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# Health effects of different amines relevant for $CO_2$ capture

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# Preface

$CO_2$ capture and storage (CCS) has been proposed for two Norwegian gas-fired power plants as a measure to reduce $CO_2$ emissions to the atmosphere, thus reducing the main contributor to global warming. A leading technology for $CO_2$ capture is through the use of amines. The *$CO_2$ and Amines Screening Project* began with *Phase I* in May 2008. The project was initiated by NILU based on the results of an expert meeting in October 2007, and discussions with SFT. The expert meeting and the following Phase I project is based upon the concern that the emissions from $CO_2$ capture using amines could be potentially harmful to the environment and human health, and that the existing information regarding these subjects were quite limited, thus demanding further examination and analysis.

The project was graciously sponsored by the following:

- Gassnova SF (CLIMIT)
- Statoil Hydro ASA
- Shell Technology Norway AS

The following institutes participated in the project:

- Centre for Theoretical and Computational Chemistry (CTCC) Department of Chemistry at the University of Oslo, responsible for the theoretical study on the atmospheric degradation of selected amines (Task 3).
- The Norwegian Institute of Public Health (FHI), responsible for the effects to human health (Task 7).
- Norwegian Institute for Nature Research (NINA), responsible for the effects to terrestrial ecosystems (Task 8).
- Norwegian Institute for Water Research (NIVA), responsible for the effects on freshwater ecosystems (Task 9).
- Norwegian Institute for Air Research (NILU), responsible for project management/coordination, including the chemical screening report, models report, worst case study report, and the summary report (Task 4, 5, 6, and 10).

The project sponsors comprised the Steering Committee, which gave useful guidance to the project and its administration. The project sponsors function within the Steering Committee also gave them an active role in reviewing all project reports and documentation.

# Contents

# Health effects of possible degradation products of different amines relevant for the CO2 capture

## 1 Introduction

In this part of the report the potential health hazards of different possible degradation products of the four amines; monoethanolamine (MEA), piperazine, aminomethylpropanol (AMP) and methyldiethanolamine (MDEA) are discussed. The choice of relevant degradation products for this hazard assessment is based on the report from the Chemical Institute, University of Oslo. The toxicological data is lacking for many of the specific compounds. Therefore available data for similar compounds belonging to the same chemical group were evaluated. A general discussion of these data and data gaps follows below.

## 2 Nitrosamines

Nitrosamines (*N*-nitrosamines) are a large and diverse family of synthetic and naturally occurring compounds having the general formula (R1)(R2) N-N=O, where R1 and R2 can be an alkyl or aryl group. Nitrosamines are typically liquids, oils, or volatile solids. Nitrosamines occur in the diet, in certain occupational settings, through use of tobacco, cosmetics, pharmaceutical products and agricultural chemicals. Nearly all commercially available alkylamines are generally contaminated by small quantities of their corresponding *N*-nitroso analogues. Factories involved either in the production or in the use of amines might be a source of nitrosamine pollution (Tricker et al 1989).

### 2.1 Classification

*N*-nitrosodimethylamine; dimethylnitrosamine (CAS-no 62-75-9) is currently classified as: Cancer2; R45T+; R26T; R25-48/25N; R51-53.

### 2.2 Exposure and metabolism

Human exposures to nitrosamines can occur via four main routes; 1) *internal* nitrosation of precursors 2) ingestion 3) inhalation 4) dermal contact. Nitrosamines may be formed in the body from nitrosation of amines via an acid- or bacterial catalyzed reaction with nitrite, or by reaction with products of nitrogen oxide generated during inflammation and infection. Because a variety of amines and reaction conditions are possible, there may be hundreds of nitrosamines. The large number of exposure sources, including formation in the body, results in a complicated matrix of total nitrosamine exposure.

The metabolic activation of nitrosamines initially involves the enzymatic hydroxylation of the carbon atom immediately adjacent to the *N*-nitroso group by members of the cytochrome P-450 enzyme family. This oxidation results in an unstable product that rapidly decomposes to an aldehyde and a diazohydroxide. The latter dissociates to a diazonium hydroxide and ultimately to a carbonium ion. The diazohydroxide and subsequent intermediates are highly electrophilic. Their

major reaction is with water yielding an alcohol, but they also react with DNA to produce a variety of alkylated DNA bases. Detoxification by denitrosation competes with this metabolic activation process. The denitrosation is also catalyzed by cytochrome P-450 and results ultimately in the production of nitrite, an aldehyde, and a primary amine. The metabolism of the short chain nitrosoalkylamines seem reasonable well understood, but the biotransformation and metabolic fate of the higher members of the homologous series need further elucidation.

## 2.3 Experimental toxicology

*Acute toxicity.* The potency of nitrosamines in causing acute tissue injury and death varies considerably (Shank 1975). Acute toxicities of nitrosamines in adult rats expressed as a single oral dose, after which 50% of the animals died (LD50) range from about 20 mg/kg bw to more than 5000 mg/kg bw, with many compounds having a LD50 between 150 and 500 mg/kg bw. In general, these compounds appear to exhibit a low to moderate acute toxicity. Structure and molecular weight play a role in determining the acute lethal toxicity. It seems that acute toxicity decreases with decreasing chain length of nitrosodialkylamines. Cyclic nitrosamines such as *N*-nitrosohexamethyleneimine and *N*-nitrosomorpholine are also acutely toxic. The liver appears to be the target organ, and liver injury is a common result of acute toxicity for a number of nitrosamines. The histopathology of *N*-nitrosodimethylamine (NDMA) and *N*-nitrosodiethylamine (NDEA) acute poisoning has been well studied. Unfortunately, this is not true for most other *N*-nitroso compounds. Detailed studies of the acute toxicity of the *N*-nitroso compunds, as a class, have not been common because the striking carcinogenicity of many of these compounds has commanded such intense interest (Olajos and Coulston 1978).

