Recommendation from the Scientific Committee on Occupational Exposure Limits for Nitrogen Monoxide

SCOEL/SUM/89
June 2014

Employment, Social Affairs and Inclusion

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8-hour TWA:	2 ppm (2.5 mg/m^3)
STEL (15-min):	Not applicable (see Recommendation)
BLV:	-
Additional categorisation:	-
Notation:	Not applicable

This Recommendation is based on compilations by WHO (1997), DFG (2010) and the National Research Council of the National Academies (2012). An additional literature search was performed in December 2013.

1. Substance identification, physico-chemical properties

Name:	Nitrogen monoxide
Synonyms:	Nitric oxide, mononitrogen monoxide
Molecular formula:	NO
Structural formula:	
EC No.:	233-271-0
CAS No.:	10102-43-9
Molecular weight:	30 g/mol
Boiling point:	-152 °C
Melting point:	-163 °C
Conversion factors: (20 °C, 101.3kPa)	1 ppm = 1.25 mg/m^3 1 mg/m^3 = 0.8 ppm

EU harmonised classification: Not classified.

2. Occurrence/use and occupational exposure

The main source of the gas into the general atmosphere is from combustion processes. Nitrogen monoxide (NO) is oxidised to nitrogen dioxide (NO_2) in the presence of oxygen and the rate of reaction is proportional to the NO concentration. Therefore, in occupational situations both gases are mostly encountered together, with higher concentrations of NO than of NO_2.

NO is manufactured for captive consumption in the production of nitric acid for use in the synthesis of nitrate fertilisers. It is also used in nitration reactions and as a respiratory stimulant in hospital intensive care therapy.

Occupational exposure to NO can arise during its production and subsequent use, or where it is produced adventitiously as a product of incomplete combustion of fossil fuels, for example in motor vehicles (Diesel and petrol fuels) and in power stations (coal). Adventitious exposure also occurs during welding and cutting processes, following explosions, during the use of heating appliances and during the heating of cooking oils, food etc. Furthermore, exposure to NO occurs where nitric acid is used in

metal treatment. It also occurs following the biological breakdown of silage (DFG 2010).

As NO has found clinical application as a vasodilator (see Section 3.2.1), health care workers might be exposed in clinical situations at levels of some ten ppb (Lindwall *et al* 2006).

2.1. Analytical measurement

There are different methods for the measurement of airborne NO (electrochemical cell, chemoluminescence). The lowest detection limit (LDL) is reached by using chemoluminescence. Chemoluminescence measurements are considered to represent the "gold standard" of NO/NO_2 analysis (LDL: 0.002 ppm; Dahmann *et al* 2007 and 2009).

3. Health significance

NO acts as a diffusible messenger molecule in various tissues. Mathematical models allow the conclusion that NO (released from a point source for some seconds) can passively diffuse about 200 µm in biological systems. It has a very rapid half-life of 0.5–5 seconds (Wood and Garthwaite 1994).

Unlike NO_2, NO is not an irritant gas. No major role is attributed to an oxidation of inhaled NO into NO_2 in the lungs since, after inhalation, NO is eliminated faster than it is oxidised (Mercer 1999).

Whereas emphysema-like alterations are the main acute toxic effects of NO_2, vasodilatory effects and, at high concentrations, methaemoglobin (MetHb) formation, are observed in the case of NO. This also confirms different modes of actions of these nitrogen oxides. Therefore, both nitrogen oxides must be evaluated separately.

In animal studies, both NO and NO_2 induced pulmonary alterations with lesions of type I cells and cilia-bearing epithelial cells, which were replaced by less sensitive cells such as type II cells. Both substances also led to inflammatory symptoms, which were caused by cellular damage mainly resulting from oxidative stress (WHO 1997).

Since NO is endogenously formed in humans, NO is measured in the respiratory tract and exhaled air. The NO concentration is 0.008–0.02 ppm in healthy persons, according to analysis by gas chromatography/mass spectrometry (Gustafsson *et al* 1991, Heutelbeck *et al* 2007).

3.1. Toxicokinetics

3.1.1. Human data

There were no studies on dermal absorption of NO.

After exposure to NO at 0.32–4.88 ppm, 85–92 % was absorbed by humans at normal respiration and 91–93 % was absorbed after physical exercise (WHO 1997).

