4,4’-Methylene dianiline

Health based calculated occupational cancer risk values

Aan de Staatssecretaris van Sociale Zaken en Werkgelegenheid

Onderwerp	: Aanbieding advies
Uw kenmerk	: DGV/BMO-U-932542
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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 om gezondheidskundige advieswaarden af te leiden ten behoeve van de bescherming van beroepsmatig aan stoffen blootgestelde personen.

Per 1 januari 1994 heeft mijn voorganger daartoe een commissie ingesteld die de werkzaamheden voortzet van de Werkgroep van Deskundigen (WGD). De WGD was een door genoemde minister ingestelde adviescommissie.

Hierbij bied ik u - gehoord de Beraadsgroep Gezondheid en Omgeving - een publicatie van de commissie aan over 4,4'-methyleen dianiline.
Deze publicatie heb ik heden ter kennisname aan de Minister van Volksgezondheid Welzijn en Sport en aan de Minister van Volkshuisvesting Ruimtelijke Ordening en Milieubeheer gestuurd.

w.g
prof. dr JJ Sixma

4,4’-Methylene dianiline

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. 2000/11OSH, The Hague, 6 September 2000

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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 methyleen dianiline. Zij heeft daarbij gebruik gemaakt van de methode die is beschreven in het rapport 'Berekening van het risico op kanker' (1995/06WGD) (Dec95).

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

- 4×10^{-5} bij 40 jaar beroepsmatige blootstelling aan 0.009 mg/m^3
- 4×10^{-3} bij 40 jaar beroepsmatige blootstelling aan 0.9 mg/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 lifetime 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 methylene dianiline. It has used the method described in the report 'Calculating cancer risks due to occupational exposure to genotoxic carcinogens' (1995/06WGD) (Dec95).

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

- 4×10^{-5} for 40 years of occupational exposure to 0.009 mg/m^3
- 4×10^{-3} for 40 years of occupational exposure to 0.9 mg/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, on 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 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-OCRVs for methylene dianiline (MDA) by the committee. 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 Institute in Zeist, by contract with the Ministry of Social Affairs and Employment.

In 1998, 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.

Chapter 2

4,4’-Methylene dianiline (MDA)

2.1 Introduction

The carcinogenicity of MDA (CAS no. 101-77-9) has been evaluated by DFG (Gre95), IARC (IARC86), and Fairhurst (Fai91). In addition, 4,4’-methylene dianiline has been classified as a category 2 carcinogen by the European Union.

The present evaluation of the carcinogenicity was based on a review by IARC (IARC86). In addition, literature was retrieved from online databases Medline, Toxline and Cancerlit covering the period 1975 to 1996.

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

No information was found to evaluate the possible carcinogenicity in humans. Liver damage is the main reported adverse effect in humans irrespective of the way of exposure (oral, dermal or inhalatory). Consumption of MDA-contaminated bread led to an outbreak of 84 cases of jaundice in Epping, UK. From analysis of the MDA content of these bread samples, it has been estimated that individuals consumed about 3 mg MDA/kg bw. All patients made a good clinical recovery (IARC86). A follow-up study after 2 years did not point to progressive hepatic disease (Fai91). A second follow-up study after 24 years did not allow firm conclusions regarding long-term health effects of MDA because of limitations in the investigation (Fai91, Hal90).

Table 1 (Annex D) summarizes the main carcinogenicity studies with experimental animals with test conditions and results. As appears from Table 1, the only studies suitable for quantitative risk assessment are the long-term studies performed in the framework of the National Toxicology Program (NTP) in mice and rats. The other studies reviewed by DFG and IARC (two subcutaneous and three gavage studies in rats, and one oral study in dogs) are suitable neither to assess the carcinogenic potentential nor for quantitative risk assessment, due to poor study design, reporting etc. (see Table 1).

