RAPPORT

2024

New knowledge on health effects of amines and their derivatives associated with CO2 capture

FHI
Folkehelseinstituttet

New knowledge on health effects of amines and their derivatives associated with CO_2 capture

NIPH
Norwegian Institute of Public Health

Published by Norwegian Institute of Public Health
Division of Climate and Environmental Health
Department of Chemical Toxicology
February 2024

Title:
New knowledge on health effects of amines and their derivatives associated with CO_2 capture

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ISBN digital 978-82-8406-426-0

Citation: Svendsen C, Låg M, Lindeman B, Andreassen M, Granum B. New knowledge on health effects of amines and their derivatives associated with CO_2 capture. Report 2023l Oslo: Norwegian Institute of Public Health, 2023.

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Acknowledgements

We would like to thank Bjørn Henrik Hansen and Eirik Falck da Silva at SINTEF and Claus Nielsen at University of Oslo for valuable input on the selection of relevant substances.

We would like to thank Bente Foss, Astrid Nøstberg, Nataliya Byelyey, and Marita Heintz (Norwegian Institute of Public Health, the library) for valuable help in designing and performing the literature searches.

Summary

Introduction

On assignment from the Norwegian Environment Agency, the Norwegian Institute of Public Health (NIPH) assessed the health effects of emissions of amines, nitrosamines, and nitramines to air and drinking water from CO_2 capture and storage facilities and published a report in 2011. The formation of carcinogenic nitrosamines and nitramines due to amine-based CO_2 capture technologies were regarded as the critical human health concern. In the 2011 report, it was concluded that the total amount of nitrosamines and nitramines should not exceed 0.3 nanograms (ng)/cubic metre (m^3) in air or 4 ng/l in drinking water. The values represent a minimal additional life-time risk of cancer. These risk estimates are conservative due to a general lack of toxicity data for the nitramines formed.

The Norwegian Environment Agency has in 2023 asked NIPH to perform a literature search to assess whether new information on health effects of amines and derivatives relevant for CO_2 capture has become available that could affect the conclusions and recommendations in the 2011 report.

Methods

The selection of amines and their derivatives relevant for CO_2 capture was done based on knowledge within the project group, meeting with external parties and information from relevant literature. The list of selected substances was discussed with, and approved by, the Norwegian Environment Agency.

Literature searches in the electronic databases MEDLINE (Ovid), Embase (Ovid), Web of Science, and CAB Abstracts were performed by the research librarian at NIPH. Both systematic reviews and primary research publications were in scope. The search for amines and nitrosamines was restricted to publications published after 1. January 2010. Also, we restricted the search for amines to studies on allergy related health outcomes and skin irritation. For nitrosamines, the search strategy was restricted to publications on genotoxicity and carcinogenicity. No restrictions were applied to the search strategy for nitramines regarding publication date or outcome. In addition to electronic databases, we searched for relevant scientific reports and for carcinogenic potency data in the Carcinogenic Potency Database (CPDB).

One person screened titles and abstracts, followed by screening of full texts and extraction of data.

Results

Based on existing knowledge six amines, 13 nitrosamines and nine nitramines were identified as relevant to include in the literature searches.

For the amines, two primary research publications with a total of three studies were identified in the search. All three studies were on piperazine (PZ) and addressed skin sensitisation or respiratory sensitisation. No systematic reviews were identified.

Of the 13 included nitrosamines, we identified studies for 11 of them. Fifty-five scientific publications were identified for the nitrosamine search: one systematic review and 54 primary research publications. In the systematic review an association with intake of *N,N*-

dimethylnitrous amide (DMA-NO) and increased risk of gastrointestinal and colorectal cancer was found. For the primary research publications, two case-control studies were found, whereas the remaining were animal studies or in vitro studies. No new chronic carcinogenicity studies or studies comparing the in vivo genotoxicity potency between nitrosamines and nitramines were identified.

Ten publications, all primary research publications were identified for the included nitramines. Three of the ten publications were published after 2010. Tumour development, genotoxicity, skin sensitisation, corrosion and irritation or eye irritation were the outcomes assessed in the identified studies. In vivo animal studies assessing tumour development were only identified for *N,N*-dimethylnitramide (DMA-NO_2) and N-methylnitramide (MA-NO_2). One chronic study which assessed tumour development in rats following exposure to DMA-NO_2 and MA-NO_2 published in 1981 was identified. No studies were identified for three of the nine nitramines in the literature search.

CPDB contained carcinogenic potency data for ten of the 13 nitrosamines and two of the nine nitramines, which was the same that was reported in the 2011 report. The data indicated a higher carcinogenic potency for the nitramine DMA-NO_2 than several of the included nitrosamines. We identified no studies that fulfilled the inclusion criteria from scientific reports that were not already identified in the literature search.

Conclusion

Since the evaluation of amines and their derivatives associated with CO_2 capture in 2011, very few relevant publications have been published on health hazard of the amines and nitramines in question. We identified over 50 publications that fulfilled the inclusion criteria for the nitrosamines, however, the majority of the publications was with two of the substances *N,N*-diethylnitrous amide (DEA-NO) and DMA-NO, which are known rodent carcinogens.

From the literature searches, only a few relevant new studies were identified and limited new knowledge could be gained. Taken together, there is not enough new information identified to support a revision of the recommendations given in NIPH's report for 2011.

Sammendrag

Innledning

På oppdrag fra Miljødirektoratet gjorde Folkehelseinstituttet (FHI) en vurdering av helseeffekter av utslipp av aminer, nitrosaminer og nitraminer i forbindelse med drift av CO_2 fangstanlegg, og publiserte en rapport, i 2011. Dannelsen av karsinogene nitrosaminer og nitraminer ble ansett som det kritiske helseendepunktet. I rapporten ble det konkludert med at den totale mengden nitrosaminer og nitraminer ikke bør overstige 0,3 nanogram (ng)/kubikkmeter (m^3) i luft eller 4 ng/liter (l) i drikkevann. Verdiene representerer en minimal ekstra livstidsrisiko for kreft. Disse risikoestimatene er konservative på grunn av en generell mangel på toksisitetsdata for nitraminene.

Miljødirektoratet har I 2023 bedt FHI om å gjøre et litteratursøk for å vurdere om det er kommet ny informasjon om helseeffekter av aminer og degraderingsprodukter som er relevant for CO_2-fangst. og om ny kunnskap kan endre konklusjonene og anbefalingene i rapporten fra 2011.

Metode

Utvelgelsen av hvilke aminer, nitrosaminer og nitraminer som er relevante for CO_2-fangst og som skulle inkluderes i litteratursøket ble basert på tidligere kunnskap, møter med eksterne fagfolk og informasjon fra relevant litteratur. Listen med utvalgte substanser ble diskutert og godkjent av Miljødirektoratet.

Litteratursøk i de elektroniske databasene MEDLINE (Ovid), Embase (Ovid), Web of Science og CAB Abstracts ble utført av en bibliotekar. Vi søkte etter både systematiske oversikter og primære forskningspublikasjoner. Søket etter aminer og nitrosaminer ble begrenset til publikasjoner publisert etter 1. januar i 2010. Vi begrenset også søket etter aminer til studier om allergirelaterte helseutfall og hudirritasjon. For nitrosaminer var søkestrategien begrenset til publikasjoner om gentoksisitet og karsinogenitet. Det ble ikke lagt begrensninger på søkestrategien for nitraminer med hensyn til publiseringsdato eller utfall. I tillegg til elektroniske databaser søkte vi etter relevante vitenskapelige rapporter og kreftpotens data i Carcinogenic Potency Database (CPDB).

En person filtrerte titler og sammendrag, etterfulgt av filtrering av fulltekst og uttrekk av data.

Resultater

Basert på eksisterende kunnskap ble seks aminer, 13 nitrosaminer og ni nitraminer inkludert i litteratursøkene.

I litteratursøket med aminer, ble to primære forskningspublikasjoner med til sammen tre studier funnet. I alle tre studiene ble respiratorisk- og hudsensibilisernde effekter av piperazin (PZ) undersøkt. Ingen systematiske oversikter ble funnet.

Av de 13 inkluderte nitrosaminene identifiserte vi studier for 11 av dem. Femtifem vitenskapelige publikasjoner ble funnet i nitrosaminsøket: en systematisk oversikt og 54 primære forskningspublikasjoner. Den systematiske oversikten fant en sammenheng med inntak av *N,N*-dimethylnitrous amide (DMA-NO) og økt risiko for tarm- og kolonkreft. For de primære forskningspublikasjonene ble det funnet to kasus-kontrollstudier, mens de resterende var dyrestudier eller cellestudier. Ingen nye kroniske karsinogenitetsstudier

eller studier som sammenlignet in vivo kreftpotens mellom nitrosaminer og nitraminer ble identifisert.

Ti publikasjoner, hvorav alle var primære forskningspublikasjoner, ble identifisert for de inkluderte nitraminene. Tre av de ti publikasjonene var publisert etter 2010. Kreftutvikling, gentoksisitet, hudsensibilisering, hudkorrosjon, hudirritasjon og øyeirritasjon var utfallene som ble vurdert i de identifiserte studiene. Dyrestudier som studerte kreftutvikling ble kun identifisert for *N,N*-dimetylnitramid (DMA-NO_2) and N-metylnitramid (MA-NO_2). Vi identifiserte en kronisk studie publisert i 1981 hvor tumorutvikling hos rotter etter eksponering for DMA-NO_2 og MA-NO_2 ble studert. Det ble ikke identifisert studier for tre av de ni nitraminene i litteratursøket.

CPDB inneholdt kreftpotens data for ti av de 13 nitrosaminene og to av de ni nitraminene som er det samme som er dokumentert i rapporten fra 2011. Dataene indikerte høyere kreftpotens for nitraminet DMA-NO_2 enn flere av de inkluderte nitrosaminene. Vi identifiserte ingen studier som oppfylte inklusjonskriteriene fra vitenskapelige rapporter som ikke allerede var identifisert i litteratursøket.

Konklusjon

Etter publisering av evalueringen av aminer og deres degraderingsprodukter knyttet til CO_2-fangst i 2011 er det publisert svært lite om helseeffekter av aminer og nitraminer. Vi identifiserte over 50 publikasjoner som oppfylte inklusjonskriteriene for nitrosaminene, men de fleste publikasjonene gjaldt to av stoffene *N,N*-dietylnitrous amid (DEA-NO) og DMA-NO som er velkjente kreftfremkallende stoffer i gnagere.

Fra litteratursøkene ble det identifisert få relevante nye studier, og det var begrenset med ny kunnskap. Samlet sett er det ikke funnet ny informasjon til å kunne gjøre en revisjon av anbefalingene i FHIs rapport fra 2011.

Terms of reference as provided by the Norwegian Environment Agency

In 2011, the Norwegian Institute of Public Health (NIPH) conducted an assessment of the health effects of emissions of amines, nitrosamines and nitramines to air from CO_2 capture and storage facilities for the Norwegian Environment Agency.

The task now being sought is to conduct a literature review to investigate whether any research has been published that would modify the conclusions and recommendations in the report from 2011.

1 Introduction

1.1 Background

Carbon capture is the capture of carbon dioxide CO_2. One of the technologies for removal of CO_2 is by using processes with chemical reagents, where amines is often used [1]. The use of amines in CO_2 capture technologies can result in the formation of potential hazardous substances such as nitrosamines and nitramines.

NIPH published a report in 2009 [2] on health hazard of four amines, 2-aminoethanol (MEA, CAS RN 141-43-5), 2-amino-2-methylpropan-1-ol (AMP, CAS RN 124-68-5), piperazine (PZ, CAS RN 110-85-0) and 2-[2-hydroxyethyl(methyl)amino]ethanol (MDEA, CAS RN 105-59-9), relevant for CO_2 capture. In this report, irritative and sensitising effects of the amines is reported. Also, there were indications in the scientific literature of reproductive and developmental toxicity in rodents after exposure to high doses for the that the amines PZ and MEA.

