Drinking-Water Quality: Guidelines for Selected Herbicides

WORLD HEALTH ORGANIZATION
Regional Office for Europe
Copenhagen
ENVIRONMENTAL HEALTH SERIES

1. Health Hazards from Nitrates in Drinking-Water: Report on a WHO Meeting
2. Effects of Occupational Factors on Reproduction: Report on a WHO Meeting
4. Reference Methods for Measuring Airborne MMMF
7. Meeting Reports: Institutional Catering and Food Inspection
8. Treatment and Discharge of Industrial Wastewater in the Mediterranean Area: Report on a WHO Meeting
10. Environmental Toxicology and Ecotoxicology: Proceedings of the Third International Course
12. Occupational Health as a Component of Primary Health Care: Report on a WHO Meeting


17. PCDD and PCDF Emissions from Incinerators for Municipal Sewage Sludge and Solid Waste: Evaluation of Human Exposure

18. Development of Environmental Health Manpower

19. Occupational Profiles of Environmental Health Personnel

20. Trace Elements in Human Health and Disease: Extended Abstracts from the Second Nordic Symposium, 17-21 August 1987

21. Drinking-water Quality and Health-related Risks


23. PCBs, PCDDs and PCDFs: Prevention and Control of Accidental and Environmental Exposures

24. Health Hazards from Radiocaesium Following the Chernobyl Nuclear Accident

25. Nuclear Accidents and Epidemiology. Reports on two meetings: Epidemiology Related to the Chernobyl Nuclear Accident; Appropriate Methodologies for Studying Possible Long-term Effects of Radiation on Individuals Exposed in a Nuclear Accident

DRINKING-WATER QUALITY:
GUIDELINES FOR SELECTED HERBICIDES
Following the successful introduction of its Guidelines for Drinking-Water Quality in 1984, the Regional Office for Europe was approached by the Government of Italy to develop, as a matter of urgency, recommendations for guideline levels of certain herbicides found in drinking-water supplies. Realizing the extent of the problem, the Regional Office for Europe, in association with the Istituto Superiore di Sanità, Rome, organized two consultations to develop drinking-water quality guidelines for the eleven herbicides most commonly used in Italy.

To deal with the complex requirements of this difficult task, comprehensive background documentation was prepared based on an extensive literature search as well as on the unpublished data provided by the main producers of herbicides. Guidelines for drinking-water quality for the 11 selected herbicides were developed during the two consultations held in Rome. The consultations were attended by 34 experts from 12 European and North American countries, and representatives of the International Programme on Chemical Safety (IPCS), the International Agency for Research on Cancer (IARC) and the International Register of Potentially Toxic Chemicals (IRPTC). The text presented here is the final report of both consultations.

Although the main purpose of these guidelines is to provide guidance to the Government of Italy in making risk management decisions, the information given may also assist the other countries of the European Region in setting standards or in developing alternative control procedures where the implementation of standards is not feasible. Although guidelines for drinking-water quality are intended to help the countries to develop standards which, if properly implemented will protect public health, it must be emphasized that the recommended levels are not standards in themselves. In order to define standards, these recommendations must be considered in the context of prevailing environmental, social, economic and cultural conditions.

That the drinking-water guidelines for herbicides were delivered in less than 6 months is a tribute to all concerned, and I would like to thank all participants for their dedication and enthusiasm, and in particular commend the Istituto Superiore di Sanità without whose combined qualities of scientific excellence, power of persuasion and organizational ability the work could not have been completed within this short time frame.

