nitrosating agents and the use of nitrosation inhibitors. Alternative vulcanisation accelerators have been developed (that are not as easily nitrosatable) and nitrate-free vulcanisation salts are available on the market. Alternative vulcanisation methods are also available to replace salt baths. However, salt bath vulcanisation is still used to produce some rubber articles (e.g. tubing, seals) as it is perceived to give the best performance.

Engineering controls such as increased ventilation in processing and storage facilities and isolating salt bath processes from other rubber processing activities have also been employed to control nitrosamine exposures. Some countries (e.g. UK[23]) have worker exposure limits for rubber dust and fumes which may help to reduce nitrosamine exposure by extension, although the link between nitrosamine concentration and rubber dust and fumes is unclear.

No specific guidance for minimum ventilation limits for rubber or tyre storage facilities was found in the literature.

5.2.2 Metal processing industry (soluble metal working fluids)

Metal-working fluids (MWFs) are used for lubricating and cooling the cutting and grinding surfaces of metals in metallurgical industries.

Nitrosamines (principally NDELA) have been detected in water-based soluble and synthetic MWFs used in tasks such as camshaft and crankshaft grinding (Park and Mirer, 1996; Ducos et al., 1999; Fadlallah et al., 1997). The formation of NDELA results primarily from the reaction between alkanol-amines (such as di- or triethanolamine, or their derivatives) used as anti-corrosives, lubricants or emulsifiers and nitrite ions frequently present as traces or intentionally added to inhibit corrosion (e.g. sodium nitrite) (IARC, 2000; Ducos et al., 1999). Ethanolamines and nitrites were first added to the machining fluids used in US vehicle production plants in the early 1950s. In these plants, the use of nitrites decreased in the mid-1980s until their exclusion by the early 1990s (Friesen et al., 2009).

Certain water-soluble MWFs can contain up to 60% diethanolamine prior to their dilution with water and subsequent use. Nitrite can also be found in the water used to dilute the MWFs (Fadlallah et al., 1997) and NOx can be present in the air of metal workshops. Most water-based fluids contain biocides, which may also catalyse the formation of nitrosamines. Nitrosamine formation has even been reported to occur during the simple peroxidation of diethanolamine, a reaction in which the nitrosating agent is apparently produced by oxidative degradation of a

[23] HSE, UK. 2011. https://www.hse.gov.uk/pubns/iacl95.htm (accessed 28/10/2022)

portion of the secondary amine. These observations suggest that NDELA can be formed in MWFs that are initially nitrite free (Fadlallah et al., 1997).

Workers handling MWFs containing NDELA can be exposed by direct contact or by inhalation of oil mists, during most machine shop operations. The concentrated water soluble MWFs are mixed with water (that may contain nitrates or nitrites) and dilute MWFs are sprayed, splashed and vaporized into the air particularly during milling and grinding operations (Fadlallah et al., 1996).

Concentrations of NDELA in MWFs have vastly reduced due to developments to greatly reduce concentrations (and co-occurrence) of the precursors; for example, since 1993, German regulations have stipulated the replacement or modification of MWFs if NDELA concentration exceeds 5 mg/l or if its concentration of nitrite/nitrate ions exceeds 20 or 50 mg/l, respectively. Also, since the early 1990s the US and Canada banned the addition of nitrites/nitrates to MWFs also containing ethanaloamines.

5.2.3 Chemical industry

There is potential for nitrosamine exposure in the chemical industry, specifically at plants manufacturing secondary amines for industrial use (Keen et al., 2000). Nitrosamines such as NDMA and NMor have been detected during material transfer processes in the production of aliphatic amines (Breuer and van Gelder, 2001). Also, EU-OSHA (2007) highlights the filling of vessels and reactors with amine in the chemical industry as a potential source of exposure to nitrosamines.

NDMA has also been found as an impurity during the manufacture and storage of certain pesticides and biocides, namely benazoline, bromacil, dicamba, 2,4-dichlorophenoxyacetic acid, mecoprop and (4-chloro-2-methylphenoxy)acetic acid (INERIS, 2014; Environment Canada, 2001). No information is available on specific process conditions for the formation of nitrosamines during the production of chemicals, pesticides and biocides.

NMor has also been reported as a reaction product of morpholine, a secondary amine, which is an intermediate for the synthesis of various active ingredients (INERIS, 2014).

5.2.4 Leather & textiles

Occupational exposure to nitrosamines (primarily NDMA but also NDEA and NMor) has previously been reported in the leather tanning industry (ECETOC, 1990; Krstev et al., 2005; Breuer and van Gelder, 2001). The formation of NDMA specifically is dependent on the use of dimethylamine sulphate as an unhairing agent in the processing of animal hides and is reported to have been discontinued some time ago (e.g. Keen et al., 2000).

The Best Available Techniques Reference Document (BREF) for the Tanning of Hides and Skins (JRC, 2013) notes the breakdown of proteins during liming and unhairing, which may contribute secondary amine precursors to the formation of nitrosamines. Ammonium salts are used for deliming, which may be converted to nitrosating agents. Deliming is conducted at approximately 35°C. Ammonium salts may be substituted by carbon dioxide or weak organic acids (e.g. magnesium lactate, lactic acid, formic acid, acetic acid) to reduce the release of nitrogen to air and wastewaters. Many plants in Europe use ammonium-free or reduced ammonium deliming processes, therefore the potential for nitrosamine formation in European leather tanning operations may be low. The deliming process takes place at the beamhouse (or limeyard), where skins and hides are prepared for tanning ("pre-tanning"). Minimal manual handling is required, as skins and hides are processed in closed drums[24,25]. There is no information on the potential for nitrosamine formation during tanning and post-tanning processes.

Exposure to nitrosamines in general textile processes may also arise from the manufacture and handling of rubber-coated textiles (IARC, 2018).

[24] Yarwood Leather, UK. 2013. https://www.youtube.com/watch?v=FT_sLxOfins (accessed 28/10/2022)
[25] ATC France. 2021. https://www.youtube.com/watch?v=YX8tKYiJYY0 (accessed 28/10/2022)

5.2.5 Foundries (Iron and steel)

The Ashland (cold-box) process for making moulds has the potential to lead to nitrosamine formation due to the use of a tertiary amine as a catalyst/reaction initiator in mould core manufacture (Ducos et al., 1988; Keen et al., 2000). Ducos et al. (1988) state that triethylamine or dimethylethylamine (both tertiary amines) are used as the amine catalyst, being injected into core moulds for the curing of sand binding materials. Keen et al. (2000) conducted an investigation of foundries in the UK and found that steel pouring into these moulds has the potential to cause exposure to nitrosamines due to the elevated temperatures generating increased NOx concentrations.

INRS (2013b) also report that during the manufacture of moulds containing cores made using the Ashland process, NDMA and NDEA can be formed from dimethylethylamine that is used as a binder, and nitrogen oxides from the combustion gases and that these two nitrosamines can subsequently be released.

5.2.6 Other industrial sources

5.2.6.1 Carbon capture

Amine-based solvents, such as monoethanolamine, diethanolamine and morpholine, are currently the most widely used system for post-combustion CO_2 capture. Nitrogen oxides (NOx) in flue gases can react with aqueous amines within the solvent loop of the absorber to form carcinogenic nitrosamines in appreciable quantities as by-products, with NDEA, NDELA and NMor as the most common nitrosamines formed (Fine et al., 2014; Aqeel and Lim, 2020; Buist et al., 2015). NDMA and NPip have also been detected. Nitrosamines can escape from the CO_2 capture system either through accidental spills, reclaimer waste, or gaseous emissions and are primarily considered to be of concern in terms of environmental emissions rather than for occupational exposure. A modelling study found the concentration of nitrosamines (in air) to be influenced by stack height and diameter, exit flue gas temperature and velocity, meteorology (e.g. wind speed, wind flow field) and background photochemistry (Manzoor et al., 2017).

5.2.6.2 Electroplating

Nitrosamines, such as NDEA, may form during the use of stripping baths in electroplating plants[26]. Stripping baths are used to remove metals from a surface by submerging a metal-plated article in a solution containing amines (e.g. triethanolamine, diethylamine, triethylamine, ethylenediamine) and applying an electric current to the system to free the metals. Nitrate salts of the amines are sometimes used in the stripping baths, thereby providing both a nitrosamine precursor (amines) and nitrosating agent (nitrates). Nitrosamines have not been detected in stripping baths containing monoethanolamine, ammonia and diethylenetriamine. Information on the specific processes (e.g. type of metal) requiring the use of amine-based stripping baths and suitable alternatives are not available.

5.2.6.3 Tobacco processing

Nitrosamines such as NDMA, NPyr, NPip, NMor and NDELA may form from natural constituents during the drying and fermentation of the tobacco plant (INERIS, 2014).
"Tobacco-specific nitrosamines" are formed when tobacco leaves are grown, cured, aged and processed[27]. Some common "Tobacco-specific nitrosamines" (Xia et al., 2021; Hecht et al., 2022) are N'-nitrosonornicotine, N'-nitrosonornicotine ketone, N'-nitrosoanabasine, N'-nitrosoanatabine.
Heat treatment (pasteurisation) has been used to prevent nitrosation reactions of tobacco plant constituents by killing microorganisms involved in the reduction of nitrate to nitrite (i.e. production of nitrosating agents) (Hecht et al., 2022).

[26] https://www.dguv.de/ifa/forschung/projektverzeichnis/bia_2031-2.jsp (accessed 12/09/2022)
[27] https://www.cancer.gov/publications/dictionaries/cancer-terms/def/tobacco-specific-nitrosamine (accessed 12/09/2022)

Finally, NDMA can also form from nicotine and during combustion.

5.2.6.4 Fuel combustion

There is a potential for nitrosamine formation during fuel combustion, as nitrous oxides (nitrosating agents) are released at elevated temperatures (INERIS, 2014; Spiegelhalder and Preussmann, 1983). NDMA has been detected during the production of rocket fuels, specifically for the rocket fuel component unsymmetrical dimethyhydrazine, which is a nitrosamine precursor (INERIS, 2014).

5.2.6.5 Industries for further consideration

BAuA (2018) state that other industrial sectors in which the occurrence of nitrosamines cannot be excluded for specific work areas include: agriculture, wastewater treatment, waste disposal and fish and meat processing. For these sectors there are indications of the occurrence of secondary amines or the possible formation of nitrosamines but there are currently not enough measurement results for these areas to enable a general assessment of the risk.

5.3 Occupational exposure

5.3.1 Nitrosamines formed in different industrial sectors

Specific nitrosamines are associated with different industrial sectors. Breuer and van Gelder (2001) have associated the occurrence of various nitrosamines with different industrial processes. However industrial processing has evolved, and the use of different raw materials, different operating conditions and improved control measures means a significant decrease in exposure levels, and reduced prominence of certain nitrosamines.

5.3.1.1 Reduction in occupational exposure levels

A marked decrease in occupational exposure to nitrosamines has been observed since the late 1970s/early 1980s. The highest exposures to nitrosamines have been measured in the rubber industry, with the highest concentrations measured during curing/vulcanisation of rubber products. Early studies in the 1980s measured concentrations up to 1060 µg/m^3 NDMA and up to 4700 µg/m^3 for NMor (Spiegelhalder and R. Preusmann 1983). Typical concentrations in this sector are now expected to be ≤1 µg/m3, although higher concentrations of up to 28 µg/m^3 NDMA have been measured in the Swedish rubber industry (Jonsson et al, 2009).
It is important to note that much of the research on exposure to nitrosamines in the rubber industry was conducted between 1980 and 2000. The decrease in nitrosamine exposures in the rubber industry was largely driven by the introduction of nitrosamine concentration limits such as those introduced in Germany in 1992 (de Vocht et al., 2007). There is little publicly available information on contemporary (i.e. post-2010) nitrosamine exposures in the rubber industry. There does not seem to be any general correlation between exposures to rubber fumes and nitrosamines, i.e. not all rubber fumes contain nitrosamines to the same extent (HSE, 2010), rather, the composition of rubber dust and fumes is strongly dependent on the mixture composition and processing conditions (Advisory Committee on Safety and Health at Work, 2021). However, the rubber industry has moved to alternative methods to reduce nitrosamine formation and increased use of engineering controls (ventilation) to reduce nitrosamine exposure as summarised in section 5.2.1.4.

A large reduction in exposure to nitrosamines associated with the use of water-soluble MWFs has also been noted in the metal processing sector. In the United States this followed the 1976 alert issued by the National Institute for Occupational Safety and Health (NIOSH) regarding the possible health threat posed by the presence of nitrosamines in MWFs. Warnings and guidance on the risk from nitrosamines have had a similar effect in Europe, e.g. since 1993, German regulations have stipulated the replacement or modification of a fluid if its NDELA concentration exceeds 5 mg/l or if its concentration of nitrite/nitrate ions exceeds 20 or 50 mg/l, respectively; also nitrosamine concentrations should be <0.0005%, the pH of used emulsions should only

differ about 0.5 from that of the original concentrate, and concentrations of secondary amines should be <0.2% in the original concentrate (BAuA, 2007). Additionally, the NMor content in the used water-mixed cooling lubricant must not exceed 0.0001%. NDELA is considered to be relatively non-volatile and NMor is considered to be volatile.

Fadlallah et al. (1997) stated that concentrations of NDELA measured in MWFs in Canada had previously been reported to have dropped considerably from 230-5,530 ppm in 1978 to 5-95 ppm in 1990 and their study in the mid-1990s found even lower concentrations of 0.02-7.53 ppm. IARC (2000) presents a comprehensive summary of NDELA concentrations in MWFs. A UK study (Simpson et al., 2002) found a median NDELA concentration of only 0.4 ppm in water-mixed MWFs.

5.3.2 Occupational exposure levels

Occupational exposure monitoring for nitrosamines is primarily performed by monitoring workplace air (static and personal air) but biological monitoring has also been undertaken for some studies of workplaces considered to have multiple exposure pathways (e.g. use of water-soluble MWFs contaminated with NDELA).
Dermal exposure is generally predicted using occupational exposure models and ECHA has previously generated an estimate of dermal exposure to NDELA for metal processing industry (ECHA, 2014) using MWFs containing the precursor secondary amine precursor DEA (2,2'-iminodiethanol).
Measurements in air are normally targeted at the nitrosamines relevant to a specific industrial sector, e.g. the most common nitrosamines in rubber manufacturing factories are NDMA and NMor but NPip and NDEA are also encountered (Hidajat et al., 2019). An alternative approach is to consider all nitrosamines considered to be volatile (Iavicoli and Cavelli, 2006).
Table 15 presents a list of studies measuring occupational exposure to nitrosamines in a range of industries that were identified during the literature review and a summary is provided of the most significant studies.

Table 15: Summary of studies measuring occupational exposure to nitrosamines in various sectors

Sector/use/activity	Substance	Air concentration data µg/m³	Year(s)	Reference
Rubber industry (Germany + UK)	Total nitrosamines*, NDMA, NMor		2002 (based on temporal trends in EU-EXASRUB database)	Hidajat et al., 2019
Crude materials & mixing: General rubber goods (GRG) Tyres		0.68, 0.16, 0.06 0.73, 0.08, 0.14		
Pre-processing & assembly: GRG Tyres		1.87, 0.58, 0.11 1.22, 0.47, 0.13		
Curing, vulcanising: GRG Tyres		2.03, 0.16, 0.59 1.05, 0.22, 0.48		
Finishing, assembly & miscellaneous: GRG Tyres		1.04, 0.31, 0.11 1.05, 0.38, 0.14		
Rubber industry (UK)	Total nitrosamines	Nd-8.85 1.64 (median); 0.99 (geo mean) Nd-2.01	1998-2001	HSE, 2010

Sector/use/activity	Substance	Air concentration data µg/m³	Year(s)	Reference
		0.3 (median); 0.33 (geo mean)	2007	
Rubber-manufacturing industry (Sweden)	Total of 6 nitrosamines^ NDMA NDEA NDBA NMor NPip NPyr	<LoD-36 Nd-4.6 Nd-28 Nd-0.53 Nd-2.0 Nd-2.8 Nd-0.79		Jonsson et al., 2009
Salt bath vulcanisation	Total of 6 nitrosamines^	Nd-36 4.2 (median)		Jonsson et al., 2009
Hot air, microwaves, fluid bed vulcanisation		Nd-13 1.3 (median)		
Compression and injection vulcanisation		Nd-2.9 0.24 (median)		
Rubber industry (Germany)	NDMA NMor	<0.07-99.0 0.13 (geo mean) <0.007-43.4 0.13 (geo mean)	Primarily 1980-2000	De Vocht et al., 2007 (EU-EXASRUB database)
Rubber industry (Netherlands)	NDMA NMor	<0.002-1.94 0.05 (geo mean) <0.002-502 0.11 (geo mean)	1997	
Rubber industry (Sweden	NDMA NMor	0.06-27.9 0.34 (geo mean) <0.06-3.66 0.17 (geo mean)	1998-2002	
Rubber industry (Poland)	NDMA NMor	<0.14-9.20 0.23 (geo mean) <0.14-1.20 0.17 (geo mean)	1992	
Rubber industry (UK)	NDMA NMor	<0.01-123 0.11(geo mean) <0.01-13.9 0.03 (geo mean)	1997-98	
Processing of rubber products (Italy)	NDMA NDEA NMor	0.14 (mean) 0.15 (mean) 0.16 (mean)		Iavicoli and Carelli, 2006
Rubber industry (Italy)	NDMA NMor	0.10-0.98 (means) 0.77-2.40 (means)		Monarca et al., 2001
Rubber vehicle seal curing-salt bath (USA)	NDMA NMor NPip Total	1.22-2.54 (means) 0.17-0.70 (means) 0.88-1.59 (means) 0.4-9.3		Reh et al., 2000
Rubber industry (France):	NDMA NDEA NDBA NPip NMor	0.25 (median), 99.9 (max) 0.12 (median), 5.6 (max) 0.17 (median), 7.6 (max) 0.24 (median), 2.1 (max) 0.22 (median), 9.4 (max)	1992-95	Oury et al., 1997
Salt bath curing	Total nitrosamines*	0.61-104.4 11.24 (median)		

Sector/use/activity	Substance	Air concentration data µg/m³	Year(s)	Reference
UHF curing		0.17-10.27 1.66 (median)		
Metalworking (Germany)	NDELA	~1 (pre TRGS 611) ~0.2 (post TRGS 611) <0.05	Pre 1989 1991-93 1999	Breuer and van Gelder, 2001;
Metalworking (Germany)	NDELA	<0.01-3.66 (mean 0.2)		Pfeiffer et al., 1996 cited in IARC 2000
Metalworking (Canada)	NDMA NDEA NDELA NDBA	Nd-0.102 Nd-0.025 Trace-0.193 Nd-0.167		Fadlallah et al., 1996
Chemical industry (Germany)	Total nitrosamines	≤1 in 91% of samples		Wolf 1989 cited in ECETOC 1990
Leather-tanning industry (Germany)	Total nitrosamines (NDEA, NDMA + NMor)	≤1		Wolf 1989 cited in ECETOC, 1990
Foundry (UK)	NDMA NDEA NMEA NMor NPip NDBA	Nd-0.78 Nd-0.06 Nd-1.16 Nd Nd Nd		Keen et al., 2000
Foundry (France)				Ducos et al., 1988
Core-making	NDMA NMEA	0.02-0.23 (means), 0.06-0.35 (maxs) 0.021 (mean)		
Molding/casting/shake-out	NDMA	<0.01-0.03 (means), 0.01-0.15 (maxs)		
Fish processing industry	NDMA	0.01-0.06		

*NDMA, NDEA, NDBA, NPip, and NMor
+NDMA, NDEA, NDPA, NDiPA, NDBA, NPip, NPyr and NMor
^NDMA, NDEA, NDBA, NMor, NPip, and NPyr
Nd – not detected

Static and personal monitoring measurements of exposure to nitrosamines in the European rubber industry have been compiled in the EXASRUB database, comprising measurements that were collected for several purposes, including research and compliance testing (Hidajat et al., 2019). The database contains >21,000 measurements of airborne nitrosamines from the rubber industries in the Netherlands, Germany, UK, Poland and Sweden, with the majority of measurements (85%) coming from the German rubber industry. Data interpretation by de Vocht et al (2007) provides a useful summary of the overall data from each country. This study determined that exposure to NDMA and NMor decreased on average 2–5-fold in the German rubber-manufacturing industry over the time period represented by the data (1980 to 2000), with comparable concentration levels in other European countries. The reduction in exposure is considered to be mainly due to the introduction of modern curing systems and reductions in nitrosamine exposure associated with curing and post-treating ranging from 3 to 19% per year.

5.3.2.1 Measurements of exposure

5.3.2.1.1 Rubber industry

Hidajat et al (2019) examined UK and German data from the EXASRUB database and developed a job exposure matrix, assigning exposure measurements to specific activity areas in rubber processing ('crude materials and mixing', 'pre-processing and assembly', 'curing/vulcanising' and 'finishing, assembly and miscellaneous'). This study determined that average nitrosamine exposure (sum of 5 nitrosamines: NDMA, NMor, NPip, NDEA and NDBA) in the general rubber goods (GRG) sector was approximately 4.5 times higher compared with the tyre industry. It is likely that the difference in total nitrosamine exposure can be attributed to the greater variation in rubber formulations that require process redesign (i.e. substitution of vulcanisation agents and accelerators) for the production of general rubber goods compared to tyres (Breuer and van Gelder, 2001). As in other studies, Hidajat et al (2019) determined that the highest average exposure was associated with curing/vulcanising activities. A slight decline was reported for NDMA exposures in rubber compounding and mixing between 1985 and 2002 in the UK and Germany. However, NDMA exposures were notably higher for extrusion processes in the same period for both tyres and general rubber goods.

Oury et al (1997) undertook an assessment of the French rubber industry in the early-mid 1990s and found that vulcanising is the most polluting step and airborne nitrosamine concentrations were strongly influenced by the type of curing process, with the concentration of total nitrosamines associated with salt bath curing being significantly higher than exposure from UHF curing (using microwaves or radio frequencies). This study assessed production of seven rubber product types and found exposure to nitrosamines to be highest for sealing strips. Exposure to nitrosamines during the production of rubber vehicle seals in the United States, using salt bath curing, is also the subject of a paper by Reh et al (2000).

The UK authorities (HSE, 2010) investigated 7 rubber facilities in 2007 and found that the median total airborne nitrosamine exposure from the survey was 0.3 µg/m^3 [28]. When HSE had previously assessed nitrosamine concentrations in the UK GRG industry between 1998 and 2001 the median exposure for measurements taken at 4 sites was 1.64 µg/m^3, indicating that there was an ongoing reduction in exposure to nitrosamines in this sector. The reduced exposures were considered to be a result of improved engineering controls and increased awareness of the nitrosamine issue leading to an effort within the industry to reduce the use of curing accelerators which are able to form nitrosamines (see section 5.2.1).

The use of nitrate/nitrite salt bath curing systems is known to generate elevated levels of airborne nitrosamines, and lead to exposure of workers operating this type of equipment and others in the area. When the 1998-2001 survey was conducted, salt bath curing systems appeared to be in widespread use in GRG companies as all four of the sites visited at this time (1998-2001) used salt bath curing for certain items. Only one site visited for the 2007 survey was using salt bath curing.

5.3.2.1.2 Metal processing industry

Fadlallah et al (1996) investigated the presence of a range of N-nitroso compounds in the ambient air of metal working factories in Canada and reported concentrations for four of them:

- NDELA was detected in the air of all 14 factories sampled, with concentrations ranging from trace levels to 0.193 µg/m^3,
- NDMA was measured at detectable concentrations in 12/14 samples at concentrations ranging from 0.011 to 0.102 µg/m^3,
- NDEA was measured at detectable concentrations in only 1/14 samples at a concentration of 0.025 µg/m^3,
- NDBA was measured at detectable concentrations in 4/14 samples at concentrations of 0.031 to 0.167 µg/m^3.

Also, levels of NDELA in metal working fluids ranged from trace levels to 7.53 ppm. The authors noted that there is no correlation between the NDELA concentration in MWFs and the levels of

[28] The principal nitrosamines detected were NDMA and NMor, being present in 29 and 24 out of 38 samples, respectively; NDEA was detected in 10 samples; NDBA was detected in 4 samples.

NDELA, NDMA, NDEA and NDBA in the corresponding air samples.
An assessment by ECHA (2014) of potential nitrosamine formation in MWFs containing 2,2'-iminodiethanol estimated dermal exposure to NDELA to be 0.0283-0.156 ug/kg bw/d, depending on the wearing of protective gloves.

Ducos et al. (1999) undertook a biomonitoring study involving urinary analysis of workers exposed to MWFs. Higher NDELA concentrations (4.3 and 10.7 µg/l) were found in the urine of two workers exposed to nitrite-formulated MWFs (contaminated with 65 and 18 mg/L NDELA, respectively) than in nine workers (range in urine, 0.4-1.3 µg/l) exposed to "nitrite-free fluids" with lower levels of NDELA (range of 0.5-6.6 mg/L).
IARC (2000) present a useful summary of biomonitoring studies focussing on the presence of NDLEA in MWFs. In preliminary investigations by Spiegelhalder et al. (1984), NDELA was found in the urine of metal grinders: of 264 analysed, 166 showed positive results (> 0.5 µg/kg) with levels up to 103 µg/kg. During biological monitoring of workers using cutting fluids with detectable levels of NDELA, only workers working with cutting fluids containing ≥ 5 mg/L NDELA excreted detectable quantities of NDELA in their urine (32% had values between 0.6 and 2.7 µg/kg urine). In a study by Monarca et al. (1996) metalworkers with low exposure to NDELA-contaminated MWFs and a control group all tested negative for NDELA.

5.3.2.1.3 Leather tanning

Occupational exposure to nitrosamines (including NDMA, NDEA and NMor) has been reported in the leather tanning industry. Elevated concentrations of NDMA (up to 47 µg/m^3) were previously measured in the air at leather tanneries by studies published in 1979 and 1982 (ECETOC, 1990) but a more recent study (Wolf, 1989, cited in ECETOC, 1990) found total nitrosamines (NDEA, NDMA and NMor) to be ≤1 µg/m^3 at 12 workplaces in Germany. The formation of NDMA specifically is dependent on the use of dimethylamine sulphate as an unhairing agent in the processing of animal hides and a UK report (Keen et al., 2000) stated that this practice had been discontinued some time ago.

5.3.2.1.4 Foundries

Ducos et al. (1988) investigated the occurrence of nitrosamines at 8 foundries in France using the Ashland core-making process (7 iron foundries and 1 aluminium foundry). NDMA was detected at all of the foundries (never exceeding 0.35 µg/m^3) with NMEA found at lower concentrations and at only 4 of the foundries, with levels ≤0.01 µg/m^3 at 3 of them. Core-making workshops had higher concentrations of NDMA than the main foundry workplace areas undertaking moulding, casting and shake-out tasks. Keen et al. (2000) undertook a survey of 2 foundries using the Ashland process in the UK. This study found that the highest total nitrosamine exposure at one foundry was 0.203 µg/m^3 in personal monitoring samples and 2.00 µg/m^3 in static samples from the steel pouring tunnel (which had LEV applied to it). At the second foundry all measurements were below the limit of detection, although traces of NDEA were evident in some of the samples.

5.3.3 Routes of exposure

Inhalation and dermal exposure are the main routes of exposure for nitrosamines; these exposure pathways are both highlighted by BAuA (2018) in Technical Note TRGS 552 with the following observations:

- Respiratory tract: Highly volatile nitrosamines are taken in primarily as trace gases, while non-volatile nitrosamines are taken in via the respiratory tract as a component of aerosols or airborne dust.
- Skin contact: nitrosamines may be absorbed through the skin. The tests carried out to date on the skin absorption of nitrosamines show that they can be easily absorbed through the skin and enter the body. Since nitrosamines easily penetrate common glove materials, skin contact cannot be ruled out even when gloves are worn

IARC (2000) state that NDELA is easily absorbed through the skin and uptake can therefore occur both via the dermal route as well as the respiratory route. Total 48 hr dermal absorption

of NDELA is reported to range from 35 to 65% of the dose depending on the formulation of the applied dose. Lower levels of skin absorption are reported in Kersemaekers et al. (1995), with 18% of applied NDELA penetrating the skin in studies on monkeys and pigs.

5.4 General population exposure

As discussed in Section 5.1, nitrosamines occur in numerous different compartments and media. General population exposure to nitrosamines occurs primarily through the diet, but exposure may occur through various other routes including from airborne emissions and contaminated medicines or personal care products.

5.4.1 Diet (including food, drinking water and alcoholic beverages)

A full scientific opinion on the risks for human health related to the presence of nitrosamines in food is currently being developed by EFSA and the initial risk assessment is currently undergoing public consultation (EFSA, 2022). The risk assessment covers NDMA, NMEA, NDEA, NDPA, NDBA, NMPA, NSAR, NMor, NPip and NPyr.

Exposure to these 10 carcinogenic nitrosamines occurring in food, is estimated to range from 0 to 208.9 ng/kg bw/day, based on data extracted from literature and occurrence databases, and meat and meat products are considered to be the highest contributing food category (EFSA, 2022b). Excluding infant-only surveys, the 'Margin of Exposure' (MoE) ranged from 3,337 to 48, at the calculated 95th percentile exposure concentration, and it is concluded that the MoE is 98-100 % certain to be less than 10,000 for all age groups (EFSA, 2022). According to EFSA a MoE above 10,000 is a low concern from a public health point of view, but only indicates a level of concern (in this case "not low") and does not quantify risk.

Herrman et al (2015a) calculated the 95th percentile total intake of non-volatile nitrosamines (NVNA) from consumption of processed meat products on the Danish market to be 90 ng/kg bw/day for children (mean 37 ng/kg bw/day) and 33 ng/kg bw/day for adults (mean 13 ng/kg bw/day); while for volatile nitrosamines (VNA) the 95th percentiles for children and adults were 1.1 ng/kg bw/day and 0.34 ng/kg bw/day, respectively. The data for this assessment was from the previous study of Herrman et al (2015b), where NDEA was identified in 16% of samples, with a mean concentration of 0.04 µg/kg, NDMA was identified in 50% of samples with a mean concentration of 0.7 µg/kg, alongside six other VNAs and five NVNAs[29].

A study on UK consumed food only identified specific VNAs in dried shrimp (NDMA at a concentration of 9.4 µg/kg) and pepperoni (NPip at a concentration of 1.3 µg/kg) (PAS, 2017).

In an assessment of the combined exposure to nitrate and nitrite via food and drinking water in the Netherlands, RIVM (2020) calculated the endogenous production of nitrosamines as 0.84 ng/kg bw/day, based the highest estimated mean combined dietary exposure of nitrate and nitrite using the model developed by Health Canada (2013). EFSA (2022) concluded that the transfer of nitrate and nitrite from feed to food products of animal origin and the nitrate- and nitrite-mediated formation of nitrosamines and their transfer into these products are likely to be negligible.

Studies have also been undertaken on the occurrence of nitrosamines in drinking water in both EU member states and other European countries. Farré et al. (2020) undertook sampling over two campaigns at 11 different drinking water treatment plants in Spain, with concentrations of NDMA ranging from below the limit of detection (LOD) to 4.2 ± 0.2 ng NDMA/L, with the highest concentration being observed in the distribution system of treatment plants without ozone treatment.

NDMA was also investigated in 41 drinking water treatment works in England and Wales, and was detected in treated water at three works at a maximum concentration of 5.8 ng NDMA/L (DEFRA, 2008).

The study of Templeton and Chen (2010) analysed samples for NDMA, NDEA, NDPA alongside NDBA, NMor, NPip, NPyr and NMEA. In the samples taken from the distribution systems furthest away from the treatment plants (i.e. closer to the consumer taps) the concentrations of NDMA, NDEA and NDPA were below the limit of detection in all samples; for some samples a trace

[29] The other nitrosamines analysed for were NSAR, N-nitrosohydroxyproline, N-nitrosodibenzylamine, N-nitrosoproline, NMPA, N-nitroso-2-methyl-thiazolidine 4-carboxylic acid and N-nitroso-thiazolidine-4-carboxylic acid, NDPA, NMEA, NPyr, NDMA and NPip.

detection was discernible but it was below the LOD, except for two samples, which had measured NDMA concentrations of 1.0 ng/L (Templeton and Chen, 2010)[30]. A notable exception was NDBA, which was consistently detected in one of the water supply systems (with a maximum concentration of 6.4 ng/L). Overall, it was concluded that there were no identifiable relationships to link source water quality characteristics or the particular treatment or distribution practices with the analysed nitrosamine concentrations (Templeton and Chen, 2010).

5.4.2 Medicine

Two main routes have been identified for the formation of nitrosamine impurities in human medicines (EMA, 2020):

1. NDMA and N-nitroso-N-methyl-4-aminoburyric acid (NMBA[31]) are formed from the nitrosation of the secondary amines N,N-dimethylamine and 4-methylaminobutyric acid, formed from the hydrolytic or thermal degradation of solvents dimethyl formamide and N-methylpyrrolidone.
2. NDEA, NMPA, NDiPA and NEiPA are formed from the N-nitrosative de-alkylation of trialkyl amine reagents (e.g. triethylamine, diisopropylethylamine and N,N-dimethylaniline).

NDMA and NDEA, as well as NDiPA, NEiPA and NMBA have been detected as impurities in Sartans, a type of blood pressure medication, and in particular Valsartan as well as Ranitidine, an indigestion treatment (EMA, 2018; EMA, 2020). A small random sampling of active pharmaceutical ingredient (API) batches was performed by the manufacturer who initially reported identifying NDMA as an impurity. This study detected NDMA concentrations in the range of 3.4 µg/g to 120 µg/g, with an average concentration of 66.5 µg/g (EMA, 2018).

A subsequent report by EMA (2019) reported NDEA concentration in the Sartan API in the range of < LoD to 42.14 µg NDEA/g and in the finished products at < LOD to 1.32 µg NDEA/g. The highest reported NDMA concentrations reported were 240.1 µg NDMA/g and 97.4 µg NDMA/g, in the API and finished product, respectively (EMA, 2019).

There is also some evidence that in batches where NDMA is high, NDEA is low and in the batch with the highest reported NDEA concentration, NDMA is low (EMA, 2019).

The study of Yang et al. (2020) compared the results of analysis for NDMA in medicines using two approved validated methods (as well as one method with severe limitations) and reported measured concentrations up to 0.314 µg NDMA/g using the FDA methods, with 24 out of 38 samples being below the LOD.

5.4.3 Atmospheric exposure

As discussed in section 5.1, nitrosamines can potentially be formed in air (WHO, 2002) and they can be released to the air via industrial practices. A study to assess NDMA formation was undertaken in the USA with samples taken in Pennsylvania and California for radiation fog and Arizona for cloudwater (Hutchings et al., 2018). NDMA was detected in radiation fogs in both California and Pennsylvania at concentrations in the range 7.5 to 497 ng/L (not blank corrected) and in cloudwater at concentrations of 153 – 208 ng/L. The blank corrected results were used to calculate ambient concentrations of 1.13 to 3.85 ng/m^3 based on thermodynamic equilibrium modelling (Hutchings et al., 2018).
NDMA, NDEA and NDPA were all monitored in airborne particulate matter in Turkey, along with nine other nitrosamines (NMEA, NPyr, NMor, NEBA, NPip, MNPiz, DNPiz, NDBA and NDPhA), with samples being taken in Zonguldak province, an area known for coal mining and the iron–steel industry, with fine ($PM_{2.5}$) and coarse ($PM_{2.5-10}$) particle samples collected (Akyüz and Ata 2013).

[30] The data from the initial sampling campaign was excluded from these results as the authors state the concentrations observed during this campaign were not repeated in subsequent sampling rounds. The cause of the elevated measurements during the initial sampling could not be assigned conclusively however they believe it was a consistent analytical instrument bias during that sampling round. Thus they concluded that although the data was included for completeness, it should be regarded with scepticism.
[31] List No. 845-897-7, CAS RN 61445-55-4

- NDMA was detected in 96 $PM_{2.5}$ samples and 93 $PM_{2.5-10}$ samples in the winter with mean concentrations of 9.43 ± 4.99 ng/m^3 and 3.23 ± 1.62 ng/m^3, respectively; in the summer 24 $PM_{2.5}$ samples had detected levels of NDMA with a mean concentration of 1.90 ± 0.76 ng/m^3, and 24 $PM_{2.5-10}$ samples had detected levels with a mean concentration of 0.68 ± 0.27 ng/m^3.
- The analysis of NDEA indicated 96 $PM_{2.5}$ and 90 $PM_{2.5-10}$ samples had detectable levels, with mean concentrations of 5.77 ± 2.49 ng/m^3 and 2.03 ± 0.78 ng/m^3, respectively in the winter, and mean concentrations of 2.73 ± 0.48 ng/m^3 (n = 17) and 0.98 ± 0.17 (n = 17) in the summer for $PM_{2.5}$ and $PM_{2.5-10}$ samples, respectively (Akyüz and Ata, 2013).
- NDPA was detected also in 96 $PM_{2.5}$ samples in the winter, and 17 samples in the summer with mean concentrations of 6.42 ± 3.19 ng/m^3 and 2.12 ± 0.38 ng/m^3; for $PM_{2.5-10}$ samples 90 samples and 17 samples had detectable levels in the winter and summer, respectively, with mean concentrations of 2.23 ± 1.03 ng/m^3 and 0.76 ± 0.14 ng/m^3 (Akyüz and Ata, 2013).
- The highest reported $PM_{2.5}$ and $PM_{2.5-10}$ concentrations were for DNPiz in the winter at concentrations was 22.85 ng/m^3 and 7.60 ng/m^3, respectively (Akyüz and Ata, 2013)

No studies were identified that monitored nitrosamines in the atmosphere in the EU. However, atmospheric exposure to nitrosamines in the air 30 cm and 100 cm above football pitches that contain rubber crumb has been investigated by RIVM (2007). Samples were analysed for NDMA, NDEA and NDPA as well as five other nitrosamines (NMEA, NMor, NPyr, NPip, NDBA. All samples analysed at the RIVM and accredited laboratories did not report any detectable concentrations of the nitrosamines of interest (RIVM, 2007).

5.4.4 Other exposures (e.g. tobacco & cosmetics)

Nitrosamines have also been detected in cigarettes and specifically tobacco smoke (Smith et al., 2000; WHO, 2002). NDELA, NDEA and NDMA have all been detected in cigarette smoke with the precursors being the alkaloids, amino acids, proteins and volatile bases present, and the extent of nitrosamine formation dependent on the nitrate level in the tobacco (Smith et al., 2000).
The concentrations for NDELA in the literature range from <LOD to 0.0076 µg/ cigarette in the vapour phase for unfiltered and filtered cigarettes, with the maximum concentration reported for filtered cigarettes. For NDEA, concentrations ranged from <LOD to 1.62 µg/ cigarette in the vapour phase of the smoke from both filtered and non-filtered cigarettes, with ~75 % of NDELA and NDMA removed by the filter (Smith et al. ,2000).
Another potential exposure pathway of the general population to nitrosamines is via cosmetics and personal care products (EC, 2013). A risk assessment has been performed on exposure of consumers to NDEA and NDELA, through the use of cosmetics (Lim et al., 2018). The study analysed samples of shampoo (n = 16), cleansing foam (n = 31), shower gel (n = 19), body lotion (n = 13), hair products (n = 4), hand (n = 5), eye (n = 4) and face creams (n = 43), skin toner (n = 23), hair conditioner (n = 8), sun screen (n = 13) and baby products (n = 15) (although the source of the cosmetics is not explicitly stated within the report). All product types had detections above the LOD, with the exceptions being sunscreens and baby products for both NDELA and NDEA and body lotions for NDEA (Lim et al., 2018).
From the use patterns of the products, the nitrosamine content and their dermal absorption, the systemic exposure dosage (SED) was calculated for each product type. SEDs ranged from 0.01 ng/kg bw/day for shampoo and cleansing foams to 0.37 ng/kg bw/day for hand creams for NDEA and 0.02 ng/kg bw/day for hair conditioner to 20.25 ng/kg bw/day for body lotions for NDELA (Lim et al. 2018).

5.5 Discussion on nitrosamines relevant to the occupational setting

After completing the review of the industrial sectors in which nitrosamines are generated (section 5.2) and the exposure studies indicating which nitrosamines are associated with those industrial sectors (section 5.3), as well as reviewing exposure to nitrosamines from non-occupational settings (section 5.4) for the purposes of this report, the focus of our further analysis towards the derivation of an OEL/ERR is on the following substances:

- NDMA, NDEA, NDELA, NDPA[32] - i.e. the substances in the request from Commission
- NMor, NPip, NDBA, NPyr, NEPA, NMPA, NDPhA and NMEA – i.e. the relevant nitrosamines that contribute to occupational exposure

The nitrosamines identified as being generated the most often across the different industrial sectors is NDMA, followed by NDEA and NDELA. NMor is also prominent in certain industrial sectors.
With the exception of the metal processing industry, individual nitrosamines are not normally generated and workers are exposed to a 'mixtures' of nitrosamines in most cases, even though one or two nitrosamines might be prevalent (Table 16).