In one study, 6 male volunteers (aged 30–38 years and weighing 67–106 kg) inhaled NO at a concentration of 100 ppm for 3 hours. Comparison of the inhaled and exhaled NO concentrations led to a pulmonary retention of 64 %. A mean absorption rate of 0.49 ± 0.08 ml/min was calculated. This corresponds to a rate of 0.61 mg/min using the ideal gas volume (Young *et al* 1994). Accordingly, a cumulative inhalation of 109.8 mg NO results from an NO absorption rate of 0.61 mg/min (at 100 ppm) after a 3-hour exposure.

More than 70 % of the inhaled NO was excreted by adults in the urine in the form of nitrate. Nitrate was eliminated from the plasma via the kidneys at a rate that almost corresponds to glomerular filtration (National Research Council of the National Academies 2012).

3.1.2. Animal data

In rats, 90 %, 60 % and 20 % of the inhaled NO concentration was absorbed after exposure to about 170, 330 and 1 080 mg/m^3 (138, 270 and 880 ppm), respectively. The relative decrease in absorption has been attributed to an exposure-induced decline in respiration (WHO 1997). In dogs that had been exposed to vehicle exhaust, 73 % of the contained NO was discharged through the nasopharynx as compared to 90 % of the contained NO_2. As in the case of NO_2, the terminal airways were the target organs, NO being even less soluble in water than NO_2. In this way, even greater amounts reach the pulmonary region, where NO may then diffuse into the blood and react with haemoglobin (WHO 1997). In a metabolism study in rats, about 55 % of the radioactivity was excreted in the urine after a 123-minute exposure to radioactively labelled ^{15}NO at 143 ppm (Yoshida and Kasama 1987).

3.1.3. Biological monitoring

There is no method for biological monitoring of NO.

3.2. Acute toxicity

3.2.1. Human data

The effects of single exposure to NO in humans have been investigated in a number of experimental studies including detailed investigations into potential effects on airway resistance, pulmonary gas exchange and pulmonary and systemic vascular tone (National Research Council of the National Academies 2012). Reviews on the therapeutic use of NO in patients with acute respiratory distress syndrome have been presented by Manktelow *et al* (1997) and Troncey *et al* (1997a,b). In relation to effects on airway resistance, at the highest concentration tested (80 ppm for 10 minutes), no changes occurred (Högman *et al* 1993). However, NO significantly reduced the bronchoconstriction induced by an external bronchoconstricting agent (methacholine). Hence, the effects of NO on the airways appear to depend on the existing state of airway smooth muscle tone. Similarly, no effects occurred on vascular tone in either the pulmonary or systemic circulation at up to the highest concentration tested, 40 ppm for up to 10 minutes (Frostell *et al* 1993). However, when the pulmonary vasculature was in a state of vasoconstriction (as induced by hypoxia), the vasoconstriction was reversed, indicating a vasodilatory effect of NO. Therefore, the effects of NO on smooth muscle tone, whether bronchial or vascular, depend on the pre-existing state of constriction.

There is no evidence for effects on pulmonary gas exchange following a single exposure for up to 40 ppm NO for up to 10 minutes in humans. There are one or two instances in the literature of findings of a statistically significantly lower value for one of several pulmonary function parameters measured in volunteers exposed to NO at lower concentrations than this, i.e. below 40 ppm (von Nieding *et al* 1973, Kagawa 1982). Some minor effects were reported in volunteers exposed for 2 hours to 1 ppm, which appear to be quantitatively and biologically insignificant (Kagawa 1982). This view is supported by WHO (1997), having considered the overall database available for NO.

Among the limited number of single exposure studies available in humans, there is evidence for a small NO induced increase in MetHb formation. At the highest concentration of NO tested (80 ppm), MetHb levels increased from 0.4 % to 0.6 % (Högman *et al* 1993). An increase of such magnitude is not of clinical significance. In relation to subjective symptoms, none have been reported in any of the single-exposure studies available with exposures up to 80 ppm (National Research Council of the National Academies 2012).

The MetHb levels caused by NO inhalation were also investigated in 1 female and 4 male healthy persons (aged 30–36 years) after a 3-hour inhalation of NO at 32, 64, 128 and 512 ppm (Young *et al* 1994). Mean maximum MetHb levels reached under these inhalation conditions were 1.04 %, 1.75 %, 3.75 % and 6.93 %, respectively.

3.2.2. Animal data

MetHb formation is the main effect after acute exposure to NO, followed by effects on the central nervous system. The studies on acute toxicity after inhalation exposure are summarised in detail by DFG (2010).

