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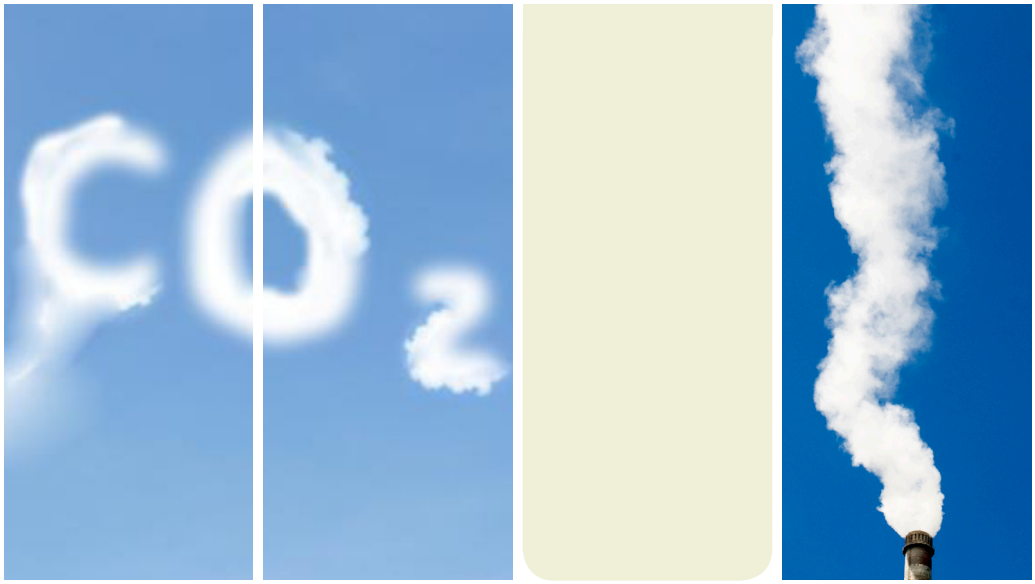

Health effects of amines and derivatives associated with CO_2 capture

Marit Låg
Birgitte Lindeman
Christine Instanes
Gunnar Brunborg
Per Schwarze

folkehelseinstituttet

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Authors:
Marit Låg
Birgitte Lindeman
Christine Instanes
Gunnar Brunborg
Per Schwarze

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Preface

The Climate and Pollution Agency (Klif) requested the Norwegian Institute of Public Health (NIPH) to carry out the following evaluations of compounds from the amine-based capture of CO_2 at the Technology Center Mongstad:

- Evaluation of potential health effects from exposure to amines, nitrosamines and nitramines from the CO_2 capture plant.
- Evaluation of existing risk estimates for *N*-nitrosodimethylamine (NDMA). This included an evaluation of EPA/IRIS cancer risk estimates for drinking water and air, and other risk evaluations of this nitrosamine in Europe and Canada. Klif asked for an evaluation of the validity of the risk estimates, how they can be used, and how they should be interpreted.

In response to Klif, NIPH has consulted existing international risk evaluations, and searched scientific literature bases for toxicological test results on relevant compounds. Evaluation and re-calculation of the existing cancer risk estimates for NDMA was carried out according to REACH guidelines. The present report does not include a health risk evaluation of amine-based CO_2 capture in the Mongstad area, since emission levels of the relevant compounds are currently not known.

The use of amine-based technology in post-combustion CO_2 capture may have more general relevance, and NIPH has therefore decided to publish the current health hazard characterization.

NIPH, April 2011,

Marit Låg, Christine Instanes, Birgitte Lindeman,

Gunnar Brunborg and Per Schwarze

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Summary

The Climate and Pollution Agency (Klif) has requested the Norwegian Institute of Public Health (NIPH) to carry out evaluations of potential health effects with regard to emissions of amine-related compounds from CO_2 capture plants. In response to Klif, NIPH has screened for existing international risk evaluations and published/unpublished toxicological test results in the following databases: ToxNet, Pubmed, INCHEM, HSDB, EPA-IRIS, IUCLID. NIPH has previously published a report (FHI rapport, 2009) with health hazard characterisations of four amines relevant for CO_2 capture. Klif has asked NIPH to update the information on these four amines with studies published after 2008. NIPH was also asked to gather information from the literature on several additional amines relevant for CO_2 capture. In addition, Klif requested an evaluation of existing cancer risk estimates of *N*-nitrosodimethylamine (NDMA) in drinking water and air and an evaluation of the health effects of nitramines.

The lower aliphatic amines are normal constituents of body tissues. Since the amines are bases that may form strongly alkaline solutions, they can be corrosive or irritating. Amines are in general mostly non-mutagenic. However, one area of concern is the possibility that some aliphatic amines may react in the body and in the environment to form nitrosamines, many of which are known to be potent carcinogens in animals. Monoethanolamine (MEA), piperazine, aminomethylpropanol (AMP) and methyldiethanolamine (MDEA) are the amines evaluated in 2009. In the present report, NIPH has included an overview of new information published after 2008 in addition to previously used key studies for the risk evaluation. However, few new studies were identified, and these did not warrant a revision of the previous risk assessments of the four amines. Furthermore, NIPH has searched for data on the toxicity of other amines, relevant for CO_2 capture, to give an overview of the available data for each substance focusing on repeated dose toxicity. These amines were the following: dimethylamine, diethylamine, dibuthylamine, *N*-methylethanamine, *N*-ethyl 1-butanamine, dipropylamine, diethanolamine, hydroxyethylimidazole (HEI), hydroxyethyl-formamide (HEF), oxazolidinone (OZD), 4,4-dimethyl-2-oxazolidinone, 2-methyl-2-(methylamino)-1-propanol, methylamine and ethylamine. The toxicity data available for the various amines was highly variable. For a few of the compounds, there is sufficient data to justify a health hazard assessment. For most of these amines, however, toxicity data retrieved was limited, and not sufficient for a quantitative health hazard characterisation.

WHO, Health Canada and EPA have all derived cancer risk estimates for exposure to the nitrosamine, NDMA, in drinking water. NIPH recommends using the dose-response modelling previously performed by WHO/Health Canada based on an extensive drinking water study by Peto and coworkers from 1991 as a basis for risk estimates for NDMA exposure. NIPH has used the dose-response data followed by a linear extrapolation to low dose exposures to estimate excess life time cancer risks at the levels of 10^{-5} and 10^{-6} for NDMA in drinking water and air exposures. The resulting estimates can be used as a basis for evaluating the human cancer risk associated with the formation of nitrosamines from CO_2 capture plants. Based on these considerations, a negligible excess risk level for cancer of 1 in 10^{-6} after lifelong exposure to NDMA was associated with a drinking water concentration of 4 ng/l and an air concentration of 0.3 ng/m^3. Although the drinking water study is the best suited study for dose-response evaluation, an inhalation study by Klein and co-workers from 1991 suggested that NDMA may be more potent by inhalation than by oral exposure.

The dose-response information reported in the inhalation study is associated with a greater uncertainty than the data from the drinking water study, and may overestimate the risk at low

exposure concentrations. Based on the inhalation study, NIPH has estimated that the proposed tolerable air concentration of 0.3 ng/m^3 is associated with a maximum excess life time cancer risk below 10^{-5}. Thus, even if NDMA is a more potent carcinogen through inhalation than via oral exposure, the excess cancer risk is considered minimal if an air concentration of 0.3 ng/m^3 is not exceeded over time. Furthermore, since NDMA belongs to the most potent nitrosamines, we suggest that the risk estimate for NDMA can also be used for other nitrosamines. A refined risk evaluation taking into account differences in cancer potencies should be performed if the total nitrosamine level exceeds the above suggested level for NDMA exposure. If the more potent *N*-nitrosodiethylamine (NDEA) were to constitute a large part of the nitrosamines, higher risks may emerge, and this will then necessitate a revised risk evaluation.

NIPH has evaluated the available data on nitramine toxicity in the open literature. Chronic toxicity data of aliphatic nitramines is very limited, and the information is not sufficient for a proper health hazard evaluation. In general, nitramines seem to be less potent as mutagens and carcinogens than the corresponding nitrosamines. However, the compound of the nitramines which has been best studied, *N*-nitrodimethylamine, should still be regarded as a highly potent carcinogen based on reported findings in a carcinogenicity study. Due to lack of toxicity data, it is not possible to carry out a cancer risk estimation for nitramines. Therefore, NIPH suggests that the risk estimate for the nitrosamine NDMA should be used also for exposure to nitramines. This is considered to be a conservative risk estimate, since NDMA is likely to be more potent than any of the nitramines. If nitramines constitute a large part of the total nitrosamines/ nitramines, and the total levels exceed the suggested level for NDMA exposure, a refined risk evaluation I recommended, taking into account differences in cancer potencies. However, there is a strong need for more information on toxic, mutagenic and carcinogenic properties of the nitramines where a significant exposure is expected in the vicinity of CO_2 capture plants.

Of the compounds released from the CO_2 capture plant, the amines seem to be of low toxicity, compared to other released compounds,. However, the area of concern is the possibility that some of the amines may react to form nitrosamines or nitramines, which may show to be potent carcinogens. NIPH recommends that the risk estimate calculated for NDMA should be used for the total concentration of nitrosamines and nitramines in air. We recommend a maximum level ensuring the public minimal or negligible risk of cancer from exposure to these substances. NIPH therefore concludes that the total amount of nitrosamines and nitramines should not exceed 0.3 ng/m^3 (nanogram/m^3) in air.

1. Health effects of selected amines

The Norwegian Institute of Public Health (NIPH) published a report in 2009 (FHI rapport, 2009) with health hazard characterisations of four amines relevant for CO_2 capture. The Climate and Pollution Agency (Klif), has asked NIPH to update the information on these four amines, with studies published after 2008. In addition, NIPH was asked to gather information from the literature on several additional amines relevant for CO_2 capture. These amines were specified by Klif (see Table 1). The literature information available for these amines has not been thoroughly evaluated by NIPH and thus definision of tolerable exposure concentrations for these additional amines was not attempted. We have searched for information in several databases containing toxicological data including ToxNet, Pubmed, INCHEM, HSDB, EPA-IRIS, IUCLID.

Amines are compounds normally present in biological tissue and food; amino acids are examples of amines. The lower aliphatic amines are normal constituents of body tissues. They occur in a large number of foods, particularly fish, to which they impart a characteristic odour. Since the amines are bases and may form strongly alkaline solutions, they can be corrosive or irritating if splashed in the eye or if allowed to contaminate the skin. Amines are in general mostly non-mutagenic. However, one area of concern at present is the possibility that some aliphatic amines may react with nitrate or nitrite *in vivo* to form nitrosamines, many of which are known to be potent carcinogens in animals.

1.2. Update on the health effects of 4 previously evaluated amines

Monoethanolamine (MEA), piperazine, aminomethylpropanol (AMP) and methyldiethanolamine (MDEA) appear to be relevant compounds for the CO_2 capture$_e$. These amines were evaluated in a previous report (FHI rapport, 2009). In this current report, NIPH has included an overview of new information published after 2008 in addition to previously used key studies for the risk evaluation. For additional information and references regarding these four amines, consult the FHI Report (2009).

