Gezondheidsraad
Health Council of the Netherlands

To the Minister of Social Affairs and Employment

Subject	: Advisory letter *Ethylene oxide*	
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Our reference	: U 8249/SV/fs/459-D71	Publication no. 2014/26E
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Dear Minister,

At the request of your predecessor (see Annex A), the Dutch Expert Committee on Occupational Safety (DECOS) of the Health Council (see Annex B) derives health-based recommended occupational exposure limits or cancer risk values for substances in air to which people can be occupationally exposed. These recommendations form the basis for occupational exposure limits, to be set by the Minister, with which the health of workers can be protected.

In this advisory letter, which has been evaluated by the Standing Committee Health and Environment, I inform you on the findings of the Committee with respect to the health risks of occupational exposure to ethylene oxide. Ethylene oxide is being used, amongst others, for the sterilisation of medical equipment, and as raw material for the production ethylene glycol ethers, ethanediol, and ethanolamines.

Classification and mode of action

The European Union has classified ethylene oxide for carcinogenicity in Category 1B ('The compound is presumed to be carcinogenic to man'). The International Agency on Research on Cancer (IARC) concluded in 2012 that there was limited evidence in humans for a causal relationship between ethylene oxide exposure and lymphatic and haematopoietic cancers, specifically lymphoid tumours (i.e. non-Hodgkin lymphoma, multiple myeloma and chronic lymphocytic leukaemia) and breast cancer. By contrast, according to IARC there is sufficient evidence for carcinogenicity of ethylene oxide in animals.[1] Since IARC also includes (convincing) positive data in its decision making, ethylene oxide has eventually been classified in category 1 (the substance is carcinogenic to humans').

At the request of DECOS, the Subcommittee on the Classification of Carcinogenic Substances of the Health Council has evaluated the carcinogenic properties and mode of action of

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ethylene oxide. This subcommittee confirms the European classification in category 1B. In addition, the Subcommittee concludes that ethylene oxide can damage the DNA directly, and should therefore be considered as a genotoxic carcinogen with a stochastic mode of action. This means that DECOS cannot derive a 'safe' exposure level below which no (carcinogenic) effects occur based on current scientific insight.[2] In such case, the Health Council calculates the concentrations in air that correspond with an extra risk of 4 per 1,000 and 4 per 100,000 of (dying from) cancer due to occupational exposure to substances, the so-called cancer risk values.[3]

Current Dutch occupational exposure limit

On the basis of an advice of the Werkgroep van Deskundigen (WGD)[a] from 1989[4], the member of government at that time set the current binding limit for ethylene oxide of 0.84 mg/m^3 (corresponding to an extra risk of dying from cancer of 4 per 1,000). For its advice, the WGD relied on data from animal studies. Since 1989, more data have become available and risk assessment methodology has changed.

Evaluations of other international organisations

The health risks of occupational exposure to ethylene oxide have recently been evaluated by some international organisations. The Scientific Committee on Occupational Exposure Limits (SCOEL) of the European Committee has published a report on ethylene oxide risks in 2012.[5] The German Ausschuss für Gefahrstoffe (AGS) has also recently published a report on ethylene oxide.[6] By both organisations, cancer risks of occupational exposure to ethylene oxide have been calculated. DECOS has reviewed the reports by SCOEL and AGS, and has considered whether the cancer risk values proposed in these reports can serve as a basis for a Dutch occupational exposure limit.

SCOEL (2012)

The SCOEL[5] notes that ethylene oxide is endogenously present at low level in the human body and low occupational exposure to ethylene oxide does not lead to a statistical significant increase of N7-(2-hydroxyethyl)guanine (HOEtG), the main DNA-adduct formed by ethylene oxide. According to SCOEL, this could imply that at low exposures the genotoxic effects of ethylene

[a] 'Working group of Experts', one of the predecessors of DECOS

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oxide are negligible. A save threshold for ethylene oxide, however, cannot be determined according to SCOEL based on current scientific data.