Dr D. Kello
Project Officer for Environmental Epidemiology and Food Safety
## CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foreword</td>
<td>v</td>
</tr>
<tr>
<td>Introduction</td>
<td>1</td>
</tr>
<tr>
<td>Conclusions</td>
<td>3</td>
</tr>
<tr>
<td>Alachlor</td>
<td>3</td>
</tr>
<tr>
<td>Atrazine</td>
<td>4</td>
</tr>
<tr>
<td>Bentazon</td>
<td>4</td>
</tr>
<tr>
<td>MCPA</td>
<td>5</td>
</tr>
<tr>
<td>Metolachlor</td>
<td>5</td>
</tr>
<tr>
<td>Molinate</td>
<td>6</td>
</tr>
<tr>
<td>Pendimethalin</td>
<td>6</td>
</tr>
<tr>
<td>Propanil</td>
<td>7</td>
</tr>
<tr>
<td>Pyridate</td>
<td>7</td>
</tr>
<tr>
<td>Simazine</td>
<td>8</td>
</tr>
<tr>
<td>Trifluralin</td>
<td>8</td>
</tr>
<tr>
<td>Recommendations</td>
<td>8</td>
</tr>
<tr>
<td>General</td>
<td>8</td>
</tr>
<tr>
<td>Specific</td>
<td>9</td>
</tr>
<tr>
<td>Mixtures of Chemical Substances in Drinking Water</td>
<td>11</td>
</tr>
<tr>
<td>References</td>
<td>12</td>
</tr>
</tbody>
</table>

### Annexes

1. Drinking-Water Quality: Guidelines for Herbicides | 14
2. Criteria for Evaluation of Evidence for Carcinogenicity | 15
3. Report of the Alachlor Subgroup | 19
4. List of Participants, Rome, 11-13 February 1987 | 20
5. List of Participants, Rome, 13-18 July 1987 | 22
INTRODUCTION

Upon the request of the Government of Italy, two consultations were organized by the WHO Regional Office for Europe in association with the Istituto Superiore di Sanità, Rome, to develop recommendations concerning guideline levels for drinking-water quality for the herbicides most commonly used in Italy:

- Alachlor
- Atrazine
- Bentazon
- MCPA
- Metolachlor
- Molinate
- Pendimethalin
- Propanil
- Pyridate
- Simazine
- Trifluralin

The presence of these and other herbicides in ground and surface water has been reported in several countries.

In view of the need to make decisions concerning the spraying of crops, particularly maize and rice which started before the end of February, a Consultation on Herbicides in Drinking Water: Atrazine and Molinate was organized - at short notice - from 11 to 13 February 1987 to establish guideline values for these two substances in drinking water. This Consultation was attended by 17 experts from nine European countries and the United States and representatives from the International Programme on Chemical Safety (IPCS) and the International Register of Potentially Toxic Chemicals (IRPTC) (Annex 4).

The Second Consultation on Herbicides in Drinking Water was held in Rome from 13 to 17 July 1987 to establish guideline values for the most commonly used herbicides in Italy (listed above). It was attended by 17 experts from eight European countries, Canada and the United States, together with representatives of IPCS and the International Agency for Research on Cancer (IARC) (Annex 5).

In preparing the recommendations for drinking-water guideline levels for the herbicides in question, the WHO publication Guidelines for Drinking-Water Quality, Vol. I. Recommendations [1], was taken into consideration. In particular, the following passage from that publication was considered particularly relevant:

"Although the guideline values describe a quality of water that is acceptable for lifelong consumption, the establishment of these guidelines should not be regarded as implying that the quality of drinking-water may be degraded to the recommended level. Indeed, a continuous effort should be made to maintain drinking-water quality at the highest possible level."
Therefore, remedial actions should be taken, based on local case-by-case analyses, when one or more substances are consistently detected at significant levels in ground or surface water.

Moreover, for a proper interpretation of the guidelines (summarized in Annex 1), the following points should be taken into consideration:

- The guideline values are based on the scientific evaluation of the toxicity data available for each individual compound;

- The possible presence of technical impurities of toxicological significance in the commercial product was taken into consideration but not incorporated in the guideline value. However, if the presence of such impurities was considered likely, this fact is mentioned in the recommendation.

- The possible presence of environmental metabolites of the parent compound in ground or surface water has not been incorporated in the guideline value. However, this subject was addressed to some extent in the evaluation of each herbicide, and if relevant, is reflected in the recommendations for specific herbicides.

- Environmental effects of the substances, their impurities and environmental metabolites have not been addressed.

- Guideline values do not take into account the possibility that during water treatment processes, products of unknown structure and toxicological properties may be formed from herbicides and/or their metabolites.

