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Sustainable OPEration of post-combustion Capture plants (SCOPE)

Human Health hazard assessment strategy for amine emissions around PCC facilities

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Abbreviations

Abbreviation	Definition
AI	Adequate Intake
AMP	2-Amino-2-methylpropanol
BW	Body Weight
CCP	Carbon Capture Plant
CCS	Carbon Capture and Storage
CDI	Chronic Daily Intake
CPDB	Carcinogenic Potency Database
CSF	Cancer Slope Factor
DEA	Diethanolamine
DEYA	Diethylamine
DGA	Diglycolamine
DMA	Dimethylamine
DMEL	The Derived Minimal Effect Level; for non-threshold effects, the underlying assumption is that a no-effect-level cannot be established and a DMEL, therefore, expresses an exposure level corresponding to a low, possibly theoretical, risk, which should be seen as a tolerable risk.
DMNA	Dimethylnitramine
DNEL	The Derived No-Effect Level; the level of exposure to a substance above which humans should not be exposed
DNPZ	Dinitrosopiperazine
DNP	Dinitrosopiperazine
EA	Ethylamine
ED	Exposure Duration
EC50	Effective Concentration causing 50 % inhibition of growth for an organism population
EIA	Environmental Impact Assessment
ET	Exposure Time
IARC	International Agency for Research on Cancer
HEI	Hydroxyethylimidazole
HEF	Hydroxyethyl-formamide
HSE	Health, Safety and Environment
Inhalation	Exposure to vapour, mist or aerosols. Experiments may use nose/mouth exposure only or the entire animal in an exposure chamber
InhR	Inhalation Rate
IR	Ingestion Rate
IRIS	Integrated Risk Information System
ISO	International Organization for Standardization
IUR	Inhalation Unit Rate
IVIS	In Vitro Irritation Score
KLIF	The Norwegian Climate and Pollution Agency
LC50	Median Lethal Concentration of a toxic substance, causing 50 % lethality for a tested organism population, after specified test duration
LD50	Median Lethal Dose of a toxic substance causing 50 % lethality for animal population, after specified test duration
LADD	Lifetime Average Daily Dose

LOEC	Lowest Observed Effect Concentration
LOAEL	Lowest Observed Adverse Effect Limit
MA	Methylamine
MDEA	Methyldiethanolamine
MEA	Monoethylamine
MMEA	Methylethanolamine [methylmonoethanolamine]
MNA	Methylnitramine
MNPZ	Mononitrosopiperazine
MoA	Mode of Action; a sequence of key events and processes, starting with interaction of an agent and a cell, proceeding through operational and anatomical changes, and resulting in cancer formation
NDBA	N-nitrosodibutylamine
NDEA	N-nitrosodiethylamine
NDELA	N-Nitrosodiethanolamine
NDMA	N-Nitrosodimethylamine
NDPA	N-nitrosodi-n-propylamine
NDPhA	N-Nitrosodiphenylamine
NDTMA	Dimethyl-nitramine
NILU	Norwegian Institute of Air Research
NMEA	N-Nitrosomethylethylamine
NMOR	N-Nitrosomorpholine
NMPA	N-Nitrosomethylaniline
NMPEA	Nitroso-N-methyl-N-(2-phenyl)ethylamine
NNK	4-(N-Nitrosomethylamino)-1-(3-pyridyl)-1-butanone
NNM	N-Nitroso-morpholine
NNN	N-Nitrosonornicotine
NNO	Nitrosopiperazine
NOAEL	No Observed Adverse Effect Limit (effect limit in toxicity tests related to human health) - the highest dose with no toxic effects
NOEC	No-Observed Effect Concentrations (effect limit in ecotoxicity tests)
NPIP	N-Nitrosopiperidine
NPYR	N-Nitrosopyrrolidine
NTMA	N-Methyl-nitramine
OECD	Organisation for Economic Cooperation and Development
OEL	Occupational Exposure Limit
Oral	Substance delivered to the stomach by lavage, food or drink
OZD	Oxazolidinone
PEC	Predicted Environmental Concentration
PNEC	Predicted No-Effect Concentration
Pow	Partition Coefficient between Octanol and Water
PZ	Piperazine
QSAR	Quantitative Structure-Activity Relationship
REACH	European Regulation for Registration, Evaluation, Authorisation and restriction of Chemicals
RSD	Risk Specific Dose
TEA	Triethanolamine
TD50	The median Toxic Dose of a drug or toxin is the dose at which toxicity occurs in 50% of cases

TCM	Technology Centre at Mongstad
TGD	Technical Guidance Document
TWA	Time Weight Average
US.EPA	United States Environmental Protection Agency
WHO	World Health Organization
WTP	Water Treatment Plant

1 Executive Summary

The general objective of the deliverable is to provide insights into the human health hazard assessment for amine emissions around Post Combustion Capture (PCC) facilities. It is a review of the available literature and previous CO_2 capture related documentation on human health and toxicology data with respect to risk assessment for amines and their degradation products. This review aims to establish a knowledge base for the environmental guidelines study to be conducted and regulatory context analysis for PCC emissions.

The deliverable addresses the following aims and objectives within the SCOPE project:

- General information on the environmental fate of amines, including their formation pathways and degradation, photodegradation rates and influence of natural organic matter.
- Environmental concerns in different compartments, surface- ground- and drinking- water.
- Human health risk assessment, assessing the relationships between occupational exposure and adverse health effects.
- Human health related data of biomarkers of biological response, critical endpoints (mutagenicity, genotoxicity and carcinogenicity) and different toxicities.
- Available toxicity models, such as dose-response or molecular modelling such as Quantitative structure activity relationships (QSAR) that predict the potential hazard/toxicity of the chemicals.
- Current safety limits used by different regulatory authorities and organisations, defined as the upper limit of the respective compounds in air and water that do not cause harmful effects to human health or to ecosystems and, therefore, appropriate to use to determine hazardous concentration zones.

Therefore, a comprehensive review of health-related scientific information on the status of occupational health and safety issues associated with potential exposure to amines and their by-products, together with concentrations and sources, has been conducted. It focused on airborne exposure to amines or exposure through drinking water for the purpose of undertaking a human health risk assessment, comparing concentrations with occupational limits and assessing and quantifying potential health risks following acute and chronic exposure to these chemicals. It aims to help to evaluate the persistence (biodegradability, toxicity and bio-accumulation) and environmental impacts of PCC emissions.

A summary of the key points is as follows:

- UV treatment and photolysis have been documented as effective degradation processes for both nitrosamines and nitramines. Especially for nitrosamines, when exposed to sunlight, photodegradation is an important depletion pathway, both in air and in water. That is that when NSA and NA are classed as being readily biodegradable, they present less of a hazard in the environment.
- Seasonal variation in temperature, sunlight, and hydrology was found to influence both the NSA and NA concentrations. During winter the effect of photodegradation was reduced to a minimum, resulting from the combined effect of weaker sunlight radiation and ice cover. This variation should be taken into account in any monitoring program.

- It is well known that concentrations and temperatures significantly influence the biodegradability of chemicals in natural waters. Results have indicated that biodegradation of nitrosamines was reduced by lower water temperatures and at lower concentrations.
- According to IARC, the majority of the nitrosamines are classified to either group 2B – possibly carcinogenic to humans – or group 2A – probably carcinogenic to humans. Although nitramines in turn seem to be less potent (~15 times less) as mutagens and carcinogens than their corresponding nitrosamines, they should also be considered as highly toxic.
- TD50 has been suggested by the CPDB as the excess cancer risk calculation, associated with a theoretical excess cancer risk of 1:100,000 or 1:1,000,000. A larger dose is indicative of a smaller carcinogenic effect. Based on the literature review TD50 values, nitramines were orders of magnitude less carcinogenic than nitrosamines.
- As these values are estimated based on animal experiments, it is important to consider assessment factors, to account mainly the differences between animals and humans, and also to allow for the variability between different population, and individual variations among people, such as age and gender.
- Special attention should be given to sensitive populations. Infants and children can be more susceptible than adults to the mutagenic effects of the nitrosamines, as they have a higher uptake from both oral and airway exposure per kg body weight due to a higher metabolic rate per body unit for children compared to adult. Children, compared to adults, were shown to be more likely to develop diseases when they were exposed to hazardous substances, especially carcinogenic chemicals.
- Because chemicals sometimes cause cancer by a mutagenic mode of action (MOA) and can therefore pose a higher risk of cancer to humans when exposure occurs during early life, it is important to apply age-dependent adjustment factors (ADAFs) for different age stages to the estimated lifetime cancer risk.
- Besides the different age stages, it is also important to consider different genders, as there are also differences in the physiological function between males and females.
- Based on a human health risk assessment for the occurrence and the carcinogenic risk of nitrosamines and nitramines, they were found to have severe eye and skin irritation and corrosion potential. However, the level of risk may depend upon the exposure concentration. The most important health risks were observed for NDMA and NMOR, which showed medium to high long term health effects for dermal and inhalation, respectively. In the case of nitramines, on the other hand, only a few toxicity studies have been conducted. Data on nitramines' toxicity showed moderate toxic health effects with an order (from highest to lowest) of the test substances being DMA > MA > MEA > PZ. Although all the compounds were genotoxic, DMA and MA were more potent and PZ slightly toxic.
- Mathematical-computational models, i.e. QSARs, have gained significance in terms of predicting the toxic activity and mutagenic properties of amines, based on their physico-chemical properties through statistical methods. These models can be very supportive for undertaking a risk assessment when experimental data is lacking.
- Several organisations and institutions have established different public health thresholds for different nitrosamines and nitramines. The Norwegian Institute of Public Health (NIPH) has recommended, based on a 10^{-6} risk of cancer, an acceptable exposure level of 4 ng lt^{-1} in drinking water, and 0.3 ng m^{-3} in air, for the total concentration of NSA and NA, based on the risk estimate calculated for NDMA. It

should, however, be pointed that this represents a conservative risk estimate, since NDMA is likely to be more potent than any of the nitramines and is one of the most potent nitrosamines.

- There is therefore the need for a continuing effort in toxicity data for both NSA and NA to derive more realistic levels that are protective of the human health.

A thorough human health hazard assessment strategy will build up on this information and together will provide information to sub-task 3.1.4 in SCOPE, to incorporate in the development of risk assessment practices.

2 Introduction

2.1 CO_2 capture context

One of the well-established, viable and prominent technologies for mitigation of CO_2 emissions from power and energy intensive industries is the amine-based post-combustion CO_2 capture (PCC). Amines are the most common solvents for PCC and have long been used in CO_2 removal processes from natural gas. They are commonly applied in post-combustion CCS due to their high CO_2 absorption capacity and reaction kinetics. They are also relatively in low cost, due to their availability as large scale bulk chemicals.

One of the drawbacks associated with post-combustion amine-based CCS technology is, however, the formation of potentially harmful by-products. These are degradation products from reactions that occur during the CO_2 capture process, which are subsequently emitted into the atmosphere. PCC activities can result in loss of amines from the absorber column, undergoing nitrosation, and be degraded into more toxic compounds, as they are released into the environment. Particularly, during the capture process, amines can react with nitrogen oxides (NOx) in the flue gas to form degradation products. Although the effluent is treated with water wash systems to remove the amines and potential degradation products, atmospheric releases of these compounds may still occur. Of particular concern among these by-products are the nitrosamine (R2NNO) and related nitramine (R2NNO2) compounds. The former are well known for their potential mutagenic as well as carcinogenic properties and pose human health and environmental risks in air, surface, ground and drinking water.

As nitrosamines can only be formed directly from secondary and tertiary amines and nitramines from primary, secondary or tertiary amines, in solvent systems where secondary and tertiary amines are the main solvent components, the potential to form nitrosamines will be higher than those operating with primary amines and, therefore, emissions of secondary and tertiary amines may also be more of an issue. Once released into the atmosphere, amine degradation products may be deposited in aquatic and terrestrial environments, where their final fate and environmental effects are determined by their resistance towards physical and microbial processes. These processes will ultimately have a significant impact on exposure and subsequently on the potential risk to human health and the environment.

For example, a worst-case study was conducted for Norway's CO_2 Technology Centre Mongstad (TCM), where a conservative 2% conversion rate from monoethylamine (MEA) to nitrosamines was used to investigate amine concentrations released into various media. It was shown that maximum MEA deposition fluxes would exceed toxicity limits for aquatic organisms by about a factor of 3–7 depending on the scenario. Due to the formation of nitrosamines and nitramines, the estimated emissions of diethylamine (DEYA) was estimated to be close to or exceed safety limits for drinking water and aquatic ecosystems (Karl et al., 2011).

Therefore, it is imperative to fully understand and evaluate health and environmental impacts from the emission of amines and their degradation products, so as to make sound decisions on advanced emission control technologies and eliminate any potential risk.

2.2 Amines of concern

Amines commonly used in chemical absorption post-combustion capture of CO_2 include monoethylamine (MEA), diethanolamine (DEA), methyldiethanolamine (MDEA), 2-amino-2-methyl-1-propanol (AMP), diglycolamine (DGA), di-isopropanolamine (DIPA), triethanolamine (TEA), and piperazine (PZ) (Låg et al. 2011). Other amines relevant for CO_2 capture include methylethanolamine [methylmonoethanolamine] (MMEA), dimethylamine (DMA), diethylamine (DEYA), dibuthylamine, N-methylethanamine, N-ethyl-1-butanamine, dipropylamine, hydroxyethylimidazole (HEI), hydroxyethyl-formamide (HEF), oxazolidinone (OZD), 4,4-dimethyl-2-oxazolidinone, 2-methyl-2-(methylamino) -1-propanol, methylamine (MA) and ethylamine (EA). These amines are used in post-combustion CCS because of their ability to selectively and strongly bind with CO_2 (Gentry et al., 2014).

The flue gas treated in PCC facilities contains various potential oxidants (O_2, SOx, and NOx) at varying concentrations depending on the combustion fuel. These compounds can react with amines, producing secondary and tertiary amines via oxidative, thermal, or nitrosative degradation pathways. Secondary amines are always present in amine solvents, initially or as a result of solvent degradation (e.g. MEA degrades into DEA) (Spietz et al 2017). Consecutively, as oxidative degradation of amine solvents can result in the formation of nitrites in the absorber, these nitrites can also react with secondary amines to form nitrosamines in the stripper (e.g. DEA leads to the formation of nitrosodiethanolamine (NDELA)). Although N-nitrosamines formation is expected in all primary, secondary, and tertiary amines used for carbon dioxide (CO_2) capture, secondary amines have a higher potential than primary and tertiary amines to form nitrosamines (Afzal et al 2017). Therefore, the potential for N-nitrosamines and N-nitramines formation, hence, depends on the degradation pathways and the structure/types of amines chosen for PCC processes (Chen et al., 2018).

Different studies, e.g. performed by Fostås et al. 2011 and Shi et al. 2017 (as seen in Shavalieva et al., 2021) indicate that, although the formation rate of nitrosamines, i.e. N-Nitrosodiethanolamine (NDELA) increases with increasing NOx and oxygen concentration, the nitrosation of MEA takes place even at low levels of NOx (5 ppm). That indicates that nitrosamines can be detected even in the absence of NOx, making it even more challenging to control their formation. Due to the formation of N-nitrosamines and N-nitramines from amines in the absorber unit, and the reactions in the flue gas, N-nitrosamines and N-nitramines may accumulate in the water wash unit, and some of them will be released to the environment through exhaust gas emission, wastewater discharge and solid waste disposal. Because most of N-nitrosamines and N-nitramines are hydrophilic, they prefer to get into the water phase, rather than adsorb to soils and sediments, resulting in preferential presence in surface, drinking or ground water (Chen et al., 2018).

Some of the nitrosamines, such as dimethylnitrosamine (NDMA), diethylnitrosamine (NDEA), diethanolnitrosamine (NDELA), nitrosomorpholine (NMOR), nitrosopiperidine (NPIP) and nitrosopiperazine (NPIPz), and the nitramines methylnitramine (MNA), dimethylnitramine (DMNA) and monoethylamine (MEA), have been clearly identified as by-products of amine based PCC technology (Buist et al., 2015). Of these, NDMA, NDEA, N-nitrosomethylethylamine (NMEA), N-Nitrosodi-n-propylamine (NDPA), N-Nitrosodibutylamine (NDBA), N-nitrosopyrrolidine (NPYR) and N-

nitrosodiphenylamine (NDPhA) have been categorized as class B2 carcinogens (probable human carcinogens) by the USEPA, 2009; whereas the International Agency for Research on Cancer (IARC) has classified NDMA and NDEA have as class A2 carcinogens (probably carcinogenic to humans), and the remaining as B2 carcinogens (possibly carcinogenic to humans).

This confirms the importance of understanding their environmental fate in order to assess the risk of human exposure to nitrosamines and nitramines. A range of natural processes, including formation mechanisms, hydrolysis, photolysis, biodegradation can determine their environmental persistence and accumulation.

3 Formation pathways of N-Nitrosamines and N-nitramines in amine-based post-combustion capture processes

The amines used as solvents (in amine scrubbing technology) can be emitted to the atmosphere where they can react with hydroxyl radical (*OH), ozone and nitric oxides present in the air and, hence, produce nitrosamines and nitramines. The presence of dissolved metals in amine solvents can also lead to the formation of N-nitrosamines (Chen et al., 2018). The nitrosamines' formation and accumulation rates vary with operating conditions like flue gas composition, operating temperature, absorber and wash water columns design, solvent choice etc.

The order of total N-nitrosamine formation from different amine structures during PCC processes has been reported as: secondary amines ≈ tertiary amines ≫ primary amines. The amine order dictates the rate and pathways of N-nitrosamine formation. Only secondary amines, where they react rapidly, can form N-nitrosamines, which are the most stable when compared with other nitrosamines and, so, their accumulation rate is higher (Mazari et al., 2019). Nitrosation of primary amines also forms a highly unstable N-nitrosamine intermediate, but degrades rapidly into nitrogen and carbocation (Zhang et al., 2014). Tertiary amines may also form stable nitrosamines, but the reactions are expected to be significantly lower than for secondary amines (Brakstad et al., 2010b). However, in a solvent system based on primary amines, there will be a certain accumulation of degradation products with secondary and tertiary amine functionality. As for N-nitramines, they can be formed directly from primary, secondary, or tertiary amines (Chen et al., 2018).

Amines, during the day, can undergo a very rapid reaction with the hydroxyl (OH) radical (photolysis), whereas during night-time, ozone and NO_3 radicals cause further amine degradation what leads to the formation of different compounds (Karl et al., 2011; Coutris et al., 2015). It becomes clear that the formation of nitrosamines and nitramines are completely dominated by gas phase reactions, which are necessary to consider (Table 3.1) (Helgesen & Gjernes, 2016). It is obvious (Table 3.1) that reactions in the aqueous phase were not found to be of importance neither for the formation or destruction of nitrosamines and nitramines. On the other hand, the high solubility of amines will pull the amines out of the gas phase reaction conditions in relation to degradation and they will not undergo reactions in the water. As such, partitioning of amines to the aqueous phase in the atmosphere will constitute an important loss process for amines (Gjernes et al., 2013).

Table 3.1 Reaction pathways of amines, nitrosamines and nitramines (Gjernes et al., 2013).

