Metronidazole

Health based calculated occupational cancer risk values

Aanbiedingsbrief

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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. 1999/11OSH, The Hague, 20 December 1999

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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 maakt zij zo'n schatting voor metronidazol. Zij heeft daarbij gebruik gemaakt van de methode die is beschreven in het rapport 'Berekening van het risico op kanker' (1995/06WGD) (DEC95a).

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

- 4×10^{-5} bij 40 jaar beroepsmatige blootstelling aan 0.12 $\mu g/m^3$
- 4×10^{-3} bij 40 jaar beroepsmatige blootstelling aan 12 $\mu g/m^3$

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 metronidazole. It has used the method described in the report 'Calculating cancer risks due to occupational exposure to genotoxic carcinogens' (1995/06WGD) (DEC95a).

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

- 4×10^{-5} for 40 years of occupational exposure to 0.12 $\mu g/m^3$
- 4×10^{-3} for 40 years of occupational exposure to 12 $\mu g/m^3$.

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, 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 by the committee for metronidazole. The members of the committee are listed in Annex B. The first draft of this report was prepared by H Stouten and MI Willems, from the TNO Nutrition and Food Research Institute in Zeist, by contract with the Ministry of Social Affairs and Employment.

Chapter 2

Metronidazole

2.1 Introduction

Metronidozole has been classified as a genotoxic carcinogen by DECOS (DEC95b).

The carcinogenicity of metronidazole has been evaluated by IARC (IARC77; IARC82; IARC87). IARC has concluded that there is sufficient evidence for carcinogenicity to animals, but inadequate evidence for carcinogenicity to humans (Group 2B, IARC87). Literature has been retrieved from online data bases covering the period 1965-1966 to June 1996.

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

Table 1 (Annex D) summarizes the carcinogenicity studies with experimental animals. Following oral administration metronidazole produced lung tumours in male and female mice, lymphomas in female mice and mammary, pituitary, testicular and liver tumours in rats. There are no inhalation studies available.

The human data underlying the conclusion of IARC regarding the inadequacy of the evidence for carcinogenicity to humans has been summarized by IARC as follows (IARC87). Two epidemiological studies of women treated with metronidazole showed some excesses of cancers of the uterine cervix, a neoplasm that has risk factors in common with vaginal trichomoniasis, the main indication in women for treatment with this drug (Bea79, Fri80a). In the study of Beard *et al*. a greater excess of cervical cancer

was observed in women with trichomoniasis who were not exposed to metronidazole than in those who were (relative risk, 2.1 versus 1.7) (Bea79). An excess of lung cancer (4 observed, 0.6 expected) seen in the study of Beard *et al*. was not found in the study of Friedman and Ury (2 observed, 2.6 expected) (Fri80b). In the former, the excess was mainly of adenocarcinoma (3/4 cases) and was concentrated after at least ten years from first use of metronidazole (3 observed, 0.3 expected) (Bea80). Further follow-up and analysis of these data suggested that the excess could be explained entirely by confounding with smoking (Bea85). Another study in which 12,280 users of metronidazole were followed up for two and one-half years gave a relative risk of 0.9 (95% confidence interval, 0.5-1.9) for all cancers (Dan82).

In 1988, Beard *et al*. published an update of their study, published in 1979 (Bea79; Bea88). The cohort defined for this study included all Rochester women with vaginal trichomoniasis diagnosed during a 10-year period who received a prescription for metronidazole as treatment. These women were followed-up for a total of 12,628 person-years. The standardized morbidity and mortality ratios were determined by using an expected number calculated by applying age-specific incidence rates from three different sources to the person-years of follow-up. The overall standardized morbidity ratios for cancer at all sites were 1.4 (Rochester), 1.5 (Iowa) and 1.2 (Connecticut).

