Ministry of Environment of Denmark
Environmental Protection Agency

Nitrosamines and nitramines

Evaluation of health hazards and proposal of health-based quality criteria and C-values for ambient air.

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Preface

The Danish Environmental Protection Agency has requested an evaluation of health hazards by inhalation exposure to relevant nitrosamines and nitramines used in the Carbon Capture (CC) technology. The aim is to derive health-based quality criteria and put forward proposals for C-values (B-værdier) in relation to ambient air.

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The project was funded by the Danish Environmental Protection Agency (Danish EPA).

The project was conducted from September to middle of December 2022.

Abbreviations

CC	Carbon Capture
CPDB	The Carcinogenic Potency Database
C-value	Contribution value (Danish: B-værdi)
DMEL	Derived Minimal Effect Level
DNP	Dinitrosopiperazin
ECHA	European Chemicals Agency
LOAEC	Lowest Observed Adverse Effect Concentration
LOAEL	Lowest Observed Adverse Effect Level
MDEA	Methyldiethanolamine
NDEA	N-nitrosodiethylamine
NDEOLA	N-nitrosodiethanolamine (NDELA may be used by others)
NDMA	N-nitrosodimethylamine
NMA	N-nitrosomethylamine
NMEA	N-nitrosomethylethylamine
NP	N-nitrosopiperazine
NOAEC	No Observed Adverse Effect Concentration
NOAEL	No Observed Adverse Effect Level
NOEL	No Observed Effect Level
NOx	Nitrogenoxides
NTEOLA	N-nitroethanolamine
NTDEA	N-nitrodiethylamine
NTDMA	N-nitrodimethylamine
NTMA	N-nitromethylamine
OECD TG	OECD Technical Guidance
PoD	Point of Departure
QC	Quality Criteria
T25	Estimated dose level causing cancer in 25% of test animals
TD05	Estimated dose level causing cancer in 5% of test animals
TD50	Estimated dose level causing cancer in 50% of test animals
UF	Uncertainty factor

1. Introduction

1.1 Background

Plants using amines in relation to the Carbon Capture technology (CO_2) may cause harmful emissions to the atmosphere, and of particular concern are the amines and their degradation products from reactions both in the CO_2 capture process and in the atmosphere. During the CO_2 capturing process, the exhaust CO_2 is initially bound to the amines. Later the CO_2 is released, compressed, and transported away for storage but the amines are re-circulated. During the re-circulation process the amines might degrade into harmful byproducts like nitrosamines and nitramines. Also, small amounts of amines might leak out and reach the atmosphere where photooxidation enhances the degradation into nitrosamines and nitramines. Very little data exist for emissions from CO_2 capture plants, but initial measurements have shown emission levels for nitrosamines and nitramines of around 2–50 ng/m^3 (Ravnum et al 2014).

Force (2022) indicated how ***nitrosamines*** may be generated from amines reacting with nitrogenoxides (NOx).
E.g. ***N-nitrosodiethanolamine*** may be generated from the reaction between methyldiethanolamine (MDEA) and NOx: [Overskrift]

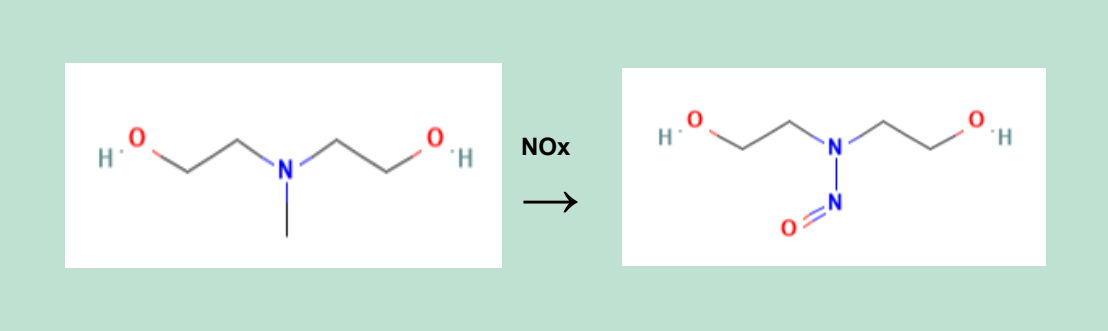


FIGURE 1. Example of *N*-nitrosodiethanolamine generation

-nitrosopiperazine may be generated from the reaction between piperazine and NOx:

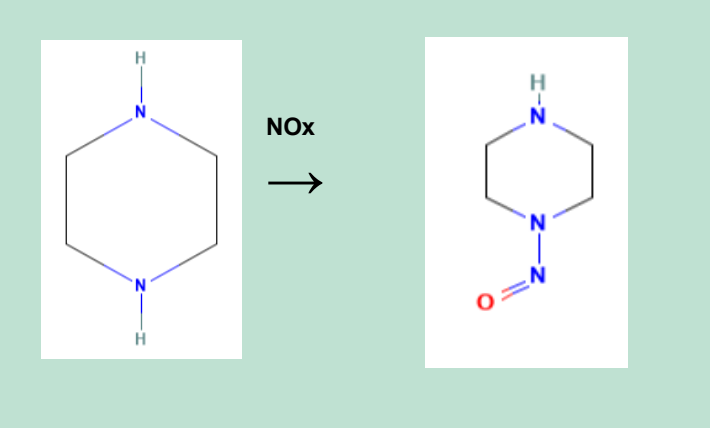


FIGURE 2. Example of *N*-nitrosopiperazine generation

Also, the formation of ***dinitrosopiperazine*** and ***N-nitrosomethylethanolamine*** was mentioned (Force 2022).

Gundersen (2018) described how formation of nitramines (and nitrosamines) may occur through degradation of the amines. This can happen both *inside the capture facility* and *in the ambient atmosphere* from volatile amines escaping the absorber tower, Examples of generation of potential ***nitramines*** were:

