Gezondheidsraad
Health Council of the Netherlands

To the Minister of Social Affairs and Employment

Subject	: Advisory letter *Acrylamide*	
Your reference	: DGV/BMO-U-932542	
Our reference	: U-8187/SV/cn/459-N70	Publication no. 2014/20E
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Date	: July 29, 2014	

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 acrylamide. The Health Council has published an advice on acrylamide previously, in 2006.[1] Recently, also the Scientific Committee on Occupational Exposure Limits (SCOEL) of the European Committee and the German Ausschuss für Gefahrstoffe (AGS) of the Bundesanstalt für Arbeitsschutz und Arbeitsmedizin (BAuA) have evaluated the health risks of occupational exposure to acrylamide.[2,3] The Committee has reviewed the literature that has been published since 2006, alongside the reports of the SCOEL and AGS.

Genotoxic carcinogens and cancer risk values

At the European level, acrylamide has been classified for carcinogenicity in category 1B ('The compound is presumed to be carcinogenic to man'). Since acrylamide can damage the DNA, it is considered a genotoxic carcinogenic compound. According to current scientific insights, no safe exposure level can be derived ed for carcinogenic compounds that can directly interact with the DNA so-called stochastic genotoxic carcinogens, below which no increased risk of cancer exists.[4] For these substances, the Committee calculates cancer risk values (HBC-OCRV's[a]): the exposure levels in air that correspond to an extra risk of dying from cancer of 4 per 1,000 (the prohibitive

[a] Health-based calculated-occupational cancer risk values.

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risk level) and 4 per 100,000 (the target risk level) due to occupational exposure to compounds.[5,6] These cancer risk values form the scientific basis of the binding occupational exposure limits.

The Committee preferably bases its calculations on epidemiological data. Only in case no (reliable) epidemiological data are available, animal data are considered as starting point.

Advice of the Health Council (2006)

In 2006, the Committee WGD (a predecessor of the DECOS) was informed on the mode of action of acrylamide by the former Committee Evaluation on Carcinogenicity of chemical substances of the Health Council. This committee concluded that acrylamide was a (weak) genotoxic carcinogen with a stochastic mode of action. At that time, the Committee WGD adopted this conclusion and subsequently calculated cancer risk values.

The Committee WGD concluded that there were no suitable epidemiological data available for deriving cancer risk values. Only two cohorts occupationally exposed to acrylamide had been described (of which one with an update).[7-9] Although in these studies no increased risks were found, the Committee noted that these studies were not suitable to detect a relatively small increase in risk, due to a limited cohort size, exposure period and latency.

At the time, the Committee therefore based its calculation of cancer risk values on animal studies. The Committee focussed on two studies with a comparable protocol, in which rats were exposed to acrylamide via drinking water (studies with exposures by inhalation were not available).[10-11] In both studies, multiple types of tumours have been attributed to the exposure to acrylamide. Eventually, the Committee based its calculation on the increased incidence of mesothelioma of the tunica vaginalis (a tumour that originates from one of the tissues that protect the testis en epididymis inside the scrotum). The Committee noted that this type of tumour is rare in humans and is possibly caused by a non-genotoxic mode of action. At the same time, the Committee concluded that a direct (stochastic) mode of action could not be ruled out.

By recalculating exposure via drinking to exposure levels in air, the Committee estimated the concentration of acrylamide that corresponds with an extra risk of dying from cancer of:

- 4 per 100,000 ($4x10^{-5}$), for 40 years of occupational exposure, to be 1,6 $\mu g/m^3$
- 4 per 1,000 ($4x10^{-3}$), for 40 years of occupational exposure, to be 160 $\mu g/m^3$.

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Reports of other European organisations

SCOEL (2012)

The SCOEL[3] concludes, after a thorough evaluation of the genotoxicity data, that acrylamide is a genotoxic carcinogen for which the existence of a threshold cannot be sufficiently supported. Although several types of tumours that have been found in animal studies are being associated with a hormonal mode of action, the SCOEL also does not exclude a role for a genotoxic mode of action.

For estimating human cancer risks of acrylamide exposure, the SCOEL has taken into account both studies on dietary exposure of the general population (evaluated by Rice[12] and Wilson et al.[13]) as studies on the two previously mentioned, occupationally exposed cohorts. Meanwhile, at the time of the SCOEL evaluation, updates had been published for both cohorts.[14,15] The SCOEL objects to the studies on dietary exposure to acrylamide, in particular with respect to the exposure estimation. Based both on the updates of the occupationally exposed cohorts as the studies on dietary exposure, the SCOEL concludes that there is no epidemiological evidence that acrylamide is carcinogenic.

Also SCOEL is of the opinion that the studies by Friedman et al.[10] and Johnson et al.[11] are the only animal studies that are suitable for risk assessment. However, the SCOEL notes that species-dependent factors play a role in the development of tumours that have been reported in the animal studies, without further explaining this statement. The SCOEL finally concludes that no meaningful risk estimation for humans can be made based on animal data.

