EURACOAL

European Association for Coal and Lignite

AISBL

EURACOAL Position Paper

on the recommendation SCOEL/SUM/53 (June 2012) of the Scientific Committee on Occupational Exposure Limits for nitrogen dioxide

Background

Mr. Costas Constantinou, Head of Unit – Health, Safety and Hygiene at Work, DG Employment, Social Affairs and Inclusion, raised the following questions in his covering letter to the revised Scientific Committee on Occupational Exposure Limits (SCOEL) recommendation SCOEL/SUM/53 (June 2012) on nitrogen dioxide (NO_2):

QUESTION 1

Are there any important or critical published papers that have not been taken into consideration?

QUESTION 2

Has any of the scientific data been misinterpreted?

QUESTION 3

Is the approach taken consistent with SCOEL's methodology?

QUESTION 4

Are you aware of any other relevant information?

EURACOAL's commentary will deal with these questions. However, this will not be done in a step-by-step procedure. We will discuss the SCOEL/SUM/53 with regard to four important topics (epidemiological evidence, uncertainty factor in the derivation of the OEL, justification of the STEL and control of OEL) and we will refer to the above questions where appropriate.

With regard to ***QUESTION 3***, we will make use of SCOEL's document Methodology for the Derivation of Occupational Exposure Limits – Key Documentation (Version 6, July 2011) (http://ec.europa.eu/social/main.jsp?catId=148&langId=en&intPageId=684). This document will be termed "SCOEL's methods document" and cited as SCOEL-METH 2011. The new SCOEL recommendation for NO_2 will be referenced as SCOEL/SUM53 2012. The abbreviations OEL, NOAEL, LOAEL, STEL and UF are as defined in SCOEL-METH 2011.

Avenue de Tervueren 168 Bte 11 ■ B-1150 Brussels ■ Belgium
Tel. +32 (0) 2 775 31 70 ■ Fax +32 (0) 2 771 41 04 ■ e-mail euracoal@euracoal.org
www.euracoal.org

1. Epidemiological Evidence

Human data are preferable in the OEL derivation according to SCOEL's method document: "In general, good quality human data are to be preferred to animal data" (section 3.3.1, SCOEL-METH 2011, p.12). Case-control, historical cohort or longitudinal prospective studies are of special value in OEL derivation: "Case-control, historical cohort or longitudinal prospective studies may be of particular value where the adverse effect in question is associated with repeated or long term exposure. Such studies represent the only satisfactory way to study long term effects in humans and well conducted studies may provide powerful evidence, particularly where adverse effects are clearly defined, exposure is well characterised and potential bias and confounding factors are well controlled." (SCOEL-METH 2011, p.13).

As a first step, SCOEL has to compile all relevant data for OEL derivation (SCOEL-METH 2011, p.11). Thus, it can be assumed that SCOEL will check if relevant high-quality studies are available (group (4) in section 3.3.1, SCOEL-METH 2011, p.12).

Indeed, at least one epidemiological study fulfils this highest quality criterion: the cohort study performed in German hard coal mining (Dahmann *et al*. 2009, Morfeld *et al*. 2010a). This is a large longitudinal study (about 1,300 workers) on clearly defined adverse endpoints (lung function deficits) that distinguishes itself by having an internationally unique combination of observation density (about nine medical examinations per person), data quality (shift data as the basis for exposure assessment plus extensive confounder adjustment) and analytical approach (GEE-regression modelling).

Due to the methodological evaluation criteria mentioned above (SCOEL-METH 2011), it is difficult to comprehend why SCOEL devotes only one sentence to this study: "In 2009, a longitudinal study was published conducted on German coalminers with a long term (1974-1998) average exposure to coal mine dust of 1.89 mg/m^3 (quartz: 0.067 mg/m^3), to NO of 0.58 ppm and to NO_2 of 0.007 ppm, without registering any effects on lung function (Morfeld *et al.* 2009)." (SCOEL/SUM53 2012, p.7).

The only reason is given by the sweeping statement on all epidemiological studies: "SCOEL considers that the available human studies conducted in working population are not reliable for deriving an 8-h OEL, taking into account that these were performed under conditions of mixed exposure to other pollutants, besides NO_2." (SCOEL/SUM53 2012, p.11).