*Mutagenicity.* As alkylating agents, *N*-nitroso compounds are extremely potent point mutagens in addition to producing chromosome breaks and aberrations (Olajos & Coulston 1978). Nitrosamines can induce mutations in *Drasophilia*, but not in microorganisms. They appear to require metabolic activation by mammalian enzyme systems before they can exert a mutagenic effect. The ability of metabolizing enzymes (NADPH-dependent microsomal) to form mutagenic compounds from nitrosodialkylamines has been demonstrated by numerous investigators. NDMA is a model compound, shown to induce gene and chromosomal mutations, as well as DNA damage, *in vivo* and *in vitro* (Olajos & Coulston 1978). Induction of mutagenesis by nitrosamines has been reported for various nitrosodialkyl (aryl)-amines, substituted nitrosodialkylamines and various cyclic nitrosamines.

*Carcinogenicity.* The carcinogenic potential of NDMA in rats was first demonstrated in 1956 (Magee and Barnes 1956). Since then nitrosamines have been studied extensively in laboratory animals. Approximately 90% of the 300 tested nitrosamines have shown carcinogenic effects in bioassay and laboratory animals. Of the approximately 40 animal species tested, none were resistant (Brown 1999). Effects of nitrosamines have been demonstrated in 29 organs. Tissues affected appear to depend upon the structure of the compound, the dosage, the route of administration, and the animal species. Changes in the alkyl chain

have elicited different tumour types. In general, the predominant sites of tumour formation include the esophagus, kidney, liver, urinary bladder, nasal cavities, brain and nervous system, oral cavity, stomach, gut, pancreas, hematopoetic system, lungs, heart and skin (Olajos and Coulston 1978; Verna et al. 1996). Studies have shown that the optimal conditions for nitrosamine tumour induction occur via exposure to small amounts of the chemical over long periods of time. Nitrosamines appear also to induce neoplasms transplacentally. Both diethylnitrosamin and N-nitrosoethylurea have been reported to induce tumors in the off-springs several months after treatment of the pregnant rats (Shank 1975). Inhalation studies concerning nitrosamines are limited, however, tumours of the nasal cavity and other neoplasms in experimental animals have been reported.

It has been reported that one of the amines relevant for the $CO_2$ capture, piperazine, can be metabolized by microorganisms in the gastrointestinal track to nitrosamines. In the presence of nitrite, the *in vivo* formation of small amounts of nitrosated products from piperazine has been demonstrated to occur in experimental animals, as well as in humans. The two nitrosated derivatives of piperazine, *N*-mononitrosopiperazine (NPZ) and *N,N'*-dinitrosopiperazine (DNPZ) have been found to be carcinogenic in rodents. Administration of NPZ to rats in the drinking water at 400 and 800 mg/l, corresponding to a daily average dose of about 27 and 54 mg/kg bw, induced a clear dose response relationship with respect to tumors in the nasal cavity.

*Teratogenicity.* *N*-nitroso compounds can also be potent teratogens. When *N*-nitrosoethylurea was given to rats before the 12$^{th}$ day of pregnancy, the compound was not carcinogenic, but it was a powerful teratogen (Shank 1975).

Human data

*Acute toxicity.* Several case studies have indicated liver injury in humans from exposure to NDMA. Both acute liver toxicity, liver necrosis and liver damage have been reported. Other acute effects of nitrosamines include irritation of eyes, lungs and skin, and also vomiting, lung damage and convulsions (Brown 1999).

*Carcinogenicity.* Most nitrosamines are suspected to be human carcinogens, but direct causal associations have not yet been found. The suspected mechanism of carcinogenesis is that nitrosamines from endogenous or exogenous sources are rapidly metabolized after absorption to reactive intermediates that can covalently bind to macromolecules (DNA), initiating the carcinogenetic process. It is generally believed that the carbonium ion is the carcinogenic species that reacts with nucleic acids to form adducts. Studies have shown that human liver tissue appears to metabolize nitrosamines in a way similar to that of rodent liver tissue. Experimental animal studies have demonstrated DNA adduct formation similar to that observed in human studies involving nitrosamines. Although a causal association has not been firmly established, there is circumstantial evidence that nitrosamines could cause cancer in humans (Olajos and Coulston 1978; Verna et al. 1996).

Evidence for cancer excess in industrial populations where nitrosamines are known to occur indicates involvement of these chemicals (Brown 1999). Because of the probable confounding effect of numerous exposures to other chemical agents in these populations, the studies do not provide adequate evidence of a

relationship between nitrosamine exposure and cancer in the humans. Several authors have suggested that nitrosamines are responsible for an excess of cancers of the bladder, lung, stomach and other sites noted in studies of workers in the rubber industry. The International Agency for Research on Cancer (IARC) has identified the exposure in rubber industry as a carcinogenic risk to humans.

*Risk assessment.* A number of quantitative risk assessments have been developed for nitrosamines under different conditions of exposure. The Environmental Protection Agency has calculated a level of 7 ppt NDMA in water as representing a $10^{-6}$ risk for cancer. On the basis of intake, the state of California has determined that 0.04 and 0.004 µg/m$^3$ of NDMA per day were equivalent to a $10^{-5}$ and $10^{-6}$ risk of cancer, respectively.

### 2.4 Regulation and occupational exposure limits

IARC has classified NDMA and NDEA as group 2A carcinogens (probable human carcinogens), and nitrosodibutylamine, nitrosodipropylamine, nitrosomorpholine, nitrosopiperdine and nitrosopyrrolidine, as group 2B carcinogens (possible human carcinogens). At present there are no established numerical exposure limits in the workplace in the US. In Germany, numerical regulations for occupational exposure to nitrosamines have been established. The guidelines are intended to apply to nitroamines as a class, and in general industry, the total exposure to nitrosamines cannot exceed a technical orientation value of 1 µg/m$^3$ (measured as an 8 hour time-weighted average).