Although acute lethality data in experimental animals are available for NO, these derive from early studies in which the exposure atmospheres are likely to have contained a substantial amount of NO_2, which would have contributed to the toxicity produced. Overall, no reliable information from animal studies concerning substantial toxicity or lethality related to single exposure, or effects relating to irritancy and sensitisation have been identified for NO (WHO 1997). It has been supposed, based on old and limited acute studies (Gray 1959), that NO was only about one fifth as toxic as NO_2 (cited by ACGIH 2001). However, there is no firm database to support this ratio.

3.3. Irritancy and corrosivity

There were no data available for local effects on skin or mucous membranes.

3.4. Sensitisation

There were no data available for allergenic/sensitisation effects.

3.5. Repeated dose toxicity

3.5.1. Human data

In terms of the effects of repeated exposure in humans, the vasodilating property of NO is used clinically in the treatment of hypertension in the new-born. Babies with persistent pulmonary hypertension of the new-born (PPHN) can be continuously exposed to up to 20 ppm NO for up to 14 days, to alleviate this condition. However, although this strongly points to only low toxicity of NO, there is no basis on which the known consequences of this clinical use can be extrapolated to predict the likely impact of workplace exposures, potentially spread over a working lifetime of many years, in adults (DFG 2010).

In a nitrogen fertiliser factory, 332 workers were exposed to various concentrations of NO (≤ 1.1 mg/m^3, corresponding to ≤ 0.9 ppm), NO_2 (≤ 1.3 mg/m^3, corresponding to ≤ 0.65 ppm), NO_3^- (≤ 0.2 mg/m^3) and NH_3 (≤ 2.8 mg/m^3). The workers were divided into groups depending on exposure at the workplace. The serum MetHb level and nitrate, urea and creatinine concentrations were measured and compared with a control group outside the factory. The highest serum nitrate levels occurred in workers who were exposed to high nitrate and ammonia concentrations. The serum creatinine

level correlated with the concentrations of NO ($r = 0.87$; $p < 0.05$) and NO_3^- ($r = 0.84$; $p < 0.05$). No correlation between the serum urea concentration and exposure to any substance in the inhaled air was established in any group. The MetHb level was highest among workers who were exposed to nitric acid and nitrate and thus to the highest NO concentration (Giroux and Ferrieres 1998), but the level of maximally 0.53 % was in the normal range. The nitrogen oxides were measured in the air by means of molecular absorption spectrophotometry.

More recently, two larger epidemiological studies have been performed in miners: by Lotz *et al* (2008) in German salt mines, and by Morfeld *et al* (2010) in German hard coal mines. The analytical part of the first study was published by Dahmann *et al* (2007), and that of the second study by Dahmann *et al* (2009). The first study (Lotz *et al* 2008) in salt mines was accompanied by a multitude of analytical measurements, covering 600–700 shift mean values in total. This data base allowed a very precise statistical analysis of the distribution of shift exposures: the 95th percentile of 8-hour shift data was slightly higher than the two-fold of the mean, both for NO and for NO_2.

The generation of a comparable body of analytical data was not possible in the coal mine study (Morfeld *et al* 2010). The main reason for this deficit of the coal mine study was that the chemoluminiscence instruments did not fulfil the very strict explosion safety requirements for underground coal mines. This led to relatively few analytical measurements reported in the coal mine study (e.g. 21 in Diesel locomotive drivers, 5 in blasting workers). However, on the basis of the pre-existing knowledge (Dahmann and Monz 2000, Dahmann *et al* 2007) it was anticipated that the general data distribution pattern of analytical data for NO/NO_2 in coal miners would be similar to those found in salt miners.

Lotz *et al* (2008) examined 410 and 463 miners (salt mines A and B) cross-sectionally; 75 and 64 % of the first cohort were again examined after a 5-year period. Exposure was measured by personal sampling. Personal lifetime exposure doses of salt dust, Diesel exhaust, NO_2 and NO were calculated for all miners. Dose-response relationships were calculated by multiple regression analysis. In the 5-year period, the adjusted (age, smoking etc.) effect of the exposure indicators resulted in a mean decrease of FEV_1 between -18 ml/year (mine A) and -10 ml/year (mine B). The personal concentrations related to this effect were 12.6 and 7.1 mg/m^3 inhalable dust, 2.4 and 0.8 mg/m^3 respirable dust, 0.09 and 0.09 mg/m^3 Diesel exhaust, 0.4 and 0.5 ppm NO_2, and 1.7 and 1.4 ppm NO (mines A and B). Exposure was related to symptoms of chronic bronchitis only in mine B. The authors concluded that the effects found in both mines indicated that the prevailing mixed exposure may cause lung function impairment in salt miners exposed over a long period of time. In this study, it was not possible to determine the effects of a single exposure component (nitrogen oxides vs. dust, Diesel exhaust etc.) separately.