This statement disregards the studies of Morfeld *et al.* 2010a and Robertson *et al.* 1984. The cited SCOEL statement may apply to studies with positive findings and mixed exposures, *i.e.*, if exposure effects were identified but could not be related to NO_2 uniquely. However, the studies from British and German hard coal mining (Robertson *et al.* 1984, Jacobsen *et al.* 1988, Morfeld *et al.* 2010a) showed negative findings – even according to SCOEL's evaluation – despite the other exposure components (that were controlled for analytically). Thus and contrary to SCOEL's evaluation, these studies are informative when deriving a limit value proposal. The exposure range covered by these studies did not produce adverse effects. A limit value proposal is bounded below by the information delivered by these studies. Therefore, scientific data have been misinterpreted.

CONCLUSION

The epidemiological studies of Morfeld *et al.* 2010a and Robertson *et al.* 1984 have been misinterpreted (*QUESTION 2*). The evaluation of these studies is incompatible with SCOEL's methodology (*QUESTION 3*).

To complete the analysis and reporting of the German cohort study in hard coal mining (Dahmann *et al*. 2009, Morfeld *et al*. 2010a), an additional analysis was performed and published (Morfeld *et al*. 2010b). This analysis dealt with questions raised during discussions of the study in Germany. This publication is missing in SCOEL/SUM53 2012. According to SCOEL's methods document there is no restriction regarding language or kind of publication to qualify for an evaluation by SCOEL: "Any relevant additional data, which may be supplied by interested parties or otherwise obtained by the Commission, will also be taken into account in the evaluation." (SCOEL-METH 2011, p.15, section 3.4).

Morfeld *et al*. 2010b summarised the exposure situation as follows. For locomotive and overhead monorail operators, 1.35 ppm NO and 0.21 ppm NO_2 have been determined to be the rough current average values of exposure during an 8-hour shift. Experts estimated that exposure values for both trace gases were lowered by approximately 25% since 1995 but constant before. It is considerably more difficult to evaluate the exposure of blasting personnel, although a series of measurements did yield rough average values of 0.84 ppm NO and 0.014 ppm NO_2. According to experts, the exposure of blasting crews has dropped by approximately 10% since 1995 and should be assumed to be almost invariant for the period between 1970 and 1995. No adverse effects on lung function were detected given these exposures. An additional analysis applying fractional polynomials showed that a cumulative exposure of up to 20 ppm-years NOx (= 99.2%-fractile of the exposure distribution, *i.e.*, covering the highest exposed) no effect on lung function was found (*c.f.* the figure in Morfeld *et al*. 2010b). Note that such averaged long-term exposures cannot be directly used as a NOAEL estimate to derive an 8h-OEL because they are far too low (Greim 1996). Reference should be made to the recent shift (8h-TWA) exposures of those most exposed. The averages are already as high as 0.2 ppm NO_2, and were even higher in former times. Measurements showed that recent shift concentration averages ranged up to 2 ppm NO_2 (Table 9 in Dahmann *et al*. 2009). These values should be taken into account when deriving any shift limit value proposal.

CONCLUSION

There is an important publication available that is not taken into account in the new SCOEL document on NO_2 (*QUESTION 1*, *QUESTION 4*): Morfeld *et al.* 2010b. The missing effects

among those subject to highest exposure in this analysis should be taken into account when establishing an OEL proposal according to SCOEL's methods document (*QUESTION 3*).

As an aside, we would like to add that the 5th paragraph on p.7 in SCOEL/SUM53 2012 does not report on long-term exposures and, thus, does not belong in the "Repeated dose toxicity" section. However, the study of Frampton *et al.* 1989 is already discussed on p.4 under the heading "Acute toxicity", but with a somewhat different description and interpretation.

The document should be rechecked for such inconsistencies.