For several years MEA and piperazine have been used in various industries and consumer products, and these two compounds may thus represent a significant potential for human exposure. Therefore, a considerable number of experimental studies have been conducted over the years to understand the potential hazards of these two compounds. Piperazine has been subject to hazard classification and an EU risk assessment report (2005) has been compiled. Few studies of AMP and MDEA were available in the toxicology databases. In the FHI Report (2009) we evaluated the toxicity of the amines from single and repeated exposures, including their potential to cause mutations, tumours and birth defects. The toxicology data were compiled and critically reviewed. For each amine either the No Observed Adverse Effect Level (NOAEL)[1] or the Lowest Observed Adverse Effect Level (LOAEL) were indicated. Based on these data we suggested an exposure guideline for the general population for each of the amines. The need to revise these guidelines is discussed in the light of new experimental data retrieved in the literature update.

[1] Alternatively used: NOAEC - No Observed Adverse Effect Concentration

1.2.2. Monoethanolamine

Monoethanolamine (MEA) (CAS No. 141-43-5) is a liquid at room temperature. It is completely miscible with water, with a low volatility. The odour is ammonia-like with a threshold of 5-8 mg/m^3. MEA is a strong base (pH 12.05 of 0.1N aq. sol.), which readily forms salts with inorganic and organic acids. The substance is widely used in industry in the production of soaps and detergents, as a cleaning and cooling agent, as an ingredient in cosmetic formulations, in the synthesis of dyestuffs, in rubber accelerators, and for the removal of acidic gases from atmospheres, such as carbon dioxide from submarines.

Current EU classification

Xn; R20/21/22 (Harmful; Harmful by inhalation, in contact with skin and if swallowed) C; R34 (Corrosive, causes burns)

Health hazard characterisation

A study by Weeks *et al.* (1960), establishing a LOAEL of 12 mg/m^3 air for behavioural effects in rats seemed to be the best available basis for proposing an exposure limit for the population. The same study was also used when establishing the occupational exposure limit (The Norwegian Labour Inspection Authority 2007). Since this LOAEL value is based on an animal experiment, an uncertainty factor had to be used. The occupational exposure limit includes 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). Use of a LOAEL value instead of a NOAEL should affect the magnitude of the uncertainty factor by a factor of 3, but as the effects seen here were minimal, a factor of 2 is justified. Furthermore, use of a subacute instead of a chronic exposure should increase the uncertainty factor by a factor of 6. Alltogether, this infers an uncertainty factor of 1200. Therefore, we suggested that the general population, over time, should not be exposed to levels in the air higher than 10 µg/m^3 MEA.

Health effects of MEA, studies published after 2008

Lessmann *et al.* (2009) described skin sensitising properties of ethanolamines in their review article. Both data analysis of a multicentre surveillance network and a review of the literature are included in this review. One of the conclusions was that animal studies indicate a very low sensitisation potential of MEA. However, industrial use of MEA in water-based metalworking fluids is regarded as a cause of occupational sensitisation to this substance. A recent paper described occupational allergic contact dermatitis in a metal worker exposed for a long time to aqueous solutions of MEA (Arias Irigoyen & Garrido Burrero, 2011).

Inhalation of MEA through a tracheal cannula (aerosol of 3.3% MEA solution, 0.1 ml/kg bw), induced bronchoconstriction in guinea pigs (Kamijo *et al.* 2009). The authors suggested that asthma-like symptoms in humans observed after MEA aspiration into the lungs may result partly from effects of MEA on specific lung receptors (histamine H1- and muscarinic receptors). In addition, a subacute inhalation rat study (28 days) from 2010 was found as summary information (IUCLID 5, ECHAs list of Registrated Substances). In this study NOAEC values for local effects to 10 mg/m^3 of MEA and for systemic effects to 150 mg/m^3 were established.

Conclusion

These recent studies support previous data, and a new health hazard characterisation of MEA does not seem to be required. Therefore, we recommend that the general population, over time, should not be exposed to levels in the air higher than 10 µg/m^3 MEA.

1.2.3. Piperazine

Piperazine (CAS No. 110-85-0) is white or translucent, and occurs as rhomboid or flake-like crystals which are highly hygroscopic at room temperature. They form a white mass in water and the solution is highly basic. It is used in veterinary pharmaceuticals as anthelmintics, i.e. drugs for infections caused by parasitic worms. Formerly, piperazine was also used in human medicine. Other industrial uses are as hardener for pre-polymers for glue, in gas washer formulations, as an intermediate for urethane catalysts, and pharmaceuticals synthesis.

Current EU classification

Xn; R42/43 (Harmfull; May cause sensitisation by inhalation and skin contact) - C; R34 (Corrosive; Causes burns) - Repr. Cat. 3; R62-63 (Possible risk of impaired fertility/harm to the unborn child)

Health hazard characterisation

The data presented in FHI Report (2009) were based on information in the EU risk assessment report – Piperazine Final Report (2005). No relevant health effect data on piperazine were found in the literature search for 2005 - 2008.

For neurotoxicity, a LOAEL in healthy humans of 30 mg/kg bw/day piperazine base for a limited 3-7 days exposure was established. A NOAEL of 25 mg/kg bw/day has been determined for induction of mild hepatic toxicity in beagle dogs. Furthermore, a LOAEL of 8.6 mg/m^3 has been estimated for the induction of occupational asthma after inhalation of piperazine during an 8-hour work day exposure. No NOAEL can be estimated for respiratory sensitisation (asthma).

Exposure to piperazine and its salts has clearly been demonstrated to cause asthma in occupational settings. The estimated exposure from human inhalation studies of 8.6 mg/m^3 was used in the risk estimation. The study by Hagmar *et al.* (1982) showed occupational asthma measured at lower concentrations than the estimated exposure level described above. However, the exposure levels could only be roughly estimated and were therefore not considered in the risk evaluation.

For 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 subchronic to chronic of 2, were included. In addition, a correction factor for work exposure versus lifetime exposure of 2.8 was included. Since both neurotoxicity, mild hepatic toxicity and reproductive effects in human and animal studies were observed, we also included a factor of 10 for severe health effects (neurotoxicity). Taken together the uncertainty factor was 1680. Therefore, we suggested that the general population should not, over time, be exposed to higher levels than 5 µg/m^3 piperazine base.

Health effects of piperazine, studies published after 2008

No relevant studies of health effects of piperazine were found for this period. In recent years, a series of new drug classes, including piperazine, has appeared on the illicit drug market. They have gained popularity and notoriety as rave drugs. Therefore, much of the recent literature is on acute toxicity at very high doses.

Conclusion

These recent studies did not give any information relevant for the risk assessment of piperazine. Our previous suggestions with regard to human risk evaluation in 2009 are still valid. Therefore, we recommend that the general population should not, over time, be exposed to higher levels than 5 μg/m^3 piperazine base.

1.2.4. Aminomethylpropanol

Aminomethylpropanol (AMP) is known as isobutanolamine or 2-amino-2-methyl-1-propanol (CAS number 124-68-5). AMP is either a colourless liquid or a white crystalline solid. Since the melting point is slightly above room temperature AMP may also appear as a paste. In liquid form AMP has a slight amine-like odour, while in solid form it is odourless. AMP is miscible with water, soluble in alcohols, slightly soluble in aromatic hydrocarbons, and insoluble in aliphatic hydrocarbons (CIR 1990). The pKa for AMP is 9.7 at 25˚C (IUCLID 2000).

Current EU classification

Xi; R36/38 (Irritant; Irritating to eyes and skin).

Health hazard characterisation

For estimation of maximal exposure level for the general population, two 90-days studies were used. Both studies have limitations and neither is optimal. In the oral dog study, there are uncertainties of the dose administered, whereas in an inhalation study with monkeys, AMP was given in hair spray which may influence the effect of AMP.

In the 90-days inhalation study, monkeys were exposed one hour daily to 2.7 or 27 μg/l of hair spray containing 0.21% AMP (CIR 1990). Effects on the target organ (liver) were observed at both dose levels. The LOAEL was set at 2.7 μg hair spray/l which compares to 0.57 mg AMP/m^{3}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 subchronic study instead of a chronic study were included. This adds 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. We have also calculated a maximal exposure level based on a 90-days beagle dog feed study. Unfortunately this study was not published and it is incompletely referred to in the report (CIR 1990). However, the data indicate that if the maximal exposure level for the general population should be calculated based on the beagle dog study, the level would be higher than 6 μg/m^3.

Health effects of AMP, studies published after 2008

Literature search resulted in no new relevant data for risk assessment of AMP.

Conclusion

The previous conclusion and recommendations are still valid, implying that, over time, the general population should not be exposed to higher levels of AMP than 6 $\mu g/m^3$.

1.2.5. Methyldiethanolamine

Methyldiethanolamine (MDEA) (CAS number 105-59-9) is a liquid at room temperature with an ammonia-like odour. It is completely miscible with water and has a low volatility.

Current EU classification

Xi; R36 (Irritating to Eye)

Health hazard characterisation

Due to a lack of studies, a proper hazard evaluation cannot be performed at the present time. The former health risk evaluation of systemic toxicity (FHI rapport, 2009) was based on the toxic effects observed in a developmental study in which rats were exposed via the dermal route to MDEA during gestation days 6-15. Maternal toxicity was apparent as a mild anaemia in dams at the 750 and 1000 mg/kg bw dose groups; the NOAELs for maternal toxicity and embryofoetal toxicity and teratogenicity were estimated to be 250, and at or above 1000 mg/kg bw/day, respectively (Leung and Ballantyne, 1998). The NOAEL was converted to an internal dose assuming 17% dermal absorption and an uncertainty factor of 1000 was used to account for intra- and interspecies variations as well as for the extrapolation from a 7 day study to the chronic situation. A human inhalation volume of 25 m^3/24 hours was used and a suggestive maximum outdoor air level for MDEA of 120 $\mu g/m^3$ for the general population was derived.

Health effects of MDEA, studies published after 2008

In a literature search for new studies published between January 2009 and February 2011 no relevant studies about health effects of MDEA were found in the open literature. However, industry has submitted a registration dossier for MDEA to the European Chemicals Agency (ECHA). NIPH has evaluated the summary information available (IUCLID 5) for relevant new studies. One new toxicity study was identified, namely a reproductive toxicity study in rats (Reproduction/Developmental Toxicity Screening Test, OECD 421) performed in 2010. From this study, a systemic NOAEL of 100 mg/kg bw/day was reported, and a NOAEL of 300 mg/kg bw/day for both reproductive performance and fertility and for developmental toxicity was given. Normally females are dosed throughout the study (approximately 54 days) and the males for 4 weeks. The systemic NOAEL was based on reduced body weight in parental males and females.

Conclusion

The information reported in the recent oral reproduction/developmental toxicity screening study supports that the air concentration level of 120 µg/m^3, derived in the former NIPH evaluation report, is protective for systemic toxicity. A refined evaluation could not be performed since only summary data are provided in IUCLID 5.

1.3. Health effects of other relevant amines

The amines specified in Table 1 were selected by Klif. Due to the time limitations of this report, NIPH has only performed a screening of the health hazard information found in the literature for the amines not treated in the former chapter. The quality of the available studies has not been assessed and a hazard characterization has not been performed. However, the data below give an overview of relevant information available for a potential future risk assessment. The need for further evaluation will depend on whether the substances are actually emitted from the CO_2 capturing process.

