Dacarbazine

Health-based calculated occupational cancer risk values

Gezondheidsraad **Voorzitter**
Health Council of the Netherlands

Aan de Staatssecretaris Sociale Zaken en Werkgelegenheid

Onderwerp : Aanbieding advies 'Dacarbazine'
Uw kenmerk : DGV/MBO/U-932542
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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 'Dacarbazine'. 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 Staatssecretaris van Volkshuisvesting, Ruimtelijke Ordening en Milieu.

Hoogachtend,

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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. 2005/01OSH, The Hague, 19 April 2005

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.

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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 dacarbazine, een genotoxisch chemotherapeuticum. Voor de schatting heeft de commissie gebruik gemaakt van de methode die beschreven is in het rapport 'Berekening van het risico op kanker' (Hea95).

Naar schatting van de commissie is de extra kans op kanker voor dacarbazine:

- $4x10^{-3}$ bij 40 jaar beroepsmatige blootstelling aan 90 $\mu g/m^3$;
- $4x10^{-5}$ bij 40 jaar beroepsmatige blootstelling aan 0,9 $\mu g/m^3$.

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 dacarbazine, a genotoxic anticancer drug. For the estimation, the committee used the method described in the report 'Calculating cancer risk due to occupational exposure to genotoxic carcinogens' (Hea95).

The committee estimated that the additional lifetime cancer risk for dacarbazine amounts to:

- $4x10^{-3}$ for 40 years of occupational exposure to 90 $\mu g/m^3$;
- $4x10^{-5}$ for 40 years of occupational exposure to 0.9 $\mu g/m^3$.

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, at request of the Minister of Social Affairs and Employment (annex A). This evaluation should lead to a health-based recommended 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 that case, an exposure-response relationship is recommended for use in regulatory standard setting, *i.e.,* 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 committee.

For the establishment of the HBC-OCRVs, 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' (Hea95). The linear model 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

This document contains the derivation of HBC-OCRVs by the committee for dacarbazine. The members of the committee are listed in Annex B. The first draft of this report was prepared by Ms MI Willems of the TNO Nutrition and Food Research, Zeist, The Netherlands, for the Ministry of Social Affairs and Employment.

In 2004, 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

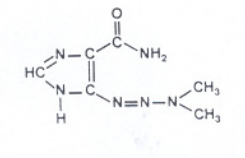
The evaluation of the carcinogenicity and other toxic effects of dacarbazine has been based on reviews by IARC (IAR81, IAR87). Where relevant, the original publications were reviewed and evaluated as indicated in the text. In addition, literature has been retrieved from the online databases Chemical Abstracts, Toxline, and Medline, covering the period 1966 to May 2004.

Chapter 2

Dacarbazine

2.1 General information

Dacarbazine is an anticancer drug that is used to treat some types of cancer, in particular melanomas, Hodgkin's lymphomas and soft tissue sarcomas. Its identity, physical and chemical properties are shown below (data obtained from IAR81 and Ric93).

Chemical name	:	dacarbazine
Chem. Abstr. Name	:	1*H*-imidazole-4-carboxamide, 5-(3,3-dimethyl-1-triazenyl)-
CAS registry number	:	4342-03-4
EU number	:	224-396-1
EINECS number	:	-
IUPAC name	:	5-(3,3-dimethyl-1-triazeno)imidazole-4-carboxamide
Synonyms	:	5-(3,3-dimethyl-1-triazenyl)-1*H*-imidazole-4-carboxamide; 5 (or 4)-(3,3-dimethyl-1-triazeno)-imidazole-4(or 5)-carboxamide
Trade names	:	deticene; DIC; DTIC; DTIC-Dome; NSC 45388
Description	:	white to ivory coloured microcrystals/powder
Molecular weight	:	182.2
Molecular formula	:	$C_6H_{10}N_6O$
Structure	:	

Melting point	:	250-255 °C (decomposes)
Water solubility	:	1 g/L at 20 °C
Stability	:	sensitive to oxidation; stable in neutral solutions in absence of light. Extremely light sensitive; rapidly undergoes chemical decomposition to form 4-diazoimidazole-5-carboxamide. When heated to decomposition it emits toxic fumes of nitrogen oxides (NO_x)
EC classification	:	not classified or labelled according to the 23rd Amendment to Annex I of Directive 67/548/EEC (dated December 5, 1997)

2.2 Carcinogenicity studies

2.2.1 Overall Conclusion

IARC (IAR87) has classified dacarbazine in group 2B (should be regarded for practical purposes as if it presented a carcinogenic risk for humans). The classification is based on sufficient evidence for carcinogenicity in animals, whereas evidence for carcinogenicity in humans was inadequate.