AGS (2012)

For the evaluation of the mode of action of acrylamide, the AGS[2] refers to a previous report of the Deutsche Forshungsgemeinschaft (DFG).[16] The AGS concludes that acrylamide can induce tumours by a genotoxic mode of action, but does not exclude non-genotoxic carcinogenic effects. The AGS considers acrylamide thereby as a genotoxic carcinogen, for which a risk-based approach is applied.

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The AGS describes the methodological limitations of the epidemiological studies published. The data on dietary exposure as well as the data on occupational exposure is considered by the AGS to be unsuitable as a basis for a risk estimation.

The AGS has therefore used animal studies and calculated the cancer risk of acrylamide exposure based on different types of tumours that have been reported in the studies by Friedman et al.[10] and Johnson et al.[11] For the determination of a starting point for a risk calculation, the AGS has applied a benchmark dose (BMD)-analysis[a]. In the AGS approach, the dose that corresponds with a 10% increase in tumour incidence is extrapolated to an exposure level that corresponds to a risk level that is applied in the working conditions policy. Since a human risk estimation based on mesothelioma of the tunica vaginalis at an anticipated mean exposure level of 1 µg acrylamide per kg body weight a day[17] would lead to an unrealistic number of cases for this rare tumour, the AGS has chosen a different point of departure. Eventually, the AGS has based its risk estimation on the combined number of breast tumours in female mice. The AGS estimates the concentration of acrylamide in the air that corresponds to an extra chance on dying from cancer of:[b]

- 4 per 100,000 ($4x10^{-5}$), at 40 years of occupational exposure, to be 7 µg/m^3
- 4 per 10,000 ($4x10^{-4}$), at 40 years of occupational exposure, to be 70 µg/m^3.

Evaluation of the Committee

Since 2006, no data have emerged that suggest an increased cancer risk due to occupational exposure to acrylamide. Recently, some associations have been reported between cancer risk and dietary intake of acrylamide.[18,19] The epidemiological studies on dietary acrylamide however, are not considered suitable by the Committee as a basis for drawing conclusions on the potential carcinogenic effects of acrylamide in humans. The findings are inconsistent, have not been reported previously and therefore need to be replicated. The Committee furthermore notes that there are major uncertainties related to the exposure estimation and many confounding variables

[a] Using the BMD-method, a relationship between dose and a response (in this case tumour incidence) is established by using mathematical models.

[b] The AGS has calculated a concentration of 700 µg/m^3 corresponding to an extra risk of cancer of 4 per 1.000. At this concentration, in addition to a increased risk of cancer also an increased risk on neurotoxic effects exists, therefore this risk level is not applied for acrylamide in German working conditions policy.

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are associated with dietary intake of acrylamide. The Committee considers these studies therefore not suitable as a basis for a quantitative risk estimation for occupational exposure to acrylamide. Further, there are no new animal studies that provide new insight in the carcinogenic mode of action of acrylamide.

The abovementioned conclusions are in line with recent evaluations of SCOEL and AGS. These organisations however, have made different choices. For instance, SCOEL did not perform a risk estimation as it considered a risk estimation based on animal data, given the great uncertainties, not meaningful. The Committee is aware of the uncertainties that are associated with a risk estimation based on animal data. The Committee emphasizes however, that the tumours that have been observed in animals, although human relevance remains unclear, can specifically be attributed to the exposure to acrylamide. For the Committee this provides sufficient reason to do a risk calculation on these data.

In contrast to SCOEL, the AGS has performed a risk estimation based on animal data. For this, the AGS used the same studies as the Committee used for its risk estimation in 2006, and used a guideline mostly similar to that of the Committee. The AGS deviates from the Committee in the choice of the type of tumour. The AGS considers a calculation based on mesothelioma of the tunica vaginalis, given its low background incidence in humans, not realistic. Therefore, the AGS based its estimation on the increased incidence in the number of – both benign and malignant – breast tumours. The Committee notes that the types of tumours that develop in animals and humans after exposure to carcinogenic substances, in practice often differ. For carcinogenic substances with a genotoxic mode of action, the Committee assumes that these can induce tumours at different sites in humans compared to experimental animals. For reasons of safety, the Committee bases its calculation on the type of tumour that shows a statistical significant increase at the lowest concentration, in this case the mesothelioma of the tunica vaginalis. Finally, the Committee questions the choice of the AGS to add numbers of benign and malignant tumours for the risk estimation.

Conclusion

The Committee states that no usable new data for risk assessment have become available. Based on the considerations outlined above, the Committee sees no reason to revise its previous report from 2006.

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I endorse the conclusions of the Committee and I trust that this letter has provided you with sufficient information.

Yours sincerely,
(signed)
Professor W.A. van Gool,
President

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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 Quality of Life, Zeist, and Professor of Translational Toxicology, Wageningen University and Research Centre, Wageningen
- P.J. Boogaard
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- H.P.J. te Riele
  Professor of Molecular Biology, VU University Amsterdam, and Antoni van Leeuwenhoek, Amsterdam
- I.M.C.M. Rietjens
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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.