Stibine

Evaluation of the carcinogenicity and genotoxicity

Gezondheidsraad **Voorzitter**
Health Council of the Netherlands

Aan de minister van Sociale Zaken en Werkgelegenheid

Onderwerp : Aanbieding advies *Stibine*
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Geachte minister,

Graag bied ik u hierbij het advies aan over de kankerverwekkendheid van stibine. Het maakt deel uit van een uitgebreide reeks waarin kankerverwekkende stoffen worden geclassificeerd volgens richtlijnen van de Europese Unie. Het gaat om stoffen waaraan mensen tijdens de beroepsmatige uitoefening kunnen worden blootgesteld.

Het advies is opgesteld door een vaste subcommissie van de Commissie Gezondheid en beroepsmatige blootstelling aan stoffen (GBBS), de Subcommissie Classificatie van carcinogene stoffen. Het advies is voorgelegd aan de Commissie GBBS en vervolgens getoetst door de Beraadsgroep Gezondheid en omgeving van de Gezondheidsraad.

Ik heb dit advies vandaag ter kennisname toegezonden aan de minister van Volksgezondheid, Welzijn en Sport en de minister van Volkshuisvesting, Ruimtelijke Ordening en Milieubeheer.

Hoogachtend,

prof. dr. J.A. Knottnerus

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Evaluation of the carcinogenicity and genotoxicity

Subcommittee on the classification of carcinogenic substances of the
Dutch Expert Committee on Occupational Standards,
a committee of the Health Council of the Netherlands

to:

the Minister of Social Affairs and Employment

No. 2008/09OSH, The Hague, April 1, 2008

The Health Council of the Netherlands, established in 1902, is an independent scientific advisory body. Its remit is “to advise the government and Parliament on the current level of knowledge with respect to public health issues...” (Section 22, Health Act).

The Health Council receives most requests for advice from the Ministers of Health, Welfare & Sport, Housing, Spatial Planning & the Environment, Social Affairs & Employment, and Agriculture, Nature & Food Quality. The Council can publish advisory reports on its own initiative. It usually does this in order to ask attention for developments or trends that are thought to be relevant to government policy.

Most Health Council reports are prepared by multidisciplinary committees of Dutch or, sometimes, foreign experts, appointed in a personal capacity. The reports are available to the public.

The Health Council of the Netherlands is a member of the European Science Advisory Network for Health (EuSANH), a network of science advisory bodies in Europe.

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INAHTA

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Contents

Samenvatting

Op verzoek van de minister van Sociale Zaken en Werkgelegenheid evalueert en beoordeelt de Gezondheidsraad de kankerverwekkende eigenschappen van stoffen waaraan mensen tijdens het uitoefenen van hun beroep kunnen worden blootgesteld. De evaluatie en beoordeling worden verricht door de subcommissie Classificatie van Carcinogene Stoffen van de Commissie Gezondheid en Beroepsmatige Blootstelling aan Stoffen van de Raad, hierna kortweg aangeduid als de commissie. In het voorliggende advies neemt de commissie stibine onder de loep. Stibine wordt gebruikt in de micro-elektronische industrie en komt vrij bij het opladen van loodaccu's.

De commissie concludeert dat stibine niet kan worden geclassificeerd door een gebrek aan gegevens over de kankerverwekkendheid.

Executive summary

At request of the Minister of Social Affairs and Employment, the Health Council of the Netherlands evaluates and judges the carcinogenic properties of substances to which workers are occupationally exposed. The evaluation is performed by the subcommittee on Classifying Carcinogenic Substances of the Dutch Expert Committee on Occupational Standards of the Health Council, hereafter called the committee. In this report, the committee evaluated stibine. Stibine is used as dopant in the microelectronics industry, and is released during charging of lead-acid batteries.

The committee concludes that stibine cannot be classified, due to a lack of carcinogenicity data.

Chapter 1

Scope

1.1 Background

In the Netherlands a special policy is in force with respect to occupational use and exposure to carcinogenic substances. Regarding this policy, the Minister of Social Affairs and Employment has asked the Health Council of the Netherlands to evaluate the carcinogenic properties of substances, and to propose a classification (see Annex A). The assessment and the proposal for a classification are expressed in the form of standard sentences (see Annex D). The criteria used for classification are partly based on an EU-directive (see Annex E). In addition to classifying substances, the Health Council also assesses the genotoxic properties of the substance in question.

This report contains the evaluation of the carcinogenicity of stibine.

