Bleomycin

Health-based calculated occupational cancer risk values

Gezondheidsraad **Voorzitter**
Health Council of the Netherlands

Aan de Staatssecretaris Sociale Zaken en Werkgelegenheid

Onderwerp : Aanbieding advies 'Bleomycin'
Uw kenmerk : DGV/MBO/U-932542
Ons kenmerk : U 1040/AvdB/459-P43
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Mijnheer de staatssecretaris,

Bij brief van 3 december 1993, nr DGV/BMO-U-932542, verzocht de Staatssecretaris van Welzijn, Volksgezondheid en Cultuur namens de Minister van Sociale Zaken en Werkgelegenheid de Gezondheidsraad om gezondheidskundige advieswaarden af te leiden ten behoeve van de bescherming van beroepsmatig aan stoffen blootgestelde personen. Tevens vroeg de Staatssecretaris om in het geval van beroepsmatige blootstelling aan genotoxisch carcinogene stoffen de risico's op sterfte als gevolg van kanker te berekenen.

In dat kader bied ik u hierbij een advies aan over bleomycine. Dit advies is opgesteld door de Commissie WGD van de Gezondheidsraad en beoordeeld door de Beraadsgroep Gezondheid en Omgeving. Ik heb dit advies vandaag ter kennisname toegezonden aan de Minister van Volksgezondheid, Welzijn en Sport en de Minister van Volkshuisvesting, Ruimtelijke Ordening en Milieu.

Hoogachtend,

prof. dr JA Knottnerus

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Health-based calculated occupational cancer risk values

Dutch Expert Committee on Occupational Standards,
a committee of the Health Council of the Netherlands

to:

the Minister and State Secretary of Social Affairs and Employment

No. 2004/04OSH, The Hague, September 2, 2004

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 21, 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.

This report can be downloaded from www.healthcouncil.nl.

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Samenvatting

Op verzoek van de Minister van Sociale zaken en Werkgelegenheid, schat de Commissie WGD van de Gezondheidsraad het extra kankerrisico bij beroepsmatige blootstelling aan stoffen die door de Europese Unie of door de Commissie WGD als genotoxisch kankerverwekkend zijn aangemerkt. In dit rapport maakt zij zo'n schatting voor bleomycine. Zij heeft daarbij gebruik gemaakt van de methode die beschreven is in het rapport ‘Berekening van het risico op kanker’ (1995/06WGD) (Hea95).

De commissie is echter van mening dat wegens een gebrek aan voldoende gegevens het niet mogelijk is om het extra kankerrisico voor bleomycine te berekenen.

Executive summary

On request of the Minister of Social Affairs and Employment the Dutch Expert Committee on Occupational Standards (DECOS), a committee of the Health Council of the Netherlands, estimates the additional cancer risk associated with occupational exposure to substances that have been classified by the European Union or the DECOS as genotoxic carcinogen. In this report the committee presents such estimates for bleomycin. It has used the method described in the report 'Calculating cancer risks due to occupational exposure to genotoxic carcinogens' (1995/06WGD) (Hea95).

The committee is of the opinion that due to a lack of sufficient data, it is not possible to estimate the additional lifetime cancer risk for bleomycin.

Chapter 1

Scope

1.1 Background

In the Netherlands, occupational exposure limits for chemical substances are set using a three-step procedure. In the first step, a scientific evaluation of the data on the toxicity of the substance is made by the Dutch Expert Committee on Occupational Standards (DECOS), a committee of the Health Council of the Netherlands, on request of the Minister of Social Affairs and Employment (annex A). This evaluation should lead to a health-based recommended occupational exposure limit for the concentration of the substance in air. Such an exposure limit cannot be derived if the toxic action cannot be evaluated using a threshold model, as is the case for substances with genotoxic carcinogenic properties.

In this case an exposure-response relationship is recommended for use in regulatory standard setting, ie. the calculation of so-called health-based calculated occupational cancer risk values (HBC-OCRVs). The committee calculates HBC-OCRVs for compounds which are classified as genotoxic carcinogens by the European Union or by the present committee.

For the establishment of the HBC-OCRV's the committee generally uses a linear extrapolation method, as described in the committee's report 'Calculating cancer risk due to occupational exposure to genotoxic carcinogens' (1995/06WGD). The linear model to calculate occupational cancer risk is used as a default method, unless scientific data indicate that using this model is not appropriate.

In the next phase of the three-step procedure, the Social and Economic Council advises the Minister of Social Affairs and Employment on the feasibility of using the HBC-OCRVs as regulatory occupational exposure limits. In the final step of the procedure the Minister sets the official occupational exposure limits.

1.2 Committee and procedure

The present document contains the derivation of HBC-OCRV's by the committee for bleomycin. The members of the committee are listed in Annex B. The first draft of this report was prepared by MI Willems, from the TNO Nutrition and Food Research in Zeist, by contract with the Ministry of Social Affairs and Employment.