In 1995, DECOS (DEC95) drew the same conclusion as IARC, in that dacarbazine should be considered as carcinogenic to humans (comparable with EU category 2). Furthermore, it classified the compound as a genotoxic carcinogen.

2.2.2 Human data

Overall, no epidemiological data on the carcinogenic effects of dacarbazine alone have been published. However, a few investigators reported on the carcinogenic effects of combined chemotherapy, including dacarbazine. One concerns a retrospective study by Valagussa *et al*. (1980), which is briefly evaluated by IARC (IAR81, IAR87). In that study no secondary malignancies were observed in a subgroup of 55 patients having Hodgkin's disease. In another study, an acute case of nonlymphomatic leukemia was reported in a woman with breast cancer, who was treated with dacarbazine in combination with other chemotherapeutics (Portugal *et al.*, 1979, see IAR81/87).

More recently, Boivin *et al*. (Boi95) reported on secondary cancers in patients with Hodgkin's disease, who were treated with chemotherapy. The cohort included 10,742 patients from 14 different cancer centers in the United States and Canada. The patients were first diagnosed as having Hodgkin's disease from 1940 through 1987. Data on dacarbazine alone did not allow assessment on secondary cancer risk. However, dacarbazine was also used in combination with other chemotherapeutics (doxorubicin, bleomycin and vinblastine). For this mixture, the authors calculated an increased relative risk for leukaemia of 1.5 (RR, 1.5; CI 95%, 0.7-3.4), which was non significant.

2.2.3 *Animal data*

No animal data on the carcinogenicity of dacarbazine by inhalation or dermal exposure have been found. However, a few animal studies are published, in which animals have been exposed to the compound by intraperitoneal or oral administration.

Intraperitoneal injections

Weisburger *et al*. (Wei75) and Weisburger (Wei77) reported on a preliminary carcinogenicity study. In that study Sprague-Dawley rats (n=25/group/sex) and Swiss Webster mice (n=25/group/sex) were given intraperitoneal injections of 50 - 100 mg/kg bw (rats, 0.5 – 1 times the maximally tolerated dose (MTD), respectively) and 25 - 50 mg/kg bw (mice, 0.5 – 1 times MTD, respectively) dacarbazine, three times per week for a total of 6 months. After stopping the exposure, the animals were observed for a further 12 months. In the study, also untreated-control and vehicle-control animal groups were included. Finally, the results obtained at both dose levels were combined to facilitate the presentation.

Concerning rats, the number of animals having tumours were: 18/34 (males) and 12/22 (females), lymphomas; 4/34 (males), renal tumours; 16/22 (females), breast carcinomas; and, 8/34 (males) and 2/22 (females), heart tumours. The number of tumours were all significantly increased compared to controls (p<0.011-0.001). Also, the authors reported on median survival time. These were: 141 days (118-191) for males and 126 days (118-135) for females at 100 mg/kg bw; and, 202 days (132-302) for males and 195 days (106-304) for females at 50 mg/kg bw. The median survival time in controls was about 500 days (males and females; reported in IAR81).

Concerning mice, the number of animals having tumours were: 21/41 (males) and 16/19 (females), lung tumours; 15/41 (males), lymphomas; 10/41 (males), splenic tumours; and 5/19 (females), uterine tumours. Again, the number of tumours were all significantly increased compared to controls (p<0.001). The median survival times were as follows: 177 days (163-270, males) and 128 days (116-179, females) at 50 mg/kg bw; and, 331 days (104-549, males) and 306 days (275-429, females) at 25 mg/kg bw. In controls the median survival time was 9.8 months (males) and 18 months (females) (reported in IAR81).

Zeller (Zel80) administered a single intraperitoneal dose of 25, 50 or 100 mg dacarbazine per kg bw to pregnant female BD IX rats (n total=8) to study the carcinogenic effects of dacarbazine in the offspring. Nine of the 39 progeny developed tumours (25 mg/kg bw, 3/11; 50 mg/kg bw, 4/15; 100 mg/kg bw, 2/13). The type of malignant tumours included neuromas, lymphomas and adenocarcinomas. A fourth group served

as untreated controls. In the offspring of that group, two of the seventeen had developed tumours: one mammary adenocarcinoma and one fibrosarcoma.