1.2 Committee and procedures

The evaluation is performed by the subcommittee on Classifying Carcinogenic Substances of the Dutch Expert Committee on Occupational Standards of the Health Council, hereafter called the committee. The members of the committee are listed in Annex B. The first draft was prepared by I.A. van de Gevel and M.I. Willems, from the Department of Occupational Toxicology of the TNO Nutrition

and Food Research, by contract with the Ministry of Social Affairs and Employment.

In 2007 the President of the Health Council released a draft of the report for public review. The individuals and organisations that commented on the draft are listed in Annex C. The committee has taken these comments into account in deciding on the final version of the report.

1.3 Data

The evaluation and recommendation of the committee is standardly based on scientific data, which are publicly available. The starting points of the committees' reports are, if possible, the monographs of the International Agency for Research on Cancer (IARC). This means that the original sources of the studies, which are mentioned in the IARC-monograph, are reviewed only by the committee when these are considered most relevant in assessing the carcinogenicity and genotoxicity of the substance in question. In the case of stibine, such an IARC-monograph is not available.

More recently published data were retrieved from the online databases Medline, Toxline, Chemical Abstracts, and RTECS. The last updated online search was in June 2007. The new relevant data were included in this report.

Chapter 2

General information

2.1 Identity and physico-chemical properties

Stibine is an antimony containing agent that is used as dopant in the microelectronics industry, and is released during charging of lead-acid batteries.[1,2]

Below is given the identity and some of its physical and chemical properties.[1,2]

Chemical name	:	stibine
CAS registry no.	:	7803-52-3
EINECS no.	:	no number
Synonyms	:	antimony hydride; antimony trihydride; hydrogen antimonide
Description	:	colourless gas
Molecular formula	:	SbH_3
Molecular weight	:	124.78
Boiling point	:	-17.1 °C
Vapour pressure	:	> 760 mm Hg at 20 °C
Vapour densitiy	:	4.36 at 15 °C (air = 1)
Solubility	:	slightly soluble in water (1.1 g/L at 0 °C)
Stability and reactivity	:	stibine is flammable when exposed to heat or flame. Decomposes slowly at room temperature but quickly at 200°C. Reacts violently with chlorine, concentrated nitric acid and ozone causing fire and explosion hazard.
Conversion factors	:	1 ppm (v/v) = 5.19 mg/m^3 1 mg/m^3 = 0.19 ppm (v/v)

EU classification	:	R20/22: Harmful by inhalation and if swallowed. R51-53: Toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment. (Based on the Annex I entry 051-003-00-9: antimony compounds, with the exception of the tetroxide (Sb_2O_4), pentoxide (Sb_2O_5), trisulphide (Sb_2S_3), pentasulphide (Sb_2S_5) and those specified elsewhere in this Annex)

2.2 IARC classification

IARC did not evaluate stibine.

Chapter 3

Carcinogenicity studies

3.1 Observations in humans

No data were available to evaluate the carcinogenicity of stibine in humans.

3.2 Carcinogenicity studies in animals

No data were available to evaluate the carcinogenicity of the agent in animals.

Chapter 4

Mutagenicity and genotoxicity

4.1 *In vitro* assays

Stibine was incubated for one hour with naked plasmid DNA.[3] Gel electrophoresis revealed single strand breaks in the plasmid DNA. The committee did not find other data on the genotoxicity *in vitro*.

4.2 *In vivo* assays

The committee did not find data on the genotoxicity *in vivo*.

4.3 Additional information

No additional information on mutagenicity and genotoxicity was available.

Chapter 5

Classification

5.1 Evaluation of data on carcinogenicity and genotoxicity

No data on the carcinogenicity of stibine in humans were available, nor were there any carcinogenicity data available in animals. Moreover, no genotoxicity data were available, except one small study on damage of isolated DNA. The committee considers this study insufficient to decide on the genotoxic potential of stibine, because the study design does not reflect the biological situation in a living organism.

Since no data are available on the carcinogenicity of stibine, it is interesting to know whether chemically related agents can give some information on the carcinogenicity of stibine. In 1989, IARC evaluated two other antimony agents, namely antimony trioxide, and antimony trisulphide.[4] The first agent was carcinogenic in animals (lung tumours in rats), and therefore, the Working Group of IARC classified the agent in Group 2. The second agent could not be classified, due to limited evidence in animals, and the absence of data in humans. Nevertheless, the committee is of the opinion that data on these two antimony agents cannot be extrapolated to stibine for several reasons. First, the induction of lung tumours by antimony trioxide and trisulphide could have been caused by sustained presence of poorly soluble antimony particles, which are not expected to occur by stibine exposure, because stibine is a gas, and has a better solubility. Second, the available data on stibine do not indicate that stibine is hydrolysed in water or transformed into the antimony oxide or sulphide.