We acknowledge that the other nitrosamines reviewed in section 5.4 may contribute to background level, but have considered that they do not fall under the remit of the request from the Commission. They are: NSAR, NDiPA, NEiPA, DNPiz, MNPiz and NEBA.

[32] NDPA is part of the request from the Commission, although it does not occur in occupational setting.

Table 16: Summary of nitrosamines present per industry sector

Report Section	Industry Sector/ Source	Process	Nitrosamine	Comments
5.2.1	Rubber	Pre-vulcanisation processing (weighing, mixing, shaping), vulcanisation, post- vulcanisation processing, salt baths, storage.	**NDMA, NDEA, NMor**, NDBA, NPip, NMPA, NEPA, NPyr, NDPhA	Although the use of NDPhA has largely been eliminated in the EU, one registrant/ manufacturer remains.
5.2.2	Metal processing	Metal working fluids: using water-based cooling lubricants containing alkanolamines and their reaction with nitrites in the water or NOx in the workshop air.	**NDELA** NMor NDMA, NDEA, NDBA (Canada)	(NDELA) is by far the most frequently occurring nitrosamine (TRGS 611). NMor is also mentioned in the TRGS 611. These are the two most relevant to the EU. Fadlallah et al. (1996) reported NDELA (all 14 sites), NDMA (12 sites), NDEA (1 site) and NDBA (4 sites) in the ambient air in metal working factories in Canada.
5.2.3	Chemical	Production and processing of aliphatic amines	**NDMA, NMor,** NDiPA	
5.2.4	Leather	Pre-tanning: deliming and unhairing	**NDMA,** NDEA NMor	
5.2.5	Foundries (Iron and steel)	Ashland mould manufacture, steel pouring	**NDMA, NDEA** NMor NMEA, NPip, NDBA (UK)	Keen et al. (2000) reports NMEA, NPip, NDBA as well as NDMA, NDEA and NMor, but that was in 2000 and in the UK, so relevance to EU is unclear.
Other industrial sources				
5.2.6.1	Carbon capture	Nitrogen oxides (NOx) in flue gases can react with aqueous amines within the solvent loop of the absorber	**NDEA, NDELA NMor,** NDMA, NPip	
5.2.6.2	Electroplating	Removing metals from a surface by submerging a metal-plated article in a solution containing amines in stripping baths.	**NDEA**	
5.2.6.3	Tobacco processing	Drying and fermentation of the tobacco plant, and from nicotine during combustion.	**NDMA**, NPyr, NPip, NMor and NDELA	"Tobacco-specific nitrosamines" are also formed when tobacco leaves are grown, cured, aged and processed[33]. Some common "Tobacco-specific

[33] https://www.cancer.gov/publications/dictionaries/cancer-terms/def/tobacco-specific-nitrosamine (accessed 12/09/2022)

				nitrosamines" (Xia et al. 2021; Hecht et al. 2022) are: N'-nitrosonornicotine, N'-nitrosonornicotine ketone, N'-nitrosoanabasine, and N'-nitrosoanatabine.
5.2.6.4	Fuel combustion	Formation possible during fuel combustion, as nitrous oxides (nitrosating agents) are released at elevated temperatures	**NDMA**	
5.2.6.5	Industries for further consideration	Occurrence of nitrosamines cannot be excluded in agriculture, wastewater treatment, waste disposal and fish and meat processing		Insufficient information generally to identify the nitrosamines present, but see entry for "diet" below for an indication of those most likely (includes meat products, drinking water including treatme nt etc.)
General population exposure				
5.4.1	Diet: food and drinking water	From consumption of processed meat and meat products. Present in drinking water, including at treatment plants, although no identifiable relationship to particular treatment or distribution practices.	**NDMA, NDEA**, **NDPA**, **NDBA**, NMEA, NMPA, NSAR, NMor, NPip and NPyr	
5.4.2	Medicine	Formation of impurities in human medicine, by the nitrosation of amine reagents	**NDMA, NDEA,** NMBA, NMPA, NDiPA, NEiPA	
5.4.3	Atmospheric exposure	Formation in air (e.g. radiation fog) or release to air via industrial practices (e.g. near coal mining or iron-steel industry).	**NDMA, NDEA, NDPA**, NMEA, NPyr, NMor, NEBA, NPip, MNPiz, DNPiz, NDBA and NDPhA	
5.4.4	Other	Tobacco (smoke) and cosmetics (hair products, and body/face creams)	NDELA, NDEA and NDMA (tobacco smoke) NDEA, NDELA (cosmetics)	

Note: the most prominent nitrosamines are in bold - almost always including NDMA and NDEA.

6. Monitoring exposure

6.1 Monitoring methods (external exposure)

Several validated methods to measure nitrosamines in air have been found and are summarised below (Table 17).

Most of the analytical methods have a similar principle: the sample is retained via active sampling in a glass filter or a sampling cartridge; then the analysis is performed by gas-chromatography (GC) with a Thermal Energy Analyser (TEA). The methods are validated for one or several nitrosamines.
A further method was also identified from the literature utilising liquid chromatography tandem mass-spectrometry (LC-MS/MS): this method was developed for eight nitrosamines: NDMA, NMEA, NPyr, NDEA, NPip, NMor, NPyr, and NDBA and utilised with samples collected through adsorption tubes at a flow rate of 1.5 L/min over three hours (Jönsson et al., 2009).

Table 17: Overview of sampling and analytical methods for air monitoring at the workplace

Method	Analytical technique	LOQ Sampling volume Time	Comments*
DFG (2022) Relative humidity below 60%	GC-TEA	LOQ: 0.010 µg/m3 400 L sample over 4 hours or 3 hours if relative humidity is in the range 40 – 60% and two samplers utilised	Method validated for NDMA, NMEA, NDEA, NDiPA, NDPA, NDBA, NPip, NPyr and NMor Similar method: DGUV 213-523
BGI 505 (DGUV, 1992) Workplace air with a maximum total dust content of 10%	GC-TEA	LOQ: 0.035 µg/m^3 or 0.17 µg/m^3 NDELA 2 m^3 sample around 2 hrs	Method only validated for analysis of NDELA.
OSHA Method 27 (OSHA 1981)	GC-TEA	LOQ: 0.12 to 0.20 µg/m^3 75 L sample at a recommended flow rate of 1L/min (min: 0.2 L/min; max: 2 L/min)	Method validated for NDMA, NDEA, NDPA, NDBA, NPip, NPyr and NMor.
Method in Jönsson et al. (2009)	LC-MS/MS	Absolute LOD: 2–50 ng Relative LOD: 0.02–0.19 µg/m^3 3 hours sampling time at a flow rate of 1.5 L/min	Method used to assess NDMA, NMEA, NDEA, NPip, NMor, NPyr, NMEA and NDBA.

* details the nitrosamines which can be analysed with each method.

Some of the methods allow to achieve very low concentrations of nitrosamines in air, being the lowest LOQ found 0.010 µg/m^3.
It is important to note that the methods do not allow to measure "total nitrosamines" as such, but allow to measure in one analysis all the nitrosamines covered by the method.

6.2 Biomonitoring of exposure (internal exposure)

No regulatory guidelines have been identified for the analysis of the nitrosamines of interest (or biomarkers) in either blood or urine. However, some methods to measure nitrosamines in urine have been found. (See section 6.2.3)

6.2.1 Background levels for general population, i.e. non-occupationally exposed

As explained in detail in section 5.4, general population exposure to nitrosamines occurs primarily through the diet, but exposure may occur through various other routes including from airborne emissions and contaminated medicines or personal care products.

Several studies have measured the concentrations of different nitrosamines in the general population. Some studies (van Maanen et al. (1996) and Vermeer et al. (1998)) studied nitrosamines excretion after nitrate intake via drinking water or food. Another study (Hu et al., 2016) studied the endogenous formation of nitrosamines as result of microorganism infection.

- In van Maanen et al. (1996) the endogenous formation of nitrosamines from nitrates in tap water and well water was investigated in female volunteers. Nitrosamines measured in urine included NDMA, NDEA and NDPA, as well as NMEA, NPyr, NPip and NMor. NMEA, NMor, NDPA, and NDBA were not detected in the urine of any of the subjects; all other nitrosamines were detected in at least two of the subjects selected for urine analysis. Detection frequencies ranged from 2 of 22 subjects for NDMA (2/11 in the tap-water groups; 0/11 in the well-water group) to 18 subjects (8/11 in the tap-water groups and 10/11 in the well-water group) for NPyr.
  Excretion quantities above the detection threshold ranged from 49 ng over a 24-hour period for NDMA to 279 ng for NPip (Table 18). Mean quantities of total nitrosamine excretion were 146 ± 173 ng/24 hr and 160 ± 95 ng/24 hr for the tap-water exposure and well-water exposure groups, respectively, with no significant difference observed between the mean concentrations. A significant correlation was observed for 24-hour urinary excretion of NPyr in relation to 24-hour nitrate excretion.

- Vermeer et al. (1998) investigated the formation of volatile nitrosamines (NDMA, NDEA, NPip, NMEA and NMor) after the consumption of nitrate at the acceptable daily intake (ADI) level in combination with a fish meal rich in amines that are nitrosatable precursors.
  Analysis detected NDMA and NPip in the urine of subjects but NDEA, NMEA and NMor were below the detection limit in all samples. The amount of NDMA excreted in 'control weeks', when participants refrained from high nitrate content foods, were 287 ± 223 and 383 ± 168 ng per 24 hour for NDMA in control weeks 1 and 2, respectively. Measured excretions for NPip were 69 ± 36 and 104 ± 55 ng/24 hour in control weeks 1 and 2, respectively.
  During 'experimental weeks', when participants were provided a dinner low in nitrate, containing cod, salmon, shrimp or pollack along with a 277 mg KNO3 solution, mean quantities of NDMA excreted ranged from 640 ± 277 to 871 ± 430 ng/24 hour and quantities of NPip per subject ranged from 69 ± 36 to 94 ± 57 ng/24 hr (Table 18)). A statistically significant relationship was observed between nitrate excretion and NDMA excretion, and between cumulative nitrate urinary excretion and cumulative NPip urinary excretion. Correlations were also observed for log nitrate concentration in saliva and NDMA urine concentration. No correlation was observed between nitrate reduction levels and NDMA excretion in urine or between nitrate excretion in urine and NPip excretion in urine.

- Hu et al. (2016) monitored nitrosamine concentrations in the urine of three groups: healthy subjects who smoke, healthy subjects who are non-smokers and subjects with urinary tract infection (UTI) patients. All nitrosamines of interest were measured above the detection limit except for NDPA.
  NDMA was the most frequently observed nitrosamine and was also detected at the highest mean concentration in all study groups.

  The highest measured concentration was 2.97 ng/mL for NDMA in the non-smokers group, 2.0 ng/mL for NPyr in the smokers group and 14.3 ng/mL for NDMA in the UTI group (Table 18), with the UTI NDMA concentration being significantly higher than for the healthy groups.

Table 18: Measured nitrosamine concentrations in urine of general population

Exposure Group (Number of group members)	Substance	Urine concentration (Detection Frequency)	Reference
Tap water exposure group (n = 11)	NDMA	<LOD – 200 ng/24 hour (18 %)	Van Maanen et al 1996
	NDEA	<LOD – 177 ng/24 hour (9 %)	
	NDPA	<LOD (0 %)	
	NMEA	<LOD (0 %)	
	NPyr	<LOD – 171 ng/24 hour (73 %)	
	NPip	<LOD – 279 ng/24 hour (18 %)	
	NMor	<LOD (0 %)	
	NDBA	<LOD (0 %)	
Well water exposure group (n = 11)	NDMA	<LOD (0 %)	
	NDEA	<LOD – 61 ng/24 hour (18 %)	
	NDPA	<LOD (0 %)	
	NMEA	<LOD (0 %)	
	NPyr	<LOD – 272 ng/24 hour (91 %)	
	NPip	<LOD – 232 ng/24 hour (36 %)	
	NMor	<LOD (0 %)	
	NDBA	<LOD (0 %)	
Female volunteers (n = 25)	NDMA	Control week 1: 287 ± 223 ng/24 hour (N.R.) Test week; days 1 – 3: 871 ± 430 ng/24 hour (N.R.) Test week; days 4 – 7: 640 ± 277 ng/24 hour (N.R.) Control week 2: 383 ± 168 ng/24 hour (N.R.)	Vermeer at al. 1998
	NPip	Control week 1: 69 ± 36 ng/24 hour (N.R.) Test week; days 1 – 3: 86 ± 49 ng/24 hour (N.R.) Test week; days 4 – 7: 94 ± 57 ng/24 hour (N.R.) Control week 2: 104 ± 55 ng/24 hour (N.R.)	
	NDEA, NMEA, NMor.	All samples: <LOD (0 %)	
Healthy smokers (n = 55)	NDMA	Mean ± SD: 0.55 ± 0.50 ng/mL Range: <LOD – 2.97 (98 %)	Hu et al. 2016
	NDEA	Mean ± SD: 0.12 ± 0.06 ng/mL Range: <LOD – 0.25 (85 %)	
	NDPA	Mean ± SD: <LOD Range: <LOD (0 %)	
	NMEA	Mean ± SD: 0.09 ± 0.08 ng/mL Range: <LOD – 0.23 (16 %)	
	NPyr	Mean ± SD: 0.30 ± 0.28 ng/mL Range: <LOD – 1.92 (80 %)	
	NPip	Mean ± SD: 0.02 ± 0.01 ng/mL Range: <LOD – 0.03 (5 %)	
	NMor	Mean ± SD: <LOD Range: <LOD (0 %)	
	NDBA	Mean ± SD: 0.03 ± 0.02 ng/mL Range: <LOD – 0.06 (18 %)	
	NDPhA	Mean ± SD: 0.03 ± 0.04 ng/mL Range: 0.001 – 0.20 (100 %)	
Healthy non-smokers (n = 55)	NDMA	Mean ± SD: 0.58 ± 0.39 ng/mL Range: 0.06 – 1.9 (100 %)	
	NDEA	Mean ± SD: 0.14 ± 0.09 ng/mL Range: <LOD – 0.42 (74 %)	
	NDPA	Mean ± SD: <LOD Range: <LOD (0 %)	
	NMEA	Mean ± SD: 0.09 ± 0.07 ng/mL Range: <LOD – 0.18 (12 %)	
	NPyr	Mean ± SD: 0.27 ± 0.36 ng/mL	

		Range: <LOD – 2.0 (46 %)
	NPip	Mean ± SD: 0.03 ± 0.01 ng/mL Range: <LOD – 0.05 (16 %)
	NMor	Mean ± SD: 0.02 ± 0.00 ng/mL Range: <LOD – 0.02 (4 %)
	NDBA	Mean ± SD: 0.03 ± 0.02 ng/mL Range: <LOD – 0.08 (39 %)
	NDPhA	Mean ± SD: 0.04 ± 0.06 ng/mL Range: <LOD – 0.28 (96 %)
Urinary Tract Infection patients (n = 73)	NDMA	Mean ± SD: 6.65 ± 14.3 ng/mL* Range: 0.12 – 73.6 (100 %)
	NDEA	Mean ± SD: 1.24 ± 1.32 ng/mL* Range: <LOD – 5.43 (44 %)
	NDPA	Mean ± SD: <LOD Range: <LOD (0 %)
	NMEA	Mean ± SD: <LOD Range: <LOD (0 %)
	NPYR	Mean ± SD: 0.35 ± 0.42 ng/mL Range: <LOD – 1.38 (14 %)
	NPip	Mean ± SD: 0.36 ± 0.45 ng/mL Range: <LOD – 1.09 (21 %)
	NMor	Mean ± SD: 0.06 ± 0.12 ng/mL Range: <LOD – 0.31 (8 %)
	NDBA	Mean ± SD: 0.09 ± 0.13 ng/mL** Range: <LOD – 0.59 (73 %)
	NDPhA	Mean ± SD: 0.04 ± 0.03 ng/mL Range: 0.005 – 0.11 (100 %)

LOD: Limit of detection
N.R.: Not reported
* The mean urinary concentration was significantly higher than that of the healthy subjects (including smokers and non-smokers) ($P < 0.001$)
** The mean urinary concentration was significantly higher than that of the healthy subjects (including smokers and non-smokers) ($P < 0.05$)

6.2.2 Correlations between internal and external exposure

No correlations between air exposure to nitrosamines and internal concentration of nitrosamines (or other biomarkers) has been found.

6.2.3 Biomonitoring analytical methods

IARC has reported been urine analysis methods for NDELA (Spieghalder et al. 1987 cited in Monarca et al. 1996). Additionally, four published studies for the analysis of nitrosamines in urine have been identified.
In the IARC method, prior to analysis, nitrite was removed from the urine samples with sulfamic analysis and then NDELA was extracted using Kieselguhr extraction columns and ethyl formate containing 2% methanol (Monarca et al. 1996). Analysis was conducted using GC-TEA analysis, a technique also utilised for air monitoring (Section 6.1), with the method detection limit reported as 0.5 ng/g (Monarca et al. 1996).
van Maanen et al. (1996) developed a method for the analysis of eight different nitrosamines in urine, namely NDMA, NDEA, NDPA, NMEA, NPyr, NPip, NMor and NDBA. Analysis was performed on buffered 24-hour urine samples that were dichloromethane extracted and analysed by GC-MS, with analysis undertaken in either high or low resolution single ion monitoring (SIM).
Vermeer et al. (1998) used the van Maanen et al. (1996) method as a basis for the analysis of nitrosamines in urine with some further modifications. These modifications included a different sample extraction procedure, elution column and oven programme, as well as all analysis being conducted in high resolution SIM. The method was utilised for the analysis of NDMA and NDEA, as well as three further nitrosamines, NMEA, NPip and NMor.
Ducos et al. (1999), developed a method for the analysis of NDELA in urine, as well as MWFs, using the GC-TEA method with NDPhA used as an internal standard. Urine samples had sulfamic acid and the internal standard added, saturated with 10 g ammonium sulphate after vortex mixing, before being loaded to a SPE cartridge and undergoing liquid-liquid extraction prior to

GC-TEA analysis; the typical detection limit of the method was 0.3 µg/L (Ducos et al. 1999) One further journal publication was identified; Hu et al. (2016) utilised online solid phase extraction (SPE) liquid chromatography with tandem mass spectrometry (LC-MS/MS) for the analysis of NDMA, NDEA and NDPA in parallel with six other nitrosamines (NPyr, NMEA, NPip, NMor, NDBA, NDPhA). A summary of these methods is presented in (Table 19).

Table 19: Summary of methods for the analysis of nitrosamines in urine

Method/Fraction	Analytical Technique	LOQ and sampling volume and time	Similar Methods/Comments
IARC method reported in Monarca et al. (1996) Urine	GC-TEA	LOQ; 0.5 ng/g Urine samples before and during shifts; 15 mL aliquot of sample used in sample preparation	Validated for NDELA. Same analytical technique used as for Ducos et al. (1999) and some air analysis
van Maanen et al. (1996) Urine	GC-MS	LOQ; 0.02 ng/mL 24-hr urine samples; 20 mL aliquot of sample used in sample preparation	Validated for NDMA, NDEA, and NDPA, NMEA, NPyr, NPip, NMor and NDBA. Vermeer et al. (1998) utilised a modified version of this method
Vermeer et al. (1998) Urine	GC-MS	LOQ: 50 ng/mL 24-hr urine samples; 20 mL aliquot of sample used in sample preparation	Validated for NDMA, NDEA, NMEA, NPip and NMor. Modified version of van Maanen et al. (1996)
Ducos et al. (1999) Urine	GC-TEA	LOQ: 0.3 µg/L Urine samples at beginning and end of shift; plus control workers. 14 mL aliquots with 10 or 12.5 µL used for analysis	Validated for NDELA. Same analytical technique used as for IARC urine method (Monarca et al. 1996) and some air analysis.
Hu et al. (2016) Urine	SPE LC-MS/MS	LOQ; 0.4 ng/mL for NDMA and NDEA; 0.037 ng/mL for NDPA Spot urine samples; 12 mL of sample used in sample preparation	Validated for NDMA, NDEA, NDPA, NPyr, NMEA, NPip, NMor, NDBA and NDPhA.

7. Health Effects

As per section 5.5, after completing the review of the industrial sectors in which nitrosamines are generated and the exposure studies indicating which nitrosamines are associated with those industrial sectors, as well as reviewing exposure to nitrosamines from non-occupational settings for the purposes of this report, the focus of our further analysis towards the derivation of an OEL/ ERR is on the following substances:

- NDMA, NDEA, NDELA, NDPA[32] - i.e. the substances in the request from Commission
- NMor, NPip, NDBA, NPyr, NEPA, NMPA, NDPhA and NMEA – i.e. the relevant nitrosamines that contribute to occupational exposure.

7.1 Toxicokinetics (ADME- absorption, distribution, metabolism and excretion)

7.1.1 Human data

7.1.1.1 Absorption

There is little to no evidence of bioavailability from oral, inhalation or dermal exposure to these nitrosamines although absorption of inhaled NDMA is inferred from human fatalities after inhalation (Hamilton and Hardy, 1974)

7.1.1.2 Distribution

Route specific distribution data for nitrosamines in humans were not identified. However, a quantitative analysis of six nitrosamines in post-mortem organs (brain, liver, kidneys, pancreas) was conducted in four human subjects (Cooper et al, 1987) with NDPA being detected in the liver of one subject only.

7.1.1.3 Metabolism

All nitrosamines require metabolism to exert their carcinogenic properties (Li and Hecht, 2022). The electrophiles produced in these simple metabolic pathways, generally catalysed by cytochrome P450 enzymes, readily alkylate DNA, thereby initiating the carcinogenic process.

For NDMA, the metabolic pathways are considered to be similar to those described for various mammalian species. In genetically-modified human cells stably expressing specific human P450s, CYP2E1 was also shown to be the primary isoenzyme involved in the demethylation of NDMA (Bellec et al, 1996). No further data was found on the metabolism in humans for NDEA, NDELA or NDPA.

7.1.1.4 Excretion

Very little human data are available on the excretion of NDMA following oral exposure. However, similar to the animal data, volunteers consuming NDMA added to drinking fluids containing ethanol, excreted only 0.5 and 2.4% of the ingested dose in the urine (Spiegelhalder et al, 1982).

7.1.2 Animal data

All nitrosamines require metabolism to exert their carcinogenic properties and the principal steps in the metabolism of NDMA, NDEA, NDELA and NDPA have been described in a recent review (Li and Hecht, 2022). The electrophiles produced in these simple metabolic pathways, generally catalysed by cytochrome P450 enzymes, readily alkylate DNA, initiating the carcinogenic process, see section 8.1.

7.1.2.1 Absorption and distribution

- NDMA: the absorption and distribution following oral dosing is reported to be rapid in several animal species (rats, mice, dogs, monkeys and swine) with maximum blood concentrations being reached within 30 minutes of dosing (Anderson et al., 1992b; Gombar et al., 1987, 1988, 1990; Streetier al., 1990a, 1990b).
  Less than 2% of 14C-NDMA administered orally to rats could be recovered 15 minutes following administration (Gomez et al., 1977). It is considered that NDMA is completely absorbed from the gastrointestinal tract and does not bind plasma proteins. The high bioavailability in many of these species is considered to result from extrahepatic metabolism (Gombar et al., 1990). The high bioavailability results in widespread tissue concentrations following oral administrations as reported for heart, forestomach, oesophagus, liver, kidney, brain and lung of mice (Daugherty and Clapp, 1976; Anderson et al., 1976).
  NDMA has also been detected in maternal blood, placenta, foetus and amniotic fluid of pregnant Syrian hamsters for up to 2 hours after a single subcutaneous injection and placental

transfer has also been demonstrated in pregnant monkeys (Chhabra et al, 1995). NDMA and its metabolites is also distributed to breast milk following oral administration to nursing rats (Chhabra et al., 2000; Diaz Gomez et al., 1986).

Transplacental transport of NDPA was also shown in pregnant hamsters (Althoff and Grandjean, 1979; Althoff et al., 1977).

- NDELA: the absorption and distribution in rats is reported to be rapid following oral administration with peak concentrations being achieved at 8 hours. Expectedly, following topical administration, absorption was found to be slower (Lethco et al., 1982; Preussman et al., 1978) and also much lower in Syrian golden hamsters (Hoffmann et al., 1983).

- The other two nitrosamines (NDEA and NDPA): whilst no specific data could be found on the absorption and distribution, gastrointestinal absorption after oral administration is expected because of the occurrence of metabolites in the urine after oral treatment and the fact that other nitrosamines are rapidly absorbed from the gastrointestinal tract after oral exposure. There is little evidence of bioavailability from inhalation or dermal exposure to these nitrosamines. However, diffusion of NDPA through rat skin *in vitro* has been demonstrated (Edwards et al., 1979) and also the induction of lung adenomas in mice was attributed to dermal exposure to NDMA (Iversen, 1980).

7.1.2.2 Metabolism

In human liver microsomes, there appears to be two principal pathways of metabolism for NDMA; one is P450 catalysed α-hydroxylation and the other is enzymatic denitrosation:

- *In vitro* assays have shown that several CYP isoenzymes are involved in the α-hydroxylation of NDMA with the most predominant enzyme being CYP2E1 (Yang et al., 1985; Yoo et al., 1990; Sulc et al., 2004). Oxidation of the methyl group of NDMA produces α-hydroxy-NDMA which is an unstable intermediate that spontaneously decomposes, generating two reactive species, formaldehyde and methyl diazohydroxide (George et al., 2019).
- Denitrosation produces formaldehyde and methylamine and it is this part of the pathway that can be considered a detoxification pathway; it has been shown to account for approximately 21% of total NDMA elimination in rats (Streeter et al., 1990a). It is the consequence of oxidation that is of most interest for carcinogenicity potential, since the methyl diazohydroxide will spontaneously form the highly electrophilic methyldiazonium ion which will alkylate DNA to form methyl DNA adducts e.g. O^6-Me-Gua (Magee and Hultin, 1962, Li and Hecht, 2022).

These processes have been demonstrated in both human and rat hepatocytes.

NDEA metabolism is also principally driven by P450-catalysed α- and β-hydroxylation with a similar outcome to that of NDMA. For this nitrosamine, it is the electrophilic ethyldiazonium ion which is formed after decomposition of the unstable intermediate ethyl diazohydroxide. The intermediate reacts with DNA producing ethyl DNA adducts such as N7-Et-Gua and O^6-Et-Gua. In addition, the hydroxylation of NDEA produces acetaldehyde which in turn, forms 2-hydroxyethyldiazonium (second reactive intermediate) when hydroxylated. This second intermediate can also alkylate DNA to form other adducts (Li and Hecht, 2022).

NDPA is metabolised via α-, β- and ɣ-hydroxylation of the propyl group catalysed by cytochrome P450 enzyme systems. The α-hydroxylation is regarded as the primary pathway producing N-nitroso-1-hydroxypropylpropylamine which decomposes to form the appropriate reactive intermediates propyl diazohydroxide and propionaldehyde, as well as propanol as metabolites, similar to NDMA and NDEA. Similarly, the electrophilic propyldiazonium ion is formed which can react with DNA. The β-hydroxylation of NDPA generates N-nitroso-2-hydroxypropylpropylamine which can be further oxidised to N-nitroso-2-oxopropylpropylamine and a secondary α-hydroxylation to form the reactive methyldiazonium ion. The ɣ-hydroxylation of NDPA predictably forms N-nitroso-3-hydroxypropylpropylamine and N-nitrosopropyl-(carboxyethyl)amine which are considered minor metabolites. NDPA would also undergo P450-catalysed denitrosation, like other N-alkylnitrosamines, and form propylamine, propionaldehyde and nitrate (Li and Hecht,

2022).

Both α- and β-hydroxylation pathways have been proposed for NDELA. The α-hydroxylation pathway is similar to the other previously described nitrosamines where action on the α-carbon of NDELA results in the formation of the 2-hydroxyethyldiazonium. Following the loss of H_2O and carbocation of this product, acetaldehyde and ethylene glycol are produced, as well as the expected glycolaldehyde which is classically converted to glycolic acid and oxalic acid for excretion.
Ethylene glycol is suggested to undergo microsome-mediated oxidation to glyoxal which is responsible for the formation of DNA adducts. It has also been demonstrated that the glycolaldehyde is catalytically converted to glyoxal by cytochrome P450 enzymes. Whilst the metabolic pathways of NDELA appear to be more complex, Li and Hecht (2022) concluded that α-hydroxylation of NDELA was necessary for DNA adduct formation. Almost contrarily, the same authors initially considered the β-hydroxylation of NDELA to be the critical metabolic step to the cause of carcinogenicity of this substance. By this pathway, two principal metabolites are formed after P450 catalysis: N-nitroso-(2-hydroxyethyl)glycine (NHEG) and N-nitroso-2-hydroxymorpholine (NHMOR), as well as the glucuronide of NDELA for excretion. NHMOR can be further metabolised by α-hydroxylation on the two methylene groups which results in glyoxal again being the major metabolite (Li and Hecht, 2022).

7.1.2.3 Excretion

Many studies involved the assessment of excretion of various nitrosamines by a variety of mammalian species following various modes of administration. In general terms, the glucuronide of hydroxylated NDMA, NDEA, NDPA and NDELA is excreted in the urine along with appropriate oxidised forms of formaldehyde, acetaldehyde, propionaldehyde or glycolaldehyde respectively, i.e. formic acid, acetic acid, propionic acid and glycolic/oxalic acid.
The other by-product of metabolism is carbon dioxide which will be exhaled along with relatively high levels of unchanged substance, particularly when given via the respiratory tract (Klein and Schmezer, 1984; Philips et al, 1975).
Only small amounts of unchanged nitrosamine were recovered in the urine of several animal species (rat, dog, hamster, monkey and swine) exposed to NDMA, at various dose levels by oral or intravenous delivery (Magee, 1956; Swann et al, 1984; Streeter et al 1990a, 1990b; Anderson et al 1992b; Harrington et al, 1987, 1990). However, higher levels of excretion via the bile following parenteral administration of NDMA was reported in pigs (Harrington et al., 1987, 1990) and rats (Alaneme and Maduagwu, 2004).
Also, large amounts (60-90%) of the unchanged form were found in the urine of rats treated with NDELA in the drinking water (Preussman et al, 1982). In Syrian golden hamsters, subcutaneous injection of NDELA yielded 49% and 11% of the dose in the urine and faeces, respectively, and only 21% and 4%, respectively, after skin application (Hoffmann et al, 1983).

7.1.3 *In vitro*

[^{14}C]-NDELA skin penetration was tested on the epidermis obtained from human abdominal skin using three different vehicles commonly present in cosmetics: water, propylene glycol and isopropyl myristate (IPM). NDELA penetration through the skin was slow in water and propylene glycol and was substantially increased when using the more lipophilic solvent (IPM). In the three solvents (water, propylene glycol and IPM) the flux rates were 7.1, 4.7 and 292 ng cm^{-2} h^{-1}, and the permeability constants $5.5 \cdot 10^{-6}$, $3.2 \cdot 10^{-6}$ and $1.1 \cdot 10^{-6}$ cm/h, respectively. (Bronaugh et al., 1981).

[^{14}C]NDELA skin penetration was measured *in vitro* through human skin to simulate the absorption when present in personal-care products. The substance was mixed in IPM, sunscreen or shampoo. When applied in concentrations up to 0.06%, the NDELA absorption was linear and ranged between 35 and 65% after 48h depending on the type of formulation. The peak absorption was found within 5h after exposure, thus the absorption was considered relatively rapid by the authors. When IPM was used as vehicle the absorption was 24.9% within the first 48h, with a permeability coefficient of $3.5 \cdot 10^{-3}$ cm/h (Franz et al., 1993).

To simulate the use of personal-care product conditions, [^{14}C]NDMA was dissolved in IPM, in oil-water emulsion and in shampoo and skin penetration was tested *in vitro*. In addition, to compare with previous studies, an IPM solution with [^{14}C]NDELA was also tested. Skin obtained from female donors was prepared and placed on a receptor chamber at constant temperature (37°C) which resulted on a temperature at surface of the skin surface of 32°C. For each vehicle, at least 4 donors were used, resulting in at least two replicates per donor per vehicle for both substances. The authors reported an average 48h absorption of 23.6 and 2.6% for NDELA and NDMA, respectively. The NDELA results were in agreement with data obtained in a previous study, i.e. absorption 24.9% and permeability coefficient of $3.5 \cdot 10^{-3}$ cm/h (Franz et al., 1993) versus $4.1 \cdot 10^{-3}$ cm/h in this study. The lower NDMA absorption was attributed to loss over time probably due to evaporation, as suggested also by the low total recovery of 7.27%, and later confirmed in a second test. The 48h absorption rates of NDMA in the other two vehicles were 3.98% and 1.10% for the oil-water emulsion and the shampoo, respectively. The highest absorption rate was observed within 3 h in all vehicles. The authors concluded that NDMA "can penetrate the skin rapidly, but that the amount of applied material actually available for penetration is, in reality, markedly reduced by a high permeant volatility" (Brain et al., 1995).

7.1.4 Toxicokinetic modelling

Physiologically based pharmacokinetic (PBPK) models are not available for nitrosamine.

7.1.5 Summary

A relatively extensive picture of the ADME profile of NDMA is reported and can be considered to largely represent all four nitrosamine substances: NDMA, NDEA, NDELA and NDPA. The ADME profile of nitrosamines could be summarised as follows:
Absorption of orally administered nitrosamine occurs primarily in the small intestine and is rapid in a variety of species tested. Bioavailability following oral administration (the proportion of an oral dose that passes unchanged through the liver into systemic circulation) varies considerably among the species tested. For NDMA in particular, absorption of inhaled material is inferred from human fatalities after inhalation and limited animal data. Rapid skin penetration of NDMA and NDELA has been demonstrated *in vitro*.
The distribution of nitrosamines following exposure is widespread in several species investigated without showing accumulation in any specific tissue. It has also been demonstrated that NDMA in particular, does not bind to plasma proteins.
The metabolic pathways shown by all four substances have distinct similarities. Metabolism occurs via microsomal membrane-bound P450 enzymes of which CYP2E1 has been frequently identified. The first step is predominantly an α-hydroxylation but can include β- or ɣ-hydroxylation for some nitrosamines to produce the appropriate hydroxyalkylnitrosamine which is then non-enzymatically converted to the appropriate aldehyde and reactive diazonium ion. Additional metabolic by-products usually following further hydroxylation steps would include alcohol and a reactive carbonium ion. Additionally, there is a denitrosation pathway yielding the appropriate aldehyde and alkylamine. Clearance of nitrosamines from systemic circulation is via these metabolic pathways.
Very little unchanged nitrosamine is excreted in the urine after oral exposure. Whilst this would increase following parenteral administrations, the amount of unchanged nitrosamine in the urine remains low in most species with enterohepatic circulation being demonstrated in the larger species in particular.

7.2 Acute toxicity

7.2.1 Human data

There are no human data on acute toxicity.

7.2.2 Animal data

The acute toxicity of nitrosamines was investigated via the inhalation and oral route of exposure in rats, monkeys, mice, guinea pigs, hamsters and cats. Details of the studies are shown in Table 20, below. No information was obtained for NDELA.

Table 20: Summary of studies on acute toxicity

Method/ route	Species, strain, sex, number/group	Doses, duration of exposure	Results	References*
NDMA				
Inhalation	Rat (10 males)	41–188 ppm 4h	LC_{50} value of 78 ppm Increased incidence of haemorrhagic necrosis in the liver (LOAEL 78 ppm)	Jacobson et al. 1955
Inhalation	Rat (10 females)	39–67 ppm 4h	LC_{50} value of 57 ppm Increased incidence of haemorrhagic necrosis in the liver (LOAEL 57 ppm)	Jacobson et al. 1955
Inhalation	Dogs – Beagle (3 females)	16–144 ppm 4h	2/3 animals died at high exposure (LOAEL 16 ppm); Increased incidence of haemorrhagic necrosis in the liver (LOAEL 16 ppm)	Jacobson et al. 1955
Oral - gavage	Monkey – African Green (6 males)	0 and 50 mg/kg	No effect on body weight (NOAEL 50 mg/kg); Increased incidence of enlarged cherry-red liver (LOAEL 50 mg/kg)	Maduagwu and Bassir. 1980
Oral – gavage	Rat – F344 / Du Crj (3 males)	0 and 20 mg/kg	Increases in serum AST and ALT (LOAEL 20 mg/kg); Increased incidence of focal necrosis in the liver (LOAEL 20 mg/kg)	Asakura et al. 1998
Oral – gavage	Rat (sex / number not specified)	40 mg/kg	LD_{50} value of 40 mg/kg	Druckrey et al. 1967
Oral – gavage	Rat – Fischer 344 (3 – 5 males)	37, 48.1, 62.5 and 81.3 mg/kg	4 / 5 died at 48.1 mg/kg (LOAEL 48.1 mg/kg)	Frank et al. 1990
Oral	Rat (7 – 8; sex not specified)	0 and 10 mg/kg	Increase in serum ALT (LOAEL 10 mg/kg)	Garland et al. 1988
Oral – gavage	Rat – Sprague Dawley (7 – 9 males)	0, 0.3, 0.7, 1.9, 5.1, 13.7, 37.0 and 100 mg/kg	Increased incidence of vacuolation in the liver (LOAEL 1.9 mg/kg) Increased incidence of necrosis in the liver (LOAEL 13.7 mg/kg)	Korsrud et al. 1973
Oral – gavage	Rat – Wistar (10 males)	0 and 50 mg/kg	Decreased body weight (LOAEL 50 mg/kg) Increased incidence of necrosis with haemorrhage into peritoneum in the liver (LOAEL 50 mg/kg)	Maduagwu and Bassir. 1980
Oral – gavage	Rat – Holtzman (21 females)	0, 15 and 20 mg/kg	No effect on body weights (NOAEL 20 mg/kg) Increased incidence of necrosis and glycogen depletion in the liver (LOAEL 15 mg/kg)	Nishie. 1983

Method/ route	Species, strain, sex, number/group	Doses, duration of exposure	Results	References*
			No effect on thyroid weight or histopathology (NOAEL 20 mg/kg)	
Oral – gavage	Rat – Wistar (12 – 20 males)	0, 8, 9 and 10 mg/kg	Increased serum ALT and AST (LOAEL 8 mg/kg) Increased incidence of necrosis in the liver (LOAEL 8 mg/kg)	Sumi and Miyakawa. 1983
Oral – gavage	Rat – Wistar (5 – 20 males)	0 and 40 mg/kg	All animals died (LOAEL 40 mg/kg)	Waynforth and Magee. 1974
Oral – gavage	Guinea pig – Hartley (10 males)	0 and 50 mg/kg	Decreased body weight (LOAEL 50 mg/kg) Increased incidence of haemorrhagic centrilobular necrosis in the liver (LOAEL 50 mg/kg)	Maduagwu and Bassir. 1980
Oral – gavage	Rat – Holtzman (21 females)	0, 15 and 20 mg/kg	No effect on body weights (NOAEL 20 mg/kg) Increased incidence of necrosis and glycogen depletion in the liver (LOAEL 15 mg/kg) No effect on thyroid weight or histopathology (NOAEL 20 mg/kg)	Nishie. 1983
Oral – gavage	Rat – Wistar (12 – 20 males)	0, 8, 9 and 10 mg/kg	Increased serum ALT and AST (LOAEL 8 mg/kg) Increased incidence of necrosis in the liver (LOAEL 8 mg/kg)	Sumi and Miyakawa. 1983
Oral – gavage	Rat – Wistar (5 – 20 males)	0 and 40 mg/kg	All animals died (LOAEL 40 mg/kg)	Waynforth and Magee. 1974
Oral – gavage	Guinea pig – Hartley (10 males)	0 and 50 mg/kg	Decreased body weight (LOAEL 50 mg/kg) Increased incidence of haemorrhagic centrilobular necrosis in the liver (LOAEL 50 mg/kg)	Maduagwu and Bassir. 1980
Oral – gavage	Cat – domestic (6 males)	0 and 50 mg/kg	2 / 6 animals died (LOAEL 50 mg/kg) Decreased body weight (LOAEL 50 mg/kg) Increased incidence of ascites and severe hemorrhage into peritoneum in the liver (LOAEL 50 mg/kg)	Maduagwu and Bassir. 1980
NDEA				
Oral	Guinea pig	Not specified	LD_{50} value of 250 mg/kg reported	Druckery et al. 1967
Oral	Rat	Not specified	LD_{50} value of 220 mg/kg reported	Schmaehl et al. 1964
Intraperitoneal exposure	Guinea pig	89, 133, 200 and 300 mg/kg	LD_{50} value of 175 – 200 mg/kg reported	Ton and Fong. 1984
Subcutaneous exposure	Hamster (5 males and 5	Not specified	LD_{50} value of 232 mg/kg reported Increased incidence of acute	Reznik et al. 1976

Method/ route	Species, strain, sex, number/group	Doses, duration of exposure	Results	References*
	females)		pulmonary and hepatic hyperaemia	
Intravenous exposure	Mouse	Not specified	LD_{50} value of 132 mg/kg reported	Simmon et al. 1979
Intraperitoneal exposure	Rat	Not specified	LD_{50} value of 216 mg/kg reported	Heath. 1962
Intravenous exposure	Rat	Not specified	LD_{50} value of 280 mg/kg reported	Druckery et al. 1967
Subcutaneous exposure	Rat	40 – 60 mg/kg	LD_{50} value of 195 mg/kg reported Increased incidence of hyperaemia, necrosis, haemorrhages of the lungs, liver, kidneys and intestines	Althoff et al. 1985
Intraperitoneal exposure	Rat	0, 50, 100 and 200 mg/kg	Increased liver and spleen weights Alterations in antioxidant enzymes in liver and kidney	Bansal et al. 2000
NDPA				
Oral – gavage	Rat (number and sex not specified)	Not specified	LD_{50} value of 480 mg/kg reported Increased incidence of necrosis in the liver (LOAEL 480 mg/kg)	Druckery et al. 1967

* References are taken from ATSDR, 2022.
ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGT: gamma-glutamyl transferase

7.2.3 Summary

There are no human data on acute toxicity.