In 2004, the President of the Health Council released a draft of this report for public review. The Individuals and organizations 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 of the carcinogenicity of bleomycin has been based on reviews by IARC (IARC81, IARC87). Where relevant, the original publications were reviewed and evaluated as indicated in the text. In addition, literature has been retrieved from the online databases Chemical Abstracts, Toxline and Medline, covering the period period 1987 to March 2004.

Chapter 2

Bleomycin

2.1 Introduction

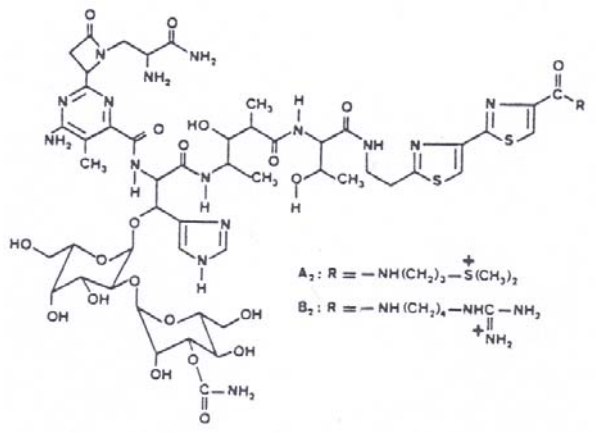
IARC considered the evidence for bleomycin-induced carcinogenicity limited to animals, and inadequate to humans (IARC87). Bleomycin has been classified by IARC as possibly carcinogenic to humans (group 2B) (IARC87).

In 1995, DECOS classified bleomycin as a genotoxic carcinogen (comparable with EU category 2) (DEC95).

2.2 Indentity and physical and chemical properties*

Chemical name	:	Bleomycin
Chem. Abstr. Name	:	Bleomycin
CAS registry number	:	11056-06-7 (sulphate: 9041-93-4; hydrochloride: 67763-87-5)
EU number	:	not available
IUPAC name	:	Bleomycin
Synonyms	:	Bleomycin A2; Blenoxane; Bleomycin sulfate; BLM; N1-(3-(dimethylsulfonio)propyl)bleomycinamide) (Bleomycin A2);
Trade names	:	Bleo; Bleomycins; NSC-125066
Description	:	Colourless or yellowish powder
Uses	:	antineoplastic antibiotic

* Data from IARC81. Bleomycin is the generic name for a mixture of antineoplastic antibiotics including bleomycins A_2 and B_2. Bleomycin sulphates and bleomycin hydrochlorides are included in this evaluation.

Molecular weight		A_2: 1415.6; B_2: 1425.5
Molecular formula	:	A_2: $C_{55}H_{84}N_{17}O_{21}S_3$; B_2: $C_{55}H_{84}N_{20}O_{21}S2$;
Structure	:	
Water solubility	:	very soluble in water
Stability	:	sterile bleomycin sulphate powder is stable for 18 months
EC-classification	:	not classified or labeled according to the 23rd Amendment to Annex I of Directive 67/548/EEC (dated July 30, 1999)

2.3 Carcinogenicity studies and selection of study suitable for risk estimation in the occupational situation

2.3.1 Human data

IARC data

IARC considered the evidence for carcinogenicity to humans inadequate. No epidemiological studies describing effects after exposure to only bleomycins were available. Although occasional case reports of exposure to bleomycins have been reported, especially in the presence of concurrent therapy with other putative carcinogens such as ionizing radiation, alkylating agents and other potent oncotherapeutic drugs, IARC did not consider these as having confirmed their carcinogenic properties (IARC81, IARC87).

In a large systematic follow-up of patients with Hodgkin's disease treated with an intensive chemotherapeutic combination including bleomycins (plus adriamycin, vinblastine and dacarbazine) but no alkylating agent, preliminary evidence suggested no excess of acute nonlymphocytic leukaemia in the first decade after therapy (San86 in IARC87).

Additional studies

No additional relevant human data, not already evaluated by IARC or DECOS, were available (IARC87, DEC95). Several follow-up studies were performed concerning patients with Hodgkin's disease treated with ABVD (doxorubicin, bleomycin, vinblastine and dacarbazine) (ie. And04, Del02, And97). However, because the patient are treated with a combination of compounds, these studies are not suitable for the assessment of the carcinogenic risk of bleomycin.

2.3.2 *Animal data*

IARC data

The animal carcinogenicity data of bleomycin have been evaluated by IARC (IARC81, IARC87). Bleomycin has been tested by subcutaneous and intramuscular injection in mice and transplacentally in rats. These studies could not be evaluated because of incomplete reporting (IARC81).

