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MX in Drinking-water

Background document for development of
WHO *Guidelines for Drinking-water Quality*

Preface

One of the primary goals of WHO and its member states is that "all people, whatever their stage of development and their social and economic conditions, have the right to have access to an adequate supply of safe drinking water." A major WHO function to achieve such goals is the responsibility "to propose ... regulations, and to make recommendations with respect to international health matters ...."

The first WHO document dealing specifically with public drinking-water quality was published in 1958 as *International Standards for Drinking-water*. It was subsequently revised in 1963 and in 1971 under the same title. In 1984–1985, the first edition of the WHO *Guidelines for Drinking-water Quality* (GDWQ) was published in three volumes: Volume 1, Recommendations; Volume 2, Health criteria and other supporting information; and Volume 3, Surveillance and control of community supplies. Second editions of these volumes were published in 1993, 1996 and 1997, respectively. Addenda to Volumes 1 and 2 of the second edition were published in 1998, addressing selected chemicals. An addendum on microbiological aspects reviewing selected microorganisms was published in 2002.

The GDWQ are subject to a rolling revision process. Through this process, microbial, chemical and radiological aspects of drinking-water are subject to periodic review, and documentation related to aspects of protection and control of public drinking-water quality is accordingly prepared/updated.

Since the first edition of the GDWQ, WHO has published information on health criteria and other supporting information to the GDWQ, describing the approaches used in deriving guideline values and presenting critical reviews and evaluations of the effects on human health of the substances or contaminants examined in drinking-water.

For each chemical contaminant or substance considered, a lead institution prepared a health criteria document evaluating the risks for human health from exposure to the particular chemical in drinking-water. Institutions from Canada, Denmark, Finland, France, Germany, Italy, Japan, Netherlands, Norway, Poland, Sweden, United Kingdom and United States of America prepared the requested health criteria documents.

Under the responsibility of the coordinators for a group of chemicals considered in the guidelines, the draft health criteria documents were submitted to a number of scientific institutions and selected experts for peer review. Comments were taken into consideration by the coordinators and authors before the documents were submitted for final evaluation by the experts meetings. A "final task force" meeting reviewed the health risk assessments and public and peer review comments and, where appropriate, decided upon guideline values. During preparation of the third edition of the GDWQ, it was decided to include a public review via the world wide web in the process of development of the health criteria documents.

During the preparation of health criteria documents and at experts meetings, careful consideration was given to information available in previous risk assessments carried out by the International Programme on Chemical Safety, in its Environmental Health Criteria monographs and Concise International Chemical Assessment Documents, the International Agency for Research on Cancer, the joint FAO/WHO Meetings on Pesticide Residues and the joint FAO/WHO Expert Committee on Food Additives (which evaluates contaminants such as lead, cadmium, nitrate and nitrite, in addition to food additives).

Further up-to-date information on the GDWQ and the process of their development is available on the WHO internet site and in the current edition of the GDWQ.

Acknowledgements

MX in Drinking-water, Background document for development of WHO *Guidelines for Drinking-water Quality*, is an update of the background document published in the second edition of the Guidelines. The update was prepared by Mr J.K. Fawell and Mr R. Mascarenhas, United Kingdom, to whom special thanks are due.

The work of the following working group coordinators was crucial in the development of this document and others in the third edition:

Mr J.K. Fawell, United Kingdom (*Organic and inorganic constituents*)
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Prof. Y. Magara, Hokkaido University, Japan (*Analytical achievability*)
Mr P. Jackson, WRc-NSF, United Kingdom (*Treatment achievability*)

The contribution of peer reviewers is greatly appreciated. The draft text was posted on the world wide web for comments from the public. The revised text and the comments were discussed at the Final Task Force Meeting for the third edition of the GDWQ, held on 31 March to 4 April 2003, at which time the present version was finalized. The input of those who provided comments and of participants in the meeting is gratefully reflected in the final text.

The WHO coordinators were as follows:

Dr J. Bartram, Coordinator, Water Sanitation and Health Programme, WHO Headquarters, and formerly WHO European Centre for Environmental Health
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Mr H. Hashizume, Water Sanitation and Health Programme, WHO Headquarters

Ms C. Vickers provided a liaison with the International Chemical Safety Programme, WHO Headquarters.

Ms Marla Sheffer of Ottawa, Canada, was responsible for the scientific editing of the document.