The acute toxicity of nitrosamines was investigated, via several routes of exposure, in rats, monkeys, mice, guinea pigs, hamsters and cats:

- Via inhalation route of exposure: only studies for NDMA were available and the LC_{50} values ranged from 57–78 ppm (ie 173–346 mg/m^3).
- Via oral route of exposure: LD_{50} values reported ranged from 40 mg/kg for NDMA, to 250 mg/kg for NDEA and 480 mg/kg for NDPA (Druckery et al. 1967).

There are no animal data on acute toxicity for NDELA.

7.3 Specific target organ toxicity/Repeated dose

7.3.1 Human data

Some epidemiologic studies were identified in industrial exposure settings with known exposure to nitrosamines, i.e. work with metalworking (metal-cutting) fluids (MWF) and rubber industry.

Four relevant articles focusing on non-cancer endpoints were identified during literature search (Meijer et al. 1998; Straif et al. 1999; Jonsson et al. 2009; Hidajat et al. 2020). However, only two of them (Jonsson et al. 2009; Hidajat et al. 2020) provided exposure information and performed dose-response analyses specifically for nitrosamines.

- Jonsson et al. 2009 evaluated the air levels of nitrosamines in Swedish rubber industry workers and estimated the risk of symptoms and changed levels of immunologic markers in relation to these levels. The study population included 8 companies working with various types

of vulcanization methods (compression and injection; hot air, microwaves, fluid-bed; salt bath). Exposure to eight different volatile nitrosamines was assessed (NDMA, NDEA, NDBA, NDPA, NMEA, NMor, NPip, NPyr). However NDPA and NMEA levels were always below the limit of detection. Exposure to nitrosamines was measured in the breathing zones of 96 rubber workers. Exposure was categorised as follows: low (<0.3 µg/m^3), intermediate (0.3–3.0 µg/m^3) and high (>3.0 µg/m^3). Workers vulcanizing with salt baths had the highest levels (median=4.2 µg/m^3). 172 rubber workers participated in a medical examination and blood analysis (only 66 of these 172 workers were included among those whose air levels of nitrosamines were monitored). The risk of symptoms (odd ratio (OR)) or immunologic markers was compared to 118 unexposed subjects (not occupationally exposed to rubber chemicals but had similar socio-economic characteristics as the exposed workers).
Compared to the unexposed subjects, the rubber workers had an increased risk of nosebleeds (OR=3.9; 95% CI=1.5-9.7), itching (OR=3; 95% CI=1.7-5.2), throat burning (OR=3.2; 95% CI=1.7-6.1), hoarseness (OR=2.4; 95% CI=1.1-5.1), cough (OR=3.9; 95% CI=1.9-7.8), nausea (OR=4.5; 95% CI=1.6-12), headache (OR=2.6; 95% CI=1.5-4.5), and changed levels of eosinophils (OR=14; 95% CI=0.6-30) and total immunoglobulin G (IgG) (OR=11; 95% CI=5.4-16). Models were adjusted for gender, age, atopy, smoking, and snuffing.
No clear exposure-response relationship was observed between the symptoms or the immunologic markers studied and exposure to nitrosamines.

It is noted that no other rubber industry related exposures than the above-mentioned nitrosamines were measured or estimated and the control group was unexposed not only to nitrosamines but also to other rubber industry chemicals. As possible reasons for lack of dose response the authors discussed healthy worker effect and differences in exposure between all exposed (N=172) and those with measured nitrosamine exposure and symptom/immunology data (N=66). However they conclude that "*More probably, other substances found in the rubber fumes and not co-varying with N-nitrosamines, caused the symptoms we registered. Rubber fumes are multitudinous and contain hundreds of compounds; the airway symptoms could, for example, be caused by particles or some reactive chemicals.*"

- Hidajat et al. 2020 examined associations between occupational exposures to rubber dust, rubber fumes and nitrosamines and non-cancer mortality in a British cohort of 36441 males aged 35+ years employed in British rubber factories. Workers were followed-up to 2015. Cumulative occupational exposures (expressed as year mg/m3) to rubber dust, rubber fumes, nitrosamines were derived based on a population-specific quantitative job-exposure matrix (JEM). Exposure estimates to total nitrosamines (quartiles: I (17.24 year µg/m3;), II (17.24–26.72 year µg/m3), III (26.72–546.51 year µg/m3), IV (>546.51 year µg/m3)), NDMA (quartiles: I (<5.77 year µg/m3), II (5.77–8.34 year µg/m3), III (8.34–11.37 year µg/m3), IV (>11.37 year µg/m3) and NMor (quartiles: I (<7.70 year µg/m3), II (7.70–12.31 year µg/m3), III (12.31–19.01 year µg/m3), IV (IV:>19.01 year µg/m3) were distinguished. Total nitrosamines were defined as a sum of lifetime cumulative exposures to NDMA, NDEA, N-nitrosodibutylamine, NPip and NMor. Statistical analyses were done to estimate subdistribution hazard ratios (SHR) and were adjusted by birth year. Total nitrosamine exposure was associated with significant increased risk of dying from circulatory (SHR=1.28, 95%CI=1.22-1.34, p for trend=0.41), ischemic heart (IHD) (SHR=1.29, 95% CI=1.22-1.37, p for trend=0.4), cerebrovascular (CVD) (SHR=1.48, 95% CI=1.33-1.64, p for trend=0.69), respiratory (SHR=1.49, 95% CI=1.37-1.62, p for trend=0.27) and digestive (SHR=1.6, 95% CI=1.31-1.95, p for trend=0.64) diseases. Similarly increased risks were observed in relation with NDMA and NMor. No evidence of increased risks of mortality from asthma, bronchitis, diseases of the oesophagus, stomach and duodenum, urinary and liver diseases was found. Multipollutant models with exposures to rubber dust, rubber fumes and total nitrosamines were conducted for a subset of causes of deaths with the highest proportions. Increased risks with exposure to total nitrosamines were found for circulatory diseases (SHR=1.2, 95% CI=1.13-1.27, p for trend=0.25), IHD (SHR=1.19, 95% CI=1.1-1.28, p for trend=0.37), CVD (SHR=1.44, 95% CI=1.26-1.65, p for trend=0.29), digestive (SHR=1.4, 95% CI=1.12-1.75, p for trend=0.46) and respiratory (SHR=1.44, 95% CI=1.3-1.59, p for trend=0.27) diseases. It is noted that no adjustment was made for smoking or other lifestyle factors.

- Meijer et al. 1998 carried out a cross-sectional study (between 1988-1991) of Dutch smoking and non-smoking 70 rubber workers employed in five various departments (compounding/mixing, calendaring, excruding, repair, curing), and 69 controls. Cumulative dust exposure to rubber fumes and dust was estimated for each rubber worker by calculating the product of the department mean exposure and the number of years employed in that department (expressed as mg/m3*year). No exposure to nitrosamines was assessed. Standardized respiratory questionnaire and pulmonary tests were used to examine lung function. Cross-sectional analyses gave indications for a small loss in pulmonary function in all rubber workers (decrease in lung function associated with 10 years of exposure to an average of 2.0 mg/m3 inhalable dust).

- Straif et al. 1999 studied mortality from nonalcohol-related chronic liver disease among 2875 German female rubber workers hired on or after 1976 and employed for at least one year. No specific exposure to nitrosamines was assessed. The mortality experience of the cohort was compared with the mortality of the general female population of former West Germany using standardized mortality ratio (SMR) analyses (stratified by plant, work area, year of hire, and years of employment in the respective work area). Authors showed a statistically significant excess in mortality from cirrhosis of the liver (10 deaths, SMR=202; 95% CI=97–372). Mortality from alcohol-related cirrhosis of the liver (3 deaths, SMR=153; 95% CI=31–446) and from other alcohol-related diseases (organic psychoses, injury, and poisoning) was not statistically significantly elevated nonalcohol-related cirrhosis of the liver (10 deaths, SMR=202; 95% CI=97–372) was not statistically increased.

7.3.2 Animal data

The specific target organ toxicity/repeat dose toxicity of NDMA was investigated, via several routes, in mice, rats, hamsters, guinea pigs, cats, dogs, minks, and monkeys. The specific target organ toxicity / repeat dose toxicity of NDEA and NDPA was investigated, via oral gavage in rats. Details of the studies are shown in Table 21. No information was obtained for NDELA.

Table 21: Summary of studies on repeated dose toxicity

Method, route	Species, strain, sex, number group	Doses, duration of exposure	Results	References
NDMA				
Oral – gavage	Mouse – CD-1 (3 males)	0, 2, 4, 7 and 10 mg/kg/day 2 weeks	All animals died by day 6 (LOAEL 7 mg/kg/day) Increased serum ALT and AST (LOAEL 7 mg/kg/day)	Doolittle et al. 1987
Oral – drinking water	Mouse – Swiss Cr:NIH(s) (10 – 20 females)	0 and 5 mg/kg/day 1 – 4 weeks	Increased haemorrhage in the liver (LOAEL 5 mg/kg/day)	Anderson et al. 1986
Oral – drinking water	Mouse – CD-1 (15 females)	0, 0.26, 1.3, 2.6 and 5.3 mg/kg/day 4 – 17 weeks	Increased death – 1 / 15 at 2.6 mg/kg/day and 3 / 15 at 5.3 mg/kg/day (LOAEL 2.6 mg/kg/day) Increased incidence of ascites in the liver (LOAEL 2.6 mg/kg/day) Decreased humoral response to sheep red blood cells and inhibition of alloantigenic response of T-cells (LOAEL 1.3 mg/kg/day)	Desjardins et al. 1992
Oral – gavage	Rat – F344 / Du Crj (3 males)	0 and 4 mg/kg/day 14 days, once daily	Increased incidence of focal necrosis in the liver (LOAEL 4 mg/kg/day)	Asakura et al. 1998
Oral – gavage	Rat – Wistar (10 males)	0 and 5 mg/kg/day 5 – 11 days, once daily	3 / 10 animals died (LOAEL 5 mg/kg/day) Decreased body weight (LOAEL 5 mg/kg/day)	Maduagwu and Bassir. 1980

Method, route	Species, strain, sex, number group	Doses, duration of exposure	Results	References
			Increased incidence of necrosis in the liver (LOAEL 5 mg/kg/day)	
Oral – gavage	Rat – Wistar (10 males)	0 and 1 mg/kg/day 30 days	Increased incidence of vacuolation and congestion in the liver (LOAEL 1 mg/kg/day)	Maduagwu and Bassir. 1980
Oral – feed	Rat – albino (6; sex not specified)	0, 5, 10 and 20 mg/kg/day 34 – 110 days	6 / 6 died at 10 and 20 mg/kg/day (LOAEL 10 mg/kg/day) Decreased body weight (LOAEL 10 mg/kg/day) Increased incidence of haemorrhage in the gastrointestinal tract (LOAEL 20 mg/kg/day) Increased incidence of necrosis in the liver (LOAEL 10 mg/kg/day)	Barnes and Magee. 1954
Oral – feed	Rat – albino (25; sex not specified)	0 and 7.2 mg/kg/day 4, 8 or 12 weeks	Increased incidence of haemorrhagic necrosis in the liver (LOAEL 7.2 mg/kg/day)	Khanna and Puri. 1966
Oral – feed	Rat – albino (25; sex not specified)	0 and 3.75 mg/kg/day 1–2 weeks; 7 days/ week	Increased incidence of haemorrhagic necrosis in the liver (LOAEL 3.75 mg/kg/day)	Khanna and Puri. 1966
Oral – drinking water	Rat – Fischer 344 (12 – 19 males)	0 and 3.9 mg/kg/day 8 weeks	No effect on body weight (NOAEL 3.9 mg/kg/day) Increased incidence of eosinophilic or mixed cell foci and hepatocellular nodules in the liver (LOAEL 3.9 mg/kg/day)	Jang et al. 1990
Oral – drinking water	Rat – Wistar (8 males)	0, 0.002 and 0.003 mg/kg/day 30 or 90 days	Increased incidence of focal necrosis; oedema, degeneration; decrease in megakaryocytes and migration to vascular sinus and myelosclerosis in the bone marrow (LOAEL 0.002 mg/kg/day) Increased incidence of degeneration, argyrophilic and collagenic fibres, inflammatory infiltrations near portal biliary tract, steatosis and parenchymatosis in the liver (LOAEL 0.002 mg/kg/day) Increased incidence of megakaryocytes in red pulp and enhanced lymphatic "texture" in the spleen (LOAEL 0.002 mg/kg/day)	Moniuszko-Jakoniuk et al. 1999
Oral – drinking water	Rat – Wistar (8 males)	0, 0.002 and 0.003 mg/kg/day 10 days	No effects on bone marrow, liver or spleen histopathology (NOAEL 0.003 mg/kg/day)	Moniuszko-Jakoniuk et al. 1999
Oral – drinking water	Rat – Wistar (7 males)	0 and 0.002 mg/kg/day 2 weeks	Increases in serum AST, ALT, ALP and GGT (LOAEL 0.002 mg/kg/day)	Roszczenko et al. 1996a
Oral – drinking water	Rat – Wistar (7 males)	0, 0.0007, 0.0016 and 0.0035 mg/kg/day 2 weeks	Decreased serum total and latent iron binding capacity (LOAEL 0.0016 mg/kg/day)	Roszczenko et al. 1996b
Oral –	Rat – Fischer	0, 0.000075,	No effect on body weight (NOAEL	Fukushima et

Method, route	Species, strain, sex, number group	Doses, duration of exposure	Results	References
drinking water	344 (81 – 91 males)	0.00075, 0.0075, 0.075 and 0.75 mg/kg/day 16 weeks	0.75 mg/kg/day) No effect on liver weight (NOAEL 0.75 mg/kg/day)	al. 2005
Oral – drinking water	Rat – SD (6 males)	0, 0.5, 2 and 4 15 days	Increased incidence of centrilobular hepatocyte degeneration and fibrosis; inflammation of central vein and subscapular region in the liver (LOAEL 2 mg/kg/day)	Rothfuss et al. 2010
Oral – drinking water	Hamster – Golden (5 – 10 males)	0 and 4 mg/kg/day 28 days	Increased incidence of portal venopathy in the liver (LOAEL 4 mg/kg/day)	Ungar. 1984
Oral – drinking water	Hamster – Golden (5 – 20 males)	0 and 4 mg/kg/day 1 – 14 days	Increased incidence of portal venopathy in the liver (LOAEL 4 mg/kg/day)	Ungar. 1984
Oral – gavage	Guinea pig – Hartley (10 males)	0 and 5 mg/kg/day 5 – 11 days, once daily	4 / 10 animals died (LOAEL 5 mg/kg/day) Decreased body weight (LOAEL 5 mg/kg/day) Increased incidence of necrosis in the liver (LOAEL 5 mg/kg/day)	Maduagwu and Bassir. 1980
Oral – gavage	Guinea pig – Hartley (10 males)	0 and 1 mg/kg/day 30 days	Increased incidence of necrosis in the liver (LOAEL 1 mg/kg/day)	Maduagwu and Bassir. 1980
Oral – gavage	Cat – domestic (6 males)	0 and 5 mg/kg/day 5 – 11 days, once daily	4/6 animals died (LOAEL 5 mg/kg/day) Decreased body weight (LOAEL 5 mg/kg/day) Increased incidence of necrosis in the liver (LOAEL 5 mg/kg/day)	Maduagwu and Bassir. 1980
Oral – gavage	Cat – domestic (6 males)	0 and 1 mg/kg/day 30 days	3/6 died (LOAEL 1 mg/kg/day) Decreased body weight (LOAEL 1 mg/kg/day) Increased incidence of necrosis in the liver (LOAEL 1 mg/kg/day)	Maduagwu and Bassir. 1980
Oral – capsule	Dog – Beagle (6 or 8 males and females)	0 and 2 mg/kg/day 24 weeks; 2 days/week	Decreased body weight (LOAEL 2 mg/kg/day) Increased serum levels of AST, ALT, ALP, GGT, bile acids, and bilirubin (LOAEL 2 mg/kg/day) Increased incidence of necrosis, inflammation, cholestasis, vacuolation, lobular collapse, fibrosis, biliary hyperplasia, ascites and hepatic encephalopathy in the liver (LOAEL 2 mg/kg/day)	Boothe et al. 1992
Oral – capsule	Dog – Mongrel (5 – 8; sex not specified)	0 and 2.51 mg/kg/day	Increased serum AST, ALT, and LDH (LOAEL 2.51 mg/kg/day) Increased incidence of necrosis, stromal collapse and fibrous structure in the liver (LOAEL 2.51 mg/kg/day)	Hashimoto et al. 1989
Oral – capsule	Dog – Mongrel (9 – 11; sex not specified)	0 and 2.51 mg/kg/day 4 weeks; 2 days/week	1 / 9 died of acute liver failure (LOAEL 2.51 mg/kg/day) Increased serum ALP, AST, and bilirubin (LOAEL 2.51 mg/kg/day) Increased incidence of extensive	Madden et al. 1970

Method, route	Species, strain, sex, number group	Doses, duration of exposure	Results	References
			necrosis, stromal collapse, destruction of lobular architecture, inflammation and cirrhosis in the liver (LOAEL 2.51 mg/kg/day)	
Oral – feed	Mink (3 males)	0, 0.32 and 0.63 mg/kg/day 23 – 34 days	Decreased survival (LOAEL 0.32 mg/kg/day) Increased incidence of necrosis in the liver (LOAEL 0.32 mg/kg/day)	Carter et al. 1969
Oral – feed	Mink (12 males and 12 females)	0, 0.04, 0.05, 0.06, 0.08, 0.13 and 0.17 mg/kg/day 122 days	Increased incidence of venopathy in the liver (LOAEL 0.13 mg/kg/day)	Koppang and Rimeslatten. 1976
Oral – gavage	Monkey – African Green (6 males)	0 and 1 mg/kg/day 30 days	Increased incidence of necrosis in the liver (LOAEL 1 mg/kg/day)	Maduagwu and Bassir. 1980
Oral – gavage	Monkey – African Green (6 males)	0 and 5 mg/kg/day 5 – 11 days, once daily	3 / 6 animals died (LOAEL 5 mg/kg/day) No effect on body weight (NOAEL 5 mg/kg/day) Increased incidence of necrosis in the liver (LOAEL 5 mg/kg/day)	Maduagwu and Bassir. 1980
NDEA				
Oral – gavage	Rat (5 males)	0, 5, 10, 20 mg/kg/day 28 days	Death in all animals at highest dose (LOAEL 20 mg/kg/day) Increased incidence of portal inflammation in the liver (LOAEL 5 mg/kg/day)	Shi et al. 2011
Oral – gavage	Rat (5 males)	0, 5, 10, 15 mg/kg/day 28 days	Decreased liver weights (LOAEL 10 mg/kg/day)	Khanal et al. 2018
Oral – drinking water	Rat (15 males)	0, 0.1, 1, 10 ppm 2, 4 or 8 weeks	No adverse effects observed (NOAEL 10 ppm)	Akagi et al. 2015
NDPA				
Oral – gavage	Rat – CD (5 males)	0, 10, 20, 40 mg/kg/day 14 days	Decreased body weight (LOAEL 40 mg/kg/day) Increased incidence of hepatocellular necrosis (LOAEL 10 mg/kg/day) Decreased liver weight (LOAEL 20 mg/kg/day) Increased incidence of minimal hepatocellular hypertrophy, mild centrilobular hepatocellular necrosis, minimal centrilobular inflammation and diffuse hepatocellular vacuolation in the liver (LOAEL 20 mg/kg/day)	Terashima et al. 2015
NDMA and NDEA				
Oral – gavage	Rabbits	12 weeks 0.5 mg/kg/day	Increased TBARS, decreased GSH levels and decreased activity of antioxidant enzymes (GHS-R, GST, SOD, CAT)	Sheweita et al., 2017

Male Wistar rats were dosed with 0, 10, 20 or 30 µg/L of NDMA in drinking water for 90 days. The authors studied the iron balance (iron concentration in serum, liver and spleen, total and latent serum iron-binding capacity, percentage of transferrin saturation and the concentration of haemoglobin and haematocrit value) after 10, 30 and 90 days of exposure. No effects were

recorded at the low dose, while at the mid dose a time-dependent increase of haemoglobin level and iron concentration in the spleen was reported. At the same dose, the latent iron-binding capacity was decreased, and the percentage of transferrin saturation was significantly increased from 30 days of exposure. At the high dose, reduced haematocrit, haemoglobin and iron level in serum were reported, as well as significant decrease of the latent iron-binding capacity and the percentage of transferrin saturation. After 30 days of exposure, iron concentrations were higher in the liver and lower in the spleen with respect to control. Overall, the authors concluded that NDMA caused disturbances of iron balance in rats from 20 µg/L (Roszczenko et al. 1996b).

Male New Zealand White (NZW) rabbits (5 group) were dosed with 0.5 mg/kg bw/day of NDEA or NDMA in drinking water for 12 weeks, and control animals received water only. The assessment of the oxidant status in the liver revealed significantly elevated levels of free radicals measured as thiobarbituric acid reactive substances (TBARS) and depleted glutathione (GSH) levels. Furthermore, a statistically significant decreased activity of antioxidant enzyme was measured (GSH-reductase (GHS-R), GHS-S-transferase (GST), superoxide dismutase (SOD) and catalase (CAT)). No effects on liver histopathology were reported for these two nitrosamines (Sheweita et al., 2017) (see also section 7.8).

7.3.3 Summary

Only two epidemiological studies, both in the rubber industry, were identified that provided exposure information and performed dose-response analyses specifically for nitrosamines (total or some specific volatile nitrosamines). There was an indication for an increase in risk of adverse respiratory symptoms, increase in certain immunologic biomarkers and mortality from circulatory, respiratory and digestive diseases when comparing the exposed and unexposed. However, no clear exposure-response patterns by intensity of exposure were identified. It is noted that potential confounding by other rubber industry exposures was not comprehensively adjusted for and adjustment for potential confounding by life-style factors was limited.

The specific target organ toxicity / repeat dose toxicity of NDMA was investigated, via oral route (gavage, feed or drinking water), in mice, rats, hamsters, guinea pigs, cats, dogs, minks, and monkeys: most studies showed target organ toxicity, evidenced as histopathological lesions in the liver in 17 studies, with Lowest Observed Adverse Effect Levels (LOAELs) ranging from 0.002–10 mg/kg/day.

The specific target organ toxicity/ repeat dose toxicity of NDEA and NDPA was investigated via oral gavage in rats: similar effects were for NDEA with similar effects on the liver at oral LOAELs up to 10 mg/kg/day in rats; after investigating NDPA in rats (gavage), the LOAEL for hepatocellular necrosis was 10 mg/kg/day.
No target organ toxicity data was available for NDELA.

7.4 Irritancy and corrosivity

7.4.1 Human data

There are no human data on irritancy and corrosivity.

7.4.2 Animal data

There are no animal data available on the skin or eye irritancy or corrosivity of nitrosamines.

7.4.3 *In vitro* data

There were no *in vitro* data available on the irritancy or corrosivity of nitrosamines on skin or eyes.

7.4.4 Summary

There are no data available on the skin or eye irritation of nitrosamines.

7.5 Sensitisation

7.5.1 Human data

There are no human data on respiratory sensitisation or on skin sensitisation.

7.5.2 Animal data

There are no animal data on respiratory sensitisation or on skin sensitisation of nitrosamine.

7.5.3 *In vitro* data

There are no *in vitro* data available on the respiratory or skin sensitisation of nitrosamines.

7.5.4 Summary

There are no data available on the sensitisation of nitrosamines.

7.6 Genotoxicity

7.6.1 Human data

Li et al. (2011) examined the relationship between DNA-damaging agents and average telomere length in peripheral blood DNA by conducting a cross-sectional study among 166 exposed to nitrosaminesfrom 8 different rubber factories (involved in vulcanisation process) in southern Sweden. Of these workers, 157 workers had information available on telomere length in peripheral blood. Nitrosamines were measured in air and the sum of nitrosamines (NDMA, NDEA, NMor, NPip, NDBA, N-Pyr, NMEA and NDPA) were used in statistical analyses. The following urinary biomarkers were measured: 1-hydroxypyrene (1-HP), 2-thiothiazolidine-4-carboxylic acid (TTCA) and p-toluidine. The effects of the individual characteristics and exposure variables on the telomere length were estimated as β-coefficients from a general linear model (all exposures were divided by 1000 times to get β-coefficients in a proper scale). Univariate analyses were carried out first, followed by multivariate analyses for adjustments with influential covariates. Potential covariates (gender, ethnicity, age, and working time) were included in multivariate analyses if they were significantly correlated to telomere length. Authors found that nitrosamine exposure (categorized in three groups: low (<5.0 μg/m^3), medium (5.0–20 μg/m^3) and high (>20μg/m^3)) was associated with shorter telomeres. A univariate linear regression analysis was performed to assess the effect estimates of the different variables on the relative telomere length. Age, working time, nitrosamines, TTCA and p-toluidine were all associated with telomere length. The association between telomere length and estimated (p=0.02; β-coefficient = -5.3, 95% CI=-9.5– -0.97) and measured (p=0.02; β-coefficient= -10, 95% CI=-17– -1.9) nitrosamine concentration in air remained statistically significant in the multivariate analysis.

7.6.2 Animal data

The genotoxicity of nitrosamines has been investigated *in vivo*, in assays testing for gene mutations, chromosomal aberrations, induction of micronuclei, sister chromatid exchange, DNA damage, DNA methylation, DNA repair synthesis and unscheduled DNA synthesis in rats, mice and hamsters, eliciting predominantly positive results.

Relevant studies with NDMA, NDEA, NDPA and NDELA are summarised in Table 22, Table 23, Table 24 and Table 25.

Table 22: Summary of *in vivo* genotoxicity studies on N-Nitrosodimethylamine (NDMA)

Species (test system)	Dose levels	Study endpoints	Results	References[1]
Rat kidney	Not specified in ATSDR report	Gene mutations	**Positive**	Horesovsky et al. 1995
Rat (transgenic Big Blue® and Big Blue® cII) liver	Administered orally or via intraperitoneal injection at doses ranging from 1.8 to 54 mg/kg/day	Gene mutations	**Positive**	Ashby et al. 1994; Butterworth et al. 1998; Cunningham et al. 1996; Davies et al. 2000; Delker et al. 2008; Hayward et al. 1995; Lefevre et al. 1994; Mirsalis et al. 1993; Shane et al. 1999, 2000a, 2000b; Shephard et al. 1995; Suzuki et al. 1996; Tinwell et al. 1994a, 1995
Mouse (transgenic Big Blue®) liver, lung, kidney		Gene mutations	**Positive**	Ashby et al. 1994; Butterworth et al. 1998; Cunningham et al. 1996; Davies et al. 2000; Delker et al. 2008; Hayward et al. 1995; Lefevre et al. 1994; Mirsalis et al. 1993; Shane et al. 1999, 2000a, 2000b; Shephard et al. 1995; Suzuki et al. 1996; Tinwell et al. 1994a, 1995
Mouse (transgenic Big Blue® cII) liver		Gene mutations	**Positive**	Shane et al. 2000b
Mouse (MutaTM mouse transgenic) liver, lung, spleen		Gene mutations	**Positive**	Fletcher et al. 1998; Jiao et al. 1997; Lefevre et al. 1994; Souliotis et al. 1998; Suzuki et al. 1998; Tinwell et al. 1994b, 1995, 1998
Mouse (transgenic Big Blue®) testes, bone marrow, bladder, forestomach		Gene mutations	Negative	Ashby et al. 1994; Shephard et al. 1996; Suzuki et al. 1996

Species (test system)	Dose levels	Study endpoints	Results	References[1]
Mouse (MutaTM mouse transgenic) bone marrow, kidney		Gene mutations	Negative	Jiao et al. 1997; Souliotis et al. 1998; Suzuki et al. 1998
Mouse intestine	Not specified in the ATSDR report	Gene mutations	**Positive**	Winton et al. 1990
Mouse lymphocytes		Gene mutations	Negative	Dass et al. 1998
Mouse lung tumours		Gene mutations	**Positive**	Chen et al. 1994; Devereux et al. 1991; Ramakrishna et al. 2000
Rat liver		Aneuploidy	**Positive**	Clawson et al. 1992
Hamster embryonic fibroblasts (transplacental)		Chromosome aberrations	**Positive**	Inui et al. 1979
Rat liver		Chromosome aberrations	**Positive**	Asakura et al. 1998; Sawada et al. 1991
Rat and mouse liver		Micronucleus assay	**Positive**	Braithwaite and Ashby 1988; Cliet et al. 1989; Hamada et al. 2015; Mehta et al. 1987; Sawada et al. 1991; Suzuki et al. 2005, 2009; Takashima et al. 2015; Tates et al. 1980
Rat kidney		Micronucleus assay	**Positive**	Robbiano et al. 1997
Rat bone marrow and spleen		Micronucleus assay	**Positive**	Krishna and Theiss 1995
Rat bone marrow		Micronucleus assay	Equivocal result	Trzos et al. 1978
Rat bone marrow		Micronucleus assay	Negative	Hamada et al. 2015; Takashima et al. 2015
Mouse bone marrow and/or spleen		Micronucleus assay	**Positive**	Bauknecht et al. 1977; Fritzenschaf et al. 1993; Krishna et al. 1990; Morrison and Ashby 1994; Odagiri et al. 1986; Sato et al. 1992; Wild 1978
Mouse bone marrow		Micronucleus assay	Negative	Cliet et al. 1989, 1993

Species (test system)	Dose levels	Study endpoints	Results	References[1]
Rat peripheral blood		Micronucleus assay	Negative	Rothfuss et al. 2010
Mouse peripheral blood		Micronucleus assay	**Positive**	Sasaki 1991; Sato et al. 1992
Rat and mouse peripheral blood		Micronucleus assay	Negative	Suzuki et al. 1996, 2005
Rat stomach and colon		Micronucleus assay	Negative	Hamada et al. 2015; Takashima et al. 2015
Hamster embryonic fibroblasts (transplacental)		Micronucleus assay	**Positive**	Inui et al. 1979
Mouse spermatid		Micronucleus assay	**Positive**	Cliet et al. 1993
Rat liver		Sister chromatid exchanges	**Positive**	Sawada et al. 1991
Hamster bone marrow		Sister chromatid exchanges	Equivocal result	Neal and Probst 1983
Mouse bone marrow		Sister chromatid exchanges	**Positive**	Bauknecht et al. 1977; Sharma et al. 1983
Human liver		DNA methylation/adducts	**Positive**	Herron and Shank 1980
Rat, mouse, hamster and/or gerbil liver		DNA methylation/adducts	**Positive**	Bamborschke et al. 1983; Bianchini and Wild 1994; Camus et al. 1990; Chin et al. 1993; Dai et al. 1991; Fadlallah et al. 1994; Fan et al. 1989; Klaude et al. 1989; Kroeger-Koepke et al. 1992; Ma et al. 2015; O'Connor et al. 1982; Pegg and Hui 1978; Pegg et al. 1981; Scherer et al. 1989; Souliotis et al. 1995; Stumpf et al. 1979; Takahashi et al. 1996
Rat kidney, mammary glands, and leukocytes		DNA methylation/adducts	**Positive**	Bianchini and Wild 1994; Chhabra et al. 2000; Fadlallah et al. 1994; Fan et al. 1989; Souliotis et al. 1995

Species (test system)	Dose levels	Study endpoints	Results	References[1]
Rat foetal liver, lung, and/or kidney		DNA methylation/adducts	**Positive**	Chhabra et al. 2000
Rat oesophagus		DNA methylation/adducts	Negative	Scherer et al. 1989
Human placenta		DNA methylation/adducts	Negative	Annola et al. 2009
Rat liver, lung, kidney, nasal cavity, and/or peripheral blood lymphocytes		DNA damage	**Positive**	Abanobi et al. 1979; Bermudez et al. 1982; Brambilla et al. 1981, 1987, 1992; Dahlhaus and Appel 1993; McNamee and Bellier 2015; Petzold and Swenberg 1978; Pool et al. 1990; Pool-Zobel et al. 1992; Rothfuss et al. 2010; Webster et al. 1996
Rat liver and kidney		DNA damage	**Positive**	Barbin et al. 1983
Rat kidney		DNA damage (double-strand breaks)	Negative	McLaren et al. 1994
Rat lung		DNA damage	Negative	Barbin et al. 1983
Mouse liver, kidney, bladder		DNA damage	**Positive**	Cesarone et al. 1982; Tsuda et al. 2001
Hamster liver		DNA damage	**Positive**	Barbin et al. 1983
Hamster lung		DNA damage	Negative	Barbin et al. 1983
Rat stomach		DNA damage	Negative	McNamee and Bellier 2015; Ohsawa et al. 1993; Okabe et al. 2019
Mouse colon		DNA damage	Negative	Tsuda et al. 2001
Foetal mouse liver and lung		DNA damage	**Positive**	Bolognesi et al. 1988
Rat liver		Unscheduled DNA synthesis	**Positive**	Asakura et al. 1994; Bakke and Mirsalis 1984; Doolittle et al. 1984, 1987; Kornbrust and Dietz 1985; Mirsalis and Butterworth 1980; Mirsalis et al. 1989; Sawada et al. 1989, 1995
Mouse liver		Unscheduled DNA synthesis	**Positive**	Mirsalis et al. 1989
Rat upper respiratory		Unscheduled DNA synthesis	**Positive**	Doolittle et al. 1984

Species (test system)	Dose levels	Study endpoints	Results	References[1]
tract				
Rat stomach		Unscheduled DNA synthesis	Negative	Ohsawa et al. 1993
Rat spermatocytes		Unscheduled DNA synthesis	Negative	Doolittle et al. 1984
Mouse testes		Unscheduled DNA synthesis	**Positive**	Cesarone et al. 1979
Rat embryo		Unscheduled DNA synthesis	**Positive**	Huang and Catalano 1994
Rat liver		Replicative DNA synthesis	**Positive**	Asakura et al. 1998
Mouse testes		Inhibition of DNA synthesis	**Positive**	Friedman and Staub 1976

[1] Source: ATSDR. 2022. Toxicological Profile for N-Nitrosodimethylamine (NDMA)

Table 23: Summary of *in vivo* genotoxicity studies on N-Nitrosodiethylamine (NDEA)

Species (test system)	Dose levels	Study endpoints	Results	References[1]
Mouse	Not specified in IARC monograph	Gene mutation	Negative	Propping et al. 1972
Mouse	Not specified in IARC monograph	Gene mutation	**Positive**	Mailing et al. 1973
Rat (liver)	Oral drinking water doses of 0.1, 1, and 10 ppm for 2, 4 or 8 weeks	Gene mutation	**Positive**	Akagi et al. 2015
Rat (blood)	Oral gavage doses of 5 and 10 mg/kg/day for 28 days	Gene mutation – Pig-a assay	Negative	Shi et al. 2011
Rat (bone marrow and blood)	Oral doses up to 12.5 mg/kg/day for 28 days	Gene mutation – Pig-a assay	**Positive**	Avlasevich et al. 2014*
Rat (blood)	Oral gavage doses of 5, 10, or 15 mg/kg/day for 28 days	Gene mutation – Pig-a assay	**Positive**	Khanal et al. 2018
Rat (liver)	Not specified in IARC monograph	Chromosome aberration	**Positive**	Hitachi et al. Grover et al. 1971; Danielsen et al. (1991)
Rat (liver)	0.5–4.0 mg/kg	Chromosome aberration	**Positive**	Horiuchi et al. 1984*
Mouse (bone marrow)	Not specified in abstract	Micronucleus assay	Not specified in abstract	Bauknecht et al. 1977*
Rat (liver)	Single intraperitoneal dose of 3.4, 23.5 or 55.1 mg/kg	Micronucleus assay	**Positive**	Mehta et al. 1987
Rat (oesophagus)	Single intraperitoneal dose of 3.4, 23.5 or 55.1 mg/kg	Micronucleus assay	**Positive**	Mehta et al. 1987
Mouse (liver)	Not specified in abstract	Micronucleus assay	**Positive**	Cliet et al. 1989*
Mouse (testes)	Not specified in abstract	Micronucleus assay	**Positive**	Cliet et al. 1993*
Rat (peripheral blood)	Oral gavage doses of 5 and 10 mg/kg/day for 28 days	Micronucleus assay	Negative	Shi et al. 2011
Rat (liver)	Oral gavage doses of	Micronucleus assay	**Positive**	Narumi et al.

Species (test system)	Dose levels	Study endpoints	Results	References[1]
	6.25 and 12.5 mg/kg/day for 5, 14 or 28 days			2012
Rat (liver)	Oral gavage doses of 6.25 and 12.5 mg/kg/day for 15 and 28 days	Micronucleus assay	**Positive**	Hagio et al. 2014
Rat (peripheral blood)	Oral gavage doses of 6.25 and 12.5 mg/kg/day for 15 and 28 days	Micronucleus assay	Negative	Hagio et al. 2014
Rat (bone marrow)	Oral doses up to 12.5 mg/kg/day for 28 days	Micronucleus assay	Negative	Avlasevich et al. 2014*
Rat (liver)	Oral gavage doses of 5, 10, or 15 mg/kg/day for 28 days	Micronucleus assay	**Positive**	Khanal et al. 2018
Rat (peripheral blood)	Oral gavage doses of 5, 10, or 15 mg/kg/day for 28 days	Micronucleus assay	Negative	Khanal et al. 2018
Hamster (bone marrow)	Not specified in abstract	Sister chromatid exchange	Negative	Bayer et al. 1978*
Rat (liver and blood)	Oral gavage doses of 5 and 10 mg/kg/day for 28 days	DNA damage	**Positive**	Shi et al. 2011
Rat (liver and kidney)	Oral gavage doses of 6.25 and 12.5 mg/kg/day for 15 and 28 days	DNA damage	**Positive**	Hagio et al. 2014

***** Abstract reviewed only – paper not obtained
[1] Source: IARC Monograph (1976) and literature search results

Table 24: Summary of *in vivo* genotoxicity studies on N-Nitrosodi-n-propylamine (NDPA)

Species (test system)	Dose levels	Study endpoints	Results	References[1]
Rat (liver)	Intraperitoneal injection of 133 mg/kg	DNA alkylation	**Positive**	Park et al. 1980
Rat (hepatocytes)	Single oral doses of 0.31 – 25 mg/kg	DNA fragmentation	**Positive**	Brambilla et al. 1981, 1987a
Mouse (liver and renal epithelial cells)	Not specified in ATSDR report	Suppressed DNA synthesis	**Positive**	Amlacher and Rudolph 1981
Mouse (bone marrow)	Intraperitoneal injection of 172 mg/kg	Sister chromatid exchange	**Positive**	Parodi et al. 1983
Rat (hepatocytes)	Oral gavage doses of 10 – 40 mg/kg for 14 days	Micronucleus assay	**Positive**	Hamada et al. 2015
Rat (bone marrow)	Oral gavage doses of 10 – 40 mg/kg for 14 days	Micronucleus assay	Negative	Hamada et al. 2015
Mouse (bone marrow)	Intraperitoneal injections of 50 –	Micronucleus assay	Negative	Morita et al. 1997

Species (test system)	Dose levels	Study endpoints	Results	References[1]
	400 mg/kg			
Mouse (peripheral blood)	Intraperitoneal injection of 250 mg/kg	Micronucleus assay	Negative	Suzuki et al. 1999

[1] Source: ATSDR. 2019. Toxicological Profile for Nitrosodi-n-propylamine

Table 25: Summary of *in vivo* genotoxicity studies on N-Nitrosodiethanolamine (NDELA)

Species (test system)	Dose levels	Study endpoints	Results	References[1]
Mouse (liver; females)	Intraperitoneal injection of 60.4 mg/kg	Gene mutation	**Positive**	Kerklaan et al. 1981
Mouse (liver; males)	Subcutaneous injection of 750 mg/kg	Gene mutation	**Positive**	Knasmüller et al. 1986
Mouse (liver and spleen)	Intraperitoneal injection of 30 mg/kg	Gene mutation	**Positive**	Knasmüller et al. 1986
Mouse (liver, lung and kidney)	Single oral dose of 600 mg/kg	Gene mutation	**Positive**	Knasmüller et al. 1986
Rat (liver)	Single oral dose of 50.3 mg/kg	DNA single-strand breaks	**Positive**	Denkel et al. 1986
Rat (liver)	Single oral dose of 100 mg/kg	DNA single-strand breaks	**Positive**	Sterzel & Eisenbrand. 1986
Rat (liver)	Single oral dose of 1.03 mg/kg	DNA strand breaks	**Positive**	Brambilla et al. 1987
Rat (hepatocytes)	Single oral dose of 1000 mg/kg	Unscheduled DNA synthesis	Negative	Mirsalis et al. 1989
Mouse (hepatocytes)	Single oral dose of 600 mg/kg	Unscheduled DNA synthesis	Negative	Mirsalis et al. 1989
Mouse	Intraperitoneal injection of 10,000 mg/kg	Micronucleus assay	Negative	Gilbert et al. 1981
Mouse	Intraperitoneal injection of 10,000 mg/kg	Chromosome aberrations	Negative	Gilbert et al. 1981

[1] Source: IARC monograph. 2000. N-Nitrosodiethanolamine

7.6.3 *In vitro* data

The genotoxicity of nitrosamines has been investigated *in vitro*, in assays testing for gene mutations, chromosomal aberrations, induction of micronuclei, sister chromatid exchange, DNA damage, DNA methylation, DNA repair synthesis and DNA synthesis assays. Relevant studies with NDMA, NDEA, NDPA and NDELA are summarised in Table 26, Table 27, Table 28 and Table 29.