Table 1: List of selected amines

Amines	CAS No.
MEA (monoethanolamine)	141-43-5
Piperazine	110-85-0
AMP (aminomethylpropanol)	124-68-5
MDEA (methyldiethanolamine)	105-59-9
Dimetylamine	124-40-3
Dietylamine	109-89-7
Dibutylamine	111-92-2
N-metylethanamine	624-78-2
N-methyl 1-butanamine	110-68-9
N-ethyl 1-butanamine	13360-63-9
Dipropylamine	142-84-7
DEA (Diethanolamine)	111-42-2
HEI (Hydroxyethylimidazole)	1615-14-1
HEF (Hydroxyethyl-formamide)	693-06-1
OZD (Oxazolidinone)	497-25-6
4,4-dimethyl-2-oxazolidinone	26654-39-7
2-methyl-2-(methylamino)-1-propanol	27646-80-6
Metylamine	74-89-5
Etylamine	75-04-7

1.3.2. Dimethylamine

Dimethylamine (DMA) (CAS No. 124-40-3) is a colourless gas (boiling point 6.8 °C) at room temperature with an ammonia or fish-like odour. Aqueous solutions of DMA are highly alkaline (pKa = 10.73), like ammonia. DMA forms explosive mixtures with air in the range between 2.8% and 14.4% by volume in air.

Current EU classification

Xn; R20/22 (Harmful; Harmful by inhalation and if swallowed) C; R34 (Corrosive; Causes burns)

Health hazard

DMA is a strong irritant to the eyes, skin, and mucous membranes. Exposure to vapours can give cloudy vision. In rats acute toxicity upon inhalation of DMA was observed at 4700 ppm (LC50) after 4 hour exposure (ACGIH 2006). An oral LD50 for rabbits was found at 240 mg/kg bw (Lewis 1996).

Repeated inhalation toxicity of DMA was investigated in Fisher 344 rats and B6C3F1 mice (175 ppm for 6 hours/day, 5 days/week, for 12 months). The animals showed significant lesions in the nasal passages (Buckley 1985). Rats developed more extensive olfactory lesions than mice. Olfactory sensory cells were highly sensitive to DMA. Even at a concentration of 10 ppm, the rodents developed minor lesions from exposure.

One study found DMA to be mutagenic in the Ames test of mutagenicity with liver metabolic activation (Green 1978). In another study, when DMA was tested using the Ames test under various conditions (varying the concentration, type of bacterial strain, degree of metabolic activation), no effect could be revealed (Zeiger *et al.*. 1987). A third study found that DMA had no mutagenic effect in the Ames test (Kilkichko *et al.* 1993), whereas sodium nitrite had a strong mutagenic effect in the same system.

DMA is found in human saliva, gastric juice, blood, urine and faeces (Tricker *et al.* 1992).

DMA can potentially react with nitrosating agents in the diet or within the body, producing the potent carcinogen *N*-nitrosodimethylamine (NDMA), which can then react with DNA (or other molecules) to form several adducts including 3-methyladenine (3-MeAde). One study (Fay *et al.* 1997) investigated whether consuming frozen fish containing very high DMA levels, with or without ingested nitrate, would result in elevated urinary 3-MeAde levels. However, no genetic damage was found as measured by the excreted urinary biomarker 3-MeAde.

Oral administration of the hydrochloride salt of DMA to pregnant Wistar rats showed no effect on offspring at any of the dose levels tested (100, 300 and 1000 mg/kg bw/day). The NOAEL for maternal toxicity was 300 mg/kg bw/day based on decreased food consumption and salivation observed in the high-dosed dams (1000 mg/kg bw/day). The NOAEL for prenatal developmental toxicity was 1000 mg/kg bw/day, because there was no evidence of an adverse effect of the test compound on foetal morphology (study report in IUCLID 5, ECHAs list of Registered Substances).

Conclusion

DMA exerts only moderate, acute toxicity, but is corrosive to eyes and skin. The olfactory sensory cells were highly sensitive to DMA. At higher doses of repeated inhalation exposure, rats showed significant lesions in nasal passages. No effect on reproduction and development was observed after dimethylamine exposure, however the data were limited.

1.3.3. Diethylamine

Diethylamine (CAS No. 109-89-7) is a primary amine. The compound exists as a colourless highly alkaline (pKa = 11.09) liquid (boiling point 55.5 °C) at room temperature with a fishy, ammonia-like odour. Diethylamine is soluble in water, alcohol, and most organic solvents. The vapours of diethylamine form explosive mixtures with air in the range between 1.8% and 10.1% by volume in air.

Diethylamine is used as a flotation agent; in dyes and pharmaceuticals, and in resins. It is also used in the rubber and petroleum industry.

Current EU classification

Xn; R20/21/22 (Harmful; Harmful by inhalation, in contact with skin and if swallowed) C; R35 (Corrosive; Causes severe burns).

Health hazard

The acute inhalation toxicity (LC50) of diethylamine to rat was 4000 ppm during 4 hour exposure time (Lewis 1996). An oral LD50 for mice was found at 500 mg/kg bw (ECB/IUCLID 2000).

Diethylamine is a strong irritant to the eyes, skin, and mucous membranes. Exposure to diethylamine vapours can give cloudy vision. Inhalation toxicity was investigated in a subchronic study with diethylamine vapour in rats (250 ppm for 6.5 h/day, 5 days/week, for 24 weeks). The animals developed sneezing, tearing, and reddened noses and lesions in the nasal mucosa (Lynch *et al.* 1986). Animals exposed to 25 ppm did not show any of these signs. In a 90-day inhalation study (OECD Guideline 413; Subchronic Inhalation Toxicity) with rat and mice exposed to 32, 62, or 125 ppm diethylamine showed significant exposure concentration-related decreases in sperm motility. No significant differences in the length of estrous cycles were observed. Read-across data were available for reproductive effects for dimethylamine hydrochloride, dibutylamine hydrochloride or tri-n-butylamine. In general there were no embryo- or fetotoxic effects except a slight and dose-related increase in foetal body weight gain, which was significant at the highest dose (ECHAs list of Registered Substances).

Diethylamine was evaluated for mutagenicity in the Salmonella/microsome pre-incubation assay (Ames test) under various conditions (varying the concentration, type of bacterial strain, degree of metabolic activation), the results were only negative (Zeiger *et al.* 1987). Male Fischer 344 rats exposed via gavage to 500 mg/kg bw diethylamine and sampled 12 hours later did not exhibit unscheduled DNA synthesis (UDS) in their kidney cells (Loury DJ *et al.*). No significant increases in the frequencies of micronucleated erythrocytes were seen in peripheral blood of male or female B6C3F1 mice from the 3-month study.

A human study with 7 healthy individuals (1 female and 6 males) aged 24 to 54 years, served as study subjects. Four participated in the 15-min experiment and another five in the 60-min experiment. All were none-smokers and none wore contact lenses. In the subjects, that were exposed to 25 ppm (75 mg/m^3) of the test substance for 15 min, neither changes in nasal volume, usually seen as acute nasal mucosa response to thermal stimuli was observed, nor acute change in nasal airway resistance. A moderate to strong olfactory response and distinct nasal and eye irritation were observed in subjects exposed to increasing concentrations from 0 to 12 ppm (average 10 ppm = 30 mg/m^3) for 60 min.

Conclusion

Diethylamine is only moderately acutely toxic, and corrosive to the eyes skin and mucous membranes. Based on the available literature, no indication of mutagenic or carcinogenic effects was found. There were significant exposure concentration-related decreases in sperm motility in exposed rats and mice. Based on read across data there were no observed effects on reproduction or development. In human subjects a moderate to strong olfactory response and distinct nasal and eye irritation were observed in subjects exposed to low concentrations of diethylamine.

1.3.4. Di-n-butylamine

Di-n-butylamine (CAS No. 111-92-2) is a colorless liquid with an ammonia-like odour.

Current EU classification

Xn, R20/21/22 (Harmful; Harmful by inhalation, in contact with skin and if swallowed).

Health hazard

Data presented in IUCLID 5 indicates that di-n-butylamine is a corrosive substance which is toxic upon inhalation (LC50 = 1.15 mg/l). An oral LD50 of 550 mg/kg bw confirms the current classification.

Potential toxic effects of di-n-butylamine on the respiratory tract were investigated in an inhalation exposure study by Buschmann and co-workers (2003). In rats, clear irritating effects in the upper part of the respiratory tract (nasal cavities) were reported. After 3 and 28 days effects were found only in the high-dose group (450 mg/m^3), but an increase in the incidence of mucous cell hyperplasia was reported also at the medium-dose (150 mg/m^3; 15 of 20 animals) and low-dose (50 mg/m^3; 2 of 20 animals) after 91 days of exposure. Body weight gain and food consumption were reduced in the treated animals.

Di-n-butylamine was judged to be non-mutagenic in an *in vitro* bacterial test and an *in vitro* mammalian cell gene mutation tests (IUCLID 5). The result from an *in vitro* mammalian chromosome aberration test was judged to be ambiguous (IUCLID 5). A mouse bone marrow micronucleus test was reported in IUCLID 5 and was found to be negative.

In a developmental toxicity study rats were fed di-n-butylamine hydrochloride (which is less corrosive than di-n-butylamine) by oral gavage during gestation days 6-19. According to the IUCLID 5 summary, the NOAEL for maternal toxicity was 15 mg/kg bw/day and the NOAEL for developmental toxicity was 150 mg/kg bw/day.

No guideline chronic toxicity and carcinogenicity studies with di-n-butylamine were found. However, several studies have investigated the *in vivo* potential of di-n-butylamine to form nitrosodibutylamine in the presence of nitrate and the preventive effects of dietary substances as e.g. soybeans (Tohamy *et al.* 1996; Fitzsimons *et al.* 1989; Medhat *et al.* 1991; Mokhtar *et al.* 1988; Airoldi *et al.* 1984). In the study by Tohamy *et al.* (1996) animals received di-n-butylamine in their drinking water (1000 ppm) in combination with sodium nitrate. Significant increases in chromosomal aberrations in bone marrow cells were observed after 3 months in animals administered a combination of di-n-butylamine and sodium nitrate. Furthermore, after 6 months, a mild to marked dysplasia with lymphocytic infiltration was observed in the liver in several animals.

Conclusion

Local irritation also seems to be a dominant health effect for di-n-butylamine. However, an oral study with di-n-butylamine hydrochloride suggests that systemic effects may be observed at levels warranting classification also for repeated dose toxicity.

1.3.5. N-methylethanamine

No relevant toxicological information was found for *N*-methylethanamine (CAS No. 624-78-2**)**.

1.3.6. N-*methyl 1-butanamine*

N-methyl 1-butanamine or butylmethylamine (CAS no 110-68-9) is a liquid with a boiling point at 91 ^{o}C. The compound is miscible with water. Its major use is as an intermediate.

Current EU classification

Not classified

Health hazard

N-methyl 1-butanamine is a skin and severe eye irritant. LD50 in rats after oral administration is reported to be 420 mg/kg bw (HSDB), indicating a relatively moderate, acute toxicity.

Conclusion

Similar to other amines, irritations of eyes, skin and airways seem to be the most affected organs upon *N*-methyl 1-butanamine exposure. Very little toxicity data of this compound was found.