For specific cancer sites, the only significantly elevated standardized morbidity ratio was that for bronchogenic carcinoma, a ratio of 3.4 was found (95% confidence interval 1.8 - 5.9). An effort was made to adjust the rates for smoking status by using the smoking habits of Rochester women of similar ages as the cohorts. After adjustment for smoking status, the standardized morbidity ratio for bronchogenic carcinoma was 2.5 (95% confidence interval of 1.3 to 4.4). Of the 12 cases of bronchogenic carcinoma, 7 were adenocarcinomas and 2 were squamous cell carcinomas; also included were 1 case each of large cell carcinoma, carcinoid and “unknown”. In addition, one case of pleural mesothelioma was identified. The standardized mortality ratios for cancer at all sites were also calculated by using death rates for all malignant neoplasms. The observed number of death was 22 while 15.4 was expected (Minnesota), resulting in a standardized mortality ratio of 1.4, with a 95% confidence interval of 0.9 to 2.2. No standardized mortality ratios were determined on specific cancer sites. Beard *et al*. concluded that the analysis of their data suggested no significant increase in cancer-related morbidity or mortality for women exposed to metronidazole for treatment of vaginal trichomoniasis (Bea88).

Falagas *et al* studied the late incidence of cancer after metronidazole use in randomly selected non-users matched on a one to one basis for age, gender and year of enrollment to persons who used metronidazole on an outpatient basis during the period January 1975 to December 1983. 5,222 metronidazole users/non-users pairs, for whom the median follow-up was 12.6 years, were analyzed. Forty-nine percent, 39.2%, 9.8%

and 2% of the users had 1, 2-4, 5-9, 10 or more prescriptions or refills of metronidazole filles, respectively. The late (after the first 7 years of follow-up) incidence of all site and site-specific cancer was nearly identical among users and non-users (652 and 662 per 100,000 person years, respectively; relative risk, 0.98; 95% confidence interval was 0.8-1.20). Age-gender stratified analysis did not reveal any association between metronidazole use and cancer. Although there was no statistically significant association between metronidazole use and the diagnosis of solid-organ cancer, the incidence of solid tumours was slightly higher for the metronidazole users in two separate subset analyses of matched pairs of metronidazole users and non-users who had at least 12 years (2,069 pairs) and 15 years (608 pairs), respectively, of cancer-free follow-up. The incidence of solid cancer in metronidazole users and non-users who had at least 15 years of cancer-free follow-up was 1,336 and 564 per 100,000 person-years, respectively (RR=2.38; 95% CI was 0.82-6.12; p=0.11). The incidence of solid cancer in metronidazole users and non-users who had at least 12 years of cancer-free follow-up was 936 and 653 per 100,000 person-years, respectively (RR=1.43; 95% CI was 0.92-2.20; p=0.11). The data reported by Falagas *et al* support no association between short-term exposure to metronidazole and cancer in humans. However, in view of the short follow-up period, ie. 7 years, the results may not extend to subjects who have used metronidazole for prolonged periods (Fag98).

Thapa *et al* did not find an increased risk of all cancers in children younger than 5 years, associated with in utero exposure to metronidazole in a retrospective cohort study of 328,846 children, born to women using or not-using metronidazole during pregnancy. However, the authors conclude that the observed increased risk of neuroblastomas, although not significant, requires further evaluation (Tha98).

From the results of the studies summarized above it is concluded that, although the evidence that metronidazole is carcinogenic to humans is still inadequate, the data accumulated in the last five years strengthen the testimony of its potential carcinogenicity. After oral administration the target organ seems to be the lung, which complements the results as found in experimental animals. The results of the epidemiological investigations published by Beard *et al*. (Bea88) are used to calculate the potential risk of cancer at the workplace. The committee is of the opinion that the available data do not indicate that the use of the linear model is not appropriate.

2.3 Estimation of the potential risk of cancer under workplace exposure conditions on the basis of epidemiological data

Beard *et al*. assessed the risk of occurrence of cancer associated with exposure to metronidazole in 770 females who were treated with metronidazole for vaginal trichomoniasis. In this group of females 12 cases of lung cancer i.e. bronchogenic

carcinomas were found, while the expected number of lung cancer for a group of this size was 3.5. After adjustment for differences in smoking habits, a relative risk of 2.5 remained. The recommended dosage of metronidazole for *Trichomonas* vaginitis during the years 1960 through 1969 was 250 mg three times a day for 10 days, and for consorts it was 250 mg three times a day for 7 days (Bea88). For the calculations in this report it is assumed that the total prescribed dose amounted to 10 x 3 x 250 mg = 7500 mg active ingredient for each course of treatment. A total dose of 7500 mg metrinadozole results in a relative risk of 2.5 for lung cancer. In the Netherlands 16.3 per 1000 deaths in females is from lung cancer (CBS92).