Table 26: Summary of *in vitro* genotoxicity studies on NDMA

Species (test system)	Dose levels	Study endpoints	Results		References[1]
			With metabolic activation	Without metabolic activation	
Salmonella typhimurium (strains not	Not specified in the ATSDR report	Gene mutation	**Positive**	Not tested or negative	Araki et al. 1984; Bartsch et al. 1980; De Flora et al.

Species (test system)	Dose levels	Study endpoints	Results		References[1]
			With metabolic activation	Without metabolic activation	
specified in the ATSDR report)					1984; Ishidate and Yoshikawa 1980; Langenbach et al. 1986; Prival and Mitchell 1981; Surh et al. 1995; Wagner et al. 2014; Wang et al. 2017
Escherichia coli		Gene mutation	**Positive**	Not tested	Araki et al. 1984; De Flora et al. 1984; Jiao et al. 1993
Saccharomyces cerevisiae		Gene mutation	**Positive**	Not tested	Frezza et al. 1983; Jagannath et al. 1981
Human lymphoblastoid (AHH-1, MCL-5, MCL-1) cells		Gene mutation	NA	**Positive**	Davies et al. 1989; Dobo et al. 1997, 1998
Chinese hamster V79 and ovary cells		Gene mutation	**Positive**	Negative	Adair and Carver 1983; Bartsch et al. 1980; Carver et al. 1981; Dickins et al. 1985; Hsie et al. 1978; Katoh et al. 1982; Kuroki et al. 1977; Langenbach 1986; Lawson and Kolar 1992; O'Neill et al. 1982; Swedmark et al. 1994
Mouse lymphoma L578Y cells		Gene mutation	**Positive**	Negative	Amacher and Paillet 1983; Clive et al. 1979
Rat hepatocyte (NRL cl-B, NRL cl-C, and ARL) cell lines		Chromosomal aberrations	Not tested	**Positive**	Kulka et al. 1993
Chinese hamster lung, ovary, or V79 fibroblast cells		Chromosomal aberrations	**Positive**	Not tested or negative	Bean et al. 1994; Ishidate and Yoshikawa 1980; Johnson et al. 1996; Kulka et al. 1993; Matsuoka et al. 1979, 1986;

Species (test system)	Dose levels	Study endpoints	Results		References[1]
			With metabolic activation	Without metabolic activation	
					Matsushima et al. 1999
Human fibroblast (L136) cells		Chromosomal aberrations	**Positive**	Not tested	Bean et al. 1994
Rat ascites hepatoma (AH66B) and rat Oesophageal (R1, R3) tumour cells		Chromosomal aberrations	Not tested	**Positive**	Ikeuchi and Sasaki 1981
Human lymphoblastoid (MCL5) cells		Micronucleus assay	Not tested	**Positive**	Crofton-Sleigh et al. 1993
Human peripheral blood lymphocytes		Micronucleus assay	Negative	Not tested	Katic et al. 2010
Human lymphoblasts (TK6) and peripheral blood lymphocytes		Micronucleus assay	Not tested	Negative	Liviac et al. 2011
Human hepatoma (HepG2) cells		Micronucleus assay	Not tested	**Positive**	Valentin-Severin et al. 2003
Rat hepatoma (H4IIEC3) cells		Micronucleus assay	Not tested	Negative	Roscher and Wiebel 1989
Mouse embryo fibroblast (NIH3T3) cells		Micronucleus assay	NA	Negative	Wang et al. 2017
Chinese hamster lung cells		Micronucleus assay	**Positive**	Not tested	Matsushima et al. 1999
Primary rat hepatocytes		Sister chromatid exchange	Not tested	**Positive**	Eckl et al. 1987
Rat hepatocyte (NRL cl-B, NRL cl-C, and ARL) cell lines		Sister chromatid exchange	Not tested	**Positive**	Kulka et al. 1993
Rat oesophageal tumor, ascites hepatoma		Sister chromatid exchange	Not tested	**Positive**	Abe and Sasaki 1982; Ikeuchi and Sasaki 1981
Human lymphocytes		Sister chromatid exchange	**Positive**	Negative	Inoue et al. 1983; Madle et al. 1987
Human fibroblasts		Sister chromatid exchange	**Positive**	Not tested	Tomkins et at. 1982
Chinese hamster ovary cells		Sister chromatid exchange	**Positive**	Not tested	Blazak et al. 1985; Johnson et al. 1996;

Species (test system)	Dose levels	Study endpoints	Results		References[1]
			With metabolic activation	Without metabolic activation	
					Okinaka et al. 1981; Tomkins et al. 1982
Chinese hamster V79 fibroblast cells		Sister chromatid exchange	**Positive**	Negative	Blazak et al. 1985; Kulka et al. 1993; Madle et al. 1987; Sirianni and Huang 1987
Chinese hamster primary lung cells		Sister chromatid exchange	**Positive**	Negative	Shimizu et al. 1984
Rat hepatocytes		DNA damage	Not tested	**Positive**	Bermudez et al. 1982; Bradley et al. 1982; Martelli et al. 1988; Pool et al. 1988; Singh and Roscher 1991
Rat hepatoma (H4IIEC3) cells		DNA damage	Not tested	**Positive**	Singh and Roscher 1991
Human hepatocytes		DNA damage	Not tested	**Positive**	Martelli et al. 1985, 1988
Human hepatoma (HepG2, HepaRG) cells		DNA damage	Not tested	**Positive**	Erkekoglu and Baydar 2010; Le Hegarat et al. 2010; Uhl et al. 1999; Valentin-Severin et al. 2003
Human lung or kidney cells		DNA damage	Not tested	**Positive**	Robbiano et al. 2006
Rat lung or kidney cells		DNA damage	Not tested	**Positive**	Robbiano et al. 2006
Rat kidney cells		DNA damage	Not tested	Negative	Brendler et al. 1992
Human lymphoblasts (TK6)		DNA damage	Negative	**Positive**	Liviac et al. 2011
Human hepatoma (HepG2) cells		DNA damage	Not tested	**Positive**	Valentin-Severin et al. 2003
Chinese hamster ovary cells		DNA damage	**Positive**	Negative	Wagner et al. 2014
Mouse splenocytes		DNA damage	**Positive**	Negative	Kim et al. 1989
Mouse embryo fibroblast (NIH3T3) cells		DNA damage	NA	Negative	Wang et al. 2017
Rat		DNA methylation/	Not tested	**Positive**	Lachapelle et al.

Species (test system)	Dose levels	Study endpoints	Results		References[1]
			With metabolic activation	Without metabolic activation	
hepatocytes		adducts			1994; Lachapelle et al. 1992
Rat hepatocytes		DNA repair synthesis	Not tested	**Positive**	Andrae and Schwarz 1981; Rossberger et al. 1987
Rat hepatoma (H4IIEC3) cells		DNA repair synthesis	Not tested	**Positive**	Rossberger et al. 1987
Human hepatocytes		DNA repair synthesis	Not tested	**Positive**	Martelli et al. 1988
Rat hepatocytes		Unscheduled DNA synthesis	Not tested	**Positive**	Martelli et al. 1988; Shaddock et al. 1993
Human lymphoblasts		Unscheduled DNA synthesis	**Positive**	Not tested	Andrae et al. 1979
Mouse hepatocytes		Unscheduled DNA synthesis	Not tested	**Positive**	McQueen et al. 1983
Hamster hepatocytes		Unscheduled DNA synthesis	Not tested	**Positive**	McQueen et al. 1983
Rat pancreatic cells		Unscheduled DNA synthesis	Not tested	Negative	Steinmetz and Mirsatis. 1984

[1] Source: ATSDR. 2022. Toxicological Profile for N-Nitrosodimethylamine (NDMA)

Table 27: Summary of *in vitro* genotoxicity studies on NDEA

Species (test system)	Dose levels	Study endpoints	Results		References[1]
			With metabolic activation	Without metabolic activation	
Salmonella typhimurium (strains not specified in IARC monograph)	Not specified in the IARC monograph	Gene mutation	**Positive**	Not reported	Bartsch et al. 1976; Bartsch et al. 1975; Malling. 1974; Sugimura et al. 1976
Salmonella typhimurium	0.52–25.5 µg/plate	Gene mutation	**Positive**	Negative	Aiub et al. 2003
Salmonella typhimurium	Not specified in abstract	Gene mutation	**Positive**	Not reported	El Torkey et al. 1983
Escherichia coli	Not specified in IARC monograph	Gene mutation	**Positive**	Not reported	Nakajima et al. 1974
Escherichia coli	Not specified in IARC monograph	Gene mutation	Negative	Not reported	Nakajima et al. 1974
Saccharomyces cerevisiae	Not specified in IARC monograph	Gene mutation	**Positive**	Negative	Brusick et al. 1974; Mayer. 1971

Species (test system)	Dose levels	Study endpoints	Results		References[1]
			With metabolic activation	Without metabolic activation	
Saccharomyces cerevisiae	Not specified in IARC monograph	Gene mutation	Not reported	Negative	Marquardt et al. 1964
Mouse lymphoma	Not specified in abstract	Gene mutation	Not specified in abstract	Not specified in abstract	Clive et al. 1979*
Chinese Hamster V79 cells	10, 50, 100 and 500 g/ml	Gene mutation	**Positive**	Not specified in abstract	Katoh et al. 1982*
Chinese Hamster V79 cells	50 mM	Gene mutation	**Positive**	Negative	Kuroki et al. 1977
Chinese hamster lung fibroblast cells	Up to 1000 µg/mL	Chromosome aberration	**Positive**	Negative	Lee and Lee. 1998*
Chinese hamster ovary cells	Not specified in abstract	Chromosome aberration	**Positive**	Not specified in abstract	Natarajan et al. 1976*
Human lymphoblasts (TK6)	0.05, 0.1, 1, 5 and 10 mM	Micronucleus assay	Not tested	Negative	Liviac et al. 2011
Chinese hamster ovary cells	Not specified in abstract	Sister chromatid exchange	**Positive**	Not specified in abstract	Natarajan et al. 1976*
Mouse hepatocytes	0.0001, 0.001 and 0.01 M	Unscheduled DNA synthesis	Not tested	**Positive**	Klaunig et al. 1984
Human lymphoblasts (TK6)	0.05, 0.1, 1, 5 and 10 mM	DNA damage	**Positive**	Negative	Liviac et al. 2011

* Abstract reviewed only – paper not obtained
[1]Source: IARC, 1976

Table 28: Summary of *in vitro* genotoxicity studies on NDPA

Species (test system)	Dose levels	Study endpoints	Results		References[1]
			With metabolic activation	Without metabolic activation	
Salmonella typhimurium (strains not specified in ATSDR report)	Not specified in the ATSDR report	Gene mutation	**Positive**	Negative	Araki et al. 1984; Bartsch et al. 1976, 1980; Dahl 1985; Guttenplan and Hu 1984; Guttenplan 1987; McMahon et al. 1979; Moore et al. 1985; Phillipson and Ioannides 1985; Probst et al. 1981; Rao et al. 1979; Rao et al. 1982; Yahagi et al. 1977

Species (test system)	Dose levels	Study endpoints	Results		References[1]
			With metabolic activation	Without metabolic activation	
Escherichia coli		Gene mutation	**Positive**	Negative	Araki et al. 1984; McMahon et al. 1979; Nakajima et al. 1974; Rao et al. 1981, 1982
Mouse lymphoma L5178Y cells		Gene mutation	**Positive**	Negative	Amacher et al. 1979; Amacher and Paillet 1982, 1983
Chinese hamster V9 cells		Gene mutation	**Positive**	Negative	Bartsch et al. 1980; Jones and Huberman 1980; Kuroki et al. 1977; Langenbach 1986
Human hepatocytes		DNA fragmentation	**Positive**	NA	Brambilla et al. 1987b; Knasmüller et al. 1998; Martelli et al. 1988
Human kidney cells		DNA fragmentation	**Positive**	NA	Robbiano et al. 1996
Rat hepatocytes		DNA fragmentation	**Positive**	NA	Bradley and Dysart 1981a, 1981b; Bradly et al. 1982; Parodi et al. 1982; Martelli et al. 1988
Rat kidney cells		DNA fragmentation	**Positive**	NA	Robbiano et al. 1996
Rat hepatocytes		DNA Repair	**Positive**	NA	Yamazaki et al. 1985
Human hepatocytes		Unscheduled DNA synthesis	**Positive**	NA	Martelli et al. 1988
Rat hepatocytes		Unscheduled DNA synthesis	**Positive**	NA	Martelli et al. 1988; Probst et al. 1981; Shu and Hollenberg 1996
HeLa cells		Unscheduled DNA synthesis	**Positive**	Negative	Martin et al. 1978
Chinese hamster fibroblasts		Chromosome aberrations	**Positive**	Negative	Kaneko et el. 1978
Chinese hamster lung cells		Chromosome aberrations	**Positive**	Negative	Matsuoka et al. 1979

[1] Source: ATSDR. 2019. Toxicological Profile for Nitrosodi-n-propylamine

Table 29: Summary of *in vitro* genotoxicity studies on NDELA

Species (test system)	Dose levels	Study endpoints	Results		References[1]
			With metabolic activation	Without metabolic activation	
Salmonella typhimurium (TA98, TA100, TA1530, TA1538)	Up to 10,000 µg/plate	Gene mutation	Negative	Negative	Gilbert et al. 1979; Gilbert et al. 1981; Lijinsky & Andrews 1983; Eisenbrand

Species (test system)	Dose levels	Study endpoints	Results		References[1]
			With metabolic activation	Without metabolic activation	
					et al. 1984
Salmonella typhimurium (TA100)	Up to 20,000 µg/plate	Gene mutation	**Positive**	**Positive**	Hesbert et al. 1979; Mori et al. 1987
Salmonella typhimurium (TA98, TA100, TA1535)	Up to 13,400 µg/plate	Gene mutation	**Positive**	Negative	Prival et al. 1982; Eisenbrand et al. 1984; Dahl 1985
Escherichia coli	Up to 20,000 µg/mL	Gene mutation	Negative	Not reported	Kerklaan et al. 1981
Escherichia coli	Up to 2680 µg/mL	Gene mutation	**Positive**	Negative	Knasmüller et al. 1986
Rat hepatocytes	Up to 3350 µg/mL	DNA single-strand breaks	Not tested	**Positive**	Denkel et al. 1986; Pool et al. 1990
Hamster hepatocytes	Up to 1675 µg/mL	DNA single-strand breaks	Not tested	**Positive**	Pool et al. 1990
Pig hepatocytes	Up to 1675 µg/mL	DNA single-strand breaks	Not tested	**Positive**	Pool et al. 1990
Human lymphoblastoid cell line	Up to 40,240 µg/mL	DNA single-strand breaks	Not tested	Negative	Scherer et al. 1991
Rat kidney cells	Up to 6700 µg/mL	DNA single-strand breaks	Not tested	Negative	Robbiano et al. 1996; Brendler et al. 1992
Human kidney cells	Up to 6700 µg/mL	DNA single-strand breaks	Not tested	Negative	Robbiano et al. 1996; Brendler et al. 1992
Human digestive tract cells	Up to 6700 µg/mL	DNA single-strand breaks	Not tested	**Positive**	Harréus et al. 1999
Chinese hamster embryo cells	Up to 1340 µg/mL	DNA amplification	Not tested	Negative	Denkel et al. 1986
Human lymphocytes	Up to 3570 µg/mL	Sister chromatid exchange	Not tested	**Positive**	Dittberner et al. 1988
Human lymphocytes	Up to 1675 µg/tube	Sister chromatid exchange	**Positive**	Not tested	Henn et al. 1989
Human lymphocytes	Up to 13,800 µg/mL	Chromosome aberrations	Not tested	**Positive**	Dittberner et al. 1988
Human lymphocytes	Up to 8380 µg/tube	Chromosome aberrations	Negative	Not tested	Henn et al. 1989
Human lymphocytes	Up to 8770 µg/mL	Micronucleus assay	Not tested	**Positive**	Dittberner et al. 1988

[1] Source: IARC monograph. 2000. N-Nitrosodiethanolamine

7.6.4 Summary

One human study showed an association between reduced telomere length in peripheral blood DNA and inhalation exposure to total of eight nitrosamines in rubber workers. Several measured variables (such as age, working time, TTCA, nitrosamine and p-toluidine exposures) were all associated with telomere length, but the association between telomere length and nitrosamines in air remained statistically significant in the multivariate analysis.

Mutagenic activity was observed in a large number of *in vivo gene* mutation assays in rats and mice (including transgenic models), in a large number of tissues (liver, lung, kidney, spleen and intestine) and dose/exposure routes/durations, with GC>AT transitions being the main

mutational class. *In vivo* genotoxicity was unequivocally demonstrated in the liver of rodents which is in concordance with the liver being the primary target of e.g. NDMA carcinogenesis. Predominantly positive results were also elicited in *in vitro* gene mutation assays, with a trend towards positive results with metabolic activation for all four substances. Positive results were also observed in studies assessing chromosomal aberrations, induction of micronuclei and sister chromatid exchange, and DNA damage assays, both *in vitro* and *in vivo,* for all four substances. These results indicate that nitrosamines are genotoxic, in the presence of metabolic activation. The critical DNA adducts formed upon bioactivation, the relevant repair mechanisms and mutagenic events are described in section 8.1.

7.7 Carcinogenicity

IARC (1987) concluded that the following nitrosamines are:

- probably carcinogenic to humans (Group 2A): NDEA, NDMA based on inadequate evidence in humans and sufficient evidence in animal studies;
- possibly carcinogenic to humans (Group 2B): NDPA, NDELA, NPip, NSAR, NMor, NMEA, NEBA based on inadequate evidence in humans and sufficient evidence in animal studies;
- not classifiable as to their carcinogenicity to humans (Group 3): NDPhA based on inadequate evidence in humans and limited evidence in animal studies.

7.7.1 Human data

Epidemiologic studies of cancer in humans focused on three main routes of exposure:

- Inhalation exposure in workers
- Dietary intake
- Consumption of contaminated drugs

7.7.1.1 Inhalation exposure in workers

Studies in occupationally exposed population were generally on two groups of workers:

- Workers exposed to metalworking fluids (MWF)
- Rubber industry workers

These studies are further described in Table 40 of Appendix 1 and are only briefly summarised below.

7.7.1.1.1 Workers exposed to metalworking fluids

Among five identified studies in workers exposed to MWF, only one (Sullivan et al. 1988) assessed exposure to nitrosamines (cumulative exposure duration in years) (described in detail in Appendix 1). The majority of studies, however, presumed exposure to NDELA from MWF containing ethanolamines and sodium nitrite, but did not quantify it.

- Sullivan et al. (1988) examined oesophageal mortality in a nested case-control study of oesophageal cancer deaths among 46384 US automobile manufacturing workers potentially exposed to MWF in machining and grinding operations. After exclusion of subjects with incomplete job history, the final study population consisted of 53 cases and 971 controls. Cumulative exposure duration (years) to nitrosamines was assessed. 15% of cases/ controls were ever exposed to nitrosamines, with a mean lifetime exposure of 5.7 years both in cases and in controls. The authors found a significant association with oesophageal cancer ("more than zero years vs zero years", OR=5.4, 95%CI=1.5-19.9). Whereas the study matched cases and controls (by race, gender, plant and year of birth) and adjusted for time since hire, it did not adjust for potential confounding by lifestyle factors (e.g. smoking) or concurrent exposures prevalent in automobile manufacturing workers. It should be noted that workers were co-exposed to MWF, metals (steel, iron, aluminium), sulphur, biocides, asbestos and solvents.
- Other studies (Jarvholm et al., 1986; Park et al., 1988; Park et al., 1996; Bardin et al., 2005) examined cause-specific cancer mortality with Standardized Mortality Ratios (SMR) or

Proportionate Mortality Ratios (PMR). Significant excess risks were found for rectal and skin cancers (Park et al., 1988). Prolonged activities of camshaft and crankshaft grinding (subject to high NDELA exposure) were associated with significant increases in pancreatic, lung and bladder cancers (Park et al., 1996).

7.7.1.1.2 Rubber industry workers

Six studies were identified in rubber industry workers, among them three studies assessed exposure to nitrosamines and examined cancer-specific mortality (described in Appendix 1).
High exposure to total nitrosamines was associated with significantly increased risks of mortality from non-Hodgkin lymphoma, lung, brain and oesophageal cancer (Hidajat et al., 2019; Straif et al., 2000).

(Hidajat et al., 2019) observed that:
- High exposure to NMor was associated with significantly increased mortality from multiple myeloma, stomach, prostate and pancreatic cancers;
- High exposure to NDMA yielded significantly increased risks from leukemia, multiple myeloma, bladder, stomach, prostate and liver cancers;

Hidajat et al., 2019 adjusted their analysis for birth year and exposure to rubber fumes and rubber dust, but not for potential confounding by any life-style factors. Fritschi et al., 2015 found a non-significant decrease in risk of dying from pancreatic cancer in workers highly exposed to total nitrosamines (>2 mg/m^3), after adjusting for age, sex and smoking.

In their analysis (Hidajat et al., 2019) described risk patterns as either absence of exposure-response, or linear (in log-space) exposure-response (increasing risk in quartiles 1–4), plateauing exposure-response (increasing risk in quartiles 1–3, but plateau or reduction in quartile 4), and increased risk without an exposure-response pattern.
Bladder cancer mortality (n=417) showed a linear exposure-response relationship for NDMA (SHR (sub-distribution hazard ratio) up to 2.82 (quartile 4) and NMor (SHR up to 2.59 (quartile 4), plateauing exposure-response for total nitrosamines (SHR up to 2.19 (quartile 3)).
For lung cancer mortality (n=3377), increased risks were found for NDMA exposure (SHR up to 1.70 (quartile 4)). Plateauing exposure-response was observed for total nitrosamines (SHR up to 1.60 (quartile 3)) and NMor (SHR 1.19 (quartile 2 and quartile 3)).
For stomach cancer mortality (n=768), a linear exposure-response relationship was found for exposures to NDMA (SHR up to 1.72 (quartile 4)) and NMor (SHR up to 1.49 (quartile 4)). Increased risks were observed for total nitrosamines (SHR up to 1.78 (quartile 3)).
A linear exposure-response association was found for leukaemia mortality (n=195) and NDMA exposures (p for trend <0.001) (SHR up to 3.47 (quartile 4)). Plateauing exposure-response were found for total nitrosamines (SHRs up to 3.08 (quartile 3)). Increased risks were found for NMor (SHRs up to 1.96 (quartile 4)).
A linear exposure-response relationship was found for multiple myeloma mortality (n=462) with exposures to NDMA (SHR up to 2.81 (quartile 4), p for linear trend <0.01) and NMor (SHR up to 1.82 (quartile 4), p for linear trend <0.01). Plateauing exposure-response was found for total nitrosamines (SHR up to 2.35 (quartile 3), p=0.02 for trend).
Increased risks for non-Hodgkin's lymphoma mortality (n=141) were observed for total nitrosamines (SHR up to 2.24 (quartile 3)), NDMA (SHR up to 2.26 (quartile 4)) and NMor (SHR up to 1.58 (quartile 3)).
A linear exposure-response relationship for oesophageal cancer mortality (n=333) was found for NMor (SHR up to 2.25 (quartile 4), p<0.001 for trend).
Linear exposure-response relationships between prostate cancer mortality (n=885) and exposures to NDMA (SHR up to 5.36 (quartile 4)) and NMor (SHRs up to 2.71 (quartile 4)) were found. Plateauing exposure-response were found for total nitrosamines (SHRs up to 3.75 (quartile 3)).
Results for brain cancer mortality (n=106) showed plateauing exposure-response relationships for NMor (SHR up to 3.16 (quartile 3)), elevated SHR in quartile 3 for total nitrosamines (SHR 1.75) and NDMA (SHR 2.50).
A linear exposure-response relationship was found for pancreatic cancer mortality (n=328) and

NMor (SHR up to 1.96 (quartile 4)). Increased risks without a trend were found for NDMA (SHR up to 2.60 (quartile 4)) and total nitrosamines (SHR up to 2.20 (quartile 2)).
A linear exposure-response relationship between liver cancer mortality (n=122) and exposures to NDMA (SHR up to 2.86 (quartile 4)) were observed. Plateauing exposure-response was found for NMor exposure (SHR up to 1.91 (quartile 3)). Increased risks were found for total nitrosamines (SHRs up to 3.20 (quartile 3)).
Three other publications examined cancer mortality (Straif et al., 1999; Boniol et al., 2016) or incidence (Boniol et al., 2017) by comparing rubber workers with the general population. They found an increased mortality risk of salivary gland cancer (2 deaths, Standardised Mortality Ratio (SMR)=9.5, 95%CI=1.2-34) in rubber workers with presumed high exposure to nitrosamines (Straif et al., 1999), and significantly increased incidence (Standardised Incidence Ratio (SRR)) of leukemia (SRR=1.29, 95%CI=1.11-1.52), lymphatic and hematopoietic system (SRR=1.16, 95%CI=1.02-1.31), bladder (SRR=1.36, 95%CI=1.18-1.57) and larynx (SRR=1.46, 95%CI=1.1-1.94) cancers (Boniol et al., 2017).

7.7.1.2 Dietary intake

The epidemiological evidence on the association between dietary exposure to nitrosamines and the risk of cancer has been investigated in several observational epidemiological studies, recently reviewed in a scientific opinion of EFSA (EFSA, 2022).
Tables in Appendix 1 summarise the results of the available 8 cohort and 16 case-control studies (Appendix 1, Table 38 and

Table **39**), for different types of cancers and nitrosamines.

Based on 8 cohort and 13 case-control studies, NDMA was associated with significant increased risks of cancers of the digestive tract (i.e. oral cavity, oesophagus, stomach, colorectum, pancreas), as well as increased risk for glioma and lung cancer. A statistically significant trend in dose-response was reported for stomach cancer, glioma, liver, colorectum and lung in at least one study.
Based on a limited number of case-control studies, statistically significant risks were reported also for NPyr (glioma), NPip (glioma and liver), NDEA (pancreas) and NMAMBA (liver).
In most studies risk estimates are adjusted for the main potential confounding factors including, age, sex, smoking, BMI energy intake, and family history of cancer. Only a few studies were able to adjust for other potential confounders, e.g. *helicobacter pylori*.
Dietary exposure to nitrosamines was estimated based on food frequency questionnaire and food history questionnaire, and data extracted from literature and chemical occurrence databases. Several limitations have been acknowledged in the studies regarding the dietary exposure estimates. These include, for example, the limited availability of occurrence data in some food items, the variation of levels found in similar items across countries, and the decreasing occurrence levels over calendar years due to risk management measures or changes in processing practices.
In conclusion, the available epidemiological evidence supports the association between dietary exposure to nitrosamines and cancer.
However, due to the exposure estimation limitations mentioned these studies do not provide a robust database for quantitative derivation of an exposure risk relationship.

7.7.1.3 Consumption of contaminated drugs

Recently, nitrosamines (more specifically NDMA) were detected as impurities in various medicines. According to the European Medicines Agency (EMA, 2020), the concentration was generally low.
Epidemiologic studies assumed Ranitidine or Valsatran contamination with NDMA:

- Ranitidine: Adami et al., 2021; Cardwell et al., 2021; Yoon et al., 2021; Kim et al., 2021.
- Valsatran: Pottegard et al., 2018; Gomm et al., 2021.

However, none of the studies quantitatively assessed NDMA exposure and conducted dose-response analyses.
Adami et al., 2021 conducted a retrospective cohort study within the Danish Prescription Registry and compared the risk of cancer (oesophageal, stomach, liver, pancreatic cancer) among first

users of histamine-2 receptor blockers (H2RBs). Ranitidine and users of proton pump inhibitors (PPIs) or others H2RBs. No association was observed between use of Ranitidine and cancer types, except for oesophageal adenocarcinoma (Ranitidine versus others H2RBs, HR=1.30, 95% CI=1.01-1.68; Ranitidine versus PPIs, HR:1.27, 95% CI: 1.04-1.56). However, when the analysis was restricted to those with at least 10 prescriptions and 10 years of follow-up no association was found.
Cardwell et al., 2021 conducted a nested case-control study within the Scottish Primary Care Clinical Informatics Unit Research database and an increased risk of bladder cancer was found among Ranitidine users, compared to no users (OR=1.22;95% CI=1.06–1.40; p-trend=0.005).
Yoon et al., 2021 conducted a cohort study using the Health Insurance Review and Assessment database in South Korea and found no association between use of ranitidine and overall cancer risk (HR=0.99, 95% CI=0.91–1.07, p-value=0.716).
Kim et al., 2021 conducted a study, using the Korean database IBM and found an inverse association between ranitidine use and risk of cancers of the oesophagus, stomach, liver, pancreas and colonrectum.
Pottegard et al., 2018 conducted a cohort study to investigate the association between the use of contaminated Valsartan products with NDMA and risk of cancer and found no increased risk for overall cancer (HR=1.09, 95% CI=0.85-1.41) and cancer sub-types.
Gomm et al. 2021, in a large cohort study, found no association between exposure to NDMA-contaminated Valsartan and the overall risk of cancer (HR: 1.01; 95%CI:0.99-1.03). However, a statistically significant association between exposure to NDMA-contaminated Valsartan and hepatic cancer (HR=1.16; 95% CI=1.03-1.31) was observed.

7.7.2 Animal data

A large number of carcinogenicity studies have been reported for the four nitrosamines under the present European Commission request, involving a wide range of:

- species such as rodents (several rat, mouse and hamster strains, gerbil, guinea pig), primates (including Bush baby, Cynomolgus, Rhesus and other species) as well as dog and swine,
- routes of administration: inhalation, oral (gavage, drinking water and diet) and parenteral routes (predominantly subcutaneous injection but also intravenous and intraperitoneal),
- duration of exposure ranging from acute (≤14 days) to chronic (up to 3.5 years)

In these studies, significantly increased incidences of tumours were regularly induced in all species, even after single administrations and a subsequent latent period of several days but, also, over medium and long-term repeated administrations with a wide range of exposure levels. The occurrence of liver tumours was most prevalent across all species with tumours of the gastro-intestinal tract also frequently seen in rats and occasionally hamsters. Tumours of the respiratory tract, including the nasal cavity, were frequently reported in mice and hamsters even via parenteral administration of the substances. Other organ systems and tissues were also occasionally affected e.g. kidneys, brain, testes, urinary tract, mammary glands and blood. There were multiple tumour types reported which were predominantly adenoma, papilloma and carcinoma.
The weight of evidence from the large data set of animal studies would indicate a strong tumorigenic potential for nitrosamines. The majority of the data summarised in the individual tables (Appendix 2; Table 41, Table 42, Table 43, Table 44) are taken from the following sources:

- Agency for Toxic Substances and Disease Registry (ATSDR) reports
- Lhasa Carcinogenicity Potency Database Reports extracted from the Lhasa Carcinogenicity Database (LCDB)[34] founded on the now retired Carcinogenic Potency Database (CPDB)[35]
- IARC Monographs

[34] Lhasa Limited. Carcinogenicity Database: https://carcdb.lhasalimited.org/
[35] Carcinogenic Potency Database: https://files.toxplanet.com/cpdb/index.html

The data from the IARC monographs dates from the 1970s and many of the studies cited in the other documents are pre-2000. Consequently, and do not often meet current design standards with regards to inclusion of appropriate control groups, dosage level/animal numbers information and statistical analysis. Discrepancies among studies cited in different reviews with regard to e.g. concentrations, have been noted. Where possible, study details have been corroborated between all sources and have been accurately presented in the summary of the studies in Appendix 2 (Table 41, Table 42, Table 43, and Table 44).

A recent analysis of rodent carcinogenicity data of a total of 228 nitrosamines, concluded that the majority of nitrosamines are carcinogenic with only 18% (41/228) considered non-carcinogenic. Further consideration of the LCDB entries, concluded that nitrosamine compounds in general are potent carcinogens, more-so than non-nitrosamines (Threser et al., 2020). Collectively, the weight of evidence for the carcinogenic potential of nitrosamines is compelling.

7.7.2.1 Carcinogenic potency ranking

The CPDB is a comprehensive source of animal carcinogenicity data, comprising 6540 chronic, long-term animal cancer studies of 1547 chemicals. Since 2016, Lhasa has adopted and consolidated the original data - supplementing with additional where available - in its repository of now 7745 long-term carcinogenicity studies covering 1727 chemicals. A key metric is the CPDB-calculated, TD_{50} value, defined as the daily lifetime dose (mg/kg body weight/day) for the induction of tumours in 50% of the test animals that would have remained tumour-free at zero dose, which serves as a numerical description and a standardised quantitative measure of carcinogenic potency. Lhasa-generated TD_{50} values –highly correlating to the CPDB-calculated TD_{50} values – have also been derived using a script based on the original methodology (Thresher et al, 2019; Note to Table 30). The LCDB contains a total of 137 nitrosamines, of which 117 were considered carcinogenic by the original study authors. Of these, 46 contain both Lhasa and CPDB TD_{50} values (Thresher et al, 2020).For the main N-nitrosamines addressed in this report, the TD_{50} values (harmonic means of all positive data across studies) calculated and extracted by the CPDB/ LCDB are presented, in descending order, in Table 30. More nitrosamine entries can be found in EMA, 2020. Additionally, the Lhasa TD_{50} values are included. A more extended set of species and site/organ-specific TD_{50} values from individual carcinogenicity studies of the four nitrosamines is presented in Table 45.

Table 30: TD_{50} values for the four main nitrosamines – NDMA, NDEA, NDPA, NDELA

Substance	TD_{50} (mg/kg/day) harmonic mean[1], rat (CPDB)	TD_{50}[2] (mg/kg/day), sensitive species (sex; tissue), key/relevant study	Lhasa TD_{50}[3], rat (LCDB)	Other species: TD_{50} (mg/kg/day; harmonic mean; CPDB)/Lhasa TD_{50}
NDEA	0.0265	0.05, rat (M/F; liver-all tumours), Peto et al 1991b; 0.026, rat (F; oesophagus-multiple tumour types, 30 weeks), Lijinsky et al 1981	0.0177	Bush baby: 0.0122/-; cynomolgus monkey 0.00725/0.229; rhesus monkey 0.0536/0.0026
NDMA	0.096	0.042 rat (F; liver-all tumours), Peto et al 1991b; 0.06, rat (F; liver), Lijinsky and Reuber, 1984	0.177	Mouse: 0.189/-
NDPA	0.186 (1 dose group)	0.186, rat (F; liver and nasal cavity carcinomas), Lijinsky and Reuber, 1983	-	Rhesus monkey: 0.0121/-
NDELA	3.17	1.9, rat (F; liver-multiple tumour types) Lijinski and Kovatch, 1985	3.38	-

Notes: [1] Taken from the respective substance-specific LCDB Summary report. The definition and formula for the derivation of the harmonic mean can be found here; Briefly, the harmonic mean is a summary measure of the most potent/lowest TD_{50} of all positive results for a chemical in each species, from experiments with varying animal strains, routes of administration, dose levels (including even one or two dose groups) and duration. If only one positive experiment is available, the harmonic mean of TD_{50} coincides with that of the most potent site; [2] Lowest, site-specific TD_{50} values from individual chronic carcinogenicity studies; [3] Taken from the LCDB Summary report. For the Lhasa TD_{50} calculation, only the terminal sacrifice tumour incidence (summary method) is considered. Not calculated for studies where no treatment-related tumourigenesis or dose-response relationship were observed or where only a single concentration of the test substance was used.

Based on the CPDB-calculated TD_{50} values (harmonic means), a carcinogenic potency ranking of the four nitrosamines evaluated in accordance with the present European Commission request, is: NDEA > NDMA > NDPA > NDELA.

A more extensive ranking (as reported in EMA, 2020 and EFSA, 2022 - with the respective TD_{50} values in mg/kg/day), including the above-mentioned nitrosamines and those identified as relevant to the occupational setting (see section 5.5, Table 16) is provided as:

NDEA (0.0265) > NMEA (0.0503) > **NDMA** (0.096) > NMoR (0.109) > NMPA (0.142) > **NDPA** (0.186) > NDBA (0.691)> NPyr (0.799)> NPip (1.1) > **NDELA** (3.17) > NDPhA (167).

It should be noted that for most of the nitrosamines in the latter ranking, TD_{50} calculations lack robustness and reliability since they are based on studies with few dose groups and different rodent strains. Especially for NDPA and NDBA, "*the TD_{50} has been calculated from studies with one or two dose groups only and therefore the reliability of the TD_{50} should be handled with caution*" (EMA, 2020).

To partly address these issues, LCDB additionally derived TD_{50} (Lhasa TD_{50}) by applying additional criteria (Note 3, Table 30), in which case the ranking as per the Lhasa TD_{50} values in mg/kg/day, calculated when possible, follows the order:

NDEA (0.0177) > NMPA (0.106) > NMOR (0.135) > **NDMA** (0.177) > NPip (1.12) > NPyr (2.02) NDPhA (167).

Preference should therefore be given to the more extensive rat carcinogenicity studies, with a sufficient number of animals and multiple dose groups (see Key studies below).

Blum et al. (2023) identified NDMA, NDEA, NMor, NPip and NPyr as having sufficient data for the derivation of OELs, employing the benchmark (BMD) approach (see section 9.2.1), ranking them as follows: **NDEA** = NPip > NPyr = **NDMA** = NMEA = **NDPA** > NMor > NDBA.
Note: due to the lack of adequate data sets, a read-across approach was applied to NMEA, NDPA and NDBA for the calculation of $BMDL_{10}$ values, with hepatocellular carcinoma as the critical endpoint.

Mirroring the Blum et al. (2023) evaluation of the quality of available studies, EFSA (2022) also concluded that no studies on NDBA or NMPA were suited for dose-response analyses. Well-documented dose-response studies with a negative control group, fit for BMD modelling, are available for NDMA, NDEA, NMor, NPip and NPyr. The derived $BMDL_{10}$ values for liver tumour incidence (in mg/kg/day) were **NDMA** (0.035), **NDEA** (0.010), NMor (0.014), NPip (0.062), and NPyr (0.127).
By any criterion, i.e. CPDB-TD_{50} values or $BMDL_{10}$, EFSA, 2022 concluded that "*NDEA, NMEA, NDMA and possibly NMor are in the group of highest concern*" with regard to carcinogenic potency.

Other ranking systems include the oral slope factor for carcinogenicity potency, as reported by the US Department of Agriculture (USDA, 2014, as reported in EMA, 2020) and they mirror the above ranking for selected Nitrosamines: **NDEA** > **NDMA** > NPip > NDBA > NPyr.

According to the California Office of Environmental Health Hazard Assessment (OEHHA) Toxicity Criteria Database, the current ranking of cancer slope factors (as per October 2020) is as follows: **NDEA** > NMEA > **NDMA** > NDBA > NPip > **NDPA** > NMor > NPyr > NDPhA (as cited in EFSA, 2022).
The carcinogenic potency, which resembles the mutagenic activity of the nitrosamines is impacted by the metabolic activation of nitrosamines and pertinent key steps/parameters such as α-hydroxylation, numbers of α-hydrogens, substitutions, steric hindrance), the formation and stability of the diazonium ions, and resulting DNA adducts. The above rankings reflect to a large extent the relative alkylation/hydrolysis rates of the alkyldiazonium ions upon the metabolic activation of nitrosamines (Manso et al, 2008). The capacity, velocity and fidelity of the repair of the DNA lesions can also determine the carcinogenic potential (see also section 8.1).

The Thresher et al, 2020 analysis of the CPDB/LCDB entries concluded that nitrosamines are potent carcinogens, exhibiting a wide range of responses, and a considerably lower mean log Lhasa TD_{50} value, than non-nitrosamines. NDEA was identified as the most potent nitrosamine for which carcinogenicity data is available, with the log Lhasa TD_{50} value for NDEA (-2.585) being considerably lower than the class mean (-0.433), with only NMPA displaying a similar value (-2.10).

Collectively, from the most common nitrosamines detected in the workplace (see section 5.5, Table 16), the primary attention with respect to risk by exposure should be paid to the most highly carcinogenic ones for which robust and reliable data from appropriately conducted studies are available. NDEA and NDMA, which form very similar DNA adducts and for which comprehensive chronic oral studies are available, consistently lead the potency rankings reported in different sources.