### 2.5 Health risk evaluation

The amines relevant for the $CO_2$ capture may be degraded to different nitrosamines. The possible concentration of the different nitrosamines in the air is uncertain. Therefore, this health risk evaluation is general. Based on experimental data, there seems little doubt that some nitrosamines are extremely potent carcinogens, that can pose a serious hazard to humans if present in the environment. In animal carcinogenicity experiments, the absence of a lower no-effect threshold for N-nitroso compounds makes it desirable to reduce the human exposure to these compounds to an absolute minimum.

## 3 Nitramines

*N*-nitramines can be produced as atmospheric pollutants when secondary amines react with $NO_2$. *N*-nitramines are structurally related to *N*-nitrosamines, with the nitroso group being replaced by a nitro group. Compared to the nitrosamines, there are few studies on the health effects of nitramines. The following is a general discussion of available data on aliphatic nitramines.

### 3.1 Metabolism

The metabolic pattern of aliphatic *N*-nitramines seems to resemble that of corresponding *N*-nitrosamines, except that N-nitromonoalkylamine metabolites were identified. *N*-nitrodimethylamine can be oxidized by the cytochrom P450 enzyme family (possibly CYP2E1) to *N*-nitro-hydroxymethyl methylamine, a stable compound that can be further metabolised to the demethylated compound

*N*-nitromethylamine and to formaldehyde. *N*-nitromethylamine has been found to be relative stable. *N*-nitrodimethylamine can also be reduced to the carcinogenic nitrosamine, *N* -nitrosodimethylamine. In a study by Hassel et al. (1990), the metabolism of radioactively labelled *N*-nitrodimethylamine in rats was compared with that of *N*-nitromethylamine. The study indicates that in contrast to *N*-nitrodimethylamine, *N*-nitromethylamine is only oxidized to a minor extent.

## 3.2 Toxicity

*Acute toxicity.* *N*-nitrodimethylamine has a $LD_{50}$ of about 1000 mg/kg bw (Druckrey et al., 1967; Andersen et al, 1978) upon oral exposure of rats. The rats appeared normal 4-24 hr after dosing, but became increasingly lethargic thereafter. Focal areas of hemorrhage were found in the stomach and intestine and variable amounts of clear fluid in the peritoneum. The liver appeared normal in all rats.

*Mutagenicity.* The mutagenic and carcinogenic activity of aliphatic *N*-nitramines seem in general to be much lower than those of the corresponding nitrosamines. However, data on mutagenicity are test system dependent. It is recognised that certain classes of mutagens including short chain aliphatic nitrosamines are not always detected using standard procedures. The technical guidelines (CPS&Q) suggest the use of *E. coli* WP2 strains or *S. typhimurium* TA102 for testing of these substances which have an AT base pair at the primary reversion site. Thus the negative results of some of the earlier bacterial mutagenicity data may be explained by the properties of the bacterial strain used in the tests.

Several of the *N* -nitramines or their metabolites have been found to be mutagenic in the E. coli WP2 $hcr^-$ assay, but were non-mutagenic in the Salmonella TA 100 and TA 1535 strains. The mono-methylated *N*-nitramines are clearly mutagenic in several assays, whereas the dimethylated analogues show borderline mutagenicity (Khudoley ;Suzuki, 1985; Frei et al, 1986). Formaldehyde has been proposed to be the mutagenic metabolite of *N*-nitrodimethylamine responsible for its mutagenicity in the Salmonella TA100 system. In contrast, both formaldehyde and *N*-nitro-hydroxymethyl methylamine were negative in mammalian cell mutagenicity assays (Frei, 1986). *N*-nitrodimethylamine, however, damaged hepatic DNA in mice *in vivo*. Although being a directly acting mutagen in the E. coli WP2 $hcr^-$ assay, results indicate that further metabolism of *N*-nitromethylamine, possible to the highly reactive *N*-nitrosomethyl compound and ultimately to the methyldiazonium ion, might occur in mammalian cells.

*Carcinogenicity.* Pliss et al. (1982) reported on the carcinogenicity of *N*-nitrodimethylamine, *N*-nitrodiethylamine and *N*-nitrobutylamine in various species including rats. Rats were given 200 ppm (15-20 mg/kg bw) daily of test substance in the drinking water for 130 weeks. In this study only *N*-nitrodiethylamine was found to be carcinogenic (liver tumours).

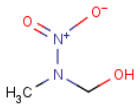
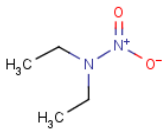
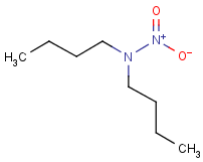
Several other studies show that *N*-nitrodimethylamine is carcinogenic to rats (Druckrey, 1967; Goodall and Kennedy, 1976; Mirvish, 1980, Scherf 1989). When *N*-nitrodimethylamine was administered via drinking water, tumours in the liver and kidney seemed to dominate. The morphology of the liver tumours after

*N*-nitrodimethylamine treatment was said to contrast with that often described after treatment with *N*-nitrosodimethylamine. In a comparative carcinogenicity study (Scherf et al, 1989), rats were administered *N*-nitrodimethylamine or *N*-nitromethylamine once weekly by oral gavage. *N*-nitrodimethylamine induced mainly neurogenic tumours of the nasal cavity, whereas *N*-nitromethylamine induced neurinoma of the spine and spinal and peripheral nerves. *N*-nitromethylamine was slightly 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. Later studies by the same authors indicate that high doses of *N*-nitrodimethylamine inhibit the hepatic effects of the nitrosamine metabolite.

### 3.3 Health risk evaluation

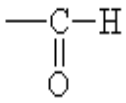
We have made a literature study of the toxicological information on the potential nitroalkylamines listed in ”Organic compounds included in the CAS Register” in the report from the University of Oslo of May 13, 2008. Data on health effects of aliphatic *N*-nitramines are sparse. However, there is sufficient information to conclude that several of the nitramines are mutagenic and carcinogenic in rodents, although they seem considerably less potent than corresponding nitrosamines. It would seem that several of the cellular mutagenicity assays are not well suited to study the mutagenic potential of nitramines, due to insufficiencies of the traditional metabolic activation systems used.