In 2011, on a request by the Norwegian Environment Agency, NIPH delivered an update on the assessment of health risk of the same four amines. NIPH was also asked to gather information from the literature on an additional 19 amines and derivatives relevant for CO_2 capture [3].

Also, in the 2011 report, an evaluation of the exposure level (in air and water) of nitrosamines and nitramines with minimal or negligible health risk was performed. The negligible excess lifetime risk level for cancer in the general population is normally 10^{5} to 10^{-6}. A 10^{-6} lifetime cancer risk means that there is one additional case of cancer during a lifetime in a population of a million persons.

Based on toxicity studies with the nitrosamine, *N,N*-dimethylnitrous amide (DMA-NO, CAS RN 62-75-9), NIPH proposed: i) recommended tolerable air concentration of 0.3 ng/m^3 based on an estimated maximum excess lifetime cancer risk below 10^{-5}, and ii) recommended tolerable drinking water concentration of 4 ng/l based on a risk level of 10^{-6}. As DMA-NO belongs to the most potent nitrosamines, the risk estimate of DMA-NO can also be used for other nitrosamines. Available data indicate that nitramines are less potent as mutagens and carcinogens than the corresponding nitrosamine. However, due to limited available data, it was not possible to carry out a cancer risk estimation for nitramines. NIPH therefore proposed the risk estimate of DMA-NO to also apply for nitramines.

The proposed risk estimate in the 2011 report is conservative and a refined risk evaluation taking into account differences in cancer potencies could be performed if i) the total nitrosamine level exceeds the above suggested level for DMA-NO exposure and ii) if nitramines constitute a large part of the total nitrosamines/nitramines, and the total levels exceed the suggested level for DMA-NO exposure. However, the last point depends on the available information on toxicity, genotoxicity and carcinogenicity of the nitramines.

As of today, the Norwegian Environment Agency have granted permission for two CO2 capture plants in Norway, and they expect receiving more applications in the future. The Norwegian Environment Agency has asked NIPH to perform a literature search to assess whether new information on amines and derivatives relevant for CO_2 capture has become available that could affect the conclusions and recommendations in the 2011 report.

1.2 Aim of the report

To provide an overview of available new knowledge on some specified health effects of amines and derivatives relevant for CO_2 capture.

1.3 Delimitations and limitations

The current report provides an overview of the available literature on specific effects on human health of the included amines, nitrosamines and nitramines. This overview includes only amines commonly used as solvent in CO_2 capture and their nitrosamine- and nitramine-degradation compounds. Other degradation compounds such as aldehydes and amides were not included.

We had only limited information on which primary amines are used for capturing of CO_2 and in what amounts as this is proprietary information.

Performing a risk assessment was out of the scope for this report. Also, no formal quality assessment of the studies and certainty of the evidence assessment were made.
Health effects was delimited to genotoxic and carcinogenic effects for nitrosamines and to allergy related health outcomes and skin irritation for amines. In addition, for nitrosamines and amines, only publications published after 1. January 2010 were included as older literature was summarised in the NIPH 2011 report.

Only one person screened titles and abstract and full texts. In addition, one person extracted data, and this has not been checked by another person.

2 Method

2.1 Selection of amines and their derivatives relevant for CO_2 capture

We had only limited information on which nitrosamines and nitramines are formed in the CO_2 capture process and in what amounts, as this is confidential information. Meetings with the Norwegian Environment Agency and external experts were held to decide an approach for the selection of substances.

It was decided that the substances included in the NIPH 2011 report [3] should be used as a starting point. In addition, several publications [4-6] were screened to complement the list with potentially relevant substances. The list was then discussed within the project group and external experts within the field, before making the final list. The list of selected substances was discussed with, and approved by, the Norwegian Environment Agency.

2.2 Literature search and study selection

A research librarian performed literature searches in the electronic databases from MEDLINE (Ovid), Embase (Ovid), Web of Science, and CAB Abstracts. The search strategies for MEDLINE (Ovid) are available in Appendix A.

The eligibility criteria were pre-defined before starting the screening of the publications. We included both primary studies and systematic reviews. For amines the search was focused on allergy related health outcomes and skin irritation, while we searched for publications on genotoxicity and carcinogenicity for nitrosamines. There was no restriction on outcome for the nitramines. The complete list of eligibility criteria is available in Appendix B.

One person screened titles and abstract from the references identified in the literature searches, as well as for full texts that were included during screening of titles and abstracts. Rayyan, a commercial program for systematic reviews, was used both for screening of titles and abstract and full texts [7].

In addition, relevant scientific reports and recent health risk assessments (published after 1. January 2010) were collected by all members of the project group.

We searched the Carcinogenic Potency Database (CPDB) [8] for carcinogenic potency data for the nitrosamines and nitramines.

2.3 Data extraction

One person extracted relevant data from the included publications and information on each study was compiled in Excel.

The following was extracted from the studies:

- Population/test system (Human, animal, in vitro)
- Exposure (substance(s))
- Outcome (e.g., genotoxicity, skin irritation)
- Method (e.g., comet assay)
- Findings

Information about concentrations and duration of exposure was only extracted for in vivo studies.

3 Results

3.1 Included amines and derivatives relevant for CO_2 capture

In this report, six amines (Table 3.1-1), 13 nitrosamines (Table 3.1-2) and nine nitramines (Table 3.1-3) are included.

Table 3.1-1. Overview of the six included amines with their IUPAC names, abbreviations and Chemical Abstracts Service (CAS) Registry Number (RN).

IUPAC name	CAS RN	Abbreviation
2-aminoethanol	141-43-5	MEA
2-[2-hydroxyethyl(methyl)amino]ethanol	105-59-9	MDEA
2-amino-2-methylpropan-1-ol	124-68-5	AMP
Piperazine	110-85-0	PZ
2-piperazin-1-ylethanol	103-76-4	PZE
2-[4-(2-hydroxyethyl)piperazin-1-yl]ethanol	122-96-3	PZDE

Table 3.1-2. Overview of the 13 included nitrosamines with their IUPAC names, abbreviations and Chemical Abstracts Service (CAS) Registry Number (RN).

IUPAC name	CAS RN	Abbreviation
N,N-dimethylnitrous amide	62-75-9	DMA-NO
N,N-bis(2-hydroxyethyl)nitrous amide	1116-54-7	DELA-NO
1-nitrosopiperidine	100-75-4	PIP-NO
N,N-diethylnitrous amide	55-18-5	DEA-NO
N-ethyl-N-methylnitrous amide	10595-95-6	MEA-NO
4-nitrosomorpholine	59-89-2	MOR-NO
1-nitrosopyrrolidine	930-55-2	PYR-NO
1-nitrosopiperazine	5632-47-3	PZ-NO
2-[2-hydroxyethyl(nitroso)amino]acetic acid	80556-89-4	HEA-NO
N,N-dipropylnitrous amide	621-64-7	DPA-NO
N,N-dibutylnitrous amide	924-16-3	DBA-NO
2-(4-nitrosopiperazin-1-yl)ethanol	48121-20-6	PZE-NO
1,4-dinitrosopiperazine	140-79-4	DPZ-NO

Table 3.1-3. Overview of the nine included nitramines with their IUPAC names, abbreviations and Chemical Abstracts Service (CAS) Registry Number (RN).

IUPAC name	CAS RN	Abbreviation
N,N-dimethylnitramide	4164-28-7	DMA-NO_2
N-(2-hydroxyethyl)nitramide	74386-82-6	MEA-NO_2
N-methylnitramide	598-57-2	MA-NO_2
1-nitropiperazine	42499-41-2	PZ-NO_2
N-(1-hydroxy-2-methylpropan-2-yl)nitramide	1239666-60-4	AMP-NO_2
N,N-diethylnitramide	7119-92-8	DE-NO_2
1,4-dinitropiperazine	4167-37-8	DPZ-NO_2
1-nitro-4-nitrosopiperazine	Not found	NPZ-NO_2
2-(4-nitropiperazin-1-yl)ethanol	42499-45-6	PZE-NO_2

3.2 Literature search and study selection

Flowcharts for the study selection of primary studies and systematic reviews for amines, nitrosamines and nitramines are presented in Appendix C.

We identified no studies that fulfilled the inclusion criteria from scientific reports that were not already identified in the literature search.

3.3 Carcinogenic potency values for the included nitrosamines and nitramines

Data on Tumourigenic dose 50 (TD50) for chronic rat carcinogenic studies were extracted the Carcinogenic Potency Database (CPDB) [8] (Table 3.3-1). TD50 is a numerical description of the carcinogenic potency of chemicals in chronic-exposure animal experiments. A lower TD50 equals a higher carcinogenic potency. DEA-NO is the most potent of the included substances followed by MEA-NO and DMA-NO.

The nitramine DMA-NO_2 has a higher carcinogenic potency than several of the nitrosamines. There was a lack of a carcinogenic potency value for three of the nitrosamines and for seven of the nitramines.

Table 3.3-1. Comparison of Tumourigenic dose 50 (TD50) values for the included nitrosamines and nitramines to indicate relative carcinogenic potencies. The substances are ranked after carcinogenic potency, where the substance that are most potent are on the top. The data were extracted from the Carcinogenic Potency Database (CPDB) [8].

Substance	CAS RN	Substance group	TD50 (mg/kg bw/day) Rat
DEA-NO	55-18-5	Nitrosamine	0.0265
MEA-NO	10595-95-6	Nitrosamine	0.0503
DMA-NO	62-75-9	Nitrosamine	0.0959
MOR-NO	59-89-2	Nitrosamine	0.109
DPA-NO	621-64-7	Nitrosamine	0.186
DMA-NO_2	4164-28-7	Nitramine	0.547
DBA-NO	924-16-3	Nitrosamine	0.691
PYR-NO	930-55-2	Nitrosamine	0.799
PIP-NO	100-75-4	Nitrosamine	1.43
DELA-NO	1116-54-7	Nitrosamine	3.17
PZ-NO	5632-47-3	Nitrosamine	8.78
MA-NO_2	598-57-2	Nitramine	17.4
HEA-NO	80556-89-4	Nitrosamine	-
PZE-NO	48121-20-6	Nitrosamine	-
DPZ-NO	140-79-4	Nitrosamine	-
MEA-NO_2	74386-82-6	Nitramine	-
PZ-NO_2	42499-41-2	Nitramine	-
AMP-NO_2	1239666-60-4	Nitramine	-
DE-NO_2	7119-92-8	Nitramine	-
DPZ-NO_2	4167-37-8	Nitramine	-
NPZ-NO_2	Not found	Nitramine	-
PZE-NO_2	42499-45-6	Nitramine	-

Abbreviations: CAS RN, Chemical Abstract Service Registry Number
For IUPAC substance names, see Table 3.1-2 and 3.1-3.

3.4 Summary of findings

Overview of all extracted data can be found in Supplementary materials 1.

Each publication can contain one or more studies or experiments (referred to as studies in these report) and one or more substances.

3.4.1 Summary of findings and conclusion for amines

The amines MEA, AMP, MDEA and PZ were evaluated in two previous reports by NIPH [2, 3]. In this current report, NIPH has included an overview of new information published after 1. January 2010. The amines PZE and PZDE was not evaluated in the two previous reports. An overview of identified studies for the included amines on sensitisation and irritation effects is shown in Table 3.4.1-1.

In total we identified two publications and three studies published in 2010 or later. We identified three studies which assessed effects of piperazine (PZ); two animal studies and

one in chemico (protein-binding) assay. No studies for the other five included amines fulfilled the inclusion criteria. Since PZE and PZDE have not been previously evaluated, it is possible that toxicity studies on these substances were published before 2010.