In the NTP studies MDA was administered in drinking water for 103 weeks followed by one week without treatment to groups of fifty male and fifty female mice and rats at concentration levels of 0, 0.015 or 0.03%. In rats given MDA there was good survival at both 78- and 105-weeks with no significant differences between the males and females. In mice on MDA, survival of high-dose males was significantly reduced when compared with the survival of the low-dose and control groups (Wei84). Treatment-related increases in the incidences of thyroid follicular-cell adenomas and hepatocellular neoplasms were observed in both male and female mice. In rats, treatment-related increases in the incidences of thyroid follicular-cell carcinomas and hepatic nodules were observed in males, and thyroid follicular-cell adenomas occurred in females (see Table 2, Annex D). The incidences of rats and mice with different tumour are listed in table 2 (Annex D).

2.3 Carcinogenic activity in experimental animals, lifetime low-dose exposure

To calculate the carcinogenic activity of MDA, the incidences of male rats and mice, given 0.03% MDA, with liver and thyroid tumours were used as starting point. For this calculation, the total number of *treatment-related* tumour-bearing animals should be used. However, since the available reports did not discriminate between animals with tumours in both thyroid and liver and those with tumours in one of these target organs only, the numbers of animals presented with liver or thyroid tumours are added up. In addition, the committee is of the opinion that the available data do not indicate that the use of the linear model is not appropriate.

The incidence per mg MDA/kg bw/day (lifespan conditions, assuming a linear dose response relationship), I_{dose}, is calculated as follows:

$$I^*_{dose} = \frac{I_e - I_c}{C \times (X_{po}/L) \times (X_{pe}/L) \times \text{exposure hours per day}/24 \times \text{exposure days per week}/7}$$

* I_{dose} = the carcinogenic activity attributable to the exposure to the substance per unit daily dose under lifespan conditions assuming a linear dose response relationship
Ie and Ic = incidence of tumour bearing animals or tumours in exposed and control amnimals, respectively,
Xpo = exposure period, Xpe = experimental period

For male rats this results in an

$$I_{dose} = \frac{(\frac{10}{48}+\frac{25}{50})-(\frac{1}{49}+\frac{1}{50})}{15[mg \cdot kg^{-1} \cdot d^{-1}] x \frac{721d}{1000d} x \frac{728d}{1000d}} = 8.5x10^{-2}[mg/kg/d]^{-1}$$

For male mice this results in an

$$I_{dose} = \frac{(\frac{29}{50}+\frac{16}{49}) - (\frac{10}{49}+\frac{0}{47})}{50\ [\text{mg x kg}^{-1}\text{x d}^{-1}]\ \text{x}\frac{721}{750}\ \text{x}\frac{728}{750}} = 1.5 \text{ x } 10^{-2}[mg/kg/d]^{-1}$$

Since the highest risk was calculated for rats, the incidence of 8.5 x 10^{-2} is used as a starting point for quantitative risk estimation in humans as a way of precaution.

For calculating the dose in mg/kg bw/day the following standard values were used:

Table 3

	standard lifespan	weight kg	water ml/day	water ml/kg bw/day
rat male	1000 days	0.5	25	50
rat female	1000 days	0.35	20	57
mouse male	750 days	0.03	5	167
mouse female	750 days	0.025	5	200

2.4 Health risk to humans

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, weights 70 kg and is exposed 24 hours per day 7 days/week, 52 weeks per year for lifetime.

and L = standard lifespan for the animals in question (L rat is assumed to be 1000 days)

2.5 Calculation of the HBC-OCRV

To estimate the additional lifetime risk of cancer in humans under workplace conditions, it is assumed that the average man lives 75 years, is exposed 8 hours per day, five days a week, 48 weeks a year, for 40 years, and inhales 10 m^3 air per 8 hour-working day. Using as starting point the estimated incidence of 8.5 x 10^{-2} per mg/kg bw/day, the additional lifetime cancer risk per mg/m^3 under occupational exposure conditions, the HBC-OCRV, amounts to:

$$\text{HBC-OCRV} = 8.5x10^{-2}\ x\frac{40y}{75y}x\frac{48w}{52w}x\frac{5d}{7d}x\frac{10m^3}{70kg} = 4.3 \times 10^{-3}[mg/m^3]^{-1}$$

Based on the HBC-OCRV of 4.3 x 10^{-3} per mg/m^3 the reference additional lifetime cancer risk amounts to:

- 4 x 10^{-5} for 40 years of exposure to 0.009 mg/m^3
- 4 x 10^{-3} for 40 years of exposure to 0.9 mg/m^3

2.6 Existing occupational exposure limits

Table 4 summarizes the occupational exposure limits established by the regulatory authorities of Germany, United Kingdom, USA-ACGIH and USA-OSHA.