*Table 1: Nitroalkylamines included in the CAS Register.*

| **Nitramine (synonyme)** | | | |
|---|---|---|---|
| Methanamine, N-nitro-<br>(N-Nitromethylamine) |  | $C H_4 N_2 O_2$ | 598-57-2 |
| Methanamine, N-Methyl-N-nitro-<br>Dimethylnitramine<br>N-Nitrodimethylamine |  | $C_2 H_6 N_2 O_2$ | 4164-28-7 |
| Methanol., (methylnitroamino)-<br>(Methylnitramino)methanol |  | $C_2 H_6 N_2 O_3$ | 32818-80-7 |
| Ethanamine, N-ethyl-N-Nitro-<br>N-Nitrodiethylamine<br>Diethylnitramine |  | $C_4 H_{10} N_2 O_2$ | 7119-92-8 |
| N-Nitrodibutylamine |  | | 4164-31-2 |

# 4 Aldehydes

An aldehyde is an organic compound containing a terminal carbonyl group. This functional group, which consists of a carbon atom bonded to a hydrogen atom and double-bonded to an oxygen atom (chemical formula O=CH-), is called the aldehyde group.



Aldehyde
Functional Group

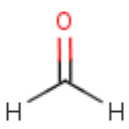
Aldehydes are major products in the photooxidation of hydrocarbons, and in the reactions of hydrocarbons with ozone, oxygen atoms, or free radicals. Formaldehyde and acrolein have been specifically identified in urban atmospheres. These materials probably contribute to the odour and eye irritation produced by photochemical smog (Amdur et al., 1991).

## 4.1 Formaldehyde

Formaldehyde (CAS No.:50-00-0), also called methanal, is a flammable, colourless and readily polymerized gas at ambient temperatures. Formaldehyde is readily soluble in water, alcohols, and other polar solvents, but has a low degree of solubility in non-polar fluids. Formaldehyde decomposes at 150 ˚C into methanol and carbon monoxide; in general it is highly reactive with other chemicals. In sunlight, it is readily photo-oxidized to carbon dioxide (EHC 89, 1989). Direct release to the aquatic compartment and soil is expected to be minor and significant removal occurs through biodegradation (NICNAS, 2006).

**The substance is currently classified as follows:**
C >= 25 %
T ; R23/24/25 (Toxic by inhalation, in contact with skin and if swallowed)
R34 (Causes burns)
R40 Cat 3 (Limited evidence of a carcinogenic effect)
R43 (May cause sensitization by skin contact)

**Structure:**



### *4.1.1 Exposure*

A considerable amount of formaldehyde comes from the exhaust emissions of motor vehicles. Formaldehyde is an important raw material in industry. It is used in the manufacture of synthetic resins and chemical compounds such as lubricants, adhesives and fertilizers. It has also applications as disinfectant, preservative and in cosmetics (EHC 89, 1989). There is some natural formaldehyde in raw food with levels ranging from 1 mg/kg up to 90 mg/kg. An accidental contamination of food may occur through fumigation, the use of formaldehyde as a preservative, or through cooking. Tobacco smoke as well as urea-formaldehyde foam insulation and formaldehyde-containing disinfectants are all important sources of formaldehyde in the indoor environment.

Formaldehyde concentrations in indoor air are generally higher than outdoors. Levels of formaldehyde in outdoor air are generally below 1 $\mu g/m^3$ in remote areas and below 20 $\mu g/m^3$ in urban settings. The levels of formaldehyde in the indoor air of houses are typically 20-60 $\mu g/m^3$ (IARC, 2006). It is estimated that several million people are exposed occupationally to formaldehyde in industrialised countries alone. The highest continuous exposures (frequently > 1 $mg/m^3$) have been measured in particle-board mills, during the varnishing of furniture and wooden floors, in foundries, during the finishing of textiles and in fur processing (IARC, 1995).

### *4.1.2 Toxicity*

*Toxicokinetic*

In humans and experimental animals, formaldehyde is readily absorbed by all exposure routes (EHC 89). More than 90% of inhaled formaldehyde gas is absorbed in the upper respiratory tract of rats and monkeys (IARC 1995). When inhaled, it reacts rapidly at the site of contact and is quickly metabolised in the respiratory tissue (EHC 89, 1989).

*Irritation*

The common effects of formaldehyde exposure to humans are various symptoms caused by irritation of the mucosa in the eyes and upper airways. Concentrations of 0.6-1.2 $mg/m^3$ (0.5 -1 ppm) are detectable by odour to most people. The suggested threshold level for exposure to formaldehyde, associated with reported mild to moderate upper respiratory tract irritation of humans in controlled studies, is also approximately 0.6-1.2 $mg/m^3$ (0.5-1.0 ppm), whilst the threshold for conjunctival eye irritation in most healthy people appears to be > 1.2 $mg/m^3$ (1 ppm). Tolerance to the irritation effects (accommodation) has been reported to occur in individuals subjects to prolonged exposure (COMEAP, 2000; Arts et al., 2006).

*Sensitisation*

In the non-industrial indoor environment, sensory reactions are typical effects, but there are large individual differences in the normal population, and between hyperreactive and sensitized people. There are a few case reports of asthma-like symptoms caused by formaldehyde, but none of these demonstrated a

sensitization effect and the symptoms were considered to be due to irritation. Skin sensitization is induced only by direct skin contact with formaldehyde solutions in concentrations higher than 2%. The lowest patch test challenge concentration in an aqueous solution reported to produce a reaction in sensitized persons was 0.05% formaldehyde (NICNAS, 2006).