Nitrosamine/Nitramine chemistry	Gas Phase	Aqueous Phase
Formation Daytime	Amine + OH	None important
Formation Night-time	Amine + NO_3	None important
Destruction, Daytime	Nitrosamine + hv	None important
Destruction, Night-time	None important	None important

3.1 Degradation of N-Nitrosamines and N-Nitramines in the natural environment

To date, the degradation mechanisms for nitrosamines have been extensively studied in the literature (Brakstad et al., 2010b-c; Brakstad & Zahlsen, 2011; Eide Haugmo et al., 2012, Brakstad et al., 2012a,b; Brakstad et al., 2014; Da Silva et al., 2012; Henry et al., 2017; Brakstad et al., 2018; Buvik, 2021).

When amines emitted to the atmosphere come in contact with biotic environments like soil, sediments and water (fresh- or seawater) they are subjected to biodegradation through aerobic or anaerobic processes, mainly conducted by the bacteria present in these environments. The Norwegian Activities Regulation has stated a minimum recommended value of 20% biodegradability. In addition, substances are defined as "ready biodegradable" when biodegradability is > 60 % under conditions of high concentration (2 – 10 mg l^{-1}) and temperature (20°C) (Brakstad et al., 2010b). However, these conditions do not often mirror the true emission conditions. That means that concentrations of compounds in PCC emissions are well below the concentrations recommended for these tests, and the temperature may not be as high all year round; whereas in temperate regions the temperature stays lower than 20°C most of the year.

It is well known that both concentrations and temperatures may be important for the biodegradability of chemicals. Brakstad and Zahlsen (2011) showed that temperature (5 to 20°C) seemed to be more important than concentration (1 to 100 µg l^{-1}) for the biodegradation of the nitrosamine N-nitrosodiethanolamine (NDELA). However, in a study of Brakstad et al. (2012b) for amine biodegradation in seawater, temperature was important for the biodegradability of some solvent amines, but less important for others, when these were tested over a range of 10-32°C. Although AMP biodegradation at 20°C and 10°C was increasing, it was delayed at 5°C. Piperazine (PZ) showed slower depletion than AMP, and this process was started after a period of 28 days. Thus, a temperature effect was not measured at temperatures < 10°C. A further study of NDELA at lower concentrations (10 µg l^{-1}) and extended biodegradation period (56 days) showed that biodegradation was affected by temperature, and when biodegradation at low concentration of NDELA was compared at 5 – 20°C over a 56-days period, the half-lives were increasing with reduced temperature (Booth et al., 2014). They also indicated that by reducing concentrations of the chemicals and extending the incubation period, biodegradation was increased for some of the compounds.

Except the clear temperature-related biodegradability of amines and their degradation products (Brakstad et al., 2014, Brakstad et al., 2010b), where cold temperatures (5 °C) can reduce the biodegradation significantly, the importance of initial concentration on biotransformation was also investigated (Brakstad et al., 2018). Biodegradation of NDELA at 20 °C for 56 days, and with initial concentrations of 100, 10 and 1 µg l^{-1}, was shown to be comparable, reaching approximately 87 ± 11% (100 µg l^{-1}), 80 ± 9% (10 µg l^{-1}) and 75 ± 1% (1 µg l^{-1}) (Brakstad et al., 2018). On the other hand, even at lower amine and nitrosamine concentrations, if the incubation period is extended, biodegradability can increase (Brakstad et al., 2014).

A striking difference was the biodegradation rates between freshwater and marine environments. A study by Henry et al. (2017) showed that biodegradability was improved under aerobic conditions in freshwater

compared to seawater. For example, DEA and MEA were rapidly degraded, while AMP, MDEA and PZ were degraded after one week incubation. This is important for AMP and MDEA, which have been reported to be persistent under marine conditions. This distinct difference could be due to the different microbial communities in the two environments.
Another observed tendency was that most of the highly degradable amines are of natural origin and the ones showing low degradability are of synthetic origin. The biodegradability of the natural compounds was in general found to be higher than the compounds which were not natural – the biodegradability range was 1 – 100% with a median value of 70.7% for the natural compounds, while it was <1–57.6% with a median value of 3.0% (Eide Haugmo et al., 2012). For example, the MEA and MA primary amines have been classified as readily biodegradable; or the parent amine PZ was also estimated as readily biodegradable; whereas all of its predicted process degradation products (nitrosamines and nitramines) were estimated as not readily biodegradable (Da Silva et al., 2010).

This indicates that particularly the primary amines with highest biodegradability, and hence the lowest half-lives, can represent the least hazardous compounds in the environment as they may produce the fewest number of environmentally persistent process degradation products. On the other hand, amines and their degradation products being classed as not readily biodegradable could present the greatest risk from an environmental perspective (Da Silva et al., 2010).

3.2 Photodegradation of N-Nitrosamines and N-Nitramines in natural waters

In the presence of light, nitrosamines are considered unstable and short-lived in the atmosphere (from ~5 min (Låg et al., 2011) up to ~40 min (Chen et al., 2018) after released from PCC facilities, as they have shown to degrade rapidly by photolysis whilst nitramines will be persistent. This means that half-lives are shorter at daytime than at night, and in summer rather than in winter. The release of nitrosamines at night or in parts of the world where there are long periods of the year with no daylight (northern latitudes) can significantly decrease the importance of this degradation pathway (Booth et al., 2014). In contrast, nitramines are considered more stable in the atmosphere, and will therefore have longer lifetimes/residence times (2 days) (Låg et al., 2011). This stability of N-nitramines brings a higher potential for its accumulation in the atmosphere compared with N-nitrosamines (Chen et al., 2018).

The photodegradation of nitrosamine and nitramines in natural waters has been well studied (Knuutila et al., 2013; Booth et al. 2014; Sorensen et al., 2015; Afzal et al., 2016, 2017; Chen et al., 2018; Mazari et al., 2019). Different half-lives ($t^{1/2}$) for a range of nitrosamines have been reported based on different concentrations and conditions (Table 3.2).

Table 3.2 Reported half-lives ($t^{1/2}$) for a range of nitrosamines.

Amines	$t^{1/2}$ Half-lives	Source
NDELA	6.2 min	Afzal et al. 2016
NDBA	4.3 min	Afzal et al. 2016
NDMA	4.9 min	Afzal et al. 2016
	21.7 min	Mazari et al. 2019
	<1 h	Spietz et al 2017
NDPA	22 min	Mazari et al. 2019
NMEA	22.7 min	Mazari et al. 2019
DMNA	2 d	Spietz et al 2017
NDEA	24 min	Mazari et al. 2019
NDEA	1d min	Spietz et al 2017
NMOR	16 min	Mazari et al. 2019
NPYR	22.7 min	Mazari et al. 2019
NPIP	18.4 min	Mazari et al. 2019
DNPZ	11.1 min	Mazari et al. 2019
MEA	1 d	Spietz et al 2017
Acetaldehyde	<1 d	Spietz et al 2017
Nitrosamines	42-178 min	Brecke-Gundersen et al. 2020

The influence of pH on UV photodegradation of different N-nitrosamines was examined over the entire pH range (2–10), reporting their strong photolability of N-nitrosamines in acidic solution. Afzal et al. (2017) showed that the degrading of the nitrosamines was quite rapid during acidic conditions, resulting in half-lives less than 25 min for all the nitrosamines. They showed that the concentration of parent secondary amines (DEA, DMA, and MOR) was increased in alkaline (pH 10) to weakly acidic conditions (pH 4). In contrast, a decrease in the concentration of primary amines (MEA and EA) was observed in the same conditions. This comes in agreement with other studies, showing that photolysis of nitrosamines has also been shown to proceed more quickly under acidic conditions compared to neutral pH conditions (Xu et al., 2009 as seen in Afzal et al., 2017; Knuutila et al., 2013; Sorensen et al., 2015). As acidic solutions have a high concentration of H^+, this can be involved in the hydrogen bonding process, and hence leading to a higher rate and accelerating the degradation of N-nitrosamines.

When the UV photolysis of the N-nitrosamines was studied at different initial concentrations, it was seen that the photolysis rate constants were affected in several studies, with decreased degradation rates observed at higher initial nitrosamine concentrations (Xu et al., 2010 as seen in Afzal et al., 2016, Da Silva et al., 2012; Knuutila et al. 2013; Afzal et al., 2016). A study of NDMA biodegradation at low nitrosamine concentration (10 µg l^{-1}) indicated rapid degradation over 15 days in both freshwater (91%) and seawater (80%) (Da Silva et al., 2012). It is therefore to note that photodegradation rates can be increased at lower concentrations.

However, when the biodegradation of three N-nitrosamines NDELA, NDMA, and MNPZ was investigated in natural surface waters, it was found that the half-life of NDELA was 28.5–38.1 days, which was much longer than its half-life for photolysis; whereas the half-lives of NDMA and MNPZ were >400 days and >1,500 days, respectively. These times indicate that N-nitrosamines may be hard to be biodegraded in natural aqueous system at low concentrations (Chen et al., 2018). In the aquatic environment, the half-lives will be influenced by day/night cycles and importantly, how much sunlight is exposed to the compounds. For example, half-lives will increase with increasing water depth. In the case of groundwater, no sunlight is expected and therefore photo-oxidation stops being a significant degradation pathway for nitrosamines (Booth et al., 2014).

When Brecke-Gundersen et al. (2020) examined the seasonal variations in temperature, sunlight, and hydrology, they found a strong impact on the photodegration rates of the nitrosamines concentrations in lake water, close to a CO_2 plant in Oslo. During winter, the effect of photodegradation was reduced due to a weaker sunlight radiation. Although the nitrosamines concentration were increased during spring time as a result of melting snow, photodegradation was the most important depletion pathway, where it was almost reducing their levels to a minimum and preventing potential accumulation. On the other hand, nitramines were found to accumulate with time, due to inefficient depletion pathways.

Potential for photolytic degradation: As natural sunlight emits radiation in the wavelength range 290–800 nm, only the nitrosamines will degrade photolytically when released to the environment. Sørensen et al. (2015) have shown nitrosamines to absorb radiation with an absorbance peak at approximately 340 nm while nitramines did not have an absorbance peak for the sunlight range. That means that nitramines life times are of several orders of magnitude higher than nitrosamines, as they are stable with regards to photolysis. Absorption peaks at ~230 nm and ~330 nm for nitrosamines have also been reported by others (Chow et al., 1972, Lee et al., 2005b, Plumlee and Reinhard, 2007, Stefan and Bolton, 2002). The $t^{1/2}$ values generated in this study (6–11 min) (Table 3.3) are generally consistent, although slightly shorter than those observed in previous studies of nitrosamine photolysis, which report $t^{1/2}$ values in the range 8–16 min depending on the study conditions (i.e. irradiation delivered, pH, nitrosamine concentration). Afzal et al. (2016) reported half-lives of 12–16 min of nitrosamines in surface water at a level of solar irradiation equal to that of a mid-day sunshine in southern California, with a nitrosamine absorption spectra at two peaks of about 230 nm and 340 nm.

Table 3.3 Half-lives ($t^{1/2}$) determined experimentally using the Atlas Sunset CPS+ solar simulator (Sorensen et al., 2015).

Amine	$t^{1/2}$ Half-life (irridation at 60 W m^{-2})
NDELA	6.4 min
NDMA	7.5 min
NMOR	6.1 min
NPZ	10.6 min

Influence of natural organic matter (NOM) on photodegradation: In aquatic systems, nitrosamines will degrade rapidly by photolysis under natural sunlight although it is also important to consider that degradation will decrease with increasing depth in the water column and be limited when nitrosamines are rapidly transported to environmental compartments where there is little or no light penetration (e.g. deeper waters and groundwater) (De Koijer et al., 2013). Dissolved organic matter and suspended particulate material in surface water is responsible for intensive light attenuation. Assessing the effect of light screening by increasing the concentration of NOM in the water, half-life of NDELA showed that a linear relationship exists between the degradation rate and the degree of light screening. Increasing the NOM concentration from 0-1 mg $l^{-1}$to 100 mg l^{-1} gave a three-fold increase in half-life for this compound (Booth et al., 2014). Similar studies, one by Sorensen et al. (2015) clearly indicated that nitrosamines $t^{1/2}$ will be significantly influenced by the concentration of NOM present in surface waters, with high NOM concentrations leading to longer residence times. At low NDELA concentrations, NOM appears to significantly reduce NDELA $t^{1/2}$, with degradation rates being significantly hindered at a NOM concentration of 10 mg l^{-1} and becoming negligible at a NOM concentration of 100 mg l^{-1} NOM (under summer conditions).

Another study by Plumlee & Reinhard (2007) (as seen in Sorensen et al., 2015) also showed that increasing concentrations of Aldrich humic acid (measured in mg DOC l^{-1}), significantly decreased the photolysis rate of NDMA. This indicates that environmentally relevant concentrations of nitrosamines may persist in natural waters under the presence of organic matter in the water as it influences the degradation rates by decreasing the nitrosamine degradation rates, acting as a light screen. Therefore, photolysis processes are normally restricted to the upper zones of water bodies, where nitrosamines have shown to have a potential for rapid degradation in the upper reaches of the photic zone of natural waters (Booth et al., 2014; Sorensen et al., 2015).

The release of nitrosamines at night or in parts of the world where there are long periods of the year with no daylight can also decrease the importance of this degradation pathway. The biodegradation processes, ultimately and secondary, are also important for toxicity, since transformation of compounds by biodegradation (and other degradation processes) may alter the toxicity of the compound.

4 Environmental Impact of amine-based CO_2 capture technology

4.1 Environmental concerns

As it has already been mentioned, amines degrade to produce nitrosamines and nitramines in amine-based post-combustion CO_2 capture. Partly these are produced during the CO_2 capture process and the rest in the environment through photochemical oxidation. Nitrosamine and nitramines may also be formed indirectly from the degradation products of primary amines (i.e. MEA) and directly from secondary and tertiary amine (i.e. PZ and MDEA). Studies have brought to light that MEA degrades into DEA, which is nitrosated to nitrosodiethanolamine (NDELA). In addition, nitrosodimethylamine (NDMA) is also detected as a degradation product of MEA, which may be produced through the degradation of NDELA (Mazari et al., 2015).

Many of these products are not only toxic but also carcinogenic. A number of nitrosamines and nitramines have been reported in literature through the degradation of amines and more than 80% of them are suspected carcinogens. As these emissions, nitrosamines and nitramines, besides contamination of air, have the tendency to accumulate in the water resources including underground water in the vicinity of PCC plants, they can cause significant damages and endanger the ecosystem.

4.2 Hazardous concentrations levels

Hazardous concentrations of substances are defined as the upper limit of concentrations in air that do not cause harmful effects to humans or ecosystems. In establishing safe concentration levels, the most perceptible unfavourable effect caused by a given group of compounds in any area of the target environment (drinking water, vegetation, terrestrial fauna, ecosystem types) and in the receptor organisms (algae, invertebrates, fish, humans) should be taken into account. The negative effects of the impact of the substances mentioned above may have an immediate character (after a few hours) or a long-term one (after a few weeks, months, years) depending on the receptor organism (a few days for algae, several years for humans) (Rusin et al., 2016).

Range of zones with amines at higher concentrations: It has been documented that the level of amines emissions and their concentration zone is dependent on the installation size and capture capacity, such as the emission source height, but also on meteorological conditions. The zones with an increased concentration of MEA, for example, will vary according to the distance from the emission source. These were shown to reach a range of about 300 m from the emission source and they are reduced if there is a rise in wind speed (Rusin et al., 2016). Namely, a MEA concentration of 2.5 mg m^{-3} will reach the range of about 300 m in the case of a lower wind speed value and about 114 m if the wind speed is 6 m s^{-1}, which means that a faster wind disperses the cloud, reducing the concentration of harmful substances. Its concentration will decrease with a rise in the distance from the emission source and may fall below 1 mg m^{-3} at a distance of 500 m, regardless of wind speed (Rusin et al., 2016).

The emission source height (i.e., the height of the stack) can also affect the amine concentration. A rise in the emission source height can decrease the range of the concentration level zone. In other words, an increase in the height of the stack through which flue gases are carried can cause a greater dispersion of the gas and a substantial reduction in their concentration. For example, Rusin et al. (2016) showed that a stack height exceeding 30 m could keep MEA concentrations in air below 0.5 mg m^{-3}. Rusin et al. (2016) also showed that the NDMA formed can create a hazardous concentration zone covering an area with a radius of more than 500 m at low wind speed values. In line with expectation, if the stack is 10 m high, the zone with the NDMA concentration of 10 µg m^{-3} may cover an area located at a distance of from 57 to 678 m away from the emission source, and if the source height is 20 m, the hazardous concentration zone will extend over a distance from 170 to 539 m. This is to say, the impact of the wind speed can be seen in that if the stack is higher than 25 m, the NDMA concentration posing a hazard to humans will not be formed. As the stack height gets higher, the hazardous zone will become smaller, and at a certain height of the emission source, no zones with the hazardous substance will arise.

5 Human Health Risk Assessment (HHRA)

A human health risk assessment is the process to estimate the nature and probability of adverse health effects in humans who may be exposed to chemicals in contaminated environmental media, now or in the future. It begins with problem formulation and includes four additional steps: (a) hazard identification, (b) hazard characterisation, (c) exposure assessment and (d) risk characterisation (Figure 5.1).

In order to establish a foundation, the initial step is crafting the problem formulation to identify the problem that needs to be addressed (i.e., regulatory requirements, data needs, and context of use). This is vital for the best course of action for the problem, to move forward and provide a problem resolution, which may include a risk treatment and reduction.

