Mitomycin C

Health-based calculated occupational cancer risk values

Gezondheidsraad **Voorzitter**
Health Council of the Netherlands

Aan de Staatssecretaris Sociale Zaken en Werkgelegenheid

Onderwerp : Aanbieding advies 'Mitomycin C'
Uw kenmerk : DGV/MBO/U-932542
Ons kenmerk : U 1041/AvdB/459-Q43
Bijlagen : 1
Datum : 2 september 2004

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 mitomycine C. 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

Bezoekadres
Parnassusplein 5
2511 VX Den Haag
Telefoon (070) 340 7017
E-mail: A.vd.Burght@gr.nl

Postadres
Postbus 16052
2500 BB Den Haag
Telefax (070) 340 75 23
www.gr.nl

Mitomycin C

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. 2004/05OSH, 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.

Preferred citation:
Health Council of the Netherlands. Dutch Expert Committee on Occupational Standards. Mitomycin C; Health-based calculated occupational cancer risk values. The Hague: Health Council of the Netherlands, 2004; publication no. 2004/05OSH.

all rights reserved

ISBN: 90-5549-536-0

Contents

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 bekijkt zij of zo'n schatting mogelijk is voor mitomycine C. 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 mitomycine C 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 examines whether such estimates can be calculated for mitomycin C. 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 mitomycin C.

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 would 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 mitomycin C. 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 mitomycin C has been based on reviews by IARC (IARC76, 87) and an update by DECOS (DEC95). 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 1987 to April 2004.

Chapter 2

Mitomycin C

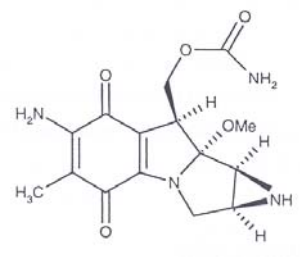
2.1 Introduction

Evidence for mitomycin C induced carcinogenicity is considered sufficient to animals, but inadequate to humans (IARC76, IARC87). As such, mitomycin C is classified by the IARC as possibly carcinogenic to humans (group 2B).

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

2.2 Identity, and physical and chemical properties

Chemical name	:	Mitomycin C
Chem. Abstr. Name	:	[1aR-(1aαb, 8, ß, 8α, 8bα)]-6-amino-8 -{[(aminocarbonyl)oxy]-methyl}-1,1a,2,8,8a,8b-hexahydro-8a-methoxy-5-methyl-azirone [2',3':3,4] pyrrolo [1,2-α]indole-4,7-dione
CAS registry number	:	50-07-7
EINECS number	:	200-008-6
IUPAC name	:	Mitomycin C

Synonyms	:	6-amino-8-[[(aminocarbonyl)oxy]methyl]-1,1a,2,8,8a,8b-hexahydro-8a-methoxy-5-methyl, [1aS-(1aα,8ß,8α,8bα)]-azirino[2',3':3,4]pyrrolo[1,2a]indole-4,7-dione; 7-amino-9α-methoxymitosane; Azirino[2',3':3,4]pyrrolo[1,2-a]indole-4,7-dione, 6-amino-8-[[(aminocarbonyl)oxy]methyl]-1,1a,2,8,8a,8b-hexahydro-8a-methoxy-5-methyl-, [1aS-(1aα,8ß,8α,8bα)]-; 6-amino-1,1a,2,8,8a,8b-hexahydro-8-(hydroxymethyl)-8a-methoxy-5-methylazirino[2',3':3,4]pyrrolo[1,2-a]indole-4,7-dione, carbamate (ester); (1ar)-6-amino-8-(((aminocarbonyl)oxy)methyl)-1,1a,2,8,8a,8b-hexahydro-8a-methoxy-5-methylazirino[2',3':3,4]pyrrolo[1,2-a]indole-4,7-dione; Ametycin; Mit-C; Mito-C; Mitocin-C; Mitomycin; Mitomycinum; MMC; Mutamycin; Mitomycin
Trade names	:	Ametycine®, Mitocin-C®, Mutamycin®
Description	:	blue-violet crystals
Uses	:	antineoplastic
Molecular weight	:	334.3
Molecular formula	:	$C_{15}H_{18}N_4O_5$
Structure		
Melting point	:	360°C
Water solubility	:	soluble
Stability		:solutions in water at pH 6-9 are stable for seven days when protected from light and stored at <5°C.
EC classification	:	not classified or labelled according to the 23rd Amendment to Annex I of Directive 67/548/EEC (dated December 5, 1997).