1.3.7. N-ethyl 1-butanamine

N-ethyl 1-butanamine or butylethylamine (CAS no 13360-63-9) is a liquid with boiling point at 107.5 ^{o}C. *N*-ethyl 1-butanamine is soluble in water. Uses of this compound are not identified in the literature.

Current EU classification

Not classified

Health hazard

N-ethyl 1-butanamin is a severe eye irritant. The LD50 in rats after oral exposure is 390 mg/kg and LC50 in rats after inhalation is 500 ppm for 4 hours (HSDB), indicating relatively moderate acute toxicity.

Conclusion

Similar to other amines irritations of eyes, skin and airways seem to be the most affected organs upon *N*-ethyl 1-butanamine exposure. Very little toxicity data of this compound was found.

1.3.8. Dipropylamine

Dipropylamine (CAS no. 142-84-7) is a secondary aliphatic amine. The compound is a colourless liquid with a strong ammonia-like odour. It is very soluble in acetone, soluble in ethanol and gives an alkaline solution in water (pKa=11). Dipropylamine is used as a starting material for herbicide synthesis. As with other lower aliphatic amines dipropylamine is a normal constituent of body tissue.

Current EU classification

Xn; R20/21/22 (Harmful; Harmful by inhalation, in contact with skin and if swallowed) - C; R35 (Corrosive; Causes severe burns)

Health hazard

Since the amines are bases and may form strongly alkaline solutions, contact with skin and eyes causes severe irritation and also oedema of the cornea of the eyes. Inhalation of dipropylamine causes severe coughing and chest pain due to irritation of the airways. The compound can cause lung oedema, and also headache, nausea, faintness, and anxiety. Ingestion causes irritation and burning of mouth and stomach (HSDB).

The acute oral toxicity of dipropylamine is similar to that of the other primary and secondary aliphatic amines, and the compound is classified as harmful to health (oral LD50 rats: 460-930 mg/kg). After neutralisation to salts, the toxicity diminishes significantly. This favours the assumption that the acute toxicity is associated mainly with the pronounced alkaline property of the substance, causing irritation (Greim *et al.* 1998).

Conclusion

Similar to other amines, irritations of eyes, skin and airways seem to be the most significant organ effects upon dipropylamine exposure. The toxicity of this compound appears to be related to the irritative effects.

1.3.9. Diethanolamine

Diethanolamine (DEA) (CAS no 111-42-2) is a secondary amine. The compound is in the form of colourless crystals or a syrupy, white liquid (melting point 28^{o} C) with mild, ammonia-like odour. The compound is very soluble with alcohol and miscible with water. DEA is used as surfactants, gas purification and in textile processing. In contrast to MEA, DEA does not occur naturally in animal phospholipids. However, at high concentrations, DEA may substitute for MEA in the phospholipids (Knaak *et al.* 1997).

Current EU classification

Not classified

Health hazard

The acute toxicity (LD50) of DEA after oral administration to rats is 1.82 g/kg bw, indicating that the compound has relatively low toxicity. The compound causes slight irritation to skin and mucous membranes and is moderately irritating to eyes. DEA is not sensitising according to animal studies. However, in humans a sensitisation risk may not be excluded at present (Lessmann *et al.* 2009).

DEA has been thoroughly evaluated for mutagenicity, but has been shown to be negative in a number of bacterial and mammalian cell assays (Knaak *et al.* 1997). Also the potential of DEA to cause chromosomal damage has been extensively evaluated, and the results of the tests seem to be uniformly negative. While purified DEA has been shown to lack genotoxic potential, it is important to note that, like secondary amines, it may react chemically with nitrosating compounds to form a nitrosamine, in this case *N*-nitrosodiethanolamine (NDELA).

After dermal application to mice DEA induced increased incidences of tumours in liver and kidney (U.S. DHHS, 2002). However, DEA was not carcinogenic in rats or in a transgenic mouse strain. Potential mechanisms of DEA-induced carcinogenicity in the mouse include its

conversion to the carcinogenic nitrosamine NDELA, as described above. However, it is questionable whether the metabolite NDELA explains the hepatocarcinogenicity observed in these mice. The second proposed mechanism involves the displacement of ethanolamine by DEA in phospholipids, an effect which may result in a reduced endogenous production of choline. Observations on the effects of DEA on choline metabolism support the proposal that DEA-induced hepatocarcinogenesis may be related to choline deficiency (U.S. DHHS, 2002)

Dietary intake of DEA by rats at levels higher than 90 mg/kg bw/ day (for 13 weeks) resulted in degenerative changes in kidneys and liver. DEA seems not to be teratogenic, but was maternal- and foetotoxic in a range-finding developmental toxicity study at dose levels of 200 mg/kg and above (Knaak *et al.* 1997). In a 90-day inhalation study (through nose only), rats were exposed to 0, 15, 150, 400 mg/m^3 DEA. Systemic toxicity was observed at or above 150 mg/m^3 (Gamer *et al.* 2008). A head-nose exposure of rats to DEA for 6 hours per working day for about 3 months (65 exposures) at the lower concentrations (1.5, 3 and 8 mg/m^3) was performed in 2002 (IUCLID 5). Exposure to 8 mg/m^3 led to upper respiratory tract irritation accompanied by some inflammatory cell infiltration. The findings were considered to represent a borderline adverse effect and were fully reversible within the 3-month recovery period. No changes were observed in the nasal cavity or the lower respiratory tract at this concentration. The NOAEC was found to be 3 mg/m^3.

The acute toxicity of DEA in humans is low and the estimated fatal amount is 20 g (HSDB). The skin, kidneys and liver are reported to be the most sensitive target tissues. However, limited respiratory data are available for DEA.

Conclusion

Similar to other amines, irritations of eyes, skin and airways seem to be important health effects of DEA. However, DEA is less irritating than the monoalkanolamine, MEA. On the other hand, DEA is slightly more acutely toxic than MEA (oral LD50 1.82 g/kg vs 2.74 g/kg, respectively). The tumours observed in the mice after DEA administration, and the fact that DEA seems not to be genotoxic, might indicate a possible non-genotoxic mechanism of carcinogenicity.

1.3.10.Hydroxyethylimidazole

No data were identified for the compound hydroxyethylimidazole (HEI) (CAS no. 1615-14-1) in the current search (data on the related compound Hydroxy*m*ethylimidazole were found, however).

1.3.11. Hydroxyethyl-formamide

No health related data was found for hydroxyethyl-formamide (HEF) (CAS no 693-06-1).

1.3.12. Oxazolidine

No health related data were found for oxazolidine (OZD) (CAS no 504-76-7).

1.3.13. 4, 4-dimethyl-2-oxazolidinone

No health related data was found for 4,4-dimethyl-2-oxazolidinone. Data were identified for the compound *3-chloro*-4,4-dimethyl-2-oxazolidinone; this compound has been used as a disinfectant.

1.3.14. 2-methyl-2-(methylamino)-1-propanol

No health related data were found for 2-methyl-2-(methylamino)-1-propanol.

1.3.15. Methylamine

Methylamine (CAS No. 74-89-5) is a primary aliphatic amine existing as a colourless gas (boiling point -6.3 °C) at room temperature with strong ammonia-like odour (at low concentrations it has a fishy odour). Aqueous solutions of methylamine are highly alkaline (pKa = 10.66). Methylamine forms explosive mixtures with air. Methylamine is soluble in water, ethanol, diethyl ether, acetone, and benzene.

Current EU classification

Xn; R20/22 (Harmful; Harmful by inhalation and if swallowed) C; R34 (Corrosive; Causes burns).

Health hazard

The acute inhalation toxicities (LC50) of methylamine to rats were 2.9 mg/l during 4 hours exposure time (ECB/IUCLID 2000). Oral LD50 for rats was 80 mg/kg bw (ECB/IUCLID 2000). Methylamine has corrosive effects on eyes, skin and respiratory tract.

Inhalation toxicity of methylamine was investigated in rats (nose-only inhalation 6 hours/day, 5 days/week for 2 weeks). Exposure to 75 ppm caused mild nasal irritation whereas 250 ppm produced damage to respiratory mucosa of the nasal turbinates. Exposure to 750 ppm produced severe body weight loss, liver damage, and nasal degenerative changes (Kinney *et al.* 1990).

When tested in mouse lymphoma cells, one study found methylamine to be mutagenic at a high concentration (3 mM) (Caspary WJ and Myhr B 1986). When methylamine was tested in the Ames test for mutagenicity under various conditions (varying concentration, type of bacterial strain, degree of metabolic activation), all results were negative (Mortelmans *et al.* 1986).

Methylamine produced neither maternal nor foetal toxicity when the female mice were given the doses 0.3, 1, and 3 mmol/kg on day 8 of gestation (ECB/IUCLID 2000). Using pregnant CD-1 mice and mouse embryo culture as experimental models, possible developmental toxicity was examined. Intraperitoneal injections (daily from d 1 to 17 of gestation) of 2.5 and 5 mmol/kg/day did not cause any obvious maternal or foetal effects. However, when added to embryos in culture methylamine caused dose-dependent decreases in their size, and in DNA, RNA, and protein content, as well as reduced embryo survival. The ability of methylamines to adversely affect foetal development suggests that methylamine may act as endogenous teratogens under certain conditions (Guest and Varma, 1991).

In addition, one study report from 2007 with methylamine hydrochloride was identified in the list of Registered Substances. The study was performed according to OECD Guideline 422: Combined Repeated Dose Toxicity Study with the Reproduction /Developmental Toxicity Screening Test. In this study male and female rats were daily administrated 0, 250, 500, or 1000 mg/kg/day methylamine hydrochloride. Increased liver weights were observed in males (≥250 mg/kg/day) and females (≥500 mg/kg/day) and kidney weights in both sexes (1000 mg/kg/day). These findings were considered to be non-adverse. The no-observed-effect level (NOEL) for systemic and reproductive toxicity in this study was 500 mg/kg/day based on reductions in parental body weights and food consumption and effects on reproductive outcome (study report in IUCLID 5, ECHAs list of Registered Substances).

Conclusion

Methylamine causes acute toxic and corrosive effects. In an inhalation study the compound caused nasal irritation at lower doses, whereas higher doses induced body weight loss, liver damage and nasal degenerative changes. In an OECD guideline study (422) with methylamine hydrochloride the NOEL for systemic and reproductive toxicity was 500 mg/kg bw/day.

1.3.16. Ethylamine

Ethylamine (CAS No. 75-04-7) is a primary amine, existing as a gas (boiling point 16.6 °C) at room temperature with an ammonia odour. Aqueous solutions of ethylamine are highly alkaline (pKa = 10.87). Ethylamine forms explosive mixtures with air in the range 3.5-14.0% by volume in air.

Current EU classification

T; R24 (Toxic; Toxic in contact with skin), Xn; R22 (Harmful; Harmful if swallowed), C; R35 (Corrosive; Causes severe burns), Xi; R37 (Irritant; Irritating to respiratory system).

Health hazard

In rats, acute toxicity upon inhalation of methylamine was observed at 12.6 mg/l (LC50) after 4 hour exposure (ECB/IUCLID 2000). An oral LD50 for rats was found at 400 mg/kg bw (Lewis 1996).

Rabbits exposed to 100 ppm ethylamine for 7 hours/day, 5 days/week for 6 weeks exhibited irritation of cornea and lung, and liver and kidney damage (ACGIH 1986). A 4-hour exposure to 3000 ppm was lethal to rats.