The lowest occupational exposure limit settled by these countries amounts to 0.08 mg/m^3 (UK, HSE95). In the United Kingdom, it was concluded that considering the carcinogenicity data, a threshold could not be identified and that consequently a maximum exposure limit (MEL)* (0.08 mg/m^3) was appropriate. This concentration is about a factor 10 lower than the concentration leading to an additional cancer risk of 4 x 10^{-3} (i.e., 0.9 mg/m^3) and about a factor 9 higher than the concentration leading to an additional cancer risk of 4 x 10^{-5} (i.e., 0.009 mg/m^3).

* In setting a Maximum Exposure Limit (MEL), not only the protection of the health of the employee is considered, also socio-economic factors are taken into account. A cost benefit assessment is prepared to assist the considerations of these. In practice, MELs have been most often allocated to carcinogens, respiratory sensitizers and to other substances for which no threshold level of exposure for the effects can be identified and for which there is no doubt about the seriousness of the hazard(s) posed by the substance.

Table 4 Occupational exposure limits for MDA.

country	level		time relation	notations	ref.
	ppm	mg/m^3			
The Netherlands[a]	-	-	-	-	-
Germany[be]	-	(0.1)	-	skin, sensibilisation	DFG96
UK	0.01	0.08 (MEL)	8-h TWA	skin, new	HSE95
Sweden[c]	-	-	-	-	NBO93
USA-ACGIH[d]	0.1	0.81	8-h TWA	skin	ACG96

[a] The substance is listed as a carcinogen

[b] The DFG classifies MDA as a category A2 carcinogen; DFG category A carcinogens are not assigned a health-based occupational limit, but a so called TRK-value (TRK = Technische Richtkonzentrationen), a concentration feasible with currently available technical means. TRK-values are given in brackets.

[c] In Sweden, MDA is placed under section 9 (carcinogen) and may only be handled by permission of the Labour Inspectorate.

[d] Classified as A3 carcinogen: animal carcinogen .

For the committee,
The Hague, 6 September 2000

dr ASAM van der Burght,
scientific secretary

Prof. dr GJ Mulder,
chairman

References

ACG96 American Conference of Governmental Industrial Hygienists (ACGIH). 1996. TLVs(R) and BEIs(R). Threshold Limit Values for chemical substances and physical agents. Biological Exposure Indices. Cincinnati OH, USA: ACGIH, 1996: 27.

DEC95 Health Council of the Netherlands: Dutch Expert Committee on Occupational Standards (DECOS). Calculating cancer risk. The Hague: Health Council of the Netherlands, 1995 publication no 1995/06WGD.

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Fai91 Fairhurst S. Toxicity review for WATCH, 4,4'-Methylene dianiline (MDA), 1991; ACTS/26/91 Annex 5.

Hal90 Hall A, Waterhouse J, Harrington JM. The 'Epping Jaundice' outbreak - A 24 year follow-up. Birmingham, UK: University of Birmingham, Institute of Occupational Health, 1990. Undated draft. Received by III Scientific Office 22 March 1990.

Gre95 Greim H, ed. 4,4'-Diaminodiphenylmethan H,S und -Dihydrochlorid. In: Gesundheitsschädliche Arbeitsstoffe. Toxikologisch-arbeitsmedizinische Begründungen von MAK-Werte (Maximale Arbeitsplatz-Konzentrationen). 1st-21st ed. Weinheim, FRG: VCH Verlagsgesellschaft mbH, 1995.

HSE95 Health and Safety Executive (HSE). Occupational exposure limits 1995. Sudbury (Suffolk), UK: HSE Books, 1995: 21, 28 (Guidance note 40/95).