To derive a risk value the following assumptions were made:

- The participants of the study followed one treatment course only, that they completed.
- A comparable carcinogenic activity is irrespective of the route by which exposure to metronidazole takes place.
- The data of Beard *et al*. regard females. The occupational situation regards males as well as females. It is assumed that in males the same effects will be found as in females. The background mortality of lung cancer in females is relatively low compared to that in males. It is assumed that the number of extra cancer cases would have been found also in a comparable group of males and not the same relative risk.
- There is no interaction with smoking.

To estimate the additional lifetime risk of cancer in humans under workplace exposure conditions it is assumed that the average worker is exposed 8 hours per day, five days a week, 48 weeks a year, for 40 years, and inhales 10 m^3 air/8 hour-working day. Under these conditions the total amount of air inhaled amounts to 100,000 m^3. Assuming a linear dose-response relationship and using as starting points the background lung cancer proportion mortality in the Netherlands of 16.3 per 1000 deaths, and the relative lung cancer risk of 2.5 (corresponding to 40.8 per 1000) derived for a total dose of 7500 mg metronidazole in 100,000 m^3 air, the additional life-time cancer risk per mg/m^3 under occupational conditions (= HBC-OCRV) amounts to 3.2×10^{-1}

Based on the HBC-OCRV of 3.2×10^{-1} the additional life-time cancer risk amounts to:

- 4×10^{-5} for 40 years of exposure to 0.12 µg/m^3
- 4×10^{-3} for 40 years of exposure to 12 µg/m^3

2.4 Existing occupational exposure limits

The regulatory authorities of The Netherlands, Germany, United Kingdom, Denmark, Sweden and the EU and USA-ACGIH have not established occupational exposure limits for metronidazole (ACG99; Arb96; DFG99; HSE99; Hun97; ISZW99; NBO93).

2.5 Toxicity profile of metronidazole

The consulted review papers (IARC77; IARC82; IARC87) did not contain information on toxicodynamic effects other than carcinogenicity and genotoxicity.

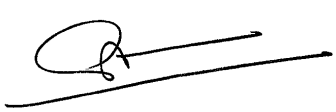
Below a short description of the general toxicology of metronidazole is given as evaluated and reported by Roe (Roe93). The oral LD_{50} of metronidazole for rats and mice is reported to lie within the range 1 to 5 g/kg bw (Roe83). Rats withstand oral dosages of up to 150 mg/kg bw daily without adverse effect, but exhibit testicular dystrophy and prostatic atrophy at higher dosage levels (no other information on experimental included). Dogs exposed orally to more than 75 mg/kg daily showed ataxia, muscular rigidity and tremors, but daily doses up to 50 mg/kg were entirely without toxic effect. At dosage levels of up to 225 mg/kg daily, monkeys displayed no evidence of toxicity apart from minimal nonspecific changes in the liver(Roe83). Properly designed tests for embryotoxicity and teratogenicity in rats, rabbits, and mice did not indicate embryotoxic or teratogenic activity, and no adverse effects on the fetus have been observed in women given metronidazole during various stages of pregnancy (Roe83).

Some human subjects given courses of 600 to 800 mg metronidazole daily for 7 or 10 days (i.e.; 10 to 15 mg/kg daily) for trichomoniasis reported transient nausea, unpleasant taste in the mouth, furring of the tongue, and gastrointestinal symptoms. On this regimen, headache, dizziness, ataxia, depression, transient leukopenia, and skin eruptions have rarely been reported (Roe83).

There are no indications that the use of metronidazole by pregnant women increase the risk of overall birth defect occurrence in the offspring (Cze98, Pip93).

Based on the lowest reported oral NOAEL of 50 mg/kg bw in animals (dogs) and the LOAEL of 10 - 15 mg/kg bw (corresponding to 60 mg/m^3) in man, it is concluded that a health-based occupational exposure limit for metronidazole derived from data other than on genotoxicity/carcinogenicity would in all likelihood be expected to be considerably higher than the concentration levels associated with the referential cancer risk levels.

The Hague, 20 December 1999,
for the committee



dr ASAM van der Burght,
scientific secretary

Prof. dr GJ Mulder,
chairman

References

ACG99 American Conference of Governmental Industrial Hygienists (ACGIH). 1999. TLVs® and BEIs®. Guide to Occupational Exposure Values, Cincinnati OH, USA: ACGIH, 1999: 126.