When ethylamine was tested in the Ames test for mutagenicity under various conditions (varying concentration, type of bacterial strain, degree of metabolic activation), all results were negative (Mortelmans *et al.* 1986).

Conclusion

Ethylamine is acutely toxic and an irritant to the eyes and lung. In addition, liver and kidney damage has been observed. Based on available literature, there were no indications of mutagenic effects. No data on reproductive effects of ethylamine were found.

1.4. Conclusions for amines

NIPH published a report in 2009 with health hazard characterisations of the amines, monoethanolamine (MEA), piperazine, aminomethylpropanol (AMP) and methyldiethanolamine (MDEA). In the present report we have updated the information on these four amines with studies published after 2008. For MEA and MDEA a few new studies were identified. However, the new studies did not warrant a revision of the previously performed risk assessment of the four amines.

In addition, NIPH has evaluated data on the toxicity of other selected amines, relevant for CO_2 capture. We have searched for information in several toxicological databases including ToxNet, Pubmed, INCHEM, HSDB, EPA-IRIS, ECHAs list of Registered Substances. The information on toxicity available for the various amines was highly variable. For a few of the compounds, there is sufficient data to justify a health risk assessment. For most of them, however, there was very limited data, and a quantitative evaluation of their health risk could not be carried out.

2. Nitrosamines and nitramines

2.2. Tolerable risk levels for cancer in the general population

The purpose of this evaluation is to provide an estimation of an exposure level (in air and water) of nitrosamines with minimal or negligible health risk. This level depends on the risk of acquiring disease associated with a dose level. Establishing an acceptable risk level is a public health policy issue and is often related to other comparable health risks in our society. The WHO drinking water quality guidelines for genotoxic carcinogens consider that a lifetime cancer risk for consumers of less than 10^{-5} represents a so-called tolerable risk. In connection with the EU Air Quality Directive and the EU Drinking Water Directive a 10^{-6} lifetime risk is used as a starting point for the derivation of limit values for the general population. In the USA, risks lower than 10^{-6} are in general considered acceptable for the general population. The REACH Guidance Document (R8) states that cancer risk levels of 10^{-5} and 10^{-6}could be seen as indicative of tolerable risks levels when setting derived minimal effect levels (DMELs) for workers and the general population, respectively. In summary, the cancer risk decision points used for *lifetime* exposure of the general population are generally in the range of 10^{-5} to 10^{-6}.

In this evaluation NIPH has calculated the concentrations of nitrosamines in air and water, associated with risks in the range 10^{-5} – 10^{-6}. This means that lifelong exposure at the indicated levels would give an excess lifelong risk of acquiring cancer of either 10 (10^{-5}) or 1 (10^{-6}) in a million. A risk of one in a million is considered negligible. A risk of 10 in a million is considered as minimal; however, measures to reduce it should be considered.

2.3. Evaluation of cancer risk from exposure to nitrosamines

Nitrosamines, (R1)(R2) N-N=O, represent a large and diverse family of synthetic and naturally occurring compounds. Approximately 90% of the 300 nitrosamines tested have shown carcinogenic effects in bioassays and laboratory animals. Among these, *N*-Nitrosodimethylamine (NDMA) has been most thoroughly studied. NDMA has been shown to be a potent mutagen and carcinogen (FHI rapport, 2009). Due to their potent carcinogenicity, other health outcomes of these compounds have been given less emphasis and are therefore less well documented.

2.3.2. Previous estimates of the carcinogenic risk of NDMA in drinking water

NDMA (CASRN 62-75-9) is carcinogenic in all animal species tested. The compound induces tumours following administration by various routes including ingestion and inhalation. The tumours are found mainly in the liver, kidney and respiratory tract. In several studies dose-response relationships have been established.

A particularly extensive study performed by Peto *et al.* (1991a; 1991b) has been used in several risk evaluations. This study is presented in more detail in Appendix 1. In brief, rats were exposed to NDMA in drinking water. Sixteen dose-groups were observed from week 6 until natural death allowing analysis of treatment effects that would not have been seen in a standard 2-years chronic exposure study. Analyses of different types of liver tumours were performed. An approximate linearity of the dose-response curve was suggested in the low dose area, whereas a cubic relationship was observed within the higher range of doses. Females were found to be the most sensitive sex and the bile duct was the most sensitive target site for tumour development. Consequently, the risk estimates presented below are based on data of bile duct

tumours in female rats. A linear extrapolation from experimental doses to concentrations associated with excess cancer risk of 10^{-5} or below is considered to give a conservative risk estimate.

The data from the Peto study have been used by WHO (2008), Health Canada (draft 2010), US EPA (1986), and California EPA (2006) to evaluate the human cancer risk due to exposure to NDMA in drinking water. In addition, US EPA has estimated the risk for developing cancer via inhalation exposure.

Table 2: Human cancer risk estimate of NDMA in drinking water

	Risk level	WHO[a]	Health[a, b] Canada	US EPA[a]	CalEPA[a,c]
Drinking water (µg/l)	10^{-5} 10^{-6}	0.1	0.04 0.004	0.007 0.0007	0.003

[a] Based on Peto *et al.,* (1991a; 1991b)

[b] The document is only a draft

[c] Public Health goal. This is not an official value. For US official risk estimates are given by EPA

The WHO evaluation of carcinogenic effects caused by NDMA in drinking water was prepared by the Canadian Health and Environmental Authorities (CICAD 2002). Hence, the Canadian (draft) and the WHO risk estimates are based on a similar dose-response model. In both reports the dose (TDL05[2]) giving a 5% increase in bile duct tumour incidence in female rats was calculated (Appendix 1). The two evaluations differ in the choice of assessment factors (interspecies extrapolation). WHO has not used any factor, unlike Health Canada, making the Canadian proposal the most conservative (Table 2). CalEPA determined the dose descriptor TDL10[3] for the induction of tumours in the bile duct in female rats. An interspecies assessment factor was included (as for the Canadian proposal). US EPA has estimated the carcinogenic risks from oral and inhalation exposure of NDMA. NIPH had only access to the IRIS summary report of this evaluation and details of the estimations are therefore not known to us.

2.3.3. Risk estimates of exposure to NDMA in air

The study by Peto *et al.* (1991a; 1991b), is by far the most suitable study for the evaluation of dose-response relationship from exposure to NDMA. The animals were exposed via drinking water only, but the dose-response values can be converted into corresponding air concentrations. However, such a route-to-route extrapolation introduces an extra uncertainty in the case of significant first-pass effects or site of entry effects that must be addressed. NIPH has therefore calculated two risk estimates for inhalation exposure; one based on the drinking water study by Peto *et al.* (1991) and another based on the best suited inhalation study available (Klein *et al.*, 1991). Both procedures are presented in the following.

[2] TDLx = lower 95%-value of the TDx. A TDx is defined as the lowest lifetime daily dose (in mg/kg bw) able to induce a statistically significant increase in tumour incidence of x% in the experimental animals. This response value is derived by fitting quantitative information available from all dose levels using a multistage model. Using the TDLx value instead of TDx is a more conservative approach.

Calculation of air concentrations based on the drinking water study

The Peto study has unusually many dose groups enabling dose-response modelling. WHO/Canada and CalEPA used linearised multistage models to calculate the dose-descriptors TDL05 and TDL10, respectively, followed by a linear extrapolation to define 10^{-5} and 10^{-6} risk levels[3]. NIPH has calculated the air concentrations (*italics* in Table 3) corresponding to risk levels of 10^{-5} and 10^{-6} based on the TDL05/10 values determined by WHO/Canada and CalEPA (cfr calculations in Appendix 1). The resulting risk estimates for these two evaluations are very similar when converted to air concentrations (Table 3). In contrast, the US EPA has estimated an approximately 4 times higher risk than WHO/Canada and CalEPA.

Calculation of risk estimates using the dose-descriptor T25[4]

Due to variations in existing risk estimates, NIPH has determined risk level based on a calculation of T25 as the dose descriptor (Dybing *et al.* 1997) and a linear extrapolation to 10^{-5} and 10^{-6} risk levels (Appendix 1). The estimated risks based on TDL05 (WHO/Canada), TDL10 (CalEPA) and T25 (NIPH) are compared in Table 3. The comparison shows that the T25 procedure gives a risk estimate approximately similar to the estimates by WHO/Canada and CalEPA. The slight difference can be explained by the extra safety factor provided in the latter evaluations by the use of the TDL instead of TD-values. The US EPA risk estimate seems conservative based on the available data.

Table 3: Concentrations of NDMA in air, recalculated from the dose descriptors TDLx and T25 by NIPH (italics). Final air concentrations are given for two different risk levels (10^{-5} and 10^{-6})

	Risk level	WHO[a]	Canada[a]	US EPA[a]	CalEPA[a,b]	NIPH[a]
TDL_x (rat) µg/kg bw/day		TDL_{05} 18	TDL_{05} 18		TDL_{10} 32	T_{25} 150
Intake[c] (rat) µg/kg bw/day	10^{-6}	0.00036	0.00036		0.00032	0.0006
Air concentration (µg/m^3)[d]	10^{-5} 10^{-6}	***0.00313*** ***0.000313***	***0.00313*** ***0.000313***	**0.0007** **0.00007**	***0.00278*** ***0.000278***	**0.0052** **0.00052**

[a]Based on Peto *et al.,* (1991a; 1991b)

[b]Public Health goal. This is not an official guideline value. For US the official guideline value is given by EPA

[c]Calculated from the TDL-values

[d]NIPH has recalculated the air concentration from the drinking water data of Peto *et al.* (1991a; 1991b), according to REACH guidance document R8 (italics). The US EPA air values are from their documents.

Choice of dose descriptor for calculation of risk estimates

According to the REACH Guidance document (REACH, Chapter R8) the T25 should be used as a default dose-descriptor unless the dose-response curve is clearly sub- or supralinear. It has been found that when risk assessments are carried out based on the same data sets, only in very few cases the dose calculated by the T25 method results in a value more than double or less than

[3] Risk level: E.g. 10^{-6}: The concentration producing an excess lifetime cancer risk of one extra case, in a population of one million.

[4] T25 = The chronic dose rate, in mg per kg body weight per day, which will give 25% of the animals tumours at a specific tissue site, after correction for spontaneous incidence, within the standard life time of that species. It is a value calculated from a single observed dose-response and is based upon the assumption of a linear dose-response relationship over the entire dose-range.

half of that calculated with dose-response modelling methods (REACH, R8; Sanner *et al.,* 2001). The T25 value gives a somewhat less conservative risk estimate than the ones based on TDL05 and TDL10, due to the extra safety implied by using the TDL instead of the TD-values as mentioned above. Furthermore, the TDL-values make use of the multidose design of the carcinogenic study in contrast to T25, which is based on one dose-level. In the opinion of NIPH it is reasonable to use the TDL-values calculated by WHO /Canada/CalEPA as the basis for estimation of the health risk associated with exposure to a certain concentration of NDMA. The reason for the conservative risk estimates of the US EPA is not known to us, but may be related to a different dose-response modelling and/or by use of different assessment factors and default values (see below).