7.7.2.2 Key studies of the most potent nitrosamines: NDMA and NDEA

7.7.2.2.1 Inhalation studies: NDMA

Only a limited number of inhalation studies is available, for NDMA only, providing some evidence for carcinogenicity in mice and rats. The relevant chronic studies are summarised in Table 31.

Moiseev and Benemansky, 1975 reported that NDMA inhalation exposure of Wistar rats and BALB/c mice for 25 and 17 months, respectively, resulted in increased incidences in:

- liver, lung and kidney tumours at 0.07 ppm (0.2 mg/m^3), in either species.

In rats, tumour incidences in both the liver and lungs were 12/61 (19.7%) in the exposed animals as opposed to 3/77 (3.9%) and 5/77 (6/5%) in controls, respectively (as reported in ATSDR 2019). A stronger effect was observed in the kidneys with tumour incidences in the exposed group of 32/61 (52.5%) vs 2/77 (2.6%) in controls.
Mice exposed to the same dose of 0.07 ppm also developed lung (19/101 vs 3/81 in control), liver (6/101 vs 3/81) and kidney (4/101 vs 0/81) tumours.
Exposure to a lower dose of 0.002 ppm (=0.005 mg/m^3) did not produce significantly increased incidences in any tumour type, compared to controls, in either species (as reported in ATSDR 2019).

Klein et al. (1989, 1991) reported a long-term NDMA inhalation study in female rats (n=36/group) exposed intermittently (4 h/day, 5 days/wk, up to 30 weeks) to 0.04, 0.2 and 1 ppm NDMA (corresponding to 0.12, 0.6 and 3 mg/m^3). Median survival was significantly reduced in the high dose group. Inhalation exposure resulted in increased incidence in:

- Local nasal cavity tumours comprising esthioneuroblastomas, mucoepidermoid tumours, squamous cell carcinomas, and neurogenic and osteogenic sarcomas in all dose groups (≥ 0.04 ppm).

At the highest dose (1 ppm), esthesioneuroblastomas were the prevalent nasal tumour type affecting 47% (9/19) of exposed animals, whereas 6% and 15% of the animals presented this tumour type at 0.2 and 0.04 ppm. Mucoepidermoid tumours were the most prevalent at the lower doses. Squamous cell carcinomas occurred in two and one animals in the mid and high dose groups, respectively. These observations suggested that tumour occurrence and tumour type were dependent on the concentrations and/or the total amount of inhaled NDMA. The nose was the most sensitive target organ. Other sites included:

- Hepatic carcinogenic effects at 0.04 and 0.2 ppm groups; with one liver carcinoma and 2 or 1 adenomas observed in each of the low and mid dose group, and none in the high dose group.
- Lung cancer occurred in one animal in the 1 ppm group.

In an earlier, lifetime inhalation study, Druckrey et al, 1976, reported increased incidences of:

- Nasal tumours at ≥ 50 ppm; 67% of BD rats exposed to either 50 ppm (150 mg/m^3; n=12, tumours in 8/12 animals) or 100 ppm (300 mg/m^3; n=6, esthesioneuroblastoma and squamous cell carcinoma in 4/6 animals) (as reported in ATSDR, 2019).

No incidences for the control group were provided.

7.7.2.2.2 Oral studies: NDMA and NDEA

The carcinogenicity of orally-administered NDMA has been demonstrated in acute, intermediate and chronic duration studies in rats, mice, hamsters, the guinea-pig, rabbit and Rhesus monkey, with the liver, lungs, kidneys and testes identified as the main sites of tumorigenicity (Table 41).

In the most comprehensive chronic, oral study, inbred Colworth rats (n=60/sex/dose; control group n=240/sex) were exposed to NDMA and NDEA in drinking water, at increasing concentrations ranging from 0.033-16.896 ppm (estimated at 0.001–0.697 mg/kg bw/day in males and 0.002-1.224 mg/kg bw/day in females) (Peto et al, 1991a, 1991b) (Table 31). This was an unusual study in size (total n=4080 of animals exposed to both nitrosamines), dose range investigated (total of 15 dose groups) and duration; interim sacrifice of 10% of animals occurred in months 12 and 18, with the rest of the animals observed until natural death or the appearance of palpable liver abnormalities (up to 3.5 years). The aim of these studies was to derive dose-response relationships for tumour induction at the sites chiefly affected: liver by both agents and the oesophagus by NDEA only. The increased sensitivity of liver to the carcinogenic effects of either nitrosamine, is in concordance with the metabolic competence of this organ, and the mechanistic basis is the intrahepatic activation of nitrosamines to unstable intermediates which produce promutagenic DNA adducts (see section 8.1.5). Average survival times in the lower 7 dose groups (0.033 – 1.584 ppm v/v) and the control group was 33 months in males and 30 months in females. In both male and female rats, higher doses of NDMA were associated with decreased survival due to liver tumours. These included malignant hepatocellular, mesenchymal, and Kupffer cell tumours as well as mostly benign tumours of the bile ducts. Bile duct neoplasms were more readily induced by NDMA in females than males and outnumbered the liver cell tumours in the range of 0.05-0.5 mg/kg. The incidences of any liver tumour (summed across cell type and fatal/incidental) were statistically significantly increased at doses ≥0.022 mg/kg/day (0.528 ppm) (as reported in ATSDR, 2019). At low dose ranges (0.1-1 ppm and probably lower), an approximately linear relationship between dose and liver neoplasms was implied, with the excess risk of liver cancer appearing to be roughly proportional to nitrosamine concentration. A "suggestively positive trend" in the lung was also observed and considered "plausible" by the authors.

Table 31: Summary of key relevant carcinogenicity studies of NDMA and NDEA

Species	Exposure route/ period	Dose levels	Tumour sites-incidences (dose) - TD_{50} [1]	Key study Reference
NDMA				
Mouse (male/female; BALB/c; n=30-68)	**Inhalation** 17 months	mg/m³ (ppm) 0 0.005 (0.002) 0.2 (0.07)	**Lung:** 3/81 (0) 19/101 (0.2 mg/m³) **Liver:** 0/81 (0) 6/101 (0.2) **Kidney:** 0/81 (0) 4/101 (0.2)	Moiseev and Benemansky, 1975
Rat (BD; n=6-12)	**Inhalation** 2x/week for 30 mins, lifetime	mg/m³ (ppm) 0 150 (50) 300 (100)	**Nasal cavity tumours:** 8/12 (150 mg/m³) 4/6 (300)	Druckrey et al, 1967
Rat (male/female; Wistar; n=36-51)	Inhalation Daily 25 months	mg/m³ (ppm) 0 0.005 (0.002) 0.2 (0.07)	**Lung:** 5/77 (0) 12/61 (0.2 mg/m³) **Liver:** 3/77 (0) 12/61 (0.2) **Kidney:** 2/77 (0) 32/61 (0.2)	Moiseev and Benemansky, 1975
Rat (female; Sprague-Dawley; n=36)	Inhalation 4-5 hours/day, 4 days/week for up to 72 weeks	mg/m³ (ppm) 0 0.12 (0.04) 0.6 (0.2) 3 (1.0)	**Nasal cavity tumours:** 0/36 (0) 13/36 (0.12 mg/m³) 31/36 (0.6) 19/36 (3.0)	Klein et al, 1991
Rat (female; F344; n=20)	**Oral**; Drinking water; 5 days/week, 30 weeks (exposure), 110 weeks (experiment) n=20	mg/kg/day (mg/L) 0 0.75 (5.5) 1.8 (13) Total dose delivered 17 and 39 mg	**Liver: multiple tumours** 2/20 (0) 14/20 (0.75 mg/kg/day) 17/20 (1.8) TD_{50}=0.0587	Lijinsky W and Reuber MD, 1984
Rat (female; Colworth; n=60, n=240)	**Oral**; Drinking water; 176 weeks	mg/kg/day (ppm) 0 0.002 (0.033) 0.005 (0.066) 0.010 (0.132) 0.019 (0.264) 0.038 (0.528) 0.076 (1.056) 0.115 (1.584) 0.153 (2.112) 0.191 (2.640) 0.229 (3.168) 0.306 (4.224) 0.382 (5.280) 0.459 (6.336) 0.612 (8.448)	**Liver: hepatocellular tumours (liver cell)** 11/240 (0) 2/60 (0.002 mg/kg/day) 2/60 (0.005) 4/60 (0.010) 2/60 (0.019) 6/60 (0.038) 6/60 (0.076) 3/60 (0.115) 7/60 (0.153) 7/60 (0.191) 4/60 (0.229) 7/60 (0.306) 13/60 (0.382) 20/60 (0.459) 40/60 (0.612)	Peto R. et al, 1991b

Species	Exposure route/ period	Dose levels	Tumour sites-incidences (dose) - TD_{50} [1]	Key study Reference
		1.224 (16.896)	41/60 (1.224) TD_{50}=0.145 **Liver: intrahepatic bile duct** malignant/benign combined 4/240 (0) 1/60 (0.002) 4/60 (0.005) 1/60 (0.010) 4/60 (0.019) 4/60 (0.038) 9/60 (0.076) 39/60 (0.115) 33/66 (0.153) 44/60 (0.191) 48/60 (0.229) 46/60 (0.306) 44/60 (0.382) 38/60 (0.459) 10/60 (0.612) 1/60 (1.224) TD_{50}=0.0752 **All malignant liver cancers (fatal+incidental):** bile duct/Kupffer cell/liver cell/mesenchyme/other 4/240 (0) 1/60 (0.002) 0/60 (0.005) 2/60 (0.010) 2/60 (0.019) 7/60 (0.038) 6/60 (0.076) 2/60 (0.115) 10/60 (0.153) 5/60 (0.191) 7/60 (0.229) 10/60 (0.306) 14/60 (0.382) 22/60 (0.459) 47/60 (0.612) 57/60 (1.224)	
Rat (male; Colworth ; n=60, n=240)	**Oral**; Drinking water, 176 weeks	mg/kg/day (ppm) 0 0.001 (0.033) 0.003 (0.066) 0.005 (0.132) 0.011 (0.264) 0.022 (0.528) 0.044 (1.056) 0.065 (1.584) 0.087 (2.112) 0.109 (2.640) 0.131 (3.168) 0.174 (4.224) 0.218 (5.280) 0.261 (6.336) 0.348 (8.448)	**Liver: hepatocellular tumours (liver cell)** 10/40 (0) 4/60 (0.001 mg/kg/day) 3/60 (0.003) 2/60 (0.005) 4/60 (0.011) 4/60 (0.022) 5/60 (0.044) 8/60 (0.065) 7/60 (0.087) 13/60 (0.109) 14/60 (0.131) 19/60 (0.174) 27/60 (0.218) 32/60 (0.261) 44/60 (0.348)	Peto R. et al, 1991b

Species	Exposure route/ period	Dose levels	Tumour sites-incidences (dose) - TD_{50} [1]	Key study Reference
		0.697 (16.896)	46/60 (0.697) TD_{50}=0.157 **Liver: intrahepatic bile duct** malignant/benign combined 3/240 (0) 2/60 (0.001) 3/60 (0.003) 2/60 (0.005) 2/60 (0.011) 1/60 (0.022) 1/60 (0.044) 4/60 (0.065) 7/60 (0.087) 13/60 (0.109) 12/60 (0.131) 12/60 (0.174) 16/60 (0.218) 18/60 (0.261) 8/60 (0.348) 0/60 (0.697) TD_{50}=0.308 **All malignant liver cancers (fatal+incidental):** bile duct/Kupffer cell/liver cell/mesenchyme/other 4/240 (0) 1/60 (0.001) 3/60 (0.003) 2/60 (0.005) 2/60 (0.011) 3/60 (0.022) 8/60 (0.044) 6/60 (0.065) 12/60 (0.087) 23/60 (0.109) 25/60 (0.131) 29/60 (0.174) 32/60 (0.218) 39/60 (0.261) 48/60 (0.348) 59/60 (0.697)	
NDEA				
Rat (female; F344; n=12-20)	**Oral;** Drinking water, 5 days/week, 30 weeks	(mg/kg/day; total dose in mg/animal) 0 0.0044; 1.35 0.0104; 3.3 0.0264; 8.4 0.119; 21 0.538; 54	**Oesophagus: multiple tumour types (carcinoma and papilloma)** 0/20 (0) 0/20 (0.0044 mg/kg/day) 3/20 (0.0104) 18/19 (0.0264) 13/20 (0.119) 10/12 (0.538) TD_{50}=0.0255 **Upper gastrointestinal tract** (animals with at least one carcinoma or papilloma of the oesophagus, forestomach, or tongue) 0/20 (0)	Lijinsky et al, 1981

Species	Exposure route/ period	Dose levels	Tumour sites-incidences (dose) - TD_{50} [1]	Key study Reference
			2/20 (0.0044) 11/20 (0.0104) 18/19 (0.264) **Liver (hepatocellular carcinoma)** 0/20 (0) 1/20 (0.0044) 5/20 (0.0104) 5/19 (0.264) 1/20 (0.119) 1/12 (0.538) TD_{50} = none derived due to lack of dose-response	
Rat (female; F344; n=20)	**Oral;** Drinking water, 60 weeks	(mg/kg/day; total dose in mg/animal) 0 0.00848; 2.7 0.0207;6.6	**Oesophagus: multiple tumour types** 0/20 (0) 2/20 (0.00848 mg/kg/day) 17/20 (0.0207) TD_{50}=0.0207 **Liver: multiple tumour types; carcinomas only** 1/20; 0/20 (0) 14/20; 6/20 (0.00848) 5/20; 3/20 (0.0207) TD_{50} = 0.00787	Lijinsky et al, 1981
Rat (female; Colworth ; n=60, n=240)	Oral; Drinking water, 176 weeks	mg/kg/day 0 0.002 0.004 0.009 0.018 0.036 0.072 0.107 0.143 0.179 0.215 0.287 0.358 0.430 0.573 1.146	**Liver: hepatocellular tumours (liver cell)** 11/240 (0) 4/60 (0.002 mg/kg/day) 4/60 (0.004) 3/60 (0.009) 4/60 (0.018) 10/60 (0.036) 31/60 (0.072) 42/60 (0.107) 45/66 (0.143) 45/60 (0.179) 45/6 (0.215) 48/60 (0.287) 50/60 (0.358) 52/60 (0.430) 57/60 (0.573) 45/54 (1.146) TD_{50}=0.0615 **Liver: intrahepatic bile duct** malignant/benign combined 4/240 (0) 2/60 (0.002) 0/60 (0.004) 1/60 (0.009) 2/60 (0.018) 1/60 (0.036) 2/60 (0.072) 2/60 (0.107) 2/66 (0.143)	Peto R. et al, 1991b

Species	Exposure route/ period	Dose levels	Tumour sites-incidences (dose) - TD_{50} [1]	Key study Reference
			0/60 (0.179) 0/60 (0.215) 0/60 (0.287) 1/60 (0.358) 0/60 (0.430) 0/60 (0.573) 0/54 (1.146) TD_{50}=0.561 **All malignant liver cancers (fatal+incidental):** bile duct/Kupffer cell/liver cell/mesenchyme/other 4/240 (0) 0/60 (0.002) 2/60 (0.004) 1/60 (0.009) 4/60 (0.018) 4/60 (0.036) 24/60 (0.072) 39/60 (0.107) 37/66 (0.143) 46/60 (0.179) 44/60 (0.215) 47/60 (0.287) 49/60 (0.358) 50/60 (0.430) 56/60 (0.573) 49/54 (1.146) **Oesophagus: multiple tumour types (malignant+benign)** 0/240 (0) 0/60 (0.002) 0/60 (0.004) 0/60 (0.009) 0/60 (0.018) 3/60 (0.036) 19/60 (0.072) 21/60 (0.107) 32/66 (0.143) 29/60 (0.179) 42/60 (0.215) 37/60 (0.287) 44/60 (0.358) 41/60 (0.430) 36/60 (0.573) 26/54 (1.146) TD_{50}=0.203	
Rat (male; Colworth ; n=60, n=240)	Oral; Drinking water, 172 weeks	(mg/kg/day) 0 0.001 0.003 0.005 0.010 0.020 0.041 0.061 0.082	**Liver: hepatocellular tumours (liver cell)** 10/240 (0) 1/60 (0.001 mg/kg/day) 2/60 (0.003) 3/60 (0.005) 0/60 (0.010) 5/60 (0.020) 9/60 (0.041) 18/60 (0.061) 10/60 (0.082)	Peto R. et al, 1991b

Species	Exposure route/ period	Dose levels	Tumour sites-incidences (dose) - TD_{50} [1]	Key study Reference
		0.102 0.122 0.163 0.204 0.245 0.326 0.653	21/60 (0.102) 20/60 (0.122) 23/60 (0.163) 27/60 (0.204) 28/60 (0.245) 28/60 (0.326) 47/60 (0.653) TD_{50}=0.0924 **Liver: intrahepatic bile duct** malignant/benign combined 3/240 (0) 2/60 (0.001 mg/kg/day) 0/60 (0.003) 1/60 (0.005) 2/60 (0.010) 0/60 (0.020) 4/60 (0.041) 3/60 (0.061) 1/60 (0.082) 2/60 (0.102) 2/60 (0.122) 2/60 (0.163) 1/60 (0.204) 0/60 (0.245) 0/60 (0.326) 0/60 (0.653) TD_{50}=0.372 **All malignant liver cancers (fatal+incidental):** bile duct/Kupffer cell/liver cell/mesenchyme/other 4/240 (0) 1/60 (0.001 mg/kg/day) 0/60 (0.003) 6/60 (0.005) 2/60 (0.010) 7/60 (0.020) 9/60 (0.041) 21/60 (0.061) 11/60 (0.082) 20/60 (0.102) 25/60 (0.122) 28/60 (0.163) 28/60 (0.204) 35/60 (0.245) 30/60 (0.326) 48/60 (0.653 **Oesophagus: multiple tumour types (malignant+benign)** 0/240 (0) 0/60 (0.001 mg/kg/day) 0/60 (0.003) 0/60 (0.005) 0/60 (0.010) 3/60 (0.020) 16/60 (0.041) 32/60 (0.061)	

Species	Exposure route/ period	Dose levels	Tumour sites-incidences (dose) - TD_{50} [1]	Key study Reference
			37/60 (0.082) 45/60 (0.102) 48/60 (0.122) 41/60 (0.163) 49/60 (0.204) 46/60 (0.245) 47/60 (0.326) 46/60 (0.653) TD_{50}=0.0949	

[1] Where available, TD_{50} values (in mg/kg/day) are provided for individual studies and for each principal carcinogenic effect, as calculated and reported by the CPDB/LCDB

In the Peto et al (1991a, 1991b) study, the principal carcinogenic effects induced by NDEA were on the oesophagus and liver, with other "apparent" effects demonstrated only on the nasopharynx (Table 31). Similarly to NDMA, a linear relationship was implied between NDEA concentration and liver tumour induction at the low dose range, at which the incidence of liver neoplasms and associated tumour risk greatly exceeds that of oesophageal tumours. The NDEA effects on the liver (nearly all fatal NDEA-induced hepatomas were malignant liver cell hepatomas) were greater in females than males (more so than NDMA). In contrast to NDMA, very few bile duct neoplasms were induced by NDEA.

The pivotal Peto et al 1991a, 1991b study allows for a direct comparison between NDMA and NDEA. Although at doses of around 1 mg/kg, NDEA and NDMA appear equipotent (on a molar basis) with regards to hepatocellular tumour induction, at moderately low dose levels – 0.1 mg/kg - where effects are directly measurable, "*NDEA appears to be about 2-3 times as potent as NDMA*". The CPDB-calculated liver-specific TD_{50} values for this study were comparable, at 42 mg/kg/day for NDMA and 50 mg/kg/day for NDEA, while the harmonic mean TD_{50} from all positive rat studies in the CPDB database is 96 mg/kg/day and 26.5 mg/kg/day for NDMA and NDEA, respectively (Table 30).

The greater potency of NDEA over NDMA has been corroborated in other studies.
Lijinsky and Reuber, 1984 assessed mortality as a measure of carcinogenic potency of four nitrosomethylamines, including NDMA, given to female F344 rats (n=20) in drinking water, 5 days/wk for 30 wks, at concentrations of 5.5 and 13 mg/L NDMA ((total dose 17 and 39 mg; 0.2 and 0.5 mmol (Table 31)). NDMA induced a large incidence of liver tumours, with more than half of the exposed animals affected at the lower dose, with all tumours being hepatocellular carcinomas. At the higher dose, hemangiosarcomas took precedence over hepatocellular carcinomas.

NDEA had been assessed in an earlier study by Lijinsky et al, 1981.
When comparing mortality between the two studies, Lijinsky and Reuber, 1984 concluded that "*NDEA is considerably more effective as a carcinogen than is NDMA. At doses of NDEA approximately equimolar with … NDMA, the animals died much more rapidly with esophageal tumors and liver tumors than the latter (40 and 50 weeks, respectively)*". The principal NDEA-induced tumours identified in the Lijinsky et al, 1981 study were of the upper gastrointestinal tract, mainly the oesophagus, exhibiting a highly significant dose-related positive trend (Table 31). Even at the lowest NDEA concentration tested (0.45 mg/L; total dose of 4.7 mg/animal) for an extended time of 104 weeks (not shown in Table 31), this tumour type was induced in 70% of exposed animals, suggesting an increased sensitivity of these tissues to the carcinogenic effects of even small amounts of this substance.

Finally, NDMA, NDEA, NDPA, NDBA and NPip have shown transplacental carcinogenic effects in the offsprings of treated dams in several rat, mouse and hamster strains (EFSA, 2022).

7.7.3 Summary

Epidemiologic evidence indicates that inhalation and oral exposure to nitrosamines may be associated with the cancer risk of various types. The majority of these studies failed to provide exposure estimates of nitrosamines, estimate dose-response relationship and adjust for major confounding factors. A handful studies among rubber industry workers retrospectively assessed exposure to several nitrosamines using JEM and examined dose-response relationship by accounting for concurrent exposure to other nitrosamines.

A large number of animal studies in different species/routes of exposure/durations resulting in the induction of tumours in many different organs, have unequivocally established the carcinogenic potential of nitrosamines which are collectively considered as highly potent carcinogens. The application of relatively reliable metrics enables the ranking of a large number of nitrosamines, with NDMA and NDEA exhibiting the greatest carcinogenic potency. Reliable, comprehensive lifetime studies identified the liver and the oesophagus as the prime sites for NDMA/NDEA-related tumour induction in orally exposed rodents.

7.8 Reproductive toxicity

7.8.1 Human data

The effects of nitrosamines between maternal dietary intake and birth defects have been investigated in human studies (Torfs et al., 1998; Huber et al., 2013).

Torfs et al. (1998) examined an association between mothers' nutrient intake and their offspring's risk of gastroschisis (a congenital defect of the abdominal wall) in a US population-based case-control study of 55 cases of gastroschisis and 182 matched controls. After the case mother was interviewed, a control was selected to match the mother's age; both case and control mothers were interviewed within 3–6 months of the delivery of their offspring. Seven nutrients' groups were assessed in mothers, such as follows: carotenoids, amino-acid compounds, nitroso compounds (nitrate, nitrite, nitrosamine), vitamins, minerals and other nutrient variables. An appropriate threshold for defining a binary version of each nutrient has been found. The cut-point for high daily nitrosamine intake was > 0.21 mg. In multivariate analysis (adjusted for age and low intake of a-carotene ang total glutathione), high nitrosamine intake was a significant risk factor of gastroschisis (OR=3.4 (95% CI=1.7-6.9), p-value=0.001). Authors noted that aspirin/ibuprofen use also partially confounded high nitrosamine intake, suggesting that beer drinkers or drug users may have taken these medicines. Low socioeconomic status variables (e.g., family income, mother's education level, ethnicity) did not retain their effect or significance in the final multivariate model.

Huber et al. (2013) examined the relationship between maternal dietary intake of nitrates, nitrites (including plant and animal sources as separate groups), and nitrosamines and several types of birth defects in offspring in a population-based case-control study of 6544 mothers of infants with neural tube defects (NTD)s, oral clefts (OC)s, or limb deficiencies (LD)sand 6807 mothers of unaffected control infants. Daily consumption of nitrate (mg/day), nitrite (mg/day) and nitrosamines (µg/day) was assessed a 58-item food frequency questionnaire based on the Willett Food Frequency Questionnaire. Nitrosamine exposure has been classified into four categories (quartiles 1-4). Logistic regression was used to estimate odds ratio (OR; quartile 2 vs. quartile 1, quartile 3 vs. quartile 1, quartile 4 vs. quartile 1) Statistical models were adjusted for energy intake, maternal race/ethnicity, maternal education, dietary folate intake, dietary fat intake and study centre. No increase in risk of birth defects after Nitrosamine exposure was observed. However, a significant deficit in risk was identified between the second quartile of nitrosamines intake and cleft palate (OR = 0.78, 95% CI=0.64-0.95).

7.8.2 Animal data

7.8.2.1 Reproductive toxicity - sexual function and fertility

The effects of nitrosamines on sexual function and fertility have been investigated in rabbits and mice. No information was obtained for NDPA or NDELA. Details of the studies are shown in Table 32.

Table 32: Summary of studies on reproductive toxicity – sexual function and fertility

Method, route	Species, strain, sex, number group	Test material	Doses, duration of exposure	Results	References
Oral – drinking water	Mice	NDMA	75 days prior to mating 0.026 mg/kg/day	No significant effects on time-to-conception in mice	Anderson et al., 1978
Oral – gavage	Rabbits	NDMA	12 weeks 0.5 mg/kg/day	Decreased serum testosterone levels (81 and 96% less than controls at 8 and 12 weeks, respectively) Testicular histopathological lesions: disorganized seminiferous tubules, interstitial oedema, degeneration of germinal epithelium in seminiferous tubules and Sertoli cells, exfoliation of cells in lumen of tubules, blood vessel congestion, and proliferation of Leydig cells Increased testicular oxidative stress parameters	Sheweita et al., 2017
Oral – gavage	Rabbits	NDEA	12 weeks 0.5 mg/kg/day	Decreased serum testosterone levels (84 and 94% less than controls at 8 and 12 weeks, respectively) Testicular histopathological lesions: disorganized seminiferous tubules, interstitial oedema, degeneration of germinal epithelium in seminiferous tubules and Sertoli cells, exfoliation of cells in lumen of tubules, blood vessel congestion, and proliferation of Leydig cells Increased testicular oxidative stress parameters	Sheweita et al., 2017

Male NZW rabbits (5 group) were dosed with 0.5 mg/kg bw/day of NDEA or NDMA in drinking water for 12 weeks, and control animals received water only. The assessment of the oxidant status in the testes revealed significantly elevated levels of free radicals measured as TBARS, depleted GSH and 17β-HSD levels, which is the main catalyst for the last step of steroid synthesis and it is expressed only in the testes. Furthermore, a statistically significant decreased activity of antioxidant enzyme activities was measured (GST, SOD and CAT). Testosterone levels were decreased gradually in the plasma during the treatment, oestradiol levels increased after the

administration of NDMA and decreased with NDEA. Consequently, the authors postulated a role of these nitrosamine in rabbit infertility. Histopathology showed disorganization of seminiferous tubules, oedema in the interstitial tissue, degenerative changes in germinal epithelium lining seminiferous tubules and degeneration of sertoli cells accompanied by exfoliation of cells in lumen of seminiferous tubules (Sheweita et al., 2017).

7.8.2.2 Reproductive toxicity - developmental toxicity

The developmental toxicity of nitrosamines has been investigated in rats and mice in NDMA. Details of the studies are shown in Table 33, below.
No information was obtained for NDEA, NDPA or NDELA.

Table 33: Summary of studies on reproductive toxicity – developmental with NDMA

Method, route	Species, strain, sex, nber group	Doses, duration of exposure	Results	References
Oral – gavage	Rats	Acute exposure – single dose administered on various gestation days (1 – 15) 30 mg/kg	Increased foetal mortality	Aleksandrov, 1974; Napalkov and Alexandrov, 1968
Oral – diet	Rats	Administered in early pregnancy - 5 mg/kg/day	Increased foetal mortality	Bhattacharyya, 1965
Oral – gavage	Rats	Administered during the first or second week of pregnancy 2.9 mg/kg/day	Increased foetal mortality	Napalkov and Alexandrov, 1968
Oral – gavage	Rats	Administered through to gestation days 17 – 21 1.4 mg/kg/day	Increased foetal mortality	Napalkov and Alexandrov, 1968
Oral – gavage	Rats	Acute exposure – administered on gestation day 15 or 20 20 mg/kg	Decreased foetal body weights	Nishie, 1983
Oral – drinking water	Mice	Administered 75 days prior to mating, during pregnancy and lactation 0.026 mg/kg/day	Increased neonatal mortality – stillbirths (19/185 versus 5/182 in controls) and deaths up to post-natal day 2 (19/186 versus 13/182 in controls)	Anderson et al., 1978

NDMA was administrated to Swiss CD-1 mice before and during pregnancy to assess the effects on reproductive toxicity.
In a preliminary study, 10 female mice received 0.1 ppm of NDMA in water for 10 weeks before mating with non-treated males. Nine females vs 10 in control were pregnant and delivered a lower number of pups than control 74 vs 100, with a slight increase in male pups (54%).
In the main study, the females (20 per group) were dosed for 75 days before mating with non-treated males, one for each 10 females. All 20 females were pregnant. However delivery time was 3 days longer on average than control (28 vs 25, respectively). No effects on the number of pups (185 vs 182 in control) were reported, despite NDMA caused an increase of neonatal mortality: 38 vs 18 (20% vs 9.9%, $p<0.05$), which included 19 stillbirths vs 5, and 19 vs 13 deaths within the first 2 days after birth (dosed group vs control). All pups died in one litter in the NDMA group (0 in control), while 11(55%) vs 8(40%) had some death in the litter (dosed group vs control). In addition, an effect on the sexual ratio was also observed in the treated group, with 51 females and 101 males out of the 152 surviving pups (34% females and 66%

males, p<0.001). In control, 84 females vs 80 males out of the 164 pups (51% female and 49 males). No effects on weight on the pups were reported (Anderson et al., 1978).

7.8.3 Summary

Two epidemiological studies examined the relationship between maternal dietary nitrosamine intake and frequency of birth defects in their offspring. One of these studies found a significantly increased risk between high maternal exposure to nitrosamines and risk of gastroschisis, while another found no increased risks between nitrosamines and a range of various birth defects. Both studies examined associations within categorical analyses and lacked to perform dose-response analyses.

The reproductive and developmental toxicity of nitrosamines has been investigated in rats, mice and rabbits. The majority of studies were conducted on NDMA, showing testicular damage in one study, and foetal deaths in five studies.

8. Other considerations

8.1 Mode of action (MoA) considerations

The bioactivation of N-nitrosamines to highly DNA reactive electrophilic species and the resulting DNA adducts which are critical for the carcinogenic properties discussed in section 7.7, were recently reviewed by Li and Hecht (2022) and Fahrer and Christmann (2023).

Nitrosamines' metabolism varies slightly depending on the chemical structure. A common scheme can be identified (Figure 2). The first step is primarily an oxidation on the α or β carbon, catalysed by cytochrome P450 monooxygenases to generate the corresponding α-hydroxynitrosamine (2) or β-hydroxynitrosamine (7). Both are subsequently further oxidised to aldehyde (6), while the nitroso group is converted to a diazonium ion (4 or 9). This ion can react with the DNA to form adducts or be solvolyzed to the corresponding alcohol (5 or 10). The second metabolic route starts with denitrosation to form an amine (12) and an aldehyde (6) via an iminium ion (11). The amine and the aldehyde can undergo normal metabolism up to carbon dioxide.

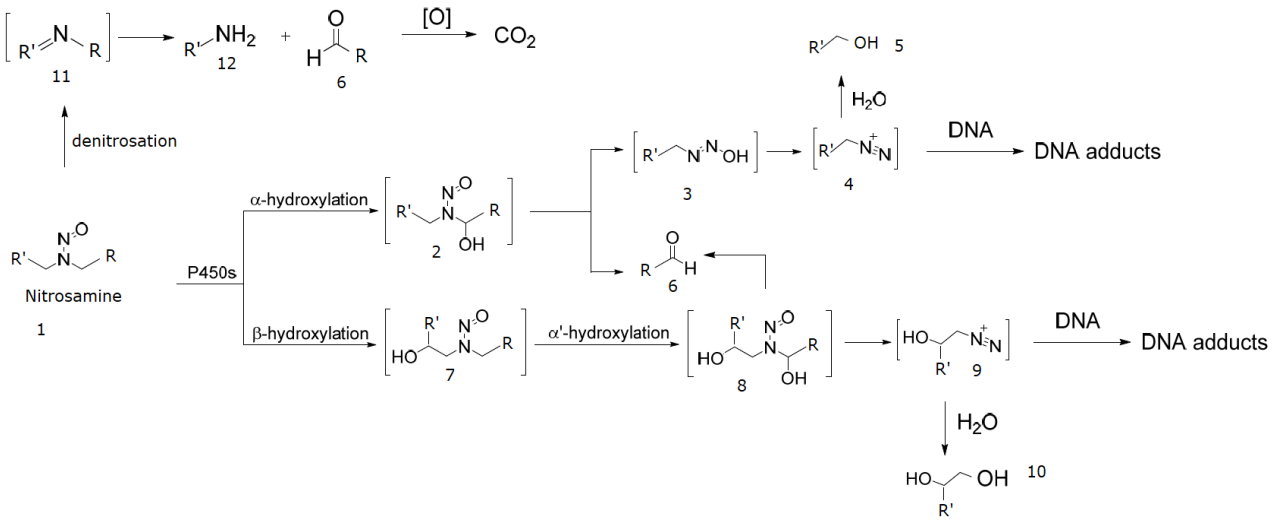


Figure 2: Nitrosamines' metabolic pathways
For NDMA, R and R' are hydrogen; for NDEA R and R' are methyl groups (-CH_3); for NDELA R and R' are methanol groups (-CH_2OH); for NDPA R and R' are ethyl groups (-CH_2-CH_3). Figure modified from Li and Hecht (2022).

The major DNA adducts produced by the four nitrosamines under consideration are presented in Table 34 and further discussed in the following sections.

Table 34: Major DNA alkylation adducts formed by NDEA, NDMA, NDPA and NDELA

Substance	Major DNA Alkylation Adducts
NDMA	N7-Me-Gua, N3-Me-Ade, O^6-Me-Gua, O^2-Me-Thy, O^4-Me-Thy
NDEA	N7-Et-Gua, N3-Et-Ade, O^6-Et-Gua, O^2-Et-Thy, O^4-Et-Thy
NDPA	N7-Me-Gua, N7-(n-propyl)-Gua
NDELA	O^6-OHEt-Gua and others; glyoxal adducts

The different DNA alkyl lesions can by repaired by multiple DNA repair mechanisms. The most prominent N7-Gua along with N3-Ade and N3-Gua adducts are substrates for alkyladenine glycosylase (AAG)-initiated base excision repair (BER). AlkB homolog (ALKBH) demethylases act directly to reverse damage on N1-Me-Ade, N1-Me-Gua, N3-Me-Thy, and N3-Me-Cyt positions. The O^6-methylguanine-DNA methyltransferase (MGMT) efficiently removes alkyl adducts from the O^4-Gua and O^6-Gua positions, except for DNA interstrand crosslinks, which are substrates to a number of complementing repair processes/pathways (NER, Homologous recombination, translesion synthesis, Fanconi anaemia proteins). NER acts mainly upon bulky replication-blocking DNA adducts, with only a limited role on smaller alkyl adducts (e.g. O^6-Eth-Gua), which depending on their DNA replication blocking ability can be bypassed, with different fidelities and efficiencies, by translesion synthesis polymerases (TLS) (reviewed by Fahrer and Christmann, 2023).

8.1.1 NDMA

8.1.1.1 Metabolism

The bioactivation of NDMA to its highly DNA reactive intermediates is primarily catalysed by CYP2E1 in human liver microsomes and CYP2A6. The oxidation of the methyl group (α-methyl hydroxylation) leads to an unstable and mutagenic intermediate which further decomposes to two reactive species—formaldehyde and methyl diazohydroxide (CH_3-N=N-OH, 3 in Figure 2). Formaldehyde can be oxidized sequentially producing formic acid and CO2 while; methyl diazohydroxide will spontaneously form the highly electrophilic methyldiazonium ion (CH_3-$N^+\equiv$N, 4 in Figure 2) and alkylate DNA or be solvolyzed to methanol.

8.1.1.2 Methyl DNA Adducts formed by NDMA Metabolism

NDMA alkylates DNA and proteins via the two reactive intermediates—methyldiazonium ion and formaldehyde. Methyl DNA adducts formed by the methyldiazonium ion are considered to play a major role in NDMA-related carcinogenesis while formaldehyde can also form DNA cross-links or hydroxymethylene adducts.

A comprehensive examination of DNA adducts in the livers of rats treated with NDMA (single i.p. dose of 10 mg/kg), demonstrated that N7-Me-Gua (67-75% of total methylated adducts) and O^6-Me-Gua (6-8%) were the major adducts produced (at a ratio of 10:1, 2 h post administration) (Den Engelse et al, 1986). Other adducts such as N3-Me-Gua, N3-Me-Ade, N7-Me-Ade, O^2-Me-Cyt, O^2-Me-Thy, O^6-Me-Thy, 3-Me-Thy, as well as methyl phosphate adducts were also observed, at lower levels (structures of the various DNA adducts and references, can be found in Li and Hecht, 2022). In rats administered 2 mg/kg dose NDMA by stomach tubing daily (5x/week, for up to 24 weeks), the content of N7-Me-Gua in liver DNA was approximately 16 times that in kidney and lung, and increased up to 16 weeks, consistent with the liver being the primary site of NDMA carcinogenicity. O^6-Me-Gua was not detected in liver DNA but was readily measured in kidney and lung DNA (Margison et al, 1977). In male F344 rats treated with NDMA (0.055 mmol/kg) by s.c. injection, N7-Me-Gua and O^6-Me-Gua were detected in hepatic DNA at 1420 µmol/mol Gua and 170 µmol/mol Gua at 4 h, respectively, with the corresponding amounts 24 h after injection, at 680 and 45 µmol/mol Gua (Hecht et al, 1986). The ratio of N7-Me-Gua to O^6-Me-Gua increases in time as the latter adduct is substrate to the repair enzyme O^6-

alkylguanine-DNA alkyltransferase (AGT/MGMT), which directly removes a methyl (and other related alkyl groups) from the O^6-position of Gua, restoring the DNA structure, without adduct excision. The resulting carcinogenicity of NDMA is therefore impacted by the enzymatic repair activity of the O^6-alky-Gua-adducts, which can be enhanced in the rat liver after repeated low-dose exposure (but depleted in chronically treated mice) or impaired by NDMA hepatic metabolism inhibitors (references in Li and Hecht, 2022).

O^6-Me-Gua and N7-Me-Gua have been identified as the major NDMA-generated DNA adducts in cultured human oesophagus cells, and in the liver DNA of an NDMA-poisoning victim (Harris et al, 1979, Herron et al, 1980, as cited in Li and Hecht, 2022). O^6-Me-Gua has also been detected in human placental DNA as well as peripheral blood leukocyte and liver DNA (Foiles et al, 1988, Kang et al, 1995, as cited in Li and Hecht, 2022).

8.1.1.3 Mutagenicity and genotoxicity of Methyl DNA Adducts

The formation and enzymatic removal of O^6-Me-Gua from DNA are critical for the tumour induction process in different organs, with the persistence of O^6-Me-Gua adducts in specific rat tissues linked to site-specific chemical carcinogenesis (Nicoll et al, 1975, Pegg et al, 1978, as cited in Li and Hecht, 2022). If not repaired, during replication O^6-Me-Gua mispairs with thymine, and the resulting O^6-MeG-T mispair is processed by mismatch repair (MMR) in a number of futile repair cycles, destablising DNA and eventually causing DNA-double strand breaks. The miscoding properties of O^6-Me-Gua are exemplified by G to A transition mutations, as those observed in the *ras* oncogene in animals (Delaney and Essigmann, 2008, Belisnky et al, 1990, as cited in Li and Hecht, 2022). The repair capacity of O^6-alkylation damage is determined by the cellular MGMT level. Transgenic C3H/HeN mice, expressing the *Escherichia coli* MGMT gene, *ada*, with MGMT levels further induced by treatment with $ZnSO_4$, exhibited reduced rates of liver tumours following an i.p dose of NDMA and NDEA (1 or 5 mg/kg) compared to non-transgenic animals, indicating that MGMT has protective effects against nitrosamine-induced hepatocarcinogenesis (Nakatsaru et al, 1993). The replication-blocking N3-Me-Ade are detected by the enzyme alkyladenine DNA glycosylase (AAG), which hydrolyses the N-glycosidic bond between the damaged DNA base and the deoxyribose moiety, generating an apurinic (AP) site and initiating the BER pathway. Kay et al, 2021 studied the role of AAG levels using *Aag*-knockout ($Aag^{-/-}$) and *Aag*-overexpressing mice. They reported that low AAG levels and therefore unrepaired N3-Me-Ade adducts increased susceptibility to NMDA methylation-induced mutations promoting liver cancer, while overexpression of AAG sensitised animals to liver damage and lethality, the latter attributed to fast removal of the N3-Me-Ade lesions, leading to an accumulation of DNA single-strand breaks (SSBs) as repair intermediates, which when colliding with the replication are converted to highly toxic DSBs.