*Carcinogenicity*
Formaldehyde is genotoxic, but only in the presence of cytotoxicity it may lead to cancer (COMEAP, 2000). For cytotoxicity of formaldehyde, concentration is more important than the duration of the exposure (IARC, 1995).Carcinogenicity bioassays in rats have shown that exposure to concentrations > 6.9 mg/m$^3$ (5.6 ppm) formaldehyde vapour induce development of tumours in the nasal cavity. The dose response curve is highly non-linear, with a disproportionate increase in tumour incidence at higher levels, suggesting that cytotoxicity may be the rate-limiting step in this process. Formaldehyde is classified as a potential human carcinogen, based on limited evidence in humans and sufficient evidence in experimental animals. Human epidemiological data relate to a potential association of nasopharyngeal cancer with occupational exposures to formaldehyde. Limited data also suggest an association between formaldehyde and nasal cancers and leukaemia. Generally exposure levels in human studies have not been well evaluated (COMEAP, 2000).

*Other effects*
There is no significant evidence that formaldehyde is toxic to the immunesystem, the reproductive system, or to developing foetuses (COMEAP, 2000).

### *4.1.3 Health risk evaluation*

In rodents and monkeys, a no-observable-effect level (NOEL) of 2.5 mg/m$^3$ for inhaled formaldehyde has been suggested (IARC, 1995). Sensory irritation and odour is first observed at a level of approximately 1.2 mg/m$^3$. However, lower levels for irritation and odour may occur. From both human and animal studies, it has been concluded that at airborne levels for which the prevalence of sensory irritation is minimal both in incidence and degree (i.e., <1.2 mg/m$^3$), risks of respiratory tract cancer are considered to be negligibly low (Arts, 2006, NICNAS, 2006). In Norway, The Board of Health Supervision has set a threshold for formaldehyde in the indoor environment at 100 μg/m$^3$ (0.1 ppm).

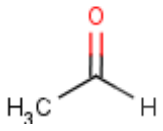
## 4.2 Acetaldehyde

Acetaldehyde (CAS No.:75-07-0) is a colorless volatile liquid with a pungent suffocating odour. Acetaldehyde is a highly flammable and reactive chemical that is miscible with water and most common solvents. Because of its high reactivity, intercompartmental transport of acetaldehyde is expected to be limited. Some transfer of acetaldehyde to air from water and soil is expected because of the high vapour pressure and low sorption coefficient. It is suggested that the photo-induced atmospheric removal of acetaldehyde occurs predominantly via radical formation. Photolysis is also expected to contribute to the removal process. Both processes cause a reported daily loss of about 80% of atmospheric acetaldehyde emissions. Reported half-lives of acetaldehyde in water and air are 1.9 h and 10-60 h, respectively (EHC 167, 1995).

**The substance is currently classified as follows:**

R12 (Extremely flammable)
R36/37 (Irritating to eyes and respiratory system)
Xn; R40 Cat 3 (Limited evidence of a carcinogenic effect)

**Structure:**




### *4.2.1 Exposure*

The main source of exposure to acetaldehyde in the general population is through metabolism of ethanol where acetaldehyde is a metabolic intermediate. Additionally the general population is exposed to acetaldehyde from food products and beverages, but to a lesser extent from air. The contribution from drinking water is negligible. Acetaldehyde is also present in vehicle exhaust and in wastes from various industries. Degradation of hydrocarbons, sewage and solid biological wastes produces acetaldehyde, as well as the open burning and incineration of gas, fuel oil and coal. Workers may be exposed in some manufacturing industries and during alcohol fermentation, where the principal route of exposure is most likely inhalation and possible dermal contact (EHC 167, 1995). WHO (1995) summarised the mean concentrations of acetaldehyde in ambient air, based on data from various locations around the world, as within the range of 2-8.6 µg/$m^3$ (0.0011-0.0048 ppm).

### *4.2.2 Toxicity*

*Toxicokinetic*

Available studies on toxicity indicate that acetaldehyde is absorbed through the lungs and gastrointestinal tract. Absorption through the skin is also probable. Following inhalation by rats, acetaldehyde is distributed to the blood, liver, kidney, spleen, heart, and other muscle tissues. Low levels were detected in embryos from rodents after maternal intraperitoneal injection of acetaldehyde and following maternal exposure to ethanol. Potential production of acetaldehyde has also been observed in rat fetuses and in the human placenta, *in vitro*. Following oral administration, virtually no unchanged acetaldehyde is excreted in the urine. Endogenous production and metabolism of acetaldehyde occurs mainly in the liver, primarily as a result of ethanol metabolism**.** The majority of ethanol is metabolised by mitochondrial enzymes (aldehyde dehydrogenases), of which a number of polymorphic forms have been identified (COMEAP, 2000). Acetaldehyde has been implicated as the putatively toxic metabolite in the induction of ethanol associated liver damage, facial flushing and developmental effects (EHC 167, 1995).

*Irritation*

Acute exposure to acetaldehyde vapour has been associated with irritation of the eyes, skin and respiratory tract. Limited studies with human volunteers showed short-term exposure thresholds of 90 mg/m$^3$ (50 ppm) for eye irritation and 241 mg/m$^3$ (134 ppm) for upper respiratory tract irritation, in most subjects. Some subjects experienced eye irritation at 45 mg/m$^3$ (25 ppm) exposure. The reported effect levels were all far above the reported odour threshold at 0.09 mg/m$^3$. All subjects showed transient conjunctivitis associated with exposure to 360 mg/m$^3$ (200 ppm) acetaldehyde vapour for 15 min (COMEAP, 2000). Respiratory effects were also noted in hamsters exposed to acetaldehyde by inhalation and degenerative changes were observed in the trachea. Degenerative changes in respiratory epithelium and larynx were noted at higher concentrations (EHC 167, 1995). No-observed-adverse-effect-levels (NOAELs) of 270 mg/m$^3$ (150 ppm) and 700 mg/m$^3$ (390 ppm) have been identified for respiratory tract lesions in rats and hamsters, respectively (COMEAP, 2000). A small number of studies have shown that inhaled acetaldehyde causes broncho-constriction and increases non-specific bronchial responsiveness in asthmatic patients, but not in healthy controls (COMEAP, 2000). In repeated dose studies, both using oral and inhalation routes, the toxic effects at relatively low concentrations were limited to the sites of initial contact (EHC 167).