In the literature it is, furthermore, reported that the acute toxicity of stibine is similar to that observed in arsine poisoning (*i.e.*, induction of haemolysis, pulmonary irritation).[2,5,6] Arsine is a gas that contains also three hydrogen atoms. In addition, some occupational exposure levels of stibine are based on analogy with arsine. However, the carcinogenicity of arsine is insufficiently investigated, and the possible carcinogenic mechanism of arsine is not yet completely understood. Therefore, the committee is of the opinion that it is not justified to extrapolate data on arsine to use these for the carcinogenic hazard assessment of stibine.

5.2 Recommendation for classification

The committee concludes that stibine cannot be classified, due to a lack of carcinogenicity data.

References

1 Agency for Toxic Substances and Disease Registry. Toxicological profile for antimony and compounds. Agency for Toxic Substances and Disease Registry U.S.Public Health Service; ATSDR/TP-91/02; 1992.

2 American Industrial Hygiene Association. Stibine. Emergency Response Planning Guidelines, American Industrial Hygiene Association, AIHA Press, Fairfax, VA, USA; 1999.

3 Andrewes P, Kitchin KT, Wallace K. Plasmid DNA damage caused by stibine and trimethylstibine. Toxicol Appl Pharmacol 2004; 194(1): 41-8.

4 International Agency for Research on Cancer. Antimony trioxide and antimony trisulfide. In: Some organic solvents, resin monomers and related compounds, pigments and occupational exposures in paint manufacture and painting (Volume 47), IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, WHO, Lyon, France, pp 291-305; 1989.

5 American Conference of Industrial Hygienists. Stibine. Documentation of the threshold limit values and biological exposure indices. American Conference of Industrial Hygienists, 7th Edition, USA; 2001.

6 National Institute for Occupational Safety & Health. Arsine (arsenic hydride) poisoning in the workplace. Current Intelligence Bulletin 32. National Institute for Occupational Safety & Health, Cincinatti, OH, USA; 1979.

A Request for advice

B The committee

C Comments on the public review draft

D Carcinogenic classification of substances by the committee

E Guideline 93/21/EEG of the European Union

Annexes

Annex **A**

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.

Annex **B**

The committee

- G.J. Mulder, *chairman*
  emeritus professor of toxicology, Leiden University, Leiden
- P.J. Boogaard
  toxicologist, SHELL International BV, The Hague
- Ms. M.J.M. Nivard
  molecular biologist and genetic toxicologist, Leiden University Medical Center, Leiden
- G.M.H. Swaen
  epidemiologist, Dow Chemicals NV, Terneuzen
- R.A. Woutersen
  toxicologic pathologist, TNO Quality of Life, Zeist
- A.A. van Zeeland
  professor of molecular radiation dosimetry and radiation mutagenesis, University Medical Center, Leiden
- E.J.J. van Zoelen
  professor of cell biology, Radboud University Nijmegen, Nijmegen
- J.M. Rijnkels, *scientific secretary*
  Health Council of the Netherlands, The Hague

The committee consulted an additional expert, Prof. dr. G. Mohn, working at Department of Radiation Genetics and Chemical Mutagenesis of the University of Leiden, with respect to the genotoxic data.

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 President 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 establishment meeting the declarations issued are discussed, so that all members of the Committee are aware of each other's possible interests.

Annex **C**

Comments on the public review draft

A draft of the present report was released in 2007 for public review. The following organisations and persons have commented on the draft document:

- E. González-Fernández, Ministerio de Trabajo y Asuntos Sociales, Spain;
- R.D. Zumwalde, National Institute for Occupational Safety and Health, the USA.