Table 3.4.1-1. Overview of the number of studies for each amine and information on population/test system, exposure route and, outcome addressed and findings.

Substance	N studies	Population/ test system	Exposure (administration route)	Outcome addressed	Findings	Ref
MEA	0					
MDEA	0					
AMP	0					
PZ	3	In chemico	NA	1 study Skin sensitisation	Minimal reactivity	[9]
		Mouse	Intratracheal	1 study Respiratory sensitisation	Increase in IL-6 in BALF	[10]
		Mouse	Dermal	1 study Respiratory sensitisation	Increase in total serum IgE	[10]
PZE	0					
PZDE	0					

Abbreviations: BALF, bronchoalveolar lavage fluid; N, number; NA, not applicable; ref, reference. For IUPAC substance names, see Table 3.1-1.

Conclusion for amines

Very few studies on allergy related health outcomes and skin irritation for the six amines were identified in the literature search. The three studies identified for PZ do not provide new knowledge on the health hazard of PZ and are not suitable for the determination of a point of departure for a risk characterisation.

3.4.2 Summary of findings and conclusion for nitrosamines

We searched for studies assessing genotoxicity and carcinogenicity for the included nitrosamines. We identified 55 scientific publications that fulfilled the inclusion criteria: one systematic review and 54 primary research publications. Each publication can have one or more studies/experiments and can have studied one or more substances. An overview of identified studies for the included nitrosamines on genotoxicity and carcinogenicity effects is shown in Table 3.4.2-1. Overview on information extracted from each study is included in Supplementary materials 1.

Of the 13 included nitrosamines, we identified studies published 2010 or later for 11 of them. The most studied of the 13 included nitrosamines was DEA-NO, followed by DMA-

NO. For the other nitrosamines, less than 10 studies were identified for each substance. No studies were identified for HEA-NO and PZE-NO.

The systematic review with a meta-analysis assessed the association between nitrate, nitrite, and nitrosamines in food and water and the risk of different types of cancer. The intake of DMA was associated with an increased risk of gastrointestinal cancer and colorectal cancer [11].

Studies on carcinogenicity in animals were only identified for DEA-NO, which is a known liver carcinogen in rodents and the substance is used to induce hepatocellular carcinomas as an experimental model for this type of cancer. No studies comparing the in vivo genotoxic potency between nitrosamines or between nitrosamines and nitramines were identified. However, two in vitro studies comparing nitrosamine and nitramine genotoxicity were identified [12, 13].

Nitrosamines are considered to be strong carcinogens that may produce cancer in diverse organs and tissues including lung, brain, liver, kidney, bladder, stomach, esophagus, and nasal sinus [14]. Eight out of the 13 included nitrosamines, DMA-NO, DELA-NO, PIP-NO, DEA-NO, MOR-NO, PYR-NO, DBA-NO, DPA-NO, have been classified as *reasonably anticipated* to be a human carcinogen based on sufficient evidence of carcinogenicity from studies in experimental animals by the National Toxicology Program (NTP) [15]. Also, DMA-NO and DEA-NO have been classified as Group 2A (Probably carcinogenic to humans), whereas the substances DELA-NO, PIP-NO, MEA-NO, MOR-NO, PYR-NO, DPA-NO and DBA-NO have been classified as 2B (Possibly carcinogenic to humans) by the International Agency for Research on Cancer (IARC) [16].

Searching the Carcinogenic Potency Database (CPDB) [8] we identified carcinogenic potency data for ten of the 13 included nitrosamines (Table 3.3-1). A value was not identified for HEA-NO, PZ-NO and DPZ-NO. Also, in the literature search for publications published after 1. January 2010, no studies were identified for PZ-NO and HEA-NO. Two in vitro genotoxicity studies, Ames test and comet assay, were identified for DPZ-NO, which both yielded positive results in the presence of metabolic activation [13].

Conclusion for nitrosamines

We identified more than 50 new publications since the literature search performed in the NIPH 2011 report. However, no new chronic carcinogenicity studies for any of the included nitrosamines were identified. The carcinogenic potency values have not been updated since the NIPH 2011 report was published. Also, no studies evaluating the in vivo genotoxic potency between nitrosamines or between nitrosamines and nitramines were identified.

Table 3.4.2-1. Overview of the number of studies for each nitrosamine and information on study design, population/test system and outcome addressed.

Substance	N studies	Study design and population/test system	Outcome addressed	Ref(s)
DMA-NO	30	Case-control, human	2 studies Carcinogenicity	[17, 18]
		Experimental, animal	5 studies Genotoxicity	[19-22]
		Experimental, in vitro	23 studies Genotoxicity	[12, 13, 23-35]
DELA-NO	2	Experimental, in vitro	2 studies Genotoxicity	[13]
PIP-NO	4	Experimental, animal	1 study Genotoxicity	[36]
		Experimental, in vitro	3 studies Genotoxicity	[12, 36]
DEA-NO	49	Case-control, human	1 study Carcinogenicity	[17]
		Experimental, animal	13 studies Tumour development	[37-49]
		Experimental, animal	18 studies Genotoxicity	[21, 50-60]
		Experimental, in vitro	17 studies Genotoxicity	[23, 26, 30, 31, 33, 34, 61-65]
MEA-NO	6	Experimental, in vitro	6 studies Genotoxicity	[25, 34]
MOR-NO	5	Experimental, in vitro	5 studies Genotoxicity	[12, 13, 26]
PYR-NO	5	Experimental, animal	1 study Genotoxicity	[66]
		Experimental, in vitro	4 studies Genotoxicity	[12, 27, 31]
PZ-NO	2	Experimental, in vitro	2 studies Genotoxicity	[13]
HEA-NO	0			
DPA-NO	8	Experimental, animal	1 study Genotoxicity	[67]
		Experimental, in vitro	7 studies Genotoxicity	[23, 25, 31, 65, 68]
DBA-NO	4	Experimental, in vitro	4 studies Genotoxicity	[23, 33, 63]
PZE-NO	0			
DPZ-NO	2	Experimental, in vitro	2 studies Genotoxicity	[13]

Abbreviations: N, number; ref, references. For IUPAC substance names, see Table 3.1-2.

3.4.3 Summary of findings and conclusion for nitramines

For nitramines, all health endpoints were included and there was no restriction on publication date.

In total we identified ten publications that fulfilled the inclusion criteria for nitramines. Three of the ten publications were published after the literature search performed in the 2011 report [3], which all contained in vitro experiments.

Each publication contained one or more studies or experiments (referred to as studies in these report) and studied one or more nitramines. An overview of identified studies for the included nitramines is shown in Table 3.4.3-1 for in vivo studies and Table 3.4.3-2 for in vitro studies.

DMA-NO_2

We identified 15 studies which assessed adverse effects of DMA-NO_2.

Three studies assessed tumour development following oral exposure in rats, where two studies showed an increase in liver tumours [69, 70] and two studies showed an increase in nasal cavity tumours [70, 71].

A total of nine studies evaluated the genotoxic potential of DMA-NO_2 in vitro. Five studies assessed the mutagenic potential of DMA-NO_2. In all five studies, DMA-NO_2 was not mutagenic without metabolic activation in any of the strains tested. Also, DMA-NO_2 was not mutagenic when tested with metabolic activation for the strains TA98, TA102, TA1535, TA1537, and TA1538 [13, 72-75]. With metabolic activation, DMA-NO_2 was mutagenic in strain YG7108 [13]. For the strain TA100, mixed results were reported, whereas two studies reported positive results for DMA-NO_2 with metabolic activation [72, 73], and two other studies reported negative results [74, 75]. DNA strand breaks, which is a measure for primary DNA damage, were assessed in three studies [13, 73, 74]. DMA-NO_2 was weakly genotoxic [73] in one study and not genotoxic in two studies [13, 74]. DMA-NO_2 did not increase the number of micronucleated cells neither with nor without metabolic activation [74].

DMA-NO_2 was not irritant or corrosive to the skin but did cause a mild eye irritation [76].

MEA-NO_2

We identified seven studies that assessed adverse effects of MEA-NO_2. No in vivo studies were identified. Seven in vitro studies were identified, and these are summarised in Table 3.4.3-2.

The genotoxic potential of MEA-NO_2 was assessed in three studies. MEA-NO_2 increased the number of micronucleated cells and show mutagenic activity in two strains in the Ames test, TA102 and TA1535. MEA-NO_2 was negative in other strains tested and was negative in the comet assay [74].

MEA-NO_2 was not irritant or corrosive to the skin, but in one study, severe eye irritation was observed. A test for dendritic cell activation indicates that MEA-NO_2 did not activate dendritic cells in the VITOSENS assay [76], which is one of three key events in the adverse outcome pathway (AOP) for skin sensitisation [77].

MA-NO_2

We identified 11 studies that assessed adverse effects of MA-NO_2. One in vivo study was identified (Table 3.4.3-1). Ten in vitro studies were identified, and these are summarised in Table 3.4.3-2.

One study assessed tumour development following oral exposure in rats, and MA-NO_2 increased the number of neurinomas of the spine, spinal nerves and peripheral nerves [71].

The genotoxic potential of MA-NO_2 was assessed in six studies. MA-NO_2 showed mutagenic activity in TA100 with metabolic activation in one of two studies [72, 75] and was positive with and without metabolic activation in TA102 (only used in one study) [74]. MA-NO_2 did not increase the mutation frequency in other strains tested, such as TA98, TA1535, TA1537, TA1538. MA-NO_2 increased the number of micronucleated cells with, but not without, metabolic activation [74]. DNA strand breaks were assessed in four different cell lines and MA-NO_2 showed DNA damaging potential in one (primary hepatocytes) [73] but was negative in the other three [74].

MA-NO_2 was not irritant or corrosive to the skin and did not activate dendritic cells in the VITOSENS assay. In the same publication, severe eye irritation in rats was observed following exposure to MA-NO_2 [76].

PZ-NO_2

Five in vitro studies assessing adverse effects of PZ-NO_2 were found (Table 3.4.3-2). No in vivo studies were identified. All five identified studies assessed the genotoxic potential of PZ-NO_2. PZ-NO_2 did not induce mutations [13, 74], chromosomal damage [74] or DNA strand breaks [13, 74].

AMP-NO_2

Six in vitro studies assessing adverse effects of AMP-NO_2 were found (Table 3.4.3-1). No in vivo studies were identified.

The genotoxic potential of AMP-NO_2 was assessed in one publication with three different genotoxic endpoints. AMP-NO_2 did not cause DNA damage in cells. AMP-NO_2 did not induce mutations, chromosomal damage or DNA strand breaks [74].

AMP-NO_2 was not irritant or corrosive to the skin. In the same publication, severe eye irritation was observed [76].

DPZ-NO_2

One publication which contained two in vitro studies of DPZ-NO_2 was found (Table 3.4.3-1). DPZ-NO_2 did not cause DNA damage in eukaryote cells with and without metabolic activation but was mutagenic in strain YG7108 in the Ames test [13].

DE-NO_2, NPZ-NO_2 and PZE-NO_2

No studies were found for DE-NO_2, NPZ-NO_2 and PZE-NO_2 that fulfilled the inclusion criteria (Table 3.4.3-1 and 3.4.3-2).

Conclusion for nitramines

The literature search in the 2011 report showed that chronic carcinogenicity data of nitramines was very limited, and the information was not sufficient for a proper health hazard evaluation. In general, nitramines seem to be less potent as mutagens and carcinogens than the corresponding nitrosamines. In the current report we performed a new literature search, with no publication date restriction or restriction on outcome. Yet, we only identified ten publications, whereas three was published after 2010.