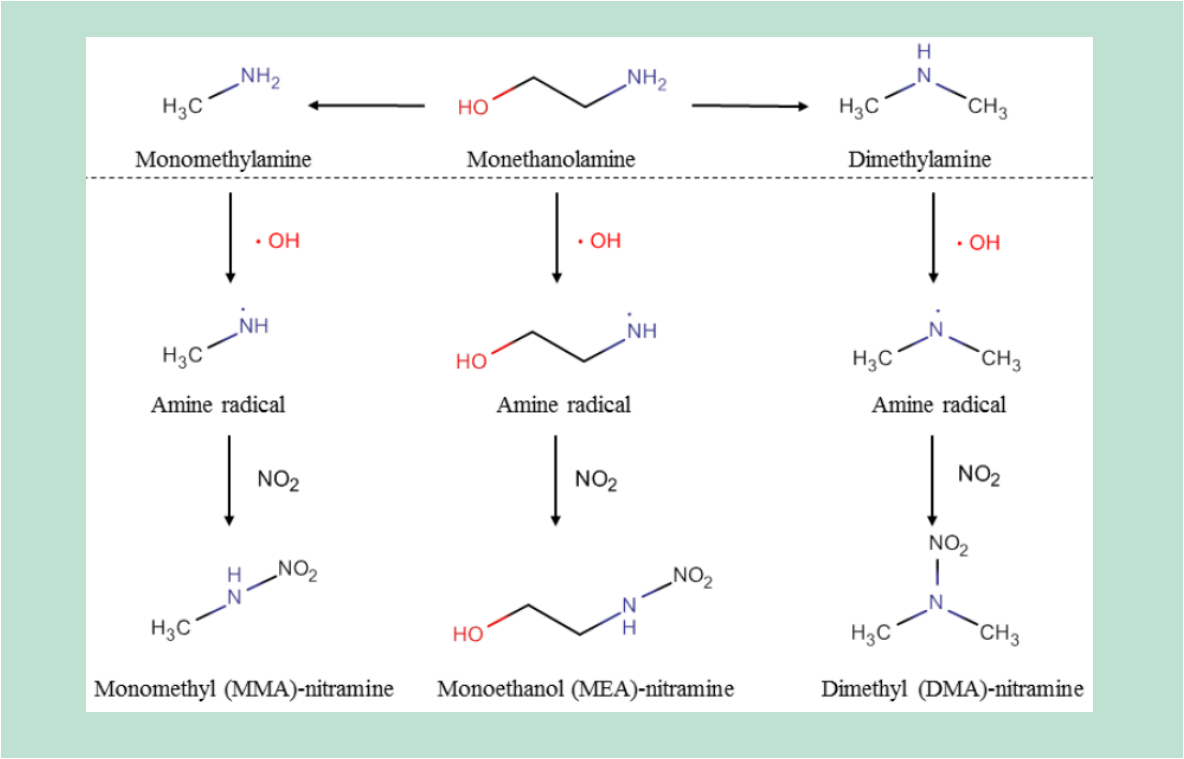


FIGURE 3. Nitramines potentially generated in CC technology (Gundersen (2018) used with permission)

The Norwegian Institute of Public Health in 2011 and Ravnum et al. in 2014 published reports concerning health effects of amines and derivatives associated with CO2 capture covering the following nitrosoamines and nitramines and together with the information of Force (2022) and Gundersen (2018) the following nitrosamines and nitramines were mentioned in these publications:

Nitrosoamines:

N-nitrosomethylamine (CAS 64768-29-2)
N-nitrosodimethylamine (CAS 62-75-9)
N-nitrosodiethylamine (CAS 55-18-5)
N-nitrosomorpholine (CAS 59-89-2),
N-nitroso-di-n-propylamine (CAS 621-64-7)
N-nitrosomethylethylamine (CAS 10595-95-6)
N-nitrosopiperidine (CAS 100-75-4)
N-nitrosopiperazine (CAS 5632-47-3)
N-nitrosodiethanolamine (CAS 1116-54-7)
N-nitrosodi-n-butylamine (CAS 924-16-3)

Nitramines:

N-nitromethylamine (CAS 598-57-2)
N-nitrodimethylamine (CAS 4164-28-7)
N-nitrodiethylamine (CAS 7119-92-8)

1.2 Purpose

The aim of the project is to collect and evaluate relevant toxicological data and to establish health-based quality criteria and C-values (B-værdier) for nitrosamines and nitramines generated from amines during the carbon capture processes.

The Danish EPA has – based on a survey conducted by Danish companies - identified the following amines and amino alcohols as most relevant for use in the Carbon Capture technology in Denmark:

ethanolamine – CAS: 141-43-5
methyldiethanolamine – CAS: 105-59-9
2-amino-2-methyl-1-propanol – CAS: 124-68-5
piperazin – CAS: 110-85-0
N-methyl-1,3-propandiamine – CAS: 6291-84-5
triethanolamine- CAS: 102-71-6
monoisopropanolamine - CAS: 78-96-6
2-(methylamino)ethanol – CAS: 109-83-1

As *dimethylamines, diethylamines, dipropylamines, morpholine, piperidine and butylamines* or alcohols thereof **are not included** in this list of relevant substances for use, we (DHI A/S) consider the formation of the following substances mentioned in section 1.1 less likely:

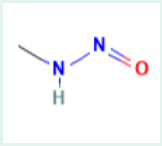
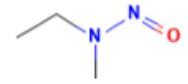
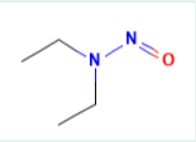
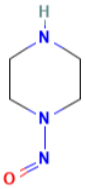
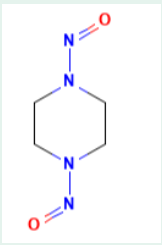
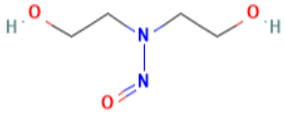
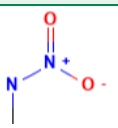
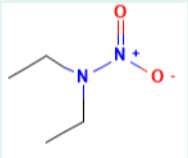
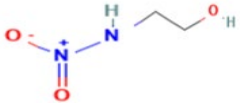
N-nitrosodimethylamine
N-nitrosomorpholine
N-nitrosopiperidine
N-nitroso-di-n-propylamine
N-nitrosodi-n-butylamine
N-nitrodimethylamine

Thus, the focus in this report is put on the remaining substances mentioned in section 1.1 as they may be considered as more likely reaction products:

Nitrosamines:
N-nitrosomethylamine (CAS 64768-29-2)
N-nitrosodiethylamine (CAS 55-18-5)
N-nitrosomethylethylamine (CAS 10595-95-6)
N-nitrosopiperazine (CAS 5632-47-3)
Dinitrosopiperazine (CAS 140-79-4)
N-nitrosodiethanolamine (CAS 1116-54-7)
Nitramines:
N-nitromethylamine (598-57-2)
N-nitrodiethylamine (CAS 7119-92-8)
N-nitroethanolamine (CAS -), named as Monoethanolnitramine by Gundersen (2018).

The nine substances are listed in Table 1 also showing the chemical structures of the substances.