The SCOEL questions the relevance of the types of tumours that have been found in experimental animals exposed to ethylene oxide and focuses on epidemiological data for its risk estimation. The SCOEL considers the epidemiological analysis of Valdez-Flores et al. (2011)[7] the most reliable. These authors have combined and analysed numbers of lymphoid tumours occurring in two occupational cohorts[8-10], and calculated cancer risk values for different risk levels. The SCOEL has directly adopted these cancer risk values, including:

- 39.1 mg/m^3, corresponding to an extra risk of cancer of 4 per 1,000
- 0.5 mg/m^3, corresponding to an extra risk of cancer of 4 per 100,000.

AGS (2011)

The AGS[6] has several arguments to consider that it is not possible to reliably establish cancer risks for ethylene oxide based on epidemiological data:

- There is no or insufficient evidence for carcinogenicity in epidemiological studies
- The individual epidemiological studies provide inconsistent results
- The published analyses show methodological limitations.

The AGS therefore calculates cancer risk values based on animal studies. Carcinogenicity data are available from rats and mice. Several tumours have been found in rats, including brain tumours, leukaemia, and peritoneal mesothelioma.[11] In mice, exposure to ethylene oxide induced lung tumours (adenoma and carcinoma in the alveoli/bronchi).[12] Based on the latter tumours, the AGS has calculated the following cancer risk values:

- 2.36 mg/m^3, corresponding to an extra risk of cancer of 4 per 1,000
- 0.02 mg/m^3, corresponding to an extra risk of cancer of 4 per 100,000.

Evaluation of the Health Council

The Committee has drafted a guideline for the calculation of risks of (dying from) cancer as a due to occupational exposure.[3] The Committee calculates cancer risk values preferably based on epidemiological research, since there are no uncertainties related to the biological differences between humans and animals. Moreover, the exposure conditions in epidemiological research are

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generally, in contrast to animal studies, a good representation of the exposure conditions at the workplace.

There is a large number of epidemiological studies available in which possible carcinogenic effects of ethylene oxide have been studied. In some of these studies, associations have been found between ethylene oxide exposure and cancer, in particular types of cancer from lymphoid/ haematopoetic origin. The Committee notes that the evaluation of these types of cancer is hampered since their classification has changed in time. As a consequence, results from studies published over the last decades are difficult to compare. Furthermore, in many of these cohort studies, employees have been exposed not only to ethylene oxide but also other carcinogenic substances. This also hampers the interpretation of the data.

The Committee concludes that there is insufficient epidemiological evidence to conclude that there is a causal relationship between exposure to ethylene oxide and the risk of cancer in humans. In the cohorts studied, on average no increase in the number of cancer cases are found compared to the general population. Moreover, most of the studies do not show increased risks at specified exposure levels. The results of studies in which increased risk have been observed, are not consistent (in other words, a study with a positive finding is not confirmed by another study). The SCOEL nevertheless uses the cancer risk values which are based of epidemiological data and derived by Valdez-Flores et al. for its evaluation.[7] The starting point for these calculations is a statistically non-significant relationship between exposure to ethylene oxide and the development of lymphoid tumours.[10] Methodologically, the Committee considers it questionable to derive cancer risk values based on an uncertain exposure-response relationship.

According to its guideline, the Committee uses animal data alternatively to epidemiological data to calculate cancer risk values. This choice corresponds with approach that the AGS uses for the derivation of cancer risk values for ethylene oxide. Also the methodology applied by the AGS is comparable to that being applied by the Health Council. The tumours that are found at the lowest concentration levels ethylene oxide are mononuclear cell (MNC) leukaemia (in rats) and lung tumours (in mice).[11,12] The AGS questions whether the type of leukaemia that develops in rats after exposure to ethylene oxide is relevant for humans. The AGS therefore uses the development of lung tumours in mice as starting point for the calculation of cancer risk values.