A human health risk assessment begins by planning the overall approach, regarding the purpose and scope of the assessment. At start, the questions to be asked when planning the risk assessment are (US. EPA, 2022):

1. Who and where is at risk?
    - Individual
    - General population
    - Life stages such as children, teenagers, elderly, pregnant/nursing women
    - Population subgroups - highly susceptible (i.e., due to asthma, genetics, etc.) and/or highly exposed (i.e., based on geographic area or gender)

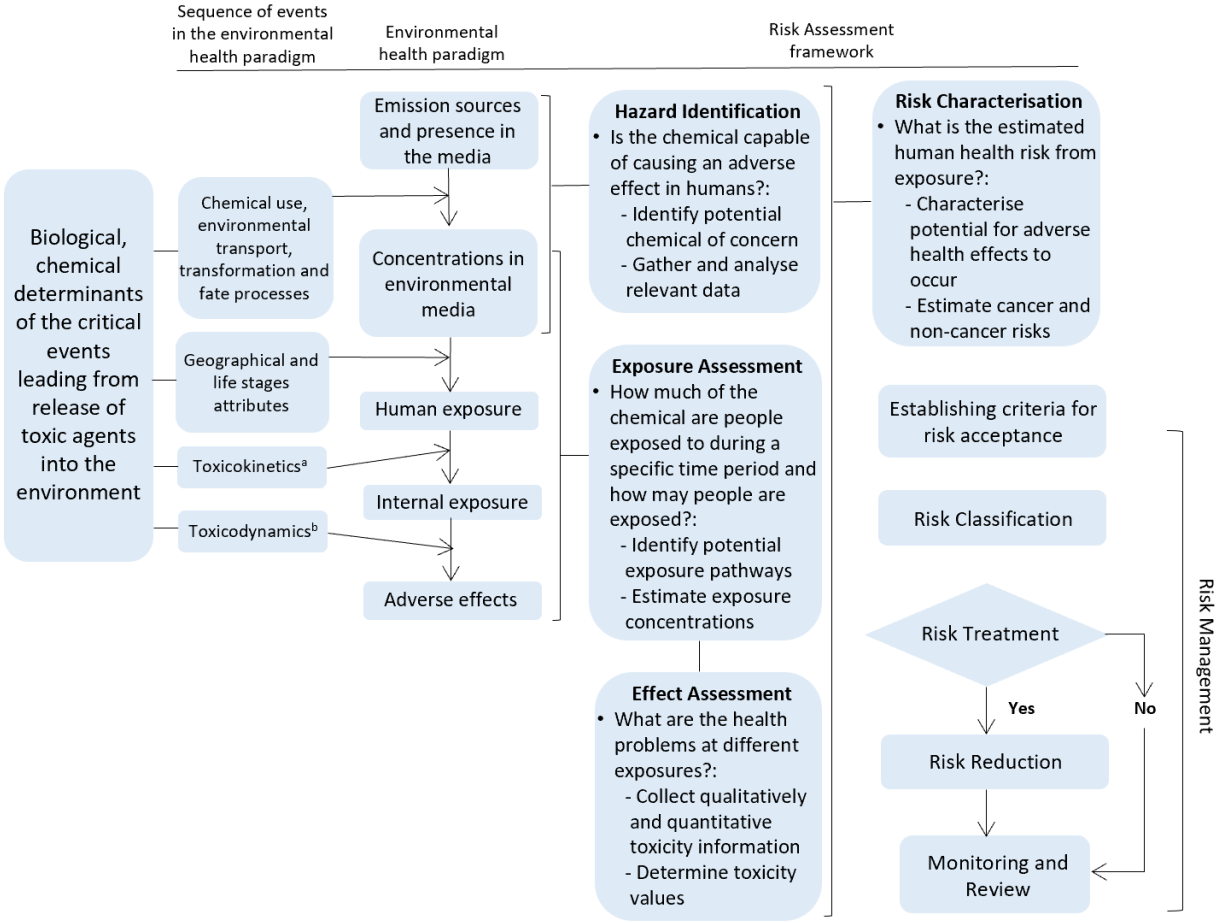
2. What is the environmental hazard of concern?
    - Chemicals (single or multiple/cumulative risk)

3. Where do these environmental hazards come from?
    - Point sources (for example, smoke or contamination/ water discharge from a plant/ factory)

4. How does exposure occur?
    - Pathways (recognising that one or more may be involved)
        1. Air
        2. Surface water
        3. Groundwater
        4. Soil
    - Routes (and related human activities that lead to exposure)
        1. Ingestion (both food and water)
        2. Contact with skin
        3. Inhalation

5. What are the health effects?
    - Example of some health effects include cancer, heart disease, liver disease and nerve disease.

6. How long does it take for an environmental hazard to cause a toxic effect? Does it matter when in a lifetime exposure occurs?
    - How long?
        1. Acute - right away or within a few hours to a day
        2. Sub-chronic - weeks or months
        3. Chronic - a significant part of a lifetime or a lifetime (for humans at least seven years)



a. Toxicokinetics: what the body does to the agent. The process of the uptake of potentially toxic substances by the body, the biotransformation they undergo, their distribution of the substances and their metabolites in the tissues and the elimination of the substances
b. Toxicodynamics: what the agent does to the body; the process of interaction of chemical substances with the target sites and the subsequent reactions leading to adverse effects

Figure 5.1: An environmental health paradigm in association to the human health risk assessment framework (US. EPA, 2022).

5.1 Conducting a HHRA

Step 1 – Hazard Identification is the process of determining whether exposure to a stressor can cause specific adverse health effects (e.g., cancer, diseases, formation of tumors, reproductive and birth defects). Identification of the adverse effects involves consultation of any toxicological and epidemiological data; that means gathering data on the types of health effects caused by a substance and characteristics of the human populations that are exposed and developing a weight of evidence to characterise the link between the negative effects and the chemical agent. The magnitude and duration of the exposure are also important (EEA, 1998; US.EPA, 2022a).

Clinical/ epidemiological studies on humans, involving a statistical evaluation of human populations to examine whether there is an association between exposure to a stressor and a human health effect, provide the best evidence linking a chemical to a resulting effect. However, such studies are frequently not available since there are significant ethical concerns associated with human testing of environmental hazards. When data from human studies are unavailable, data from animal studies (rats, mice, rabbits, etc.) are relied on to draw inference about the potential hazard to humans; but there are also uncertainties associated with extrapolating results from animal subjects to humans (US. EPA, 2022).

Step 2 – Dose-Response Assessment (or Effect Assessment) is the "estimation of the relationship between dose, or level of exposure to a substance, and the extent of that toxic effect or disease. It describes how the likelihood and severity of adverse health effects (the responses) are related to the amount and condition of exposure to an agent (the dose provided) and is therefore ascertained from epidemiological and toxicological data. Typically, as the dose increases, the measured response also increases.

No-Observed-Adverse-Effect Levels (NOAELs), which are derived from laboratory studies, are the highest exposure levels that do not pose a statistically or biologically significant adverse effect at the exposed population. The next dose above NOAEL (i.e. the lowest dose at which adverse effects may be seen) is the Lowest-Observed Adverse Effect Level (LOAEL). However, when these levels are observed from animal studies, they are often at much higher doses that would be anticipated for humans, so both these doses must be extrapolated to lower ones and from animal species to humans in order to predict the relationship for humans. These extrapolations to determine NELs (DNELs) for humans introduce some uncertainty into the dose-response analysis and this can be applied by assessment factors (EA, 2009). Assessment factors are notably aiming to include potential differences in human response compared to that of another animal species – as it is expected that humans may be more sensitive per unit dose – and the variability in response in human population due to factors such as age and health status. Examples of generic assessment factors used in chemical risk assessment can be seen in Table 5.1 (EA, 2009).

The selection of assessment factors will therefore depend on a number of considerations. These include the types of study available (kinetic, chronic toxicity, reproductive toxicity, genotoxicity, carcinogenicity), the species for which data are available (i.e. rodents, humans) and the critical adverse effects observed.

It is often sensible to focus on the most sensitive members of the population; therefore, regulatory efforts are generally made to keep exposures below the population threshold, which is defined as the lowest of the thresholds of the individuals within a population (US. EPA, 2022).

Table 5.1 Assessment Factors examples used in a chemical risk assessment (EA, 2009).

Consideration	Typical assessment factor applied
Interspecies variability	A 10-fold factor is normally used to account for variability in species susceptibility between human and animal species
Intraspecies variability	A 10-fold factor is normally used to account for variability of responses in human populations
LOAEL to NOAEL	A 10-fold factor may be used when a LOAEL instead of a NOAEL is used in the derivation
Data gaps	A factor usually 3- to 10-fold may be used for 'incomplete' databases (with missing studies, such as no chronic bioassays or no reproductive toxicity data). It accounts for the failure of a study to consider all toxic endpoints

Step 3 – Exposure assessment is the process of measuring or estimating the magnitude, frequency, and duration of human exposure to a chemical in the environment. Determining the emissions, pathways and rates of a substance as well its transformation and degradation is vital in in order to estimate the concentration/ doses to which human populations are or may be exposed (EEA, 1998).

Environmental exposure to chemicals can be direct - as a result of emission to the environment (air, land, water) of a substance through industrial manufacture, use or disposal, or indirect - through drinking water or the food chain. It is therefore important to consider models of chemical transport and fate in the environment, and estimates of human intake over time (US. EPA, 2022).

Range of Exposure. For any specific agent or site, there is a range of exposures actually experienced by individuals. Some individuals may have a high degree of contact for an extended period (e.g., factory workers exposed to a substance on the job). Other individuals may have a lower degree of contact for a shorter period. Hence, there is a range of exposures for any substance by individuals (Figure 5.2).

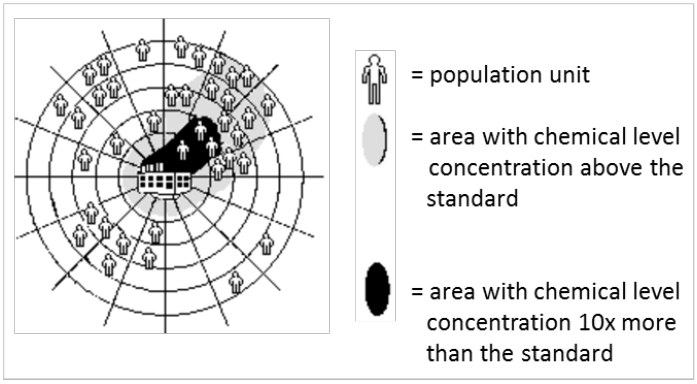


Figure 5.2: A schematic exemplar of the range of population exposure

Step 4 – Risk Characterisation is defined as the estimation of the incidence and severity of the adverse effects likely to occur in a human population due to actual or predicted exposure to a substance (EEA, 1998). If the level of exposure to a chemical exceeds the known hazard thresholds, a certain risk is assumed. If not, then it is concluded that no risks are emerging. However, there is no direct relation between hazard and risk; a chemical with a high potential hazard may have a small risk if the (probability of) exposure is very small. Accordingly, a chemical with a low potential hazard may have a high risk if the exposure is high (Hillebrand et al., 2016).

An intermediate step in risk characterisation can be a risk classification, which is described as the valuation of risk so as to decide if risk reduction is required. The acceptability of risk is a value-laden issue. Risk levels either numerical (below or lower than a value) or categorical (based on a consequence/ likelihood risk matrix (ISO 31010, 2009) are commonly associated with this. If these levels are used, it is common to accept risk below them; whereas levels above a value are defined as unacceptable which will require the use of risk management measures.

Monitoring and review form the final step in the risk management process, as illustrated in Figure 5.1, where a repetitive observation of one or more chemical or biological elements over space and time is required to review health management performances. Risk management decisions are developed based on these results for the studied site.

5.1.1 Cancer Risk Assessment

5.1.1.1 Estimation of cancer risk using the slope factor approach

For chemicals that may exert a carcinogenic effect, the risk characterisation is sometimes expressed as the excess lifetime cancer risk. Characterisation of cancer risk over a lifetime has become a convention primarily because cancer is thought to be a function of long-term rather than short-term exposure. Excess lifetime cancer risk is an estimate of the likelihood of excess cancer associated with a given level of exposure averaged over a lifetime. To estimate cancer risk in the environmental media, the slope factor determined from dose–response assessment, expressed in the appropriate units for relevant media (the "unit risk" or the estimated number of cases of a cancer associated with a unit of exposure), is compared to measured or estimated concentrations in those media, with the risk increasing proportionately with exposure. For example, a two-fold increase in exposure would be estimated to be associated with a double increase in the number of projected cases in a population (WHO, 2021).

5.1.1.2 Parameters

Cancer Slope Factor (CSF): These are used to estimate the risk of cancer associated with exposure to a carcinogenic or potentially carcinogenic substance. A slope factor is an upper bound, approximating a 95% confidence limit, on the increased cancer risk from a lifetime exposure to an agent by ingestion or inhalation. The development of a slope factor entails applying a model to the available data set and using the model to extrapolate from the relatively high doses administered to experimental animals (or the exposures noted in epidemiologic studies) to the lower exposure levels expected for human contact in

the environment. This estimate is usually expressed in units of proportion (of a population) affected per mg of substance kg^{-1} body weight-day^{-1} and is generally for use in the low-dose region of the dose-response relationship, that is, for exposures corresponding to risks less than 1 in 100 (US.EPA, 2005).

NOAELs/ LOAELs are used by applying assessment factors (AFs) to derive a reference dose (RfD) which is an oral, dermal or inhalation dose to be used in the dose-response relationship. As it is already mentioned, these uncertainty factors take into account the variability and uncertainty that are reflected in possible differences between test animals and humans (generally 10-fold) and variability within the human population (generally another 10×); the AFs are multiplied together: 10 × 10 = 100×.

If a LOAEL is used, another uncertainty factor, generally 10×, is also used. In the absence of key toxicity data (duration or key effects), an extra uncertainty factor(s) may also be employed. Thus, the RfD is determined by use of the following equation: RfD = NOAEL (or LOAEL) / AFs

In general, the RfD is defined as an estimate of a daily oral exposure to the human population (including sensitive groups or life stages, such as children or the elderly) that is likely to be without an appreciable risk of deleterious effects during a lifetime.

The RfD is generally expressed in units of milligrams per kilogram of body weight per day: mg kg^{-1} bw day^{-1} for daily oral exposure; while for inhalation risks, where concentration refers to levels in the air, is generally expressed in the units of milligrams agent per cubic meter of air: mg/m^3 (US.EPA, 2022a).

The CSF is also called a "potency factor" and can be used to calculate the Incremental Lifetime Cancer Risk by multiplying the CSF by the chronic daily intake (CDI). The CDI is the dose over a lifetime and is expressed in mg kg^{-1} bw day^{-1}.

Risk Specific dose (RSD): The Cancer Slope Factor is used to derive the Risk Specific Dose (RSD) (mg kg^{-1} bw day^{-1}) for direct-acting carcinogenic agents, those that cause chemical changes. It is also the default choice for carcinogens when there are insufficient data to demonstrate the mode of action of the chemical. RSD can be calculated by CSF and a tolerable risk level. It has been reported that tolerable risk levels for consumers during lifetime exposure should not exceed 10^{-4} or 10^{-6} (Zhang et al., 2014).

The RSD is often calculated based on a one-in-a-million extra risk (10^{-6} risk) or a one-in-a-hundred-thousand risk (10^{-5} risk) for other-than highly exposed individuals. The formula to calculate the RSD for a chemical based on a one-in-a-million extra risk (10^{-6} risk) is: RSD = 0.000001/CSF. According to the relationship between RSD and CSF, at high CSF, the RSD is low and hence the potent carcinogenic risk is high.

5.1.1.3 Classification of potential health hazards and endpoints

Based on the REACH Regulation, part of the chemical safety assessment is substances of specific concern, or of particular hazardous properties, to be comprehensively evaluated when they are supposed to pose a risk to human health and the environment. This evaluation relates substances classified as:
- Carcinogenic, mutagenic and/or toxic for reproduction (CMR substances)
- Persistent, bioaccumulative and toxic (PBT substances)
- Very persistent and very bioaccumulative (vPvB substances)

Especially, in case of persistence, ECHA (2017) recommends a list of criteria that these substances need to fulfil:
- Persistent (P): $T^{1/2}$ > 60 d in marine water; $T^{1/2}$ > 40 d in fresh- or estuarine water
- Very persistent (vP): $T^{1/2}$ > 60 d in marine- or freshwater
- Bioaccumulative (B): BCF > 2,000
- Very Bioaccumulative (vB): BCF > 5,000
- Toxic to the environment (T): Chronic NOEC < 0.01 mg l^{-1} for marine or freshwater organisms

Acute short-term exposure at relatively high concentrations may not be a good indicator of health hazards which may occur after low level and long-term exposure. There is therefore of prime interest to focus on compounds which cause the following potential health effects, when regulations are set for permissible exposure to population at or near a plant:

- Carcinogenicity (C): shown to induce or increase cancer in humans;
- Mutagenicity (M): shown to give rise to an increased occurrence of mutations, that is applying permanent changes in the amount or structure of the genetic material. It is recognized that genetic events are central in the overall process of cancer development. Therefore, evidence of mutagenicity indicates that a substance has a potential to induce carcinogenic effects;
- Reproductive effects (R): shown to cause adverse effects on reproductive ability or capacity or the development of offspring;
- Sensitisation, primarily by inhalation (S)/ corrosion of skin and eyes: shown to induce a condition of hypersensitivity in individuals following inhalation (respiratory sensitiser) or skin contact (contact sensitiser); in case it requires light to become active subsequently induce a condition of contact sensitivity then the effect is photosensitising (Sp).

These are the most important endpoints to evaluate (Brakstad et al. 2010a). In order to support this evaluation of chemicals, GESAMP Hazard Evaluation Procedure (2019) provides a set of criteria for categorising these hazard end-points, based on the intrinsic properties of the chemicals, and assess their importance (Table 5.2).

Table 5.2 Hazard system classification according to GESAMP (2019).

Label	Toxicity level	Explanation
C1	Oral toxicity LD50 rating levels	0: >2,000 1: 300-2,000 2: 50-300 3: 5-50 4: <5 mg kg^{-1} bw
C2	Dermal toxicity LD50 rating levels	0: >2,000 1: 1,000-2,000 2: 200-1,000 4: <50 mg kg^{-1} bw
C3	Inhalation toxicity LC50 4 hours exposure rating levels	0: >20 1: 10-20 2: 2-10 3: 0.5-2 4: <0.5 mg l^{-1} (4hrs)
D1	Skin irritation / Corrosion	0: non-irritating 1: Mildly irritating 2: Irritating 3: Severely irritating or corrosive 3A: Corrosive >1 hr-4hr 3B: Corrosive >3 min <1hr 3C: Corrosive < 3 min
D2	Eye irritation / Corrosion	0: non-irritating 1: Mildly irritating 2: Irritating 3: Severely irritating with irreversible corneal injury
D3	Long term effects	C, M, R, S
	Expert Judgement	For oral/ dermal/ inhalation the numbers in columns indicate: • Negligible toxicity: 0 • Slight toxicity: 1 • Moderate toxicity: 2 • Moderately high toxicity: 3 • High toxicity: 4 OEL: Occupation exposure limit – TWA: Time weight average (of exposure for 8 hours)

5.2 Human Health Impact Assessment of Nitrosamines and Nitramines

N-nitrosamines have been studied for many years with well documented mutagenic and carcinogenic effects, as humans have been exposed to nitrosamines in general via tobacco smoke for long time. Most nitrosamines have proven to be highly toxic and carcinogenic at a μg g^{-1} level and, while less is known about nitramines, they appear mutagenic and carcinogenic although are typically less potent in their biological activity than their nitrosamines analogue (Låg et al., 2011; Selin, 2011 Fjellsbø et al., 2013; Wagner et al., 2014). For example, the nitramines 2-Nitroaminoethanol (MEA) and dimethylnitramine (DMNA) were shown to have carcinogenic effects on laboratory animals, but their potency was lower than nitrosamines (Booth et al., 2014). Specifically, Wagner et al. (2014) showed that N-nitrosamines were ~15-fold more mutagenic than their N-nitramines analogues. It was interesting to note, however, at the same study, that the nitramines associated with diethanolamine (DEA) and piperazine (PZ) were more toxic than their nitrosamine analogues when tested for chronic cytotoxicity in Chinese hamster ovary (CHO) cells.

In any case, both nitrosamines and nitramines are considered to exert a potential risk to human health, especially to those people living in close proximity to the capture facility and may be exposed to these compounds for lifetime. It is therefore essential to further investigate their mutagenic and carcinogenic potential and hence determine their potential adverse effects, derived from the amine-based CO_2 capture technology.

5.2.1 Exposure routes

The primary exposure pathways for the general population to amines and their degradation products are through inhalation of the air surrounding a post-combustion plant and (drinking) water consumption of supplies nearby. Other human exposure routes except ingestion or inhalation could be also dermal contact. As amines are hydrophilic, it is therefore more likely that they will partition to the water phase rather than adsorb to soils and sediments, with the possibility of reaching ground and drinking water via precipitation and run-off, where further degradation process can occur.