Table 1 Relevant nitrosamines and nitramines to be assessed for this project

Substance	CAS	Chemical structure
Nitrosamines		
N-nitrosomethyllamine NMA	64768-29-2	
N-nitrosomethylethylamine NMEA	10595-95-6	
N-nitrosodiethylamine NDEA	55-18-5	
N-nitrosopiperazine NP	5632-47-3	
Dinitrosopiperazine DNP	140-79-4	
N-nitrosodiethanolamine NDEOLA	1116-54-7	
Nitramines		
N-nitromethylamine NTMA	598-57-2	
N-nitrodiethylamine NTDEA	7119-92-8	
Monoethanolnitramine (N-nitroethanolamine) NTEOLA	-	

Among these substances, only the substance **N-nitrosodiethanolamine** (NDEOLA) is subjected to an EU-harmonised classification with the classification as **Carc. 1B H350** according to Regulation (EC) No 1272/2008 (CLP Regulation).

2. Hazard evaluation

2.1 Selection of data

There is a great amount of data when making literature search on the term *nitrosamine* and cancer,* thus more than 8000 hits were obtained from a data search in PubMed. Using the search term *diethylnitrosamine* resulted in more than 4700 hits in PubMed.

Therefore, a focused approach was to be used in this project. Besides literature search in PubMed on the individual substances included in Table 1 (search terms were CAS numbers and substance names), the literature search was directed to identify the most recent expert assessments describing the most critical effects of nitrosamines and nitramines and assessing the dose-response and potency in relation to these effects.

References specifically addressing assessment of substances in relation to the Carbon Capture technology and references addressing critical effects and dose-response relationships for nitrosamines and nitramines were prioritized. Among this further prioritization were given to assessment conducted by international or national expert groups in order to ensure highest possible validity of the data used.
Based on these criteria the following key references for use in this project were selected:

Table 2 Key references

Reference	Information
The Carcinogenic Potency Database (CPDB).	Provides TD50 levels for carcinogens. This includes more than 80 nitrosamines and nitramines
NTP (2021). *"Report on Carcinogens"* Fifteenth edition.	Provides short overviews on cancer data on specific nitrosamines
EMA (2020). *"Assessment report. Nitrosamine impurities in human medicinal products"*	Provides most recent update on cancer potency estimation and tolerable exposure levels for nitrosamines
NIPH (2011). *"Health effects of amines and derivatives associated with CO2 capture"*	Provides risk assessment of nitrosamines and nitramines relevant for CO_2 capture technology
Ravnum et al. (2014). *"Human health risk assessment of nitrosamines and nitramines for potential application in CO2 capture"*	Provides risk assessment of nitrosamines and nitramines relevant for CO_2 capture technology

2.2 Critical effect

Nitrosamines
In all these references, the carcinogenic properties are considered as the most critical effects of the nitrosamines. Thus, NIPH (2011) found that approximately 90% of the 300 nitrosamines tested have shown carcinogenic effects in bioassays and laboratory animals.

Therefore, the further assessment in this report will focus specifically on the carcinogenic properties of the substances.

In the most recent EU expert group assessment made by EMA (2020) it was concluded that *N*-nitrosamines in general, are both mutagenic and carcinogenic, but with extensive difference in potency between the most and least potent nitrosamines.

In relation to the carcinogenic mode of action the nitrosamines are described to be activated metabolically to form diazoniums ions that directly react with DNA thereby forming stable alkylated adducts mainly with nitrogen and oxygen of guanine, cytosine and thymidine. The alkylating potential is considered to be highest for nitrosamines with substitution of the smallest alkyl-groups, i.e. the alkylating potency is decreasing from methyl- to ethyl- to propyl- to butyl- substitution. Based on the mutagenic mode of action EMA (2022) considered nitrosamines as non-threshold carcinogens.

Nitramines
NIPH (2011) indicated that only a few studies on health effects of aliphatic nitramines are available. As N-nitramines are structurally related to N-nitrosamines which are potent carcinogens, the focus of the studies has been on carcinogenicity and mutagenicity. N-nitrodimethylamine has been the most studied of the N-nitramines, but the studies are either small, have too few doses and/or they are of too short duration and the available study documentation is limited. However, based on these studies it may be possible to achieve a rough estimation of the carcinogenic potencies of the two nitramines, N-nitrodimethylamine and N-nitromethylamine.

2.3 Carcinogenicity

Although not included in Table 1 the nitrosamine *N-nitrosodimethylamine* (NDMA) is also described below as this substance is the most widely tested of the nitrosamines and as such often is used as a reference substance when discussing the carcinogenic properties of nitrosoamines.

2.3.1 N-nitrosomethylamine (NMA), CAS 64768-29-2

No relevant data was found on this substance.

2.3.2 N-nitrosodimethylamine (NDMA), CAS 62-75-9

NDMA is subject to EU-harmonised classification as:
Carc. 1B H350; Acute Tox. 2 H330; Acute Tox. 3 H301; STOT RE 1 H372; Aquatic Chronic 2 H411 according to Reg. (EC) No 1272/2008.

Furthermore, NDMA is the only nitrosamine listed in “Vejledning om B-værdier” with a C-value of 0.0001 mg/m^3 and placed in main group 1 and appointed to class I (Danish EPA 2016).

According to EMA (2021) this is the most tested substance among the nitrosamines.
Although this substance has not been identified as a likely reaction product from the amines and the amine alcohols used for the CC technology in Denmark (no dimethylamine and dimethylamine alcohols were reported to be used for this purpose), the substance is described below. The substance is often used as a reference substance when discussing the carcinogenic properties of the nitrosamines.

Toxicokinetics

Oral absorption of NDMA is rapid and complete in all species tested. However, the fraction of an oral dose that passes through the liver unchanged and enters systemic circulation varies widely across species (about 10% in rats; above 90% in beagles).
No data is available regarding absorption of NDMA following inhalation exposure.

NDMA is metabolized by microsomal membrane-bound CYP2E1, to hydroxymethyl-nitrosamine that is nonenzymatically converted to formaldehyde and the reactive methyldiazonium ion. Other metabolic products include methanol and a reactive methyl carbonium ion. Clearance of NDMA from blood is primarily via metabolism (ATSDR 2022).

Carcinogenicity
ATSDR (2022) identified 89 animal studies (conducted by inhalation, oral, or dermal exposure) with N-nitrosodimethylamine where most of the studies were oral studies using doses ranging from 0.0007 to 50 mg/kg/day and in which hepatic effects, cancer, and/or survival were assessed. From these studies, a LOAEL of 0.022 mg/kg bw/day for cancer and lethality was given in relation to long-term exposure. In relation to adverse effects on the liver a LOAEL of 0.002 mg/kg bw/day was given for acute/short-term exposure.