Many individuals from various countries contributed to the development of the GDWQ. The efforts of all who contributed to the preparation of this document and in particular those who provided peer or public domain review comment are greatly appreciated.

Acronyms and abbreviations used in the text

CAS	Chemical Abstracts Service
CMCF	3-chloro-4-(chloromethyl)-5-hydroxy-2[5H]furanone
DNA	deoxyribonucleic acid
GST	glutathione-*S*-transferase
IC_{50}	median inhibitory concentration
LD_{50}	median lethal dose
MCA	3,4-dichloro-5-hydroxy-2[5H]furanone
MNNG	*N*-methyl-*N*'-nitro-*N*-nitrosoguanidine
MX	3-chloro-4-dichloromethyl-5-hydroxy-2(5H)-furanone
UDS	unscheduled DNA synthesis
USA	United States of America

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1. GENERAL DESCRIPTION

1.1 Identity

CAS No.:	77439-76-0
Molecular formula:	$C_5H_3Cl_3O_3$

MX is the common name for 3-chloro-4-dichloromethyl-5-hydroxy-2(5H)-furanone.

1.2 Major uses

MX does not have any commercial uses.

1.3 Environmental fate

In drinking-water, at normal pH, MX exists in the open ring form, i.e., as (Z)-2-chloro-3-(dichloromethyl)-4-oxobutenoic acid.

2. ANALYTICAL METHODS

MX in drinking-water can be determined by first concentrating organics using XAD resins, followed by high-pressure liquid chromatography, capillary column gas chromatography and mass spectroscopy (Hemming et al., 1986; Kronberg & Vartiainen, 1988).

3. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

3.1 Water

MX is formed by the reaction of chlorine with complex organic matter in drinking-water and is present in the chlorinated effluents of pulp mills. It has been identified in chlorinated humic acid solutions and drinking-water in Finland, the United Kingdom and the USA and was found to be present in 37 water sources at levels of 2–67 ng/litre (Hemming et al., 1986; Meier et al., 1989). Five drinking-water samples from different Japanese cities contained MX at concentrations ranging from <3 to 9 ng/litre (Suzuki & Nakaniski, 1990). In a study in the USA, tap water samples were collected from 36 towns in Massachusetts during 1997 and 1998; MX was found at mean concentrations ranging from 4 to 80 ng/litre (Wright et al., 2002).

4. KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS

A number of studies with laboratory animals have been carried out to examine the fate of radiolabelled MX.

The oral administration by gavage of 7.9 mg of ^{14}C-radiolabelled MX to F344 rats resulted in an estimated 40% absorption of the administered dose. The highest levels of radioactivity were found in liver, muscle, kidney, skin and blood. However, the

amount of radioactivity found in these tissues was small, indicating that MX and its metabolites were not selectively concentrated in any tissue. Neither the parent compound nor any specific metabolites were identified in any body compartment or fluid (Ringhand et al., 1989).

The disposition of ^{14}C-labelled MX was studied in male CD-1 mice (Horth et al., 1991). The study demonstrated that the ^{14}C was rapidly absorbed, reaching peak values in blood within 15 min of administration. Approximately 57% of the radioactivity was eliminated in the urine and 28% in the faeces. Less than 1% of the initial dose was retained in the carcass 120 h after administration, and most of this was associated with the stomach. It was stated that the urinary metabolites were polar, but no specific identifications were made.

The toxicokinetics of MX were investigated following the administration of a single oral or intravenous dose of ^{14}C-labelled compound to male Wistar rats. Approximately 20–35% of the dose was absorbed into circulation from the gastrointestinal tract, and the mean half-life of radioactivity in the blood was 3.8 h (Komulainen et al., 1992). The main route of elimination of the radioactive label was excretion via the urine.

Single doses of 0, 200, 300, 400 or 600 mg/kg of body weight were administered to male Wistar rats by oral gavage in distilled water (pH 5.0) in a study assessing the excretion of MX. This high-dose study indicated a low excretion of the unmetabolized parent compound, suggesting a rapid and extensive metabolism of MX (Komulainen et al., 1994).

There are no data available in the scientific literature on the metabolism of MX or related compounds in humans.

5. EFFECTS ON LABORATORY ANIMALS AND IN VITRO TEST SYSTEMS

5.1 Acute exposure

Acute oral LD_{50}s of 128 and 144 mg/kg of body weight have been estimated for mice (Meier et al., 1987; Mullins & Proudlock, 1990).