Although N-nitrosamines are subject to sunlight photolysis and they can pose less of a problem from an ecotoxicological and toxicological perspective, this can be inhibited by light-shielding constituents and then they can disperse more into aerosols. The safety distance of exposure to the atmosphere for a 1 Mt CO_2 per year PCC plant has been estimated to be less than 5,700 m for the direction with low wind velocity (Chen et al., 2018). However, building another PCC plant within a distance of 100 – 200 Km downwind of an existing PCC plant will cause interferences, and amine emissions released from the neighbouring PCC plant will add to the already chemically produced N-nitrosamines and N-nitramines and so will be continuously accumulated in the surrounding environment and endanger human health.

On the other hand, the biodegradation rate of N-nitramines is very low, as they more stable compounds in the atmosphere, and generally have a lifetime more than 2 days. It can be expected that nitramines are transported over and deposited at longer distances from the plant (Chen et al., 2018).

5.2.2 Toxicity classification of nitrosamines and nitramines

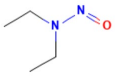
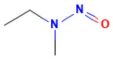
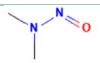
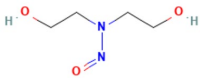
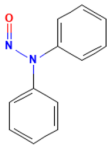
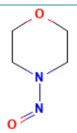
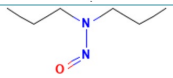
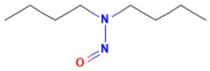
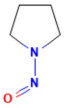
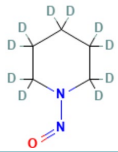
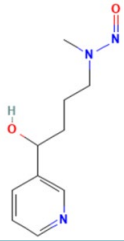
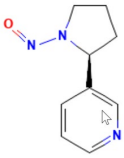
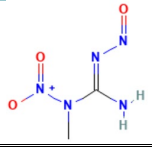
The IARC (2021) have devised a system of categories to evaluate the carcinogenicity of an agent to humans. An agent is classified based on scientific evidence derived from human and experimental animal studies. The list of categories and their definition is shown in Table 5.3.

According to IARC, nitrosamines are classified as either group 2B – possibly carcinogenic to humans – or group 2A – probably carcinogenic to humans (i.e., NDEA and NDMA). Nitramines in turn seem to be less potent as mutagens and carcinogens than the corresponding nitrosamines; however, the DMNA, which has been best studied, should still be regarded as a highly potent carcinogen (Table 5.4). Although nitramines are less mutagenic and carcinogenic than their corresponding nitrosamines, they should also be considered as highly toxic. Of highest concern with respect to mutagenic and carcinogenic potential are some of the so-called volatile N-nitrosamines such as NDMA, NDEA, NPYR, NPIP, NMPEA, NDBA, NMOR, NMEA and NDPA (EMA, 2020).

Table 5.3 IARC Classification of carcinogenic agents

Group	Description	Definition
Group 1	Carcinogenic to humans	• Sufficient evidence of carcinogenicity, Or • Evidence of carcinogenicity in humans is less than sufficient but there is sufficient evidence of carcinogenicity in experimental animals and strong evidence in exposed humans that the agent acts through a relevant mechanism of carcinogenicity
Group 2A	Probably carcinogenic to humans	• Limited evidence of carcinogenicity in humans and sufficient evidence of carcinogenicity in experimental animals, Or • Inadequate evidence of carcinogenicity in humans and sufficient evidence in experimental animals, Or • Limited evidence of carcinogenicity in humans but belongs to a class of agents for which one or more members have been classified in Group 1 or Group 2A
Group 2B	Possibly carcinogenic to humans	• Limited evidence of carcinogenicity in humans and less than sufficient evidence of carcinogenicity in experimental animals, Or • Inadequate evidence of carcinogenicity in humans but sufficient evidence in experimental animals, Or • Inadequate evidence of carcinogenicity in humans and less than sufficient in experimental animals
Group 3	Not classified as to its carcinogenicity to humans	• Evidence of carcinogenicity is inadequate in humans and inadequate or limited in experimental animals, Or • Evidence of carcinogenicity is inadequate in humans but sufficient in experimental animals Agents in Group 3 are not determined to be non-carcinogenic or safe overall, but often means that further research is needed

Table 5.4 IARC classification of nitrosamines and nitramines formed in Carbon Capture plants

Agent	Abbreviation	Chemical structure	IARC Classification
N-Nitrosodiethylamine	NDEA		2A
N-Nitrosomethylethylamine	NMEA		2B
N-Nitrosodimethylamine	NDMA		2A
N-Nitrosodiethanolamine	NDELA		2B
Nnitrodiphenylamine	NDPha		3
N- Nitrosomorpholine	NMOR		2B
N-Nitrosodi-n-propylamine	NDPA		2B
Nitrosodibutylamine	NDBA		2B
N- nitrosopyrrolidine	NPYR		2B
N-nitrosopiperidine	NPIP		2B
4-(N- Nitrosomethylamino-1-(3-pyridyl)-1-butanole	NNK		1
N- Nitrosonornicotine	NNN		1
N- Methyl- N' –nitro- N-nitrosoguanidine	MNNG		2A

5.2.3 Excess risk calculations for humans

A generally accepted approach to calculate the excess risk for humans for nitrosamine contaminations has followed the definition of the Adequate Intake (AI). The AI is defined as an intake level that poses negligible cancer risk. Because reliable human data are currently not available for most chemicals, and are also lacking for N-nitrosamines, animal data generated in lifetime bioassays are the most reliable source to conclude on the carcinogenicity of chemicals and human relevance (EMA, 2020). The Carcinogenic Potency Database (CPDB) is the most comprehensive source for animal carcinogenicity data.

5.2.3.1 Estimation of acceptable environmental concentrations

DNEL (the Derived No-Effect Level) and DMEL (derived Minimal-Effect Level) have been considered as estimated acceptable levels, e.g. the highest safe level of exposure of a substance above which humans should not be exposed or the maximum level in the environment at which the substance poses no or minimal health hazards to human in order to establish 'safe exposure levels'. In the risk characterisation, the exposure of each human population likely or known to be exposed is compared with the appropriate DNEL.

First, the NOAEL is determined, which is the highest dose with no toxic effects. The "NOAEL approach" is the standard approach for evaluating dose–effect data for threshold effects. A large safety factor is then added – usually by dividing the level in animals by 100 – to arrive at a safe level for humans. For example, if the no effect level in animals is found to be 100mg kg^{-1}, then the human acceptable environmental concentration would be set at 1mg kg^{-1}. However, the NOAEL approach is not considered suitable for genotoxic carcinogens, due to a lack of a dose-threshold. As a biological threshold for cancer may occur, this threshold cannot be derived from a NOAEL on a dose–response curve. Thus, other extrapolation models and reference doses need to be determined, i.e. T25 or TD50 as reference doses to be used for the derivation (Dye et al., 2011).

The dose-descriptor value of T25 is defined as the chronic dose rate that will give 25% of the animals' tumours at a specific tissue site and is calculated from a single observed dose-response (i.e., a tumour incidence within the standard lifetime of that species), based upon the assumption of a linear dose-response relationship over the entire dose-range. Usually, the lowest dose that gives a significant increase in tumours is used for extrapolation to a 25% incidence value. On the other hand, the standardised measure of carcinogenic potency, TD50, is the daily dose rate in mg kg^{-1} body weight day^{-1} to induce tumours in half of test animals that would have remained tumour-free at zero dose (Ravnum et al., 2014).

A dose descriptor (e.g. carcinogenicity as endpoint) is first selected, and the toxic dose (e.g. T25/ TD50) is then divided by the assessment factor for determination of DNEL/DMEL.

5.2.3.2 Methodology to calculate excess risk for humans

CPDB recommends to use the TD50 as the point of departure for the calculation of excess cancer risk and to calculate the AI as the dose associated with a theoretical excess cancer risk of 1:100,000 to define the limit. The extrapolation to the excess risk level for cancer is performed by a linear back extrapolation to the dose theoretically causing a 1:100,000 risk by dividing the TD50 by 50,000 (50% or 0.5 × 100,000). For

a person with a body weight of 50 kg the AI level is then calculated as AI = 50 × (TD50 / 50,000) (EMA, 2020).

Table 5.5 presents TD50 values from the Carcinogenic Potency Database for available nitramines and nitrosamines; a larger dose is indicative of a smaller carcinogenic effect. The corresponding value for NDMA is 0.096 mg kg^{-1} d^{-1} for rats, which is indicative of much stronger carcinogenic potency. Based on TD50 values, it is indicative that nitramines are orders of magnitude less carcinogenic than nitrosamines.

Table 5.5 TD50 values from the Carcinogenic Potency Database for available Nitrosamines and Nitramines.

Agent	TD50 (mg kg^{-1} day^{-1}) rat	TD50 (mg kg^{-1} day^{-1}) sensitive species (tissue)	TD50 (mg kg^{-1} day^{-1}) other species	Mutagenicity
NMPEA	0.00998	0.00788, rat (ugi)		Ames test positive
NDEA	0.026	0.05, rat (liv) 0.026, rat (eso)	0.00725, cynomolgus; 0.012 bush babies 0.054, rhesus	Ames test positive
NMEA	0.053			Ames test positive
NDMA	0.096	0.04 rat (liv) 0.06, rat (liv)	0.189, mouse	Ames test positive
NDELA	3.17	0.19 rat (liv)		Ames test positive
NDPha	167		mouse, no positive	Ames test negative
NMOR	0.109	0.127 rat (liv)	3.57 hamster	Ames test positive
NMPA	0.142		0.034 rat	Positive in the Salmonella strain
NDPA	0.186		0.012 rhesus (liv)	Ames test positive
NDBA	0.691		1.09 mouse (liv)	Ames test positive
NPYR	0.799		1.7 rat (liv) 2.43 rat (liv) 0.697 mouse	Ames test positive
NPIP	1.43	1.31 rat (eso)	1.3 mouse	Ames test positive
NPZ	8.78			
NNK	0.0999	0.182 rat (lun)		
NNN	0.096		10.8 (hamster)	Ames test positive
NNM	0.109			
DNP	3.6			
MNNG	0.803	0.284 rat (pyl)	2.03 mouse	Ames test positive
NMBA	0.982			Ames test positive
NTMA*	17.4			
NDTMA**	0.54			

Abbreviations: eso: esophagus; liv: liver; lun: lung; pyl: pylorus; ugi: upper gastrointestinal tract

* Nitraminine Melthylnitramine

**Nitramine Dimethylnitramine

On the other hand, T25 is mostly used by the European Guidelines for calculations of the carcinogens' concentration limits, non-thresholds and for risk characterization of chemicals in general. Ravnum et al. (2014) has used T25 as a dose descriptor to undertake a risk assessment for five nitrosamines NDMA, NDEA, N-Nitroso-morpholine (NNM), N-Nitroso-piperidine (NPIP), and Dinitrosopiperazine (DNP) and two nitramines N-Methyl-nitramine (NTMA), dimethyl-nitramine (NDTMA), which are potentially emitted from the CO_2 capture plant.

They assumed a liner dose-response relationship for T25 by estimating the dose in mg kg^{-1} bw day^{-1} from the amount of tumours detected in 25% of the animals in specific tissues. The calculation of T25 was based on the following equation (eq. 1):

$$T25 = (f)^2 \times d \qquad \text{eq. 1}$$

where f = (duration of exposure)/(standard lifespan) and d = the dose rate; the duration is divided by the lifespan in order to correct T25 in case the experiment is terminated before the standard lifespan, which then the number of tumours found will be reduced, and the dose d needed to give 25% of the animal tumours will be greater than the true T25. Standard lifespan was taken either as 24 months, 104 weeks or as 730 days, based on different studies (Table 5.6).

Table 5.6 T25 calculation for nitrosamines and nitramines (as seen in Ravnum et al., 2014).

Compound	Dose (d) (mg kg^{-1} bw d^{-1})	Exposure time	% tumours	T25 (=f^2 x d) (mg kg^{-1} bw d^{-1})
NDMA	0.109	30.48 months	13/60 – 10/240 =17.5%	(30.48/24) × (30.48/24) × (25/ 17.5) × 0.109 = **0.251**
	0.131	28.48 months	14/60 – 10/240 =19.66%	(28.48/24) × (28.44/24) × (25/ 19.66) × 0.131 = **0.315**
	0.174	25.44 months	19/60 – 10/240 =27.5%	(25.44/24) × (25.44/24) × (25/ 27.5) × 0.174 = **0.178**
NDEA	0.061	29.04 months	18/60 – 10/240 =25.83%	(29.04/24) × (29.04/24) × (25/ 25.83) × 0.061 = **0.086**
	0.082	28.08 months	10/60 – 10/240 =12.5%	(38.08/24) × (28.08/24) × (25/ 12.5) × 0.082 = **0.225**
	0.102	23.3 months	21/60 – 10/240 =30.8%	(23.3/24) × (23.3/24) × (25/ 30.8) × 0.102 = **0.078**
NNM	6.00	27 weeks	2/6 =33%	(27/104) × (27/104) × (25/ 33) × 6.00 = **0.306**
NPIP	0.12	800 days	6/75 =7%	(800/730) × (800/730) × (25/7) × 0.12= **0.515**
	0.60	816 days	16/34 =47%	(816/730) × (816/730) × (25/ 47) × 0.6= **0.398**
	3.00	392 days	11/34 =32%	(392/730) × (392/734) × (25/ 32) × 3.0= **0.675**
DNP	4.00	466 days	5/31 =16.1%	(466/730) × (466/730) × (25/ 16.1) × 4.0= **2.531**
NTMA	5.43	725 days	5/10 =50%	(725/730) × (725/730) × (25/ 50) × 5.43= 2.67
NDTMA	5.01	365 days	8/10 – 1/107 =79.1%	(365/730) × (365/730) × (25/ 79.1) × 5.01= **0.806**

Based on the estimated T25, they calculated the DMEL by first extrapolating this T25 for the general public at 10^{-6} risk. This was done by multiplying T25 with a high to low dose extrapolation factor (HtLF) of $10^{-6}/0.25 = 1/250{,}000$ (eq. 2; Table 5.7):

$$\text{DMEL in mg/ kg bw/ day} = \text{T25}/250{,}000 \qquad \text{eq. 2}$$

In order to adjust for the route of exposure from rat oral exposure (DMEL mg/kg bw/day) to human inhalational exposure (DMEL ng m^{-3}), an additional adjustment factor for route of exposure was used, from rat (in mg/kg bw/day for 6 h) to human (in m^3 min^{-1} kg^{-1} bw for 24 h), which is 1/1.15 m^3 kg^{-1} bw (eq. 3; Table 5.7).

$$\text{DMEL mg m}^{-3}\text{ in human} = \text{DMEL (in rat mg kg}^{-1}\text{ bw day}^{-1}) \times 1/1.15\ \text{m}^3\ \text{kg}^{-1}\text{ bw 24h}^{-1} \qquad \text{eq. 3}$$

Table 5.7 Calculation of DMELs for nitrosamines and nitramines from the rat oral route to human inhalation (as seen in Ravnum et al., 2014).

Compound	TD50 oral rat (mg kg^{-1} bw d^{-1})	Average T25 oral rat (mg kg^{-1} bw d^{-1})	DMEL[a] (mg kg^{-1} bw d^{-1}) 10^{-6} risk	DMEL[b] (mg m^{-3}) 10^{-6} risk	DMEL[c] (ng m^{-3}) 10^{-6} risk	DMEL[d] (ng m^{-3}) 10^{-6} risk
NDMA	0.096	0.248	0.992×10^{-6}	0.863×10^{-6}	0.86	0.31; 0.28; 0.07
NDEA	0.026	0.130	0.520×10^{-6}	0.452×10^{-6}	0.45	0.52
NNM	0.109	0.306	1.224×10^{-6}	1.064×10^{-6}	1.06	
NPIP	1.43	0.530	2.120×10^{-6}	1.843×10^{-6}	1.84	
DNP	3.6	2.531	10.12×10^{-6}	8.803×10^{-6}	8.80	
NTMA	17.4	2.673	10.69×10^{-6}	9.297×10^{-6}	9.30	
NDTMA	0.547	0.792	3.168×10^{-6}	2.755×10^{-6}	2.76	

[a]DMEL in mg kg^{-1} bw day^{-1} is calculated by multiplying the T25 with the high to low dose extrapolation factor: (T25/250,000)
[b]DMEL in mg m^{-3} is calculated by correcting the T25 to the relevant endpoint: (T25/250,000) × (1/1.15 m^3 kg^{-1} bw $24h^{-1}$)
[c]DMEL in ng m^{-3} is calculated by correcting the T25 to the relevant endpoint: (T25/250,000) × (1/1.15 m^3 kg^{-1} bw $24h^{-1}$) × 10^6
[d]DMEL in ng m^{-3} based on other studies; 0.31 (WHO, 2002; Canada, 2010); 0.28 (Cal EPA, 2006); 0.07 (EPA, 2011) and 0.52 (calculated by Låg et al., 2011 for all nitrosamines and nitramines as a group, from only NDMA rat oral exposure data)

Ravnum et al. (2014) concluded that since both their DMELs and the DMELs from other studies were in the same range of concentrations; that it is possible to extrapolate calculated risks from these compounds among each other, if there are no or limited data on the toxicity of each compound. They consider a DMEL of 0.45 ng m^{-3}, which is for NDEA, to be an acceptable level in human risk estimation when it comes to genotoxic non-threshold nitrosamines and nitramines produced in a CO_2 capture process, as all the nitrosamines and nitramines had a DMEL higher than the one for NDEA.

Låg et al. (2011) estimated the Derived Minimal Effect Level for induction of cancer due to inhalation exposure, from T25, based on literature review and assigning the "large Assessment Factor" approach (Table 5.8). They calculated T25 from the lowest exposure concentration and the % of animals that developed tumours in that concentration. They consider corrections for reduced weekly, daily and the duration exposure and for differences in survival time, in order to transform the exposure to chronic lifetime exposure. The exposure concentration was adjusted based on these corrections and it was extrapolated from the dose that was associated with the equivalent percentage of tumour incidents.

A large AF was assigned to the corrected T25 to derive the DMEL for human exposure (DMEL=T25/AF).

Table 5.8 Assessment Factors used in the DMEL calculations.

	AF	Comments
Interspecies extrapolation	2.5	This factor is reduced from the default value of 10 as the dose is given in air concentration and an allometric scaling factor (4×) is thus not applied. The remaining factor of 2.5 is proposed to account for potential differences in chemical deposition in the respiratory track and tissue metabolism.
Intraspecies extrapolation	10	Human variability; physiological and metabolic differences
Nature of carcinogenic process	10	Inter-individual human variability in cell cycle control and DNA repair
Transformation of T25	2.5	Extrapolation from a 25% effect dose to a 10% effect dose
Point of comparison	10	Compensation for the dose descriptor being a 10% response and not a NOEL
Total Assessment Factor	**6,250**	

The assessment factor is mainly to account for the differences between animals and humans, and also to allow for the variability between different populations, and individual variations among people, such as age, gender, health. They consider many uncertainty factors, such as the variability in the experimental information and or inter and intra-species variation; the nature and severity of the effect; the sensitivity of the human (sub-) population to which the quantitative and/or qualitative information on exposure applies, etc. For example, DMELs must consider populations (general population), exposure routes (inhalation, dermal/eye, oral), duration of exposure (long-term or short term).