Habs and Schmähl (Hab84), see Annex D, examined the possible carcinogenicity of bleomycin in Sprague-Dawley rats of both sexes. Four groups of rats (n=30/group/sex) were given subcutaneously, injections of 0.35, 0.70, 1.40, and 2.80 mg bleomycin per kg bw, once a week for 10 weeks. Thereafter the doses were given once every fortnight either for one year (groups given 1.40 and 2.80 mg/kg bw) or for life (groups given 0.35 and 0.70 mg/kg bw). Sixty male and sixty female rats served as solvent-treated (physiological saline) controls. The animals were observed for life and housed in the same laboratory as the treated animals.

Main results are summarised in tables 1 and 2 (Annex D). Repeated doses of bleomycin reduced body weight gain and life expectancy of the animals in a dose-related pattern. Pulmonary infections were seen in treated animals and in controls. However, the authors considered it likely that the life-reducing infections could be, at least in part, attributed to bleomycin (because cross-infections could not be excluded).

Tubular cell changes and cell proliferations were seen as a symptom of major toxicity in the kidneys. Nephrotoxicity characterised by amyloidosis, protein casts, cyst formation, and tubular necrosis was observed already at the lowest dose applied. The application of bleomycin resulted in a significant dose-related carcinogenic response at the site of injection (fibrosarcomas) and in the kidneys (adenomas, adenocarcinomas, fibrosarcomas). Increases in treatment-related tumours were observed for the combined sex data even at the lowest doses; the incidence of tumour bearing animals (combined male and female) amounting to 0/120, 3/60, 4/60, 8/60, 2/60 for renal tumours (benign and malignant tumours combined) and 0/120, 13/60, 18/60, 20/60, 3/60 for local malig-

nant tumours at the site of injection in rats given doses of 0, 0.35, 0.70, 1.4 and 2.8 mg/kg bw, respectively (Hab84). The lower incidence of tumour bearing animals in the highest dose groups (ie 2/60 for renal tumours and 3/60 for local tumours) is probably a result of a higher mortality in these male and female animals.

There were no inhalatory, dermal or oral studies.

Additional studies

The literature search did not reveal relevant additional animal carcinogenicity data.

2.3.3 Conclusion

The study of Habs and Schmähl clearly demonstrated carcinogenic properties of bleomycin (Hab84). However, besides (systemic) renal tumours also local skin tumours at the site of injection were observed in animals to which the lowest dose was applied. Because the relevance of these local skin tumors for the riskassessment after inhalation exposure is unknown, the committee is of the opinion that the results of this study with subcutaneous exposure are inappropriate for quantitative risk assessment regarding inhalatory exposure. Therefore, the committee finds the study of Habs and Schmäl not suitable for establishing a health-based occupational cancer risk value based on inhalatory exposure. As a result and due to a lack of other sufficient data, the committee concludes that it is not possible to estimate the additional lifetime cancer risk of bleomycin for the inhalation route of exposure.

2.4 Existing occupational exposure limits

No occupational exposure limits are available for bleomycin in Europe, including the Netherlands, and in the USA. IARC has classified bleomycin as possibly carcinogenic to humans (Group 2B) (IARC87).

2.5 Toxicity profile of bleomycin

Animals

The i.p. LD_{50} of bleomycin A in mice is reported to be 200 mg/kg bw after a single application, and 15 mg bleomycin/kg after daily administration for 14 days to young mice. In older mice, bleomycin was more toxic. The main signs of toxicity were bad hair condition, nail deformations and salivation. Intraperitoneal administration of 0.1-0.5 mg bleomycin/kg bw in mice, twice weekly for 8 weeks was lethal to 50% of the animals. It

also produced pulmonary fibrosis after 4 weeks. The earliest changes, observed 2 weeks after the start of injections, involved the endothelium of pulmonary arteries and veins.

After i.v. application to rabbits, the LD_{50} is reported to be 150-200 mg/kg bw. A single injection of 50 mg/kg bw to dogs was lethal after 12-14 days. Dogs and monkeys receiving multiple doses of bleomycin i.v., developed pyrexia, footpad ulceration, dermatitis, alopecia and pulmonary lesions (IARC 81).

Humans

The principal toxic effects of bleomycin include diffuse interstitial pneumonitis and mucocutaneous toxicity seen as pigmentation, striae, blistering, inflammation of mucous membranes and hyperkeratosis and alopecia. Rarely, cardiorespiratory failure has been noted, distinct from anaphylaxis. Further toxicities of bleomycin consist of abdominal pain, fever, occasional shivering, headache, nausea and vomiting (IARC 81).

Systemic absorption of bleomycin was reported to be 40% or 80% of the dose, following intrapleural or intraperitoneal administration, respectively. The pharmacokinetics of large, single i.m. or i.v. injections are almost identical. Bleomycin has a short half life of 115 minutes (mean value) (IARC81).