Methylated thymidines are poorly repaired and are therefore likely to contribute to the mutagenicity and carcinogenicity of NDMA. O^2-Me-Thy and O^4-Me-Thy specifically, have been shown to – unlike O^6-Me-Gua – strongly block DNA replication (Andersen et al, 2012). Straight chain O^2-alkyl-Thy lesions (e.g. O^2-Me-Thy, O^2-Et-Thy) have been shown to be bypassed by Pol η and Pol κ, but not Pol ι. In the case of O^4-alkyl-Thy, all straight-chain lesions except O^4-Eth-Thy are bypassed by Pol η, Pol ζ but not Pol κ and Pol ι (Fahrer and Christmann, 2023; references therein).

8.1.2 NDEA

8.1.2.1 Metabolism

NDEA metabolic activation for carcinogenicity is principally catalysed by CYP2E1 and CYP2A6 at the α- and β-carbon. Hydroxylation at the α-carbon of the ethyl group of NDEA, results in the formation of the electrophilic ethyldiazonium ion (CH_3-CH_2-$N^+{\equiv}N$, 4 in Figure 2), via the unstable intermediate ethyl diazohydroxide (CH_3-CH_2-N=N-OH, 3 in Figure 2), and acetaldehyde (CH_3CHO, 6 in Figure 2). Intermediate 3 reacts with DNA producing ethyl DNA adducts such as N7-Et-Gua, N3-Et-Ade, O^6-Et-Gua, O^2-Eth-Thy and O^4-Et-Thy. The other catalytic pathway involves the hydroxylation of the β-carbon followed by a secondary α-carbon hydroxylation on the other ethyl group of NDEA, generating ($CH_2(OH)CH_2N(NO)CH(OH)CH_3$, 8 in Figure 2), which

is further converted to the reactive intermediate 2-hydroxyethyldiazonium ion ($CH_2(OH)CH_2$-$N^+\equiv N$, 9 in Figure 2). The diazonium ions 9 can hydroxyethylate DNA and form minor DNA adducts, such as N7-HOEt-Gua.
Finally, NDEA can also undergo denitrosation to form ethylamine (CH_3-CH_2-NH_2, 12 in Figure 2) and acetaldehyde (CH_3CHO, 6 in Figure 2).

8.1.2.2 Ethyl DNA Adducts Formed by NDEA Metabolism

Ethyl DNA adducts are readily formed by NDEA metabolism *in vivo* after a single administration (Singer et al, 1985). The main ethyl DNA adducts were ethyl DNA phosphate adducts $B_1p(Et)B_2$, as well as ethyl DNA base adducts after deglycosylation. The most abundant adducts comprise: N7-Et-Gua, O^6-Et-Gua, O^2-Et-Thy, and N3-Et-Ade with minor base adducts including N1-Et-Ade N7-Et-Ade, O^2-Et-Cyt, N3-Et-Cyt, N3-Et-Gua, N3-Et-Thy, and O^4-Et-Thy (structures of the various ethyl DNA adducts can be found in Li and Hecht, 2022). It should be noted that 58% of the ethyl adducts detected in relevant *in vivo* studies were formed at the hydrogen-linked phosphotriester oxygen. Relevant DNA adducts have been detected in various human tissues including leucocyte DNA, lower respiratory tract, lung, salivary DNA and in human urine at increased levels in smokers vs non-smokers. Ethyl DNA adducts generated via dietary exposure and endogenous formation have been detected in hepatic DNA samples (Li and Hecht, 2022; references therein).

8.1.2.3 Mutagenicity and Genotoxicity of Ethyl DNA Adducts

The rate of ethyl groups' removal by MGMT is four times slower compared to methyl groups (Pegg, 1984). Ethyl adducts such as O^6-Et-dGua and O^4-Et-Thy, are differentially repaired and are not comparable substrates for ATG/MGMT, which is reflected in the half-lives of the adducts *in vivo*, with O^4-Et-Thy adducts being both persistent, accumulating in time and mutagenic; half-lives between 11-19 days have been reported in rat liver after a single-dose of NDEA (Verna et al 1996; references therein). Diverse mutagenic consequences have been observed for the three regioisomeric ethyl thymidine adducts; O^4-Et-Thy (major-groove lesion), induces A to G transitions when incorporated into polynucleotides, while O^2-Et-Thy (a minor groove lesion) is only slightly mutagenic and N3-Et-Thy does not induce mutations. O^4-Et-Thy lesions moderately block DNA replication with a bypass efficiency of 20–33% in human cells and induce substantial frequencies of T to C transition mutations (Wu et al, 2016). The role of individual translesion synthesis DNA polymerases in alkylated thymidine lesions bypass was further probed in the same study; Pol η or Pol ζ deficiencies, but not Pol κ or Pol ι, led to pronounced drops in bypass efficiencies for all the O^4-alkyldT lesions except O^4-MedT (Wu et al, 2016). Pol η and Pol ζ are therefore the predominant polymerases responsible for bypassing O^2- and O^4-Et-Thy, causing the respective T to A/G and T to C mutations. In *E. coli*, both Pol IV and Pol V are essential for the misincorporation of dCMP opposite to O^2-Et-Thd, whereas Pol V is necessary for the T to A transversions (Li and Hecht, 2022; references therein). Oncogene activation (in *ras* proto-oncogenes) at different frequencies, has been reported in NDEA-induced liver and lung tumours in different mouse and rat strains, consistent with the formation of either 0^4-Et-Thy or O^6-Eth-Gua adducts. Mutation in the p53 tumour-suppressor gene has also been reported in mice (Verna et al, 1996; reference therein). Guanine O^6 adducts (but not N3 or N7) can potentially cause mispairing, but are repaired relatively rapidly, potentially mitigating mutagenicity (Verna et al, 1996; references therein). N3-Et-Ade and N7-Et-Gua adducts are prone to undergo spontaneous depurination resulting in the formation of AP sites (Fahrer and Christmann, 2023).

8.1.3 NDPA

8.1.3.1 Metabolism

NDPA undergoes hydroxylation at the α-, β- and γ-carbon; the α-hydroxylation is considered the main bioactivation pathway, catalysed primarily by CYP2E1 and CYP2B1 and results in the formation of the electrophilic propyldiazonium ion (CH_3-CH_2-CH_2-$N^+\equiv N$, 4 in Figure 2) via the reactive intermediate propyl diazohydroxide (CH_3-CH_2-CH_2-N=N-OH, 3 in Figure 2) and propionaldehyde (CH_3CH_2CHO, 6 in Figure 2).

The solvolysis of (4) results in propan-1-ol ($CH_3CH_2CH_2OH$, 5 in Figure 2) and propan-2-ol ($CH_3CHOHCH_3$) which have both been identified *in vitro*. The β-hydroxylation yields (($CH_3CH(OH)CH_2N(NO)CH_2CH_2CH_3$, 7 (NHPPNA) in Figure 2)), which is in equilibrium with its ketone NOPPA ($CH_3CHOCH_2N(NO)CH_2CH_2CH_3$), as detected in rat urine. Due to the presence of the ketonic form, the successive hydroxylation on the α-carbon results in the electrophilic methyldiazonium ion (CH_3-$N^+\equiv N$, 4 in Figure 2) and acetic acid (CH_3COOH), via the formation of unstable intermediates ($CH_3COCH_2N(NO)CH(OH)CH_2CH_3$) and ($CH_3COCH_2N{=}NOH$). The γ-hydroxylation of NDPA forms the minor metabolites N-nitroso-3-hydroxypropylpropylamine and N-nitrosopropyl-(carboxyethyl)amine (Li and Hecht, 2022; references therein).

8.1.3.2 DNA Adducts Formed by NDPA Metabolism

Krüger et al, 1975 first reported the simultaneous detection of N7-Me-Gua and N7-(n-propyl)guanine (N7-n-Pr-Gua) in the liver RNA of rats treated with NDPA, consistent with an NDPA metabolism by both the α- and β-hydroxylation pathways (structures of the various propyl/ hydroxypropyl and butyl/ hydroxybutyl DNA adducts can be found in Li and Hecht, 2022).

DNA alkylation has been demonstrated *in vitro*, using [α-^{14}C]NDPA (Shu et al, 1997). Methyl (N7-Me-Gua, O^6-Me-Gua) and hydroxypropyl DNA adducts (N7-(2-hydroxypropyl)guanine, O^6-(2-hydroxypropyl)guanine, and O^6-(1-methyl-2-hydroxyethyl)guanine) have been detected in the tissues of hamsters and rats, exposed to NDPA analogues (Kokkinakis 1991, 1992).

8.1.4 NDELA

8.1.4.1 Metabolism

NDELA can undergo hydroxylation at the α- and β-carbon. The α-carbon hydroxylation catalysed by CYP2E1 results in the formation of the 2-hydroxyethyldiazonium ion ($HOCH_2$-CH_2-$N^+\equiv N$, 4 in Figure 2) and glycolaldehyde ($HOCH_2CHO$, 6 in Figure 2). The solvolysis of (4) results in acetaldehyde (CH_3CHO) and ethane-1,2-diol (or ethylene glycol, $HOCH_2CH_2OH$, 5 in Figure 2). Both ethane-1,2-diol and glycolaldehyde can further be oxidised to glyoxal (CHOCHO).
Alternatively, the hydroxylation of the β-carbon, primarily catalysed by CYP2E1, yields *N*-nitroso-(2-hydroxyethyl)glycine (NHEG, $HOCOCH_2N(NO)CH_2CH_2OH$)) which has been identified in rat urine at concentrations about 6% of the initial NDELA dose. Another minor metabolite derived from the β-hydroxylation is *N*-nitroso-2-hydroxymorpholine (NHMOR, C1COC(CN1N=O)O). Successive α-hydroxylation can occur on the 3- or 5-carbon, to generate glyoxal (CHOCHO) and 2-acetoxyacetaldehyde (CH_3COOCH_2CHO) (Li and Hecht, 2022).

8.1.4.2 DNA Adducts Formed by NDELA Metabolism

The metabolic activation via α-hydroxylation is linked to DNA adduct formation and NDELA-related carcinogenesis. The DNA hydroxyethyl guanine adducts O^6-OHEt-dGua and N7-OHEt-Gua and glyoxal adducts (N1,N^2-glyoxal-dGua, N1,N^2-etheno-dGua), formed by NDELA and its analogues have been detected *in vitro* and *in vivo,* (structures can be found in Lin and Hecht, 2022).

8.1.5 Conclusion and other considerations

The genotoxicity of nitrosamines has been documented in numerous *in vitro* and *in vivo* studies. Metabolic activation produces reactive intermediates which directly interact and alkylate DNA, generating promutagenic DNA adducts. Genotoxic mechanisms are the underlying mode of action for the carcinogenic activity of the nitrosamines under consideration which can be influenced by several factors: the ability of the substances to be metabolically activated and form diazonium/carbenium ions, the nature and stability of the DNA adducts formed, the capacity, kinetics and accuracy of the different cellular repair mechanisms involved in the processing of the pertinent adducts, and the inherent sensitivity of the exposed tissues.

The above parameters can therefore render certain individuals/groups particularly sensitive to the genotoxic and carcinogenic effects of nitrosamines.

On an organ level, nitrosamine alkylation reflects the local level of bioactivation capacity; the regiospecific expression, bioavailability and inducibility of relevant CYPs can modulate the carcinogenic organotropism; in rats, the use of disulfiram, an effective CYP2E1 inhibitor in both rat and human liver microsomes, favoured NDEA-induced carcinogenicity in the oesophagus over liver. The switch in the primary target site was attributed to greater systemic availability of unchanged NDMA and enhanced metabolic activation coupled to the slower repair of single-strand DNA breaks in the oesophagus (Frank et al, 1984 as cited in Verna et al, 1996).

The protective effects of CYP-mediated NDEA bioactivation inhibition has been shown for a number of inhibitors (Verna et al, 1996; references therein). Conversely, the role of elevated CYP2E1 expression in NDEA-induced hepatocarcinogenesis has been confirmed *in vivo*, in experiments with wild-type and *Cyp2e1*-null mice, the latter showing significantly decreased liver tumour incidence and multiplicity (Kang et al, 2007). In Sprague-Dawley rats, greater liver fibrosis – a precursor to hepatocellular carcinoma - occurred in rats with higher CYP2E1 innate activity, while the use of a CYP2E1 inhibitor prevented or reversed NDEA-induced hepatofibrosis, identifying CYP2E1 as a risk factor for this nitrosamines effect. Mirroring this effect, CYP2E1 activity was found to be significantly higher in human fibrotic than in normal liver tissues (Gao et al, 2017).

However, CYP2E1 plays multiple independent roles at different stages of hepatocarcinogenesis, as it was recently revealed that it is markedly downregulated in established malignant phenotypes (hepatocellular carcinoma) and acts as a tumour suppressor when expressed ectopically (Zhu et al, 2022). The metabolic activation of NDMA and NDEA can vary greatly among individuals as suggested by the large interindividual variation in the amount of CYP2A6 and CYP2E1 detected in human liver microscomes (Camus et al, 1993). CYP2E1 has been shown to be inducible by ethanol, acetone, diabetes and fasting in experimental animals (Verna et al, 1996; references therein). Induction of CYP2E1 by ethanol ingestion in Wistar rats, resulted in increased preneoplastic changes (nodules and enzyme-altered foci) following exposure to very low NDMA doses (11 ng/kg/bw-37 μg/kg/bw), suggesting that "*in alcoholic individuals cancer may develop from exposure to small doses of carcinogen in real life*" (Tsutsumi et al, 1993). CYP450 induction by chronic ethanol consumption in mice has been shown to be mediated by oxidative stress (Lu et al, 2012).

Similarly to enzymes involved in the bioactivation of nitrosamines, the species/tissue-specific expression of key repair enzymes like MGMT and the repair efficiency and kinetics of the critical DNA adducts could influence mutagenesis and tumour induction. Human tissues have a greater MGMT content/activity compared to equivalent rodent tissues (Pegg, 1984). The enzyme is differentially expressed in various normal tissues in humans ranging from high amounts in the liver to negligible levels in the brain and bone marrow, with some human cancers (including brain tumours) expressing MGMT at elevated, albeit variable, levels (Pegg, 2000). However, a subset of CNS malignancies is MGMT-deficient due to epigenetic silencing via promoter methylation rendering these tumours more responsive to alkylating agents-based chemotherapy (Gerson, 2002).
The tissue-related variation is coupled to a large range of interindividual variability in humans (Margison et al, 2003). A 7.6-fold difference in MGMT levels in peripheral blood mononuclear cells (PBMCs) from healthy individuals (n=40), has been reported (Janssen et al, 2001). Apart from the epigenetic silencing, a genetic component to the MGMT methylation was recently identified (Wang et al, 2021). In rats, the repair of O^6-Et-Gua adducts has been shown to be age-related, being lower in younger and older rats compared to middle-aged ones (Likhachev et al, 1991). In humans, MGMT activity in paediatric brain tumours was highest in those aged 3±12 years but an inverse correlation between age and enzyme expression has been reported in the normal brain tissues, and no correlation in ovarian tumours. Most studies have reported no relationship between MGMT and gender, age, and alcohol consumption, whilst for smoking, diet and medication, associations are more frequent (as cited in Margison, et al 2003).

Collectively, it is envisaged that variable human risk could be associated with a number of factors

pertinent to the inducibility of CYP enzymes (e.g ethanol ingestion), the bioactivation and subsequent mutagenicity/genotoxicity/carcinogenicity of nitrosamines, and the genetic/epigenetic regulation of factors mitigating these effects (e.g. MGMT expression).

8.2 Lack of specific scientific information

Not identified.

8.3 Groups at extra risk

No groups at extra risk were identified.

9. Evaluation and recommendations

9.1 Cancer risk assessment

9.1.1 Published approaches for cancer risk assessment

9.1.1.1 AGS

AGS (2015) reviewed the genotoxicity and carcinogenicity studies on NDMA and concluded that a direct interaction with the DNA and a linear dose-response relationship without a threshold value can be assumed for NDMA. It was also noted that numerous animal studies provide insights into additional secondary genotoxic effects. AGS did not identify any human study suitable for the estimation of the reference risk levels.

AGS derived workplace air concentrations corresponding to tolerable (4:1000) and acceptable (4:10000 or 4:100000) cancer excess risks for NDMA. AGS used as starting point a BMD10 value of 18.66 µg/m^3 for human equivalent exposure at the workplace, calculated from the nasal tumour incidences observed in the inhalation experiment with rats published by Klein et al. (1991).

The following lifetime excess risk were estimated:

- Risk of 4 per 1 000 arising from exposure to 0.75 µg/m³
- Risk of 4 per 10 000 arising from exposure to 0.075 µg/m³ (75 ng/m³)
- Risk of 4 per 100 000 at exposure to 7.5 ng/m³

Carcinogenicity data from oral experimental studies were also analysed to identify dose levels at which systemic tumours may develop. However, in view of the uncertainties regarding a possible first-pass effect with oral exposure, the findings from the most comprehensive chronic study by Peto et al. (1991a, 1991b) were not considered for the derivation of the ERR. Long-term oral exposure to low doses of NDMA, which did not cause any significant increase in mortality, mainly led to an induction of liver tumours, while short-term exposure to high doses mainly induced kidney tumours. This confirms a relevant first-pass effect at low doses.

AGS also reviewed the information on non-carcinogenic effects. Teratogenic effects observed in a drinking water study in mice (Andersson et al. 1978) were considered to be the most sensitive non-carcinogenic findings: a human equivalent air concentration of 3 µg/m^3 (assumed values: 70 kg body weight, 10 m^3 breathing volume for 8 hours, 5 days/week) was derived. This level is significantly higher than the tolerance value calculated on the basis of the carcinogenic effects.

The technical regulation for hazardous substances (TRGS 552) that applies to all carcinogenic nitrosamines with Cat 1A and 1B (BAuA, 2018), states that in the absence of any other toxicologically justified assessment principles, the acceptable and tolerable concentration values of NDMA are also transferred to other carcinogenic nitrosamines.

TRGS 552 further specifies that "*for the potent N-nitrosodiethylamine (NDEA) an increased risk cannot be ruled out even if these values are met. If the NDEA content plays a significant role, further reduction of exposure should be sought in line with the minimisation requirement*".

9.1.1.2 DECOS

Health Council of the Netherlands (DECOS, 1999) estimated the additional lifetime cancer risk associated with occupational exposure to NDMA.

DECOS found no information on the possible carcinogenicity in humans. However, similarities in metabolism between human and rodent tissues had been demonstrated. DECOS then reviewed the main oral and inhalatory carcinogenicity studies in experimental animals. Studies with subcutaneous, intramuscular or intraperitoneal administration were considered to be less relevant for estimation of long-term cancer risk under workplace exposure conditions than dermal, inhalation and oral studies. No dermal studies were found.

DECOS considered the inhalation experiment with rats published by Klein et al. (1991) the most sensitive and most reliable study for estimation of the potential risk of cancer at the workplace. The lowest concentration (120 µg/m^3) resulting in the induction of the tumour of interest i.e. tumours of the nasal mucosa was used as starting point to calculate the incidence per µg NDMA per m^3. DECOS considered that the available data do not indicate that the use of the linear model would not be appropriate.

The following so-called health-based calculated occupational cancer risk values (HBC-OCRVs) were estimated for NDMA:

- Risk of 4 per 1000 for 40 years of occupational exposure to 0.2 mg/m^3.
- Risk of 4 per 100 000 for 40 years of occupational exposure to 0.002 mg/m^3

DECOS (1999) also concluded that due to a lack of toxicity data the concentration levels associated with the referential cancer risk levels cannot be compared with a tentatively estimated health-based occupational exposure limit derived from data other than those on genotoxicity/carcinogenicity.

9.1.1.3 EFSA

EFSA assessed the risks to public health related to the presence of nitrosamines in food (EFSA, 2022). The risk assessment was confined to the carcinogenic nitrosamines occurring in food, i.e. NDMA, NDEA, NDPA, NMEA, NMor, NPip, NPyr, NDBA, (NMA) and (NSAR) (TCNAs)[36].

As regards human data and quantitative risk assessment, EFSA (2022) concluded that *"In all the studies on nitrosamines and cancer assessed, selection bias, information bias, and confounding were present to some degree. In addition, in all studies nitrosamines intake was estimated from data obtained from food frequency and food history questionnaires. Food intake questionnaires are imperfect measures of exposure and thus misclassification of exposure is likely to occur. It is important to note that food frequency questionnaires are used to rank subjects according to food or nutrient intake, but not to estimate absolute levels of intake. Based on the exposure tools used in these studies and in the possibility of residual confounding by other exposure sources (e.g. smoking, occupation) and/or other unmeasured factors (e.g.* Helicobacter *for gastric cancer, fruits and vegetables intake, chemicals contained in meat other than nitrosamines) the possibility of using data from these studies for hazard characterisation is limited. Therefore, these studies cannot be used to establish tumour target sites and Reference Points for nitrosamines."*. However, EFSA (2022) considered that these studies could support an association between nitrosamines and cancer.

For risk assessment purpose, EFSA then performed BMD analyses on rat liver tumour incidence data and obtained $BMDL_{10}$ values of:

- 35 µg/kg bw/day for NDMA,
- 10 µg/kg bw/day for NDEA,
- 14 µg/kg bw/day for NMor,
- 62 µg/kg bw/day for NPip, and
- 127 µg/kg bw/day for NPyr.

[36] Note: some (in brackets), as identified in section 5.5 are not 'relevant' nitrosamines in relation to occupational settings under the scope of this report.

Based on this, NDEA was identified as the most potent of the substances and in its risk assessment, EFSA used a conservative approach using the lowest $BMDL_{10}$ (NDEA 10 µg/kg bw/day) as the 'reference point' in the Margin of Exposure approach they applied.

9.1.1.4 EMA

The Committee for Medicinal Products for Human Use of the European Medicines Agency (EMA, 2020) reviewed the nitrosamine impurities in human medicinal products, including quantification of cancer risk from such exposure.

As regards to the human data and quantitative risk assessment, EMA (2020) considered that "*Epidemiological studies are not yet providing convincing evidence for a quantification of the carcinogenic potential of Nitrosamines in humans*" and consequently concluded that "*Animal data generated in lifetime bioassays are the most reliable source to conclude on the carcinogenicity of chemicals and human relevance*".

Based on animal carcinogenicity data, limits for nitrosamines in medicinal products were calculated from mean TD_{50} values, considering a lifetime daily nitrosamine exposure, to ensure an excess lifetime cancer risk below 1:100 000 as follows:

- NDMA and NMBA 96.0 ng/day,
- NDEA, NDBA 26.5 ng/day.

The limits were said to be "*applicable only if a finished product contains a single N-nitrosamine*" and "*If more than one N-nitrosamine is identified in a given finished product (or its API), it must be ensured that the total risk level of the sum of all detected N-nitrosamines does not exceed 1 in 100,000 life-time risk. An alternative approach where the sum of all detected N-nitrosamines does not exceed the limit of the most potent N-nitrosamine identified may also be used*".

9.1.2 Cancer risk assessment

As discussed in section 8.1 , all nitrosamines containing an α-hydrogen that can be metabolically activated are considered to be potentially mutagenic and carcinogenic to humans.

The human data on cancer risk by exposure to nitrosamines concern mainly cohort and case-control studies addressing dietary (oral) uptake. Only few studies via inhalation exposure in the occupational setting in rubber industry and through exposure to metal working fluids have assessed quantitatively exposure specifically to nitrosamines (total or some specific nitrosamines. These studies support a carcinogenic effect of nitrosamines.
However, they do not provide a robust database for deriving an exposure risk relationship (ERR) for any specific N-NA or for comparing potencies of different N-NA and generating an exposure profile dependent overall N-NA ERR. The underlying reasons are further outlined in section 7.7.1, both for oral and inhalation studies, but concern especially quantification of exposure and lack of adjustment for potential confounding by relevant known risk factors; these include, in the case of occupational studies, also potential confounding by multiple other occupational exposures (including other nitrosamines in case of assessing the effect of a given nitrosamines) in the industries/occupational settings concerned.

When human data cannot be used for the derivation of an ERR, ECHA use chronic animal study results. As discussed in section 7.7, clear differences in the carcinogenicity potency have been identified, with NDEA and NDMA being the most potent ones of the nitrosamines. They are also the most widely occurring nitrosamines at workplaces. However, exposure to NDEA and NDMA has not been reported in the metal processing sector, where NDELA is the most common nitrosamines.
Therefore, we present below ERRs for NDMA and NDEA, and also present ERR for NDELA for comparison.

9.1.2.1 Exposure risk relationship for NDMA

Two studies were identified as key studies:

- Klein et al. (1991): in this 2-year inhalation study in female rats, there was a significant increase in nasal cavity tumours and kidney cancer at a NDMA dose of 0.12 mg/m^3. Nasal cavity tumours were identified as the most sensitive findings.
- Peto et al. (1991a,b). in this is an oral study, male and female rats were exposed to NDMA for 176 weeks and exhibited significant increases in several tumour types. The total malignant liver tumours were identified as the most sensitive endpoint.

9.1.2.1.1 ERR based on the inhalation study

The dose-response correlations reported by Klein et al. (1991) were not suitable for benchmark dose modelling. Therefore, T25 was used to identify the point-of-departure[37], using the LOAEC of 0.12 mg/m^3 related to the nasal cavity tumours.

The calculations included the following steps:

1) T25 was calculated as:

T25 = C*[reference incidence / (incidence at C – control incidence)] * (1-control incidence) / 1;

with C being the LOAEC of 0.12 mg/m^3 for nasal cavity tumours as identified above and 0.25 being the reference incidence.

T25 = 0.12 mg/m^3 * [0.25 / (13/36 – 0/36)] * (1 – 0/36)/1 = 0.08 mg/m^3 NDMA

2) The T25 value was adjusted to correspond to worker exposure conditions (40 years, 48 weeks/year, 8 h/day, and correction for the inhalation volume for workers at light physical activity. No allometric scaling is needed for inhalation exposure.[43]

T25(worker)= 0.08 mg/m^3 * (75 years/40 years) * (52 weeks/48 weeks) * (4 days/5 days) * (4.5 h/8 h) * (6.7 m^3/10 (m^3) = 0.049 mg/m^3

3) Additional lifetime cancer risks were calculated as follows according to a linearised approach (high to low dose extrapolation)

Exposure concentration representing a 1*10^{-5} risk: 0.049 mg/m^3 / 25.000=0.000002 mg/m^3 (corresponding to 0.0000006 ppm).

Assuming linearity, excess life-time cancer risks were calculated and are presented in Table 35.

Table 35: Cancer exposure-risk relationship (nasal cavity tumours) after working life exposure to a given 8-hour air concentration of NDMA for five working days a week over a 40-year working life period

NDMA concentration in air (mg/m^3)	NDMA in air (ppm)	Excess life-time cancer risk (Cases per 100 000 exposed)
0.000002	0.0000006	1
0.000008	0.000003	4
0.00002	0.000006	10
0.00008	0.00003	40
0.0002	0.00006	100
0.0008	0.0003	400
0.002	0.0006	1000
0.008	0.003	4000

[37] https://echa.europa.eu/documents/10162/17224/information_requirements_r8_en.pdf/e153243a-03f0-44c5-8808-88af66223258?t=1353935239897

9.1.2.1.2 ERR based on the oral study

We used the BMD approach using EFSA Open Analytics software (quantal response, with model averaging, sex as a covariate, extra-risk: $BMD_{10\%}$, 95%CI) on the total malignant liver cancers in male rats in the Peto et al. (1991a,b) study, which yielded a BMDL of 0.0421 mg/kg bw/day, assuming the benchmark response (BMR) of 10%.

For the cancer risk estimate, the calculations included the following steps:

1) Conversion of the oral rat dose to the corresponding air concentration using the standard breathing volume for the rat (0.38 m^3/kg bw for 8 h exposure of workers)[44]:

BMDL(inhalation)= 0.0421 mg/kg bw/d / 0.38 m^3/kg bw= 0.11 mg/m^3 (8 h)

2) Correction for exposure duration (considering 40 years of work, 5 days/week), and inhalation volume (rats in rest vs worker light activity) using default values:

BMDL(worker)= 0.11 mg/m^3 ∗ (75 years/40 years) * (52 weeks/48 weeks) * (7 days/5 days) * (6.7 m^3/10 m^3) = 0.21 mg/m^3.

As indicated in section 7.1.2., a high degree of absorption is assumed for oral exposure and therefore no correction for bioavailability is needed.

3) Additional lifetime cancer risks were calculated as follows according to a linearised approach (high to low dose extrapolation)

The exposure concentration representing a $1*10^{-5}$ risk would be: 0.21 mg/m^3 / 10 000 = 0.00002 mg/m^3 (0.000006 ppm)

As this concentration is higher than the one derived from the inhalation study, no further ERR derivation is presented.

9.1.2.2 Exposure risk relationship for NDEA

No NDEA long-term inhalation study was found. Therefore we used the study by Peto et al (1991a,b) was used for the ERR calculations on NDEA. Significant increases in several tumour types were observed, with the total malignant liver tumours identified as the most sensitive ones.

We used the BMD approach using EFSA Open Analytics software (quantal response, with model averaging, sex as a covariate, extra-risk: BMD10%, 95%CI) on the total malignant liver cancers in female rats upon chronic NDEA exposure (Peto et al., 1991 a,b), which yielded a BMDL of 0.0142 mg/kg, assuming the BMR of 10%.

The BMDL of 0.0142 mg/kg was used for the ERR calculations, which included the following steps:

1) Conversion of the oral rat dose to the corresponding air concentration using the standard breathing volume for the rat (0.38 m^3/kg bw for 8 h exposure) [38]:

BMDL(inhalation)= 0.0142 mg/kg bw/d / 0.38 m^3/kg bw= 0.037 mg/m^3 (8 h)

2) Correction for exposure duration (considering 40 years of work, 5 days/week), and inhalation volume (rats in rest vs worker light activity) using default values:

BMDL(worker)= 0.037 mg/m^3 ∗ (75 years/40 years) * (52 weeks/48 weeks) * (7 days / 5 days) * (6.7 m^3/10 m^3) = 0.070 mg/m^3.

As indicated in section 7.1.2., a high degree of absorption is assumed for oral exposure and therefore no correction for bioavailability is needed.

3) Additional lifetime cancer risks were calculated as follows according to a linearised approach (high to low dose extrapolation)

[38] https://echa.europa.eu/documents/10162/17224/information_requirements_r8_en.pdf/e153243a-03f0-44c5-8808-88af66223258?t=1353935239897

The exposure concentration representing a $1*10^{-5}$ risk would be: 0.070 mg/m^3 / 10 000 ≈ 0.000007 mg/m^3 (0.0000002 ppm)

Assuming linearity, excess life-time cancer risks were calculated and are presented in Table 36.

Table 36: Cancer exposure-risk relationship (incidental and fatal liver cancer) after working life exposure to a given 8-hour air concentration of NDEA for five working days a week over a 40-year working life period

NDEA concentration in air (mg/m^3)	NDEA concentration in air (ppm)	Excess life-time cancer risk (Cases per 100 000 exposed)
0.000007	0.000002	1
0.00003	0.000007	4
0.00007	0.00002	10
0.0003	0.00007	40
0.0007	0.0002	100
0.003	0.0007	400
0.007	0.002	1000
0.03	0.007	4000

9.1.2.3 Exposure risk relationship for NDELA

The oral route study by Lijinsky and Kovatch (1985) was identified as the key study. Total liver tumours in female rats (LOAEL 0.879 mg/kg/day) were identified as the most sensitive endpoint. We attempted to use the BMD approach but the software exerted a (too) low BMD/BMDL ratio of <3. Therefore we instead calculated the T25 of 1.01 mg/kg[39].

This dose of 1.01 mg/kg was used for the cancer risk calculations, which included the following steps:

1) Conversion of the oral rat dose to the corresponding air concentration using the standard breathing volume for the rat (0.38 m^3/kg bw for 8 h exposure of workers)[45]:

T25(inhalation)= 1.01 mg/kg bw/d / 0.38 m^3/kg bw= 2.66 mg/m^3 (8 h)

2) Correction for exposure duration (considering 40 years of work, 5 days/week), and inhalation volume (rats in rest vs worker light activity) using default values:

T25(worker)= 2.66 mg/m^3 ∗ (75 years/40 years) * (52 weeks/48 weeks) * (7 days/5 days) * (6.7 m^3/10 m^3) = 5.07 mg/m^3.

As indicated in section 7.1.2. a high degree of absorption is assumed for oral exposure and therefore no correction for bioavailability is needed.

3) Additional lifetime cancer risks were calculated as follows according to a linearised approach (high to low dose extrapolation)

The exposure concentration representing a $1*10^{-5}$ risk would be:

5.07 mg/m^3 / 25 000 = 0.0002 mg/m^3.

Assuming linearity, excess life-time cancer risks were calculated and are presented in Table 37.

Table 37: Cancer exposure-risk relationship (incidental and fatal liver cancer) after working life exposure to a given 8-hour air concentration of NDELA for five working days a week over a 40-year working life period

[39] https://echa.europa.eu/documents/10162/17224/information_requirements_r8_en.pdf/e153243a-03f0-44c5-8808-88af66223258?t=1353935239897

NDELA concentration in air (mg/m³)	NDELA concentration in air (ppm)	Excess life-time cancer risk (Cases per 100 000 exposed)
0.0002	0.00004	1
0.0008	0.0001	4
0.002	0.0004	10
0.008	0.001	40
0.02	0.004	100
0.08	0.01	400
0.2	0.04	1000
0.8	0.1	4000

9.1.2.4 Conclusion on ERR

Based on inhalation study data, an ERR for NDMA was derived from nasal cavity tumour findings. Additional cancer risk calculations were performed on NDMA oral study data (liver tumours), and indicated a higher cancer risk for NDMA nasal tumours than liver tumours.
The ERR derived for NDEA from liver tumour findings in an oral study show a clearly higher potency compared to the oral study data on NDMA.

The ERR for NDEA (based on oral study data) shows excess lifetime risk levels very similar to those presented in the ERR for NDMA (based on inhalation study data). The potency of NDELA is markedly lower.

9.2 Derived Occupational Exposure Limit (OEL) values

9.2.1 Published approaches to establish OELs

No robust OEL setting reports by regulatory bodies have been identified.

A recent publication in a scientific journal presents an approach to derive OELs for nitrosamines by considering them as genotoxic carcinogens with thresholds (Blum et al., 2023). The authors applied BMD modelling to identify point-of-departure concentrations for total malignant liver tumours of different nitrosamines, and then derived two OELs using a risk-based approach (with an acceptable excess cancer risk of 1:100 000) and assuming a threshold mechanism, respectively. A third OEL was derived using TD50 values as point-of-departure.
BMDL10 concentrations were considered as LOAELs, and assessment factors were applied to take into account interspecies variability, intraspecies variability, LOAEL to NOAEL extrapolation, severity of effects, duration of exposure, dataset completeness, route to route extrapolation, and bioaccumulation.

In their conclusion, the authors compared the derived limit values and recommended the following OELs:
- 0.2 µg/m³ for **NDEA** and NPip
- 0.4 µg/m³ for NPyr
- 0.5 µg/m³ for **NDMA**, NMEA, **NDPA**
- 1 µg/m³ for NMor
- 2.5 µg/m³ for NDBA.

They also identified a need to set a limit value for total nitrosamine concentrations on the basis of mixed exposure in different occupational settings and taking into account the potency of the substances. A skin notation was also recommended. (Blum et al., 2023)

9.2.2 OEL – 8h TWA

Nitrosamines have been shown to cause carcinogenicity in experimental animals and it is assumed to be related to a non-threshold MoA. For that reason, it is not possible to derive a health-based OEL and ERRs were calculated from animal data (see section 9.1.2).

As occupational exposure typically includes a mixture of several nitrosamines, it is recommended that the ERRs derived for NDMA and NDEA (both showing cancer risk levels in the same order of magnitude), which are the most potent of the nitrosamines occurring at workplaces, are used for the setting of a BOEL for total nitrosamines levels.
However, we note that in specific occupational situations with no exposure to NDMA or NDEA, like in metal processing, the ERR derived for NDELA may be more appropriate.

´Regarding (non-threshold) non-cancer adverse health effects, the human studies do not provide a robust database for quantifying a hypothetical limit value. if a hypothetical limit value was derived from data on threshold effects in animal studies, the developmental effects caused by exposure to NDMA in a reproductive toxicity study (Anderson et al, 1978) is considered as the critical study that could be used for such limit value calculations.
A LOAEL of 0.026 mg/kg bw/day was identified (increased incidences of stillbirths and deaths up to post-natal day 2).
Other studies with NDMA or other nitrosamines showed non-cancer effects only at higher dose levels.

The calculations of a hypothetical limit would include the following steps:

1) Conversion of the oral mouse dose to the corresponding worker air concentration (allometric scaling mouse factor 7, inhalation volume 10 m^3):

LOAEL(worker) = 0.026 mg/kg bw/d * 70 kg bw / 10m^3 / 7 = 0.026 mg/m^3 [40]

2) Application of assessment factors: a factor of 3 for conversion from LOAEL to NOAEL, a factor 2.5 to cover interspecies differences, and a factor of 5 for worker intraspecies differences. As the exposure time of the study covered 75 days prior to mating and full pregnancy and lactation period, no assessment factor is applied for the study duration. Application of these factors would lead to:
0.026 mg/m^3 / 3*2.5*5 ≈ 0.0007 mg/m^3 (corresponding to 0.0002 ppm).

At this exposure level the excess life-time cancer risk would be around 4 cases per 1000 NDMA exposed workers (see section 9.1.2).

9.2.3 OEL – Short-Term Exposure Limits (STELs)

The available data does not indicate a need to propose a STEL.

9.2.4 Biological Limit Value (BLV)

No correlation between air exposure to nitrosamines and internal concentration of nitrosamines (or other biomarkers) has been found. No limit value is proposed.

9.2.5 Biological Guidance Value (BGV)

No guidance value is proposed.

9.3 Notations

Although the data is limited, there is information indicating absorption of nitrosamines via the skin. Therefore a 'skin' notation is recommended.

[40] https://echa.europa.eu/documents/10162/17224/information_requirements_r8_en.pdf/e153243a-03f0-44c5-8808-88af66223258?t=1353935239897

There are no data on skin or respiratory sensitisation of nitrosamine. Therefore, no notation for ‘Sensitisation’ is proposed.

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Appendix 1. Summaries of epidemiologic studies on cancer risk and exposure to nitrosamines

This Appendix summarises cancer epidemiology studies that assessed dietary exposure to N-nitrosamines. Studies are described according to the main route of exposure and to the study design.