Beal *et al*. (Bea75) performed a series of experiments, of which one concerned intraperitoneal administration. In that study, female Sprague-Dawley rats (n=16/group) received a single injection of dacarbazine at a dose of 100, 250 or 400 mg per rat. Another group, containing 20 rats, received a dose of 2.5 mg per rat, three times per week for a total of 12 weeks. In the vehicle control (n=16) no tumours were found. Data on tumour incidence of the exposed animals at week 66, are shown in Table 2.1.

Oral administration

In another experiment by Beal *et al*. (Bea75), male and female Sprague-Dawley rats, and female Buffalo rats were given dacarbazine orally. The males concerned one group only. Dacarbazine was put in the diet at doses of 100, 500 or 1,000 mg/kg diet. The exposure and experimental periods, the cumulative doses and the tumour incidences are shown in Table 2.2. In none of the control groups (each exposed group had its own non-treated control group) tumours were found, with two exceptions; 2 mammary adenofibromas were found in a group of 24 female controls at 66 weeks; and, 6 mammary adenofibromas were found in a group of 52 female controls at week 60.

Table 2.1 Tumour incidence of mice treated intraperitoneally with dacarbazine (Bea75).

dose (mg/rat)	mammary[a]		lymphocarcoma		other tumours
	adeno-carcinoma	adeno-fibroma	thymic	splenic	
100	1 (1)	7 (1)	-	-	1 leiomyosarcoma of the uterus; 1 ependymoblastoma; 1 adrenal cortical adenoma
250	5 (2-3)	4 (2)	-	2	1 leiomyosarcoma of the uterus; 2 embryonal adenosarcomas
400	11 (2)	5 (2)	7	9	2 leiomyosarcomas of the uterus; 1 cerebral ependymoma
2.5 (3x/wk, 12 wk)	-	6 (2)	-	1	7 leiomyosarcomas of the uterus; 1 cerebral ependymoma; 2 bronchogenic adenocarcinomas; 1 kidney cortical adenocarcinoma

[a] Number in parentheses indicate average number of tumours per animal.

Table 2.2 Experimental design and tumour incidence in rats fed dacarbazine (Bea75).

sex (no.)	X_{po} (weeks)	X_{pe} (weeks)	cumulative dose (mg/rat)	mammary[a]		lymphosarcoma		other tumours
				adeno-carcinoma	adeno-fibroma	thymic	splenic	
Spr-Daw								
M (16)	14	18	974	8 (1-2)	-	15	5	1 hemangioma
F (16)	10	15	346	10 (1-2)	-	1	-	-
F (16)	46	60	570	1 (4)	12 (3)	3	2	2 leiomyosarcoma of the uterus; 2 leiomyosarcomas (eye, blood vessel)
F (12)	14	24	608	6 (2-3)	-	5	3	-
F (24)	14	18	740	24 (5)	-	24	21	10 cerebral ependymomas; 4 pulmonary alveolar carcinomas
Buffalo								
F (16)	6 mo	18 mo	354	15 (4-5)	-	5	-	-

[a] Number in parentheses indicate average number of tumours per animal; M, males; F, females; X_{po}, exposure period; X_{pe}, total experimental and observation period; mo, months.

2.3 Selection of the suitable study for estimating occupational cancer risk

In the absence of well-performed human studies, and in the absence of animal inhalation studies, the committee selected the oral carcinogenic experiment by Beal *et al*. (Bea75), to estimate the potential cancer risk in humans under workplace conditions. In this experiment, the carcinogenic effects of dacarbazine at various doses and exposure periods were studied in male and female rats (see Table 2.2).

For cancer risk analysis, the group with the longest exposure and observation period is of most interest. This concerns a group of female rats, which were given dacarbazine in the diet (100 mg/kg diet) for 46 weeks, followed by an observation period of 14 weeks (=98 days) on diet without the compound. The committee has chosen this group as starting point for estimating occupational cancer risk.