*Genotoxicity and carcinogenicity*
Acetaldehyde is classified by IARC, US EPA and ECB as possibly carcinogenic to humans.
A LOAEL of 1350 mg/m$^3$ (750 ppm) was set for hyperplastic changes and tumour incidence (adenocarcinomas of the olfactory epithelium) in rats (COMEAP, 2000). Acetaldehyde is genotoxic *in vitro*, inducing gene mutations, clastogenic effects and sister chromatid exchanges (SCEs) in mammalian cells in the absence of exogenous metabolic activation. Negative results were found in tests for bacterial mutacenicity (Ames` test). Following intraperitoneal injection, acetaldehyde induced SCEs in the bone marrow of Chinese Hamsters and mice.

Increased incidences of tumours have been noted in inhalation studies on rats and hamsters**.** In rats, there were dose related increases in nasal adenocarcinomas and squamous cell carcinomas (significant at all dose levels). In hamsters, increases in nasal and laryngeal carcinomas were non-significant (EHC 167, 1995). It has been suggested that the mechanism of carcinogenicity observed with acetaldehyde is very similar to the mechanism of carcinogenicity of formaldehyde, but higher doses of acetaldehyde were required to observe the same effects as with formaldehyde (COMEAP, 2000).

*Developmental toxicity*
Exposure of pregnant rats and mice to acetaldehyde induced fetal malformations (EHC 167, 1995). Several animal studies have demonstrated direct teratogenic effects of acetaldehyde when applied to embryos *in vitro* and *in vivo*, and it has been suggested that the compound may contribute to the congenital abnormalities seen in human foetal alcohol syndrome. There are, however, no data regarding the developmental and reproductive toxicity of inhaled acetaldehyde in humans or experimental animals (COMEAP, 2000).

### *4.2.3 Health risk evaluation*

On the basis of data on irritancy in humans, a tolerable concentration of 2 mg/m$^3$ has been derived for acetaldehyde. The mechanism of carcinogenicity observed with acetaldehyde has been suggested to be very similar to the mechanism of carcinogenicity of formaldehyde (COMEAP 2000). Hence, exposure to acetaldehyde concentrations < 2 mg/m$^3$ is not likely to cause respiratory tract cancer. However, in 1995 WHO suggested a tolerable concentration of 0.3 mg/m$^3$ for lifetime cancer risk (EHC 167, 1995).

# 5 Amides

There seems to be a common effect pattern of formamides as one group and of acetamides as the other. The majority of the animal studies are performed on N,N-dimethylformamide (DMF), N-methylformamide (MMF), N,N-dimethylacetamide (DMAC) and N-methylacetamide (MMAC). In this part we will discuss health effects only of formamide and acetamide.

## 5.1 Formamide

Formamide (CAS no: 75-12-7) , $CONH_2$, known as methanamide, is derived from formic acid. Formamide is a clear liquid which is miscible with water and has an ammonia-like odour. It is used primarily for manufacturing sulfa drugs, synthesizing vitamins, as a softener for paper and fiber as well as in the dye industry. Formamide, in its pure state, has been used as an alternative solvent for the electrostatic self-assembly of polymer nanofilms (Vimal et al.,2007). Formamide will begin to partially decompose into carbon monoxide and ammonia at 180°C. When heated strongly, formamide decomposes to hydrogen cyanide (HCN) and vapor ($H_2O$).

**Classification:** Repr. Cat 2 R61.

### *5.1.1 Metabolism*

Formamide is a metabolite of DMF. DMF is oxidised by cytochrome P450 (probably Cyp2E1) to N-hydroxymethyl-N-methylformamide (HMMF) which is demethylated to MMF, which is further demethylated to formamide. In humans the most important target organ is the liver and the metabolites is excreted in the urine. More than 90% of DMF is retained in the respiratory tract of exposed human volunteers (Mraz, 1992). The metabolic pathway of DMF seems to be qualitatively different in rodents and humans, since in rodents the major excreted metabolite in urine is HMMF followed by formamide, while in humans it is DMF>HMMF>N-acetyl-S-(N-methylcarbamoyl)cystein (Tulip, 1989; Kestell, 1986).

### *5.1.2 Experimental toxicity*

The toxicity data is based on ECBI/59/98-Add.4 (2000).

*Acute toxicity*. The $LD_{50}$ values in rats was between 3,200 mg/kg bw and 7,500 mg/kg bw, a $LC_{50}$ value after inhalation was $\geq$ 21 mg/l/4 hours (furthermore no toxic effects at 7.2mg/l/6h) and acute dermal toxicity values in rats and rabbits $\geq$ $LD_{50}$ 17,000 mg/kg (ECBI 2000). Repeated sublethal treatment by various exposure routes shows the liver to be the target organ with the degree of damage being proportional to the amount absorbed. However, massive doses can also produce damage to other organs and tissues (Kennedy 1986).

*Skin irritation.* Three older tests in rabbits show either no irritancy (two tests) or only erythema after 20-hour exposure. .

*Eye irritation.* Whereas some older studies showed some slight to moderate irritant effects, in a more recent study no irritating effects according to EC criteria were observed. Two of the older studies excluded iris damage or showed only mild iritis in part of the animals.

*Subacute, subchronic and chronic toxicity.* In a 4-week study 113 mg/kg bw did not show toxic effects besides some retarded body weight gain at the end of the treatment, whereas 340 mg/kg bw caused severe toxicity (mortality). It can be assumed that at the limit of 150 mg/kg bw (28-day study) no "severe lesions" will be caused.

There are no appropriate, subchronic (90 days) studies to assess effects by inhalation. From a 2-week study a definitive conclusion cannot be made, but it may be assumed that serious damage is not likely to be achieved at the limit dose of 0.25 mg/l/6 h/d also taking into account the results of the 90-day dermal studies.