Table 3.4.3-1. Overview of the number of in vivo studies for each nitramine and information on species, exposure route, outcomes addressed and findings.

Substance	N studies	Species	Exposure (administration route)	Outcome addressed	Findings	Ref(s)
DMA-NO_2	3	Rat	Oral	Tumour development	2 studies; increase in liver tumours, 2 studies: increase in nasal cavity tumours	[69-71]
MEA-NO_2	0					
MA-NO_2	1	Rat	Oral	Tumour development	Increase in neurinoma of the spine, spinal nerves and peripheral nerves	[71]
PZ-NO_2	0					
AMP-NO_2	0					
DPZ-NO_2	0					
DE-NO_2	0					
NPZ-NO_2	0					
PZE-NO_2	0					

Abbreviations: N, number; ref, references. For IUPAC substance names, see Table 3.1-3.

Table 3.4.3-1. Overview of the number of in vitro studies for each nitramine and information on outcomes addressed and findings.

Substance	N studies	Outcome addressed	Findings	Ref(s)
DMA-NO_2	12	Genotoxicity, DNA strand breaks	3 studies Negative in two studies, and weakly positive in one.	[13, 73, 74]
		Genotoxicity, mutation	5 studies Negative in the absence of metabolic activation, some negative and some positive results with metabolic activation.	[13, 72-75]
		Genotoxicity, chromosomal damage	1 study Negative	[74]
		Eye irritation	1 study Mild eye irritation response	[76]
		Skin irritation	1 study Not irritant to the skin	[76]
		Skin corrosion	1 study Not corrosive to the skin	[76]
MEA-NO_2	7	Genotoxicity, DNA strand breaks	1 study Negative	[74]
		Genotoxicity, mutation	1 study Positive in TA102 and 1535 with and without metabolic activation. Negative in strains TA98, TA100, TA1537.	[74]
		Genotoxicity, chromosomal damage	1 study Positive with and without metabolic activation	[74]
		Eye irritation	1 study Severe eye irritation response	[76]
		Skin irritation	1 study; not irritant to the skin	[76]
		Skin corrosion	1 study Not corrosive to the skin	[76]
		Skin sensitisation	1 study No activation of dendritic cells	[76]
MA-NO_2	10	Genotoxicity, mutation	3 studies Positive in TA102 with and without metabolic activation, positive in TA100 with metabolic activation. Negative in other strains tested.	[72, 74, 75]
		Genotoxicity, chromosomal damage	1 study Positive with metabolic activation	[74]
		Genotoxicity, DNA strand break	2 studies Positive in primary hepatocytes, negative in three other cell lines.	[73, 74]
		Eye irritation	1 study Severe eye irritation response	[76]
		Skin irritation	1 study Not irritant to the skin	[76]
		Skin corrosion	1 study Not corrosive to the skin	[76]

Substance	N studies	Outcome addressed	Findings	Ref(s)
		Skin sensitisation	1 study No activation of dendritic cells	[76]
PZ-NO_2	5	Genotoxicity, mutations	2 studies Negative in all strains tested both with and without metabolic activation.	[13, 74]
		Genotoxicity, chromosomal damage	1 study Negative with and without metabolic activation	[74]
		Genotoxicity, DNA strand break	2 studies Negative with and without metabolic activation	[13, 74]
AMP-NO_2	6	Genotoxicity, mutations	1 study Negative in all strains tested both with and without metabolic activation.	[13, 74]
		Genotoxicity, chromosomal damage	1 study Negative with and without metabolic activation	[74]
		Genotoxicity, DNA strand break	1 study Negative	[74]
		Eye irritation	1 study Severe eye irritation response	[76]
		Skin irritation	1 study Not irritant to the skin	[76]
		Skin corrosion	1 study Not corrosive to the skin	[76]
DPZ-NO_2	2	Genotoxicity, mutations	1 study Positive with and without metabolic activation.	[13]
		Genotoxicity, DNA strand break	1 study Negative with and without metabolic activation	[13]
DE-NO_2	0			
NPZ-NO_2	0			
PZE-NO_2	0			

Abbreviations: N, number; ref, references. For IUPAC substance names, see Table 3.1-3.

Discussion

For each of the included substances, numerous different chemical names and abbreviations are used in the published literature. In addition, only a few of the included publications reported the CAS RN, which makes the identification of the substances more difficult and uncertain.

Nitrosamines are potent carcinogens and cancer risk has been identified as a main concern for amine-based CO_2 capture [2, 3]. Nitramines are structurally related to nitrosamines, but data on their health effect in the previous reports were scarce. Due to possible human exposure to nitramines from CO_2 capturing processes, a need for more information on toxic, mutagenic and carcinogenic properties of the nitramines was stressed in the NIPH 2011 report.

No new cancer bioassays were identified for the selected substances, but there are a few newer publications reporting in vitro genotoxicity and mutagenicity assays. Although several nitrosamines are known mutagenic carcinogens, in vitro genotoxicity assays may display low sensitivity due in part to insufficient metabolic activation and to specificities of the bacterial strains used [13, 78]. Thus, these genotoxicity results must be interpreted with care. Wagner (2014) [13] compared the genotoxic potencies of nitrosamines and nitramines, and the findings support the concept of higher potencies of nitrosamines compared to the related nitramines.

Fjellsbø and co-workers (2013) [76] examined four of the nitramines included in the present study and showed that they are mild to very severe eye irritants, but not irritating to skin, based on in vitro assays in accordance with OECD guidelines. An in vitro Dendritic cell activation assay was used to predict skin sensitisation of nitramines, but no complete predictions according to current guidelines have been performed.

The amines are all classified or suggested classified for corrosion or irritation (skin and/or eye). In addition, PZ is classified for skin and respiratory sensitisation (ECHA, CLP harmonised classification). No new data were identified to expand on these classifications.

Conclusion

Since the evaluation of potential health effects of amines and their derivatives associated with CO_2 capture in 2011, very few relevant publications have been published on health hazard of the amines and nitramines in question. We identified over 50 publications that fulfilled the inclusion criteria for the nitrosamines, however, the majority of the publications included data on the two substances DEA-NO and DMA-NO, which are well known rodent carcinogens. This updated literature review show that there are still significant knowledge gaps hampering the assessment of potential health effects of nitramines.

In the NIPH 2011 report, it was recommended that the total amount of nitrosamines and nitramines should not exceed 0.3 ng/m^3 in air and/or 4 ng/l in drinking water. These risk estimates are conservative and if the total amount of nitrosamines and nitramines exceed the recommended value, a more refined risk evaluation taking into account differences in cancer potencies could be performed. Toxicity data from chronic studies are lacking for some of the nitrosamines and most of the nitramines. When cancer potency value for a substance is lacking, NIPH recommends that the potency for DMA is used. To perform a refined risk evaluation, the substances, their toxicities, and the environmental concentration of each substance have to be known.

In conclusion, no data was identified in this updated literature review that would change the recommendation from 2011.

Appendix A: Search strategies

Search strategy for amines

Drafting the search strategy and performing the search	Bente Foss
Critical review of the search strategy	Nataliya Byelyey
Duplications	Before removal of duplicates: 1224 primary studies and 111 reviews Result after removal of duplicates: 969 primary studies and 110 reviews

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) <1946 to July 06, 2023>
Date: 07.07.2023
Result: 244 primary studies; 2 reviews

1	amines/ or ethanolamine/ or propanolamines/ or piperazine/	43007
2	(Ethanolamine? or colamine? or "2-Aminoethanolor Monoethanolamine" or "Mono ethanolamine" or "2-Ethanolamine" or Alkanolamine? or "N-Methyldiethanolamine" or Methyldiethanolamine? or "Methyl diethanolamine?" or "MDEA amine?" or "2,2'-(methylimino)diethanol" or "2-[2-hydroxyethyl(methyl)amino]ethanol").tw,kf.	7861
3	("aminomethyl propanol" or "2-amino-2-methyl-1-propanol" or "2-amino-2-methyl-1-propanol hydrochloride" or "2-amino-2-methyl-1-propanol mesylate" or "2-amino-2-methyl-1-propanol nitrate salt" or "2-amino-2-methyl-1-propanol tosylate" or "2-amino-2-methylpropanol" or aminopropanol? or propanolamine?).tw,kf.	384
4	(Piperazine? or "1,4 Diazacyclohexane" or "1,4-piperazineor piperazine diacetate" or "piperazine dihydrochloride" or "piperazine hexahydrate" or "piperazine hydrate" or "piperazine hydrobromide" or "piperazine hydrochloride" or "piperazine monohydrochloride" or "piperazine mono hydrochloride" or "piperazine phosphate" or "piperazine salt" or "piperazine sulfate" or "Piperazine Tartrate" or "piperazine tartrate (1:1), (R-(R*,R*))-isomer" or "piperazine tartrate, (R-(R*,R*))-isomer" or "piperazinium oleate" or Pripsen).tw,kf.	8558
5	("2-piperazin-1-ylethanol" or "N-(2-Hydroxyethyl)piperazine" or "1-PIPERAZINEETHANOL" or "1-(2-Hydroxyethyl)piperazine" or "2-Piperazinoethanol" or "Hydroxyethylpiperazine" or "2-(piperazin-1-yl)ethan-1-ol" or "1-Piperazinethanol" or "2-(1-Piperazinyl)ethanol" or "2-Hydroxyethylpiperazine" or "2-(piperazin-1-yl)ethanol" or "USAF DO-22" or "4-(2-Hydroxyethyl)piperazine" or "Ethanol, 2-(1-piperazinyl)*" or "Piperazine-1-ethanol" or "N-(beta-Hydroxyethyl)piperazine" or "1-(beta-Hydroxyethyl)piperazine" or "2-Piperazin-1-yl-ethanol" or MFCD00005970 or "NSC 26884" or "NSC26884" or "1-(2-hydroxyethyl)-piperazine").tw,kf.	562
6	("2-[4-(2-hydroxyethyl)piperazin-1-yl]ethanol" or "1,4-Piperazinediethanol" or "2,2'-(Piperazine-1,4-diyl)diethanol" or "1,4-Bis(2-hydroxyethyl)piperazine" or "1,4-Di(2-hydroxyethyl)piperazine" or "N,N'-Dihydroxyethylpiperazine" or "N,N'-Bis(2-hydroxyethyl)piperazine" or "N,N'-Di(2-hydroxyethyl)piperazine" or "Piperazine-1,4-diethanol").tw,kf.	10
7	("141-43-5" or "105-59-9" or "124-68-5" or "110-85-0" or "205-483-3" or "602-036-8" or "602-038-9" or "618-436-0" or "682-672-0" or "685-828-6" or "690-	2

	571-8" or "203-312-7" or "204-709-8" or "203-808-3" or "103-76-4" or "203-142-3" or "122-96-3" or "204-586-0").mp.	
8	or/1-7	57798
9	exp Hypersensitivity/ or exp Dermatitis/ or exp Haptens/ or exp Urticaria/	448397
10	(allergy or allergies or allergic or hypersensitivit* or allergenicit* or hapten? or urticar* or (skin adj1 (sensiti#ation or irritation or inflamma*))).tw,kf.	290099
11	(respiratory hypersensitivity* or (airway adj1 (hyper-responsitiveness* or hyperresponsitiveness*))).tw,kf.	359
12	Asthma*.tw,kf.	181472
13	(dermatitides or dermatitis or rhinitis or rhinitides).tw,kf.	101262
14	((atopic or disseminated or infantile) adj1 (e#zema or e#sema or neurodermatitides or neurodermatitis)).tw,kf.	3577
15	(contact adj1 (dermatitides or dermatitis or e#zema or e#sema or hypersensitivity* or sensitiv*)).tw,kf.	20858
16	or/9-15	636498
17	8 and 16	985
18	limit 17 to yr="2010 -Current"	250
19	limit 18 to (danish or dutch or english or multilingual or norwegian or swedish)	246
20	limit 19 to "reviews (maximizes specificity)"	2
21	Meta-Analysis/ or Network Meta-Analysis/ or ((systematic* adj2 review*) or metaanal* or "meta anal*" or (review and ((structured or database* or systematic*) adj2 search*)) or "integrative review*" or (evidence adj2 review*)).tw,kf,bt.	511767
22	20 or (19 and 21)	2