2.4 Lifetime low-dose exposure: carcinogenic activity in experimental animals

The incidence of malignant tumours in the treated rats was for: mammary adenocarcinoma, 1/16; thymic lymphosarcoma, 3/16; splenic lymphosarcomas, 2/16; uterine leiomyosarcomas, 2/26; and, leiomyosarcomas elsewhere, 2/16. Not included are mammary adenofibromas, because these type of tumours are not relevant for humans. In addition, the total incidence of tumour bearing animals is 10/16, compared to no malignant tumours in control rats (0/52). The committee remarks that the incidence of 10/16 is

a ‘worst-case’, because in the original paper it is not indicated whether some animals had more than one type of tumour.

For estimating additional lifetime cancer risk values the dose should be expressed in mg/kg bw/day. The average daily intake is calculated from the reported cumulative dacarbazine dose per rat (570 mg/rat), the average weight of female rats (350 gram, see Hea95), and the duration of the experimental period. Taking these into account, the average daily intake amounts to 5.1 mg dacarbazine/kg bw/day.

Furthermore, the committee is of the opinion that the available data do not indicate that the use of the linear model is inappropriate. Therefore, under lifespan conditions, the calculated incidence of tumour-bearing animals per mg/kg bw/day is calculated as follows*:

$$I_{dose} = \frac{I_e - I_c}{D \times \left(X_{po}/L\right) \times \left(X_{pe}/L\right) \times \left(\textit{days per week}/7\right)}$$

$$I_{dose} = \frac{\left(10/16\right) - \left(0/52\right)}{5.1 \times \left(322/1{,}000\right) \times \left(420/1{,}000\right) \times \left(7/7\right)}$$

I_{dose} = 0,91 *[mg/kg bw/day]*

2.5 Human lifetime low-dose exposure

To estimate the additional lifetime risk of cancer in humans under lifespan conditions on the basis of results in animal experiments, it is assumed that no difference exists between experimental animals and man with respect to toxicokinetics, mechanism of tumour induction, target susceptibility, etc., unless specific information is available which justifies a different approach. Furthermore, it is assumed that the average man lives 75 years, weighs 70 kg, and is exposed 24 hours per day, 7 days per week, 52 weeks per year for lifetime.

2.6 Calculation of the HBC-OCRV

To estimate the potential additional lifetime risk of cancer in humans under workplace exposure conditions, it is assumed that the average man lives 75 years, is exposed 8 hours per day, 5 days per week, 48 weeks per year for 40 years, and inhales 10 m^3 per 8-

* I is estimated tumour incidence; I_e and I_c are tumour incidences in exposed and control animals, respectively; X_{po} and X_{pe} are exposure and experimental period, respectively (days); L is the standard lifespan for the animal species in question (L rats is assumed to be 1,000 days)

hour-working day. Using as starting point the estimated incidence of 0.91 per mg/kg bw/day, the additional lifetime cancer risk per mg/m^3 under occupational exposure conditions, the HBC-OCRV, amounts to

$$HBC-OCRV = I_{dose} \times \left({}^{40}\!/\!_{75\ years} \right) \times \left({}^{48}\!/\!_{52\ weeks} \right) \times \left({}^{5}\!/\!_{7\ days} \right) \times \left(10\ m^3 \right) \times \left(70\ kg\ bw \right)^{-1}$$

$$HBC-OCRV = 0.91 \times (0.53) \times (0.92) \times (0.71) \times (10) \times (70)^{-1}$$

$$HBC-OCRV = 4.5 \times 10^{-2} \left[mg/m^3 \right]^{-1}$$

Based on the HBC-OCRV of 4.5 x 10^{-2} per mg/m^3, the additional lifetime cancer risk for dacarbazine amounts to:

- 4 x 10^{-3} for 40 years of exposure to 90 µg/m^3;
- 4 x 10^{-5} for 40 years of exposure to 0.9 µg/m^3.

2.7 Existing occupational exposure limits

No occupational exposure limits have been set in the Netherlands (SZW04) nor in Germany (DFG03, Bun98), the United Kingdom (HSE02), Scandinavian countries (Arb02, NBO00), the USA (ACG04), and the European Union (Hun97).

In the Netherlands and in Denmark, dacarbazine is listed as a carcinogenic compound (Arb02, SZW04). Furthermore, the Occupational Safety and Health Administration (the USA) has regulated dacarbazine under the Hazard Communication Standard and as a chemical hazard in laboratories (ACG04).