Calculation of air concentrations based on the inhalation studies

As described above, the exposure medium of NDMA in the study by Peto and coworkers (1991a; 1991b) was drinking water. However, there may be differences in response depending on the route of exposure. Therefore, we have searched for studies addressing carcinogenicity of NDMA after inhalation exposure. Only a few studies are available.

Following administration of NDMA to mice by inhalation (0.005 or 0.2 mg/m^3 for 17 months) or to rats (0.005 or 0.2 mg/m^3 for 25 months), tumours were induced by the highest concentration in the lung, liver, and kidney (Moiseev and Benemansky, 1975 as reported in IARC, 1978). Furthermore, marked increases in tumours of the nasal cavity were observed in female rats administered NDMA by inhalation (Klein *et al.,* 1991). In the latter study, four groups of 36 animals were exposed to 0, 0.04, 0.2 or 1.0 ppm (corresponding to 0, 120, 600 and 3000 µg/m^3 air, respectively), four times a week, 4-5 hours a day for up to 207 days and tumour incidences were recorded. Median age at sacrifice was above 2 years in all but the highest exposure groups. The incidences of nasal tumours (all types) were 0%, 36% and 86% at the 0 µg/m3, 120 µg/m^3 and 600 µg/m^3 concentrations, respectively. In the 120 µg/m^3 and 600 µg/m^3 exposure groups two cases of hepatocellular carcinomas were reported. Tumours of the nasal cavity were also observed in an earlier study by Druckrey in 1967. In that study nasal tumours were found in 4 out of 6 BD rats exposed by inhalation to NDMA twice weekly at a concentration which resulted in a dose equivalent to 4 mg/kg, and 8 of 12 rats at half that concentration (Druckrey, 1967 as reported in IARC, 1978).

The inhalation studies confirm the liver as a target organ in addition to tumours at the primary sites of exposure in the lung and in particular the nasal cavity. The study by Klein *et al.* (1991) showed induction of tumours in the nasal cavity and was used by a Dutch expert committee (1999) in an evaluation of occupational cancer risk. A marked increase in nasal tumours at the lowest of the exposure concentrations was reported. The study by Klein and coworkers is important since it confirms that NDMA is a potent carcinogen by the inhalatory route. The information provided in the report is, however, limited and the exposure duration was only approximately 25% of lifetime exposure making it less useful than the Peto study for evaluation of dose-response relationships. Furthermore, there are uncertainties related to the actual exposure regimen and the lifetime of the animals seems to vary greatly (between 5 and 39 months), partly unrelated to the exposure. However, this study involves large study groups and is the best study available for inhalation exposure. NIPH has used the “large assessment factor” approach (Appendix 2) as described in REACH (guidance R8) to establish a derived minimal effect level (DMEL) that can be compared with the risk estimates based on the study by Peto *et al.* (1991). This comparison indicates a higher tumour risk from inhalation than from drinking water exposure. However, based on this inhalation study an exposure level of 0.0003 µg/m^3 or below will be sufficient to obtain a maximal lifetime excess cancer risk below 10^{-5}.

2.3.4. Inter- and intraspecies differences (assessment factors)

Usually, and in accordance with REACH guidance (R8), only an assessment factor for toxicokinetic differences between species should be applied for systemic non-threshold effects such as interactions with DNA, which is suspected to be the mechanism for carcinogenic effects of nitrosamines. Allometric scaling, correction for physiological differences in metabolic rate, is hence often used. When calculating the air concentration values given in Table 3, a factor for interspecies difference in metabolic rate is included in the equation for conversion of oral dose into air concentration (see Appendix 1).

In contrast to threshold effects as a default, there will be no assessment factor to account for remaining uncertainties i.e. intraspecies differences (in the absence of substance-specific information). The reason for this is that the linear model used for high-to-low dose extrapolation, which is more than four orders of magnitude, is considered sufficiently conservative to account for differences in human sensitivity. Based on our current knowledge, no further assessment factors are proposed by NIPH.

2.3.5. Excess lifetime cancer risk for exposure to drinking water and air suggested by NIPH

NIPH recommends using the dose-response modelling performed by WHO/Health Canada based on the study by Peto *et al.* 1991 followed by linear extrapolation to tolerable exposure levels. To perform the risk estimates in drinking water we suggest including an assessment factor for interspecies extrapolation and thus the proposal by Health Canada is recommended (Table 4).

NIPH suggests the use of the study by Peto *et al.* for estimating risk also from exposure via air. However, the estimated minimal effect level (DMEL) based on the inhalation study by Klein *et al.* (1991) indicates that there is a higher tumour risk from inhalation exposure than from oral exposure. Taken together, this result strongly supports 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.

Table 4: Recommended tolerable drinking water and air concentrations of NDMA

Drinking water (µg/l)	Air concentration (µg/m^3)
0.04[a] - 0.004[b]	0.0003[c]

[a]Risk level 10^{-5}
[b]Risk level 10^{-6}
[c]Risk level *below* 10^{-5}

2.3.6. Comparison of potency of different nitrosamines

NDMA is not the only nitrosamine generated and possibly emitted during CO_2 capture with amines. In Table 5 we have ranged different nitrosamines based on their oral cancer slope factor (CSF)[5] as reported by US EPA (1999). This gives an indication of the relative carcinogenic

[5] Oral Cancer Slope Factor (CSF): An upper bound, approximating a 95% confidence limit, on the increased cancer risk from a lifetime oral exposure to an agent. This estimate, usually expressed in units of proportion (of a population) affected per mg/kg-day, is generally reserved for use in the low-dose region of the dose-response relationship, that is, for exposures corresponding to risks less than 1 in 100.

potencies of these nitrosamines. The CSFs depend on the dose-responses in the studies available and also vary between studies.

Table 5: Relative carcinogenic potencies of different nitrosamines

Substance	CAS No	Oral CSF* (mg/kg bw/day)$^{-1}$
N-Nitrosodiethanolamine	1116-54-7	2.8
N-Nitrosodi-n-butylamine	924-16-3	5.4
N-Nitrosomorpholine	59-89-2	-
N-Nitroso-di-n-propylamine	621-64-7	7
N-Nitrosomethylethylamine	10595-95-6	22
N-Nitrosopiperidine	100-75-4	37.5
N-Nitrosodimethylamine	62-75-9	51
N-Nitrosodiethylamine	55-18-5	150

*Intigrated Risk Information System EPA

Table 5 shows that the various nitrosamines have different abilities to induce cancer with *N*-Nitrosodiethylamine (NDEA) being the most potent. The other nitrosamines are, however, less potent than NDMA. US EPA had not derived CSF for *N*-Nitrosomorpholine, but a unit risk factor was given. A comparison of the unit risk factors for these nitrosamines showed that the carcinogenicity potency of *N*-Nitrosomorpholine seemed to be among the nitrosamines with lowest potency.

The oral CSF for NDMA is 51 and the T25 is 0.15 mg/kg bw/day (Table 3). According to the "Setting of Specific Concentration Limits for Carcinogens" (Annex I of Directive 67/548/EEC), carcinogens of high potency are those with a T25 value < 1 mg/kg bw/day. Based on a rough evaluation, more than half of the nitrosamines in Table 5 has a T25 value lower than 1 and should be characterised as carcinogens of high potency.

2.3.7. Conclusions for nitrosamines

To derive cancer risk estimates for exposure to NDMA in both drinking water and air we recommend that the dose-response modelling performed by WHO/Health Canada based on the extensive drinking water study (Peto *et al.* 1991) is used. A linear extrapolation to low dose exposure is performed. The resulting estimates should be used as a basis for evaluating the human health risk. Based on these considerations a negligible risk level for cancer of 1 to 10^{-6} after lifelong exposure is associated with an air concentration of 0.3 ng/m^3. Although the drinking water study is best suited for dose-response evaluation, the inhalation study by Klein *et al.* suggests that NDMA is more potent by the inhalation route than by oral exposure. NIPH has therefore estimated a Derived Minimal Effect Level (DMEL) for the inhalatory route based on the study by Klein *et al.* This DMEL is slightly above 0.3 ng/m^3 and it refers to a maximal excess lifetime cancer risk of 10^{-5}. Based on an evaluation of both the drinking water study by Peto *et al.* and the inhalation study by Klein *et al.,* NIPH recommends the use of 0.3 ng/m^3 as a tolerable air concentration. This NDMA concentration is associated with a maximal excess lifetime cancer risk *below* 10^{-5}.

Based on these considerations, an air quality guideline could be established; with the available information this level might be set at 0.3 ng/m^3. The activity to establish a final air quality

guideline is still ongoing and a recommendation will ultimately be included in Klif/NIPHs upcoming report on air quality guidelines, which will be completed later in 2011.

Furthermore, since NDMA belongs to the most potent nitrosamines, we suggest that the risk estimates for NDMA can be used also for other nitrosamines. A refined risk evaluation taking into account differences in cancer potencies should be performed if the total nitrosamine level exceeds the above suggested level for NDMA exposure. If NDEA constitutes a large part of the nitrosamines, higher risks may emerge, and this will then necessitate a revised risk evaluation.

2.4. Evaluation of cancer risk from exposure to nitramines

N-nitramines can be formed in the atmosphere when secondary amines react with NO_2. In general, the nitramines are more stable than the nitrosamines and thus the potential for exposure is likely to be higher.

There are only a few studies on health effects of aliphatic nitramines. A general discussion of available data is presented in the NIPH report (FHI rapport, 2009). *N*-nitramines are structurally related to *N*-nitrosamines, which are potent carcinogens. Due to this similarity there has been a general interest in the potential mutagenicity and carcinogenicity of the nitramines. Other important health endpoints have not been addressed. Thus, the following presentation focuses on data related to the potential carcinogenicity of aliphatic nitramines. A few carcinogenicity studies are available, most of which concern *N*-nitrodimethylamine. These studies generally do not satisfy the standards of present carcinogenicity testing as they are either small, have too few doses and/or they are of too short duration and the available study documentation is limited. However, based on these studies and the data present in the carcinogenic potency database (CPDB) it is possible to achieve a rough estimation of the carcinogenic potencies of the two nitramines, *N*-nitrodimethylamine and *N*-nitromethylamine. Caution must be used in the evaluation of health risk from nitramine exposure as there are important data gaps and uncertainties in the available toxicity data.

2.4.2. Mutagenicity

Several of the aliphatic *N*-nitramines or their metabolites have been found to be mutagenic in bacterial assays (Khudoley *et al.* 1981; Frei *et al.* 1984; Suzuki *et al.* 1985). Furthermore, *N*-nitromethylamine and *N*-nitroethylamine, but not *N*-nitrodimethylamine were shown to induce DNA single strand breaks in primary rat hepatocytes *in vitro* (Frei *et al.* 1986). The mutagenic activities of the *N*-nitramines seem in general to be considerably lower than those of the corresponding nitrosamines and are highly dependent on the bacterial assay used. More studies are needed to adequately define the mutagenic potencies of different nitramines.

2.4.3. Carcinogenicity

Several studies show that some of the nitramines are indeed carcinogenic to rats (Druckrey *et al.*, 1967; Goodall and Kennedy, 1976; Mirvish *et al.,* 1980, Pliss 1982 *et al.*, Hassel *et al,*, 1987, Scherf *et al.,* 1989). Both the nitrosamine metabolite and formaldehyde are among the metabolites proposed as possible mediators of the carcinogenic effect of *N*-nitrodimethylamine, but the mechanism of *N*-nitramine carcinogenicity is still unclear.