In calculating guideline values for levels of these herbicides in drinking-water, the daily consumption of water was assumed to be 2 litres per person per day, and that an average adult consuming this amount of water weighs 70 kg [1]. For toxic agents whose effect becomes apparent only after a dose threshold has been exceeded, an acceptable daily intake (ADI) was calculated from the available toxicological studies by applying a "safety factor" to the no-adverse-effect dose. In setting guideline levels, 10% of the total ADI of these substances was allocated to drinking water. This allocation of dietary intake to drinking water is higher than for many of the substances included in the Guidelines for Drinking-Water Quality because residues of the herbicides reviewed are unlikely to be present to any significant extent in food at the time of consumption.
DRINKING-WATER QUALITY: GUIDELINES FOR SELECTED HERBICIDES

The decision to consider a substance as a carcinogen is based on the qualitative evaluation of all available information on carcinogenicity, assuming that the evaluation criteria of IARC [2] have been applied (see Annex 2). Following principles outlined in the Guidelines for Drinking-Water Quality, the linearized multistage model was used to estimate from the animal cancer bioassays the incremental risks from a lifetime exposure to a particular daily amount of a substance.

The general philosophy of the Guidelines for Drinking-Water Quality has recently been reviewed by a group of expert, specifically in the context of microorganic pollutants, and its continuing soundness and validity was agreed [3].

CONCLUSIONS

Alachlor

Alachlor is considered not be be persistent under aerobic conditions and can undergo photodecomposition. This compound has intermediate mobility. The presence of alachlor in ground and well water has been frequently analysed in several countries but has only occasionally been detected.

On the basis of available experimental data, the evidence for genotoxicity or mutagenicity of alachlor is considered to be limited.

IARC has not evaluated alachlor. Available data from two studies in rats clearly indicate that this compound is carcinogenic, causing benign and malignant tumours of the nasal turbinate, malignant stomach tumours, and benign thyroid tumours (see Annex 3). A similar study in mice showed some increase in the incidence of malignant tumours, but the study failed to produce clear evidence of carcinogenicity in this species (Annex 3). Taking the available evidence into account, alachlor may pose a carcinogenic hazard to humans.

In the long-term experiments in rats, the most prominent non-carcinogenic finding associated with treatment with alachlor was progressive uveal degeneration syndrome (of the eye).

By adopting the principles of the Guidelines for Drinking-Water Quality, the calculation of risk is based on a linearized multistage model using a body surface area correction and assuming a 10% contribution of water to total dietary intake. The guideline value was based on the incidences of nasal tumours only.

In consideration of the carcinogenic potential of alachlor, it was concluded that alachlor in drinking water at a concentration of 0.3 μg/l may produce an excess lifetime cancer risk no greater than 1 in 10^5.
Atrazine

Measurement of atrazine in the most important maize-producing regions in Italy showed that levels higher than 1 ug/l were found in a very low percentage of water supplies, and mostly in private wells. However, the extent of the public health significance cannot be adequately evaluated until current investigations have been completed. The persistence of atrazine in water and soil has been well documented; even where its use has been discontinued, atrazine persists for some years. Therefore, the environmental fate of atrazine in deeper soil layers and ground water should be studied.

IARC has not evaluated atrazine. The limited information available suggests that atrazine might be a weak, non-genotoxic carcinogen in rats. Based on the available data from animal studies in dogs and rats receiving repeated oral doses over a 2-year period, 0.7 mg/kg of body weight per day could be assumed to represent the no-observed-effect level (NOEL). Bearing in mind the uncertainty inherent in available toxicological information, a safety factor of 1000 was adopted. On this basis, an ADI for humans would be 0.7 ug/kg of body weight.

A guideline value for atrazine of 2 ug/l is recommended. However, until more comprehensive toxicological information becomes available, this value should be regarded as tentative.

Bentazon

Bentazon is a molecule with high mobility and high affinity for the water compartment. Further, this compound is not readily degraded and is relatively persistent in the environment (half-life of 10 weeks). Therefore, the probability of finding this chemical in underground water supplies is high.

No significant mutagenic or genotoxic potential was evident in several in vitro and in vivo mutagenicity studies.