Table 38: Summary of Epidemiological studies on dietary intake of nitrosamines and cancer: cohort studies*

References*	N-NA compound	Exposure levels	Population (n)	Cases	Age	Country	Confounding factors	Risk estimate (95% CI)
Knekt, 1999	NDMA	Q4 vs Q1 no values	9,985	48	15-99	Finland	age, sex, municipality, smoking, energy intake.	Head and neck, 1.37 (0.50-3.74)
Michaud, 2009	NDMA	Q5 (0.08-0.09) vs Q1 (0.02-0.04)	230,655	335	25-75	USA	Age, calory intake, calendar year	Glioma, 0.88 (0.57-1.36)
Michaud, 2009	NPyr	T3 (0.02-0.03) vs T1 (0.01)	230,655	335	25-75	USA	Age, calory intake, calendar year	Glioma, 0.81 (0.62-1.05)
Keszei, 2013 (case-cohort)	NDMA	0.1 ug/d increase	120,852	110 Oesophagus	55-69	The Netherlands	age, smoking, BMI, alcohol, education, energy intake, fruits, vegetables, physical activity	Oesophagus and stomach, 1.15 (1.05-1.25)
Keszei, 2013	NDMA	0.1 ug/d increase	120,852	497 Stomach	55-69	The Netherlands	age, smoking, BMI, alcohol, education, energy intake, fruits, vegetables, physical activity	Oesophagus and stomach, 1.06 (1.01-1.10)
Knekt, 1999	NDMA	Q4 vs Q1 no values	9,985	68	15-99	Finland	age, sex, municipality,	Stomach, 0.75 (0.37-1.51)

References*	N-NA compound	Exposure levels	Population (n)	Cases	Age	Country	Confounding factors	Risk estimate (95% CI)
							smoking, energy intake.	
Larsson, 2006	NDMA	Q5 (>=0.19) vs Q1 (<=0.04)	61,433 women	156	58-92	Sweden	age, education, BMI, energy, alcohol, fruits, vegetables	Stomach, 1.96 (1.08-3.58)**
Jakszyn, 2006	NDMA	Per 1 ug/day increase	521,457	314	35-70	10 EU countries	age, sex, BMI, education, alcohol, smoking, physical activity, energy intake, fruits and nitrites.	Stomach, 1.00 (0.70-1.43)
Nothlings, 2005	Nitrosamines	Q5 Vs Q1 no values	190,545	482	45-75	USA	age, sex, ethnicity, time on study, diabetes, smoking, energy intake, family history of pancreatic cancer	Pancreas, 1.26 (1.01-1.56)
Knekt, 1999	NDMA	Q4 vs Q1 no values	9,985	73	15-99	Finland	age, sex, municipality, smoking, energy intake.	Colorectum, 2.12 (1.04-4.33)
Loh, 2011	NDMA	Per 1 standard deviation increase	23,363	1,055	40-79	UK	age, sex, education, smoking, alcohol, energy intake, physical activity, BMI, menopausal status for	Digestive tract, 1.13 (1.00-1.28) Rectum, 1.46 (1.16-1.84)

References*	N-NA compound	Exposure levels	Population (n)	Cases	Age	Country	Confounding factors	Risk estimate (95% CI)
							women	
Jakszyn, 2011	NDMA	Q4 (>=0.19) vs Q1 (<=0.05)	521,457	1001	Not reported	10 EU countries	age, sex, center, BMI, education, smoking, physical activity, energy intake.	Bladder, 1.12 (0.88-1.44)
Jakszyn, 2012	NDMA	Q5 (0.87) vs Q1 (0.045)	139,005	4606	Not reported	8 EU countries	age, sex, center, BMI, education, marital status, smoking, protein from diary, physical activity, energy intake	Prostate, 1.04 (0.92-1.18)
Loh, 2011	NDMA	Q4 (0.13) vs Q1 (0.02)	23,363	3,268	40-79	UK	age, sex, education, smoking, alcohol, energy intake, physical activity, BMI, menopausal status for women	All cancers, 1.10 (0.97-1.24)

*all cancer sites from the original publication are reported
**p-trend statistically significant

Table 39: Summary of Epidemiological studies on dietary intake of nitrosamines and cancer: case-control studies

References*	N-NA compound	Exposure levels (ug/d)	Cases	Controls	Age	Country	Confounding factors	Risk estimate (95% CI)
Rogers, 1995	NDMA	T3 (0.18) vs T1 (0.06)	645	458	20-74	USA	age, sex, education, alcohol, smoking, BMI, energy intake	Larynx, 1.70 (0.91-3.18) Oesophagus, 1.86 (0.87-3.95), Oral cavity, 1.82 (1.10-3.00)
Ward, 2000	Nitrosamines	Q4 vs Q1	375	327	<75	Taiwan	Age, gender, ethnicity, vegetables	Nasopharynx, 2.6 (1.0-7.0)
Boeing, 1993	NDMA	T3 vs T1 no values	115	418	25-75	Germany	Age, sex, smoking, alcohol	Glioma, 2.8 (1.5-5.3)**
Giles, 1994	NDMA	T3 vs T1	409	409	20-79	Australia	Age, sex, alcohol, smoking	Glioma, 1.78 (1.12-2.84) males 1.45 (0.78-2.68) females
Boeing, 1993	NPyr	T3 vs T1 no values	115	418	25-75	Germany	Age, sex, smoking, alcohol	Glioma, 3.4 (1.8-6.4)**
Boeing, 1993	NPip	T3 vs T1 no values	115	418	25-75	Germany	Age, sex, smoking, alcohol	Glioma, 2.7 (1.4-5.2)**
Boeing, 1993	NDMA	T3 vs T1 no values	81	418	25-75	Germany	Age, sex, smoking, alcohol	Meningioma, 1.4 (0.7-2.6)
Boeing, 1993	NPyr	T3 vs T1 no values	81	418	25-75	Germany	Age, sex, smoking, alcohol	Meningioma, 1.8 (0.7-0.3)
Boeing, 1993	NPip	T3 vs T1 no values	81	418	25-75	Germany	Age, sex, smoking, alcohol	Meningioma, 2.0 (1.0-3.8)

References*	N-NA compound	Exposure levels (ug/d)	Cases	Controls	Age	Country	Confounding factors	Risk estimate (95% CI)
Risch, 1985	NDMA	10 ug/day	246	246	35-79	Canada	Total food intake, ethnicity	Stomach, 0.94 (0.14-6.13)
Gonzales, 1994	Nitrosamines	Q4 vs Q1	354	354	31-88	Spain	Total calories	Stomach, 2.09**
Pobel, 1995	NDMA	T3 (0.51) vs T1 (0.20)	92	128	66 (mean)	France	Age, sex, occupation, energy intake	Stomach, 7.0 (1.85-26.46)*
La Vecchia,1995	NDMA	T3 (>=0.19) vs T1 (<=0.13)	746	2053	19-74	Italy	age, sex, education, family history, food score index, intake of β-carotene, vitamin C, nitrates, nitrites and total calories	Stomach, 1.4 (1.1-1.7)**
De Stefani, 1998	NDMA	Q4 (>=0.27) vs Q1 (<=0.14)	340	698	25-84	Uruguay	Age, sex, residence, smoking, urban/rural, mate consumption	Stomach, 3.6 (2.4-5.5)
Zheng, 2019	NDMA	Q4 vs Q1	957	938	61.9/60.2	USA	Age, sex, race, education, BMI, alcohol, history of diabetes, smoking, family history of pancreatic cancer	Pancreas, 1.93 (1.42-2.61) NDMA from plant sources
Zheng, 2019	NDEA	Q4 vs Q1	957	938	61.9/60.2	USA	Age, sex, race, education, BMI, alcohol, history of diabetes,	Pancreas, 2.28 (1.71-3.04)

References*	N-NA compound	Exposure levels (ug/d)	Cases	Controls	Age	Country	Confounding factors	Risk estimate (95% CI)
							smoking, family history of pancreatic cancer	
Zheng, 2019	NDBA	Q4 vs Q1	957	938	61.9/60.2	USA	Age, sex, race, education, BMI, alcohol, history of diabetes, smoking, family history of pancreatic cancer	Pancreas, 0.64 (0.48-0.85)
Zheng, 2019	NPyr	Q4 vs Q1	957	938	61.9/60.2	USA	Age, sex, race, education, BMI, alcohol, history of diabetes, smoking, family history of pancreatic cancer	Pancreas, 0.79 (0.60-1.05)
Zheng, 2021	NDMA	Q4 vs Q1	827	1013	All age groups	USA	Age, sex, race, education, BMI, alcohol, smoking, diabetes, HCV, HBV, total calories	Liver, 0.80 (0.53-1.21)
Zheng, 2021	NDEA	Q4 vs Q1	827	1013	All age groups	USA	Age, sex, race, education, BMI, alcohol, smoking, diabetes, HCV, HBV, total calories	Liver, 1.10 (0.72-1.69)
Zheng, 2021	NDBA	Q4 vs Q1	827	1013	All age groups	USA	Age, sex, race, education, BMI, alcohol,	Liver, 0.39 (0.25-0.61)**

References*	N-NA compound	Exposure levels (ug/d)	Cases	Controls	Age	Country	Confounding factors	Risk estimate (95% CI)
							smoking, diabetes, HCV, HBV, total calories	
Zheng, 2021	NDPA	Q4 vs Q1	827	1013	All age groups	USA	Age, sex, race, education, BMI, alcohol, smoking, diabetes, HCV, HBV, total calories	Liver, 0.88 (0.56-1.39)
Zheng, 2021	NMAMBA	Q4 vs Q1	827	1013	All age groups	USA	Age, sex, race, education, BMI, alcohol, smoking, diabetes, HCV, HBV, total calories	Liver, 1.24 (0.81-1.87), 1.54 (1.01-2.35) plant sources
Zheng, 2021	NPyr	Q4 vs Q1	827	1013	All age groups	USA	Age, sex, race, education, BMI, alcohol, smoking, diabetes, HCV, HBV, total calories	Liver, 0.89 (0.58-1.37)
Zheng, 2021	NPip	Q4 vs Q1	827	1013	All age groups	USA	Age, sex, race, education, BMI, alcohol, smoking, diabetes, HCV, HBV, total calories	Liver, 2.52 (1.62-3.94)**
Zhu, 2014	NDMA	Q5 vs Q1	1760	2481	20-74	Canada	Age, sex, energy intake, BMI, alcohol, smoking, physical activity, FANS, education,	Colon-rectum, 1.42 (1.03-1.96)**

References*	N-NA compound	Exposure levels (ug/d)	Cases	Controls	Age	Country	Confounding factors	Risk estimate (95% CI)
							dietary supplements	
Wilkens, 1996	Nitrosamines	T3 vs T1	195 men	390	30-93	Hawaii, USA	Age, smoking, occupation, vegetables, vitamin C	Lower urinary tract, 3.0 (1.4-6.4)
Wilkens, 1996	Nitrosamines	T3 vs T1	66 women	132	30-93	Hawaii, USA	Age, smoking, occupation, vegetables, vitamin C	Lower urinary tract, 1.9 (0.6-5.8)
Catsburg, 2014	Nitrosamines	Q5 (>= 0.06) vs Q1 (<= 0.015)	1307 men 353 women	1237 men 349 women	25-64	USA	BMI, smoking, ethnicity, education, history of diabetes, vegetable intake, vit A, C, carotenoid, total serving of food per day	Bladder, 1.03 (0.78-1.36)
Goodman, 1992	NDMA	Q4 (0.70) vs Q1 (0.07)	326	865	30-84	Hawaii, USA	Age, ethnicity, smoking, beta-carotene	Lung, 3.3 (1.7-6.2)**
De Stefani, 2009	Nitrosamines	Q4 (>0.12) vs Q1 (<= 0.05)	866 males	1346	30-89	Uruguay	Age, residence, family history, BMI, smoking, energy intake, vegetables, fruits, non-meat fatty food, reduced glutathione	Lung, 1.89 (1.30-2.73)**

*all cancer sites from the original publication are reported
**p-trend statistically significant

Table 40: Summary of epidemiologic studies and nitrosamines exposure: inhalation exposure in workers.

Ref.	Description	Nitrosaminecompound	Exposure assessment	Confounding factors adjusted for	Risk estimate (95% CI)	Comments
Workers of metalworking fluids (MWF)						
Sullivan et al. 1988	US Nested case-control study of 60 esophageal cancer deaths among 46384 automobile manufacturing workers potentially exposed to MWF in machining and grinding operations	Total N-NA	Cumulative exposure for MWF (mg/m3-years), type of MWF operation (grinding with synthetic MWF/grinding with soluble MWF/machining with soluble MWF) and duration (years) for N-NA and other chemicals. 15% ever exposed to N-NA, mean lifetime exposure of cases/controls: 5.7 years	Cases and controls matched on race, gender, plant, and year of birth, adjusted for time since hire	N-NA (years("more than zero years vs zero years"): OR=5.4 (1.5-19.9)	Co-exposure to MWF, metals (steel, iron, aluminium), sulfur, biocide, asbestos, solvent
Rubber industry workers						
Straif et al. 2000	German cohort study of cancer mortality among 8933 rubber workers from 5 plants employed after 1950 and worked for at least one year (oesophagus (n=13) and pharynx and oral cavity cancers (n=17))	NDMA, NMor, NDPhA (unspecified exposure level)	Exposure categories included a combination of air concentration, (µg/m3) and type of work. Broad ranges: Low (NDMA: 0.1-2, NMor: 0.1-3) Medium: (NDMA: 0.1-4.5, NMor: 0.1-17) High: (NDMA: 1-130, NMor: 0.1-380)	Age	Oesophagus cancer, RR high vs. low combined N-NA exposure = 7.3 (1.9-27.8) Oral cavity and pharynx, RR high vs. low combined N-NA exposure = 3.9 (1.4-11.1)	Stomach and lung cancer RR adjusted for exposure to asbestos, talc, and carbon black (non-increased RR)
Fritschi et al. 2015	Australian case-control study of pancreatic cancer deaths (504 cases and 643 controls)	Total N-NA	Exposure categories (ever vs. never) and levels (low(<1 mg/m3)/medium(1–2 mg/m3)/high(>2 mg/m3))	Age, sex, cigarette pack years smoked	OR ever vs. never= 0.85 (0.51-1.42) OR high vs. low exposure: 0.65 (0.15-2.81)	Co-exposure to pesticides, insecticides and herbicides
Hidajat et al. 2019	UK cohort study of cancer mortality among 36441 male rubber workers employed since 1967 (cancers of bladder (n=417), stomach (n=768), multiple	Total N-NA, NDMA, NMor, NDBA (unspecified exposure level), NDEA (unspecified exposure level), NPip (unspecified exposure level)	Job-exposure matrix to estimate cumulative exposure (year* µg/m3). Divided into 4 quartiles for each individual N-NA compound: Total N-NA: Q1 :<10.03 year µg/m3, Q2: 10.03–	Birth year, rubber dust, rubber fumes	*NMor (Q4 vs. Q1)*: Bladder, SHR=2.59 (1.99-3.38) Stomach, SHR=1.49 (1.22-1.81) MM, SHR=1.82 (1.4-2.36) Oesophagus, SHR=2.25	Increased risks also observed with sum N-NA score and cancers of the lung, non-Hodgkin's

Ref.	Description	Nitrosaminecompound	Exposure assessment	Confounding factors adjusted for	Risk estimate (95% CI)	Comments
	myeloma (n=462), oesophagus (n=333), prostate (n=885), leukemia (n=195), pancreas (n=328))		21.38 year µg/m3, Q3: 21.38–442.93 year µg/m3, Q4: >442.93 year µg/m3. NDMA: Q1: <3.12 year µg/m3, Q2: 3.12–5.96 year µg/m3, Q3: 5.96–9.67 year µg/m3, Q4: >9.67 year µg/m3 NMor: Q1: <4.69 year µg/m3, Q2: 4.69–9.77 year µg/m3; Q3: 9.77–16.40 year µg/m3; Q4: >16.40 year µg/m3		(1.64-3.08) Prostate, SHR=2.71 (2.2-3.38) Pancreas, SHR=1.96 (1.46-2.64) *NDMA (Q4 vs. Q1)*: All cancers, SHR=2.08 (1.96-2.21) Bladder, SHR=2.82 (2.16-3.67) Stomach, SHR=1.72 (1.41-2.1) Leukemia, SHR=3.47(2.35-5.13) MM, SHR=2.81 (2.17-3.64) Prostate, SHR=5.36 (4.27-6.73) Liver, SHR=2.86 (1.78-4.59) *Total N-NA (Q4 vs. Q1)*: All cancers, SHR=1.49(1.41-1.58) Lung, SHR=1.36(1.25-1.49) NHL, SHR=1.54(0.95-2.48) Brain, SHR=1.75(1.06-2.9)	lymphoma and brain

Notes: OR, odds ratio; RR, relative risk; N-NA, nitrosamines; NHL, Non-Hodgkin's lymphoma; MM, multiple myeloma; MWF, metalworking fluids; SHR, subdistribution hazard r

Appendix 2. Summaries of animal carcinogenicity data

Table 41: Summary of animal carcinogenicity studies of N-Nitrosodimethylamine (NDMA)

Species	Exposure route	Exposure period	Dose levels	Tumour types observed	Tumours incidence	Reference
Mouse (male) Strain A	Drinking water	16 weeks	0.5, 1 or 5 ppm (with or without 10 or 20% ethanol)= 0, 0.12, 0.25, 1.2 mg/kg/day	Lung: tumours	Dose-dependent increase 1.5- to 3-fold increase (0.5, 1) 2–3.5 increase in multiplicity (5 + 10% ethanol)	Anderson LM, 1988[3]
Mouse (male) Strain A	Drinking water	72 weeks	0, 167 µg/kg/day	Liver: hepatocellular adenoma Lung: alveolar adenoma	1/47 (control) 0/48 (167) 39/47 (control) 42/48 (167)	Anderson LM et al, 1992a[2]
Mouse (male) A/JNCr strain	Oral gavage	16 weeks	Single dose of 5 or 1 mg/kg on Day 1. Controls received vehicle only	Lung: tumours	4/30 (control) 15/30 (5)	Anderson LM et al, 1992b[1]
Mouse (female) BALBc strain	Drinking water	85 weeks	0, 600 µg/kg/day	Lung: adenoma Multiple sites: multiple tumour types	20/62 (control) 44/62** (600) 56/62 (control) 59/62 (600)	Terracini B et al, 1973[2]
Mouse (female) C57BL strain	Oral gavage	50 weeks	0, 238 µg/kg/day	Brain: olfactory neuroepithelioma Liver: olfactory neuroepithelioma Liver: benign/malignant tumours	0/32 (control) 12/30** (238) 0/38 (control) 12/36** (198) (2/0)/38 (control) (2/11**)/36 (198)	Griciute L et al, 1981[2]

Species	Exposure route	Exposure period	Dose levels	Tumour types observed	Tumours incidence	Reference
Mouse, (male, female), Swiss	Predominantly oral via drinking water	Treatment duration ranged from one week to 38 weeks (details not given in the IARC monograph)	Lowest effective dose levels were quoted at 50 mg/L or 0.4 mg/kg/day (equivalent to a total dose of 89 mg/kg)	After one week at 50 mg/L in drinking water of females (10 mg/kg/day): Kidney: tumours Lung: tumours Lung: adenoma Liver: Haemangiocellular tumours Liver: haemangiomas, haemangioendotheliomas, haemangioendothelial sarcomas, adenomas, hepatocellular carcinomas Lung: adenomas and adenocarcinomas	 0/17 (control) 6/10 (10) 2/17 (control) 10/10 (10) 13/17 treated animals at 89 mg/kg 2/10 treated animals at 89 mg/kg No incidences given in IARC monograph	Terracini B et al, 1966[3,1] Clapp and Toya, 1970[3] Clapp et al, 1968[3], 1971[3] Den Engelse et al, 1969/1970[3] Kuwahara et al, 1972[3] Otsuka and Kuwahara, 1971[3] Shabad and Savluchinskaya, 1971[3] Takayama and Oota, 1963[3], 1965[3] Toth et al, 1964[3] Zwicker et al, 1972[3]
Mouse (sex not given) BALB/c and SJL/J strains	Subcutaneous injection	1-25 weeks	Weekly injection of 0.15 mg in 0.2 mL saline (total dose of 0.15-3.75 mg/animal)	Liver: haemangioendothelial sarcomas Retroperitoneal and abdominal soft tissue: haemangioendothelial	No incidences given in IARC monograph	Kuwahara et al, 1972[3] Otsuka and Kuwahara, 1971[3]

Species	Exposure route	Exposure period	Dose levels	Tumour types observed	Tumours incidence	Reference
				sarcomas Lung: adenomas or adenocarcinomas		
Mouse (sex and strain not given)	Subcutaneous injection	Not specified in IARC monograph	Single injections at 1, 2, 4 and 8 mg/kg	Lung: adenomas and carcinomas	29% (1) 35% (2) 39% (4) 67% (8)	Cardesa et al, 1974[3]
Mouse (sex and strain not given)	Subcutaneous injection	Not specified in IARC monograph	Single injections of 15-75 µg/animal	Liver: parenchymal-cell and vascular tumours Lung: adenomas	No incidences given in IARC monograph	Terracini et al, 1966[3] Toth and Shubik, 1967[3] Toth et al, 1964[3]
Mouse (male and female) Mastomys strain	Subcutaneous injection	10-44 weeks	Twice weekly at 0.1 mg/animal	Liver: multiple tumour types	Zero incidence in control males 6/36 treated males 4/82 control females Zero incidence in treated females	Fujii and Sato, 1970[3]
Mouse (sex not given) RF strain	Intraperitoneal injection	Not specified in IARC monograph	Single dose of 0 (control), 5, 10, 15 mg/kg	Lung: tumours (papillomas, adenomas, carcinomas)	25/52 (control) 9/18 (5) 16/19 (10) 4/5 (15)	Clapp, 1973[3]
Mouse (sex not given) GR and CFW/D strains	Intraperitoneal injection	Not specified in IARC monograph	Single dose of 7 or 14 mg/kg	Lung: adenomas	No incidences given in IARC monograph	Den Engelse et al, 1969/1970[3] Frei, 1970[3]
Mouse (male and female) Swiss strain	Intraperitoneal injection	10 weeks	Weekly injections of 6 mg/kg	Retroperitoneum: vascular tumours	40% increase**(females) 15% increase (males) NS	Cardesa et al, 1973[3]
Mouse (male and female) NZO/BL strain	Intraperitoneal injection	Not specified in IARC monograph	Single doses of 0 (control), 7.5 and 15 mg/kg given at 60 days of age	Lung: tumours Kidney: adenomas (males only)	19-25% incidence in controls 76-100% incidence in treated animals 1/268 (control) 7/21 (7.5) 10/33 (15)	Noronha, 1975[3]
Mouse (male)	Intraperitoneal	13 weeks	Single dose of 7 mg/kg	Liver: hepatomas (males	38% of treated animals	Den Engelse et

Species	Exposure route	Exposure period	Dose levels	Tumour types observed	Tumours incidence	Reference
C3Hf strain	injection			only)		al, 1974[3]
Mouse (sex not given) Swiss, ASW/SN and A strains	Intraperitoneal injection	Not specified in IARC monograph	Single doses of 0 (control), 0.5, 1.0, 2.0, 4.0, 8.0 mg/kg	Lung: adenomas	15% (control) 17% (0.5) 29% (1.0) 35% (2.0) 39% (4.0) 67% (8.0)	Ii et al, 1976[3]
Mouse (sex and strain not given)	Intraperitoneal injection	Not specified in IARC monograph	Single dose of 8 mg/kg to newborn animals	Liver: hepatomas Lung: adenomas	No incidences given in IARC monograph	Frei, 1970[3]
Mouse (sex and strain not given)	Intraperitoneal injection	Not specified in IARC monograph	Six injections of 1-4 mg/kg to 7-day old animals	Liver: hepatomas and hepatocarcinomas Lung: adenomas and haemangiomas	No incidences given in IARC monograph	Vesselinovitch, 1969[3]
Mouse (pregnant female) strain not given	Intraperitoneal injection	During last days of pregnancy	Single or repeated injections of 12.5-75 mg/kg	Liver: hepatomas Lung: adenomas	Increased incidences reported in F_1 offspring of treated mothers	Smetanin, 1971[3]
Mouse (sex and strain not given although a hairless strain was used)	Dermal	20 weeks	Once weekly at 33.3 mg/kg	Lung: adenomas	13% in treated animals	Iversen, 1980[1]
Rat (male) Buffalo strain	Diet	26 weeks	0, 500 µg/kg/day	Liver: hepatocellular carcinoma	0/14 (control) 1/21 (500)	Angsubhakorn S et al, 1981[2]
Rat (male) Wistar	Drinking water	30 weeks	0, 10 and 25 ppm (alone or in combination with 1% 2-amino-4,5-diphenylthiazole; DPT) = (0, 1.5, 3.7 mg/kg/day as per ATSDR)	Liver: multiple tumour types	0/11 (control) 10/11 (10) 8/10 (25) DPT treatment showed a tendency to increased incidences of both renal cell and mesenchymal tumours, compared to controls/or NDMA-only treatments)	Takahashi et al, 2000[3]

Species	Exposure route	Exposure period	Dose levels	Tumour types observed	Tumours incidence	Reference
Rat (male) Fischer 344 strain	Oral gavage	30 weeks	0, 527 µg/kg/day	Kidney: mesenchymal neoplasm Liver: multiple tumour types Lung: multiple tumour types	0/19 (control) 10/19** (527) 0/19 (control) 10/19** (527) 0/19 (control) 16/19** (527)	Lijinsky W et al, 1987[2]
Rat (female) MRC Porton strain	Diet	108 weeks	0, 100, 250, 500, 1000, 2500 µg/kg/day	Liver: multiple tumour types	0/29 (control) 0/18 (100) 4/62 (250) 2/5 (500) 15/23 (1000) 10/12 (2500)	Terracini B et al, 1967[2]
Rat (female) MRC Porton strain	Diet	52 weeks	0, 108 µg/kg/day	Liver: multiple tumour types	0/29 (control) 3/15** (108)	Terracini B et al, 1967[2]
Rat (male) MRC Porton strain	Diet	120 weeks	0, 80, 200 µg/kg/day 0, 2, 5, 10, 20, 50 mg/kg diet	Liver: multiple tumour types Liver: hepatocellular carcinomas	0/12 (control) 1/19 (80) 1/6 (200) 0/41 (control) 1/37 (2) 5/68 (5) 2/5 (10) 15/23 (20) 10/12 (50)	Terracini B et al, 1967[2]
Rat (female) Wistar strain	Diet	96 weeks	0, 5, 50, 500 µg/kg/day	Liver: hepatocellular carcinoma Liver: haemangioendothelioma Liver: nodular hyperplasia	0/18 (control) 0/24 (5) 3/24 (50) 2/24 (500) 0/18 (control) 0/24 (5) 1/24 (50) 3/24 (500) 0/18 (control) 0/24 (5) 6/24 (50)	Arai M et al, 1979[2]

Species	Exposure route	Exposure period	Dose levels	Tumour types observed	Tumours incidence	Reference
					4/24 (500)	
				Multiple sites: leukaemia	0/18 (control) 1/24 (5) 0/24 (50) 5/24 (500)	
Rat (male, female) Wistar strain	Diet	96 weeks	0, 4, 40, 400 µg/kg/day	Liver: hepatocellular carcinoma	0/18 (control) 0/24 (4) 1/24 (40) 1/24 (400)	Arai M et al, 1979[2,1]
				Liver: haemangioendothelioma	0/18 (control) 0/24 (4) 0/24 (40) 3/24 (400)	
				Liver: nodular hyperplasia	0/18 (control) 0/24 (4) 1/24 (40) 6/24 (400)	
			0, 0.13, 1.3 mg/kg/day	Testes: tumours	28.6% (control) 60% (0.13) 52.9% (1.3)	
Rat (male) Wistar strain	Diet	54 weeks	0, 313 µg/kg/day	Liver: carcinoma	0/29 (control) 0/14 (313)	Terao K et al, 1978[2]
				Testes: Leydig cell tumour	0/29 (control) 7/14** (313)	
Rat (sex and various strains not specified in IARC monograph)	Oral via drinking water or diet	Duration of studies not specified in IARC monograph	Low dose levels compatible with good survival rates i.e 50-100 mg/kg or 4 mg/kg/day	Liver: hepatocellular carcinomas, cholangiocellular tumours; haemangioendothelial tumours	High incidences (no data given in IARC monograph)	Argus and Hoch-Ligeti, 1961[3] Geil et al, 1968[3] Magee and Barnes, 1956[3], 1962[3] Schmähl and Preussmann, 1959[3] Hadjiolov and

Species	Exposure route	Exposure period	Dose levels	Tumour types observed	Tumours incidence	Reference
			High dose levels by single dose or short-term i.e. 100-500 mg/kg diet or up to 30 mg/kg body weight	Kidney: tumours Lung: adenocarcinomas and squamous cell carcinomas	No incidences given in IARC monograph	Markow, 1973[3] Taylor et al, 1974[3] Magee and Barnes, 1959[3], 1962[3] Riopelle and Jasmin, 1969[3] Shinohara et al, 1976[3] Terracini et al, 1969[3] Zak et al, 1960[3] Argus and Hoch-Ligeti, 1961
Rat (sex not given) Sprague-Dawley strain	Not specified in IARC monograph	24 weeks	5 times weekly at 0.4 mg/rat/day up toa total dose of 48mg/rat	Liver: hepatocellular carcinoma (3) and sarcoma(2)	5/19 treated animals	Hoch-Ligeti et al, 1968[3]
Rat (sex and strain not given)	Parenteral injection not specified in IARC monograph	Latent period of 286-369 days	Single injections of 0 (control), 10, 20 or 30 mg/rat given on Days 21 and 70 after birth	Kidney: tumours (41% renal cell; 59% stromal nephromas)	Incidence in control given as zero but no incidences for treated animals given in the IARC monograph	Campbell et al, 1974[3]
Rat (sex not given) Wistar strain	Subcutaneous injection	40 weeks	Weekly injections of 0.1 mg/rat beginning at birth	Kidney: tumours mainly nephroblastomas, adenomas and clear-cell carcinomas	6/11 treated animals	Ito, 1973[3]
Rat (sex not given) Wistar strain	Subcutaneous injection	Latent period of 218-237 days	Single injection of 0.125 mg/rat on Day 1 of age and 0.125 or 10 mg/rat on Day 7	Kidney: tumours (mainly stromal nephromas	63% incidence. Details of distribution not given in IARC monograph	Campbell et al, 1974[3]
Rat (sex not given) Wistar	Intraperitoneal injection	Not specified in IARC monograph	Single injection of 18 mg/kg	Kidney: tumours	No incidences given in IARC monograph	Murphy et al, 1966[3]
Rat (sex not	Intraperitoneal	Not	Single injection of 20	Nasal cavity: squamous cell	No incidences given in IARC	Noronha and

Species	Exposure route	Exposure period	Dose levels	Tumour types observed	Tumours incidence	Reference
given) NZR strain	injection	specified in IARC monograph	mg/kg	carcinomas	monograph	Goodall, 1972[3]
Rat (female) strain not given	Not specified in IARC monograph	Animals treated during the last week of pregnancy or during the whole of pregnancy	Total dose given as 11 mg/animal	Kidney: tumours	Low incidence in F_1 offspring of treated mothers	Alexandrov, 1968[3]
Rat (pregnant female) strain not given	Oral gavage	Dose administered on gestation day 21	Single dose of 30 mg/kg to F_0 parents	Tumours reported but sites not given	5/20 treated animals (no control data reported)	Aleksandrov 1974[1]
Rat (sex and strain not given)	Not specified in ATSDR	6 days	8 mg/kg/day	Kidney: epithelial and mesenchymal tumours	8.6% and 14.5% respectively Toxicological significance of these figures are uncertain with the inclusion of a control group	Ireton et al, 1972[1] McGiven and Ireton, 1972[1]
Hamster (sex not given) Syrian golden strain	Oral gavage	5 weeks	1.0 and 1.6 mg/animal over 5 weeks or 1.6 mg/animal as a single dose	Liver: cholangioadenomas,cholangiocarcinomas, haemangiosarcomas, haemangioendotheliomas	No incidences given in IARC monograph	Tomatis and Cefis, 1967[3]
Hamster (sex and strain not given)	Drinking water	11 weeks	25 mg/L	Liver: hepatocellular carcinoma, cholangiocarcinomas, haemangioendotheliomas	No incidences given in IARC monograph	Kowalewski and Todd, 1971[3] Tomatis et al, 1964[3]
Hamster (sex not given) Syrian strain	Drinking water	60 weeks	1 mg/L	Glandular stomach: adenocarcinoma	1/40 treated animals	Homburger et al, 1976[3]
Hamster (sex not given) Syrian golden strain	Subcutaneous injection	6-20 weeks	Weekly injections of 0.5-1.0 mg/animal up to a total dose of 6-14 mg/animal	Liver: haemangioendothelial sarcomas and cholangiocarcinomas	No incidences given in IARC monograph	Herrold, 1967[3]

Species	Exposure route	Exposure period	Dose levels	Tumour types observed	Tumours incidence	Reference
				Nasal cavity: aesthesioneuroepithelialomas		
Hamster (male and female) Syrian golden strain	Subcutaneous injection	Lifespan (actual duration not specified in IARC monograph)	Weekly injections of 1.5, 3 and 6 mg/kg	Liver: hepatocellular carcinomas, hepatomas, cholangiocarcinomas Respiratory tract: tumours (3) Kidney: tumour (1) Forestomach: tumour (1)	10/30 (1.5) 14/32 (3) 7/32 (6)	Haas et al, 1973[3] Stenback et al, 1973[3]
Hamster (sex not given) Chinese strain	Subcutaneous injection	Lifespan (actual duration not specified in IARC monograph)	Weekly injections of 0.89, 1.77 and 3.54 mg/kg	Liver: haemangioendotheliomas Nasal cavity: adenocarcinoma of the endoturbinals	70-100% incidence in treated groups 3/108 treated animals	Reznik, 1975[3] Reznik et al, 1976[3]
Hamster (sex not given) European strain	Subcutaneous injection	Not specified in IARC monograph	Weekly injections of 0 (control) and 1.4-8.6 mg/kg	Liver: malignant haemangioendotheliomas, hepatocellular carcinomas and cholangiocellular carcinoma Kidney: malignant haemangioendotheliomas	0/20 (control) No incidences given for treated animals	Mohr et al, 1974[3]
Hamster (male) Golden	Drinking water	8, 12 or 16 weeks	4 mg/kg/day	Liver: cholangiocellular adenocarcinomas	High incidences reported in treated animals but no figures given in ATSDR	Ungar, 1986[1]
Hamster (sex and strain not given)	Oral gavage	Up to 20 weeks	Twice weekly at 5.4 mg/kg for 6.5 weeks; once weekly with 10.7 mg/kg for 4 weeks; once weekly with 5.4 mg/kg for 20 weeks	Liver: tumours	High incidences reported in treated animals but no figures given in ATSDR	Linjinsky et al, 1987[1]
Hamster (sex and strain not given)	Drinking water	7 months	1.1 mg/kg/day	Liver: tumours	High incidences reported in treated animals but no figures given in ATSDR	Bosan et al, 1987[1]
Guinea-pig (male) strain not given	Oral via dietary inclusion	6-49 weeks	25 or 50 mg/kg diet	Liver: papillary cholangiomas and hepatocellular carcinomas	No incidences given in IARC monograph	Le Page and Christie, 1969a[3]

Species	Exposure route	Exposure period	Dose levels	Tumour types observed	Tumours incidence	Reference
Rabbit (sex and strain not given)	Oral via dietary inclusion	17-60 weeks	25 or 50 mg/kg diet	Liver: hepatocellular carcinomas with lung metastases and benign papillary cholangiomas	No incidences given in IARC monograph	Le Page and Christie, 1969b[3]
Rhesus monkey (male and female)	Intraperitoneal injection	507 weeks	0, 1010 µg/kg/day	Multiple sites: malignant tumour	1/74(control) 0/2 (1010)	Adamson RH, 1982[2]

Notes: *p<0.05, **p<0.01; [1] Agency for Toxic Substances and Disease Registry (ATSDR) January 2022; [2] Lhasa Carcinogenicity Potency Database Report August 2022; [3] IARC Monograph May 1978

Table 42: Summary of animal carcinogenicity studies of N-Nitrosodiethylamine (NDEA)

Species	Exposure route	Exposure period	Dose levels	Tumour types observed	Tumours incidence	Reference
Bush baby (male and female)	Intraperitoneal injection	137 weeks	0; 897 µg/kg/day	Liver: hepatocellular carcinoma Nasal cavity- mucosa: Carcinoma-mucoepidermoid	0/9 (control) 2/3** (897) 0/9 (control) 10/13** (897)	Adamson RH, 1982[2]
Cynomolgus monkey (male and female)	Intraperitoneal injection	817 weeks	0, 6.3, 322, 910, 1350, 2290 µg/kg/day	Liver: hepatocellular carcinoma	0/105 (control) 2/7 (6.3) 3/3 (322) 5/5 (910) 5/5 (1350) 38/40 (2290)	Adamson RH, 1982[2]
Cynomolgus monkey (male and female)	Diet	812 weeks	0, 8070 µg/kg/day	Liver: hepatocellular carcinoma	0/104 (control) 13/16** (8070)	Adamson RH, 1982[2]
Rhesus monkey (male and female)	Intraperitoneal injection	1019 weeks	0, 7.4, 80, 340, 650, 1590, 2090 µg/kg/day	Liver: hepatocellular carcinoma	0/120 (control) 0/4 (7.4) 4/8 (80) 6/6 (340) 5/5 (650) 6/6 (1590) 51/53 (2090)	Adamson RH, 1982[2]
Rhesus monkey (male and female)	Diet	1030 weeks	0, 6870 µg/kg/day	Liver: hepatocellular carcinoma	0/102 (control) 11/14** (6870)	Adamson RH, 1982[2]

Species	Exposure route	Exposure period	Dose levels	Tumour types observed	Tumours incidence	Reference
Rhesus monkey (sex not given) newborn animals	Intraperitoneal injection	>10-15 months	Dose level not given but administered every 2 weeks	Liver: tumours	100% incidence in treated animals	Adamson et al, 1974[3]
Monkey (sex not specified in IARC monograph) Rhesus and cynomolgus breed	Oral (not specified in IARC monograph)	Up to 24 months	2 mg/kg/day to young animals increasing up to 30 mg/kg/day. Cumulative oral dose ranged from 6-26 g/monkey	Liver: hepatocellular carcinoma	6/15 treated animals	O'Gara and Kelly, 1965[3] Kelly, 1966[3]
Monkey (sex not given) *Ceropethicus aethiops*	Intraperitoneal injection	26 months	20-40 mg/kg every 2 weeks	Liver: hepatocellular carcinomas	2/2 treated animals	Kelly et al, 1966[2,3]
Monkey (sex not given) *Ceropethicus aethiops*	Intraperitoneal injection	>15 months	40 mg/kg every 2 weeks	Liver: hepatomas and hepatocellular carcinomas	25/25 treated animals	O'Gara et al, 1970[3]
Prosimian primates (sex not given) *Galago crassicaudatus*	Intraperitoneal injection	Duration not specified in IARC monograph	10-30 mg/kg every 2 weeks	Nasal cavity: mucoepidermoid carcinomas Liver: primary carcinomas	10/14 treated animals 2/10 treated animals	Dalgard et al, 1975[3], 1976[3]
Rat (female) Fischer strain	Drinking water	86 weeks	0, 51.6 µg/kg/day	Liver: hepatoma	0/15 (control) 0/15 (51.6)	Nixon JE et al, 1974[2]
Rat (male) Fischer strain	Drinking water	86 weeks	0, 46 µg/kg/day	Liver: hepatoma	0/16 (control) 0/13 (46)	Nixon JE et al, 1974[2]
Rat (female) Wistar strain	Drinking water	60 weeks	0, 136 µg/kg/day	Liver: hepatoma	0/18 (control) 10/20** (136)	Nixon JE et al, 1974[2]
Rat (male) Wistar strain	Drinking water	60 weeks	0, 104 µg/kg/day	Liver: hepatoma	0/17 (control) 4/18* (104)	Nixon JE et al, 1974[2]
Rat (female) Fischer strain	Drinking water	104 weeks	0, 14.8 µg/kg/day	Liver: multiple tumour types Forestomach: basal cell papilloma	1/20 (control) 7/20* (14.8) 0/20 (control) 5/20** (14.8)	Lijinsky W et al, 1981[2]

Species	Exposure route	Exposure period	Dose levels	Tumour types observed	Tumours incidence	Reference
				Oesophagus: multiple tumour types	0/20 (control) 13/20** (14.8)	
Rat (female) Fischer strain	Drinking water	30 weeks	0, 132 µg/kg/day	Liver: multiple tumour types Oesophagus: multiple tumour types	1/20 (control) 1/20 (132) 0/20 (control) 16/20** (132)	Lijinsky W et al, 1983[2]
Rat (male) Sprague-Dawley strain	Drinking water	116 weeks	0, 71.4 µg/kg/day	Liver: multiple tumour types Oesophagus: multiple tumour types	0/90 (control) 36/90** (71.4) 0/90 (control) 33/90** (71.4)	Habs M and Schmahl D, 1980[2]
Rat (male) Sprague-Dawley strain	Drinking water	149 weeks	0, 7.14, 22.9, 71.4 µg/kg/day	Gastrointestinal tract: multiple tumour types Liver: multiple tumour types Oesophagus: carcinoma/papilloma Urinary tract: multiple tumour types	26/500 (control) 9/80 (7.14) 7/80 (22.9) 25/80 (71.4) 3/500 (control) 2/80 (7.14) 3/80 (22.9) 36/80 (71.4) (1/0)/500 (control) (0/0)/80 (7.14) (0/0)/80 (22.9) (4/17)/80 (71.4) 1/500 (control) 2/80 (7.14) 1/80 (22.9) 1/80 (71.4)	Berger MR et al, 1987[2]
Rat (female) Wistar strain	Oral gavage	120 weeks	0, 10.2 µg/kg/day	Liver: hyperplastic nodule Mammary gland: adenocarcinoma	1/59 (control) 1/58 (10.2) 1/59 (control) 5/58 (10.2)	Kroes R et al, 1974[2]
Rat (male) Wistar strain	Oral gavage	120 weeks	0, 7.14 µg/kg/day	Liver: multiple tumour types Multiple sites: benign/malignant tumours	0/39 (control) 0/40 (7.14) (8/4)/39 (control) (9/7)/40 (7.14)	Kroes R et al, 1974[2]