Arb96 Arbejdstilsynet. Exposure Limit value for substances and materials. Copenhagen, Danmark: Arbejdstilsynet, 1996:10.

Bea79 Beard CM, Noller KL, O'Fallon WM, *et al*. Lack of evidence for cancer due to use of metronidazole. N Eng J Med 1979; 301: 519-22.

Bea80 Beard CM , Cancer after metronidazole. N Eng J Med 1980; 302: 520.

Bea85 Beard CM, Noller KL, O'Fallon WM. Metronidazole and subsequent malignant neoplasms (Abstract). Am J Epidemiol 1985; 122: 529.

Bea88 Beard CM, Noller KL, O'Fallon WM, *et al*. Cancer after exposure to metronidazole. Mayo Clin Proc 1988; 63: 147-53.

Cav83 Cavaliere A, Bacci M, Amorosi A , et al. Induction of lung tumors and lymphomas in BALB/c mice by metronidazole. Tumori 1983; 69: 379-82.

CBS92 Netherlands Central Bureau of Statistics (CBS): Department of Health Statisitics. Atlas of cancer mortality in the Netherlands. The Hague, The Netherlands: SDU/publishers / CBS publications, 1992.

Cze98 Czeizel AE, Rockenbauer M. A population based case-control teratologic study of oral metronidazole treatment during pregnancy. Brit J Obstetics and Gynaecology 1998; 105:322-327.

Dan82 Danielson DA, Hannan MT, Jick H. Metronidazole and cancer (letter to the editor). J Amer Med Assoc 1982; 247: 2498-9.

DEC95a Health Council of the Netherlands: Dutch Expert Committee on Occupational Standards (DECOS). Calculating cancer risk. The Hague: Health Council of the Netherlands, 1995; pub no 1995/06WGD.

DEC95b Dutch Expert Committee on Occupational Standards (DECOS). Scientific documentation on the Dutch list of Occupational Carcinogens (I), 1995. The Hague: RA1/95; .

DFG99 Deutsche Forschungsgemeinschaft (DFG): Senatskommission zur Prüfung gesundheitsschädlicher Arbeitsstoffe. MAK- und BAT-Werte-Liste 1999. MAK- und BAT-Werteliste 1999. Maximale Arbeitsplatzkonzentrationen und biologische Arbeitsstofftoleranzwerte. Weinheim, (Mitteilung 35).

Fal98 Falagas ME, Walker AM, Herschel J *et al*. Late incidence of cancer after metronidazole use: a matched metronidazole user/nonuser study. Clin Infect Dis 1998; 26:384-388.

Fri80a Friedman GD, Ury HK. Initial screening for carcinogenicity of commonly used drugs. J NatlCancer Inst 1980; 65: 723-33.

Fri80b Friedman GD. Cancer after metronidazole (letter to the editor). N Engl J Med 1980; 302: 519.

Fri89 Friedman GD, Selby JV. Metronidazole and cancer (letter to the editor) J Amer Med Assoc 1989; 261: 866.

HSE99 Health and Safety Executive (HSE). Occupational exposure limits 1999. Sudbury (Suffolk), UK: HSE Books, 1999; Guidance note EH 40/96.

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

IARC77 International Agency for Research on Cancer (IARC). Metronidazole. In: Some miscellaneous pharmaceutical substances. Lyon, France: IARC, 1977: 113-22 (IARC monographs on the evaluation of carcinogenic risk of chemicals to man; Vol 13).

IARC82 International Agency for Research on Cancer (IARC). Metronidazole. In: Chemicals, industrial processes and industries associated with cancer in humans IARC monographs, volumes 1 to 29. Lyon, France: IARC, 1982: 160-2 IARC Monographs on the evaluation of the carcinogenic risk of chemicals to humans; Suppl 4).

IARC87 International Agency for Research on Cancer (IARC). Metronidazole. In: Overall evaluations of carcinogenicity: an updating of IARC monographs volumes 1 to 42. Lyon, France: IARC, 1987: 250-2 (IARC monographs on the evaluation of carcinogenic risks to humans; Suppl 7).

ISZW99 Inspectiedienst van het Ministerie van Sociale Zaken en Werkgelegenheid (I-SZW). De nationale MAC-lijst 1999. The Hague, The Netherlands: Sdu Servicecentrum Uitgeverijen, 1999.