IARC86 International Agency for Research on Cancer (IARC). 4,4'-Methylenedianiline and its dihydrochloride. Some chemicals used in plastics and elastomers. Lyon, France: IARC, 1986: 347-65. In: IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans; Vol 39.

ISZW95 Inspectiedienst van het Ministerie van Sociale Zaken en Werkgelegenheid (I-SZW). De Nationale MAC-lijst 1995. The Hague, The Netherlands: Sdu Servicecentrum Uitgeverijen, 1995: 42, 63 (pub no P145).

NBO93 National Board of Occupational Safety and Health (NBOSH). Occupational exposure limits. Solna, Sweden: NBOSH, 1993: 74 (Ordinance AFS 1993/9).

Wei84 Weisburger EK, Krishna Murthy AS, Lilja HS *et al*. Neoplastic response of F344 rats and B6C3F1 mice to the polymer and dyestuff intermediates 4,4'-methylenebis- (N,N-dimethyl)-benzenamine, 4,4'-oxydianiline, and 4,4'-methylenedianiline. J Natl Cancer Inst 1984; 72: 1457-63.

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
- PJ Borm
  toxicologist; Heinrich Heine Universität Düsseldorf (Germany)
- JJAM Brokamp, *advisor*
  Social and Economic Council, The Hague
- VJ Feron,
  professor of toxicology; TNO Nutrition and Food Research Institute, Zeist
- DJJ Heederik
  epidemiologist; Wageningen University, Wageningen
- LCMP Hontelez, *advisor*
  Ministry of Social Affairs and Employment, The Hague
- G de Jong
  occupational physician; Shell International Petroleum Maatschappij, The Hague
- J Molier-Bloot
  occupational physician; BMD Akers bv, Amsterdam
- IM Rietjens
  professor in Biochemical toxicology; Wageningen University, Wageningen.

- H Roelfzema, *advisor*
  Ministry of Health, Welfare and Sport, Den Haag
- T Smid
  occupational hygienist; KLM Health Safety & Environment, Schiphol and professor of working conditions, Free University, Amsterdam
- GMH Swaen
  epidemiologist; Maastricht University, Maastricht
- HG Verschuuren
  toxicologist; DOW Europe, Horgen (Switzerland)
- F de Wit
  occupational physician; Labour Inspectorate, Arnhem
- CA Bouwman, *scientific secretary*
  Health Council of the Netherlands, Den Haag
- ASAM van der Burght, *scientific secretary*
  Health Council of the Netherlands, Den Haag

The first draft of the present advisory report was prepared by M Willems, from the Department of Occupational Toxicology of the TNO Nutrition and Food Research Institute, by contract with the Ministry of Social Affairs and Employment.

Secretarial assistance: J Toet.
Lay-out: J van Kan.

Annex **C**

Comments on the public draft

A draft of the present report was relased in 1998 for public review. The following organisations and persons have commented on the draft document:

- WF ten Berge, DSM, Heerlen

Annex **D**

Animal studies

See tables on the next pages.

Table 1 Carcinogenicity studies with 4,4'-methylene dianiline (MDA).