2. Uncertainty factor in the derivation of the OEL

The derivation of the OEL proposal for NO_2 of 0.2 ppm depends considerably on the applied uncertainty factor (UF). SCOEL correctly describes that the 13-week inhalation study (BASF 2006) showed no effect on BALF parameters, cell proliferation or apoptosis up to an exposure of **2.15 ppm NO_2** (SCOEL/SUM53 2012, p.9). SCOEL's comment that the measured concentrations are not reliable (SCOEL/SUM53 2012, p.9) appears to be speculative. We wish to emphasize that this study did not test higher exposures than 2.15 ppm. It remains unclear where exactly the NOAEL was because no LOAEL could be determined. Thus, for this study 2.15 ppm is a lower bound for the NOAEL. SCOEL applies an uncertainty factor of UF = 10 and uses the highest exposure category of the BASF study to derive the OEL proposal of 0.2 ppm = 2 ppm/ 10 (SCOEL/SUM53 2012, p.11). The relevance of the UF is evident. When we set UF = 1, 2, 5, 10, 20 *etc.*, we will get 2 ppm, 1 ppm, 0.4 ppm, 0.2 ppm, 0.1 ppm *etc.* as OEL proposals. This high sensitivity of the OEL to uncertainty factor points to the need to follow up ***QUESTION 3*** with an examination of whether SCOEL's methods document and SCOEL's document on NO_2 can actually justify the chosen UF value of 10.

SCOEL explains that uncertainty factors (UFs) will be applied usually, and that the limit value proposal will be derived as OEL = NOAEL / UF (SCOEL-METH 2011, pp.18, 23). The derivation of an UF is discussed in section 6 of the methods document (SCOEL-METH 2011, pp.22-24).

SCOEL explains: "When developing limit values (*e.g.* ADIs for food additives and contaminants, water/air quality standards) for lifetime exposure of the general public it is internationally accepted that safety factors of 10, 100 or 1000 should be used, depending on the available experimental and epidemiological evidence. 100 is usually used as a default value" (SCOEL-METH 2011, p.22). Furthermore SCOEL makes clear: "… it is often appropriate to apply lower UFs for the development of scientifically based OELs than those which are used to develop limit values for the general population exposed to environmental and consumer chemicals." (SCOEL-METH 2011, p.22). The factors 10, 100 and 1000 were introduced to specifically protect the general population ("environmental UFs") and, thus, are usually not applied in the occupational setting ("occupational UFs").

Unfortunately, SCOEL does not quote any occupational UFs in SCOEL-METH 2011. However, due to the arguments developed in section 6.3 it appears to be obvious that the occupational UFs should be smaller than the environmental UFs (SCOEL-METH 2011, p.22). In section 6.5 (SCOEL-METH 2011, p.23), SCOEL presents a ranking of the occupational UFs in terms of categories (as mentioned, unfortunately without quoting any actual UF values). The lowest two categories ("fall[s] short of accepted standards") are not applicable to the situation of NO_2 because the BASF study (BASF 2006) was judged to be of high quality (see SCOEL's evaluation of this study: "performed according to modern standards", SCOEL/SUM53 2012, p.11). Moreover, large and reliable epidemiological investigations are available (see section 1 above on "Epidemiological evidence"). Thus, an allocation to the first category appears to be appropriate. This means that for NO_2, the lowest UF should have been chosen from the occupational UFs and certainly not a value from the list of environmental UFs. Note that the value UF = 10 applied by SCOEL was taken from the list of environmental UFs and has no justification: SCOEL/SUM53 2012 gives no explanation of why the value 10 was chosen. Note, however, that the methods document asks for such a justification: "The SCOEL will justify their decision on the choice of UF in their recommendation for an OEL" (SCOEL-METH 2011, p.24).

CONCLUSION

The chosen UF = 10 is unjustified und not compatible with SCOEL's methods document (*QUESTION 3*).

3. Justification of the STEL

SCOEL proposes a STEL (15 min) = 1.0 ppm for NO_2 (SCOEL/SUM53 2012, p.11). The methods document demands a scientific basis for the derivation of a STEL: "When … there is a need for a specific STEL, and sufficient data exist on which to make a scientifically based recommendation, a numerical limit will be proposed" (SCOEL-METH 2011, p.21). Thus, we will follow up on ***QUESTION 3*** and explore the scientific basis of the proposed STEL. SCOEL bases its STEL recommendation on NO_2 chamber experiments with volunteers (Frampton *et al.* 1989, Frampton *et al.* 1991, Frampton *et al.* 2002, Sandström *et al.* 1992, Blomberg *et al*. 1999, Solomon *et al*. 2000, Devlin *et al*. 1999). These studies evaluated a large number of parameters in a small number of subjects. Thus, statistically significant findings can only be expected to occur by chance. However, an adjustment for multiple testing was not performed. It is important to note that in none of these investigations were the same parameters described as being significantly different between exposed and controls. Just one of these investigations was repeated (Frampton *et al.* 1989) and the authors report as a main finding of their study the impairment of virus inactivating after NO_2 exposure. Frampton *et al*. 2002 could not replicate this finding, but focused on other endpoints such as certain lymphocyte ratios. However, the authors themselves judged these changes as of no clinical significance. These chamber studies with human volunteers performed at a concentration of 2 ppm