Kra85 Krause JR, Ayuyang HQ, Ellis LD. Occurrence of three cases of carcinoma in individuals with Crohn's disease treated with metronidazole. Amer J Gastroenterol 1985; 80: 978-82.

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

Roe83 Roe FJC. Toxicologic evaluation of metronidazole with particular reference to carcinogenic,mutagenic, and teratogenic potential. Surgery 1983; 93: 158-64.

Rus79 Rustia M, Shubik P. Experimental induction of hepatomas, mammary tumors, and other tumors with metronidazole in noninbred Sas: MRC(WI)BR rats. J Natl Cancer Inst 1979; 63: 863-7.

Pip93 Piper JM, Michel EF, Ray WA. Prenatal use of metronidazole and birth defects: no association. Obstet Gynecol 1993;82:348-352.

Tha98 Thapa PB, Whitlock JA, Brockman Worrell KG *et al*. Prenatal exposure to metronidazole and risk of childhood cancer; A retrospective cohort study of children younger than 5 years. Cancer 1998; 83:1461-1468.

A	Request for advice
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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)
- AAE Wibowo
  toxicologist; Coronel Institute, Amsterdam
- 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 H Stouten and 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: E Vandenbussche-Parméus.
Lay-out: J van Kan.

Annex **C**

Comments on the public draft

A draft of the present report was released in 1999 for public review. The following organizations and persons have commented on the draft document:

- mr P Ridgeway, Health and Safety Executive, United Kingdom
- mr A Aalto, Tampere, Finland
- mw Van Lent-Evers, Nederland

Annex **D**

Animal studies

See next page.

Table 1 Carcinogenicity studies with metronidazole.[a]

authors	species/route	exposure characteristics	findings	remark
Rustia & Shubik (1972) in IARC77	mouse[b] diet	diet, dose levels: 0, 0.06, 0.15, 0.3, 0.5% Xpo=Xpe is lifetime.	Lung tumours in male: 13/70, 3/9, 11/19, 12/18, 27/35; in female: 14/70, 4/10, 10/20, 14/20, 16/36 (respectively in the 0, 0.06, 0.15, 0.3, 0.5% groups) Lymphomas significantly increased in females at 0.5%	The difference was statistically significant at dose levels $\geq$ 0.15%. Original publication not available.
Cavaliere *et al*. (1983) in IARC87	mouse[c]	not given	Induction of lung tumours and lymphomas.	Original publication not available (see IARC, 1987).
Cohen *et al*. (1973) in IARC77	rat[d](only females were treated)	diet, dose levels: 0, 0.135% X_{po}: 66 weeks, X_{pe}: 76 weeks.	Control group: mammary fibroadenomas 12/71; mammary adenocarcinomas 6/71. Treatment group: mammary fibroadenomas 12/36; mammary adenocarcinomas 3/36	The difference was statistically not significant (Fischer Exact Probability test).
Rus79	rat[e] Controls 100/ sex/group Test 30/ sex/group	diet, dose levels: 0, 0.06, 0.3, 0.6% X_{po}=X_{pe} is 140 weeks.	Statistically significant increase in tumour incidences: *females* *control* *0.6%* *p* mammary tumours 34/97 23/30 < 0.02 hepatomas 0/97 7/30 < 0.05 *males* testis tumours 18/100 14/30< 0.04 pituitary adenomas 20/100 15/30 < 0.04	
Cav84	rat[d] (n=50 per sex/ group)	gavage, dose levels: 0, 30 mg/kg bw X_{po}: 100 days; X_{pe}: 140 weeks	Mammary tumours: 15/50 females (control), 36/50 females (treatment group)	Exposure was less than one-fourth the standard lifespan.

[a] Two lifespan carcinogenicity studies in hamsters gave unequivocally negative results (FCJ Roe Metronidazole, Tumorgenicity studies in mice, rats and hamsters. In SM Finegold, JA McFadzean, FCJ Roe editors, Metronidazole - preceedings of the International Metronidazole Conference, Montreal, Quebec, Canada, Amsterdam 1977, Excerpta Medica (see also Roe, 1983).

[b] Swiss mice

[c] BALB/c mice

[d] Sprague-Dawley

[e] Sas: MRC(WI)BR rats