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NBO93 National Board of Occupational Safety and Health (NBOSH). Occupational exposure limit values. Solna, Sweden: National Board of Occupational Safety and Health, 1993: (Ordinance AFS1993/9).

SZW99 Ministerie van Sociale Zaken en Werkgelegenheid (SZW) De Nationale MAC-lijst 1999, The Hague, The Netherlands: Servicecentrum Sdu Uitgevers, 1999.

A	Request for advice
B	The Committee
C	Comments on the public draft
D	Animal studies

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. The membership of the Committee is given in annex B.

Annex **B**

The committee

- GJ Mulder, *chairman*
  professor of toxicology; Leiden University, Leiden
- RB Beems
  toxicologic pathologist; National Institute of Public Health and the Environment, Bilthoven
- LJNGM Bloemen
  epidemiologist; Dow Benelux NV, Terneuzen
- PJ Boogaard
  toxicologist; Shell International BV, The Hague
- PJ Borm
  professor of inhalation toxicology; Heinrich Heine Universität Düsseldorf (Germany)
- JJAM Brokamp, *advisor*
  Social and Economic Council, The Hague
- DJJ Heederik
  epidemiologist; IRAS, Utrecht University, Utrecht
- AAJP Mulder, *advisor*
  Ministry of Social Affairs and Employment, The Hague
- TM Pal
  occupational physician; Netherlands Centre for Occupational Diseases, Amsterdam
- IM Rietjens
  professor of toxicology; Wageningen University, Wageningen.

- H Roelfzema, *advisor*
  Ministry of Health, Welfare and Sport, The Hague
- T Smid
  occupational hygienist; KLM Health Safety & Environment, Schiphol and professor of working conditions, Free University, Amsterdam
- GMH Swaen
  epidemiologist; Maastricht University, Maastricht
- RA Woutersen,
  toxicologist and pathologist; TNO Nutrition and Food Research, Zeist
- P Wulp
  occupational physician; Labour Inspectorate, Groningen
- ASAM van der Burght, *scientific secretary*
  Health Council of the Netherlands, The Hague
- JM Rijnkels, *scientific secretary*
  Health Council of the Netherlands, The Hague

The first draft of the present advisory report was prepared drs MI Willems, from the TNO Nutrition and Food Research in Zeist, by contract with the Ministry of Social Affairs and Employment.

Secretarial assistance was provided by F smith.
Lay-out: J van Kan.

Annex C

Comments on the public draft

A draft of the present report was released in 2004 for public review. The following organizations and persons have commented on the draft document:

- JA Wess, National Institute of Occupational Safety and Health, USA.

Annex **D**

Animal studies

Abbreviations used:

Xpo	exposure period
Xpe	total experimental/observation period
MST	mean survival time
MTD	maximally tolerated dose
TBA	tumour bearing animals

Table 1 Experimental design, weight development, survival times and total doses[1] in the investigation on carcinogenicity of bleomycin after repeated subcutaneous administration to Sprague-Dawley rats (Table taken from Hab84).

Individual dose mg/kg	Initial number of animals		Median survival times[2], (days)/95% confidence limit		Median total dose, mg/kg body weight	Mean weight gain (in gram)[3]	
	M	F	M	F		M	F
0	60	60	472 (424-542)	554 (489-582)	0.00	+140	+80
0.35	30	30	476 (406-520)	519 (477-547)	13.65	+130	+55
0.70	30	30	344 (301-403)	520 (478-545)	26.60	+100	+45
1.40	30	30	435 (394-468)	455 (411-517)	51.80	+ 50	+30
2.80	30	30	296 (283-312)	330 (315-365)	72.80	- 50	-10

[1] For details see text, evaluation 650 days after start of the experiment.
[2] After start of the experiment.
[3] After first 10 weeks of treatment.

Table 2 Tumour-inducing activity of bleomycin after repeated subcutaneous administration to Sprague-Dawley rats[a] (Table taken over from Hab84).

Individual dose mg/kg	Animals with malignant tumours (all sites)				Animals with renal tumours								Animals with local tumours							
	M		F		M benign		M malign.		F benign		F malign.		M benign		M malign.		F benign		F malign.	
	n	%	n[b]	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Bleomycin																				
0.0	2	4	3	7	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
0.35	9	30	14	50	0	0	1	3	0	0	2	7	1	3	6	20	0	0	7	25
0.70	10	33	17	57	0	0	0	0	3	10	1	3	0	0	6	20	0	0	12	40
1.40	15	50	14	47	5	17	2	7	1	3	0	0	0	0	11	37	0	0	9	30
2.80	1	3	3	10	2	7	0	0	0	3	0	0	0	0	1	3	0	0	2	7

[a] Evaluation after day 650 on experiment

[b] referring to the number of animals to be evaluated on day 650