Rats tolerated doses of 200 mg/kg of body weight administered in drinking-water but displayed severe symptoms, including dyspnoea, laboured breathing, depressed motor activity and cyanosis, at higher doses (Komulainen et al., 1994). A 48-h LD_{50} of 230 mg/kg of body weight was identified in this study.

5.2 Short-term exposure

MX in distilled water was administered to Swiss-Webster mice (five per sex per dose) by gavage at 10, 20, 42, 88 or 184 mg/kg of body weight per day for 2 days. At 184 mg/kg of body weight per day, all animals died within 1 day following the second dose; enlarged stomachs and haemorrhagic areas of the forestomach were observed.

At lower doses, no deaths occurred, no effect on body weight was noted during the 2-week observation period and gross necropsy results were normal (Meier et al., 1990).

A study was carried out in which groups of rats were administered a dose of 64 mg/kg of body weight by gavage for 4 days. The study examined the effects of such a dose on a number of enzyme activities in the livers of the rats. MX treatment resulted in the reduction of levels of a number of hepatic enzymes, including catalase, cytochrome P450 reductase, aminopyrine demethylase and aromatic hydrocarbon hydroxylase. It did not affect fatty acyl coenzyme A oxidase, glutamylcysteine synthetase, glutathione-*S*-transferase (GST) or glutathione peroxidase (Meier et al., 1996).

Daniel et al. (1994) administered MX to B6C3F1 mice and F344 rats by oral gavage for 14 days. The doses used were 0, 8, 16, 32 and 64 mg/kg of body weight per day. No target organ for toxicity was clearly identified. Treatment-related effects included increased plasma cholesterol levels and increased liver and kidney weights. Decreased thymus weights were observed in rats and female mice, and decreased spleen weights were observed in male mice. Epithelial hyperplasia, hyperkeratosis, chronic inflammation and ulceration were observed in rats treated with 64 mg/kg of body weight per day. Epithelial hyperplasia was observed in mice at the same dose as for rats.

A study was carried out by Nishikawa et al. (1994) examining cell proliferation and lipid peroxidation in the glandular stomach mucosa in Wistar rats given 0, 6.25, 12.5, 25 or 50 mg of MX per litre in their drinking-water for 5 weeks. At doses up to 25 mg/litre, a dose-dependent and statistically significant increase in cell proliferation was observed. The MX treatment was also associated with increased lipid peroxidation levels in the gastric mucosa as well as in the urine, although this was not apparent at 50 mg/litre. Histopathology revealed gastric erosion at 25 and 50 mg/litre.

Heiskanen et al. (1995) conducted a study examining the effect of MX on enzyme activities in various tissues. A constant daily dose of 30 mg/kg of body weight was administered by gavage for a period of 18 weeks as the low dose. A higher dose was achieved by initiating treatment at 45 mg/kg of body weight per day (7 weeks), raising it to 60 mg/kg of body weight per day for 2 weeks and then further raising it to 75 mg/kg of body weight per day for 5 weeks. A dose-related decrease in ethoxyresorufin-*O*-deethylase activity was observed in liver and kidney. The treatment also increased the activities of uridine diphosphate-glucuronosyltransferase and GST in the kidneys in a dose-dependent manner, but only in female rats.

Vaittinen et al. (1995) investigated the subchronic toxicity of MX in Wistar rats. In a range-finding study, groups of five male rats were administered doses of 12.5, 25, 50, 100 or 200 mg/kg of body weight per day by gavage in deionized water for 14 days. Doses above 50 mg/kg of body weight per day were lethal, and three of the five animals died at the 50 mg/kg of body weight per day dose. The range-finding study was repeated with doses of 5, 10 and 20 mg/kg of body weight per day given 5 days per week for 2 weeks to groups of 10 male and 10 female rats. The doses were not overtly toxic, but changes in plasma clinical chemistry were observed at the 10 and 20

mg/kg of body weight per day doses when compared with the controls. In the actual subchronic study, groups of 15 rats were given MX by gavage, 5 days per week, at doses of 0 or 30 mg/kg of body weight per day for 18 weeks and in the high-dose group at doses increasing from 45 to 75 mg/kg of body weight per day for 14 weeks. The high dose was eventually lethal, and effects were observed in clinical chemistry at both doses. It was concluded that the repeated administration of MX disturbed the fluid electrolyte balance and induced diuresis, caused mucosal hyperplasia in the gastrointestinal tract as a local effect and affected lipid metabolism.