In a recent dermal 90-day study the NOAEL with respect to effects was 300 mg/kg bw/day for females, whereas only slight hematological effects were found at this dose for males.

*Mutagenicity.* The National Toxicology Program tested formamide for mutagenicity in the Salmonella/microsome preincubation assay using the standard protocol. Formamide was tested at several doses in five Salmonella typhimurium strains in the presence and absence of rat or hamster liver enzymes. Formamide was negative in these tests and the highest ineffective dose tested in any S. typhimurium strain was 10 mg/plate (Mortelmans et al; 1986).

*Carcinogenicity*. Formamide appear to be non-carcinogenic (Kennedy, 1986).

*Reproductive toxicity.* Embryotoxicity can be demonstrated at high doses, which generally show toxicity to the maternal animals. Structural abnormalities in sensitive species such as the rabbit are produced following exposure at near-lethal levels. The spectrum of abnormalities seen is broad and fails to show any time or site specificity in terms of developing organs/organ systems.

The developmental toxicity potential of orally administered formamide was evaluated in rats (25 animals/group). Formamide (50, 100, or 200 mg/kg bw/day) was administered by gavage on gestation day 6-19. At 200 mg/kg/day, maternal body weight, weight gain and pregnant uterine weight were significantly

decreased. Maternal gestational weight gain (corrected for gravid uterine weight), liver weight, food and water consumption were not affected. Formamide did not affect prenatal viability or incidences of fetal malformations or variations. Average fetal body weight/litter was decreased at 100 and 200 mg/kg bw/day. Fetal body weight was affected at lower daily doses than in previous studies, possibly due to the longer total exposure period and lack of a recovery period between cessation of exposure and termination. In summary, the maternal toxicity NOAEL was 100 mg/kg bw/day. The developmental toxicity NOAEL was 50 mg/kg bw/day (Price et al., 1999).

### *5.1.3 Human toxicity*

Liver damage can be produced by overexposure to these chemicals in man. Airborne concentrations need to be controlled and care should be taken to avoid excessive liquid contact as the chemicals are absorbed through the skin and the respiratory tract (Kennedy 1986 and 2001).

## 5.2 Acetamide

Acetamide (CAS no: 60-35-5) or acetic acid amide or ethanamide ($CH_3CONH_2$) the amide of acetic acid, is a white crystalline solid in pure form and produced by dehydrating ammonium acetate. Acetamide is used primarily as a solvent and a plasticizer and a wetting and penetrating agent (US EPA, 2000). The derivative N,N-dimethylacetamide (DMA), which has two methyl groups replacing the amine protons, is used as a solvent.

**Classification**: Xn; Carc. Cat 3; R40
Acetamide is a metabolite of N,N-dimethylacetamide (DMAC). DMAC is metabolised through an analogous pathway as DMF to N-methylacetamide (MMAC), which is demethylated to acetamide.

### *5.2.1 Experimental toxicity*

The toxicity data is based on US EPA (2000) and Lakes environmental software air toxics index.

*Acute Effects.* Acetamide causes mild skin irritation in humans from acute exposure. (US EPA, 2000). Tests involving acute exposure of rats and mice have shown acetamide to have low to moderate acute toxicity from oral exposure. (US EPA, 2000). Tests involving acute exposure of animals, such as the $LD_{50}$ test in rats and mice, 7 g/kg bw and 12.9 g/kg bw, respectively, have shown acetamide to have low to moderate acute toxicity from oral exposure. (US EPA, 2000).

*Subacute, subchronic and chronic toxicity*. No information is available on subacute, subchronic or chronic effects of acetamide in humans or animals.

*Reproductive/developmental effects.* No information is available on the reproductive or developmental effects of acetamide in humans. Animal studies have not reported any significant developmental effects from exposure to acetamide (US EPA, 2000).

*Mutagenicity.* Acetamide is considered a non-genotoxic carcinogen that was negative in at least six separate genotoxicity assays (Parodi et al., 1991). There were no evidence for genotoxicity in *Salmonella typhimurium*, for DNA damage in rat hepatoma cells or for DNA repair in isolated rat hepatocyte (Dybing et al.,1987). Mice exposed orally to acetamide (50 mg/kg bw 30 and 6 h prior to sacrifice), produced increases in the bone marrow micronuclei (Chieli et al., 1987; Arni, 1989). In contrast to these findings, in a study by Mirkova (1996), acetamide is inactive as a micronucleus inducing agent in mouse bone marrow. Positive effects were seen in micronuclei from Syrian hamster embryos exposed *in vitro* (Fritzenschaf et al., 1993).

*Carcinogenicity.* The carcinogenicity bioassay by Fleischman *et al*. (1980) indicated that acetamide causes hematopoietic tumors in male C57BL/6 mice, and hepatocellular carcinomas in male and female Fischer 344 rats. Rats were more sensitive than mice, and male rats were more sensitive than female rats in this study. Several animal studies have reported liver tumors from oral exposure to acetamide. (US EPA, 2000; IARC, 1987, 1974; California environmental protection agency, 1999).

### *5.2.2 Human toxicity*

No studies on the potential carcinogenic effects of acetamide on humans are known to exist. Occupational exposure to acetamide may occur for workers in the plastics and chemical industries (US EPA, 2000). The acute exposure (short-term) causes mild skin irritation. No information is available on the chronic (long-term), reproductive/developmental, or carcinogenic effects of acetamide in humans. Reference Concentration (RfC) for acetamide is under review by EPA. EPA has not classified acetamide for carcinogenicity. The International Agency for Research on Cancer (IARC) has classified acetamide as a Group 2B, possible human carcinogen. (IARC, 1987) and ECB (CPS&Q) has classified acetanmide as a carc. cat.3 R40 (Limited evidence of a carcinogenic effect). The California Environmental Protection Agency (1999) has established an inhalation unit risk estimate of $2.0x10^{-5}(\mu g/m^3)^{-1}$ and an oral cancer slope factor of $7.0x10^{-2}$ $(mg/kg/d)^{-1}$ for acetamide.