Search strategy for nitrosamines

Drafting the search strategy and performing the search	Astrid Nøstberg
Critical review of the search strategy	Marita Heintz
Duplications	Before removal of duplicates: 8417 primary studies and 61 reviews Result after removal of duplicates: 3678 primary studies and 44 reviews

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions <1946 to September 15, 2023>
Date: 18.09.2023
Result: 2368 primary studies; 9 reviews

#	Searches	Resultat
1	Dimethylnitrosamine/ or ("N,N-dimethylnitrous amide?" or Dimethylnitrosamin* or Nitrosodimethylamin* or "N-Nitroaodimethylamin*" or "N-Nitroso-N,N-dimethylamin*" or "N-Methyl-N-nitrosomethanamin*" or NDMA or "dimethyl n nitrosamin*" or "dimethyl nitrosamin*" or "dimethyl nitrosoamin*" or dimethylnitrosoamin* or ww17d4 or "62-75-9" or "200-549-8").tw,kf,nm.	4953
2	("N,N-bis(2-hydroxyethyl)nitrous amide?" or Nitrosodiethanolamin* or diethanolnitrosamin* or Diethanolnitrosoamin* or "bis(2 hydroxyethyl)nitrosamin*" or "n nitroso bis(2 hydroxyethyl)amin*" or "nitrosamin*,bis(2 hydroxyethyl)" or NDELA or "1116-54-7" or "214-237-4").tw,kf,nm.	197
3	(nitrosopiperidin* or "N-nitrosopentamethyleneimin*" or "N-Nitroso-piperidin*" or "1-Nitroso-piperidin*" or "NPIP 100-75-4" or "202-886-6").tw,kf,nm.	282
4	Diethylnitrosamine/ or ("N,N-diethylnitrous amide?" or Diethylnitrosamin* or "Diethyl nitrosamin*" or Nitrosodiethylamin* or "N-Ethyl-N-nitrosoethanamin*" or NDEA or dena or "diethyl n nitrosamin*" or diethylnitrosamide? or diethylnitrosoamin* or "nitroso diethylamin*" or "nitroso n,n diethylamin*" or "55-18-5" or "200-226-1").tw,kf,nm.	6070
5	("N-ethyl-N-methylnitrous amide?" or ethylmethylnitrosamin* or ethylnitrosomethylamin* or methylethylnitrosamin* or nitrosoethylmethylamin* or nitrosomethylethylamin* or "N-Methyl-N-nitrosoethanamin*" or "N-Methyl-N-nitrosoethylamin*" or "N-nitroso-methyl-ethylamin*" or "n nitroso n methylethylamin*" or "nitrosamin*,ethylmethyl" or NMEA or "10595-95-6" or "621-991-1").tw,kf,nm.	163
6	(Nitrosomorpholin* or "4 nitroso morpholin*" or "morpholin*,n nitroso" or NMOR or "59-89-2" or "627-564-6").tw,kf,nm.	652
7	N-Nitrosopyrrolidine/ or (Nitrosopyrrolidin* or "N-Nitroso-pyrrolidin*" or "1-nitroso-Pyrrolidin*" or NPYR or "930-55-2" or "213-218-8").tw,kf,nm.	526
8	(nitrosopiperazin* or mononitrosopiperazin* or "N-nitroso piperazin*" or NPZ or "5632-47-3" or "803-995-7" or "fk 960" or fk960 or "fr 59960" or fr59960 or "n (4 acetyl 1 piperazinyl) 4 fluorobenzamide?").tw,kf,nm.	177
9	("2-[2-hydroxyethyl(nitroso)amino]acetic acid" or "N-(2-hydroxyethyl)-N-carboxymethylnitrosamin*" or "nitroso-(2-hydroxyethyl)glycine" or "Nitroso(2-Hydroxyethyl)glycine" or "N-(2-Hydroxyethyl)-N-nitrosoglycine" or "2-[(2-Hydroxyethyl)nitrosoamino]acetic Acid" or "N-Nitroso-N-(2-hydroxyethyl)glycine" or NHEG or OHECMN or "NO-HeGly" or "80556-89-4").tw,kf,nm.	23
10	("N,N-dipropylnitrous amide?" or "N-nitroso(di-n-propyl)amin*" or dipropylnitrosamin* or "N-nitrosodipropylamin*" or "Nitrosodi-n-propylamin*" or "N-Nitroso-di-n-propylamin*" or "N-Nitroso-N-propyl-1-propanamin*" or "N-	289

	Nitroso(di-n-propyl)amin*" or "di n propyl n nitrosamin*" or "di n propylnitrosamin*" or "nitrosamin*,dipropyl" or NDPA or "621-64-7" or "210-698-0").tw,kf,nm.	
11	("N,N-dibutylnitrous amide?" or dibutylnitrosamin* or "Nitrosodi-n-butylamin*" or nitrosodibutylamin* or "N-Nitroso-di-n-butylamin*" or Dibutylnitrosoamin* or "di n butyl n nitrosamin*" or "di n butyl nitrosamin*" or "di n butylnitrosamin*" or "nitrosamin*,dibutyl" or NDBA or "924-16-3" or "213-101-1").tw,kf,nm.	327
12	("2-(4-nitrosopiperazin-1-yl)ethanol" or "2-(4-nitroso-piperazin-1-yl)-ethanol" or "2-(4-nitrosopiperazin-1-yl)ethan-1-ol" or SCHEMBL18650422 or AKOS040822781 or "1-Nitroso-4-(2-hydroxyethyl)piperazin*" or "1-(2-Hydroxyethyl) 4-nitroso piperazin*" or "1-(2-Hydroxyethyl)4-nitrosopiperazin*" or "EN300-7759346" or Z1736780064 or "48121-20-6" or "691-848-6").tw,kf,nm.	0
13	(Dinitrosopiperazin* or "Dinitroso piperazin*" or "1,4-Dinitroso-piperazin*" or "140-79-4" or "205-434-6").tw,kf,nm.	71
14	or/1-13	11683
15	Mutation/ or Chromosome Aberrations/ or Aneuploidy/ or Chromosome Breakage/ or Chromosome Duplication/ or Frameshift Mutation/ or Gene Duplication/ or Point Mutation/ or Mutagens/ or Aneugens/ or Mutagenesis/ or Mutagenicity Tests/ or Comet Assay/ or Micronucleus Tests/ or DNA Damage/ or DNA Adducts/ or DNA Breaks/ or DNA Breaks, Double-Stranded/ or DNA Breaks, Single-Stranded/ or Cytogenetics/ or Sister Chromatid Exchange/ or Noxae/	749008
16	(Mutation? or mutagen* or (gene? adj2 alteration?) or mutator? or Genotoxi* or "Genetic Toxicity Test?" or "Ames test*" or "ames salmonella assay?" or "mouse lymphoma tk assay?" or "mouse lymphoma assay?" or "mouse spot test*" or mutamouse or (Muta adj2 Mouse) or "Big Blue" or BigBlue or "LacZ mouse" or "LacI mouse" or "cII gene" or "gpt delta" or (("deoxyribonucleic acid" or DNA) adj (damage* or injur* or lesion? or break* or adduct? or reactivity)) or "strand* break*" or "doublestrand* break*" or "singlestrand* break*" or "dna nick?" or "DNA chain break*" or "comet assay*" or "single cell gel electrophores#s" or "singlecell gel electrophores#s" or SCGE or "alkaline elution" or "unscheduled DNA synthes*" or "unscheduled deoxyribonucleic acid synthes*" or "Rec assay? with Bacillus subtilis" or "SOS test with Escherichia coli" or ((chromosom* or autosom*) adj1 (aberration? or abnormal* or anomal* or defect? or error? or duplication? or break* or endoreduplication?)) or "abnormal karyotype" or cytogen* or clastogen* or aneugen* or "Aneuploidyinducing Agent?" or "Polyploidy Inducing Agent?" or "Polyploidyinducing Agent?" or "micronucleus assay?" or "micronucleus test*" or "MN assay?" or (SOS adj1 chromotest*) or (SOS adj1 "chromo test*") or "sister chromatid exchange*" or "reading frame shift" or ((OutofFrame or "Out of Frame") adj (Insertion? or Deletion?)) or gentox* or "gene duplication?" or "gene doubling?" or aneuploid* or aneploid* or monosomics or polysomics or (toxic adj (substance? or agent? or chemical? or compound?)) or noxae).tw,kf.	1091561
17	exp Neoplasms/ or Carcinogenicity Tests/	3877836
18	(carcinogen* or cancer* or oncogenicity or tumorigenicity or tumourigenicity or neoplasm* or neoplasia? or malignanc* or tumor? or tumour?).tw,kf.	3752352
19	or/15-18	5996597
20	14 and 19	8428
21	limit 20 to yr="2010 -Current"	2416
22	limit 21 to (danish or dutch or english or multilingual or norwegian or swedish or undetermined)	2377
23	limit 22 to "reviews (maximizes specificity)"	7
24	Meta-Analysis/ or Network Meta-Analysis/ or ((systematic* adj2 review*) or metaanal* or "meta anal*" or (review and ((structured or database* or systematic*) adj2 search*)) or "integrative review*" or (evidence adj2 review*)).tw,kf,bt.	523254
25	23 or (22 and 24)	9
26	22 not 25	2368

Search strategy for nitramines

Drafting the search strategy and performing the search	Bente Foss
Critical review of the search strategy	Nataliya Byelyey
Duplications	Before removal of duplicates: 2884 primary studies and 0 reviews Result after removal of duplicates: 1883 primary studies

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) <1946 to September 19, 2023>
Date: 20.09.2023
Result: 481 primary studies, 0 reviews

#	Searches	Results
1	(nitramine? or dimethylnitramine? or "Dimethyl nitramine?" or "N-nitrodimethylamine?" or "DMA-nitramine?" or "N,N-dimethylnitramide?" or DMNA or "DMA-NO2" or NDTMA).tw,kf.	462
2	("N-(2-hydroxyethyl)nitramide?" or Ethanolnitramine? or "Ethanol nitramine?" or monoethanolnitramine? or "mono ethanolnitramine?" or "MEA-nitramine?" or "2-nitroaminoethanol" or "2-nitro aminoethanol" or "MEA-NO2").tw,kf.	5
3	("N-methylnitramide?" or "N-methyl nitramide?" or "N-nitromethylamine?" or "NTDMA" or "MA-NO2" or "NTMA" or "Methylnitramine?" or "Methyl nitramine?" or "MMA-nitramine?" or "N-Nitromethanamine?").tw,kf.	43
4	("1-nitropiperazine?" or Nitropiperazine? or "N-Nitropiperazine?" or "N-mononitropiperazine?" or "PZ-NO2").tw,kf.	6
5	("N-(1-hydroxy-2-methylpropan-2-yl)nitramide?" or "2-methyl-2-(nitroamine)-1-propanol" or "AMP-NO2").tw,kf.	2
6	("N,N-diethylnitramide?" or diethylnitramine? or "diethyl nitramine?" or "N-nitrodiethylamine?").tw,kf.	13
7	("1,4-dinitropiperazine?" or "N,N-Dinitropiperazine?" or "N,N'-Dinitropiperazine?" or "1,4-Dinitro-1,4-diazacyclohexane?").tw,kf.	5
8	("1-nitro-4-nitrosopiperazine?" or "N-nitroso-N'-nitropiperazine?").tw,kf.	0
9	("2-(4-nitropiperazin-1-yl)ethanol" or "2-(4-Nitropiperazin-1-yl)ethan-1-ol").tw,kf.	0
10	("4164-28-7" or "74386-82-6" or "598-57-2" or "42499-41-2" or "7119-92-8" or "1239666-60-4" or "4164-37-8" or "224-010-1" or "42499-45-6").mp.	0
11	or/1-10	490
12	limit 11 to (danish or dutch or english or multilingual or norwegian or swedish)	481
13	limit 12 to "reviews (maximizes specificity)"	0
14	Meta-Analysis/ or Network Meta-Analysis/ or ((systematic* adj2 review*) or metaanal* or "meta anal*" or (review and ((structured or database* or systematic*) adj2 search*)) or "integrative review*" or (evidence adj2 review*)).tw,kf,bt.	523833
15	13 or (12 and 14)	0

Appendix B: Eligibility criteria

We included both primary studies and systematic reviews. The classification of systematic reviews will be based on criteria developed by the Cochrane collaboration. In short, the publications will be considered as systematic reviews if they have described or presented (i) a specific research question and clear criteria for relevant studies to include, (ii)) a systematic literature search, and (iii) quality assessment of the included studies [79].