5.3 Reproductive and developmental toxicity

Teramoto et al. (1998) evaluated the teratogenic properties of MX using the micromass *in vitro* assay with 12-day-old rat embryo midbrain and limb bud cells. In the presence of the S9 fraction, MX had little or no effect; in the absence of the S9 fraction, there was a significant decrease in the number of differentiated foci in central nervous system and limb bud cells, indicative of a potential teratogenic effect. The IC_{50} for these effects was 3 µg/ml. The significance of this finding is uncertain in view of the findings *in vivo*, discussed below.

The developmental toxicity of MX has been evaluated in a study conducted in Han:Wistar rats. Doses of 0, 3, 30 and 60 mg/kg of body weight per day were administered to pregnant rats by gavage on gestation days 6–19. The animals were sacrificed on day 20. Maternal toxicity was observed at the highest dose, indicated by reduced body weight gain, decreased absolute and relative kidney weights and decreased water consumption. Although there was a slight reduction in the mean body weights of the fetuses at all doses, the observation was not statistically significant. There were no increases in gross, visceral or skeletal malformations in the fetuses in the MX-dosed groups compared with the control group, and fetal mortality was not affected. The authors concluded that MX was not teratogenic in this strain of rat (Huuskonen et al., 1997).

5.4 Mutagenicity and related end-points

There have been several studies concerning the mutagenic activity of MX and related chemicals.

MX was reported to be an extremely potent mutagen in *Salmonella typhimurium* strain TA100 without metabolic activation by the S9 fraction of rat liver homogenate. The responses were also positive, but not as strong, in strains TA92, TA97, TA98, TA102 and TA1535. No mutagenic response was found with TA1537. The addition of rat liver S9 fraction dramatically decreased the responses in strains TA100, TA98 and TA1535 (Holmbom et al., 1984; Meier et al., 1987).

MX has been examined for genotoxic activity in cultured mammalian cells. In Chinese hamster ovary cells (CHO-K1), it induced significant increases in structural chromosomal aberrations with and without metabolic activation. It also induced DNA strand breaks in suspensions of rat hepatocytes, rat testicular cells and V79 Chinese

hamster cells (Meier et al., 1987; Brunborg et al., 1991). However, there was no increased frequency of micronuclei in mouse bone marrow *in vivo* following two consecutive daily doses of 70% of the LD_{50}, despite its relatively high clastogenic activity in mammalian cells *in vitro*.

The mutagenic effect of MX has been shown to be effectively inhibited by sulfhydryl compounds such as cysteine, glutathione, dithiothreitol and 2-mercaptoethanol. The suggested mechanism for this effect is that sulfhydryl compounds inactivate the MX by a direct chemical interaction before the MX induces DNA damage (Watanabe et al., 1994). However, investigations with antioxidants other than sulfhydryl compounds showed no inhibitory effects. Further examination of the structural activities of cysteine analogues indicated that the sulfhydryl group was indispensable for antimutagenic activity and that an amino moiety enhanced the MX-inactivating reaction of the sulfhydryl group (Watanabe et al., 1994).

In vitro studies in which rat and mouse hepatocytes were incubated with MX resulted in a dose-dependent increase in unscheduled DNA synthesis (UDS) at sub-cytotoxic concentrations (1–10 µmol/litre; 20-h incubation). Depletion of glutathione stores by pretreatment of rat hepatocytes with buthionine sulfoximine did not result in a significant increase in UDS produced by MX (Nunn et al., 1997). MX did not induce UDS in mouse hepatocytes *ex vivo* either 3 or 16 h following administration of a single oral dose of 100 mg/kg of body weight. Despite the ability of MX to produce repairable DNA damage, restricted access of MX to the liver may prevent a measurable UDS response *in vivo* (Nunn et al., 1997).

A study by Mullins & Proudlock (1990) observed slight increases in nuclear anomalies in the non-glandular stomach, urinary bladder, jejunum and ileum in rats administered 144 mg of MX per kg of body weight. Significant irritation, inflammation and evidence of apoptotic cells in the gastrointestinal tract were also observed, and it was concluded that these changes render the significance of the observed nuclear anomalies uncertain.

Structure–activity relationships for MX and related compounds have identified chlorine substitution on C3 as being important to the mutagenic activity of MX (Ishiguro et al., 1988).