The Committee is of the opinion that the relevance for humans of both types of tumour is unclear. MNC leukaemia is common in Fischer 344 rats but not in humans, and is indeed usually considered not relevant.[13] However, this is also the case for the lung tumours in mice, which commonly develop spontaneously and differ strongly from lung tumours in humans in their

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biological behaviour. The Committee stresses that the exposure to carcinogenic substances can lead to different types of tumours in different species. The Committee would therefore, for reasons of safety, use those data that result in the lowest cancer risk values, in this case the leukemias observed in rats. For ethylene oxide, cancer risk values based on leukaemia in rats are slightly lower than the cancer risk values that would be based on lung tumours in mice.

Summary and recommendation

The Committee notes that recently, both SCOEL and AGS have published reports concerning the risk of cancer due to occupational exposure to ethylene oxide. The SCOEL uses the cancer risk values that have been derived by Valdez-Flores[7] based on epidemiological data. The exposure-response relationship used in this study is, however, uncertain. The Committee finds this approach therefore questionable.

Alternatively to the use of epidemiological data, the Committee uses animal data for the calculation of cancer risk values. This choice corresponds with the approach that the AGS applies for ethylene oxide. The AGS methodology does lead to cancer risk values that are somewhat higher than those that would be derived by the Committee based on its own guideline. On the other hand, the cancer risk values of the AGS are lower than the cancer risk values that can be calculated based on epidemiological data.

Considering all of the above mentioned, the Committee recommends to use the cancer risk values derived by the AGS as a starting point for a occupational exposure limit. The Committee does note that these cancer risk values probably overestimate the cancer risk for humans.

I subscribe the conclusions and recommendation of the Committee and trust to have informed you sufficiently.

Yours sincerely,
(signed)
Professor J.L. Severens,
Vice President

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References

1 IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 100F. 2012.

1 Health Council of the Netherlands. Guideline to the classification of carcinogenic compounds. The Hague: Health Council of the Netherlands, 2010; publication no. A10/07E.

2 Health Council of the Netherlands. Guideline for the calculation of risk values for carcinogenic compounds. The Hague: Health Council of the Netherlands, 2012; publication no. 2012/16E.

3 Directoraat-Generaal van de Arbeid van het Ministerie van Sociale Zaken en Werkgelegenheid. Raport inzake grenswaarde Ethyleenoxide: Gezondheidskundig advies van de werkgroep van Deskundigen ter vaststelling van MAC-waarden. 1989.

4 Scientific Committee on Occupational Exposure Limits (SCOEL). Recommendation from the Scientific Committee on Occupational Exposure Limits for ethylene oxide. 2012: SCOEL/SUM/160.

5 Federal Institute for Occupational Safety and Health (BAuA). Committee on Hazardous Substances (AGS). Exposure-risk relationship for ethylene oxide in BekGS 910. 2011.

6 Valdez-Flores C, Sielken RL, Jr., Teta MJ. Quantitative cancer risk assessment for ethylene oxide inhalation in occupational settings. Arch Toxicol 2011; 85(10): 1189-1193.

7 Steenland K, Stayner L, Deddens J. Mortality analyses in a cohort of 18 235 ethylene oxide exposed workers: follow up extended from 1987 to 1998. Occup Environ Med 2004; 61(1): 2-7.

8 Swaen GM, Burns C, Teta JM, Bodner K, Keenan D, Bodnar CM. Mortality study update of ethylene oxide workers in chemical manufacturing: a 15 year update. J Occup Environ Med 2009; 51(6): 714-723.

9 Valdez-Flores C, Sielken RL, Jr., Teta MJ. Quantitative cancer risk assessment based on NIOSH and UCC epidemiological data for workers exposed to ethylene oxide. Regul Toxicol Pharmacol 2010; 56(3): 312-320.