Badr et al. (2017) accounted for the interspecies differences by using the ratio of inhalation rate per body weight of the studied species to humans as a correction factor. Table 5.9 shows the correction factors used for the different species and the human-equivalent LC50 and LOEC values. The corrected value for LOEC for dogs was in this case higher than the corrected LC50 for mice and thus the corrected mice value was used as the corrected human equivalent LOEC.

Table 5.9 LC50 inhalation values for different species (Badr et al., 2017).

Species	Concentration mg m^{-3}	Correction Factor	Concentration corrected for humans, mg m^{-3}
Rat	240 ($LC50_{inhalation}$)	10.6	22.7
Mouse	176 ($LC50_{inhalation}$)	23.3	7.55 (new LOEC)
Dog	49	4.62	10.6
Humans	**6,250**	1	

5.2.4 Potency of Nitrosamines and Nitramines

Various nitrosamines have different abilities to induce cancer with N-Nitrosodiethylamine (NDEA) being the most potent; whereas the carcinogenicity potency of N-Nitrosomorpholine (NMOR) seemed to be

among the nitrosamines with the lowest potency (Table 5.10). The oral cancer slope factor (CFS) gives an indication of the relative carcinogenic potencies of the nitrosamines together with T25. The majority of nitrosamines have a T25 value lower than 1 and should be characterised as carcinogens of high potency. The CSFs can vary between studies as CSF depends on the dose-response. For example, the oral CSF for NDMA is 51 and the T25 is 0.15 mg kg^{-1} bw day^{-1}. Carcinogens of high potency are those with a T25 value < 1 mg kg^{-1} bw day^{-1}.

Table 5.10 Relative carcinogenic potency of nitrosamines (Låg et al., 2011; MEA, 2020).

Compound	Oral Slope Factor (mg kg^{-1} bw d^{-1})
NDMA	51
NDEA	150
NDBA	5.4
NDPA	7
NPYR	2.1
NPIP	37.5
NDELA	2.8
NMEA	22
NDPha	0.0049
NPIP	9.4

5.2.5 Toxic Effects and Health data

5.2.5.1 Nitrosamines

Nitrosamines and their toxicity have been studied for many years with well documented mutagenic and carcinogenic effects because humans have been exposed for a long time to nitrosamines via tobacco smoke.

Acute oral toxicities (LD50- the oral dose where 50% of treated animals die) of nitrosamines in rats have a high degree of variation, ranging from about 20 mg kg^{-1} bw to more than 5,000 mg kg^{-1} bw, with many compounds exhibiting a LD50 between 150 and 500 mg kg^{-1} bw. In general, nitrosamines exhibit a low to moderate acute toxicity, although structure and molecular weight play a role in determining the acute lethal toxicity. The liver appeared to be the target organ, and liver injury was a common result of acute toxicity for a number of nitrosamines. Other acute effects of nitrosamines have included irritation of eyes, lungs and skin, and also vomiting, lung damage (Booth et al., 2014).

Considerable concern has been expressed about their chronic toxicity due to their mutagenicity and genotoxicity. Mazari et al. (2019) showed the most mutagenic nitrosamines being in the following order NDMA > NMOR > DNPZ > NDELA, with the cancer risk for some of the most commonly found nitrosamines being also shown in Table 5.11. The most widely studied nitrosamine is NDMA due to its toxicity and potential environmental effects. Recent research has however suggested that N-NDEA may be more toxic than NDMA (Ravnum et al, 2014). Both are in the group 2A (probably human carcinogenic) of the IARC.

Table 5.11 Nitrosamines Cancer Risk (Mazari et al., 2019).

Nitrosamine species	10^{-6} Cancer Risk concentration (ng l^{-1})
NDMA	0.7
NMEA	2
NPYR	20
NDEA	0.2
NPIP	3.5
NMOR	5
NDPA	5
NDBA	6
NDPhA	7,000
MNPZ	140
DNPZ	10

Ambient air surveys (41) (Ng, A. & De Brou, G., 1991; as seen in WHO, 2002) considered together with surface and groundwater samples (390) (Ng, A. & Lusis, M., 1992; as seen in WHO, 2002) taken in the vicinity of a chemical production facility in Ontario were used to investigate human exposure of NDMA in different media. Air NDMA concentrations ranged from 0.003 to 0.230 µg m^{-3}; with the highest concentration measured within the perimeter of the production facility, while the max concentration beyond the perimeter was 0.08 µg m^{-3}. In addition, average surface water NDMA concentration was 1.3 $\times 10^{-3}$ µg lt^{-1} with the highest being at 0.008 µg lt^{-1}; whereas NDMA concentrations in the municipal aquifer ranged from 1.3 to 2.9 µg lt^{-1}, attributing to a contamination from the facility. Point estimates of daily intake (per kilogram body weight) for NDMA, based on available historic data and reference values for body weight, inhalation volumes, and amounts of drinking-water consumed daily were produced for the Concise International Chemical Assessment Documents (Table 5.12; as seen in WHO, 2002). These were ranges of reasonable worst-case estimates of daily intake and indicated that daily intake of NDMA was as high as 3.0×10^{-6} mg kg^{-1} body weight per day.

Intake of NDMA due to inhalation of air contaminated by atmospheric contributed somewhat less to the total daily intake and an even smaller contribution was attributed to consumption of drinking-water. However, these estimates indicated that contaminated groundwater in the vicinity of the industrial point source can, in some cases, lead to intakes that were greater than those from all other media combined. Reasonable worst-case estimates of daily intake of NDMA for all age groups from ingestion of contaminated groundwater range from 0.03 to 0.31×10^{-3} mg kg^{-1} body weight per day (WHO, 2002).

Table 5.12 Reasonable worst-case estimates for daily intake of NDMA by the general population (WHO, 2002).

Media	0 – 0.5 years[a] mg kg^{-1} bw d^{-1}	0.5 – 4 years[b] mg kg^{-1} bw d^{-1}	5 – 11 years[c] mg kg^{-1} bw d^{-1}	12 – 19 years[d] mg kg^{-1} bw d^{-1}	20 – 59 years[e] mg kg^{-1} bw d^{-1}	60^{+} years[f] mg kg^{-1} bw d^{-1}
Air[g]	$0.5 – 5 \times 10^{-6}$	$1 – 11 \times 10^{-6}$	$0.8 – 9 \times 10^{-6}$	$0.4 – 5 \times 10^{-6}$	$0.4 – 4 \times 10^{-6}$	$0.3 – 4 \times 10^{-6}$
Water[h]	$1.3 – 4 \times 10^{-6}$	$0.6 – 2 \times 10^{-6}$	$0.4 – 1 \times 10^{-6}$	$0.2 – 1 \times 10^{-6}$	$0.3 – 1 \times 10^{-6}$	$0.3 – 1 \times 10^{-6}$
Indoor-air[i]	60×10^{-6}	130×10^{-6}	100×10^{-6}	60×10^{-6}	50×10^{-6}	40×10^{-6}
Ground water[j]	$140 – 310 \times 10^{-6}$	$60 – 130 \times 10^{-6}$	$50 – 100 \times 10^{-6}$	$30 – 60 \times 10^{-6}$	$30 – 60 \times 10^{-6}$	$30 – 60 \times 10^{-6}$

[a]Assumed to weigh 7.5 kg, to drink 0.8 lt day^{-1} of tap water and to breathe 2.1 m^3 of air per day
[b]Assumed to weigh 15.5 kg, to drink 0.7 lt day^{-1} of tap water and to breathe 9.3 m^3 of air per day
[c]Assumed to weigh 31.0 kg, to drink 1.1 lt day^{-1} of tap water and to breathe 14.5 m^3 of air per day
[d]Assumed to weigh 59.4 kg, to drink 1.2 lt day^{-1} of tap water and to breathe 16.2 m^3 of air per day
[e]Assumed to weigh 70.9 kg, to drink 1.5 lt day^{-1} of tap water and to breathe 2.1 m^3 of air per day
[f]Assumed to weigh 72.0 kg, to drink 1.6 lt day^{-1} of tap water and to breathe 14.3 m^3 of air per day
[g]These worst-case estimates of inhalation intake were based on short term measurements of NDMA in outdoor air in the close vicinity of point sources of atmospheric discharge in Ontario. The minimum estimates were based on the lowest limit of detection (i.e. 0.0017 µg m^{-3}) for half-hour averaging times; the maximum estimates were based on the censored mean concentration (i.e. 0.019 µg m^{-3}) for half-hour averaging times. Concentrations equivalent to one-half the detection limit were assumed for half-hour averages during which NDMA was not detected. It was assumed that the population would be exposed to similar concentrations for 24h daily, and that concentrations in the indoor air would be the same as those in outdoor air, in the immediate vicinity of the point sources.
[h]The minimum estimates of drinking water ingestion intake were based on the mean concentrations (i.e. 0.012 µg l^{-1}); whereas the maximum estimates were based on the maximum concentration (i.e. 0.04 µg l^{-1}).
[i]Based on the assumption that the population spends 21 h day^{-1} breathing contaminated indoor air containing NDMA at the maximum reported concentration (0.24 µg m^{-3}).
[j]Based on the minimum (i.e. 1.3 µg l^{-1}) and maximum (2.9 µg l^{-1}) of NDMA concentration in well water in Ontario, resulting from contamination of groundwater by a nearby industrial facility, and average daily rates of water consumption.

It should be noted that in case the No-Effect Dose Levels cannot be derived due to limited data, an alternative and provisional option for evaluating the intrinsic hazards of that compounds would be to use established exposure standards such as occupational exposure limits (OEL; OEL for nitrosamines 0.001 mg m^{-3}) and apply a safety factor. The safety factor needs to cover characteristics that haven't been encountered for the work exposure limits:

- Continuous exposure
- Age range
- Gender
- Health status

For example, OELs have been developed for an adult population and do not take into account age dependent changes, which for long term exposure is of special importance for children; or in case of gender, nitrosamines are reprotoxic and they may act both on the parental side as well as being fetotoxic and cause developmental effects. As they are mutagenic the parenteral effects might be both on the female and male side. A correction factor of 2-10 has also been introduced to include a continuous life-long exposure for an adult healthy population, for a range of effects from temporary discomfort to carcinogenesis. Brakstad et al. (2010a-b) have suggested a correction factor of 10 and this would be

multiplied by 10, to get a combined factor. Then the lowest available OEL was divided by this factor, 100, to represent a permissible exposure limit for the general population.

Based on this OEL extrapolation, Brakstad et al. (2010a-c) conducted a provisional health risk evaluation of the nitrosamines' degradation products (Table 5.14). These health risks, associated with the nitrosamines and mainly related to the exposure from air and drinking water were evaluated given a numerical value (Table 5.13) for a better assessment.

Table 5.13 Health hazard rating for risk assessment (Brakstad et al., 2010a).

Rating	Description
0	None or very long-term health risk
1	Low long-term health risk
2	Medium long-term health risk
3	High long-term health risk
4	Very high long-term health risk

Humans are potentially exposed to the N-nitrosamines, mainly through oral ingestion. Luo et al. 2020 conducted a human health risk assessment to investigate the occurrence and carcinogenic health risk of the nitrosamines, NDMA, NDEA and NPIP, in terms of exposure via ingestion and dermal absorption, in a drinking water system in China. The exposure estimates were calculated based on the following equations:

$$LADD_{ingestion} = \frac{C_w \times IR \times EF \times ED}{BW \times LT} \quad \text{eq. 4}$$

$$LADD_{dermal} = \frac{C_w \times SA \times K_p \times ET \times EF \times ED}{BW \times LT} \quad \text{eq. 5}$$

where $LADD_{ingestion}$ and $LADD_{dermal}$ are the lifetime average daily intake (LADD) for the corresponding nitrosamine through oral ingestion and dermal exposure, respectively (mg kg^{-1} bw day^{-1}); C_w (ng l^{-1}) is the average or 95th percentile concentration of the nitrosamine in tap water; IR is the ingestion rate of drinking water (l day^{-1}); EF is the exposure frequency (day $year^{-1}$); ED is the exposure duration (year); BW is body weight (kg); LT is lifetime (days); SA is the skin surface area available for contact during bathing or other activities (cm^2); k_p is the chemical specific dermal permeability constant in water measured at 25°C (cm h^{-1}) and ET is exposure time (min day^{-1}).

The estimated lifetime cancer risk ($ELCR$) was calculated based on the average daily intakes ($LADD$) for ingestion and dermal absorption (eq. 6 & 7) to estimate the general exposure.

$$ELCR_{ingestion} = LADD_{ingestion} \times CSF \times \text{ADAF} \quad \text{eq. 6}$$

$$ELCR_{dermal} = LADD_{dermal} \times \frac{CSF}{GAF} \times ADAF \quad \text{eq. 7}$$

Table 5.14 Health hazard of nitrosamines (compiled by Brakstad et al., 2010a).

Compound	LD50 (mg kg bw^{-1})	Percutaneous toxicity[a]	Oral[b]	Dermal[c]	Inhalation[d]	Long Term	Toxicity	Comment to Human Health hazard
NDMA	37 (rat) 26 (rat) 28 (hamster)	15 (rat)	3	(3)	4	C M R	Fetotoxic	Very high acute toxicity Serious long term effects OEL-TWA: 0.001 mg m^{-3} LD low (human/ woman): 20 mg kg^{-1} 2.5Y^{-1}
NMOR	282 (rat) 956 (hamster)	170 (rat)	2	(2)	(4)	C M		High acute toxicity Very high inhalation hazard Moderate toxicity by oral route Serious long term effects OEL-TWA: 0.001 mg m^{-3} LC lo= 1,000 mg m^{-3} for 10 min
NDEA	220	195	0	(0)	-	C M	Fetotoxic Skin: positive Eye: positive	OEL: 0.001 mg m^{-3} Non toxic by oral or dermal route
NDELA	7,500 (rat)	11,000 (hamster)	0	(0)	-	C M (R)		OEL: 0.001 mg m^{-3} Non toxic by oral or dermal route Serious long term effects
NNO			0	-	-	C M		Remarkable low oral toxicity -in question Serious long term effects
DNPZ			2	3	-	C M R		High acute toxicity Expect inhalation hazard Serious long term effects
N-AEP			-	-	-	C M R		
Nitrosamines (NOS)			3	(3)	4	C M R		High acute toxicity Very high inhalation hazard Serious long term effects OEL-TWA: 0.001 mg m^{-3}

[a]Percutaneous Toxicity: 0: >2,000; 1: 1,000-2,000; 2: 200-1,000; 3: 50-200; 4: <50 mg kg^{-1} bw
[b]Oral Toxicity: 0: >2,000; 1: 300-2,000; 2: 50-300; 3: 5-50; 4: <5 mg kg^{-1} bw
[c]Dermal/ Skin iiritation: 0: non-irritating; 1: Mildly irritating; 2: Irritating; 3: Severely irritating/ corrosive; 3A: Corrosive >1-4 hr; 3B: Corrosive 3 min <1 hr; 3C: Corrosive <3 min
[d]Inhalation Toxicity: 0: >20; 1: 10-20; 2: 2-10; 3: 0.5-2; 4: <5 mg (4 hrs)

where CSF is the cancer slope factor via ingestion (mg kg^{-1} bw day^{-1}); GAF is the gastrointestinal absorption factor; and $ADAF$ is an age-dependent adjustment factor, which has been recommended by the US.EPA (2016) due to different sensitivities in different age stages.

They found that children, compared to adults, were more likely to develop diseases when they were exposed to hazardous substances, especially carcinogenic chemicals, due to their susceptibility at the early stage of life and longer life years to develop diseases related to exposure. The average total lifetime cancer risk for the three main nitrosamines was 4.83×10^{-5} mg kg^{-1} bw day^{-1}, exceeding the negligible risk level (10^{-6}) that has been proposed (Table 5.15). Exposure to nitrosamines in drinking water posed a higher cancer risk for children than for adults, and children aged 0.75 to 1 year suffered the highest cancer risk. Specifically, in terms of oral ingestion, the highest ELCR was observed for NDEA for infants aged from 0.75 to 1 years; while for dermal contact, it was observed for age 0.5 to 0.75 year (Luo et al., 2020).

Table 5.15 Estimated lifetime cancer risk (Luo et al., 2020).

Compound	Ingestion		Dermal	
	LADD	ELCR	LADD	ELCR
NDMA	6.64×10^{-7}	3.39×10^{-5}	1.68×10^{-10}	8.58×10^{-9}
NDEA	9.48×10^{-8}	1.42×10^{-5}	8.34×10^{-11}	1.25×10^{-08}
NPIP	7.66×10^{-8}	1.61×10^{-7}	4.81×10^{-11}	1.01×10^{-10}
Total	8.35×10^{-7}	4.83×10^{-5}	3×10^{-10}	2.12×10^{-08}

It is important to note that as there are also differences in physiological function between males and females; therefore, cancer risks need to be calculated for different age stages and for different genders.

5.2.5.2 Nitramines

Under the European Union's regulation on safe use of chemical substances, substances that are of very high concern are those that are carcinogenic, mutagenic or reproductive toxins, or those that are very persistent and very bioaccumulative. Nitramines are potential carcinogens. In addition, they may fulfil criteria for persistence. According to a model estimate based on physical properties, overall persistence in water was estimated at ≈40 days, half-life in soil≈75 days and sediment ≈300 days. This puts these substances near the "very persistent" criteria used by REACH, which is >60 days in water, >180 days in soil, or >180 days in sediment (Selin, 2011).

Only a few toxicity studies have been focusing on the nitramines. Dye et al. (2011) was one of the first to investigate the potential toxic effects that might occur from acute exposure to nitramines, most likely produced during amine-based CO_2 capture, dimethylnitramine (DMNA), methylnitramine (MNA), ethanolnitramine, 2-methyl-2-(nitroamino)-1-propanol (AMP) and piperazine (PZ). All four test substances showed mild cytotoxicity (60-75% PE; Table 5.16) in concentrations range up to around 500 µg ml^{-1}, with DMA and AMP being the least toxic, inducing low cytotoxic effect for all concentrations

tested; while the MA and MEA showed dose dependent cytotoxicity, with high toxicity at the highest concentrations; at concentrations of 5.5 and 3.7 mg/ml respectively.

Table 5.16 Classification of the test substances according to their % PE cytotoxicity, (Dye et al., 2011).

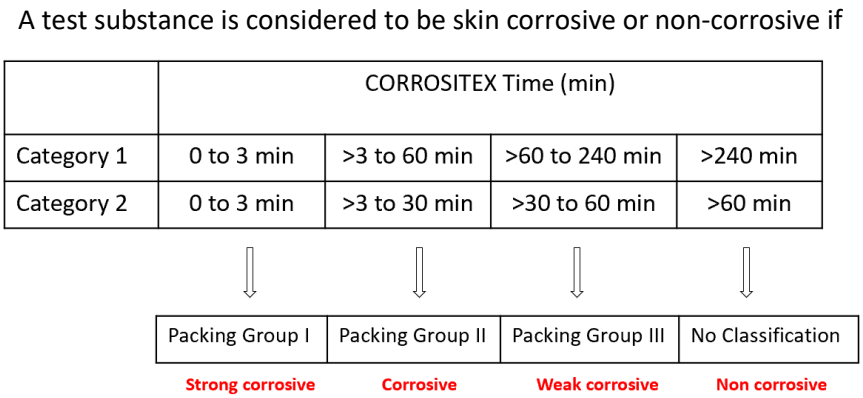
Classification	PE %	Test substance	% PE
Extremely toxic	< 40	**DMA**	60-75%
Strong Toxic	40 – 60	**MA**	
Mild Toxic	60 – 80	**MEA**	
Of control	> 80	**AMP**	
		PZ	

Data on long term toxicity of DMA and MA showed that both compounds were genotoxic with actually DMA being more potent and PZ slightly toxic. The order of chronic toxicity (from highest to lowest) of the test substances were DMA > MA > MEA > PZ. Experimental data for oral acute toxicity was tested in rats. They showed that all the nitramines tested (based on LD_{50}; Table 5.17) induced low or mild toxicity and were classified as harmful (if swallowed). In addition to genotoxicity, Dye et al. (2011) indicated that DMA, MA and MEA might cause mutagenic effects on mammals and/or bacteria and should be considered as mutagenic compounds category 3: Substances which cause concern for man owing to possible mutagenic effects (Figure 5.3). However, when these were tested for mutagenicity towards *Salmonella typhimurium*, DMA, AMP and PZ showed no evidence of mutagenic activity. However, MEA and MA induced mutagenic activity towards selected strains.