2.8 Toxicity profile

Overall, IARC commented that in view of the extreme light sensitivity of dacarbazine, the data below should be interpreted with caution, since most reports did not describe whether precautions to protect the compound from light were taken into account (IAR81).

2.8.1 Humans (IAR81)

The toxic effects of dacarbazine are mainly myelosuppression and gastrointestinal upset. Leucopenia and thrombocytopenia occurred from 5 to 21 days after a dose of 4.5 mg/kg bw per day for up to 10 days; blood counts recovered only after 2-3 weeks. Nausea and vomiting limit the therapeutic dose which can be given either intravenously or orally

(Skibba *et al*., 1969; evaluated in IAR81). High doses may cause gastrointestinal bleeding. Furthermore, in three patients hepatic vein thrombosis leading to fatal hepatic necrosis have been reported. The patients were treated for melanoma with 200-260 mg/m^2 daily intravenously for one cycle of five days.

No other human data were available to the committee.

2.8.2 *Animal data*

Lethality. The oral LD_{50} of dacarbazine in mice is reported to be up to 1,000 mg/kg bw; the LD_{50} amounts to 350 and 567 mg/kg bw in rat and mouse, respectively, when given as a single intraperitoneal injection; and, the intravenous LD_{50} in rat is 411 mg/kg bw (Ric93).

Maximally tolerated doses (MTDs). In dogs, the maximum tolerated dose over 28 days was reported to be 2.5 mg/kg bw per day when given intraperitoneally, and 5 mg/kg per day when given orally; in monkeys the respective doses were 15-30 and 10 mg/kg bw per day. In all animal studies (rats, monkeys, and dogs), the major toxicity involved damage to the gut, bone marrow, and lymphoid tissue. Recovery from toxic effects may be complete within 6 weeks of finishing treatment (IAR81).

Reproduction and prenatal toxicity. Dacarbazine given to mice as a single intraperitoneal injection at doses of 50 or 200 mg/kg bw adversely affected spermatogenesis (Mar89). IARC reports on several studies in which dacarbazine, when given intraperitoneally, causes teratogenic effects (anomalies in several organs and skeletal system) in rats and rabbits at doses as low as 30 to 70 mg/kg bw (rats) or 10 mg/kg bw (rabbits) (IAR81).

Mutagenicity and genotoxicity

Dacarbazine is a methyling cytostatic drug that possesses genotoxic potential. The compound has been shown to be mutagenic in prokaryotic and eukaryotic cells *in vitro* and clastinogenic to mouse bone marrow *in vivo* (Bar82, Haw82, IAR81, Psa00).

2.8.3 *In conclusion*

The toxicity data, as summarized in the previous sections, are too limited to allow a conclusion with regard to risk of adverse effects other than carcinogenicity at concentration levels associated with the referential cancer risk levels.

References

ACG04 American Conference of Governmental Industrial Hygienists (ACGIH). Guide to occupational exposure values 2004. Cincinnati OH, USA: ACGIH, 2004.

Arb02 Arbejdstilsynet. Grænseværdier for stoffer og materialer. Copenhagen, Danmark: Arbejdstilsynet, Oktober 2002. [In Danish]

Bar82 Bartolli-Klugmann F, Pani B, Badudri N, Montibragadin C, Tamaro M, *et al*. In vitro mutagenic activity of DTIC in eukaryotic and procariotic cells. Carcinogenesis 1982; 3: 467-471.

Bea75 Beal DD, Skibba JL, Croft WA, Cohen SM and Bryan GT. Carcinogenicity of the antineoplastic agent, 5-(3,3-dimethyl-1-triazeno)-imidazole-4-carboxamide, and its metabolites in rats. J Natl Cancer Inst 1975; 54: 951-957.

Boi95 Boivin JF, Hutchison GB, Zauber AG, Bernstein L, Davis FG, *et al*. Incidence of second cancers in patients treated for Hodgkin's disease. J Natl Cancer Inst 1995; 87: 732-741.

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

DEC95 Dutch Expert Committee on Occupational Standards. Scientific documentation on the Dutch list of occupational carcinogens (I). The Hague, The Netherlands: Sdu Servicecentrum Uitgeverijen, 1995; rep no RA 1/95.