NO_2 (Blomberg *et al*. 1999, Solomon *et al*. 2000, Devlin *et al*. 1999) or 1.5 ppm NO_2 (Sandström *et al.* 1992, Frampton *et al.* 1989a, Frampton *et al.* 2002) generated no convincing evidence. Without a replication of the findings in larger study groups, without having the chance to study the same endpoints across different investigations and without control of the multiple testing, the results are not reliable. The data are thus insufficient to derive a STEL proposal scientifically.

CONCLUSION

Sufficient data are necessary to derive a numerical value for a STEL and to justify a proposal scientifically. This is not the case in the case of NO_2. Hence, the SCOEL recommendation is not in agreement with SCOEL's methodological framework (*QUESTION 3*).

4. Control of OEL

The proposed OEL for NO_2 cannot be controlled adequately with the available measurement instruments in underground mining. Dahmann *et al*. 2007 and Dahmann *et al*. 2009 listed and discussed the possible instruments/procedures to measure NO_2 in mining. Dräger Multiwarn instruments may be used and these direct-reading instruments can measure NO_2 concentrations as low as 1 ppm reliably, with lower gas detection levels. However, the CEN standard EN 482 defines specific requirements for compliance measurements. This is related to the extended measurement uncertainty and the minimal value the instrument must be able to measure. For control measurements, the measurement range must cover the interval from 1/10 of the limit value up to twice the limit value. Uncertainty of measurements must be bounded by 50% for concentrations up to half of the limit value and by 30% if the values are higher. SCOEL acknowledges these requirements: "It is accepted that no measurement difficulties are foreseen when the limit of quantification of the method fit the requirement set by the EN 482 to be above a tenth of the OEL proposed." (SCOEL-METH 2011, p.16). Thus, proposing an OEL at 0.2 ppm means that NO_2 concentration as low as 0.02 ppm must be measurable with a bounded uncertainty.

SCOEL's methods document requires that SCOEL investigates the feasibility of measurements when proposing an OEL: "(14) assess the technical measurement feasibility of the air and biological values recommended." (SCOEL-METH 2011, p.11). SCOEL comments on this regarding NO_2 as follows "The lowest detection limit of 0.002 ppm is reached by using chemiluminescence. However, there are some restrictions to the applicability of this method, for instance in underground mining (Dahmann *et al.* 2007, 2009)" (SCOEL/SUM53 2012, p.4). However, Dahmann *et al*. 2007 and Dahmann *et al*. 2009 clearly stated that chemiluminescence devices cannot be applied in hard coal mining because of explosion hazards and that these devices could only be used in low exposure environments such as workshops in potash mining. Thus, a control of the recommended OEL of 0.2 ppm is not possible in underground mining. The wording used by SCOEL ("some restrictions") is therefore somewhat misleading.

CONCLUSION

The proposed OEL for NO_2 of 0.2 ppm cannot be controlled adequately in underground mines. The requirements laid down in SCOEL's methods document are not fulfilled (*QUESTION 3*).

6. Overall evaluation of SCOEL/SUM53 2012

In summary, SCOEL's proposals for nitrogen dioxide are unconvincing due to missing scientific evidence and with regard to the epidemiological data. We call for a strict adherence to SCOEL's methods document. The number used as an uncertainty factor must be chosen appropriately and the choice of this number must be justified. In addition, the proposed limit value must be controllable. SCOEL should revise the NO_2 recommendation accordingly, while applying evidence-based procedures and while strictly adhering to SCOEL's methods document.

References

BASF (2006). Nitrogen dioxide – Subchronic 90-day inhalation study in Wistar rats –gas exposure. Project No. 9910375/03055, BASF AG Ludwigshafen, unpublished.