10 Snellings WM, Weil CS, Maronpot RR. A two-year inhalation study of the carcinogenic potential of ethylene oxide in Fischer 344 rats. Toxicol Appl Pharmacol 1984; 75(1): 105-117.

11 National Toxicology Program. NTP Toxicology and Carcinogenesis Studies of Ethylene Oxide (CAS No. 75-21-8) in B6C3F1 Mice (Inhalation Studies). Natl Toxicol Program Tech Rep Ser 1987; 326: 1-114.

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Annex **A**

The request for advice

In a letter dated October 11, 1993, ref DGA/G/TOS/93/07732A, to, the State Secretary of Welfare, Health and Cultural Affairs, the Minister of Social Affairs and Employment wrote:

Some time ago a policy proposal has been formulated, as part of the simplification of the governmental advisory structure, to improve the integration of the development of recommendations for health based occupation standards and the development of comparable standards for the general population. A consequence of this policy proposal is the initiative to transfer the activities of the Dutch Expert Committee on Occupational Standards (DECOS) to the Health Council. DECOS has been established by ministerial decree of 2 June 1976. Its primary task is to recommend health based occupational exposure limits as the first step in the process of establishing Maximal Accepted Concentrations (MAC-values) for substances at the work place.

In an addendum, the Minister detailed his request to the Health Council as follows:

The Health Council should advice the Minister of Social Affairs and Employment on the hygienic aspects of his policy to protect workers against exposure to chemicals. Primarily, the Council should report on health based recommended exposure limits as a basis for (regulatory) exposure limits for air quality at the work place. This implies:

- A scientific evaluation of all relevant data on the health effects of exposure to substances using a criteria-document that will be made available to the Health Council as part of a specific request for advice. If possible this evaluation should lead to a health based recommended exposure limit, or, in the

case of genotoxic carcinogens, a ‘exposure versus tumour incidence range’ and a calculated concentration in air corresponding with reference tumour incidences of 10^{-4} and 10^{-6} per year.

- The evaluation of documents review the basis of occupational exposure limits that have been recently established in other countries.
- Recommending classifications for substances as part of the occupational hygiene policy of the government. In any case this regards the list of carcinogenic substances, for which the classification criteria of the Directive of the European Communities of 27 June 1967 (67/548/EEG) are used.
- Reporting on other subjects that will be specified at a later date.

In his letter of 14 December 1993, ref U 6102/WP/MK/459, to the Minister of Social Affairs and Employment the President of the Health Council agreed to establish DECOS as a Committee of the Health Council. The membership of the Committee is given in Annex B.

Annex **B**

The Committee

- R.A. Woutersen, *chairman*
  Toxicologic Pathologist, TNO Innovation for Life, Zeist; and professor of translational toxicology, Wageningen University and Research Centre, Wageningen
- P.J. Boogaard
  Toxicologist, Shell International BV, The Hague
- D.J.J. Heederik
  Professor in Risk Assessment in Occupational Epidemiology, Institute for Risk Assessment Sciences, Utrecht University, Utrecht
- R. Houba
  Occupational Hygienist, Netherlands Expertise Centre for Occupational Respiratory Disorders, Utrecht
- H. van Loveren
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The Health Council and interests

Members of Health Council Committees are appointed in a personal capacity because of their special expertise in the matters to be addressed. Nonetheless, it is precisely because of this expertise that they may also have interests. This in itself does not necessarily present an obstacle for membership of a Health Council Committee. Transparency regarding possible conflicts of interest is nonetheless important, both for the chairperson and members of a Committee and for the President of the Health Council. On being invited to join a Committee, members are asked to submit a form detailing the functions they hold and any other material and immaterial interests which could be relevant for the Committee's work. It is the responsibility of the President of the Health Council to assess whether the interests indicated constitute grounds for non-appointment. An advisorship will then sometimes make it possible to exploit the expertise of the specialist involved. During the inaugural meeting the declarations issued are discussed, so that all members of the Committee are aware of each other's possible interests.