Species	Exposure route	Exposure period	Dose levels	Tumour types observed	Tumours incidence	Reference
Rat (sex not given) Fischer 344 strain	Intraperitoneal injection	12 or 23 weeks	Daily dose of 0.55 mg/animal	Liver: hepatomas	>80% of treated animals	Svoboda and Higginson, 1968[3]
Rat (pregnant female) Sprague-Dawley	Subcutaneous injection	From Day 10 to Day 21 of gestation	4 or 8 mg/animal/day	Kidney: tumours including 5 animals with carcinomas	14/26 treated mothers and some offspring	Wrba et al, 1967[3]
Rat (pregnant female) Wistar strain	Oral or subcutaneous injection	Not reported in IARC monograph	Not specified in IARC monograph	Liver and kidney: carcinomas and adenomas leading to death Mammary gland: benign and malignant tumours	Majority of treated mothers Majority of F_1 offspring	Thomas and Bollmann, 1968[3]
Rat (female) strain not given	Oral	F_1 offspring observed for lifetime duration	1 mg/animal/day before and during pregnancy up to a total dose of 60-90 mg/animal	Kidney: carcinoma	3/4 mothers treated at a total dose of 60 mg No increased tumour rate in F_1 offspring	Sydow, 1970[3]
Mouse (male and female) various strains	Not reported in IARC monograph	Not reported in IARC monograph	Effect dose levels have been cited at 2-13 mg/kg/day	Liver: haemangioendothelioma, adenoma, hepatoma Oesophagus and forestomach: squamous cell carcinoma Lung: adenoma	The tumour incidences were reported to be very high, approaching 100% in many cases at the dose levels cited	Clapp et al, 1970[3] Clapp et al, 1971[3] Clapp NK and Craig AW, 1967[3] Schmähl et al, 1963[3] Schmähl and Thomas, 1965[3] Shvemberger, 1965[3] Takayama and Oota, 1965[3]
Mouse (sex not given) SWR strain	Intraperitoneal injection	Not reported in IARC monograph	Two injections of 100 mg/kg	Lung: adenomas	28/29 treated animals	Mirvish and Kaufman, 1970[3]
Mouse (sex not given) AKR/J, SWR/J and C57BL/6J	Intraperitoneal injection	Not reported in IARC monograph	Single injection of 90 mg/kg	AKR/J mice Lung: adenomas Leukaemia	0 (control) 24% (90) 68% (control and 90)	Diwan and Meier, 1976a[3]

Species	Exposure route	Exposure period	Dose levels	Tumour types observed	Tumours incidence	Reference
strains				SWR/J mice Lung: adenomas Leukaemia C57BL/6J mice Hepatomas and bile duct adenoma	22% (control) 70% (90) 18% (control) 28% (90) Total 7 animals	
Mouse (sex not given) BTO and C57BL/60 strains	Oral gavage	Not reported in IARC monograph	Single dose of 60 mg/kg	Liver: hepatomas Lung: adenomas	7/24 in BTO mice only 7/24 in BTO mice only	Akamatsu Y, 1975[3]
Mouse (sex and strain not given)	Dermal	Twice weekly for 10 months	2 drops of a 0.2% solution on each treatment day	Nasal cavity: squamous cell carcinoma	17/24 treated animals	Hoffmann and Graffi, 1964a[3]
Mouse (sex and strain not given)	Dermal	Daily or Twice weekly (duration not given)	0.2% solution given in 3 drops daily or 2 drops twice weekly on each treatment day giving a total dose of >8mg/animal	Nasal cavity: squamous cell carcinoma	100% incidence in both treated groups	Hoffmann and Graffi, 1964b[3]
Mouse (sex and strain not given)	Subcutaneous injection	Duration not specified in IAR monograph	50 mg/kg once or twice weekly up to a total dose of 200 or 400 mg/kg	Lung: adenoma	15% in untreated controls 25-90% in treated animals	Hilfrich et al, 1971[3]
Mouse (male and female) Swiss strain	Subcutaneous injection	88 weeks	Single injections of: 0 (control), 2, 4, 8, 16, 32 mg/kg	Lung: tumours (adenomas and carcinomas)	33/218 (controls) 16/39 (2) 18/38 (4) 24/39 (8) 25/39 (16) 21/40 (32)	Cardesa et al, 1974[3]
Mouse (pregnant female) NMRI strain	Subcutaneous injection	Treatment to parent from Day 15-20 of gestation. Offspring killed after 8	80-240 mg/kg/day	Lung: pulmonary adenomas	Increased incidence up to 63% in offspring from treated animals	Mohr and Althoff, 1965a[3]

Species	Exposure route	Exposure period	Dose levels	Tumour types observed	Tumours incidence	Reference
		or 12 months				
Mouse (pregnant female) C3H strain	Route of administration not specified in IARC monograph	Duration of treatment given as last days of pregnancy. Termination of offspring not specified	Not specified in IARC monograph	Lung: adenomas Liver: benign and malignant tumours Oesophagus and forestomach: benign and malignant tumours	Observed in the offspring of treated dams	Likhachev, 1971[3], 1974[3]
Mouse (pregnant female) AKR/JxSWR/J strain	Route of administration not specified in IARC monograph	Single dose administered on Day 18 of gestation	Single dose of 50 mg/kg	Lung: adenomas	87% of F_1 offspring of treated dams	Diwan and Meier, 1976b[3]
Rat (male and female) various strains	Oral but specifics not reported in IARC monograph	Not specifically reported in IARC monograph but often referred to as lifetime studies	Not specifically reported in IARC monograph but a range of dose levels from 0.15-10 mg/kg/day have been cited together with single doses of 280 mg/kg and 4-weekly doses of 25 or 35 mg/kg	Liver: hepatocellular tumours often with lung metastases; cholangiomas Oesophagus: squamous cell carcinoma and papilloma Kidney tumours	In drinking water studies all dose levels higher than 0.15 mg/kg/day gave tumour incidences approaching 100%	Argus and Hoch-Ligeti, 1961[3] Druckrey et al, 1963ab[3], 1964[3] Grundmann and Sieburg, 1962[3] Hadjiolov, 1972[3] Hoch-Ligeti et al, 1964[3] Lacassagne et al, 1967[3] Reid et al, 1963[3] Reuber, 1975[3] Reuber and Lee, 1968[3] Schmähl et al, 1960[3] Takayama et al, 1975[3] Thomas, 1961[3]
Rat (sex and strain not	Intravenous injection	Duration not specified in	Single injection of 280 mg/kg	Kidney: tumours	4/4 treated animals	Druckrey et al, 1963ab[3], 1964[3]

Species	Exposure route	Exposure period	Dose levels	Tumour types observed	Tumours incidence	Reference
given)		IARC monograph				
Rat (sex and strain not given)	Spray inhalation	4 months duration	Dilute aqueous solution but concentration and frequency not specified in IARC monograph	Liver carcinoma	8/17 treated animals	Dontenwill and Mohr, 1962[3]
Rat (male and female) Sprague-Dawley strain	Intravenous injection	Total duration nor specified in IARC monograph	Single injection of 1.25-160 mg/kg	Multiple sites: multiple tumour types	Increased incidence (>40 mg/kg)	Mohr and Hilfrich, 1972[3], 1974[3]
Rat (sex and strain not given)	Intrarectal	Lifespan although actual duration not specified in IARC monograph	11.2 mg/kg twice weekly	Liver: hepatocellular carcinomas	100% of treated animals	Schmähl et al, 1963b[3]
Hamster (male and female) Syrian and Chinese strains	Oral by gavage or drinking water	Not consistently reported in IARC monograph	Not specifically reported in IARC monograph but details given where present in the tumour incidence data	Trachea and lung tumours Liver: malignant tumours Nasal cavity tumours Oesophagus and forestomach tumours	37/68 (0.4 mL of 1:250 solution o.g. No incidence given 20/20 males and 20/20 females (40mg/L in drinking water for 17-26 weeks)	Dontenwill and Mohr, 1961[3] Dontenwill et al, 1962[3] Herrold and Dunham, 1963[3] Baker et al, 1974[3]
Hamster (sex not given) Syrian strain	Intradermal	Weekly injections for 5-6 months	3.5 mg/animal/week	Nasal cavity: epithelial papilloma	10/19 treated animals	Herrold, 1964a[3]
Hamster (sex and strain not given)	Intraperitoneal injection	4-7 months	2 mg/animal once per week	Trachea: squamous cell papillomas Nasal cavity: epithelial papillomas, carcinomas and neuroepithelial tumours Bronchi: squamous cell papillomas Liver: hepatocellular	Incidences not specified in IARC monograph	Herrold, 1964b[3]

Species	Exposure route	Exposure period	Dose levels	Tumour types observed	Tumours incidence	Reference
				carcinomas		
Hamster (sex not given) Syrian golden strain	Spray inhalation	5 months	1-2 mg twice weekly	Trachea and/or lung: tumours	18/33 treated animals	Dontenwill et al, 1962[3]
Hamster (sex not given) Syrian golden strain	Intratracheal instillation	Weekly for 6 months	0.05 mL of an aqueous solution(1:14)	Trachea/Bronchi: tumours	(14/10)/14 treated animals	Herrold and Dunham, 1963[3]
Hamster (sex and strain not given)	Subcutaneous injection	12 weeks	Once weekly doses of: 0.5, 1, 2 or 4 mg/animal	Nasal cavity and larynx tumours Tracheal tumours	17-72% in treated animals 88-100% in treated animals	Montesano and Saffiotti, 1968[3]
Hamster (sex and strain not given)	Subcutaneous injection	Lifespan (exact duration not specified in IARC monograph)	4.6-9.3 mg/kg (frequency of dosing not specified in IARC monograph)	Tracheal papilloma	10% in treated animals	Dontenwill, 1968[3]
Hamster (sex not given) Syrian golden strain	Subcutaneous injection	Duration not specified in IARC monograph	20 mg/kg per dose (dosing frequency not specified in IARC monograph)	Liver: 19 tumours Trachea: 31 papillomas Nasal cavity: 18 tumours	Incidences not specified in IARC monograph	Mennel et al, 1974[3]
Hamster (female) Syrian golden strain	Subcutaneous injection	30 days	5-20 mg/kg/day	Respiratory tract: papillomas in trachea, larynx, bronchi, nasal cavity and lung	Increased incidence in mothers and offspring (F_1)	Mohr et al, 1972a[3]
Hamster (sex not given) Chinese strain	Subcutaneous injection	22 weeks	77 mg/kg once per week	Oesophagus: papilloma Forestomach: multiple papillomas	30% incidence 82% incidence	Mohr et al, 1967[3]
Hamster (sex not given) Chinese strain	Subcutaneous injection	Lifespan (exact duration not specified in IARC monograph)	11.5, 23, 46 mg/kg once per week	Squamous cell papillomas (and occasional carcinoma) of the cheek pouch, tongue, pharymx, oesophagus, forestomach	Up to 100% incidence in 40 treated animals	Reznik et al, 1976[3]
Hamster (male) Wild European	Subcutaneous injection	Lifespan (exact duration not	20 mg/kg once per week	Respiratory system tumours (nasal cavity, larynx, trachea, bronchi):	100%incidence in 10 treated animals	Mohr et al, 1972b[3]

Species	Exposure route	Exposure period	Dose levels	Tumour types observed	Tumours incidence	Reference
strain		specified in IARC monograph)		squamous cell papillomas		
Hamster (pregnant female) Syrian golden strain	Subcutaneous injection	For 7 consecutive days during the second half of gestation	2 mg/animal/day	Trachea: multiple papillomas	42% of F_1 offspring 25 weeks post partum	Mohr et al, 1965[3]
Hamster (pregnant female) Syrian golden strain	Subcutaneous injection	Daily dosing for 2-5 days during pregnancy	4 mg/animal/day	Trachea: papillomas	75% of F_1 offspring 25 weeks post partum 73% treated mothers	Mohr and Althoff, 1965b[3] Mohr et al, 1966b[3]
Hamster (pregnant female) Syrian golden strain	Subcutaneous injection	Single dose on one of the last 4 days of pregnancy (Days 12-15)	45 mg/kg	Respiratory tract: tumours	95% F_1 offspring 0% in F_1 offspring from mothers treated during the first 11 days of pregnancy	Mohr et al, 1975[3]
Newborn hamster (sex and strain not given)	Subcutaneous injection	Duration not specified in IARC monograph	0.015, 0.03, 0.09, 0.15 mg/animal	Upper respiratory tract tumours	30-65% of 144 animals	Montesano and Saffiotti, 1970[3]
Gerbil (sex and strain not given)	Subcutaneous injection	Lifespan (exact duration not specified in IARC monograph)	6, 12, 24 mg/kg once per week	Nasal cavity: multifocal tumours Tracheobronchial: papillomas Lung: adenomas and carcinomas Cholangiocellular and hepatocellular carcinomas	66-80% incidence in treated groups	Cardesa et al, 1976[3] Haas et al, 1975[3]
Gerbil (sex and strain not given)	Intravenous injection	Duration not specified in IARC monograph	Single injection of 50 or 100 mg/kg	Nasal cavity: carcinomas originating mainly from the respiratory-olfactory mucosal junction	Increased but no incidences given in IARC monograph	Cardesa et al, 1976[3]
Hedgehog (sex not given) Algerian strain	Subcutaneous injection	Duration not specified in IARC monograph	Total dose of 375-1050 mg/kg	Liver: necrosis of parenchyma and benign and malignant tumours Lung: benign and	Incidences of pathological findings not given in IARC monograph	Graw et al, 1974[3]

Species	Exposure route	Exposure period	Dose levels	Tumour types observed	Tumours incidence	Reference
				malignant tumours		
Guinea-pig (male and female)	Drinking water	Not specified in IARC monogr. but estimated at 240 days	5 mg/kg/day with a total dose of 1200 mg/kg	Liver: hepatocellular carcinoma and adenocarcinoma	11/11 treated animals	Druckrey and Steinhoff, 1962[3]
		Not reported in IARC monogr.	3 mg/kg/day	Liver tumours	7/8 treated animals	Thomas and Schmähl, 1963[3]
		Not reported in IARC monogr.	Dose level not reported in IARC monograph	Liver: hepatocellular carcinoma	14/15 treated animals	Argus and Hoch-Ligeti, 1963[3]
		Groups treated for 4, 8, 12 or 24 weeks	Average daily intake of 1.2 mg/animal (total dose, <75 mg/animal)	Tumour types not specified in IARC monograph	21% incidence after 12 weeks;100% incidence after 24 weeks	Arcos et al, 1969[3]
Guinea-pig (sex and strain not given)	Subcutaneous injection	Not specified in IARC monograph	Frequency of dosing not specified in IARC monograph but animals dosed up to t total dose of 341-1310 mg/kg	Liver: malignant tumours Trachea and ethmoid region: benign and malignant tumours	Incidence in treated animals not specified in IARC monograph	Lombard, 1965[3]
Rabbit (sex not specified in the IARC monograph)	Drinking water	Not specified in IARC monogr.	3.4 mg/kg/day	Liver cell carcinoma	2/2 treated animals	Schmähl and Thomas, 1965b[3]
		6 days/week; duration not specified	0.042 g/L	Liver: metastasising hepatic carcinoma	13/13 treated animals	Rapp et al, 1965[3]
Dog (male) mongrel breed	Drinking water	2-50 weeks	0 (control), 50, 100, 500 mg/L	Multiple sites: multiple tumour types (fibroma, leiomyoma, haemangioma, haemangioendothelioma, fibrosarcoma, leiomyosarcoma, hepatocellular carcinoma, cholangiocarcinoma)	14/14 treated animals	Hirao et al, 1974[3]

Species	Exposure route	Exposure period	Dose levels	Tumour types observed	Tumours incidence	Reference
Dog (sex and strain not given)	Oral and subcutaneous injection	One oral dose and weekly s.c. doses up to total dose	Individual doses of 3 mg/kg up to a total dose of 565 mg/kg	Liver: leiomyosarcoma	1/1 treated animal	Schmähl et al, 1964[3]
Pig (sex not specified in IARC monograph)	Oral (not specified in IARC monograph)	Not specified in IARC monograph	4.4 mg/kg	Liver: various tumour types Kidney: adenoma	4/4 treated animals	Schmähl et al, 1967[3]
			1.5 mg/kg/day (11 months) then 3 mg/kg/day until death	Liver: hepatoma	1/2 (total dose of 750 mg/kg after 470 days)	Schmähl et al, 1969[3]
				Kidney: adenoma	1/2 (total dose of 1090 mg/kg after 594 days)	
		42 weeks per year for 5 years	0.4 mg/kg for 5 days per week. Total dose of 420 mg/kg in three long term survivors	Liver: tumours include hepatocellular adenoma and carcinoma 1 renal carcinoma and 1 brain tumour also observed	5/6 treated animals	Graw and Berg, 1977[3]

Notes: *p<0.05, **p<0.01; [1] No data available; [2] Lhasa Carcinogenicity Potency Database Report August 2022; [3] IARC Monograph May 1978

Table 43: Summary of animal carcinogenicity studies of N-Nitrosodi-n-propylamine (NDPA)

Species	Exposure route	Exposure period	Dose levels	Tumour types observed	Tumours incidence	Reference
Mouse (sex and strain not given)	Oral gavage	50 weeks	1 mg/kg twice per week Positive control of 40% ethanol	Forestomach: papillomas and carcinomas Lung: pulmonary adenomas	Higher in treated animals when compared with the positive control	Griciute et al, 1982[1]
Mouse (sex and strain not given)	Subcutaneous injection	Not specified in ATSDR report	Weekly	Liver, nasal cavity, oesophagus and respiratory system: tumours	No incidences given in ATSDR report	Dickhaus et al, 1977[1]
Rat (sex and strain not given)	Drinking water	30 weeks	2.6 and 5.1 mg/kg/day for 5 days/week	Liver, nasal cavity, oesophagus and forestomach: tumours of various types	Typically in the range of 60-100% incidence in treated animals	Lijinsky W and Reuber MD, 1981[1] Lijinsky and Taylor, 1978[1], 1979[1]
Rat (female) Fischer 344	Oral gavage	30 weeks	0, 898 µg/kg/day[2] Also reported as 0, 6.3	Liver: hepatocellular carcinoma	0/20 (control) 8/12** (898)	Lijinsky W, Reuber MD,

Species	Exposure route	Exposure period	Dose levels	Tumour types observed	Tumours incidence	Reference
strain			and 12.6 mg/kg/day (2 days/week)[1]	Nasal cavity: carcinoma Oesophagus: multiple tumour types	0/20 (control) 8/12** (898) 0/20 (control) 4/12** (898)	1983[2,1]
Rat (sex not given) BD strain	Drinking water	Not specified in IARC monograph	0 (control), 4, 8, 15, 30 mg/kg/day	Liver: carcinomas Oesophagus: papillomas or carcinomas Tongue: carcinomas	45/48 treated animals at induction times of: 300 days (4) 202 days (8) 155 days (15) 120 days (30) 8 animals (8 or 15) 6 animals (8 or 15)	Druckrey et al, 1967[3]
Rat (male and female) Sprague-Dawley strain	Subcutaneous injection	Lifespan (actual duration not specified in IARC monograph)	Weekly doses at: 0 (control), 24.35, 48.7, 97.4 mg/kg Average total dose range 0.93 and 2.7 g/kg	Nasal cavity: tumours Liver: carcinomas Lung: adenomas and carcinomas Oesophagus: squamous cell papillomas Kidney: tumours	The was a total of 58 viable treated animals of which at least 45 developed tumours	Althoff et al, 1973a[3,1] Reznik et al, 1975[3,1]
Hamster (male and female) Syrian golden strain	Subcutaneous injection	Lifespan (actual duration not specified in IARC monograph)	Weekly doses at 0 (control), 3.75, 7.5, 15, 30 or 60 mg/kg	Nasal and paranasal cavities: tumours Laryngobronchial tract: tumours Lung: tumours	0/40 (control) 134/185 (treated animals) 0/40 (control) 163/185 (treated animals) 0/40 (control) 56/185 (treated animals)	Althoff et al, 1973b[3,1], 1977[1] Pour et al, 1973[3,1], 1974[1]
Hamster (sex and strain not given)	Intratracheal instillation	15 weeks	1.5 mg once per week	Tracheal tumours	72% in treated animals	Ishinishi et al, 1988[1]
Hamster (female) strain not given	Subcutaneous injection	Single dose to F_0 female during gestation	100 mg/kg	Respiratory and digestive tract tumours in F_0 dams and F_1 offspring	No incidences given in ATSDR report	Althoff and Grandjean, 1979[1]

Species	Exposure route	Exposure period	Dose levels	Tumour types observed	Tumours incidence	Reference
Rhesus monkey (male and female)	Intraperitoneal injection	133 weeks	0, 3520 µg/kg/day	Liver: hepatocellular carcinoma	0/102 (control) 4/4 (3520)	Adamson RH, 1982[2]
Monkey (sex and species not given)	Intraperitoneal injection	Average duration of 28 months	Weekly injections of 40 mg/animal	Death due to hepatocellular carcinoma	No incidences given in ATSDR report	Adamson and Sieber, 1979[1]

Notes: *p<0.05, **p<0.01; [1] Agency for Toxic Substances and Disease Registry (ATSDR) February 2019; [2] Lhasa Carcinogenicity Potency Database Report August 2022; [3] IARC Monograph May 1978

Table 44: Summary of animal carcinogenicity studies of N-Nitrosodiethanolamine (NDELA)

Species	Exposure route	Exposure period	Dose levels	Tumour types observed	Tumours incidence	Reference
Rat (female) Fischer 344 strain[1,2]	Drinking water	55 weeks	0, 7.77, 14.4, 31.4, 99.8 mg/kg/day (equivalent to 0 control for 45 weeks; 400 mg/L for 50 weeks; 400 mg/L for 75 weeks; 1000 mg/L for 50 weeks; 2500 mg/L for 45weeks)1 mg/kg twice per week Positive control of 40% ethanol	Kidney: multiple tumour types	0/40 (control) 0/16(7.77) 0/16 (14.4) 4/20 (31.4) 2/20 (99.8)	Lijinsky W and Reuber MD, 1984[1,2]
				Liver: hepatocellular carcinoma	0/40 (control) 15/16 (7.77) 16/16 (14.4) 19/20 (31.4) 20/20 (99.8)	
				Liver: cholangiocarcinoma	0/40 (control) 3/16 (7.77) 1/16 (14.4) 3/20 (31.4) 5/20 (99.8)	
				Nasal cavity: adenocarcinoma	0/40 (control) 3/16 (7.77) 2/16 (14.4) 8/20 (31.4) 1/20 (99.8)	
				Nasal cavity: olfactory carcinoma	0/40 (control) 1/16 (7.77)	

Species	Exposure route	Exposure period	Dose levels	Tumour types observed	Tumours incidence	Reference
					0/16 (14.4) 4/20 (31.4) 1/20 (99.8)	
				Nasal cavity: squamous cell carcinoma	0/40 (control) 3/16 (7.77) 1/16 (14.4) 2/20 (31.4) 1/20 (99.8)	
				Oesophagus: papilloma	0/40 (control) 0/16 (7.77) 0/16 (14.4) 0/20 (31.4) 1/20 (99.8)	
Rat (female) Fischer 344 strain[1,2]	Drinking water	75 weeks	0, 0.879, 1.0, 2.01, 2.51 mg/kg/day (equivalent to 0 control; 28 mg/L for 100 weeks; 64 mg/L for 50 weeks and 100 weeks; 160 mg/L for 50 weeks)	Kidney: multiple tumour types	0/20 (control) 0/39 (0.879) 0/20 (1.0) 1/20 (2.01) 3/27 (2.51)	Lijinsky W and Kovatch RM, 1985[1,2]
				Liver: multiple tumour types	1/20 (control) 10/39 (0.879)* 5/20 (1.0) 14/20 (2.01)** 27/27 (2.51)**	
Rat (female) Fischer 344 strain[1,2]	Drinking water	50 weeks	0, 2.56 mg/kg/day	Liver: hepatocellular carcinoma	0/20 (control) 14/20** (2.56)	Hecht SS et al, 1989[1,2]
				Liver: haemangiosarcoma	0/20 (control) 1/20 (2.56)	
Mouse (female) A/J strain[2]	Drinking water	10 weeks	0, 0.2 µmol/mL	Lung: tumours	40% (control); 0.5±0.6 tumours/mouse 70%** (0.2 µmol/mL); 1.4±1.2 tumours/mouse	Hecht SS et al, 1989[2]
Rat (male) Fischer 344 strain[1,2]	Drinking water	48 weeks	0, 6.02, 9.02, 16.8, 48.4 mg/kg/day (equivalent to 0 control for 45 weeks; 400 mg/L for 50 weeks; 400 mg/L for 75 weeks; 1000	Kidney: multiple tumour types	0/28 (control) 0/16 (6.02) 1/16 (9.02) 2/20 (16.8) 5/20 (48.4)	Lijinsky W and Reuber MD, 1984[1,2]

Species	Exposure route	Exposure period	Dose levels	Tumour types observed	Tumours incidence	Reference
			mg/L for 50 weeks; 2500 mg/L for 45weeks)	Liver: hepatocellular carcinoma	1/28 (control) 14/16 (6.02) 14/16 (9.02) 18/20 (16.8) 20/20 (48.4)	
				Liver: cholangiosarcoma	0/28 (control) 4/16 (6.02) 2/16 (9.02) 6/20 (16.8) 4/20 (48.4)	
				Nasal cavity: adenocarcinoma	0/28 (control) 5/16 (6.02) 9/16 (9.02) 8/20 (16.8) 14/20 (48.4)	
				Nasal cavity: olfactory carcinoma	0/28 (control) 0/16 (6.02) 1/16 (9.02) 5/20 (16.8) 2/20 (48.4)	
				Nasal cavity: squamous cell carcinoma	0/28 (control) 0/16 (6.02) 0/16 (9.02) 0/20 (16.8) 3/20 (48.4)	
				Oesophagus: carcinoma	0/28 (control) 0/16 (6.02) 0/16 (9.02) 1/20 (16.8) 1/20 (48.4)	
				Oesophagus: papilloma	0/28 (control) 0/16 (6.02) 0/16 (9.02) 0/20 (16.8) 4/20 (48.4)	

Species	Exposure route	Exposure period	Dose levels	Tumour types observed	Tumours incidence	Reference
Rat (male and female) Fischer 344 strain[2]	Drinking water	34 weeks (5 days/week)	0, 3900, 7800, 15600, 31250, 62500 ppm (mg/L)	Liver: hepatocellular carcinoma Liver: cholangiocellular carcinoma males/females	100% incidence at 31250, 15600, 7800 and 3900 ppm when compared to 0% in controls (0/0)/10 (control) (1/3)/10 (3900) (6/5)/10 (7800) (8/8)/10 (15600) (10/7)/10 (31250)	Lijinsky W et al, 1980[2]
Rat (male) Fischer 344 strain[1,2]	Drinking water	75 weeks	0, 0.64, 0.795, 1.46, 1.83 mg/kg/day (equivalent to 0 control; 28 mg/L for 100 weeks; 64 mg/L for 50 weeks and 100 weeks; 160 mg/L for 50 weeks)	Kidney: multiple tumour types Liver: multiple tumour types	0/20 (control) 1/39 (0.64) 1/20 (0.795(2/20 (1.46) 2/27 (1.83) 4/20 (control) 6/39 (0.640) 2/20 (0.795) 11/20 (1.46)** 19/27 (1.83)**	Lijinsky W and Kovatch RM, 1985[1,2]
Rat (male) Fischer 344/DuCrj strain[1]	Drinking water	40 weeks	0, 1.47 mg/kg/day	Liver: multiple tumour types	0/10 (control) 0/15 (1.47)	Hasegawa R et al, 1998[1]
Rat (male) Sprague-Dawley strain[1,2]	Drinking water	118 weeks	0, 1070, 4290, 17900, 71400, 286000 ppm (equivalent to 0, 1.5, 6, 25, 100 and 400 mg/kg/day)	Liver: multiple tumour types (principally adenocarcinomas) Nasal cavity: multiple tumour types (principally squamous cell carcinomas and neuro-epitheliomas)	0/88 (control) 7/72 (1.5) 43/72 (6) 33/36 (25) 32/36 (100) 31/36 (400) 0/88 (control) 2/72 (1.5) 0/72 (6) 6/36 (25) 6/36 (100) 1/36 (400)	Preussman R et al, 1982[1,2]
Rat (male) Sprague-Dawley	Drinking water	162 weeks	0, 143, 450, 1430 ppm (equivalent to 0 control; 0.2, 0.63 and 2.0	Gastrointestinal tract: multiple tumour types	26/500 (control) 7/80* (0.2) 3/80 (0.63)	Berger MR et al, 1987[1,2]

Species	Exposure route	Exposure period	Dose levels	Tumour types observed	Tumours incidence	Reference
strain[1,2]			mg/kg/day)		6/80 (2.0)	
				Liver: multiple tumour types	3/500 (control) 2/80* (0.2) 1/80 (0.63) 6/80** (2.0)	
				Nervous system: multiple tumour types	54/500 (control) 8/80 (0.2) 16/80* (0.63) 11/80 (2.0)	
				Multiple sites: tumours benign/malignant	(362/144)/500 (control) (61/29)/80 (0.2) (60/29)/80 (0.63) (64/28)/80 (2.0)	
Hamster (male and female) Syrian golden strain[2]	Subcutaneous injection (twice weekly)	45 weeks maximum	0 (controls, 78 injections of 0.5 mL saline); 7 injections of 2260 mg/kg over 3 weeks; 27 injections of 565 mg/kg over 45 weeks. All survivors killed after 78 weeks	Nasal tumours male and female (principally adenocarcinomas)	0/15 and 0/12) (control) 7/13 and 5/14 (565) 6/15 and 5/15 (2260)	Hilfrich J et al, 1977[2]
				Tracheal tumours male and female	0/15 and 0/12 (control) 2/13 and 5/14 (565) 5/15 and 3/13 2260)	
Hamster (male and female) Syrian golden strain[2]	Subcutaneous injection (weekly)	Life (not specified)	0 (control, saline)), 250, 500, 1000 mg/kg	Nasal cavity tumours (principally adenocarcinomas) in males and females	0/15 and 0/15 (control) 8/13 and 5/14 (250) 8/14 and 6/15 (500) 11/15 and 11/15 (1000)	Pour P and Wallcave L, 1981[2]
Hamster (male and female) Syrian golden strain[2]	Subcutaneous injection (weekly)	80 weeks approximately	0 (control, saline), 58, 170, 500 mg/kg	Nasal cavity tumours (ranging from squamous papillomas to olfactory esthesioneuroepitheliomas) in males and females	0/10 and 0/8 (control) 0/15 and 0/14 (58) 2/15 and 2/14 (170) 11/15 and 5/15 (500)	Hoffman D et al, 1983[2]
				Tracheal tumours in males and females	0/10 and 0/8 (control) 2/15 and 0/14 (58) 1/15 and 3/14 (170) 3/15 and 4/15 (500)	
Hamster (male and female)	Dermal (three times per week)	36 weeks (all surviving animals killed	0 (control), 5, 16, 50mg/mL	Nasal cavity tumours in males and females	No data reported (control, 5 and 16) 2/15 males and 2/15	Hoffman D et al, 1983[2]

Species	Exposure route	Exposure period	Dose levels	Tumour types observed	Tumours incidence	Reference
Syrian golden strain[2]		at 80 weeks)			females	
Hamster (male and female) Syrian golden strain[2]	Oral cavity swab (three times per week)	45 weeks (all surviving animals killed at 80 weeks)	0 (control), 50mg/mL	Nasal cavity tumours in males/females Tracheal tumours in males/females	(0/0)/20 (controls) 12/20 males and 4/18 females (50) (0/0)/20 (controls) 4/20 males and 2/18 females (50)	Hoffman D et al, 1983[2]
Rats (sex not reported)[2]	Drinking water	Actual duration not reported but dose schedule would suggest at least 300 days	Concentrations equivalent to 600-1000 mg/kg/day up to a total dose of 150-300 g/kg	Liver: hepatocellular carcinoma (developed between 242-325 days after the start of treatment) Kidney: renal adenoma	20/20 (treated animals) 4/20 (treated animals)	Druckrey H et al, 1967[2]

Notes: *p<0.05, **p<0.01; [1]Lhasa Carcinogenicity Potency Database Report August 2022; [2] IARC Monograph February 2000

Table 45: Summary of TD_{50} values from carcinogenicity studies for NDMA, NDEA, NDPA and NDELA, taken from the CPDB

Species	Exposure route	Exposure period	Dose levels (mg/kg/day)	Derived TD50 (mg/kg/day)	References[1]
NDMA					
Mouse (male)	**Oral** Drinking water	72 weeks	0, 167	Lung (alveolar adenoma): TD50 177	Anderson LM et al, 1992
Mouse (female)	Drinking water	85 weeks	0, 600	Lung (adenoma): TD50 324	Terracini B et al, 1973
Mouse (female)	Oral gavage	50 weeks	0, 238	Brain (neuroepithelioma): TD50 153 Liver (benign/malignant tumours): TD50 350/429	Griciute L et al, 1981
Mouse (male)	Oral gavage	50 weeks	0, 198	Brain (olfactory neuroepithelioma): TD50 161 Liver (benign/malignant tumours): TD50 508/179	Griciute L et al, 1981
Mouse (male)	Diet	26 weeks	0, 500	Liver (hepatocellular carcinoma): TD50 1760	Angsubhakorn S et al, 1981
Rat (female)	**Oral** Drinking water	176 weeks	0, 1, 3, 5, 10, 20, 41, 61, 82, 102, 122, 163, 204	Liver (malignant/benign tumours): TD50 237/145 Liver (intrahepatic duct benign): TD50 76.3	Peto R et al, 1991
Rat (male)	Drinking water	176 weeks	0, 1, 3, 5, 10, 20, 41, 61, 82, 102, 122, 163, 204	Liver (malignant/benign hepatocellular tumours): TD50 218/157 Liver (intrahepatic bile duct benign and malignant combined): TD50 308	Peto R et al, 1991
Rat (female)	Drinking water	30 weeks	0, 63.1, 168	Liver (all tumour types): TD50 59.5	Lijinsky and Reuber, 1984
Rat (male)	Oral gavage	30 weeks	0, 527	Kidney (mesenchymal neoplasm): TD50 189 Liver (all tumour types): TD50 189 Lung (all tumour types): TD50 76.5	Lijinsky W et al, 1987
Rat (female)	Diet	108 weeks	0, 100, 250, 500, 1000, 2500	Liver (all tumour types): TD50 1420	Terracini B et al, 1967
Rat (female)	Diet	52 weeks	0, 108	Liver (all tumour types): TD50 443	Terracini B et al, 1967
Rat (male)	Diet	120 weeks	0, 80, 200	Liver (all tumour types): TD50 1190	Terracini B et al, 1967
Rat (female)	Diet	96 weeks	0, 5, 50, 500	Liver (hepatocellular carcinoma): TD50 4150 Liver (haemangioendothelioma): TD50 1850 Liver (nodular hyperplasia): TD50 115 Multiple sites (leukaemia): TD50 1480	Arai M et al, 1979
Rat (male)	Diet	96 weeks	0, 4, 40, 400	Liver (hepatocellular carcinoma): TD50 5600 Liver (haemangioendothelioma): TD50 1980 Liver (nodular hyperplasia): TD50 791	Arai M et al, 1979
Rat (male)	Diet	54 weeks	0, 313	Testes (leydig cell tumour): TD50 136	Terao K et al, 1978
Rhesus monkey (male and female)	**i.p. injection**	507 weeks	0, 1010	None derived	Adamson RH, 1982
NDEA					
Bush baby	**i.p. injection**	137 weeks	0, 897	Liver (malignant): TD50 18.4 Nasal cavity (malignant):	Adamson RH, 1982

Species	Exposure route	Exposure period	Dose levels (mg/kg/day)	Derived TD50 (mg/kg/day)	References[1]
				TD50 12.2	
Cynomolgus monkey	**i.p. injection**	817 weeks	0, 6.3, 322, 910, 1350, 2290	Liver (malignant): TD50 229	Adamson RH, 1982
Cynomolgus monkey	Diet	812 weeks	0, 8070	Liver (malignant): TD50 2080	Adamson RH, 1982
Rhesus monkey	**i.p. injection**	1019 weeks	0, 7.4, 80, 340, 650, 1590, 2090	Liver (malignant): TD50 266	Adamson RH, 1982
Rhesus monkey	**Diet**	1030 weeks	0, 6870	Liver (malignant): TD50 2620	Adamson RH, 1982
Rat (female)	**Oral** Drinking water	176 weeks	0, 2, 4, 9, 18, 36, 72, 107, 143, 179, 215, 287, 358	Liver (all tumour types/malignant): TD50 61.5/105 Oesophagus (all tumour types/malignant): TD50 203/729	Peto R et al, 1991
Rat (male)	Drinking water	172 weeks	0, 1, 3, 5, 10, 20, 41, 61, 82, 102, 122, 163, 204	Liver (all tumour types/malignant): TD50 92.4/136 Oesophagus (all tumour types/malignant): TD50 94.9/236	Peto R et al, 1991
Rat (female)	Drinking water	86 weeks	0, 51.6	None derived	Nixon JE et al, 1974
Rat (male)	Drinking water	86 weeks	0, 46	None derived	Nixon JE et al, 1974
Rat (female)	Drinking water	60 weeks	0, 136	Liver: (hepatoma): TD50 53.7	Nixon JE et al, 1974
Rat (male)	Drinking water	60 weeks	0, 104	Liver: (hepatoma): TD50 104	Nixon JE et al, 1974
Rat (female)	Drinking water	30 weeks	0, 4.4, 10.4, 26.4, 119, 538	Oesophagus (all tumour types): TD50 25.8	Lijinsky W et al, 1981
Rat (female)	Drinking water	60 weeks	0, 8.48, 20.7	Liver (all tumour types): TD50 8 Oesophagus (all tumour types): TD50 21	Lijinsky W et al, 1981
Rat (female)	Drinking water	104 weeks	0, 14.8	Forestomach (papilloma): TD50 54.9 Liver (all tumour types): TD50 41.6 Oesophagus (all tumour types): TD50 15	Lijinsky W et al, 1981
Rat (female)	Drinking water	30 weeks	0, 132	Oesophagus (all tumour types): TD50 21.9 µg/kg/day	Lijinsky W et al, 1983
Rat (male)	Drinking water	116 weeks	0, 71.4	Liver (all tumour types): TD50 119 Oesophagus (all tumour types): TD50 133	Habs M and Schmahl D, 1980
Rat (male)	Drinking water	149 weeks	0, 7.14, 22.9, 71.4	GI-tract (all tumour types): TD50 405 Liver (all tumour types): TD50 273 Oesophagus (carcinoma/papilloma): TD50 3390/723 Urinary tract (all tumour types): TD50 6680	Berger MR et al, 1987
Rat (female)	Oral gavage	120 weeks	0, 10.2	Liver (hyperplastic nodule): TD50 31300 Mammary gland (adenocarcinoma): TD50 127	Kroes R et al, 1974
Rat (male)	Oral gavage	120 weeks	0, 7.14	Multiple sites benign/malignant: TD50 257/77.4	Kroes R et al, 1974
NDPA					
Rat (female)	**Oral** gavage	30 weeks	0, 898	Liver (hepatocellular carcinoma): TD50 186 Nasal cavity (carcinoma): TD50 186 Oesophagus (all tumour	Lijinsky and Reuber, 1983

Species	Exposure route	Exposure period	Dose levels (mg/kg/day)	Derived TD50 (mg/kg/day)	References[1]
				types): TD50 505	
Rhesus monkey (male and female)	**i.p. injection**	133 weeks	0, 3520	Liver (hepatocellular carcinoma): TD50 12.1	Adamson RH, 1982
NDELA					
Rat (female)	**Oral** Drinking water	55 weeks	0, 7770, 14400, 31400, 99800	Kidney (all tumour types): TD50 327000 Liver (hepatocellular carcinoma): TD50 3300 Liver (cholangiocarcinoma): TD50 192000 Nasal cavity (adenocarcinoma):TD50 44500 Nasal cavity (olfactory carcinoma): TD50 128000 Nasal cavity (squamous cell carcinoma): TD50 713000 Oesophagus (papilloma): TD50 2070000	Lijinsky and Reuber, 1984
Rat (female)	Drinking water	75 weeks	0, 879, 1000, 2010, 2510	Kidney (all tumour types): TD50 42600 Liver (all tumour types): TD50 1920	Lijinsky and Kovatch, 1985
Rat (female)	Drinking water	50 weeks	0, 2560	Liver (hepatocellular carcinoma): TD50 1940 Liver (haemangiosarcoma): TD50 45400	Hecht SS et al, 1989
Rat (male)	Drinking water	48 weeks	0, 6020, 9020, 16800, 48400	Kidney (all tumour types): TD50 101000 Liver (hepatocellular carcinoma): TD50 2800 Liver (cholangiosarcoma): TD50 24100 Nasal cavity (adenocarcinoma): TD50 15700 Nasal cavity (olfactory carcinoma): TD50 50800 Nasal cavity (squamous cell carcinoma): TD50 282000 Oesophagus (carcinoma): TD50 437000 Oesophagus (papilloma): TD50 203000	Lijinsky and Reuber, 1984
Rat (male)	Drinking water	75 weeks	0, 640, 795, 1460, 1830	Kidney (all tumour types): TD50 19300 Liver (all tumour types): TD50 2880	Lijinsky and Kovatch, 1985
Rat (male)	Drinking water	40 weeks	0, 1470	None derived	Hasegawa R et al, 1998
Rat (male)	Drinking water	118 weeks	0, 1070, 4290, 17900, 71400, 286000	Liver (all tumour types): TD50 8330 Nasal cavity (all tumour types): 169000	Preussman R et al, 1982
Rat (male)	Drinking water	162 weeks	0, 143, 450, 1430	Gastrointestinal tract (all tumour types): TD50 145000 Liver (all tumour types): TD50 38900 Nervous system (all tumour types): TD50 43100 Multiple sites (benign/malignant tumours): TD50 8030/23800	Berger MR et al, 1987

[1] References obtained from the Carcinogenicity potency database (CPDB)