Annex **D**

Carcinogenic classification of substances by the committee

The committee expresses its conclusions in the form of standard phrases:

Judgment of the committee	*Comparable with EU class*
This compound is known to be carcinogenic to humans • It is stochastic or non-stochastic genotoxic • It is non-genotoxic • Its potential genotoxicity has been insufficiently investigated. Therefore, it is unclear whether it is genotoxic	1
This compound should be regarded as carcinogenic to humans • It is stochastic or non-stochastic genotoxic • It is non-genotoxic • Its potential genotoxicity has been insufficiently investigated. Therefore, it is unclear whether it is genotoxic	2
This compound is a suspected human carcinogen. • This compound has been extensively investigated. Although there is insufficient evidence for a carcinogenic effect to warrant a classification as 'known to be carcinogenic to humans' or as 'should be regarded as carcinogenic to humans', they indicate that there is cause for concern. • This compound has been insufficiently investigated. While the available data do not warrant a classification as 'known to be carcinogenic to humans' or as 'should be regarded as carcinogenic to humans', they indicate that there is a cause for concern.	3 (A) (B)
This compound cannot be classified • There is a lack of carcinogenicity and genotoxicity data. • Its carcinogenicity is extensively investigated. The data indicate sufficient evidence suggesting lack of carcinogenicity.	not classifiable

Annex **E**

Guideline 93/21/EEG of the European Union

4.2 Criteria for classification, indication of danger, choice of risk phrases

4.2.1 Carcinogenic substances

For the purpose of classification and labelling, and having regard to the current state of knowledge, such substances are divided into three categories:

Category 1:

Substances known to be carcinogenic to man.

There is sufficient evidence to establish a causal association between human exposure to a substance and the development of cancer.

Category 2:

Substances which should be regarded as if they are carcinogenic to man.

There is sufficient evidence to provide a strong presumption that human exposure to a substance may result in the development of cancer, generally on the basis of:

- appropriate long-term animal studies
- other relevant information.

Category 3:

Substances which cause concern for man owing to possible carcinogenic effects but in respect of which the available information is not adequate for making a satisfactory assessment.

There is some evidence from appropriate animal studies, but this is insufficient to place the substance in Category 2.

4.2.1.1 The following symbols and specific risk phrases apply:

Category 1 and 2:

T; R45 May cause cancer

However for substances and preparations which present a carcinogenic risk only when inhaled, for example, as dust, vapour or fumes, (other routes of exposure e.g. by swallowing or in contact with skin do not present any carcinogenic risk), the following symbol and specific risk phrase should be used:

T; R49 May cause cancer by inhalation

Category 3:

Xn; R40 Possible risk of irreversible effects

4.2.1.2 Comments regarding the categorisation of carcinogenic substances

The placing of a substance into Category 1 is done on the basis of epidemiological data; placing into Categories 2 and 3 is based primarily on animal experiments.

For classification as a Category 2 carcinogen either positive results in two animal species should be available or clear positive evidence in one species; together with supporting evidence such as genotoxicity data, metabolic or biochemical studies, induction of benign tumours, structural relationship with other known carcinogens, or data from epidemiological studies suggesting an association.

Category 3 actually comprises 2 sub-categories:

a substances which are well investigated but for which the evidence of a tumour-inducing effect is insufficient for classification in Category 2. Additional experiments would not be expected to yield further relevant information with respect to classification.

b substances which are insufficiently investigated. The available data are inadequate, but they raise concern for man. This classification is provisional; further experiments are necessary before a final decision can be made.

For a distinction between Categories 2 and 3 the arguments listed below are relevant which reduce the significance of experimental tumour induction in view of possible human exposure. These arguments, especially in combination, would lead in most cases to classification in Category 3, even though tumours have been induced in animals:

- carcinogenic effects only at very high levels exceeding the 'maximal tolerated dose'. The maximal tolerated dose is characterized by toxic effects which, although not yet reducing lifespan, go along with physical changes such as about 10% retardation in weight gain;
- appearance of tumours, especially at high dose levels, only in particular organs of certain species is known to be susceptible to a high spontaneous tumour formation;
- appearance of tumours, only at the site of application, in very sensitive test systems (e.g. i.p. or s.c. application of certain locally active compounds);
- if the particular target is not relevant to man;
- lack of genotoxicity in short-term tests *in vivo* and *in vitro*;
- existence of a secondary mechanism of action with the implication of a practical threshold above a certain dose level (e.g. hormonal effects on target organs or on mechanisms of physiological regulation, chronic stimulation of cell proliferation;
- existence of a species - specific mechanism of tumour formation (e.g. by specific metabolic pathways) irrelevant for man.

For a distinction between Category 3 and no classification arguments are relevant which exclude a concern for man:

- a substance should not be classified in any of the categories if the mechanism of experimental tumour formation is clearly identified, with good evidence that this process cannot be extrapolated to man;
- if the only available tumour data are liver tumours in certain sensitive strains of mice, without any other supplementary evidence, the substance may not be classified in any of the categories;
- particular attention should be paid to cases where the only available tumour data are the occurrence of neoplasms at sites and in strains where they are well known to occur spontaneously with a high incidence.