Blomberg A, Krishna MT, Helleday R, Söderberg M, Ledin MC, Kelly FJ, Frew AJ, Holgate ST, Sandström T (1999). Persistent airway inflammation but accommodated antioxidant and lung function responses after repeated daily exposure to nitrogen dioxide. Am J Respir Crit Care Med 159:536-543

Dahmann D, Monz C, Sönksen H (2007). Exposure assessment in German potash mining. Int. Arch. Occup. Environ. Health 81:95-107

Dahmann D, Morfeld P, Monz C, Noll B, Gast F (2009) Exposure assessment for nitrogen oxides and carbon monoxide in German hard coal mining. Int Arch Occup Environ Health 82: 1267-1279

Devlin RB, Horstman DP, Gerrity TR, Becker S, Madden MC, Biscardi F, Hatch GE, Koren HS (1999). Inflammatory response in humans exposed to 2.0 ppm nitrogen dioxide. Inhal Toxicol 11:89-109

Frampton MW, Smeglin AM, Roberts Jr. NJ, Finkelstein JN, Morrow PE, Utell MJ (1989). Nitrogen dioxide exposure in vivo and human alveolar macrophage inactivation of influenza virus in vitro. Environ Res 48:179-192

Frampton MW, Morrow PE, Cox C, Gibb FR, Speers DM, Utell MJ (1991). Effects of nitrogen dioxide exposure on pulmonary function and airway reactivity in normal humans. Am Rev Respir Dis 143:522-527

Frampton MW, Boscia J, Roberts NJ Jr, Azadniv M, Torres A, Cox C, Morrow PE, Nichols J, Chalupa D, Frasier LM, Gibb FR, Speers DM, Tsai Y, Utell MJ (2002). Nitrogen dioxide exposure: effects on airway and blood cells. Am J Physiol Lung Cell Mol Physiol 282:L 155-165

Greim H. Ableitung von schichtbezogenen MAK-Werten für Stäube aus Langzeitgrenzwerten. Toxikologisch-arbeitsmedizinische Begründungen von MAK-Werten (Maximale Arbeitsplatzkonzentrationen) der Senatskommission zur Prüfung gesundheitsschädlicher Arbeitsstoffe. Deutsche Forschungsgemeinschaft. Vol. 23.Weinheim: Wiley-VCH, 1996; 1-22

Jacobsen M, Smith TA, Hurley JP, Robertson A, Roscow R (1988). Respiratory infections in coal miners exposed to nitrogen oxides. Institute of Health Effects, Research Report No. 18, Cambridge, MA, USA

Morfeld P, Noll B, Büchte SF, Derwall R, Schenk V, Bicker HJ, Lenaerts H, Schrader N, Dahmann D (2010a) Effect of Dust Exposure and Nitrogen Oxides on Lung Function Parameters of German Coalminers - a Longitudinal Study applying GEE regression 1974-1998. Int Arch Occup Environ 83:357-371

Morfeld P, Noll B, Büchte SF, Bicker HJ, Lenaerts H, Schrader N, Schenk V, Derwall R, Dahmann D (2010b) Einfluss von Stickoxiden auf die Lungenfunktionsparameter deutscher Steinkohlenbergleute: Eine Längsschnittstudie auf der Basis von GEE-Regressionsmodellen. 50. Wissenschaftliche Jahrestagung der Deutschen Gesellschaft für Arbeitsmedizin und Umweltmedizin e.V. in Dortmund 272-276
(http://www.dgaum.de/images/stories/jahrestagungen/dgaum50_jahrestagung_2010_dortmund.pdf)

Robertson A, Dodgson J, Collings P, Seaton A (1984) Exposure to oxides of nitrogen: respiratory symptoms and lung function in British coalminers. Brit J Industr Med 41:214-219

Sandström T, Ledin MC, Thomasson L, Helleday R, Stjernberg N (1992). Reductions in lymphocyte subpopulations after repeated exposure to 1.5 ppm nitrogen dioxide. Br J Ind Med 49:850-854

SCOEL-METH 2011 Methodology of the Scientific Committee on Occupational Exposure Limits for the Derivation of Occupational Exposure Limits – Key Documentation (Version 6, July 2011) (http://ec.europa.eu/social/main.jsp?catId=148&langId=en&intPageId=684)

SCOEL/SUM53 2012 Recommendation from the Scientific Committee on Occupational Exposure Limits on Occupational Exposure Limits for nitrogen dioxide, June 2012

Solomon C, Christian DL, Chen LL, Welch BS, Kleinman MT, Dunham E, Erle DJ, Balmes JR (2000). Effect of serial-day exposure to nitrogen dioxide on airway and blood leukocytes and lymphocyte subsets. Eur Respir J 15:922-928

EURACOAL, 3 September 2012