This limitation was avoided in the study of hard coal miners by Morfeld *et al* (2010) by use of General Estimation Equation (GEE) models. This allowed the discrimination of effects of nitrogen oxides from those of other exposure component variables. A longitudinal inception cohort study (1974–1998) was conducted on miners who started working underground at two coal mines between 1974 and 1979. The authors determined the number of shifts underground, the exposure to coal mine dust, quartz dust, NO, NO_2, smoking behaviours, and the lung function parameters FVC, FEV_1 and FEV_1/FVC. In total, 1 369 miners worked on average 3 017 shifts underground per person. The total mean respirable coal mine dust concentration was 1.89 mg/m^3 (quartz: 0.067 mg/m^3), and nitrogen oxide concentrations were 0.58 ppm NO and 0.007 ppm NO_2. However, the exposure in defined subgroups was consistently higher (mean 8-hour shift concentrations: Diesel engine drivers, 1.35 ppm NO and 0.21 ppm NO_2; Diesel train drivers, 1.35 ppm NO and 0.52 ppm NO_2, blasting specialists, 0.84

ppm NO and 0.014 ppm NO_2; Dahmann *et al* 2009). The GEE-regression models did not reveal clear adverse dust exposure effects. Nitrogen oxides combined (NO + NO_2) showed small, statistically insignificant, effects on lung function, which were not considered as being adverse. It was concluded that nitrogen oxide exposures, including those in the subgroups, showed no adverse influence on lung function in this long-term longitudinal study.

Regarding the distribution of exposure data, the 95th percentiles of the 8-hour shift data (Dahmann *et al* 2009, Morfeld *et al* 2010) were slightly higher than the two-fold of the means, which was supported by the data of the preceding study in salt miners (Dahmann *et al* 2007, Lotz *et al* 2008).

If the distribution of exposures (95th percentile of 8-hour shift data slightly higher than the two-fold of the mean, see above) is taken into account, the data for the Diesel engine and Diesel train drivers (Dahmann *et al* 2009, Morfeld *et al* 2010) point to a NOAEC (lung function, chronic exposure) for NO of about 2.5 ppm, under relevant human workplace conditions.

3.5.2. Animal data

In relation to the effects of repeated exposure, no reliable information was available concerning the effects in animals of intermittent (6–8 hours per day) repeated exposures. However, there were studies involving continuous (or approaching continuous) exposure regimes. In one study in rats exposed continuously for 9 weeks to a background of 0.5 ppm NO with 2 daily 1-hour peak exposures of 1.5 ppm, light microscopic examination revealed slight pulmonary structural changes (fenestrations in the interstitial spaces of the alveolar septa) suggestive of the early stages in the development of emphysema (Mercer *et al* 1995), but it seems that these findings could not be reproduced by continuous exposure to 2 and 6 ppm of NO (Mercer 1999). Mercer (1999) reported a follow-up investigation, in which groups of rats (of the same strain as previously) were exposed continuously to 2 or 6 ppm NO for 6 weeks. Immediately after the end of the exposure period, bronchiolar lavage and detailed light and electron microscopic examination of the lungs were performed. This time, no increase in alveolar septum fenestrations was seen in NO exposed rats; the explanation for the discrepancy between the two studies is unknown. In this latter study, there were no toxicologically significant findings in the bronchiolar lavage. Morphometric analysis of the histological preparations revealed some proliferation of alveolar Type II cells at both NO exposure levels, which the author described as a "proinflammatory" response; the response was more evident in the higher (6 ppm) exposure group.