Overall, NTP (2021) concluded that N-nitrosodimethylamine have caused tumors in numerous species of experimental animals, at several different tissue sites, and by several different routes of exposure.
Benign and malignant tumors of the liver (hepatocellular adenoma and carcinoma) or bile duct (cholangioma or cholangiocellular tumors) have been observed following oral administration in mice, rats, hamsters, rabbits, guinea pigs, and after inhalation exposure in mice.
Exposure to *N*-nitrosodimethylamine by most of these routes also caused tumors of the respiratory tract. Thus, oral exposure caused lung tumors in mice; inhalation exposure caused lung tumors in mice and rats and nasal-cavity tumors in rats (NTP 2021).

Cancer Potency
Based on the overall set of cancer data on the substance, the Carcinogenic Potency Database has estimated harmonic mean TD50 values of 0.0959 mg/kg bw/day for rats and 0.189 mg/kg bw/day for mice.

2.3.3 N-nitrosomethylethylamine (NMEA), CAS 10595-95-6

Cancer Potency
Based on a study showing carcinogenic effects in male rats the Carcinogenic Potency Database estimated a harmonic mean TD50 value of 0.0503 mg/kg bw/day. No TD50 value was given for mice.

No further relevant data was found on this substance.

2.3.4 N-nitrosodiethylamine (NDEA), CAS 55-18-5

Carcinogenicity
Nitrosodiethylamine have caused tumors in several species of experimental animals, at several different tissue sites, and by several different routes of exposure.

Benign and malignant liver tumors were found in mice, rats, hamsters, guinea pigs, rabbits, dogs, and pigs orally exposed to *N-nitro*sodiethylamine. Liver tumors also occurred in rats following inhalation exposure.

Tumors of the lung and upper respiratory tract occurred in mice, rats, hamsters, dogs, and pigs following oral administration of *N*-nitrosodiethylamine.
Inhalation exposure caused tumors of the trachea, bronchi, and lungs in hamsters, and dermal exposure caused tumors of the nasal cavity in mice and hamsters.

Tumors of the kidney occurred in rats following oral, intravenous, or prenatal administration of *N*-nitrosodiethylamine. Oral administration also caused kidney tumors in pigs and tumors of the upper digestive tract in mice, rats, and hamsters.

Cancer Potency
Based on the overall set of cancer data on the substance the Carcinogenic Potency Database has estimated a harmonic mean TD50 value of 0.0265 mg/kg bw/day for rats. No TD50 value was given for mice.

2.3.5 N-nitrosopiperazine (NP), CAS 5632-47-3

Cancer Potency
Based on the overall set of cancer data on the substance the Carcinogenic Potency Database has estimated a harmonic mean TD50 value of 8.78 mg/kg bw/day for rats in relation to tumor bearing animals (all tumors). No TD50 value was given for mice.

No further relevant data was found.

2.3.6 Dinitrosopiperazine (DNP), CAS 140-79-4

Cancer Potency
Based on the overall set of cancer data on the substance the Carcinogenic Potency Database has estimated a harmonic mean TD50 value of 3.6 mg/kg bw/day for mice based on increased incidences of stomach tumors. No TD50 value was given for rats.

No further relevant data was found.

2.3.7 N-nitrosodiethanolamine (NDEOLA), CAS 1116-54-7

Carcinogenicity
According to NTP (2021), *N*-nitrosodiethanolamine caused tumors in two rodent species, at several different tissue sites, and by two different routes of exposure.

Administration of *N*-nitrosodiethanolamine in the drinking water caused liver cancer (hepatocellular carcinoma) and benign kidney tumors (adenoma) in rats. Some of these studies also found increased incidences of nasal-cavity cancer (adenocarcinoma and squamous-cell carcinoma).

In female strain A/J mice (a strain with a high spontaneous incidence of lung tumors), administration of *N*-nitrosodiethanolamine in the drinking water increased the incidence of benign lung tumors and the number of tumors per animal.

Subcutaneous injection of *N*-nitrosodiethanolamine caused cancer of the nasal cavity (adenocarcinoma) and at the injection site (fibrosarcoma) and benign tumors of the trachea (papilloma) and liver (hepatocellular adenoma) in hamsters of both sexes.

Cancer Potency
Based on the overall set of cancer data on the substance the Carcinogenic Potency Database has estimated a harmonic mean TD50 value of 3.17 mg/kg bw/day for rats. No TD50 value was given for mice.

2.3.8 N-methylnitramine (MNTA), CAS 598-57-2

Cancer Potency
Based on the overall set of cancer data on the substance the Carcinogenic Potency Database has estimated a harmonic mean TD50 value of 178.4 mg/kg bw/day for rats in relation to tumors in the nervous system. No TD50 value was given for mice.

No further relevant data was found.

2.3.9 N-nitrodiethylamine (NTDEA), CAS 7119-92-8

Cancer Potency
No TD50 value was given for nitrodiethylamine. For nitrodimethylamine (CAS 4164-28-7) a harmonic mean TD50 value of 0.547 mg/kg bw/day for rats in relation to tumors in the liver and the nasal cavity. No TD50 value was given for mice.
No further relevant data was found.

2.3.10 Monoethanolnitramine (NTEOLA), CAS -

No relevant data was found on this substance.

3. Estimation of cancer risk levels

In this chapter short descriptions of the methodology and findings will be given in relation to the key references identified in section 2.1.

3.1 The Carcinogenic Potency Database (CPDB)

In this database, carcinogenicity data/results are included from 6540 experiments on 1547 chemical agents. Based on carefully selection and an analysis of the data, a TD50 value is established for each carcinogenic substance based on an overall assessment of the carcinogenic dose-response relationship from the experimental data. The TD50 value is defined as the chronic dose-rate in mg/kg bw/day, which would induce tumors in half the test animals at the end of a standard lifespan for the species.
When an experiment is terminated before the standard lifespan (e.g. due to a shorter study design or due to high degree of severe toxicity/ mortality), animals are not at risk of developing tumours later in life. Thus, the number of tumours found might be reduced, and the TD50 will be higher than the true lifetime TD50, i.e., the compound will appear to be less potent.
Because tumour incidence increases markedly with age, a correction factor "f^2" was used by CPDB to obtain a TD50 for lifetime exposure, where "f" = experiment time / standard lifespan.

Taken together the TD50 values are numerical descriptions of carcinogenic potency, and the values can be used for further ranking of carcinogenic substances and/or used for risk estimation of specific exposure levels to the substances.