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

2.3.1 Human data

IARC data

No case reports or epidemiological studies were available to the IARC-Working Group (IARC76, IARC87).

Additional data

No additional relevant human data were available concerning the incidence of cancer due to exposure to mitomycin C.

2.3.2 *Animal data*

IARC data

The animal carcinogenicity data are summarised in Annex D. Routes of administration of the test substance include subcutaneous, intraperitoneal, intravenous injection and instillation into the urinary bladder. There were no oral, inhalatory or dermal carcinogenicity studies.

None of the experiments summarised in Annex D fulfilled the criteria for calculating the additional lifetime cancer risk. The exposure periods applied in the experiments of Ikegami *et al*., Ohtani *et al*., and Schmähl and Osswald were less than 25% of the standard lifespan (Ike67, Oht83, Sch70).

Moreover mean survival time in the study of Schmähl and Osswald was clearly affected by the dose administered (Sch70). In the study of Ikegami *et al*. only tumours at the site of contact were reported (Ike67).

Only in the study of Weisburger, the exposure and experimental time (duration) were considered long enough for calculating the additional lifetime cancer risk. However, the tumour incidence in the two treatment groups (Sprague-Dawley CD rats and Swiss-Webster-derived mice; n=25/species/group/sex) was not reported separately for both dose levels. The authors wrote “mitomycin C was active in inducing peritoneal sarcomes in a considerable number of male and female rats, but no real effect was noted in mice” (Wei75). In addition, the committee noted that the data concerning the control animals are insufficiently described.

Additional data

No additional relevant data were available concerning the incidence of cancer due to exposure to mitomycin C in experimental animals.

2.3.3 *Conclusion*

From the data presented by Schmäll and Oswald (Sch70), the committee believes that mitomycin C is an animal carcinogen, but an additional life time cancer risk cannot be

established from these limited data. Also the study of Weisburger *et al*. (Wei75) is inadequate for establishing a lifetime cancer risk.

In conclusion, due to a lack of other sufficient data, the committee is not able to calculate the health-based occupational cancer risk value of mitomycin C in air.

2.4 Existing occupational exposure limits

No occupational exposure limits have been established for mitomycin C in European countries and in the USA. In several countries, mitomycin C is listed as animal carcinogen, such as in the Netherlands. IARC concluded that mitomycin C is possibly carcinogenic to humans (IARC76).

2.5 Toxicity profile of mitomycin C*

No information is available on uptake, distribution, and excretion after oral, inhalation, or dermal exposure. Following i.v. injection of 2 mg/kg bw mitomycin C in Wistar rats, 18% was recovered unchanged in the urine within 24 hours. At higher doses (8 mg/kg bw), 35% was recovered in the urine, but none in the faeces or tissues. Thirty minutes after i.v. injection of 8 mg/kg bw to mice traces mitomycin C remained in the blood. In guinea-pigs the drug was concentrated in the kidneys and not in the liver, spleen or brain and was excreted in the urine.

In humans, mitomycin C rapidly disappears from the blood upon i.v. injection, and is widely distributed but does not cross the blood-brain barrier. It is metabolised mainly in the liver, about 10% is excreted unchanged in the urine, but small amounts are also found in the bile and faeces in humans (Ric94).