A study was carried out by Fekadu et al. (1994) in which mice were injected intravenously with mixtures of repair-competent and repair-deficient *Escherichia coli* K-12 cells as test cells and the animals were subsequently treated with 200 mg of test chemical per kg of body weight. Two hours later, the mice were sacrificed and cells recovered from various organs. MX, 3-chloro-4-(chloromethyl)-5-hydroxy-2[5H]furanone (CMCF) and 3,4-dichloro-5-hydroxy-2[5H]furanone (MCA) were the test chemicals. The differential survival of the DNA repair-deficient strain versus a repair-competent variant was used to detect mutagenic activity. All three compounds significantly reduced recovery of the repair-deficient strain in the stomach, lung, intestine, liver, kidney and spleen.

The effects of lower doses of MX were investigated in a second study in which doses of 4.3, 13 and 40 mg/kg of body weight were administered intravenously. Significantly depressed recovery was seen with MX doses as low as 4.3 mg/kg of body weight. MCA did not modify recovery of the repair-deficient strain at any dose. These data suggest that significant amounts of MX or a mutagenic metabolite reach the systemic circulation and at least the extracellular fluid. They do not clearly demonstrate effects in the target tissue of the experimental animals (Fekadu et al., 1994).

Brunborg et al. (1990, 1991) studied DNA damage induced by MX and other compounds in organs of rats using the alkaline elution assay (to detect strand breaks). While clear evidence of strand breaks was obtained with dibromochloropropane and 2-amino-3,4-dimethylimidazol[4,5-f] quinoline, no significant effects were observed with MX after an intraperitoneal dose of 18 mg/kg of body weight or at oral doses of up to 125 mg/kg of body weight. The organs examined included the small and large intestine, stomach, liver, kidney, lung, bone marrow, urinary bladder and testis.

The view expressed by the United Kingdom's expert advisory Committee on Mutagenicity of Chemicals in Food, Consumer Products and the Environment (Committees on Mutagenicity, Carcinogenicity and Toxicity of Chemicals in Food, Consumer Products and the Environment, 1991) was that negative data in the bone marrow micronucleus assay at doses approaching the LD_{50} and the fact that MX would be extensively detoxified in the gut by GST suggested that the compound would not have any significant mutagenic activity *in vivo*. These data were supported by marginal activity in the nuclear anomaly assay seen only at toxic dose levels.

5.5 Carcinogenicity

Carcinogenicity studies in experimental animals have been summarized in detail by US EPA (2000). Komulainen et al. (1997) conducted an oral study in Wistar rats over a period of 104 weeks. Groups of 50 rats per sex per group were provided with drinking-water containing MX at concentrations of 5.9, 18.7 or 70 µg/ml. The pH of the drinking-water was adjusted to values between 3.5 and 5.0 in order to ensure the stability of MX in solution, and the controls were provided with acidified drinking-water in the same pH range. The animals were examined on a daily basis for clinical signs of toxicity. The administered concentrations resulted in average daily doses of 0, 0.4, 1.3 and 5.0 mg/kg of body weight per day for males and 0, 0.6, 1.9 and 6.6 mg/kg of body weight per day for females, as calculated by the authors using water consumption data.

Body weight, food consumption and water consumption were monitored weekly for the first 13 weeks of the experiment. Body weight and food consumption were then monitored monthly, and water intake was monitored every 2 months. At termination of the experiment, blood samples were collected for the analysis of serum levels of the thyroid hormones thyroxine and triiodothyronine and thyroid stimulating hormone. All organs and tissues were examined for gross lesions at necropsy, and organs and tissues were processed for histopathological examination.

No clinical signs of toxicity were observed in any of the test animals. Food consumption was the same among all groups, but water consumption was reduced in a dose-dependent manner, suggesting that the drinking-water containing the compound was unpalatable. Dose-dependent increases in the incidence of some tumours were observed, while the same MX doses had no obvious toxic effects on the animals. Increases were recorded in tumours of the lung, mammary gland, haematopoietic system, liver, pancreas, adrenal gland and thyroid, but few showed a clear dose–response. The incidence of follicular adenomas and carcinomas of the thyroid in males was 2, 20, 34 and 21 and 0, 1, 9 and 27, respectively, for control, 0.4 mg/kg of body weight per day, 1.3 mg/kg of body weight per day and 5.0 mg/kg of body weight per day. In females, the incidence was 4, 16, 36 and 36 and 1, 3, 6 and 22 for control, 0.6 mg/kg of body weight per day, 1.9 mg/kg of body weight per day and 6.6 mg/kg of body weight per day, respectively. The incidence of cholangiomas, which are rarely found spontaneously in this strain, was 0, 0, 1 and 4 in control, 0.4 mg/kg of body weight per day, 1.3 mg/kg of body weight per day and 5.0 mg/kg of body weight per day, respectively, in males and 0, 4, 10 and 33 in controls, 0.6 mg/kg of body weight per day, 1.9 mg/kg of body weight per day and 6.6 mg/kg of body weight per day, respectively, in females.