Table B-1. Inclusion criteria for amines.

Population	Human, animal (non-human primates, dogs, rats, mice, rabbit, pig and guinea pigs) and in vitro (only for skin sensitisation and irritation), in chemico (only for skin sensitisation), in silico (only for skin sensitisation)		
Exposure	Exposure route: oral, dermal and inhalation		
	IUPAC name	CAS RN	Abbreviation
	2-aminoethanol	141-43-5	MEA
	2-[2-hydroxyethyl(methyl)amino]ethanol	105-59-9	MDEA
	2-amino-2-methylpropan-1-ol	124-68-5	AMP
	Piperazine	110-85-0	PZ
	2-piperazin-1-ylethanol	103-76-4	PZE
	2-[4-(2-hydroxyethyl)piperazin-1-yl]ethanol	122-96-3	PZDE
Comparison	Placebo, no treatment, dose comparison		
Outcome	Allergy related health outcomes and skin irritation		
Study design/ publication type	Primary Studies and systematic reviews Scientific reports		
Publication year	From 1. January 2010		
Country/ context	No restrictions		
Language	Danish, Dutch, English, Norwegian and Swedish		

Table B-2. Inclusion criteria for nitrosamines.

Population	Human, animal (non-human primates, dogs, rats, mice, rabbit, pig and guinea pigs) and in vitro studies (only for genotoxicity endpoints).		
Exposure	Exposure route: oral and inhalation		
	IUPAC name	CAS RN	Abbreviation
	N,N-dimethylnitrous amide	62-75-9	DMA-NO
	N,N-bis(2-hydroxyethyl)nitrous amide	1116-54-7	DELA-NO
	1-nitrosopiperidine	100-75-4	PIP-NO
	N,N-diethylnitrous amide	55-18-5	DEA-NO
	N-ethyl-N-methylnitrous amide	10595-95-6	MEA-NO
	4-nitrosomorpholine	59-89-2	MOR-NO
	1-nitrosopyrrolidine	930-55-2	PYR-NO
	1-nitrosopiperazine	5632-47-3	PZ-NO
	2-[2-hydroxyethyl(nitroso)amino]acetic acid	80556-89-4	HEA-NO
	N,N-dipropylnitrous amide	621-64-7	DPA-NO
	N,N-dibutylnitrous amide	924-16-3	DBA-NO
	2-(4-nitrosopiperazin-1-yl)ethanol	48121-20-6	PZE-NO
	1,4-dinitrosopiperazine	140-79-4	DPZ-NO
Comparison	Placebo, no treatment, dose comparison		
Outcome	Genotoxicity and carcinogenicity		
Study design/ publication type	Primary Studies and systematic reviews Scientific reports		
Publication year	From 1. January 2010		
Country/ context	No restrictions		
Language	Danish, Dutch, English, Norwegian and Swedish		

Table B-3. Inclusion criteria for nitramines.

Population	Human, animal (non-human primates, dogs, rats, mice, rabbit, pig and guinea pigs) and in vitro studies (only for genotoxicity endpoints, skin sensitisation and skin irritation).		
Exposure	Exposure route: oral and inhalation		
	IUPAC name	CAS RN	Abbreviation
	N,N-dimethylnitramide	4164-28-7	DMA-NO_2
	N-(2-hydroxyethyl)nitramide	74386-82-6	MEA-NO_2
	N-methylnitramide	598-57-2	MA-NO_2
	1-nitropiperazine	42499-41-2	PZ-NO_2
	N-(1-hydroxy-2-methylpropan-2-yl)nitramide	1239666-60-4	AMP-NO_2
	N,N-diethylnitramide	7119-92-8	DE-NO_2
	1,4-dinitropiperazine	4167-37-8	DPZ-NO_2
	1-nitro-4-nitrosopiperazine	Not found	NPZ-NO_2
	2-(4-nitropiperazin-1-yl)ethanol	42499-45-6	PZE-NO_2
Comparison	Placebo, no treatment, dose comparison		
Outcome	All adverse effects		
Study design/ publication type	Primary Studies and systematic reviews Scientific reports		
Publication year	No restrictions		
Country/ context	No restrictions		
Language	Danish, Dutch, English, Norwegian and Swedish		

Exclusion criteria

We excluded non-systematic reviews, editorials, letters to editor, commentaries, book chapters and meeting abstracts and posters.
We excluded studies on other endpoints than specified in the inclusion criteria.
We excluded other exposure routes than those listed for in vivo studies.

Appendix C: Results of study selection

Figure C-1. Prisma flowchart for the selection of primary studies and systematic reviews for amines (adapted from Page 2021) [80].

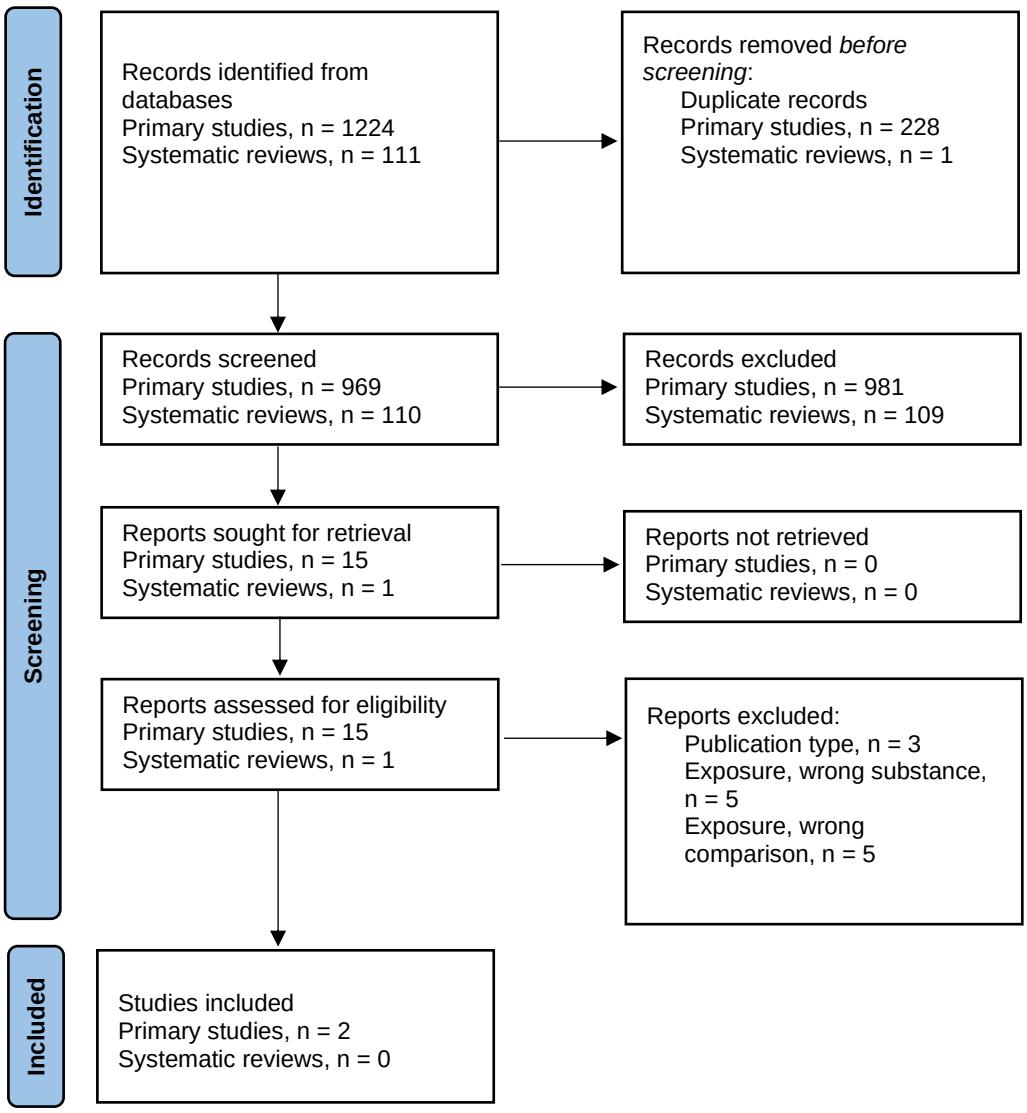


Figure C-2. Prisma flowchart for the selection of primary studies and systematic reviews for nitrosamines (adapted from Page 2021) [80].