An earlier study performed by a different group, involved rats exposed continuously for 6 weeks to 0 (controls) or 2 ppm NO (Azoulay *et al* 1977). Light microscopy of the lungs from these animals revealed some evidence of "emphysema-like" changes in the NO exposed animals, relative to the controls. However, the electron microscopic observations made were inconclusive. The authors concluded that the light microscopy findings "might result from the exposure to NO". There is also a study in dogs, in which groups of 10 beagles were exposed to 0 or 1.64 ppm NO (contaminated with 0.14 ppm NO_2) for 16 hours per day for 68 months (Hyde *et al* 1978). The dogs were then maintained for an exposure-free period of 3 years and then sacrificed for lung histopathology. The results showed that in dogs exposed to NO, there was alveolar air space enlargement, destruction of alveolar septa and an increase in alveolar pores, observations indicative of emphysema-like changes. Although a low concentration of NO_2 was also present, the overall toxicological database on NO_2, as evaluated by WHO, suggests that it would not produce effects on the lung, evident by light microscopy, at such a low concentration (WHO 1997).

In contrast to the general pattern of the above findings, no pulmonary structural changes were found in mice following 23 months of continuous exposure to 2.4 ppm. No histopathological changes were identified in this study in any other organs and tissues including the reproductive organs. Continuous exposure of mice to 10 ppm NO (contaminated with about 1 ppm NO_2) for 6.5 months produced lung damage (increased relative lung weight, hyperaemia and congestion, bronchiolar epithelium hyperplasia) but no increase in MetHb formation (Oda *et al* 1976). However, the same author reported four years later that circulating MetHb concentrations of up 15 % can be achieved following inhalation of 80 ppm (Oda 1980). In the meantime, it has been demonstrated that the primary reaction of NO exposure is that between haemoglobin and NO yielding nitrosyl-haemoglobin (NOHb), a compound that is incapable of oxygen transport (Oda 1975).

3.6. Genotoxicity

Concerning its mutagenic potential, available data are equivocal (Stepnik 2002). At cytotoxic concentrations, NO was mutagenic in some bacterial and mammalian cell assays, such as *Salmonella typhimurium* TA 100, Don hamster cells and TK 6 human cells (Zhuang *et al* 2000, Nguyen *et al* 1992), but not in others (*Salmonella* SOS repair, V79 hamster cells (Victorin 1993 and 1994). There is evidence for its ability to produce single-strand breaks in DNA (Felley-Bosco 1998). It has been demonstrated that this genotoxic activity of NO is not a function of it inducing pH changes (Nguyen *et al* 1992), and several pathways have been discussed (Tamir *et al* 1996). In the only available *in vivo* mutagenicity study, which did not follow a validated test method, mutagenic changes were found in cells removed from the lungs of rats given a single 3-hour exposure to 27 ppm, but not after exposure to 9 or 19 ppm (Isomura *et al* 1984). According to Stopper *et al* (1999), all available evidence suggests that the pronounced cytotoxicity of NO and its oxidative metabolites outweighs any genotoxic potential.

3.7. Carcinogenicity

Mechanistically, both pro- and anti-tumourigenic effects of NO have been discussed (Stepnik 2002). However, no data of chronic bioassays are available.

3.8. Reproductive toxicity

There were no data available for reproductive toxicity.

4. Recommendation

Genotoxic activity has been seen in some mutagenicity studies in bacteria and mammalian cells with NO *in vitro*, but not in others (Section 3.6) In the only *in vivo* study available, mutagenic changes were found in the lung cells removed from rats following exposure to NO at 27 ppm; no such changes were produced with exposures to 9 or 19 ppm. This was not a validated study, and the correct interpretation to place on the results is unclear. However, the half-life of NO is very short, and NO is an endogenous messenger compound that is regulated by a tight homeostasis. In view of this homeostasis, a threshold for mutagenicity would be likely. In general, it appears that there is no practical relevance of genotoxic activity of NO at levels of the occupational exposure limit (OEL) recommended below.

Unlike NO_2, NO is not an irritant gas upon acute exposure. Whereas emphysema-like alterations are the main acute toxic effects of NO_2, vasodilatory effects and, at high concentrations, MetHb formation, are observed in the case of NO.