In the CPDB the following TD50 values listed in Table 3 have been derived for the substances in Table 1:

Table 3 TD50 values from CPDB of the 9 substances listed in Table 1

Substance	CAS	TD50 value mg/kg bw/day
Nitrosamines		
N-nitrosomethyllamine NMA	64768-29-2	-
N-nitrosomethylethylamine NMEA	10595-95-6	0.0503 in rats
N-nitrosodiethylamine NDEA	55-18-5	0.0265 in rats
N-nitrosopiperazine NP	5632-47-3	8.78 in rats
Dinitrosopiperazin DNP	140-79-4	3.6 in mice
N-nitrosodiethanolamine NDEOLA	1116-54-7	3.17 in rats
Nitramines		
N-nitromethylamine	598-57-2	17.4 in rats

NTMA		
N-nitrodiethylamine NTDEA	7119-92-8	- (0.547 in rats for N-nitrodimethylamine)

Table 3 shows that there is a large variation in the TD50 values from 0.0265 mg/kg bw/day for N-nitrosodiethylamine to 17.4 mg/kg bw/day for N-nitromethylamine, i.e. a variation with a factor of more than 650.

3.2 EMA (2020)

The publication by EMA (2020) was performed for deriving tolerable exposure level of nitrosamines as impurities in medicines. As indicated in section 2.2, EMA considers the nitrosamines as genotoxic carcinogens and as non-threshold substances, i.e. any residual exposure relates to an increased risk for development of cancer. Generally, an impurity level for impurities in medicines corresponding to a 10^{-5} lifetime cancer risk level is considered tolerable.

According to the guidelines of accessing genotoxic impurities in medicines, such a risk can be determined by linear extrapolation from a TD50 value (i.e. a lifetime risk level of 0.5) down to a risk level of 0.00001 by dividing the TD50 value by 50,000 (0.5/0.00001=50000).

Although some human epidemiological studies were available, EMA (2020) considered the amount of experimental animal data as the most relevant data for cancer potency estimations. Especially the extensive data on N-nitrosodimethylamine (NDMA) and N-nitrosodiethylamine (NDEA) were considered as robust data for low-risk extrapolation.

EMA (2020) considered the TD50 value as estimated by the CPDB as a valid starting point for low-dose extrapolation. For obtaining a tolerable daily lifetime dose for a patient the TD50 values was multiplied by 50 and divided by 50,000 as the assumed body weight of a patient was set to 50 kg (i.e. the TD50= value was divided by a figure of 1000), see Table 4.

Table 4 Tolerable lifetime exposure limits for NDMA and NDEA

Substance	CAS	TD50 value from CPDB mg/kg bw/day	Tolerable lifetime exposure mg/day
N-nitrosodimethylamine (NDMA)	62-75-9	0.0959 in rats	96×10^{-6} (or 96 ng)
N-nitrosodiethylamine (NDEA)	55-18-5	0.0265 in rats	26.5×10^{-6} (or 26.5 ng)

EMA (2020) also evaluated several other nitrosamines relevant as medical impurities e.g.:

Table 5 Other nitrosamines relevant as medical impurities

Substance	CAS	TD50 value from CPDB mg/kg bw/day
N-nitrosoethylisopropylamine (EIPNA)	16339-04-1	no TD50 value available
N-nitrosodiisopropylamine (DIPNA)	601-77-4	no TD50 value available
N-nitrosomethyl-amino butyric acid (NMBA)	61445-55-4	0.982
N-nitrosodibutylamine (NDBA)	924-16-3	0.691

However, they found the data used for TD50 values for NMBA and NDBA too limited (one rat study each) for the derivation of a tolerable exposure level.
Instead, EMA applied the NDMA value of 96 ng/day for NMBA (containing one methyl-group), and the NDEA value of 26.5 ng/day for EIPNA, DIPNA and NDBA (containing either an ethyl group or larger alkyl-groups) based on analysis of the chemical structures.

As an overall result of the evaluation, EMA recommended the following for deriving tolerable exposure levels for nitrosamines:

- When N-nitrosamines are identified with sufficient substance specific animal carcinogenicity data to calculate a reliable TD50, then this should be used to derive a substance specific limit for lifetime exposure.

- If more than one N-nitrosamine were identified, 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 is that the sum of all detected N-nitrosamines must not exceed the limit of the most potent of the N-nitrosamines identified.

- When N-nitrosamines are identified with insufficient substance specific data to derive a substance specific limit for lifetime exposure, then a class specific TTC for nitrosamines of 18 ng/d* can be used as default option. This TTC has been derived from the Lhasa carcinogenic potency database where a further selection of the data from the CPDB database has been made.

(*It should be noted that a value of 18 ng/day would equal a TD50 value of 0.018 mg/kg bw/day. Only two nitrosamines among 80 nitrosamines having a TD50 value in the CPDB have values below 0.018 mg/kg bw/day. The lowest TD50 of 0.00998 mg/kg bw/day is for nitroso-N-methyl-N-(2-phenyl) ethylamine).

3.3 Ravnum et al. 2014

Ravnum et al. (2014) derived DMEL-values according to the ECHA guidance document R8 for dose-response characterisation and DN(M)EL derivation (ECHA 2012).
The basis for the assessments were the TD50 values and experimental data behind these values extracted from the CPDB.

As ECHA (2012) recommends making low-dose extrapolation from a T25 value (a dose level given cancer in 25% of the animals) and not a TD50 value, Ravnum et al. (2014) used the background data from the CPDB to calculate T25 values for each substance from the specific data on cancer incidences in the studies observed at various time-points. This was done for five nitrosamines and two nitramines among these: NDEA, DNP and NTMA that are relevant for this project.

Having derived the T25 value (i.e., a dose level corresponding to a risk level of 0.25) linear extrapolation was made down to a risk level of 10^{-6} by multiplying the T25 dose with a factor of 10^{-6} / 0.25 = 1/ 250,000 i.e.:

DMEL (mg/ kg bw/day) = T25 (mg/kg bw/day) x 1/250 000

The next step was conversion to an inhalation dose. As rats inhale 1.15 m^3 air/ kg bw per day the following expression was used to convert the dose from mg/kg bw/day to mg/m^3:

DMEL (mg/m^3) = DMEL (mg/kg bw/day) / 1.15 (m^3/ kg bw/day)

Using these steps, DMEL values as indicated in Table 6 below were calculated,

Table 6 Calculated DMEL values

Substance	CAS	TD50 value from CPDB mg/kg bw/day	T25* mg/kg bw/day	DMEL* (oral) 10^{-6} risk mg/kg bw/day	DMEL* (inhalation) 10^{-6} risk mg/m^3
N-nitrosodiethylamine (NDEA)	55-18-5	0.0265 in rats	0.130	0.520 x 10^{-6}	0.452 x 10^{-6}
Dinitrosopiperazine (DNP)	140-79-4	3.6 in mice	2.531	10.12 x 10^{-6}	8.803 x 10^{-6}
N-nitromethylamine NTMA	598-57-2	17.4 in rats	2.673	10.69 x 10^{-6}	9.297 x 10^{-6}

*Calculated by Ravnum et al. (2014) based on reevaluation of selected data sets.

