Health effects of amines and derivatives associated with CO$_2$ capture:

Nitrosamines and nitrarnines

The Climate and Pollution Agency (Klif) has requested the Norwegian Institute of Public Health (NIPH) to carry out evaluations related to emission of amine-related compounds from the CO$_2$ Technology Center Mongstad:

1. Evaluation of potential health effects with regard to exposure to amines, nitrosamines and degradation products from the CO$_2$ capture plant. Klif will decide which amines and degradation products that should be evaluated and will also be responsible for the information about the emission of these compounds.

2. Furthermore, NIPH was asked by Klif to evaluate existing risk estimates for N-nitrosodimethylamine (NDMA). This includes an evaluation of EPA/IRIS risk estimates for drinking water and air, and other risk estimates of this nitrosamine in Europe or Canada. Klif wanted an evaluation of the validity of the values, how they can be used, and how they should be interpreted. NIPH was also asked to consider establishing guidelines ("luftkvalitetskriterier") for this nitrosamine.

In response to Klif, NIPH has consulted existing international risk evaluations of the relevant compounds, and scientific literature bases have been searched for in open publications on toxicological test results. Re-calculations of risk evaluations were carried out according to REACH guidelines.

1. 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 US, 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 (DME$L$s) 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 life-long exposure at the indicated levels would give an excess lifetime risk of acquiring cancer of either $10^{-5}$ or $10^{-6}$ in a million. A risk of one in a million is considered negligible. A risk of 1 in a million is considered as minimal, however, measures to reduce it should be considered.
2. 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 (NIPH report, 2009). Due to their potent carcinogenicity, other health outcomes of these compounds have been given less emphasis and are therefore less well documented.

2.1 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. Shortly, 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 1: **Human cancer risk estimate of NDMA in drinking water**

<table>
<thead>
<tr>
<th>Risk level</th>
<th>WHO1</th>
<th>Health1,2 Canada</th>
<th>US EPA1</th>
<th>CalEPA1,3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drinking water (µg/l)</td>
<td>10^{-5}</td>
<td>0.1</td>
<td>0.04</td>
<td>0.007</td>
</tr>
<tr>
<td>10^{-6}</td>
<td></td>
<td>0.004</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1 Based on Peto et al., (1991a; 1991b)
2 The document is only a draft
3 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*) 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 such factor, whereas Health Canada has, making the Canadian proposal the most conservative (Table 1). CalEPA determined the dose descriptor TDL10* 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.

### 2.2. 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 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 the best suited inhalation study available (Klein et al, 1991). Both procedures are presented in the following.

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*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.*
2.2.1. 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 linearized 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. NIPH has calculated the air concentrations (italics in Table 2) 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 2). In contrast, the US EPA has estimated an approximately 4 times higher risk than WHO/Canada and CalEPA.

2.2.1.1. Calculation of risk estimates using the dose-descriptor T25

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 2. 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 2: 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 $10^{-6}$)*

<table>
<thead>
<tr>
<th>Risk level</th>
<th>WHO</th>
<th>Canada</th>
<th>US EPA</th>
<th>CalEPA</th>
<th>NIPH</th>
</tr>
</thead>
<tbody>
<tr>
<td>TDLx (rat)</td>
<td>µg/kg bw/day</td>
<td>TDL05</td>
<td>TDL05</td>
<td>TDL10</td>
<td>T25</td>
</tr>
<tr>
<td>Intake (rat)</td>
<td>µg/kg bw/day</td>
<td>10^{-6}</td>
<td>0.00036</td>
<td>0.00036</td>
<td>0.00032</td>
</tr>
<tr>
<td>Air concentration (µg/m³)</td>
<td>10^{-5}</td>
<td>0.000313</td>
<td>0.000313</td>
<td>0.00007</td>
<td>0.000278</td>
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<tr>
<td></td>
<td>10^{-6}</td>
<td>0.00000313</td>
<td>0.0000313</td>
<td>0.000007</td>
<td>0.0000278</td>
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</tbody>
</table>

*Based on Peto et al., (1991a; 1991b)
Public Health goal. This is not an official guideline value. For US the official guideline value is given by EPA
Calculated from the TDL-values
NIPH (Norwegian Institute of Public Health) 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.

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

§ 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.
2.2.1.2. Choice of dose descriptor for calculation of risk estimates

According to the REACH Guidance document (REACH, Chapter R8) the \( T_{25} \) 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 \( T_{25} \) method results in a value more than double or less than half of that calculated with dose-response modelling methods (Reach, R8; Sanner et al., 2001). The \( T_{25} \) value gives a somewhat less conservative risk estimate than the ones based on TD05 and TD10, due to the extra safety implied by using the TD instead of the TD-values as mentioned above. Furthermore, the TD-values make use of the multidose design of the carcinogenic study in contrast to \( T_{25} \), which is based on one dose-level. In the opinion of NIPH it is reasonable to use the TD-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).

2.2.2. Calculation of air concentrations based on 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/m\(^3\), 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 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 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 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/m³ or below will be sufficient to obtain a lifetime excess cancer risk below 10⁻⁵.