authors	species	exposure characteristics	findings	remark
Steinhoff and Grundmann (1975) reviewed in Gre95; Fair91; IARC86	rat, Wistar 25/sex/group	subcutaneous Dose: 30-50 mg/kg bw at one to 3-week intervals (total dose 1.4 g/kg bw) Xpo: 705 days Xpe: 970 - 1060 days (MDA); 1007 days (controls)	MDA group: 29 benign tumours, 33 malignant tumours controls: 15 benign tumours, 16 malignant tumours	limited reporting. Study not suitable for assessment of carcinogenic potential of MDA
Steinhoff and Dycka (1981) reviewed in Gre95	rat, Sprague- Dawley 30/sex/group	subcutaneous close: 0_1 ? Xpo: ? Xpe: lifetime	no significant increases in tumour incidence in MDA-treated animals compared to controls	data not sufficiently reported
NTP-Study 1983 (Wei84)	rat, F344/N 50/sex/group	p.o. drinking water dose levels: 0, 0.015, 0.03% Xpo: 103 weeks Xpe: 104 weeks	treatment related increases in the incidences of thyroid follicular-cell carcinomas and hepatic nodules in males and thyroid follicular-cell adenomas in females (see Table 2 for actual numbers)	
NTP-Study 1983 (Wei84)	mouse, B6C3F1 50/sex/group	p.o. drinking water dose levels: 0, 0.015, 0.03% Xpo: 103 weeks Xpe: 104 weeks	treatment related increases in the indidences of thyroid follicular- cell adenomas and hepatocellular neoplasms (see Table 9.2 for actual numbers)	
Schoental (1968) reviewed in Gre95 IARC86 Fai91	rat, strain? N =16 (8/sex)	p.o. gavage dose levels: 4 or 5 x 20 mg/animal Xpo: < 8 months Xpe: lifetime	tne hepatoma and a hemangioma-like tumour of the kidney in a male (18 months). Uterus adenocarcinoma in one female (24 months)	study not suitable for evaluation of carcinogenic potential of MDA
Munn (1967) reviewed in Gre95, IARC86, Fai91	rat, strain? males N = 24 similar experiment	1) p.o. gavage, total dose 3300 mg/kg Xpo: 121 days Xpe: lifetime 2) p.o. gavage, total dose 6000 mg/kg Xpo: 18 months Xpe: lifetime	all of the 24 animals had liver cirrhosis and two developed benign hepatomas two animals developed "liver tumours" (type unspecified)	studies not suitable for evaluation of carcinogenic potential of MDA
Griswold et al. (1968) reviewed in Gre95 IARC86 Fai91	rat, Sprague-Dawley females N = 20 controls: 140 females	p.o. gavage dose: 30 mg every 3 days for 30 days (total dose: 300 mg/rat) Xpo: 30 days Xpe: 9 months Limited histopathology	mammary lesions were found in 5/132 controls and in 1 of 14 MDA-treated animals	no MDA induced tumours were found. Study design focussed on the appearance of mammary tumours in female SD-rats
Deichmann et al. (1978) reviewed in Gre95 IAR86 Fai91	dog, Beagle females N = 5 pure MDA N = 4 "crude" MDA	p.o. gelatineous capsules dose: 70 mg/dog, 3 times a week Xpo: 4 - 7 years No control group included	no tumours of liver and bladder were found. MDA-induced liver damage was seen in all animals pure MDA: one survivor crude MDA: two survivors	study not suitable for assessment of carcinogenic potential of MDA

Xpo = exposure period, Xpe = experimental period.

Table 2 Tumour incidences in rats and mice treated with MDA (from Wei84; Gre95; IARC86; Fai91)[a].

rats		% MDA in drinking water					
		males			females		
		0	0.02	0.03	0	0.02	0.03
MDA, mg/kg bw/day							
calculated[b]		0	7.5	15	0	8.6	17.1
measured[c]		0	9	16	0	10	19
thyroid gland	n =	49	47	48	47	47	48
follic. cell adenoma		1	4	3	0	2	17 [<.001]
follic. cell carcinoma		0	0	7 [.012]	0	2	2
C-cell adenoma		1	2	1	0	3	6 [<0.05]
liver	n =	50	50	50	50	50	50
neoplastic nodule		1	12 [.002]	25 [<.001]	4	8	8

mice		% MDA in drinking water					
		males			females		
		0	0.015	0.03	0	0.015	0.03
MDA, mg/kg bw/day							
calculated[b]		0	25	50	0	30	60
measured[c]		0	25	57	0	19	43
thyroid gland	n =	47	49	49	50	47	50
follic. cell adenoma		0	3	16 [<.001]	0	1	13 [<.001]
follic. cell carcinoma		0	0	0	0	0	2
liver	n =	49	50	50	50	50	50
adenoma		7	10	8	3	9 [.049]	12 [<.008]
carcinoma		10	33 [<.001]	29 [<.001]	1	6	11 {<.002]

[a] Numbers in brackets are P-values.

[b] See Table 3, page 17.

[c] Fai91. MDA intake was calculated from measured water intake.