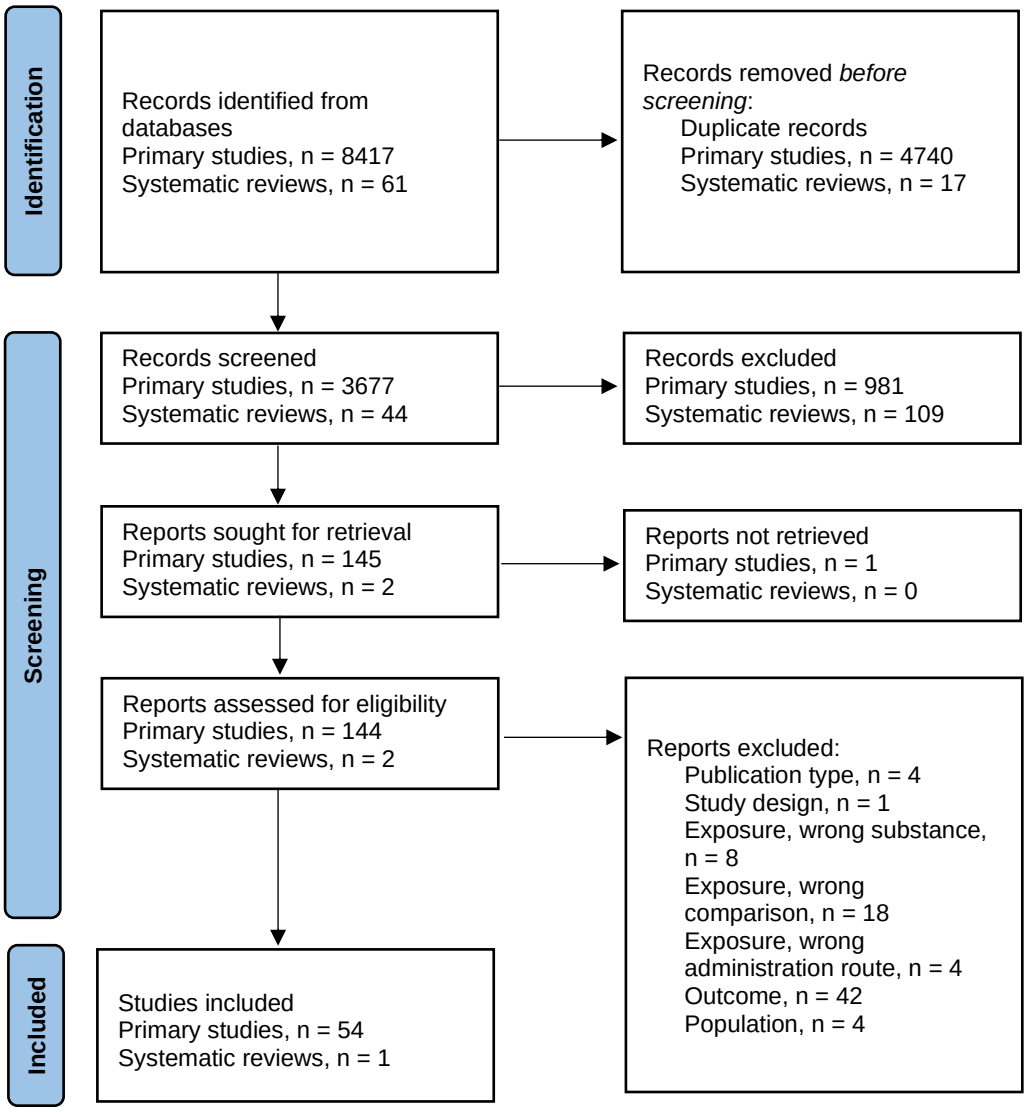
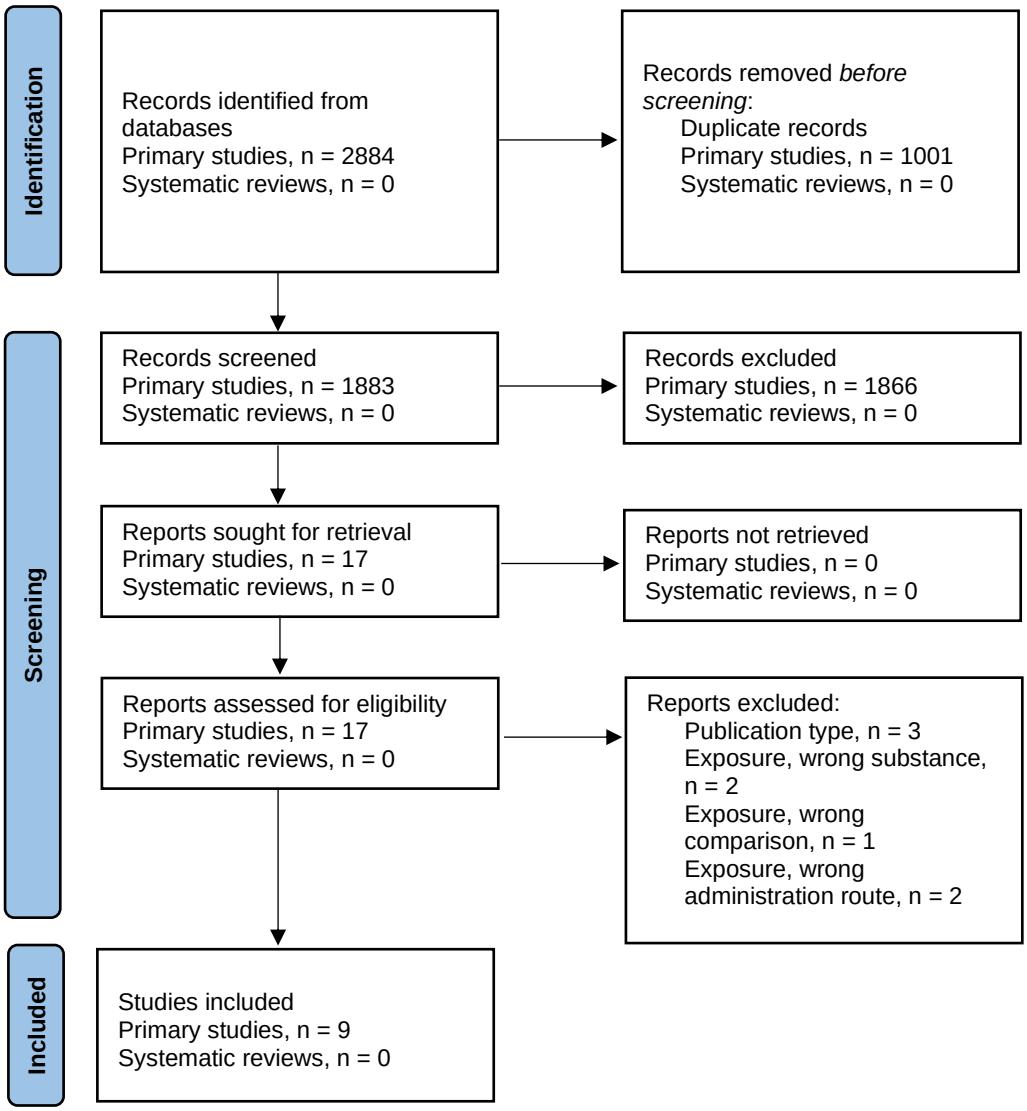


Figure C-3. Prisma flowchart for the selection of primary studies and systematic reviews for nitramines (adapted from Page 2021) [80].



References

1. Luis, P., *Use of monoethanolamine (MEA) for CO2 capture in a global scenario: Consequences and alternatives.* Desalination, 2016. **380**: p. 93-99.
2. Låg, M., Andreassen, Å., Instanes, C., Lindeman, B., *Health effects of different amines and possible degradation products relevant for CO2 capture*. 2009, Norwegian Institute of Public Health.
3. Låg, M., Lindeman, B., Instanes, C., Brunborg, G., Schwarze, P., *Health effects of amines and derivatives associated with CO2 capture*. 2011, The Norwegian Institute of Public Health.
4. EFSA, *Risk assessment of N-nitrosamines in food.* EFSA Journal, 2023. **21**(3): p. e07884.
5. (SCOPE), S.O.o.p.-c.C.p., *PNECs and degradation data for amines and amine degradation products*. 2023.
6. (SCOPE), S.O.o.p.-c.C.p., *Human Health hazard assessment strategy for amine emissions around PCC facilities*. 2022.
7. Ouzzani, M., et al., *Rayyan—a web and mobile app for systematic reviews.* Systematic Reviews, 2016. **5**(1): p. 210.
8. CPDB, *The Carcinogenic Potency Database*. University of California, Berkeley.
9. Lalko, J.F., et al., *Reactivity of chemical respiratory allergens in the Peroxidase Peptide Reactivity Assay.* Toxicology in Vitro, 2013. **27**(2): p. 651-61.
10. Mori, T., et al., *Comparison of cytokine profiles in bronchoalveolar lavage fluid of mice exposed to respiratory and contact sensitizers.* Journal of Toxicological Sciences, 2012. **37**(2): p. 337-43.
11. Seyyedsalehi, M.S., et al., *Association of Dietary Nitrate, Nitrite, and N-Nitroso Compounds Intake and Gastrointestinal Cancers: A Systematic Review and Meta-Analysis.* Toxics, 2023. **11**(2).
12. Wagner, E.D., et al., *Comparative genotoxicity of nitrosamine drinking water disinfection byproducts in Salmonella and mammalian cells.* Mutation Research, 2012. **741**(1): p. 109-15.
13. Wagner, E.D., et al., *Comparative in vitro toxicity of nitrosamines and nitramines associated with amine-based carbon capture and storage.* Environmental Science & Technology, 2014. **48**(14): p. 8203-11.
14. Robles, H., *Nitrosamines*, in *Encyclopedia of Toxicology (Third Edition)*, P. Wexler, Editor. 2014, Academic Press: Oxford. p. 584-585.
15. NTP, *(National Toxicology Program). Report on Carcinogens, Fifteenth Edition.* . 2021, Research Triangle Park, NC: U.S. Department of Health and Human Services, Public Health Service. .
16. IARC, *(International Agency for Research on Cancer). Agents classified by the IARC Monographs, Volumes 1–135*.
17. Zheng, J., et al., *Dietary N-nitroso compounds and risk of pancreatic cancer: results from a large case-control study.* Carcinogenesis, 2019. **40**(2): p. 254-262.
18. Zhu, Y., et al., *Dietary N-nitroso compounds and risk of colorectal cancer: a case-control study in Newfoundland and Labrador and Ontario, Canada.* British Journal of Nutrition, 2014. **111**(6): p. 1109-17.
19. Hobbs, C.A., et al., *Comet assay evaluation of six chemicals of known genotoxic potential in rats.* Mutation Research-Genetic Toxicology & Environmental Mutagenesis, 2015. **786**: p. 172-81.
20. McNamee, J.P. and P.V. Bellier, *Use of a standardized JaCVAM in vivo rat comet assay protocol to assess the genotoxicity of three coded test compounds; ampicillin trihydrate, 1,2-dimethylhydrazine dihydrochloride, and N-nitrosodimethylamine.*

Mutation Research-Genetic Toxicology & Environmental Mutagenesis, 2015. **786**: p. 158-64.
21. Dertinger, S.D., et al., *3Rs friendly study designs facilitate rat liver and blood micronucleus assays and Pig-a gene mutation assessments: Proof-of-concept with 13 reference chemicals.* Environmental & Molecular Mutagenesis, 2019. **60**(8): p. 704-739.
22. Takashima, R., et al., *Evaluation of a repeated dose liver micronucleus assay in rats treated with two genotoxic hepatocarcinogens, dimethylnitrosamine and 2-acetylaminofluorene: the possibility of integrating micronucleus tests with multiple tissues into a repeated dose general toxicity study.* Mutation Research-Genetic Toxicology & Environmental Mutagenesis, 2015. **780**: p. 18-24.
23. Bringezu, F. and S. Simon, *Salmonella typhimurium TA100 and TA1535 and E. coli WP2 uvrA are highly sensitive to detect the mutagenicity of short Alkyl-N-Nitrosamines in the Bacterial Reverse Mutation Test.* Toxicology Reports, 2022. **9**: p. 250-255.
24. Deng, H., H. Gao, and Y. Liu, *Biotransformation enzyme-dependent formation of micronucleus and multinuclei in cell line V79-hCYP2E1-hSULT1A1 by 2-nitropropane and N-nitrosodimethylamine.* Mutation Research, 2011. **726**(1): p. 84-7.
25. Dong, L., et al., *The genotoxic potential of mixed nitrosamines in drinking water involves oxidative stress and Nrf2 activation.* Journal of Hazardous Materials, 2022. **426**: p. 128010.
26. Erkekoglu, P. and T. Baydar, *Evaluation of the protective effect of ascorbic acid on nitrite- and nitrosamine-induced cytotoxicity and genotoxicity in human hepatoma line.* Toxicology Mechanisms & Methods, 2010. **20**(2): p. 45-52.
27. Haza, A.I. and P. Morales, *Spanish honeys protect against food mutagen-induced DNA damage.* Journal of the Science of Food & Agriculture, 2013. **93**(12): p. 2995-3000.
28. Katic, J., et al., *Evaluation of the genotoxicity of 10 selected dietary/environmental compounds with the in vitro micronucleus cytokinesis-block assay in an interlaboratory comparison.* Food & Chemical Toxicology, 2010. **48**(10): p. 2612-23.
29. Le Hegarat, L., et al., *Assessment of the genotoxic potential of indirect chemical mutagens in HepaRG cells by the comet and the cytokinesis-block micronucleus assays.* Mutagenesis, 2010. **25**(6): p. 555-60.
30. Liviac, D., A. Creus, and R. Marcos, *Genotoxic evaluation of the non-halogenated disinfection by-products nitrosodimethylamine and nitrosodiethylamine.* Journal of Hazardous Materials, 2011. **185**(2): p. 613-8.
31. Mestankova, H., et al., *Development of mutagenicity during degradation of N-nitrosamines by advanced oxidation processes.* Water Research, 2014. **66**: p. 399-410.
32. Misik, M., et al., *Cytome micronucleus assays with a metabolically competent human derived liver cell line (Huh6): A promising approach for routine testing of chemicals?* Environmental & Molecular Mutagenesis, 2019. **60**(2): p. 134-144.
33. Seo, J.E., et al., *Genotoxicity assessment of eight nitrosamines using 2D and 3D HepaRG cell models.* Archives of Toxicology, 2023. **97**(10): p. 2785-2798.
34. Wang, H.Y., et al., *Genotoxicity of a Low-Dose Nitrosamine Mixture as Drinking Water Disinfection Byproducts in NIH3T3 Cells.* International Journal of Medical Sciences, 2017. **14**(10): p. 961-969.
35. Yoneda, K., et al., *Novel antimutagenic proteins in the edible mushroom Agrocybe cylindracea.* Genes and Environment, 2012. **34**: p. 9-17.
36. Totsuka, Y., et al., *DNA Adductome Analysis Identifies N-Nitrosopiperidine Involved in the Etiology of Esophageal Cancer in Cixian, China.* Chemical Research in Toxicology, 2019. **32**(8): p. 1515-1527.