Table 5.17 Classification of the test substances according to their LD_{50} values, determined from OECD TG 425 Oral Toxicity (Dye et al., 2011).

Classification	LD_{50} orally to rat mg kg^{-1} bw)	Test substance	LD_{50} (mg kg^{-1} bw)	LD_{50} (mg kg^{-1} bw) (from other studies)
Very toxic	< 25	**DMA**	770	400[1]; 600[2]; 897[1]; 1,095
Toxic	25 – 200	**MA**	834	500
Harmful	200 – 2,000	**MEA**	970	67[1,6]; 225[2,6]; 1,750[3,6]; 10,200[4,6]; 600[5,6]
Non toxic	> 2,000	**AMP**	> 1,600	-
		PZ	1,750	-

[1]mice intraperitoneal [3]rat intramuscular [5]Guinea pig
[2]rat intravenous [4]rat oral [6]Brakstad et al., 2010a-b



Screening test is applied to distinguish between either category 1 (high acidity/alkalinity) or category 2 (low acidity/alkalinity). Two different breakthrough timescales are used for determining corrosivity, based on the acid or alkali reserve of the test substance solution.

Figure 5.3: Corrosive test classification based on skin corrosion test methods (Corrositex)

No signs of toxicity were observed for skin corrosion/irritation/sensitisation; but both MA and MEA were found to cause severe eye corrosion, whilst and DNA elicited a mild response.

Dye et al. (2011) estimated the acceptable concentration levels of DMA and MA as Derived Minimal Effect Levels (DMELs) (Table 5.18), using a non-threshold mode of action approach, where adequate animal cancer data are taken of a semi-quantitative reference value. This is normally suggested for mutagens and genotoxic carcinogens, with the use of an endpoint-specific large assessment factor (AF), i.e. 10,000 to ensure that the exposure causes a minimal risk. Then, the specific dose descriptor was divided by that AF.

Table 5.18 Derived Minimal Effect based on LD_{50} values, determined from OECD TG 425

Test substance	DMEL ($\times 10^{-5}$ mg kg^{-1})
DMA	0.547
MA	17.4

Confirming the study by Dye et al. (2011), Fjellsbø et al. (2013) also examined DMA, MA, MEA and AMP, with emphasis on irritation, corrosion and/or sensitisation of human skin and eye. Both studies showed no skin irritating potential and eye corrosion.

In terms of corrosion, exposure to DMA induced a mild eye irritation response, though it was not OECD classified as ocular corrosive; while MA, MEA and AMP were shown to be very severe eye irritants. These three nitramines are classified as an ocular corrosive or severe irritant. MA and MEA were tested for skin sensitisation and found to be non-sensitizers to the skin (Table 5.20) (Fjellsbø et al., 2013).

The following formula was used to determine the in vitro score (Table 5.19):

$$IVIS = \text{mean opacity value} + (15 \times \text{mean OD490 value}) \quad \text{eq. 8}$$

Table 5.19 In Vitro irritancy scores (IVIS).

IVIS Classification range	IVIS Category
3.0	Non eye irritant
3.1 to 25.0	Mild eye irritant
25.1 to 55.0	Moderate eye irritant
55.1 to 80.0	Severe eye irritant
≥ 80.1	Very severe eye irritant

Table 5.20 Eye irritancy classifications for DMA; MA; MEA and AMP (Fjellsbø et al., 2013).

Test substance	IVIS (mean ± standard deviation)	IVIS Category	OECD classified as ocular corrosive or severe irritant
DMA	5.2 ± 4.6	Mild eye irritant	No
MA	187.9 ± 4.4	Very severe eye irritant	Yes
MEA	85.4 ± 3.2	Very severe eye irritant	Yes
AMP	112.1 ± 17.9	Very severe eye irritant	Yes

In terms of skin sensitisation test, the concentration that yields around 20% reduction of cell viability (IC_{20}) after 24 h exposure, was found to be above the threshold concentration of 0.05% (w/v) only for DMA and AMP, presenting a very low cytotoxicity. No skin irritating potential was observed for MA and MEA, and can be classified as non-sensitising compounds. In addition, based on the Corrositex, MA, MEA and AMP were found to be non-corrosive (Fjellsbø et al., 2013), as they all had a mean CB of >60 min (Dye et al., 2011). MEA, MA and AMP were categorised in group 2 (Figure 5.3) and were assigned to Packing Group No Classification which is non-corrosive. The mild level of irritancy of DMA could be due to the low concentration applied (7.7%), compared with the other nitramines (~19%) due to its low solubility.

A follow up study by Fjellsbø et al. (2014) tested the four nitramines (DMA, MA, MEA and AMP) and also the PZ for genotoxic and mutagenic effects by Ames test, micronucleus and comet assay. The potential to induce reverse mutations was evaluated in five standard Salmonella typhimurium strains TA98, TA100, TA102, TA1535 and TA1537 in the absence and in the presence of liver metabolising enzymes. While DMA, MEA and PZ did not show any mutagenicity, MA induced a clear mutagenic response at all concentrations with the Salmonella typhimurium strain TA102. Both MA and MEA were positive in the micronucleus assay showing clastogenic potential. The results on DNA damage measured by the comet assay were negative. The concentrations used in this study were higher than what can be expected near the capture facility, in the range of 2–50 ng N m^{-3}. The authors showed MA and MEA to have genotoxicity/mutagenicity potential but with different responses in the Ames tests. DMA, AMP and PZ were considered non-genotoxic, with DMA to be the least potent nitramine (Fjellsbø et al., 2014). However, Dye et al. (2011) studied mutagenic potential of DMA and MEA in mammalian gene mutation

test and found that both DMA and MEA induced mutations in the mammalian gene mutation test, with DMA to be more potent.

In general, nitramines have shown to have a similar metabolism as the corresponding nitrosamines, but can form more stable intermediates, which can explain their low toxicity levels for acute toxicity, cytotoxicity, skin-eye corrosion and sensitisation (Hillebrand et al., 2016). However, they showed positive (in vitro) genotoxicity results (Dye at al., 2011; Fjellsbø et al., 2014; Gjernes et al., 2013). Among these positive results, the monomethylated nitramines induced more mutations in bacteria compared to the dimethylated ones (Fjellsbø et al., 2014) but DMA was more potent in mammalian gene mutation test (Dye et al., 2011).

A related provisional health risk evaluation of the nitramines was also conducted, compiled by different studies (Table 5.21), together with the main health effects that have been reported (Table 5.22).

Låg et al. (2009) established a LOAEL of 12 mg m^{-3} air for MEA from behavioural effects in rats as the best available basis for an exposure limit for the population. Since this LOAEL value was based on an animal experiment, an uncertainty factor had to be used. The occupational exposure limit included an uncertainty factor of only 5. For the general population a factor of 10 is normally applied to account for uncertainties in extrapolation from animal studies (rat) and a further factor of 10 for the variability between the individuals (in a human a population). The use of a LOAEL value instead of a NOAEL affected the magnitude of the uncertainty factor by a factor of 3. Furthermore, the use of a subacute instead of a chronic exposure increased the uncertainty factor by a factor of 6. Altogether, this inferred an uncertainty factor of 1,200. Therefore, they suggested that the general population, over time, should not be exposed to levels in the air higher than 10 µg m^{-3} for MEA (Table 5.23).

The same study pointed a LOAEL of 8.6 mg m^{-3} for piperazine (PZ) being estimated for the induction of occupational asthma after inhalation during an 8-hour workday exposure, which was used for a risk evaluation. The need for using uncertainty factors was considered. A factor of 10 for the variability between the individuals in a population was used. Both a factor of 3 for extrapolation from a LOAEL to a NOAEL, and an exposure factor for sub-chronic to chronic of 2, were also included. In addition, they counted for a correction factor for work exposure versus lifetime exposure of 2.8. Since both neurotoxicity, mild hepatic toxicity and reproductive effects in human and animal studies were observed, a factor of 10 for severe health effects (neurotoxicity) was added. Having taken together all these, the final uncertainty factor was 1,680; suggesting a higher level of 5 µg/m^3 for the general population not be exposed, over time (Table 5.23).

Furthermore, a health hazard characterisation was also undertaken for AMP. Based on a LOAEL of 0.57 mg m^{-3} in air, an uncertainty factor of 5 for the variability between species (monkeys to humans), an uncertainty factor of 10 for variations in the human population and an uncertainty factor of 2 for using a sub-chronic study instead of a chronic study were included. This added up to a total uncertainty factor of 100. Based on this, it was suggested that, over time, the general population should not be exposed to higher levels of AMP in the air than 6 µg/m^3 (Låg et al., 2009; Table 5.23).

Table 5.21 Health hazard of amines and nitramines (compiled by Dye et al. 2011, Låg et al., 2011 and Brakstad et al., 2010a).

Compound	LD50 (mg kg^{-1} bw)	Oral	Dermal	Inhalation	Long Term	Comment to Human Health hazard
DEA	Oral: 780-3,460 Dermal: 12,200-13,000	1	0	(0)	C M R	Slight Irritating to skin and moderate irritating to eyes NOAEL: <32 mg kg^{-1} bw (repeated dose toxicity) 0.05 mg l^{-1} (reproduction toxicity) NOAEC: 3 mg m^{-3} Exposure to 8 mg m^{-3} led to upper respiratory tract irritation
DEYA	Oral: 540-1000 Dermal: 12.1-17.3	1	2	3		Irritating and corrosive to eyes and skin NOAEL: 0.076 mg l^{-1} (repeated dose toxicity) OEL: 30 mg m^{-3}
DMA	240 (rabbit) 1,600 (rabbit) 698 (rat) 1,000 (rat) 8100 (rat) 316 (mice) 240 (guinea pig) 1,070 (guinea pig) Dermal: 3,900	2	3	2	M S	Skin and eye: severely irritating LC50: 12.79 (rat) 1.5 (rat) 12.53 (rat) 8.8 (rat) 1.85 (rat) 4.44 (rat) 0.035 (mice) 7.038 (mice) 2.5 (mice) 3.7 (mice) 0.07 OEL: 3.5 mg m^{-3} 10 ppm: rodents developed minor lessions NOAEL: >225 mg kg^{-1} bw (reproduction toxicity) NOAEL: 0.02-0.19 mg l^{-1} (repeated dose toxicity)
DMNA	1095 (rat) 600 (i.v. rat) 897 (i.p. rat) 399 (i.p. mice)	1	-	-	C M	Slight oral toxicity Serious long term effects No OEL/TWA available
Dipropylamine	Oral: 200-1,600 Dermal: 925	2	2	2		Irritating and corrosive to skin and eyes
EA	400 (rats)	2	2	1		Irritating and corrosive to skin

	Dermal: 265-360					OEL: 18 mg m^{-3} LC50: 12.6 (rats) after 4h exposure NOAEL: 0.18 mg l^{-1} (repeated dose toxicity) Acutely toxic and irritant to eyes and lungs
MEA	80 (rat) 100-200 (rat) 375 (rat) 689 (rat) 1,600-3,200 (rat)	2	3	3	M	Irritating to severe eye and skin irritation Moderate acute toxicity OEL: 6.4 mg m^{-3} LC50: 0.97 (rat after 2.5hr exposure) 0.362 (rat) 2.1-2.9 (rat) 1.2 (mice) NOAEL: >351 mg/kg/day (reproduction toxicity) NOAEL: 320 mg/kg/day (repeated dose toxicity) TCLo: 0.01 gm m^{-3} (Humans)
MNA	500 (oral; rat)				C M?	Confirm C Slight oral toxicity No OEL/TWA available Serious long term effects
PZ	2,500-4,500 (oral) 4,000 (dermal)	2	0	2	(M) (S)	Irritating and corrosive to eyes and skin Moderate acute toxicity NOAEL: 7.5 mg/kg bw (repeated dose toxicity) > 5000 (reproduction toxicity) OEL: 0.3 mg m^{-3}
1-butanamine	420 (rats) 366-720 (oral) 850 (dermal)	2	2	3		Severe Irritating to eyes and skin OEL: 15 mg m^{-3}
Dibutylamine	189-550 (oral) 768-1,010 (dermal)	2	2	3		Irritating and corrosive to eyes and skin OEL: 26 mg m^{-3}
N-methyl 1-butanamine	Oral: 420 Dermal: 627	1	1	(2)		Irritating and corrosive to eyes and skin
N-ethyl 1-butanamine	Oral: 310	1	1	2		

Table 5.22 Most commonly health effects reported for nitramines (Gushgari & Halden, 2018).

Amines	Inhalation hazard	Skin hazard	Eye hazard	Effect of short-term exposure	Effect of long-term exposure
MEA	Cough; Headache; Shortness of breath; Sore throat	Redness; Pain; Skin burns	Redness; Pain; Severe deep bums	The substance is corrosive on ingestion to the respiratory tract, skin and eyes. The vapour is irritating to the eyes, skin and respiratory tract. The substance may cause effects on the central nervous system. Exposure could cause lowering of consciousness.	Repeated or prolonged contact may cause skin sensitisation.
DEA	Redness; Pain; Severe deep bums	-	-	The substance is corrosive to the eyes.	Repeated or prolonged contact may cause skin sensitisation. The substance may have effects on the liver and kidneys.
MDEA	Cough; Nausea; Sore throat	Redness; Pain	Redness; Pain	The substance is irritating to the eyes and skin.	-

In MDEA case, a hazard assessment was not possible based on existing data and therefore an extrapolation from dermal to an inhalative dose was conducted. The LOAEL value for MDEA (Table 5.23) is equivalent to the extrapolated intern systematic exposure of the dermal NOAEL. A human inhalation volume of 25 m^3 /24 hours was used and a suggestive maximum outdoor air level for MDEA of 120 µg m^{-3} for the general population was derived (Låg et al., 2009).

Table 5.23 Amines inhalative threshold values after uncertainty factors application (Låg et al., 2009).

Substances	LOAEL	Uncertainty Factors	Threshold (µg m^{-3})
MEA	12 mg m^{-3}	1,200	10
PZ	8.6 mg m^{-3}	1,680	5
AMP	0.57 mg m^{-3}	100	6
MDEA	42.5 mg kg^{-1} bw^{-1} [a]	1,000	120

[a] An extrapolation from dermal NOAEL to an inhalative dose

To outline, among the PCC originated substances, NDEA, NDMA and NPIP have been shown to be the three most hazardous nitrosamines (Chen et al., 2018; Luo et al., 2020). Table 5.24 contains a summary of the health hazard for the most studied post-combustion capture derived substances.

Table 5.24 Health Hazard Information of PCC-derived Nitrosamines and Nitramines (Chen et al., 2018).

Substances	Health Hazard	Target Organ	Signal
NDMA	Carcinogen, Mutagen, Flammable – 2nd degree	Liver, kidney, lungs	Danger
NDEA	Carcinogen, Mutagen, Flammable – 2nd degree, Reactive – 1st degree	Liver, esophagus, stomach	Danger
NDELA	Carcinogen	Liver, esophagus, stomach	Warning
NMOR	Carcinogen, Mutagen	Liver, lungs	Warning
NPIP	Carcinogen, Mutagen, Flammable – 2nd degree, Reactive – 1st degree	Eyes, esophagus, liver, nasal cavity, stomach	Danger
NDBA	Carcinogen, Mutagen	-	Warning
DMNO	Carcinogen	Liver, eyes	Danger
MNPZ	Carcinogen	Central nervous system, liver	-
MEA	Carcinogen	Eyes	-
MA	Carcinogen	Central nervous system, liver	-
DMA	Carcinogen	Eyes	-

5.2.6 Sensitive population

Infants and children can be more susceptible than adults to the mutagenic effects of the nitrosamines, as they have a higher uptake from both oral and airway exposure per kg body weight due to a higher metabolic rate per body unit for children compared to adult.

A spatial study of children age 2 – 14 in Alberta, Canada, which assessed the association between residential proximity to a coal-fired power plant and a disease clustering, showed an inverse association with distance from the power plant and children asthma after adjusting for age and gender. A similar study with children living in three communities near a major coal-fired power plant in Hadera, Israel, had also a significant rise in asthma and respiratory-related conditions (Amster, 2021).

In addition, Zhang et al. (2014) calculated the safety distance (D') of nitrosamines on a 10^{-6} risk. Nitrosamine intake caused by inhalation was calculated using the following equation (eq. 9):

$$IC = \frac{CA \times CR \times EF \times ED \times RR \times ABS}{BW \times AT} \qquad \text{eq. 9}$$

where IC is the daily intake through inhalation (mg kg^{-1} d^{-1}), CA is the concentration in the air (mg m^{-3}), CR is the inhalation rate (7.6 m^3 d^{-1} for children and 20 m^3 d^{-1} for adults), EF is the exposure frequency, ED is exposure duration, RR is retention factor, ABS is absorption fraction (assumed to be equal 1), BW is body weight (15 kg for children and 70 kg for adults), and AT is the average lifetime (lifetime in years x 365 days per year × 24 hours per day).

They showed that for children, NDMA concentrations based on a one-in-ten-thousand extra risk (10^{-4} risk) and on a one-in-a-million extra risk (10^{-6} risk) were 9.0 and 0.09 µg m^{-3}, respectively, while NMEA

concentrations for the same risks were 3.1 and 0.03 μg m^{-3}, respectively. For adults, NDEA concentrations based on a one-in-ten-thousand extra risk (10^{-4} risk) and a one-in-a-million extra risk (10^{-6} risk) were 16 and 0.16 μg m^{-3}, while NMEA concentrations for the same risks were 5.4 and 0.05 μg m^{-3}, respectively.

Table 5.25 shows the safety distance from five CO_2 capture power plants under different capacities, based on exposure concentrations on a 10^{-6} risk, at downwind direction and wind speed of 5 m s^{-1}. The safety distance for children was longer than that for adults, and D' for NDEA was also longer than that for NDMA.

Table 5.25 Safety Distance (D') of the five capture scenarios on 10^{-6} risk (Zheng et al., 2014).

D' (Km) Capture Capacities (tpa)		Plant 1 365	Plant 2 3,000	Plant 3 40,000	Plant 4 146,000	Plant 5 1,000,000
Children	NDMA	0	0	0	0	2.88
	NDEA	0	0	0	1.58	5.7
Adult	NDMA	0	0	0	0	0
	NDEA	0	0	0	0.86	3.5

Following a sensitivity analysis, they demonstrated that the results of the model will show a large variance depending on the input variables. The safety distances D' for the capture capacity of 1 million tonnes per year (tpa) were 3.9 and 4.7 km, under the conditions of 70% CO_2 capture, with absorber inlet temperature at 30°C and the reboiler operating temperature at 120°C. These were shorter than the safety distance D' 5.7 km when the absorber inlet temperature was 45°C.