## 5.3 Health risk evaluation of amides

We have made a literature study of the human toxicological information on the potential formamides and acetamides. The studies on formamide indicates concern for developmental toxicity. The carcinogenicity studies on acetamide indicate liver tumour formation in rats. Occupational exposure to acetamides induces mild skin irritation.

# 6 Concluding remarks

The amines relevant for the $CO_2$ capture may be degradated to different nitrosamines, nitramines, aldehydes and amides. Data on health effects of the specific degradation products are sparse. This report of health risk evaluation is, therefore, general. Based on experimental data, there seems little doubt that some nitrosamines are extremely potent carcinogens, that can pose a serious hazard to humans if present in the environment. It is desirable to reduce the human exposure to these compounds to an absolute minimum. Several of the nitramines are mutagenic and carcinogenic in rodents, although they seem considerably less potent than the corresponding nitrosamines.

With regard to the aldehydes, it has been concluded that at airborne levels for which the prevalence of sensory irritation is minimal, both in incidence and degree (<1.2 $mg/m^3$), risks of respiratory tract cancer are considered to be negligibly low. The degradation products formamide and acetamide has been reported to induce development toxicity and carcinogenicity, respectively, in experimental animals. Acetamide may also induce skin irritation. The irritating potential of the aldehydes and amides might in this context be the most relevant adverse health effect of these compounds, as also the amines thought to be used in the $CO_2$ capture also has such effects. Therefore, all these compounds have to be evaluated together with respect to irritating potential of the air around the gas plants.

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| TITLE | PROJECT LEADER |
|---|---|
| Health effects of possible degradation products of different amines relevant for the $CO_2$ capture | Svein Knudsen |
| | NILU PROJECT NO.<br>N-108068 |
| AUTHOR(S)<br>Marit Låg, Åshild Andreassen, Christine Instanes and Birgitte Lindeman | CLASSIFICATION *<br>A |
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REPORT PREPARED FOR
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ABSTRACT

The toxicity studies of the amines, MEA, piperazine, AMP and MDEA, together with relevant groups of degradation products, nitrosamines, nitramines, aldehydes and amides, have been evaluated. However, the toxicological data are generally sparse. The amines, and the degradation products aldehydes and amides, seem to be irritative, piperazine is also reported to be sensitizing. For piperazine and MEA there are indications of reproductive and developmental toxicity. The aldehydes; formamide and acetamide, have in experimental animals induced developmental toxicity and carcinogenicity, respectively. Based on experimental data some nitrosamines are extremely potent carcinogens. Several of the nitramines are mutagenic and carcinogenic in rodents, although they seem considerably less potent than the corresponding nitrosamines.

The suggested exposure guidelines for the amines are based on the available literature. Particularly for AMP and MDEA there are few high quality studies. We suggest that the general population, over time, should not be exposed to levels in the air higher than 10 µg/m$^3$ MEA, 5 µg/m$^3$ piperazine base, 6 µg/m$^3$ AMP or 120 µg/m$^3$ MDEA. These values should be used as an indication and not as limit values for safety. Furthermore, it is desirable to reduce the human exposure of nitrosamines to an absolute minimum. Due to the serious effects of nitramines, exposure should also be kept at a low level. The irritating potential of the amines, aldehydes and amides may be the most relevant adverse health effect. Therefore, all these compounds have to be evaluated together with respect to irritating potential of the air around the $CO_2$ capture plants.


NORWEGIAN TITLE

Helseeffekter av mulige nedbrytningprodukter fra aminer som er relevante for $CO_2$-fangst


| KEYWORDS | | |
|---|---|---|
| $CO_2$ capture | Amines | Human toxicology |

ABSTRACT (in Norwegian)
Toksikologiske studier av aminene, MEA, piperazin, AMP and MDEA, samt relevante grupper av nedbrytningsprodukter, nitrosaminer, nitraminer, aldehyder and amider, er gjennomgått i denne rapporten. Det mangler imidlertid mye kunnskap om de fleste av disse stoffene. Aminene, aldehyder og amider har irritasjonseffekter, og piperazin er også rapportert å være sensibiliserende. Videre er det indikasjoner på at piperazin and MEA kan gi reproduksjons- og utviklingsskader. Aldehydene, formamid and acetamid, kan gi henholdsvis utviklingsskader og være kreftfremkallende i forsøksdyr. Basert på eksperimentelle data synes noen nitrosaminer å være ekstremt kreftfremkallende. Flere nitraminer er også mutagene og karsinogene i gnagere, men de er mindre potente enn de tilsvarende nitrosaminer.
De foreslåtte retningslinjene for aminer er basert på tilgjenglig litteratur. Spesielt for AMP og MDEA er det få relevante og gode studier. Vi foreslår at den generelle befolkningen, over tid, ikke skal eksponeres for høyere nivåer i luften enn 10 $\mu g/m^3$ MEA, 5 $\mu g/m^3$ piperazin base, 6 $\mu g/m^3$ AMP eller 120 $\mu g/m^3$ MDEA. Disse verdier er en veiledning og ikke ment som grenseverdi for helseeffekter. Det er ønskelig å holde befolkningens eksponering for nitrosaminer så lavt som mulig. Også eksponering for nitraminer bør holdes på et lavt nivå på grunn av mulige, alvorlige helseeffekter. De irriterende egenskapene til aminer, aldehyder og amider synes imidlertid å være de mest relevante helseskadelige effektene i forbindelse med utslipp fra gasskraftverk med $CO_2$-fangst. Den totale forekomsten av slike forbindelser i lufta rundt $CO_2$-fangstanleggene bør vurderes samlet.

** Classification*

| | | |
|---|---|---|
| | *A* | *Unclassified (can be ordered from NILU)* |
| | *B* | *Restricted distribution* |
| | *C* | *Classified (not to be distributed)* |