In laboratory animals, the LD_{50} after a single mitomycin C treatment and an observation period of 14 days, using different application routes, were as follows:

Application route	LD_{50} rat (mg/kg bw)	LD_{50} mouse (mg/kg bw)
Intraperitoneal	2.5	8.5
Oral	30	23
Subcutaneous	3250 (Ric94)	7800 (Ric94)

* The toxicity data are derived from IARC76, unless indicated otherwise.

LD_{50} values after intravenous application in cats, dogs and monkeys, ranged between 1 and 2.5 mg/kg bw. Anorexia, weight loss, diarrhoea and dehydration were the main signs prior to death. The main pathological changes were petechiae in the colon and other organs, and depression of the haematopoietic tissues.

Patients receiving intravesical mitomycin C can develop severe eczematous symptoms, which appear to be due to a hypersensitivity reaction (Ric94). Other main adverse effects in humans are delayed cumulative bone-marrow suppression (Ric94).

Teratogenic and reproductive effects were observed in ICR mice given once i.p. mitomycin C at doses of 1.5-5 mg/kg bw on day 1, 2 or 3 of pregnancy (Ric94).

Many studies reveal that mitomycin C has genotoxic properties in bacteria, in mammalian cells *in vitro*, in *Dros. melanogaster* and in mammals *in vivo*, inducing DNA cross-linking, mutations, chromosomal aberrations, micronuclei and SCEs (IARC87, DEC95).

References

ACG99 American Conference of Governmental Industrial Hygienists (ACGIH). Guide to occupational exposure values-1999. Cincinnati OH, USA: ACGIH, 1999.

Aka84 Akaza H, Murphy WM, Soloway MS. Bladder cancer induced by noncarcinogenic substances. Journal of Urology 1984; 131: 152-155.

Arb96 Arbejdstilsynet. Exposure limit values for substances and materials. Copenhagen, Danmark: Arbejdstilsynet, 1996: 12 (Instruction no. 3.1.0.2).

Bun98 Bundesministerium für Arbeit und Sozialordnung. Grenzwerte in der Luft am Arbeitsplatz; Technische Regeln für Gefahrstoffe; TRGS900. FRG: Verlag W. Kolhammer, 1998; Bundesarbeitsblatt 10.

EPA93 Evaluation of the potential carcinogenicity of mitomycin C. EPA document no. PB93-196376 1993;17

DEC95 Dutch Expert Committee on Occupational Standards (DECOS). (II). Mitomycin C. Ministry of social affairs and employment 1995; RA 2/95:125-127.

DFG98 Deutsche Forschungsgemeinschaft (DFG): Senatskommission zur Prüfung gesundheitsschädlicher Arbeitsstoffe. MAK- und BAT-Werte-Liste 1998. Maximale Arbeitsplatzkonzentrationen und biologische Arbeitsstofftoleranz-werte. Weinheim: Wiley-VCH Verlagsgesellschaft mbH, 1998; Mitteilung 34.

HSE98 Health and Safety Executive (HSE) 40/98. Occupational exposure limits 1998. Sudbury (Suffolk), UK: HSE Books, 1998.

Hun97 Hunter WJ, Aresini G, Haigh R, et al. Occupational exposure limits for chemicals in the European Union. Occup Environ Med 1997; 54: 217-22.

IARC76 International Agency for Research on Cancer (IARC). Mitomycin C. In: Some naturally occurring substances. Lyon, France: IARC 1976: 171 (IARC monographs on the evaluation of carcinogenic risks to humans; Vol 10).

IARC87 International Agency for Research on Cancer (IARC). Mitomycin C. In: Overall Evaluations of Carcinogenicity: An Updating of IARC Monographs Volumes 1 to 42. Lyon, France: IARC 1987: 67. (IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans; suppl. 7).

Ike67 Ikegami R, Akamatsu Y, Haruta M. Subcutaneous sarcomas induced by mitomycin C in mice. Acta path Jap 1967; 17: 495-501.

Kos86 Koseki K, Akaza H, Niijima T. Mutual neoplastic promotion by instillation of mitomycin C and cauterization on rat bladder urothelium. Cancer 1986; 57: 774-778.