In a lifetime study of mice and rats with *N*-nitrodimethylamine administered via the drinking water, tumours were induced predominantly in the liver and kidney (Goodall and Kennedy, 1976). Rats (10 males and 10 females) were exposed to approximately 5 mg/kg bw/day via the drinking water from 35 days of age, for one year, and thereafter given drinking water only (total dose, 1.83 g/kg bw). Mice (10 males and 10 females) were exposed by repeated subcutaneous

injection from birth to 7 months of age followed by administration in drinking water. Liver tumours (hepatocellular carcinomas) were observed in 85% of the rats. Mice developed predominantly hepatocellular carcinomas and renal adenocarcinomas. Statistically significant increases of other tumour types also occurred in mice. The morphology of the liver tumours after *N*-nitrodimethylamine treatment was said to contrast with that often described after treatment with the nitrosamine NDMA (Goodall and Kennedy 1976) suggesting that the nitramine carcinogenicity is not solely mediated through formation of the nitroso metabolite.

Misvish *et al.* (1980) exposed rats to large doses of *N*-nitrodimethylamine, *N*-nitroso-L-proline, and sodium nitrite in the drinking water for one year or more, and the rats were maintained for life. *N*-Nitrodimethylamine (total dose, 20 g/kg bw) was reported to produce liver tumours in 25 of 36 male rats and nasal cavity tumours (predominantly adenocarsinomas) in 9 of 36 of male rats. The liver tumours were of various types (hepatocellular carcinomas, cholangiosarcomas, hemangioendotheliomas, hemangiosarcomas and cholangiomas).

Two studies compared the carcinogenicity of several *N*-nitroalkylamines. Pliss *et al.* (1982) reported on the carcinogenicity of *N*-nitrodimethylamine, *N*-nitrodiethylamine, and *N*-nitrodibuthylamine in various species including outbred rats. Rats (50 animals per substance) were given 200 ppm (15-20 mg/kg bw) daily of the test substance in the drinking water for 130 weeks. In this study only *N*-nitrodiethylamine was found to be carcinogenic to rats (multiple liver tumours and vascular neoplasms in 2 of the 5 rats that survived during the whole experiment). The authors refer to unpublished information suggesting that high dose exposure of rats to *N*-nitrodimethylamine (1000 mg/l) induced tumours in liver, kidney, breast and other sites. This study suggests that *N*-nitrodiethylamine is a more potent carcinogen than *N*-nitrodimethylamine. In the second study by Scherf *et al.* (1989), rats were administered *N*-nitrodimethylamine or *N*-nitromethylamine once weekly by oral gavage. Ten male and 10 female rats were exposed to 0.5 mmol/kg bw/week (38 mg/kg bw/week) or 1 mmol/kg bw/week (76 mg/kg bw/week) by weekly oral gavage. *N*-Nitrodimethylamine induced mainly neurogenic tumours of the nasal cavity while *N*-nitromethylamine induced neurinoma of the spine, spinal nerves and peripheral nerves. Both nitramines were shown to be carcinogenic and *N*-nitromethylamine was less potent than the dimethyl compound. It was suggested that a bolus effect could explain the differences in target organ seen between this study and the drinking water studies by Goodall and Kennedy. Later studies by the same authors indicate that high doses of *N*-nitrodimethylamine inhibit the hepatic effects of the nitrosamine metabolite (Frei *et al.,* 1999).

The nitramines seem in general to be less potent than the corresponding nitrosamines. However, there are significant differences in response in the available rat studies suggesting important variability in sensitivity of different strains of rats. Furthermore, the study by Scherf *et al.* (1989) suggests differences in tumour response in high-dose versus low-dose regimen.

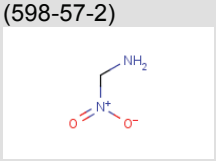
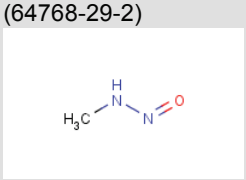
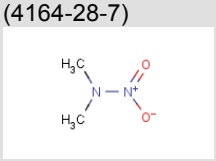
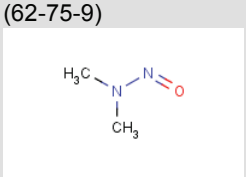
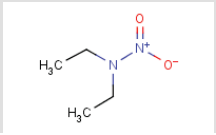
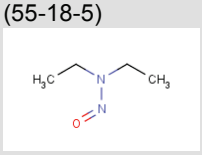
2.4.4. Carcinogenic potency of nitramines compared to nitrosamines

The Carcinogenic Potency Database (CPDB), developed at the University of California, Berkeley, and Lawrence Berkeley Laboratory, provides standardised analysis of a great number of animal cancer tests. A numerical descriptor (TD50) of carcinogenic potency is provided in this database. TD50 values were found for two nitramines and several nitrosamines in the CPDB database (Table 6). The calculated TD50 values vary depending on the studies and their quality and should only be taken as indications of relative potencies.

TD50 as defined in The Carcinogenic Potency Database (CPDB):

TD50 is the "*dose-rate in mg/kg body wt/day which, if administered chronically for the standard lifespan of the species, will halve the probability of remaining tumourless throughout that period*".

Table 6: Comparison of TD50 values for selected nitramines and nitrosamines to indicate relative carcinogenic potencies

Substance		**Indicative TD50s***		**Comments**
Nitramine (CAS No)	**Nitrosamine** (CAS No)	Nitramine	Nitrosamine	
N-Nitromethylamine (598-57-2) 	*N*-Nitrosomethanamine (64768-29-2) 	17.4	-	TD50 for *N*-nitromethylamine is based on Scherf *et al.* (1989) This study might underestimate the carcinogenic potency
N-Nitrodimethylamine (4164-28-7) 	*N*-Nitrosodimethylamine (62-75-9) 	0.54	0.0959	TD50 for *N*-nitrodimethylamine is based on Scherf *et al.* (1989) and on Goodall and Kennedy (1976).
N-Nitrodiethylamine (7119-92-8) 	*N*-Nitrosodiethylamine (55-18-5) 	-	0.0265	The study by Pliss *et al.* (1992) indicates that *N*-nitrodiethylamine is more potent than *N*-nitrodimethylamine
	N-Nitrosomorpholine (59-89-2)		0.109	
	N-Nitroso-di-n-propylamine (621-64-7)		0.186	
	N-Nitrosomethylethylamine (10595-95-6)		0.0503	
	N-Nitrosopiperidine (100-75-4)		1.43	
	N-Nitrosopiperazine (5632-47-3)		8.78	
	N-Nitrosodiethanolamine (1116-54-7)		3.7	
	N-Nitrosodi-n-butylamine (924-16-3)		0.691	

* Values taken from CPDB

- No TD50 value in the CPDB

2.4.5. Conclusions for nitramines

NIPH has evaluated the data on nitramine toxicity available in the open literature. The data on chronic toxicity of aliphatic nitramines are very limited and there is not sufficient toxicological information for a proper evaluation of their health hazard. In general they seem to be less potent as mutagens and carcinogens than the corresponding nitrosamines. However, the compound among these nitramines that has been best studied, *N*-nitrodimethylamine, should still be regarded as a carcinogen of high potency based on the findings reported in the carcinogenicity study by Goodall and Kennedy (1976). Due to lack of toxicity data, it is not possible to perform any cancer risk estimates for nitramines. Therefore, NIPH suggests that the risk estimate for the nitrosamine NDMA should be used also for exposure to nitramines based on current information. This is considered to be a conservative risk estimate as NDMA is likely to be more potent than any of the nitramines. If nitramines constitute a large part of the total nitrosamines/nitramines and the total levels exceed the suggested level for NDMA exposure, a refined risk evaluation taking into account differences in cancer potencies is recommended. However, there is a strong need for more information on toxic, mutagenic and carcinogenic properties of the nitramines to which there is expected to be a significant exposure.

2.5. Recommendation

For compounds released from the CO_2 capture plant, NIPH recommends that the risk estimate calculated for NDMA should be used for the total concentration of nitrosamines and nitramines in air and water. We recommend maximum levels ensuring minimal or negligible risk of cancer for the public from exposure to these substances. NIPH therefore concludes that the total amount of nitrosamines and nitramines should not exceed 0.3 ng/m^3 (nanogram/m^3) in air.

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Appendix 1

Calculation of cancer risk estimates based on T25 as the dose descriptor and air concentrations according to REACH guidelines

In the main document concerning the estimation of tolerable air and water concentrations of NDMA, NIPH introduces a cancer risk estimation based on the T25 and linear extrapolation-approach as described in the REACH guidance (R8). This was done due to the differences in the existing cancer risk estimates, although moderate, and was meant to assure that the risk estimate chosen is sufficiently protective. In Appendix 1 calculations and decisions used in the derivation of this extra risk estimate (T25) are presented.

Data for calculation of the T25 value

To calculate the chronic dose rate of NDMA which gives tumours in 25% of the animals at a specific tissue site (T25) NIPH used the same data set as used by WHO to calculate the lowest lifetime daily NDMA dose that would induce an increase in tumour incidence in 5% in the experimental animals (TD05) (Table 1).

In the WHO report (CICAD 38) the dose-response curve to compute TD05 for NDMA was based on the study by Peto and co-workers (1991a, 1991b). In this study rats were continuously exposed to NDMA in drinking water. Sixteen dose-groups ranging from 0 to 1.224 mg/kg bw/day for both sexes were observed from week 6 until natural death (up to about 3.5 years in the low-dose groups), allowing to demonstrate treatment effects that would not have been seen in a standard 2-years chronic exposure study. After 1 and 1.5 years 12 rats per group were exanguinated for analyses of liver tumours. In each of the 16 dose-groups there were 60 rats per sex in addition to 240 in the control groups. Analyses of different types of liver tumours (parenchymal liver cell, bile duct, mesenchymal liver cell and Kupffer cell) were performed. An approximately linearity of the dose-response curve was suggested in the low dose area of the experiment, whereas a cubic relationship was observed within the higher range of doses. The females were found to be the most sensitive sex and bile duct was the most sensitive target site for liver tumour development.

To calculate the dose-descriptors the upper dose groups for which there was downturn in the dose–response curve were eliminated in the WHO dataset. These dose groups did not give any information to the shape of the dose–response curve for tumours and the results indicate that animals are dying of some other cause before having a chance to develop the tumour of interest. To fit the curve the number of dose groups was reduced to 10 by first eliminating upper dose groups with downturn and then collapsing similar dose groups together. Collapsing was accomplished by averaging the dose level and totalling the number of tumours for the two groups. The software Global82 was then used to fit full multistage models to the reduced data. Generally the models overestimated the risk and resulted in conservative TD05 values. The data from the Peto study was adjusted as described above and used to compute TD05 for biliary cystadenomas in rats in the WHO report. Biliary cystadenomas originates in the bile ducts. The adjusted data are presented in Table A and NIPH has used these data for female rats to calculate the dose descriptor T25.

Table A: Incidence of biliary cystadenoma in female rats used for modelling

Biliary cystadenoma	
Intake (mg/kg body weight per day)	Incidence
0	4/192
0.002	1/48
0.005	4/48
0.010	0/48
0.019	3/48
0.038	5/48
0.076	7/48
0.115	34/48

Data in Table A is taken from WHO Concise International Chemical Assessment Document 38, *N*-Nitrosodimethylamine, page 38.