Regarding long-term repeated exposure, the critical endpoint of concern is lung damage, based on experimental data in animals. However, studies in experimental animals have employed daily exposure regimes encompassing most or all of the day, rather than a 6–8-hour period that would be representative of the workplace situation, and these studies have produced varying results. Studies in rats suggest that NO has a potential to cause pro-inflammatory or detrimental changes in the lungs with continuous exposure to 2–6 ppm over a few weeks. An initial finding of fenestrations in the alveolar septa, microscopic changes possibly indicative of the early stages in the development of emphysema, with twice-daily exposures to 1.5 ppm, each of 1-hour duration, set against a continuous background of 0.5 ppm, was not reproduced by the same author in a later study using exposure levels of 2 and 6 ppm; there is no explanation for this. A repeated exposure (16 hours/day) study in dogs exposed to 1.6 ppm NO (with 0.14 ppm NO_2) showed evidence of exposure-induced emphysema-like changes; the level of NO_2 contamination involved here was too low for it to be responsible for such changes. There are obvious species differences, as mice appear to be more resistant to these respiratory effects than rats or dogs, with a NOAEC of 2.4 ppm in a lifetime exposure study.

The extent to which the extended or continuous exposure regimes used have exacerbated the consequences, in comparison with a repeated (6–8 hours/day) regime, are not determinable from the available experimental data. Hence, an overall NOAEC for the adverse effects of NO on the lungs of experimental animals is not available. The results of experimental studies in which rats and mice were continuously exposed to NO, instead of a repeated regime (6–8 hours/day) cannot be used to derive a numerical point of departure to assess a recommended OEL for human working conditions. In any case, it may be expected that a NOAEC for "working conditions" (8-hour time weighted average, TWA) should be consistently higher than NAOEC values found for continuous long-term exposure.

Given this situation, the derivation of a recommended OEL for NO must exclusively rely on data obtained in humans. Laboratory studies in humans under controlled short-term exposures to NO have been performed (Section 3.2.1); single exposures to 40 ppm NO for 10 min or to 1 ppm NO for 2 hours did not lead to adverse changes in lung function tests (body plethysmography). This very low human acute toxicity (compared to NO_2) is in line with clinical experience, e.g. in the NO treatment of newborns with persistent pulmonary hypertension (Section 3.5.1). With this toxicological profile of NO, there is no requirement for a specified short-term exposure limit (STEL).

The major problem in deriving a recommended OEL for NO from occupational field studies is that NO reacts with air to form NO_2, which is more toxic than NO due to local irritation of the pulmonary system. At occupational settings, both nitrogen oxides occur together, besides other components such as dust or Diesel particles. This complicates the interpretation of available occupational field studies, as it is difficult to determine the effects of a single exposure component separately.

A suitable basis for deriving a recommendation for an OEL (8-hour TWA) is provided by a recent longitudinal study (1974–1998) in German coal miners, in which discrimination of effects of nitrogen oxides was performed using General Estimation Equation (GEE) models (Morfeld *et al* 2010). In this study, underground miners were exposed to mean NO concentrations of 0.58 ppm (NO_2: 0.007 ppm). However, there were sub-collectives with higher exposures: for Diesel engine drivers and for Diesel

train drivers, mean exposures were 1.35 ppm NO (NO_2: 0.21 and 0.52 ppm, respectively). These NO_x exposures caused no adverse influence on lung function in the longitudinal long-term study (Section 3.5.1). By contrast, a previous study of the same group in two German salt mines (Lotz *et al* 2008) with higher mean exposures (1.7 ppm NO [0.4 ppm NO_2] in the 1st mine; 1.4 ppm NO [0.5 ppm NO_2] in the 2nd mine) pointed to the possibility of lung function impairment in miners exposed over a long period of time. However, this study could not dissociate the effects of nitrogen oxides from those of other variables (dust, Diesel exhaust etc.). If the distribution of exposures (95th percentile of 8-hour shift data slightly higher than the two-fold of the mean) is taken into account, the data for the Diesel locomotive and Diesel train drivers in the coal mine study (Dahmann *et al* 2009, Morfeld *et al* 2010) point to a NOAEC (lung function, chronic exposure) for NO at relevant human workplace conditions of about 2.5 ppm. This conclusion is generally compatible with the results of the salt mine study.

Therefore, based on experience from human field studies and considering the "preferred value approach" of SCOEL, an OEL of 2 ppm NO (8-hour TWA) can be considered to be safe under realistic working conditions. Such a level is seconded by the available experimental animal data (*v.s.*), if differences between continuous and intermittent exposure conditions are considered. It is also consistent with the proven low acute human toxicity of NO.

Therefore, SCOEL recommends an OEL for NO of 2 ppm.

There is no requirement for a skin notation.

At the recommended level, no measurement difficulties are foreseen (Dahmann *et al* 2007 and 2009).

The present Recommendation was adopted by SCOEL on 11 June 2014.

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