DFG03 Deutsche Forschungsgemeinschaft (DFG): Commission for the investigation of health hazards of chemical compounds in the work area. List of MAK and BAT Values 2003. Maximum concentrations and biological tolerance values at the workplace. Weinheim: Wiley-VCH Verlagsgesellschaft mbH, 2003; Report no. 39.

Haw82 Al Haward BA and Al-Saleh AA. Cytogenetic effects of dacarbazine on mouse bone marrow cells in vivo. Mutat Res 1982; 223: 259-266.

Hea95 Health Council of The Netherlands: Dutch Expert Committee on Occupational Standards (DECOS). Calculating cancer risk. The Hague, The Netherlands: Health Council of the Netherlands, 1995; pub no 1995/06WGD.

HSE02 Health and Safety Executive (HSE). EH 40/02. Occupational Exposure Limits 2002. Sudbury (Suffolk), UK: HSE Books, 2002.

Hun97 Hunter WJ, Aresini G, Haigh R, *et al*. Occupational exposure limits for chemicals in the European Union. Occup Environ Med 1997; 54: 217-222.

IARC81 International Agency for Research on Cancer (IARC). Dacarbazine. In: Some antineoplastic and immunosuppressive agents. Lyon, France: IARC, 1981: 203-215 (IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans; Vol 26).

IARC87 International Agency for Research on Cancer (IARC). Dacarbazine. In: Overall evaluations of carcinogenicity: an updating of IARC monographs volumes 1 to 42. Lyon, France: IARC, 1987: 184-185. (IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans; Supplement 7).

Mar89 Martinova YS, Nikolova DB, Michova Z. Early effect of the anticancer drug biocarbazin (DTIC synonym) on mice spermatogenesis. Z Mikrosk Anat Forsch 1989; 103: 431-436.

NBO00 National Board of Occupational Safety and Health (NBOSH). Occupational exposure limit values and measures against air contaminants. Solna, Sweden: National Board of Occupational Safety and Health, 2000 (Ordinance AFS 2000:3).

Psa00 Psaroudi MC and Kyrtopoulos SA. Toxicity, mutation frequency and mutation spectrum induced by dacarbazine in CHO cells expressing different levels of O^6-methylguanine-DNA methyltransferase. Mutat Res 2000; 447: 257-265.

Ric93 Richardson ML, Gangolli S, ed. D18. Dacarbazine In: The dictionary of substances and their effects. Cambridge, UK: Royal Society of Chemistry, 1993: 22-25 (Vol 1).

ROC98 Report on carcinogens, eighth edition. 1998. U.S. Department of health and human services, Public Health Service, National Toxicology Program 1998; 85.

SZW04 Ministerie van Sociale Zaken en Werkgelegenheid (SZW) De Nationale MAC-lijst 2004, The Hague, The Netherlands: Servicecentrum Sdu Uitgevers, 2004. [In Dutch]

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

Wei77 Weisburger EK. Bioassay program for carcinogenic hazards of cancer chemotherapeutic agents. Cancer 1977; 40: 1935-1951.

Zel80 Zeller WJ. Pränatal karzinogene Wirkung von 5-(3,3-Dimethyl-1-triazeno)-imidazol-4-carboxamid (DTIC) bei den Nachkommen von BD IX Ratten. Arch Geschwulstforsch 1980; 50: 306-308.

A Request for advice

B The Committee

C Comments on the public review draft

Annexes

Chapter 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.

Chapter **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; Environ, the Netherlands
- PJ Boogaard
  toxicologist; SHELL International BV, The Hague
- PJ Borm
  professor of inhalation toxicology; Heinrich Heine Universit‰t, D¸sseldorf (Germany)
- JJAM Brokamp, *advisor*
  Social and Economic Council, The Hague
- DJJ Heederik
  professor of risk assessment in occupational epidemiology; IRAS, University of Utrecht, Utrecht
- TM Pal
  occupational physician; Dutch 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; DOW Benelux NV, Terneuzen
- AA Vijlbrief, *advisor*
  Ministry of Social Affairs and Employment, The Hague
- RA Woutersen
  toxicologic 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 this report was prepared by MI Willems, from the Department of Occupational Toxicology of the TNO Nutrition and Food Research, by contract with the Ministry of Social Affairs and Employment.

Secretarial assistance: F Smith.
Lay-out: J van Kan.

Chapter C

Comments on the public review draft

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

- R Zumwalde, National Institute for Occupational Safety and Health, the USA.