3.4 NIPH (2011)

The Norwegian Institute of Public Health (NIPH) in 2011 published a report assessing the health effects of amines and derivatives associated with CO2-capture.

Data was collected on 10 nitrosamines and 3 nitramines, among these NMA, NDEA, NMEA, NP, NDEOLA and NTMA, NTDEA that are relevant for this report.

The following TD50 values were extracted from the CPDB for these substances by NIPH (2011) that noted that the calculated TD50 values might vary depending on the studies and their quality and thus, should only be taken as indications on relative potencies, see Table 7.

Table 7 TD50 values from CPDB (NIPH (2011))

Substance	CAS	TD50 value mg/kg bw/day	T25
Nitrosamines			
N-nitrosodimethylamine NDMA	62-75-9	0.0959	0.076 mg/kg bw/day
N-nitrosomethyllamine NMA	64768-29-2	-	ND
N-nitrosomethylethylamine NMEA	10595-95-6	0.0503 in rats	ND
N-nitrosodiethylamine NDEA	55-18-5	0.0265 in rats	0.0025 mg/m^3
N-nitrosopiperazine NP	5632-47-3	8.78 in rats	ND
N-nitrosodiethanolamine NDEOLA	1116-54-7	3.7* in rats	ND
Nitramines			
N-nitromethylamine NTMA	598-57-2	17.4 in rats	ND
N-nitrodiethylamine NTDEA	7119-92-8	-	ND

*Should most probably be 3.17 as this is the value in the current CPDB

ND: not determined

NIPH (2011) provided examples for using the current test data on N-nitrosodimethylamine (NDMA) as the best tested substances to derive T25 values and low dose-extrapolation down to low risk levels. Using two different data sets for the substance and using two different low-dose extrapolation methods - the non-threshold linear extrapolation approach and the large assessment factor approach as described by ECHA (2012).

For N-nitrosodimethylamine (NDMA), NIPH (2011) modelled data from a drinking water study in rats in which 16 dose levels were used in the range of 0 to 1.224 mg/kg bw/day. Biliary cystadenoma in female rats was found to be the most sensitive cancer end-point. Using the cancer incidences from 10 of the dose groups and using a multistage carcinogenicity model a T25 dose of 0.076 mg/kg bw/day was calculated, based on an output of a TD05 value.
Using the methodology as described by ECHA (dose conversion to mg/m3 and extrapolation down to a low-risk level of 10-5 lifetime risk (same methodology as also used by Ravnum et al. (2014)) a DMEL value at a concentration of 5.2 ng/m3 (0.0000052 mg/m3) was calculated.

For the same substance (NDEA), NIPH (2011) also used data from an inhalation study in rats in which female rats were exposed to 0, 0.04, 0.2 or 1.0 ppm NDMA (corresponding to 0, 120, 600 and 3000 µg/m3 air), four times a week, 4 - 5 hours a day for up to 207 days.
A T25 value of 2.5 µg/m3 for lifetime exposure was calculated from the lowest exposure concentration of 120 µg/m3 at which 36% of the animals developed tumors in the nasal cavity.
NIPH (2011) then used the large assessment factor approach as described by ECHA, and by using a total assessment factor of 6250 in relation to the T25 value of 2.5 µg/m3 a DMEL value of 0.4 ng/m3 was derived. This level was considered to represent a risk level below 10-5 lifetime risk.
Further, NIPH (2011) referred to a cancer risk estimate derived by WHO (2002), and from a TD05 level of 34 µg/ kg bw/day for development of biliary cystadenomas in female rats, NIPH

(2011) calculated an exposure level in air of 0.3 ng/m3 (0.0000003 mg/m3) as an 10-5 lifetime risk level.

Based on these calculations and using NDMA as representative for all nitrosamines and nitramines NIPH (2011) concluded that the total amount of nitrosamines and nitramines should not exceed 0.3 ng/m3 (0.0000003 mg/m3) in air for ensuring minimal or negligible risk of cancer below a 10-5 lifetime risk level.

(It can be mentioned that for NDMA, Ravnum et al. (2014) used the incidences for hepatocellular carcinoma in rats and derived 10-6 lifetime risk at a concentration level of 0.86 ng/m3).

4. Derivation of C-values

In this chapter the findings from chapter 3 will be evaluated for the further use in the context of derivation of QCs and C-values for ambient air.

4.1 Evaluation of methods for deriving QC

According to Danish EPA guidance documents, EPA (2006 + 2016), a health-based quality criteria (QC) expressing a 10^{-6} lifetime risk should be derived for genotoxic carcinogens and based on this value, a C-value can be proposed. In the extrapolation of the low-dose / low risk area, it is key to define a reliable dose-level to form a point of departure (PoD) from which to make extrapolation.

4.1.1 PoD

EMA (2020) used TD50 values from the CPDB as PoD for the extrapolation, where the TD50 value used is a harmonic mean TD50 value that is derived from the overall data set of experiments and the most sensitive cancer-type from the experiments.
When using harmonic mean TD50 values all datapoints are used and CPDB indicates that it generally makes little difference in the TD50 value whether one uses the most potent target site in the CPDB or the harmonic mean derived from the most potent TD50 values from all positive experiments (CPDB-website).

NIPH (2011) and Ravnum et al. (2014) derived their own T25 values to be used for low dose extrapolation. The T25 levels were in both cases based on selecting relevant studies and using the specific cancer rates for a specific cancer type for the estimation of a T25 value. Thus, a **T25 value of 0.248 mg/kg bw/day** for NDMA was derived by Ravnum et al. (2014) while NIPH (2011) derived a **T25 value of 0.15 mg/kg bw/day** for this substance, i.e. nearly a factor 2 lower.

If the harmonic mean TD50 value of 0.0959 mg/kg bw/day from CPDB was used with a linear extrapolation to a T25 value, this would result in a value half of the TD50 value, namely **T25 value of 0.048 mg/kg bw/day**, i.e. a 4-6 times lower PoD compared to the values derived by Ravnum et al. (2014) and NIPH (2011).

To make a comparison/ analysis regarding the use of the TD50 value from the CPDB and the use of T25 values derived by Ravnum et al. (2014), the values can be compared as shown in Table 8. In this table the TD50 values from the CPDB is converted to a T25 value by dividing by a factor of two. The T25 values by Ravnum et al. (2014) were derived by revaluation of specific test data from a selected part of the data on the substances.