Farren et al. (2015) calculated the cumulative lifetime cancer risk (eq.10), for the nine compounds, NDMA, NDEA, NDPA, NPYR, NMOR, NPIP, NDBA, NDPhA and NNN, based on the exposure concentration:

$$risk_{inhalation} = \sum_{i=1}^{n} IUR_i \times EC_i \qquad \text{eq. 10}$$

where IUR_i is the inhalation unit risk specific for each carcinogen (μg m^{-3}) and EC is the exposure concentration. The IUR can be defined as the upper-bound excess lifetime cancer risk estimated to result from continuous exposure to an agent at a concentration of 1 μg m^{-3} in air. IUR values were taken by the Integration Risk Information System (IRIS).

As chemicals sometimes cause cancer by a mutagenic mode of action (MOA) and can therefore pose a higher risk of cancer to humans when exposure occurs during early life, US. EPA (2016) requires that the potential increased cancer risk due to early-life exposure should be taken into account. In these cases, age-dependent adjustment factors (ADAFs) can be applied to assess the additional risk:

$$risk_{inhalation} = \sum_{i=1}^{n} IUR_i \times EC_i \times ADAF_j \qquad \text{eq. 11}$$

where $ADAF_j$ is the age-dependent adjustment factor specific for the age group under consideration.

The Superfund Program (US.EPA, 2022b) released an updated approach for estimating cancer risk via inhalation. This new approach relies on the concentration of the chemical in air as the exposure metric (µg m^{-3}), rather than the intake of a contaminant in air (mg kg^{-1} day^{-1}). This is considered more accurate as it accounts for the fact that the amount of chemical reaching the target site is not a simple function of IR and BW. An estimation of exposure duration (ED) is also required to assess lifetime cancer risks using this approach. The ED was increased from 1 to 8 h in 1 h increments to represent a range of different individual scenarios. Parameters and their respective values used for the cancer risk assessment, based on age groups, can be seen in Table 5.26.

Table 5.26 Parameters for the cancer risk assessment; age intervals chosen according to US.EPA guidelines (Farren et al., 2015).

Age groups/ yrs	EF[a] / days yr^{-1}	ED[b] / yrs	AT[c] / hrs	ADAF[d]
0 to < 1	365	1	613,200	10
1 to < 6	365	5	613,200	5.33
6 to < 21	365	15	613,200	2.33
21 to 70	365	49	613,200	1.00

[a]Exposure frequency; [b]Exposure duration; [c]Average time; [d]Age-dependent adjustment factor

Farren et al. (2015) showed that the cancer risk associated with nitrosamine exposure was most prevalent in adults; all of the lifetime cancer risks calculated for the adult group (21 to 70 years) exceeded the U.S. EPA guideline of negligible risk. The estimates of cancer risks were approximately 41 and 68 excess cancer cases per 1 million people in winter and summer, respectively. The minimal cancer risk (defined by the U.S. EPA as 10 excess cancer cases per 1 million population exposed) was exceeded after 4 h of exposure to outdoor ambient air in the summer; whereas the risk was lower in winter for the adult age group, with the minimal cancer risk level reached after 6 h.

5.2.7 Quantitative Structure Activity Relationship (QSAR) models

In recent years, predictive toxicology approaches based on Structure–Activity Relationships have emerged as fundamental tools in the regulatory assessments of chemicals, especially in cases of data gaps, where regulatory constraints and assessment schemes limit the amount of data available from experimental test methods, in order to predict the biological activity of compounds of interest using structural features of known toxicants. The structure of the chemical compounds is the basis for their toxicity and affects the metabolism of toxic chemicals in the body. QSARs are considered flexible tools, due to their cost effectiveness and independence of animal testing.

Specifically, these mathematical-computational models can be used to estimate the biological activity (i.e. toxicity or biodegradation) of a compound in relation to its physico-chemical properties through statistical means (Chinen and Malloy, 2020). Benigni and Bossa (2012) have noted QSAR's reliability as a tool for the prediction of the mutagenicity of aromatic amines, and discussed how the results of the QSAR analyses agree with and are supported by the mechanistic knowledge on their mechanisms of action.

Different descriptors and statistical methods have been used to develop toxicity models for amines, investigating their mutagenic properties and their acute toxicities toward fish and other aquatic species, including the analysis of QSARs for elucidating the underlying modes of action and their link to the characteristics of molecular structures of these compounds. However, QSAR involving amines in rats via oral LD50 have been lacking.

The Organisation for Economic Cooperation and Development (OECD, 2006) has taken the lead in the definition of principles for the validation of (Q)SAR models for regulatory purposes and has undertaken the development of an ambitious software tool for the regulatory use of Structure–Activity based approaches (OECD (Q)SAR Toolbox).

5.3 Safety Limits

Safety limits have been defined as the upper limit of the respective compounds in air and in deposition that do not cause harmful effects to human health or to ecosystems. Following the most precautionary principle, the most sensitive adverse effect caused by the respective compound group in each environmental target compartment (drinking water, vegetation, terrestrial fauna, ecosystem types) and receptor organism (algae, invertebrates, fish, humans) is to be considered when establishing the proposed safety limits.

Several organisations and institutions have established different public health thresholds for different nitrosamines and nitramines (Table 5.27). For instance, the Australian Guidelines for Water Recycling have recommended a 10 ng lt^{-1} for NDMA, while the California's Department of Public Health (CDPH) has recommended a 1, 3 and 5 ng lt^{-1} limit for three nitrosamines NDEA, NDMA and NDPA, respectively. They have also established notification levels for these nitrosamines at 10 ng lt^{-1} to take into account the very low detection limits and their potential presence in association with drinking water treatment. Response levels, that is the levels at which a drinking water source should be removed from service, and have been set at 100 ng lt^{-1}, 300 ng lt^{-1} and 500 ng lt^{-1}, respectively. The State of Massachusetts has also outlined a regulatory drinking water limit of 10 ng lt^{-1} for NDMA, Arizona has set regulatory limits for NDMA (1 ng lt^{-1}), NDPhA (7,100 ng lt^{-1}), and NDPA (5 ng lt^{-1}) and New Jersey 0.7 ng lt^{-1} for NDMA and 5 ng lt^{-1} for NDPA in groundwater (Gushgari & Halden, 2018). Furthermore, according to WHO and Health Canada, the NDMA limit in drinking water are at 100 ng lt^{-1} (risk 10^{-5}) and 4 ng lt^{-1} (risk 10^{-6}), respectively (Spietz et al., 2017).

The Environmental protection Agency (EPA), on the other hand, has set health reference levels for NMBA (30 ng lt^{-1}), NDEA (0.4 ng lt^{-1}), NDMA (0.6 ng lt^{-1}), NDPA (7 ng lt^{-1}), NMEA (3 ng lt^{-1}), and NPYR (2 ng lt^{-1})

(US.EPA, 2016). In Germany, control limits for NDMA in drinking water are at 10 ng lt^{-1} and considered as health-based according to the German Umweltbundesamt (UBA) for lifetime and less than lifetime exposure.

The Norwegian Institute of Public Health (NIPH) has recommended, based on a 10^{-6} risk of cancer, an acceptable exposure level of 4 ng lt^{-1} in drinking water, and 0.3 ng m^{-3} in air (Låg et al., 2011). Due to lack of toxicity data, it is not possible to perform any cancer risk estimates for nitramines. Therefore, NIPH has suggested that the risk estimate for the nitrosamine NDMA can be used as a proxy of exposure to nitramines. This is considered to be a conservative risk estimate, either an overestimate of the risk, as NDMA is likely to be more potent than any of the nitramines, or could be an underestimate of the risk, if total levels of nitramines exceed the suggested level for NDMA exposure (Låg et al., 2011).

Table 5.27 Permissible concentrations of compounds on 10^{-6} risk (reproduced by Selin et al., 2011; Låg et al., 2011; Rusin et al, 2016; US.EPA, 2016; Gushgari & Halden, 2018).

	Safety limits	Regulatory Country and Enacted Law
NDMA	2 ng lt^{-1}	California Action Level in Drinking water
	3 ng lt^{-1}	California Public health goal in Drinking water
	10 ng lt^{-1}	Massachusetts Regulatory Limit in Drinking water
	1 ng lt^{-1}	Arizona Regulatory Limit in Discharge
	40 ng lt^{-1}	Canada Maximum Limit in Drinking water
	10 ng lt^{-1}	Germany Maximum Limit in Drinking water
	10 ng lt^{-1}	UK Maximum Limit in Drinking water
	200 ng lt^{-1}	UK Emergency Action in Drinking water
NDEA	2 ng lt^{-1}	US. EPA Maximum Permissible concentration
NDPA	5 ng lt^{-1}	Arizona Regulatory Limit in Discharge
NDPha	7,100 ng lt^{-1}	Arizona Regulatory Limit in Discharge
MEA	10 µg m^{-3}	Air: Inhalation
	6, 7.5, 8 & 15 mg m^{-3}	United States OEL
	5.1 mg m^{-3}	Germany OEL
	7.5 & 15 µg m^{-3}	Canada OEL
DEA	75 mg m^{-3}	Air: Inhalation of 8-hour average
	1 & 15 mg m^{-3}	United States OEL
	1 mg m^{-3}	Germany OEL
	2, 13 & 26 mg m^{-3}	Canada OEL
piperazine	0.1 mg m^{-3}	United States OEL
	0.3 & 1 mg m^{-3}	Canada OEL
	0.1 & 0.3 mg m^{-3}	UK OEL
Nitrosamines	0.02 ng m^{-3}	Air: Inhalation of monthly average
	7 ng lt^{-1}	Drinking water
Nitramines	1 µg lt^{-1}	Drinking water

While occupational exposure limits (OELs) specific to amine mixtures released from CCS facilities have not been developed, OELs for certain individual amines including MEA, DEA, and PZ are available (Table 5.27). In the USA, the Occupational Safety and Health Administration (OSHA) have established a permissible exposure limit (PEL) for MEA of 3 ppm (Gentry et al., 2014). OSHA PELs are based on an 8-h time-weighted average (TWA) exposure. Similarly, the National Institute of Occupational Safety and Health (NIOSH) has established 8-h TWA exposure limits and short-term exposure limits for MEA of 3 and 6 ppm, respectively, based on skin, eye, and respiratory irritation, and narcotic effects. The 8-h TWA is the level at which a worker can be exposed for 8 h a day, 40 h a week without adverse effects. Alberta, Quebec, and British Columbia have established an 8-h exposure limit for MEA of 3 ppm and an acceptable, over a short period of time, usually 15 min exposure limit of 6 ppm.

The UK has set an OEL for MEA at 7.6 mg m^{-3}; while Norway has implemented an administrative norm for occupational exposure to MEA of 2.5 mg m^{-3} (Karl et al., 2011). However, previously, Låg et al. (2009) had suggested that the general population, over time, should not be exposed to ambient air levels of MEA higher than 10 µg m^{-3}. This safety limit was used as a monthly average concentration in air. For piperazine, Norway and Denmark have long-term occupational exposure limits at 0.3 mg m^{-3} and 0.1 mg m^{-3}, respectively, whilst Finland has both a long-term OEL of 0.1 mg m^{-3} and a short-term OEL of 0.3 mg m^{-3}.

For DEA, NIOSH have established TWA exposure limits of 3 ppm; same in Canada, the provinces of Quebec and Alberta have established 8-h exposure limits of 3 ppm, and Alberta reports a 15-min exposure limit of 6 ppm. British Columbia also reports a TWA exposure limit of 2 mg m^{-3} for DEA based on skin sensitisation and a carcinogen designation of 2B. The German 8-h average exposure limit for DEA is 1 mg m^{-3} based on skin sensitisation effects (Gentry et al., 2014).

The assessment level of 0.3 ng m^{-3} for NDMA developed by NIPH was derived from established drinking water dose-response modelling and linear extrapolation. There are uncertainties associated with the approach of using an oral dose to derive inhalation concentration (route-to-route extrapolation). Route-to-route extrapolation increases toxicological uncertainty in two ways (the uncertainty in applying animal data to human exposure and the link between oral and inhalation exposures) resulting in reduced confidence in the risk assessment. NIPH has therefore calculated two risk estimates for inhalation exposure; one based on the drinking water study by Peto et al. (1991) (as seen in Booth et al., 2014) and another based the best suited inhalation study available. However, the estimated effect of an inhalation study showed that there is a higher tumour risk from inhalation exposure than from oral exposure. Based on the available data, NIPH strongly supported the use of the most conservative risk estimate of 0.3 ng m^{-3} to protect the general population from health hazards in relation to inhalation exposure of nitrosamines.

The UK approach for deriving health guidelines for non-threshold mutagenic carcinogens is based on categorical risk level (as opposed to the NIPH quantitative risk assessment). There is, therefore, continuing effort in research for dose-response inhalation toxicity data from which to derive more realistic levels that are protective of human health (SEPA, 2015).

5.3.1 Health Reference Levels for Nitrosamines

The Health Reference Levels (HRL) is a risk-derived concentration in drinking water against which available data can be compared to determine if a nitrosamine occurs with a frequency and at levels of public health concern. In the case of chemicals that are known or are likely to cause cancer, the HRL is the concentration in drinking water associated with an increased risk of one excess cancer among a million exposed persons over a lifetime exposure (i.e., estimated lifetime excess cancer risk of one-in-a-million, 1×10^{-6}). The HRL is a benchmark that is set to compare the risks of different chemicals based on drinking water being the sole route of exposure; it does not integrate added risks associated with other exposure media (i.e., food, air) (US.EPA, 2016).

In cases where data are lacking, US. EPA (2016) uses a default low dose linear extrapolation to calculate a cancer factor slope (CSF). The unit risk (eq. 12) is the estimated upper-bound excess lifetime cancer risk from a continuous exposure to a chemical at a concentration of 0.001 mg l^{-1} in drinking water and expressed in units of (µg l^{-1}). The exposure estimate assumes an adult body weight of 70 kg and the 90th percentile adult drinking water intake of 2 l per day.

$$Unit\ risk\ (\mu g\ lt^{-1}) = CSF \times [(DWI \times UA) / BW] \qquad \text{eq. 12}$$

where CFS = cancer factor slope (mg kg^{-1} bw day^{-1}), DWI = Drinking Water Intake, for an adult assumed to be 2 l day^{-1} UA = Unit Adjustment from mg to µg, BW = Body weight for an adult, assumed to be 70 kg.

The cancer HRL (eq. 13) is the concentration of a contaminant in drinking water corresponding to an excess estimated lifetime cancer risk of one-in-a-million (1×10^{-6}). It needs to be clarified, however, that they are not final determinations about the level of a contaminant in drinking water that must not be exceeded to protect any particular population. They are rather risk derived concentrations against which to evaluate the available data to determine if contaminants occur at levels of potential public health concern (US. EPA, 2016).

$$HRL\ (\mu g\ lt^{-1}) = Risk\ Level \text{ of } 10^{-6} / Unit\ risk\ (\mu g\ l^{-1}) \qquad \text{eq. 13}$$

When chemical-specific data to quantify the increased risk are lacking, then Age Dependent Adjustment Factors ($ADAFs$) are applied to estimate age-adjusted unit risks. The age-adjusted unit risk (eq. 14) is determined by using the sum of the unit risks for each of the three ADAF developmental groups (birth to < 2 yrs; 2 yrs to < 16 yrs; 16 yrs to 70 yrs). The age adjusted unit risks include a ten-fold adjustment for early life (birth to < 2 yrs) exposures, a three-fold adjustment for childhood/adolescent (2 yrs to < 16 yrs) exposures, and no additional adjustment for exposures later in life (16 yrs to 70 yrs), in conjunction with age-specific drinking water intake values and the fraction of a 70-year lifetime applicable to each age period.

$$Age\text{-}Adjusted\ Unit\ Risk\ (\mu g\ l^{-1}) = \sum CSF \times ADAF \times DWI\ /\ BWR \times UA\ /\ F) \qquad \text{eq. 14}$$

where CFS = Cancer Factor Slope (mg kg^{-1} bw day^{-1}), $ADAF$ = Age Dependent Adjustment Factor for the age group birth to two years (ADAF=10), two to sixteen years ($ADAF$ =3) and sixteen to seventy years ($ADAF$ =1), DWI / BWR = Drinking Water Intake Body Weight Ratio expressed as litres per day per kg body weight for the age specific group, UA = Unit Adjustment from mg to µg and F = the fraction of a 70-year lifetime applicable to the age period: 2/70 to the age group birth to two years, 14/70 for two to sixteen years and 54/70 from sixteen to seventy years.

Then, the cancer HRL can be re-calculated based on the age adjustment risk (eq. 15).

$$HRL\ (\mu g\ l^{-1}) = Risk\ Level \text{ of } 10^{-6} \text{ / } Age\text{-}adjusted\ unit\ risk\ (\mu g\ l^{-1}) \qquad \text{eq. 15}$$

The HRLs for the nitrosamines NDMA, NDPA, NDEA, NPYR, NMEA and NDBA (Table 5.28) were derived from the CSF using the age-adjusted unit risk. Since the nitrosamines were determined to cause cancer by a mutagenic mode of action, the unit risk was adjusted for the increased risk associated with early life exposures through the application of ADAFs and age-specific exposure factors.

Table 5.28 US.EPA (2016) Cancer Risk Values and HRLs for six nitrosamines.

Nitrosamines	Cancer Slope Factor[a] (mg kg^{-1} bw day^{-1})	Age-Adjusted Unit Risk (µg l^{-1})	HRL[b] (µg l^{-1})	HRL (ng l^{-1})
NDBA	0.4	3.0×10^{-5}	3.0×10^{-2}	30
NDEA	30	2.3×10^{-3}	4.0×10^{-4}	0.4
NDMA	21	1.6×10^{-3}	6.0×10^{-4}	0.6
NDPA	2	1.5×10^{-4}	7.0×10^{-3}	7
NMEA	4	3.0×10^{-4}	3.0×10^{-3}	3
NPYR	7	5.3×10^{-4}	2.0×10^{-3}	2

[a]CSF was established by different studies; liver and oesophageal tumours in rats

[b]The cancer HRL was determined by dividing the population risk level of one in a million (1×10^{-6}) by the age adjusted unit risk

6 Final Considerations

It is well documented that the highest health risk to the general population from CO_2 capture facilities has been associated with nitrosamines and nitramines dispersed to the surrounding ambient air and drinking water. There is, therefore, a critical need to characterise the potential health effects of both nitrosamines and nitramines and their degradation products formed within the capture system or downwind of their release.