37. Ajitha, A. and P. Subramanian, *Dose-dependent protective features of lobophora variegata methanolic extract (LVME) in n-nitrosodiethylamine induced experimental hepatocarcinogenesis in rats.* International Journal of Current Pharmaceutical Research, 2021. **13**: p. 65-70.
38. Fathy, A.H., et al., *Sequential analysis and staging of a diethylnitrosamine-induced hepatocellular carcinoma in male Wistar albino rat model.* Canadian Journal of Physiology & Pharmacology, 2017. **95**(12): p. 1462-1472.
39. Krishnan, P., et al., *Citral inhibits N-nitrosodiethylamine-induced hepatocellular carcinoma via modulation of antioxidants and xenobiotic-metabolizing enzymes.* Environmental Toxicology, 2020. **35**(9): p. 971-981.
40. Nitha, A., et al., *Curative effect of woodfordia fruticosa kurz flowers on n-nitrosodiethylamine induced hepatocellular carcinoma in rats.* International Journal of Pharmacy and Pharmaceutical Sciences, 2014. **6**: p. 150-155.
41. Nota, T., et al., *Safety and Feasibility of Contrast-Enhanced Computed Tomography with a Nanoparticle Contrast Agent for Evaluation of Diethylnitrosamine-Induced Liver Tumors in a Rat Model.* Academic Radiology, 2023. **30**(1): p. 30-39.
42. Patial, V., et al., *Synergistic effect of curcumin and piperine in suppression of DENA-induced hepatocellular carcinoma in rats.* Environmental Toxicology & Pharmacology, 2015. **40**(2): p. 445-52.
43. Ranju, P. and N. Thirumoorthy, *Chemo-preventive effect of ethanolic extract of Morinda citrifolia root on N-nitrosodiethylamine induced oxidative stress in rat liver.* World Journal of Pharmaceutical Research, 2012. **1**(3): p. 893-908.
44. Sadeeshkumar, V., et al., *Protective effects of dieckol on N-nitrosodiethylamine induced hepatocarcinogenesis in rats.* Biomedicine & Pharmacotherapy, 2016. **84**: p. 1810-1819.
45. Sulaimon, L.A., et al., *Mitoquinol mesylate alleviates oxidative damage in cirrhotic and advanced hepatocellular carcinogenic rats through mitochondrial protection and antioxidative effects.* Advances in Redox Research, 2021. **3**.
46. Venkateswararao, R., B. Arul, and R. Kothai, *Chemopreventive effects of Costus comosus Linn against diethylnitrosamine-induced hepatocellular carcinoma in rats.* Journal of HerbMed Pharmacology, 2022. **11**: p. 375-382.
47. Sharma, V. and P. Janmeda, *Chemopreventive Role of Euphorbia neriifolia (Linn) and its Isolated Flavonoid Against N-Nitrosodiethylamine-induced Renal Histopathological Damage in Male Mice.* Toxicology International, 2013. **20**(1): p. 101-7.
48. Sharma, V. and P. Janmeda, *Protective Assessment of Euphorbia neriifolia and its Isolated Flavonoid Against N-nitrosodiethylamine-induced Hepatic Carcinogenesis in Male Mice: A Histopathological Analysis.* Toxicology International, 2014. **21**(1): p. 37-43.
49. Thuy le, T.T., et al., *Promotion of liver and lung tumorigenesis in DEN-treated cytoglobin-deficient mice.* American Journal of Pathology, 2011. **179**(2): p. 1050-60.
50. Avlasevich, S.L., et al., *Diethylnitrosamine genotoxicity evaluated in sprague dawley rats using pig-a mutation and reticulocyte micronucleus assays.* Environmental & Molecular Mutagenesis, 2014. **55**(5): p. 400-6.
51. Bercu, J.P., et al., *Comparison of the transgenic rodent mutation assay, error corrected next generation duplex sequencing, and the alkaline comet assay to detect dose-related mutations following exposure to N-nitrosodiethylamine.* Mutation Research - Genetic Toxicology and Environmental Mutagenesis, 2023. **891**.
52. Khanal, S., et al., *Integration of liver and blood micronucleus and Pig-a gene mutation endpoints into rat 28-day repeat-treatment studies: Proof-of-principle with diethylnitrosamine.* Mutation Research-Genetic Toxicology & Environmental Mutagenesis, 2018. **828**: p. 30-35.

53. Wada, K., et al., *Evaluation of the PIGRET assay as a short-term test using a single dose of diethylnitrosamine.* Mutation Research-Genetic Toxicology & Environmental Mutagenesis, 2016. **811**: p. 70-74.
54. Ali, F., et al., *Protective Role of Curcumin against N-Nitrosodiethylamine (NDEA)-Induced Toxicity in Rats.* Scientia Pharmaceutica, 2016. **84**(2): p. 361-77.
55. Hagio, S., et al., *Repeated dose liver micronucleus assay using adult mice with multiple genotoxicity assays concurrently performed as a combination test.* Journal of Toxicological Sciences, 2014. **39**(3): p. 437-45.
56. Itoh, S., et al., *Gender differences in the liver micronucleus test in rats with partial hepatectomy.* Toxicology Letters, 2012. **214**(3): p. 296-300.
57. Itoh, S., et al., *Assessment of a twice dosing regimen both before and after partial hepatectomy in the rat liver micronucleus test.* Mutation Research-Genetic Toxicology & Environmental Mutagenesis, 2015. **782**: p. 18-23.
58. Nagasue, R., et al., *Effectiveness of the liver micronucleus assay using juvenile mice.* Journal of Veterinary Medical Science, 2017. **79**(7): p. 1310-1317.
59. Narumi, K., et al., *Development of a repeated-dose liver micronucleus assay using adult rats: an investigation of diethylnitrosamine and 2,4-diaminotoluene.* Mutation Research, 2012. **747**(2): p. 234-9.
60. El Mesallamy, H.O., et al., *The chemopreventive effect of Ginkgo biloba and Silybum marianum extracts on hepatocarcinogenesis in rats.* Cancer Cell International, 2011. **11**(1): p. 38.
61. Alvarez-Moya, C., et al., *Comparison of the in vivo and in vitro genotoxicity of glyphosate isopropylamine salt in three different organisms.* Genetics & Molecular Biology, 2014. **37**(1): p. 105-10.
62. Kligerman, A.D., et al., *An evaluation of 25 selected ToxCast chemicals in medium-throughput assays to detect genotoxicity.* Environmental and Molecular Mutagenesis, 2015. **56**: p. 468-476.
63. Li, X., et al., *Genotoxicity evaluation of nitrosamine impurities using human TK6 cells transduced with cytochrome P450s.* Archives of Toxicology, 2022. **96**(11): p. 3077-3089.
64. Liu, W., et al., *An Adaption of Human-Induced Hepatocytes to In Vitro Genetic Toxicity Tests.* Mutagenesis, 2019. **34**(2): p. 165-171.
65. Peng, X., J. Zhang, and Q. Liu, *A Genetic Toxicology Study of the Rapid Detection of Nitrosamine Compounds by the rpsL Gene Mutation Assay.* 2022.
66. Ogawa, I., et al., *Evaluation of repeated dose micronucleus assays of the liver using N-nitrosopyrrolidine: a report of the collaborative study by CSGMT/JEMS.MMS.* Mutation Research-Genetic Toxicology & Environmental Mutagenesis, 2015. **780**: p. 25-30.
67. Terashima, Y., et al., *Detection of micronuclei in hepatocytes isolated from young adult rats repeatedly treated with N-nitrosodi-n-propylamine.* Mutation Research-Genetic Toxicology & Environmental Mutagenesis, 2015. **780**: p. 36-40.
68. Reiter, M., et al., *DNA repair and mutagen sensitivity of epithelial cells and lymphocytes in oropharyngeal cancer.* Oncology Letters, 2012. **3**(1): p. 100-106.
69. Goodall, C.M. and T.H. Kennedy, *Carcinogenicity of dimethylnitramine in NZR rats in NZO mice.* Cancer Letters, 1976. **1**(5): p. 295-8.
70. Mirvish, S.S., et al., *Study of the carcinogenicity of large doses of dimethylnitramine, N-nitroso-L-proline, and sodium nitrite administered in drinking water to rats.* Journal of the National Cancer Institute, 1980. **64**(6): p. 1435-42.
71. Scherf, H.R., E. Frei, and M. Wiessler, *Carcinogenic properties of N-nitrodimethylamine and N-nitromethylamine in the rat.* Carcinogenesis, 1989. **10**(11): p. 1977-81.

72. Malaveille, C., et al., *Hydroxylation and nitroreduction are required to activate dimethylnitramine into alkylating and mutagenic agents.* Carcinogenesis, 1983. **4**(11): p. 1477-81.
73. Frei, E., et al., *Determination of DNA single strand breaks and selective DNA amplification by N-nitrodimethylamine and analogs, and estimation of the indicator cells' metabolic capacities.* Journal of Cancer Research & Clinical Oncology, 1986. **111**(2): p. 123-8.
74. Fjellsbo, L.M., et al., *Genotoxic and mutagenic potential of nitramines.* Environmental Research, 2014. **134**: p. 39-45.
75. Pool, B.L., et al., *Formaldehyde as a possible mutagenic metabolite of N-nitrodimethylamine and of other agents which are suggested to yield non-alkylating species in vitro.* Carcinogenesis, 1984. **5**(6): p. 809-14.
76. Fjellsbo, L.M., et al., *Screening for potential hazard effects from four nitramines on human eye and skin.* Toxicology in Vitro, 2013. **27**(4): p. 1205-10.
77. OECD, *Guideline No. 497: Defined Approaches on Skin Sensitisation*. 2023.
78. McCann, J., et al., *Statistical analysis of Salmonella test data and comparison to results of animal cancer tests.* Mutation Research/Genetic Toxicology, 1988. **205**(1): p. 183-195.
79. Higgins JPT, T.J., Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). *Cochrane Handbook for Systematic Reviews of Interventions version 6.4 (updated August 2023).*
80. Page, M.J., et al., *The PRISMA 2020 statement: an updated guideline for reporting systematic reviews.* BMJ, 2021. **372**: p. n71.

Utgitt av Folkehelseinstituttet
Februar 2024
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