Table 8 T25 values derived from TD50 values or from experimental data by Ravnum et al. (2014)

Substance, CAS	TD50 oral rat from CPDB mg/kg bw/day	T25 value oral rat (½ x TD50) mg/kg bw/day	T25 oral rat, derived from a specific experiment data set by Ravnum et al. mg/kg bw/day
Nitrosamines			
N-nitrosodimethylamine (NDMA), 62-75-9	0.0959	0.0479	0.248
N-nitrosodiethylamine (NDEA), 55-18-5	0.0265	0.0133	0.130
N-nitrosomorpholine (NNM), 59-89-2	0.109	0.0545	0.306
N-nitrosopiperidine (NPIP), 100-75-4	1.43	0.715	0.530
Dinitrosopiperazine (DNP), 140-79-4	3.6	1.8	2.531
Nitramines			
N-nitromethylamine (NTMA) 598-57-2	17.4	8.7	2.673
Dimethylnitramine (DMNTA) 4164-28-7	0.547	0.274	0.792

From Table 8, it can be seen that a T25 value derived from the harmonic mean TD50 value from the CPDB, in all cases except two (N-nitrosopiperidine and N-methylnitramine), were considerably lower than the T25 values derived by Ravnum et al. (2014). N-nitrosodiethylamine was the substance with the highest difference, as a T25 value ten times higher was calculated by Ravnum et al. (2014).

Also, it can be seen that the derived T25 values by Ravnum et. al. (2014) for 4 of 7 substances result in higher values than the corresponding TD50 values from the CPDB. An explanation/ discussion for this was not further given by Ravnum et al. (2014).

Conclusion on PoD for this project

While EMA (2020) used harmonic TD50 values from the CPDB as a PoD for low-dose extrapolation, NIPH (2011) and Ravnum et al. (2014) based their low-dose extrapolation on T25 values derived after further data selection and analysis of the cancer incidences in the studies. Although very comparable approaches by NIPH (2011) and Ravnum et al. (2014) it can be seen that the selection of the relevant studies for the T25 derivation may be different and different values for the same substance may be obtained (e.g.in the case of derivation of T25 for NDMA).

In this project for obtaining administrative C-values, we find it important to use the most transparent approach for PoD selection for low dose extrapolation and here we find the approach presented by EMA (2020) expert group using the TD50 values from the CPDB to be the most transparent approach to use. This method also allows for differences in the carcinogenic potencies of the substances that will influence the calculation of the health-based quality criteria and the proposed C-values.

4.1.2 Conversion of oral PoD to inhalation PoD

When the PoD is from an oral study and a DMEL for inhalation should be derived, the first step according to ECHA (2012) is to convert the oral dose to an inhalation dose.

As used by Ravnum et al. (2014) and NIPH (2011) and as recommended by ECHA (2012), the oral dose should be converted to an inhalation concentration by dividing the oral dose with the daily inhalation volume (1.15 m^3/kg bw) of rats i.e.

PoD (inh) mg/m^3 = PoD (oral) (mg/kg bw/day) / 1.15 m^3/kg bw/day x $ABS_{oral\text{-}rat}$ / $ABS_{inh\text{-}human}$

In the evaluation by NIPH (2011) the oral absorption rate in rats was found to > 90% for NDEA and therefore no correction regarding differences in absorption rates was done. Assuming this would be very much the same for the other nitrosamines and nitramines, the equation can be reduced to:

PoD (inh) mg/m^3 = PoD (oral) (mg/kg bw/day) / 1.15 m^3/kg bw/day

4.1.3 Low dose extrapolation

The default assumption for conducting low dose extrapolation for genotoxic carcinogens is according to the guidance in Danish EPA (2006) and ECHA (2012) to use linear extrapolation from a PoD in the high-risk area (a T25 value is recommended by ECHA 2012) down to a low risk level assuming the straight line going through (0,0) as an intersection point.

In the case of a T25 value, ECHA (2012) divide this value by 250 000 to obtain a 10^{-6} lifetime risk level.

When using a TD50 as a PoD the linear extrapolation down to a risk level of 10^{-6} should instead be conducted by dividing by 500 000.

Thus, a QC representing a 10^{-6} risk level can be calculated by:

QC (inh.) mg/m^3 = TD50 (inh) mg/m^3 / 500 000.

4.2 QC calculations

In Table 9 below QCs are calculated using the equations given above.

Table 9 Calculation of QC-values with TD50 values as starting point

Substance CAS	TD50 value mg/kg bw/day	TD50 value mg/m^3	QC mg/m^3
Nitrosamines			
N-nitrosodimethylamine* NDMA, 62-75-9	0.0959 in rats multiple studies	0.083	1.7×10^{-7}
N-nitrosomethyllamine NMA, 64768-29-2	-	-	-
N-nitrosomethylethylamine NMEA, 10595-95-6	0.0503 in rats two studies	0.044	9.0×10^{-8}
N-nitrosodiethylamine NDEA, 55-18-5	0.0265 in rats multiple studies	0.023	4.6×10^{-8}

N-nitrosopiperazine NP, 5632-47-3	8.78 in rats more than one study	7.63	1.5×10^{-5}
Dinitrosopiperazin DNP, 140-79-4	3.6 in mice 4 studies	1.71**	3.4×10^{-6}
N-nitrosodiethanolamine NDEOLA, 1116-54-7	3.17 in rats more than one study	2.76	5.5×10^{-6}
Nitramines			
N-nitrodimethylamine 4164-28-7	0.547 in rats more than one study	0.476	1×10^{-6}
N-nitromethylamine NTMA, 598-57-2	17.4 in rats more than 1 test	15.1	3.0×10^{-5}
N-nitrodiethylamine NTDEA 7119-92-8	-	-	-
Monoethanolnitramine (N-nitroethanolamine) NTEOLA	-	-	-

* the substance is not one of the 9 selected substances but it is included because of read-across from this substance may be relevant due to its chemical structure resembling some of the selected substances

**calculated by using 2.1 m^3/kg bw/day for daily inhalation volume/ kg bw for mice

4.3 Proposal for C-values

According to Danish EPA (2016), substances where the toxicity is dependant of the total dose over longer time period such as genotoxic carcinogens, the C-value for a substance can be obtained from the QC by multiplication with 40. This factor is used as the average exposure to a substance for a neighbour and is set to generally 40 times lower than the numerical value of the C-value. This is because of different meteorological conditions during a year and because the C-value should be met 99% of the time during a year.

Thus, based on the QCs the following C-values can be proposed as indicated in Table 10.