Based on the foregoing literature review, the following key points need to be highlighted:

- UV treatment and photolysis have been documented as effective degradation processes for both nitrosamines (NSA) and nitramines (NA). Especially for nitrosamines, when exposed to sunlight, photodegradation is an important depletion pathway, both in air and in water. That is that when NSA and NA are classed as being readily biodegradable, they present less of a hazard in the environment.
- Seasonal variation in temperature, sunlight, and hydrology was found to influence both the NSA and NA concentrations. During winter the effect of photodegradation was reduced to a minimum, resulting from the combined effect of weaker sunlight radiation and ice cover. This variation should be taken into account in any monitoring program.
- It is well known that concentrations and temperatures significantly influence the biodegradability of chemicals in natural waters. Results have indicated that biodegradation of nitrosamines was reduced by lower water temperatures and at lower concentrations.
- According to IARC, the majority of the nitrosamines are classified as group 2B – possibly carcinogenic to humans – or group 2A – probably carcinogenic to humans. Although nitramines in turn seem to be less potent (~15 times less) as mutagens and carcinogens than their corresponding nitrosamines, they should also be considered as highly toxic.
- TD50 has been suggested by the CPDB as the excess cancer risk calculation, associated with a theoretical excess cancer risk of 1:100,000 or 1:1,000,000. A larger dose is indicative of a smaller carcinogenic effect. Based on the literature review TD50 values, nitramines were orders of magnitude less carcinogenic than nitrosamines.
- As these values are estimated based on animal experiments, it is important to consider assessment factors, to account mainly the differences between animals and humans, and also to allow for the variability between different population, and individual variations among people, such as age and gender.
- Special attention should be given to sensitive populations. Infants and children can be more susceptible than adults to the mutagenic effects of the nitrosamines, as they have a higher uptake from both oral and airway exposure per kg body weight due to a higher metabolic rate per body unit for children compared to adult. Children, compared to adults, were shown to be more likely to develop diseases when they were exposed to hazardous substances, especially carcinogenic chemicals.
- Because chemicals with mutagenic potential can cause cancer by a mutagenic mode of action (MOA), they can therefore pose a higher risk of cancer to humans when exposure occurs during early life. Therefore, it is important to apply age-dependent adjustment factors (ADAFs) for different age stages to the estimated lifetime cancer risk.

- Besides the different age stages, it is also important to consider different genders, as there are also differences in the physiological function between males and females.
- Based on a human health risk assessment for the occurrence and the carcinogenic risk of nitrosamines and nitramines, they were found to have genotoxic/mutagenic potential. Additionally, severe eye and skin irritation and corrosion potential was observed. However, the level of risk may depend upon the exposure concentration. The most important health risks were observed for NDMA and NMOR, which showed medium to high long term health effects for dermal and inhalation exposure, respectively. In the case of nitramines, on the other hand, only a few toxicity studies have been conducted. Data on nitramines' toxicity showed moderate toxic health effects with an order (from highest to lowest) of the test substances being DMA > MA > MEA > PZ. Although all the compounds were genotoxic, DMA and MA were more potent and PZ slightly toxic.
- Mathematical-computational models, i.e. QSARs, have gained significance in terms of predicting the toxic activity and mutagenic properties of amines, based on their physico-chemical properties through statistical methods. These models can be very supportive for undertaking a risk assessment when experimental data is lacking.
- Several organisations and institutions have established different public health thresholds for different nitrosamines and nitramines. The Norwegian Institute of Public Health (NIPH) has recommended, based on a 10^{-6} risk of cancer, an acceptable exposure level of 4 ng lt^{-1} in drinking water, and 0.3 ng m^{-3} in air, for the total concentration of NSA and NA, based on the risk estimate calculated for NDMA. It should, however, be pointed that this represents a conservative risk estimate, since NDMA is likely to be more potent than any of the nitramines and is one of the most potent nitrosamines.
- There is therefore the need for a continuing effort in toxicity data for both NSA and NA to derive more realistic levels that are protective of the human health.

7 References

AFZAL, A., KANG, J., CHOI, B.-M. & LIM, H.-J. 2016. Degradation and fate of N-nitrosamines in water by UV photolysis. *International Journal of Greenhouse Gas Control,* 52**,** 44-51.

AMSTER, E. 2021. Public health impact of coal-fired power plants: a critical systematic review of the epidemiological literature. *Int J Environ Health Res,* 31**,** 558-580.

AFZAL, A., KIM, C.J. & LIM, H.J. 2017. Influence of pH on the UV photolysis of N-nitrosamines in water: Kinetics and products. *International Journal of Greenhouse Gas Control,* 64**,** 194-203.

BADR, S., FRUTIGER, J., HUNGERBUEHLER, K. & PAPADOKONSTANTAKIS, S. 2017. A framework for the environmental, health and safety hazard assessment for amine-based post combustion CO2 capture. *International journal of greenhouse gas control,* 56**,** 202.

BENIGNI, R. & BOSSA, C. 2012. Flexible use of QSAR models in predictive toxicology: a case study on aromatic amines. *Environ Mol Mutagen,* 53**,** 62-9.

BOOTH, A., SØRENSEN, L., BRAKSTAD, O. G., FALCK DA SILVA, E., KORRE, A., MANZOOR, S., DURUCAN, S., SIMPERLER, A., ZAHLSEN, K., HYLDBAKK, A. & VERNESTAD, K. 2014. Fate of nitramine and nitrosamine emissions in air, water and soil environments around amine-based post combustion CO2 capture plants. Trondheim, Norway: SINTEF. Materials and Chemistry.

BRAKSTAD, O. G., SØRENSEN, L., ZAHLSEN, K., BONAUNET, K., HYLDBAKK, A. & BOOTH, A. M. 2018. Biotransformation in water and soil of nitrosamines and nitramines potentially generated from amine-based CO2 capture technology. *International journal of greenhouse gas control,* 70**,** 157-163.

BRAKSTAD, O. G., HYLDBAKK, A. & ZAHLSEN, K. 2014. Biodegradation of nitramines in water. Norway: SINTEF Materials and Chemistry. Marine Environmental Technology.

BRAKSTAD, O. G., BOOTH, A. M., EIDE-HAUGMO, I., SKJÆRAN, J. A., SØRHEIM, K. R., BONAUNET, K., VANG, S.-H. & SILVA, E. F. D. 2012a. Seawater biodegradation of alkanolamines used for CO2-capture from natural gas. *International Journal of Greenhouse Gas Control,* 10**,** 271-277.

BRAKSTAD, O. G., ZAHLSEN, K. & VANG, S. H. 2012b. Environmental Impacts of Solvent Technology – Phase 2 SOLVit Delivery D1.3.3 - Biodegradation studies Norway: SINTEF Materials and Chemistry. Marine Environmental Technology.

BRAKSTAD, O. G. & ZAHLSEN, K. 2011. Biodegradation of nitrosamines in water. Biodegradation studies at low nitrosamine concentrations. Norway: SINTEF Materials and Chemistry. Marine Environmental Technology.

BRAKSTAD, O. G., BOOTH, A., MELBYE, A. G., NORDTUG, T., HANSEN, B. H., VANG, S. H., ZAHLSEN, K., WITTGENS, B., SYVERSEN, T., KAUR, P., DUSINSKA, M., FJELLSBO, L. B. & RAVNUM, S. 2010a. TQPAmine3 Protocol for Evaluation of Solvents – Emission compound Toxicity. Norway: SINTEF Materials and Chemistry.

BRAKSTAD, O. G., FALCK DA SILVA, E. & SYVERSEN, T. 2010b. TCM Amine project: Support on input to environmental discharges. Evaluation of degradation components Version 3. Norway: SINTEF Materials and Chemistry.

BRAKSTAD, O. G., VANG, S. H. & SYVERSEN, T. 2010c. TCM Amine project: Support on input to environmental discharges: Quality checks of data sheets for alternative solvents. Norway: SINTEF Materials and Chemistry.

BRECKE-GUNDERSEN, C., NORLING, M. D. & CLAYER, F. 2020. Modeled Nitrosamine and Nitramine concentrations in Lake Elvåga following amine-based CO2 Capture at FOV Waste Incineration Plant at Klemetsrud. Norway NIVA. Norwegian Institute for Water Research.

BUIST, H. E., DEVITO, S., GOLDBOHM, R. A., STIERUM, R. H., VENHORST, J. & KROESE, E. D. 2015. Hazard assessment of nitrosamine and nitramine by-products of amine-based CCS: alternative approaches. *Regul Toxicol Pharmacol,* 71**,** 601-23.

BUVIK, V., HØISÆTER, K. K., VEVELSTAD, S. J. & KNUUTILA, H. K. 2021. A review of degradation and emissions in post-combustion CO2 capture pilot plants. *International journal of greenhouse gas control,* 106**,** 103246.

CHEN, X., HUANG, G. H., AN, C., YAO, Y. & ZHAO, S. 2018. Emerging N-nitrosamines and N-nitramines from Amine-based Post-combustion CO2 Capture - A Review. *Chemical Engineering Journal,* 335**,** 921-935.

CHINEN, K. & MALLOY, T. 2020. QSAR Use in REACH Analyses of Alternatives to Predict Human Health and Environmental Toxicity of Alternative Chemical Substances. *Integr Environ Assess Manag,* 16**,** 745-760.

CHOW, Y.L., LAU, M.P., PERRY, R.A. & TAM J.N.S. 1972. Photoreactions of nitroso compounds in solution. XX. Photoreduction, photoelimination, and photoaddition of nitrosamines Can. J. Chem., 50, 1044-1050

COUTRIS, C., MACKEN, A. L., COLLINS, A. R., EL YAMANI, N. & BROOKS, S. J. 2015. Marine ecotoxicity of nitramines, transformation products of amine-based carbon capture technology. *Sci Total Environ,* 527-528**,** 211-9.

CPDB 2007. https://toxnet.nlm.nih.gov/cpdb/.

DYE, C., FJELLSBØ, L. & DUSINSKA, M. 2011. Nitramine Analysis Procedures development and screening toxicity study. NILU Norwegian Institute for Air Research.

EA 2009. Human health toxicological assessment of contaminants in soil Bristol: Environment Agency.

ECHA 2017. Guidance on information requirements and chemical safety assessment. Part C: PBT/vPvB assessment. . Finland.

EEA 1998. Environmental Risk Assessment - Approaches, Experiences and Information Sources. Brussels.

EIDE-HAUGMO, I., BRAKSTAD, O. G., HOFF, K. A., SILVA, E. F. D. & SVENDSEN, H. F. 2012. Marine biodegradability and ecotoxicity of solvents for CO2-capture of natural gas. *International Journal of Greenhouse Gas Control,* 9**,** 184-192.

EMA 2020. Assessment report. Procedure under Article 5(3) of regulation EC (No) 726/2004. Nitrosamine impurities in human medicinal products. *Procedure number EMEA/H/A-5(3)/1490.* The Netherlands: European Medicines Agency.

FALCK DA SILVA, E., BOOTH, A. & SØRENSEN, L. 2012. Emissions from post-combustion CO2 capture plants. Review: Environmental fate and effect of emissions from post-combustion CO2 capture plants. . Norway: SINTEF. Materials and Chemistry. Marine Environmental Technology.

FALCK DA SILVA, E., BOOTH, A., LOEPPKY, R., MA'MUN, S., KARL, M., HEIMSTAD, E., JOHNSON, M. & FEILBERG, K. 2010. Protocol for evaluation of solvents - process and atmospheric chemistry *Report for H&ETQP Amine 4 project.* Trondheim, Norway: SINTEF. Materials and Chemistry.

FARREN, N. J., RAMÍREZ, N., LEE, J. D., FINESSI, E., LEWIS, A. C. & HAMILTON, J. F. 2015. Estimated Exposure Risks from Carcinogenic Nitrosamines in Urban Airborne Particulate Matter. *Environmental Science & Technology,* 49**,** 9648-9656.

FJELLSBØ, L. M., VERSTRAELEN, S., KAZIMIROVA, A., VAN ROMPAY, A. R., MAGDOLENOVA, Z. & DUSINSKA, M. 2014. Genotoxic and mutagenic potential of nitramines. *Environ Res,* 134**,** 39-45.

FJELLSBØ, L. M., VAN ROMPAY, A. R., HOOYBERGHS, J., NELISSEN, I. & DUSINSKA, M. 2013. Screening for potential hazard effects from four nitramines on human eye and skin. *Toxicol In Vitro,* 27**,** 1205-10.

GENTRY, P. R., HOUSE-KNIGHT, T., HARRIS, A., GREENE, T. & CAMPLEMAN, S. 2014. Potential occupational risk of amines in carbon capture for power generation. *Int Arch Occup Environ Health,* 87**,** 591-606.

GESAMP. 2019. GESAMP Hazard Evaluation Procedure for Chemicals Carried by Ships. UK: Joint Group of Experts on the Scientific Aspects of Marine Environmental Protection, Rep. Stud.

GJERNES, E., HELGESEN, L. I. & MAREE, Y. 2013. Health and environmental impact of amine based post combustion CO2 capture. *Energy procedia,* 37**,** 735-742.

GUSHGARI, A. J. & HALDEN, R. U. 2018. Critical review of major sources of human exposure to N-nitrosamines. *Chemosphere,* 210**,** 1124-1136.

HELGESEN, L. I. & GJERNES, E. 2016. A Way of Qualifying Amine Based Capture Technologies with Respect to Health and Environmental Properties. *Energy procedia,* 86**,** 239-251.

HENRY, I. A., KOWARZ, V. & ØSTGAARD, K. 2017. Aerobic and anoxic biodegradability of amines applied in CO2-capture. *International Journal of Greenhouse Gas Control,* 58**,** 266-275.

HILLEBRAND, M., PFLUGMACHER, S. & HAHN, A. 2016. Toxicological risk assessment in CO2 capture and storage technology. *International Journal of Greenhouse Gas Control,* 55**,** 118-143.

IARC. 2021. *Agents Classified by the IARC Monographs, Volumes 1–129* [Online]. Lyon: International Agency for Research on Cancer. Available: http://monographs.iarc.fr/ENG/Classification/index.php. [Accessed 01 August 2022].

ISO 31010 2009. Risk management - Risk assessment techniques. International Electrotechnical Commission / International Organization for Standardization.

KARL, M., WRIGHT, R. F., BERGLEN, T. F. & DENBY, B. 2011. Worst case scenario study to assess the environmental impact of amine emissions from a CO_2 capture plant. *International Journal of Greenhouse Gas Control,* 5**,** 439-447.

KNUUTILA, H., SVENDSEN, H. F. & ASIF, N. 2013. Destruction of nitrosamines with UV-light. *Energy procedia,* 37**,** 743-750.

LÅG, M., LINDEMAN, B., INSTANES, C., BRUNBORG, G. & SCHWARZE, P. 2011. Health effects of amines and their derivatives associated with CO_2 capture. Norwegian Institute of Public Health.

LÅG, M., INSTANES, C., LINDEMAN, B. & ANDREASSEN, Å. 2009. Health effects of possible degradation products of different amines relevant for the CO2 capture. Oslo, Norway: NILU. Norwegian Institute of Public Health.

LEE, C. , CHOI, W. & YOON, J. 2005. UV photolytic mechanism of N-nitrosodimethylamine in water: roles of dissolved oxygen and solution pH. Environ. Sci. Technol., 39 (24), 9702-9709.

LUO, Q., BEI, E., LIU, C., DENG, Y. L., MIAO, Y., QIU, Y., LU, W. Q., CHEN, C. & ZENG, Q. 2020. Spatial, temporal variability and carcinogenic health risk assessment of nitrosamines in a drinking water system in China. *Sci Total Environ,* 736**,** 139695.

MAZARI, S. A., ALABA, P. & SAEED, I. M. 2019. Formation and elimination of nitrosamines and nitramines in freshwaters involved in post-combustion carbon capture process. *Journal of environmental chemical engineering,* 7**,** 103111.

MAZARI, S. A., ALI, B. S., JAN, B. M., SAEED, I. M. & NIZAMUDDIN, S. 2015. An overview of solvent management and emissions of amine-based CO_2 capture technology. *International Journal of Greenhouse Gas Control,* 34**,** 129-140.

OECD 2006. Report on the regulatory uses and applications in OECD member countries of (quantitative) structure-activity relationship [(Q)SAR] models in the assessment of new and existing chemicals. . *OECD Series on Testing and Assessment.* Paris: OECD.

PLUMLEE, M.H. & REINHARD, M. 2007. Photochemical attenuation of N-nitrosodimethylamine (NDMA) and other nitrosamines in surface water. Environ. Sci. Technol., 41 (17), 6170-6176.

RAVNUM, S., RUNDÉN-PRAN, E., FJELLSBØ, L. M. & DUSINSKA, M. 2014. Human health risk assessment of nitrosamines and nitramines for potential application in CO_2 capture. *Regulatory Toxicology and Pharmacology,* 69**,** 250-255.

RUSIN, A. & STOLECKA, K. 2016. An Analysis of Hazards Caused by Emissions of Amines from Carbon Dioxide Capture Installations. *Polish Journal of Environmental Studies,* 25**,** 909-916.

SELIN, N. E. 2011. Environmental Regulations and Guidelines for Nitramines: A Policy Summary. Report for CO2 Technology Centre Mongstad.

SEPA 2015. A review of amine emissions from carbon capture systems. *Version 2.01.* Scottish Environment Protection Agency.

SHAVALIEVA, G., KAZEPIDIS, P., PAPADOPOULOS, A. I., SEFERLIS, P. & PAPADOKONSTANTAKIS, S. 2021. Environmental, health and safety assessment of post-combustion CO2 capture processes with phase-change solvents. *Sustainable production and consumption,* 25**,** 60-76.

SØRENSEN, L., ZAHLSEN, K., HYLDBAKK, A., SILVA, E. F. D. & BOOTH, A. M. 2015. Photodegradation in natural waters of nitrosamines and nitramines derived from CO2 capture plant operation. *International Journal of Greenhouse Gas Control,* 32**,** 106-114.

SPIETZ, T., DOBRAS, S., WIĘCŁAW-SOLNY, L. & KRÓTKI, A. 2017. Nitrosamines and nitramines in Carbon Capture plants. *Environmental Protection and Natural Resources,* 28**,** 43-50.

STEFAN, M.I. & BOLTON, J.R. 2002. UV direct photolysis of N-nitrosodimethylamine (NDMA): kinetic and product study. Helv. Chim. Acta, 85 (5), 1416-1426.

US.EPA. 2022a. *Human health risk assessment. Conducting a human health risk assessment.* [Online]. US. Environmental Protection Agency. Available: https://www.epa.gov/risk/human-health-risk-assessment [Accessed].

US.EPA. 2022b. *The Superfund Program - Risk Assessment: Human Health topics* [Online]. Washington, DC. Available: https://www.epa.gov/risk/superfund-risk-assessment-human-health-topics [Accessed 25/8/2022 2022].

US.EPA. 2016. Six-Year Review 3 Technical report Document for Nitrosamines. Washington, DC: US. Environmental Protection of Agency. Office of Water (4607M).

WAGNER, E. D., OSIOL, J., MITCH, W. A. & PLEWA, M. J. 2014. Comparative in Vitro Toxicity of Nitrosamines and Nitramines Associated with Amine-based Carbon Capture and Storage. *Environmental Science & Technology,* 48**,** 8203-8211.

WHO. 2021. Human Health Risk Assessment Toolkit. Chemical Hazards. Harmonization Project. Geneva.

WHO. 2002. Concise International Chemical Assessment N-NITROSODIMETHYLAMINE. Geneva.

ZHANG, X., ZHOU, Z., LIU, Y., FAN, X., LI, H. & WANG, J.-T. 2014. Predicting the Acute Toxicity of Aromatic Amines by Linear and Nonlinear Regression Methods. *Chinese Journal of Structural Chemistry,* 33**,** 244-252