Calculation of T25 for developing billary cystadenoma in female rats

To calculate T25 NIPH used the lowest dose level with significantly increased incidence of biliary cystadenoma (Table A). This dose level was 0.076 mg/kg bw/day. Biliary cystadenoma in females was the most sensitive type of analysed liver tumours and females were the most sensitive sex.

Adjustment of background tumour incidences: (Dybing et al., 1997)

Net increase in tumour incidence (%): ((A*100/B) – (C*100/D)) / (100 – (C*(100/D))

A: The number of animals with tumours (at dose x)
B: The total number of animals in the group (at dose x)
C: The number of animals in the control group with tumours
D: The total number of animals in the control group

Dose level 0.076 mg/kg bw/day:

A: The number of animals with tumours: 7 (at dose 0.076 mg/kg bw/day)
B: The total number of animals in the group: 48 (at dose 0.076 mg/kg bw/day)
C: The number of animals in the control group with tumours: 4
D: The total number of animals in the control group: 192

((A*100/B) – (C*100/D)) / (100 – (C*(100/D)) =
((7*100/48) – (4*100/192)) / (100 – (C*(100/192)) =
((7*2.083) – (4*0.521)) / (100 – (4*(0.521)) =
(14.58 – 2.084) / 97.916 = 0.128

At 0.076 mg/kg bw/day 13% of the animal developed biliary cystadenoma.

The chronic dose rate giving tumours in 25% of the animals at a specific tissue site (T25) for NDMA is calculated from 0.076 mg/kg bw/day at which 13% of the animals developed biliary cystadenoma: (25/13)*0.076 mg/kg bw/day = **0.15 mg/kg bw/day**

Calculation of air concentration from oral dose

According to REACH "Guidance on information requirements and chemicals safety assessment" Chapter R.8: Characterisation of dose [concentration]-response for human health (December, 2010) a conversion of an oral dose (experimental) into a corrected inhalatory concentration to assess human inhalatory exposure may be performed according to the following equation:

For general population (in case of 24 hours exposure per day):

$$\text{Corrected inhalatory concentration} = \text{oral dose} * \frac{1}{sRV_{rat}} * \frac{ABS_{oral\text{-}rat}}{ABS_{inh\text{-}rat}} * \frac{ABS_{inh\text{-}rat}}{ABS_{inh\text{-}human}}$$

$$= \text{oral dose} * \frac{1}{1.15\ m^3/kg/d} * \frac{ABS_{oral\text{-}rat}}{ABS_{inh\text{-}human}}$$

ABS: Absorption, sRV: standard Respiratory Volume

Oral absorption of NDMA in rats is shown to be high (> 90%), whereas absorption by the inhalatory route is less well known. We have assumed an absorption value of 100% for both inhalation and oral exposure.

Conversion of oral dose (using T25) into inhalation concentration

Experimental dose 0.076 mg/kg bw/day:

High to low dose extrapolation: Extrapolation from the calculated dose were 25% developed biliary cystadenoma to the risk of 10^{-5} and 10^{-6}

$(10^{-5}/0.25) * 0.15 = 0.006$ µg/kg bw/day

$(10^{-6}/0.25) * 0.15 = 0.0006$ µg/kg bw/day

Corrected air concentration = 0.006 µg/kg bw/day * 1/1.15m^3/kg bw/day * 1

= **0.0052 µg/m^3 for 10^{-5} risk**

Corrected air concentration = 0.0006 µg/kg bw/day * 1/1.15m^3/kg bw/day * 1

= **0.00052 µg/m^3 for 10^{-6} risk**

Appendix 2

Derived minimal effect level (DMEL) for NDMA based on the inhalation study by Klein *et al.* 1991

NDMA is metabolised to alkylating, carcinogenic component(s) in particular by enzymes present in liver, lung and nasal epithelium. Due to possible first-pass effects and effects at the site of entry, the potency of NDMA carcinogenicity may be different following exposure by inhalation than exposure via the drinking water. There are a few inhalation studies available. The study by Klein *et al.* (1991) shows effects of NMDA at lower concentrations than the other studies and is thus the most sensitive study. NIPH regards the study by Klein *et al.* (1991) as the best of the inhalatory studies for estimation of carcinogenicity of NDMA. We have therefore used the data presented in the published report to estimate a DMEL for human exposure via inhalation.

In the study by Klein *et al.,* marked increases in tumours of the nasal cavity were observed in rats administered NDMA. Four groups of 36 female rats were exposed to 0, 0.04, 0.2 or 1.0 ppm NDMA (corresponding to 0, 120, 600 and 3000 $\mu g/m^3$ air), four times a week, 4-5 hours a day for up to 207 days. Median age at sacrifice was above 2 years in all but the highest exposure group in which the survival time was markedly reduced. The incidences of nasal tumours (all types) were 0%, 36% and 86% at the 0 $\mu g/m^3$, 120 $\mu g/m^3$ and 600 $\mu g/m^3$ concentrations, respectively.

The information provided in the published report is limited, for example there is no information on histological data other than tumours. Such data could have indicated whether other nasal lesions, such as irritation and inflammation could have influenced the tumourigenic response. The exposure duration was only approximately 25% of lifetime exposure and there are uncertainties related to the actual exposure regimen and the lifetime of the animals seems to have varied greatly (between 5 and 39 months), partly unrelated to the exposure.

NIPH has calculated the dose descriptor T25 based on the study by Klein *et al.* and estimated the derived minimal effect level (DMEL) for induction of cancer due to inhalatory exposure. The DMEL indicates that NDMA may be more potent by the inhalatory route than by drinking water administration. Although there are several uncertainties in this evaluation as described above, NIPH strongly recommends that this information is taken into consideration when deciding on a tolerable exposure level for NDMA in air as mentioned in the report on nitrosamines.

Calculation of T25

T25 is defined as the chronic dose rate, in mg per kg body weight per day, which will give 25% of the animals tumours at a specific tissue site, after correction for spontaneous incidence, within the standard life time of that species. It is a value calculated from a single observed dose-response and is 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.

To calculate the chronic dose rate of NDMA which gives tumours in 25% of the animals at a specific tissue site (T25) NIPH used the data set from the study by Klein *et al.* (1991) as presented in Table A.

Table A: Animal data from the study by Klein *et al.* 1991

Exposure concentration (µg/m^3 air)	No of animals	Length of exposure (days)	Median age at death (days)	No of animals with nasal tumours
0	36	77-207	795	-
120	36	95-207	860	13
600	36	57-207	772	31
3000	36	49-207	524	19

T25 for NDMA was calculated from the lowest exposure concentration (120 µg/m^3; 0.04 ppm). At this dose 36% of the animals developed tumours in the nasal cavity.

Nasal tumours (all tumour types): 1 nasal tumour reported in 13 of the 36 exposed animals. No nasal tumours reported in the control group. Thus, an adjustment of background tumour incidence was not needed.

For non-threshold carcinogens, lifetime risks for consumers and for humans exposed indirectly via the environment is associated with daily exposure of 24 hours (7 days a week) for 75 years. This exposure duration is considered equivalent to the life-time exposure in experimental studies, usually 2 years for rats.

The exposure was transformed to chronic lifetime exposure by the following calculations:

Correction for reduced daily exposure: 4.5 hours/day : 24 hours/day = **0.19**

Correction for reduced weekly exposure: 4 days/week : 7 days/week = **0.57**

Correction for reduced exposure duration: 207 days : 795 days = **0.26**

Correction for differences in survival time between the exposure groups: 860 : 795 = **1.08**

Total correction factor: 0.03

Tumour incidence: 13/36 animals (36%) at a concentration of 120 µg/m^3.

Adjusted exposure concentration giving rise to 36% increase in nasal tumour incidence:

120 µg/m^3 * 0.03 (total correction factor) = 3.6 µg/m^3

Extrapolation from the dose that was associated with a 36% tumour incidence to the T25:

Corrected T25: 0.25/0.36*3.6 µg/m^3/day = 2.5 µg/m^3/day

Derivation of DMEL by the “large assessment factor” approach

Due to the limited information in the published report of the study a large assessment factor approach was considered an appropriate procedure for the derivation of a DMEL (The procedure is described in Reach guidance, R8). The assessment factors used are listed in Table B.

Table B: Assessment factors (AF) used in the calculation of the DMEL.

	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 (4x) is thus not applied. The remaining factor of 2.5 is proposed to account for potential differences in chemical deposition in the respiratory tract 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 to BMD10	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 NOAEL
Total assessment factor (AF)	**6250**	

Following application of the assessment factors in Table B to the corrected T25 the following DMEL for human exposure is derived: DMEL: T25/AF = 2.5 $\mu g/m^3$ / 6250 = 0.0004 $\mu g/m^3$

This DMEL is related to an estimated lifetime excess cancer risk below 10^{-5}.

KLIMA- OG FORURENSNINGS- DIREKTORATET

Klima- og forurensningsdirektoratet
Postboks 8100 Dep, 0032 Oslo
Besøksadresse: Strømsveien 96
Telefon: 22 57 34 00
Telefaks: 22 67 67 06
E-post: postmottak@klif.no
Internett: www.klif.no

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Forfatter(e)
Marit Låg, Birgitte Lindeman, Christine Instanesm, Gunnar Brunborg, Per Schwarze

Tittel - norsk og engelsk
Health effects of amines and derivatives associated with CO2 capture

Sammendrag – summary
Klima- og forurensningsdirektoratet ba Folkehelseinstituttet (FHI) om å gjøre vurderinger av risiko for helseskade i forhold til utslipp av aminer, nitrosaminer og nitraminer i forbindelse med drift av CO_2 fangst anlegg. FHI gjorde også konkrete vurderinger om risikoestimat av eksponering av nitrosaminer og nitraminer som kan dannes i slik bruk, spesifikt Nitrosdimetylamin (NDMA). Selv om det antas at nitraminer er mindre potente som kreftfremkallende enn nitrosaminer anbefaler FHI pga usikkerheter og kunnskapsmangel at man benytter risikoestimatet for nitrosaminet NDMA også for nitraminene. FHI anbefaler maksimalnivåer som gir neglisjerbar eller minimal risiko for kreft ved eksponering for disse stoffene. FHI finner derfor at den samlede mengden av nitrosaminer og nitraminer ikke bør overstige 0,3 ng/m3 (nanogram/m3) luft.

The Climate and Pollution Agency (Klif) requested the Norwegian Institute of Public Health (NIPH) to carry out evalutaions of amines, nitrosamines and nitramines associated with CO2 capture. NIPH was also asked to evaluate existing risk estimates for N-nitrosodimethylamine (NDMA). Due to the lack of data on nitramines, and NIPH therefore recommends using the risk estimates for NDMA for nitramines as well, even though there are indications that nitramines are less carcinogenic than nitrosamines. NIPH recommends a maximum level ensuring the public minimal or negligible risk of cancer from exposure to these substances. NIPH therefore concludes that the total amount of nitrosamine and nitramines should not exceed 0,3 ng/m3 in air.

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www.fhi.no

Utgitt av Nasjonalt folkehelseinstitutt
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Postboks 4404 Nydalen
NO-0403 Oslo
Telefon: 21 07 70 00