Table 10 Proposed C-values derived from substances with a QC

Substance **CAS**	**QC** **mg/m³**	**C-value** **mg/m³**
Nitrosamines		
N-nitrosodimethylamine* NDMA, 62-75-9	1.7×10^{-7}	7×10^{-6}
N-nitrosomethylethylamine NMEA, 10595-95-6	9.0×10^{-8}	4×10^{-6}
N-nitrosodiethylamine NDEA, 55-18-5	4.6×10^{-8}	2×10^{-6}
N-nitrosopiperazine NP, 5632-47-3	1.5×10^{-5}	6×10^{-4}
Dinitrosopiperazin DNP, 140-79-4	3.4×10^{-6}	1×10^{-4}
N-nitrosodiethanolamine NDEOLA, 1116-54-7	5.5×10^{-6}	2×10^{-4}

Nitramines		
N-nitromethylamine NTMA, 598-57-2	3.0 x 10^{-5}	1 x 10^{-3}

* the substance is not one the selected substances but is included because of their chemical structure very similar to some of the selected substances

For the substances where a QC could not be calculated based on lack of a TD50 value, C-values may be derived by read-across based on structural similarity to either NDMA or NDEA for the nitrosamines and structural similarity to NTMA or NTDMA for the nitramines, see Table 11.

Table 11 Proposed C-values derived from read-across

Substance **CAS**	**QC** **mg/m^3**	**C-value** **mg/m^3**
Read-across nitrosamines		
N-nitrosodimethylamine NDMA, 62-75-9	1.7 x 10^{-7}	7 x 10^{-6}
N-nitrosodiethylamine NDEA, 55-18-5	4.6 x 10^{-8}	2 x 10^{-6}
Nitrosamines without TD50 and QC values		
N-nitrosomethylamine NMA, 64768-29-2	-	7 x 10^{-6}*
Read-across nitramines		
N-nitromethylamine NTMA, 598-57-2	3.0 x 10^{-5}	1 x 10^{-3}
N-nitrodimethylamine NTDMA, 4164-28-7	1 x 10^{-6}	4 x 10^{-5}
Nitramines without TD50 and QC values		
N-nitrodiethylamine NTDEA 7119-92-8	1 x 10^{-6} *	4 x 10^{-5}*
Monoethanolnitramine (N-nitroethanolamine) NTEOLA	-	-

*** values based on read-across**

For N-nitrosomethylamine (NMA) the closest structural similarity can be found to the read-across substance N-nitrosodimethylamine (NDMA) and therefore, the C-value of 7 x 10^{-6} mg/m^3 is applied for NMA.

For N-nitrodiethylamine (NTDEA) the closest structural similarity can be found to the read-across substance N-nitrodimethylamine (NTDMA) as both substances contain two alkyl-groups (dimethyl- and diethyl., respectively) and therefore, the QC-value of 1 x 10^{-6} mg/m^3 and the C-value of 4 x 10^{-5} mg/m^3 are applied for NTDEA.

For monoethanolnitramine (NTEOLA) it is not - based on its structure as a mono-alcohol - considered possible to do read-across to either of the two potential read-across substances.

Conclusion and overall results

For specific nitrosamines and nitramines that potentially may be generated by reactions between NOx and amines / amino-alcohols used in the carbon capture technology toxicological data was gathered and health based quality criteria were derived.

As all the specific nitrosamines and nitrosamines were considered as genotoxic carcinogens TD50 dose levels as reported in the Carcinogenic Potency Data Base (CPDB) were used as starting point for low-dose extrapolation. TD50 dose levels are substance-specific dose levels derived from experimental animal carcinogenicity testing and represent an everyday lifetime dose level estimated to cause cancer in 50% of the animals). Based on these values linear low-dose extrapolation down to a QC-value representing a 10^{-6} lifetime risk level in humans can be made (a 10^{-6} lifetime risk level is considered acceptable according to Danish EPA (2006)).
Based on the QC-values proposals for C-values can be made by multiplying the QC value with 40 according to the methodology given in *"B-værdivejledningen"* (Danish EPA 2016).

Overall, it was possible to provide proposals for C-values of eight of the nine relevant substances + 2 structural closely related substances used for read-across, see Table 12.

Table 12 Proposed C-values derived for the selected nitrosamines and nitramines + the substance N-nitrosodimethylamine (NDMA) used for read-across.

Substance CAS	QC mg/m³	C-value mg/m³
Nitrosamines		
N-nitrosodimethylamine* NDMA, 62-75-9	1.7 x 10^{-7} *	(0.000007 7 x 10^{-6}) *
N-nitrosodiethylamine NDEA, 55-18-5	4.6 x 10^{-8}	0.000002 2 x 10^{-6}
N-nitrosomethylethylamine NMEA, 10595-95-6	9.0 x 10^{-8}	0.000004 4 x 10^{-6}
N-nitrosopiperazine NP, 5632-47-3	1.5 x 10^{-5}	0.0004 6 x 10^{-4}
Dinitrosopiperazin DNP, 140-79-4	3.4 x 10^{-6}	0.0001 1 x 10^{-4}
N-nitrosodiethanolamine NDEOLA, 1116-54-7	5.5 x 10^{-6}	0.0002 2 x 10^{-4}
N-nitrosomethylamine NMA, 64768-29-2	-	0.000007 7 x 10^{-6}
Nitramines		
N-nitromethylamine NTMA, 598-57-2	3.0 x 10^{-5}	0.001 1 x 10^{-3}
N-nitrodimethylamine** NTDMA, 4164-28-7	1 x 10^{-6} **	(0.00004 4 x 10^{-5})**
N-nitrodiethylamine NTDEA 7119-92-8	1 x 10^{-6}	0.00004 4 x 10^{-5}

*NDMA data used for read-across to N-nitrosomethylamine NMA (NDMA is not considered a relevant degradation product from the used amines for CC in DK, see section 1.2 and thus, the C-value calculated is not relevant for the CC technology). However, the C-value is an update of the Danish EPA (2016) C-value of 0.0001 mg/m³ for NDMA)

**NTDMA data used only for read-across to N-nitrodiethylamine NTDEA (NTDMA is not considered a relevant degradation product from the used amines for CC in DK, see section 1.2 and thus, the C-value calculated is not relevant for the CC technology).

According to Danish EPA (2001), C-values for substances with *identical effects* should be added up when:

- the substances are *homologous* (i.e. substances from the same chemical substance group, e.g. alcohols, ketones, ethers, etc.), *and*
- the substances belong to the *same substance group* (i.e. in the same main group of C-values) *and*
- the substances have health-related C-values (i.e. they are not marked L (L: odour based C-values)).

For the substances in this evaluation the nitrosamines fulfil these criteria as they all belong to the same homologue chemical group and as they all result in carcinogenic effects via a genotoxic mechanism. Also, they are all placed in main group 1.

Currently, the data on the nitramines is considered being too limited to apply the same additive criteria on these substances.

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Nitrosamines and nitramines

The Danish Environmental Protection Agency has requested an evaluation of health hazards by exposure to nitrosamines and nitramines. This resulted in the present report, which includes a healthbased quality criterion for the substances in ambient air

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