The cancer-promoting effects of MX in the glandular stomach were investigated by Nishikawa et al. (1999). Three groups of 30 male Wistar rats each were administered 100 mg of the initiator *N*-methyl-*N*'-nitro-*N*-nitrosoguanidine (MNNG) per litre in drinking-water for 8 weeks. In addition, 5% sodium chloride was administered in the diet as a co-initiating factor. Following the pretreatment period, the MNNG-treated animals were exposed to 0, 10 or 30 mg of MX per litre in drinking-water for 57 weeks. There were three additional groups of rats that were exposed to 0, 10 or 30 mg of MX per litre in drinking-water without pretreatment with MNNG/sodium chloride. At termination of the study, the animals were sacrificed and organ weights (liver, heart, kidney, spleen and lungs) were measured. Histological examination of stomach, liver, kidney and thyroid tissues was performed.

The average daily doses of MX were 0.4 and 1.2 mg/kg of body weight in the 10 and 30 mg/litre groups, respectively. There was no apparent difference in final body weight or weights of the measured organs in animals treated with MNNG and/or MX. There was a significant increase in the incidence of adenocarcinomas in rats given MNNG and 30 mg of MX per litre compared with MNNG alone. The incidence of the indicator of precancerous lesions (i.e., atypical hyperplasia of the glandular stomach) in the stomach of rats fed MNNG and MX at 10 or 30 mg/litre was also elevated compared with the group of rats given MNNG alone. Cholangiomas, cholangiocarcinomas, cholangiofibrosis and bile duct hyperplasia were found in the liver of animals treated with MX and/or MNNG. The combined incidence of cholangiomas and cholangiocarcinomas was not, however, statistically significant in the MNNG plus MX treatment groups, although there appeared to be a trend of increasing incidence at 10 and 30 mg of MX per litre. Thyroid follicular hyperplasias were detected only in the MNNG plus MX treatment groups, whereas C-cell adenomas and C-cell hyperplasia of the thyroid were detected in all treatment groups.

6. EFFECTS ON HUMANS

It would be extremely difficult to carry out meaningful epidemiological studies on MX. This is because MX is always present in drinking-water, along with a wide range of other chlorination by-products. A number of epidemiological studies have been carried out on chlorinated drinking-water that show a weak association between chlorinated drinking-water and a range of cancers, including cancers of the bladder, colon, rectum, stomach, pancreas and lymphomas. An IPCS (2000) working group concluded that "The hypothesis of a causal relationship between consumption of chlorination by-products and the increased relative risk of any cancer remains an open question."

7. CONCLUSIONS

MX is a potent mutagen in bacteria and in cells *in vitro* and has undergone a lifetime study in rats in which some tumorigenic responses were observed (Komulainen et al., 1997). These data indicate that MX induced thyroid and bile duct tumours. An increased incidence of thyroid tumours was seen at the lowest dose of MX administered (0.4 mg/kg of body weight per day). A dose-related increase in the incidence of cholangiomas was also observed, with tumours observed at the low dose in female rats and a more modest response in male rats. The increase in cholangiomas in female rats was utilized to derive a slope factor for cancer of 0.18 per mg/kg of body weight per day using the linearized multistage model. This slope factor does not incorporate a surface to body weight correction (US EPA, 2000). Based on this slope factor, the 95% upper confidence limit for a 10^{-5} lifetime risk of excess cancer was calculated to be 0.06 µg/kg of body weight per day. Therefore, assuming a 60-kg adult drinking 2 litres of water per day, the concentration associated with a 10^{-5} risk would be 1.8 µg/litre. However, this is significantly above the concentrations that would be found in drinking-water, and there remains uncertainty over whether MX is genotoxic *in vivo*, particularly at the low doses encountered from drinking-water.

In view of the above and of the analytical difficulties in measuring MX at such low concentrations, it is considered unnecessary to propose a formal guideline value for MX in drinking-water.

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