2.3. 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 2, 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.

2.4. 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 3).

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/m³ to protect the general population from health hazards in relation to inhalation exposure of nitrosamines.
Table 3: Recommended tolerable drinking water and air concentrations of NDMA

<table>
<thead>
<tr>
<th>Drinking water (µg/l)</th>
<th>Air concentration (µg/m³)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.04¹</td>
<td>0.0003³</td>
</tr>
<tr>
<td>0.004²</td>
<td></td>
</tr>
</tbody>
</table>

¹Risk level 10⁻⁷  
²Risk level 10⁻⁸  
³Risk level below 10⁻⁸

2.5. Comparison of potency of different nitrosamines

NDMA is not the only nitrosamine generated and possibly emitted during CO₂ capture with amines. In Table 4 we have ranged different nitrosamines based on their oral cancer slope factor (CSF)** as reported by US EPA (1999). This gives an indication of the relative carcinogenic potencies of these nitrosamines. The CSFs depend on the dose-responses in the studies available and also vary between studies.

Table 4: Relative carcinogenic potencies of different nitrosamines

<table>
<thead>
<tr>
<th>Substance</th>
<th>CAS No</th>
<th>Oral CSF³ (mg/kg bw/d)¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>N-Nitrosodiethanolamine</td>
<td>1116-54-7</td>
<td>2.8</td>
</tr>
<tr>
<td>N-Nitrosodi-n-butylamine</td>
<td>924-16-3</td>
<td>5.4</td>
</tr>
<tr>
<td>N-Nitrosomorpholine</td>
<td>59-89-2</td>
<td>-</td>
</tr>
<tr>
<td>N-Nitroso-di-n-propylamine</td>
<td>621-64-7</td>
<td>7</td>
</tr>
<tr>
<td>N-Nitrosomethylisopropylamine</td>
<td>62-75-9</td>
<td>51</td>
</tr>
<tr>
<td>N-Nitrosodiethylamine</td>
<td>55-18-5</td>
<td>150</td>
</tr>
</tbody>
</table>

**Intigrated Risk Information System EPA

Table 4 shows that the various nitrosamines have different ability to induce cancer with N-Nitrosodiethanolamine 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.

**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.
The oral CSF for NDMA is 51 and the T25 is 0.15 mg/kg bw/d (Table 2). 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 4 has a T25 value lower than 1 and should be characterized as carcinogens of high potency.

2.6. Conclusions for nitrosamines

We recommend that the dose-response modelling from WHO/Health Canada in drinking water and linear extrapolation to low dose exposure is applied and converted into air concentrations. 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. This means that in a population of 1 mill exposed to 0.3 ng/m^3 during their whole life, 1 extra case of cancer due to the exposure will be expected. 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 estimated a Derived Minimal Effect Level (DMEL) from the inhalatory route, based on Klein et al. This DMEL is close to 0.3 ng/m^3.

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 further risk evaluation.

3. 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 (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 potency 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.

3.1. 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.

3.2. Carcinogenicity

Several studies show that some of the nitramines are indeed carcinogenic to rats (Druckrey, 1967; Goodall and Kennedy, 1976; Mirvish, 1980, Pliss 1982, Hassel, 1987, Scherf 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 1 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 adenocarcinomas) 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-nitromethylamine, 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 nitrosamine. 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.

3.3. Carcinogenic potency of nitramines compared to nitrosamines

The Carcinogenic Potency Database (CPDB), developed at the University of California, Berkeley, and Lawrence Berkeley Laboratory, provides standardized 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 5). The calculated TD50 values vary depending on the studies and their quality and should only be taken as indications on 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 tumorless throughout that period”.

Table 5: Comparison of TD50 values for selected nitramines and nitrosamines to indicate relative carcinogenic potencies

<table>
<thead>
<tr>
<th>Substance</th>
<th>Indicative TD50s*</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitramine (CAS No)</td>
<td>Nitrosamine (CAS No)</td>
<td>Nitramine</td>
</tr>
<tr>
<td>N-Nitromethylamine (598-57-2)</td>
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<td>N-Nitrodimethylamine (4164-28-7)</td>
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<td>N-Nitrodiethylamine (7119-92-8)</td>
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<td></td>
</tr>
</tbody>
</table>

* Values taken from CPDB
- No TD50 value in the CPDB
3.4. 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 which 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 do 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 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 might be performed. 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.
REFERENCES


5. Draft: N-Nitrosodimethylamine (NDMA) in Drinking Water, Health Canada 2010

6. Public Health Goal for N-Nitrosodimethylamine in Drinking Water, N-Nitrosodimethylamine December 2006, California Environmental Protection Agency

7. EPA/IRIS, N-Nitrosodimethylamine ; http://www.epa.gov/iris/subst/0045.htm


12. REACH "Guidance on information requirements and chemicals safety assessment" chapter R.8: Characterisation of dose [concentration]-response for human health; December, 2010

correlations between carcinogenic potency and species/site specificity and mutagenicity. Pharmacol Toxicol 80, 272-279.


27. The Carcinogenic Potency Database (CPDB); http://potency.berkeley.edu/