Mer97 Merck index on CD-rom 1997: version 12:2.

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).

Oht83 Ohtani M, Fukushima S, Ito N, Koiso K, Niijima T. Effects of intravesical instillation of antitumor drugs on the induction of preneoplastic bladder lesions in rats. Cancer Chemotherapy and Pharmacology 1983; 11: S64-66.

Ric94 Richardson M, ed. M315. Mitomycin C. In: The dictionary of substances and their effects. Cambridge, UK: Royal Society of Chemistry, 1994: 747-750 (Vol 5).

Sch70 Schmähl D, Osswald H. Experimentelle Untersuchungen uber carcinogene Wirkungen von Krebs-Chemotherateutica und Immunosuppressiva. Arzneimittel-Forsch 1970; 20: 1461-1467.

Wei75 Weisburger JH, Griswold DP, Prejean JD, Casey AE, Wood HB Weisburger EK. The carcinogenic properties of some of the principal drugs used in cancer chemotherapy. Recent Results Cancer Res 1975; 52: 1-17

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
  toxicologic pathologist; TNO Nutrition and Food Research, Zeist
- P Wulp
  occupational physician; Labour Inspectorate, Groningen
- JM Rijnkels, *scientific secretary*
  Health Council of the Netherlands, The Hague
- ASAM van der Burght, *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 review 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 Carcinogenicity studies with mitomycin C.

Ref.	Species/route	Experimental	Findings, tumours	Remark(s)
Bladder instillation				
Oht83 DEC95	female rat, F344 n=10; control, n=12.	0.15 mg/rat/wk for 12 wks by intravesical instillation, controls were treated with saline alone. Xpo: 12 wks, Xpe: 17 wks	No bladder tumours were found in control or mitomycine C-treated animals	
Subcutaneous administration				
Ike67 EPA93 IARC76,	Mouse, males, strains btk, n=7; C57BL, n=10; C3H, n=10; ddO, n=10.	35 x 0.2 µg. The injections were given twice weekly, cumulative dose: 7 µg/mouse. Xpo: 18 wks, Xpe: 66 wks	Incidence, local sarcoma: btk mice 7/7 and C57B1 mice 2/10; C3H and ddO strains 0/10; Control group: no tumours found (0/10), all strains	
Intraperitoneal administration				
Wei75 EPA93 IARC76	Rat, Charles River CD, n=25/group/sex.	3 times per week 0.038 or 0.15 mg/kg bw for 6 months. Xpo: 6 months, Xpe: 18 months	Tumour incidences, both dose groups combined, mitomycin C-treated animals, peritoneal sarcomas, males 27/29, females 30/31. Tumour data for concurrent controls not reported.	0.15 mg/kg bw = MTD
Intravenous administration				
Sch70 Ano93 IARC76	male BR 46 rat, n=96; control, n=89	Five injections of 0.52 mg/kg bw, total dose 2.6 mg/kg bw. The injections were given two weeks apart. Xpo 10 weeks, Xpe lifespan	Tumour incidence: mitomycin C-treated rats: TBA, malignant 34/79, TBA, benign 4/79 [lymphosarcoma (2), abdominal polymorph-cell sarcomas (4), mammary sarcomas or carcinomas (5), subcutaneous fibrosarcoma (4), squamous cell carcinomas of the lung (3), carcinoma (1) and sarcoma (1) of the bladder, phaeochromocytoma (1), reticulumcell sarcoma of the liver (1), carcinosarcoma of the oesophagus (1), adenocarcinoma of the pyloric mucosa (1), sarcoma of the salivary gland (1), abdominal haemangioendothelioma (1), haemangiosarcoma in the paw (1). Controls: TBA, malignant 6/65, TBA, benign 5/65	Dose applied was 17% of lethal dose. MST, controls 25±5 months. MST, mitomycin C-treated animals 5 months less. Tumour latency time, controls 23±5, mitomycin C-treated animals 18±4 months.