IARC has not evaluated bentazon. Chronic toxicity studies have been conducted in rats and mice; no evidence of carcinogenic potential has been shown. A NOEL for chronic toxicity of 10 mg/kg/day was indicated by rodent data. However, a NOEL of 7.5 mg/kg/day was established based on a 90-day feeding study in dogs (a longer-term study in this species has apparently not been conducted).

An ADI of 0.0075 mg/kg/day was established for bentazon based on the subchronic feeding study in dogs and a 1000-fold safety factor.

A guideline value of 25 ug/l was calculated.
MCPA

MCPA, a chlorophenoxy post-emergence herbicide, is a very soluble, highly mobile molecule that is easily leached from the soil. MCPA is metabolized by bacteria and can be photochemically degraded. The rate of disappearance varies, but under favourable conditions MCPA is degraded in a few weeks. Therefore, this compound has only limited persistence and has not been frequently detected in drinking water.

Limited evidence of mutagenicity was noted for MCPA, although a final conclusion could not be reached because of the inadequacy of the available data.

IARC evaluated MCPA in 1983 and concluded that the available data on humans and experimental animals were inadequate for an evaluation of carcinogenicity. Further evaluations on chlorophenoxy herbicides made in 1986 and 1987 concluded that evidence is limited for the carcinogenicity of chlorophenoxy herbicides (as a class) to humans. No adequate epidemiological data on exposures to MCPA alone are available.

Subchronic toxicity studies are available in rats and dogs. A 1-year feeding study in dogs indicated that the lowest NOEL overall was 0.15 mg/kg/day. No long-term toxicity or carcinogenicity studies in rodents were available. An ADI of 0.00015 mg/kg/day was established, based on the NOEL from the 1-year dog study and a safety factor of 1000.

A guideline value of 0.5 ug/l was calculated.

Metolachlor

Metolachlor is a molecule with an intermediate mobility and a partial affinity for soil. It is not considered to be persistent, being biodegraded in different media. This compound can also undergo some photodegradation. Based on a small number of samples, metolachlor has only occasionally been detected in drinking-water supplies.

On the basis of available experimental data, metolachlor appears to be devoid of significant mutagenic or genotoxic activity.

IARC has not evaluated metolachlor. Available studies provide no evidence that metolachlor is carcinogenic in mice. In rats, a few nasal tumours and a slight increase in the incidence of liver tumours in females have been observed, but these findings do not provide clear evidence of carcinogenicity.

Chronic toxicity data are available from rodents and dogs. A NOEL of 1.5 mg/kg/day was established based on data for the rat. Using a safety factor of 1000, an ADI of 0.0015 mg/kg/day was derived.

A guideline value of 5 ug/l was calculated.
**Molinate**

The available data suggest that ground-water pollution by molinate is restricted to rice-growing regions. In Italy, the number of ground-water sources polluted by molinate is rather small compared to that for atrazine, and the concentration of molinate rarely exceeds 1 µg/l. The low persistence of molinate in water and soil has been well documented; with a half-time of about 5 days, molinate in the environment is likely to pose few problems.

Based on the limited information available, molinate does not seem to be carcinogenic to animals. A review of epidemiological data based on examinations of workers involved in molinate production does not indicate any effect on human fertility.

Evidence suggests that impairment of the reproductive performance of the male rat represents the most sensitive indicator of molinate exposure, even though the effect was shown to be completely reversible on withdrawal of the chemical. Studies in rabbits and monkeys were negative. The NOEL was found to be the equivalent of 0.2 mg/kg of body weight per day, and this value was chosen as a basis for calculating an ADI of molinate by humans.

Using a safety factor of 100 for extrapolating laboratory animal data to humans, an ADI of 0.002 mg/kg was indicated and a guideline value for molinate of 7 g/l in drinking water was recommended. In addition, adherence to good agricultural practice would do much to ensure that such a value was unlikely to occur in a supply of potable water.

**Pendimethalin**

Pendimethalin is a moderately persistent herbicide in soil, which can give rise to several longlasting metabolites, mainly by photodegradation. This herbicide and most of its aerobic metabolites bind tightly to soil particles, and the leaching potential is negligible. However, under anaerobic conditions more-polar metabolites with higher mobility are formed and these can potentially reach ground and surface water.

On the basis of available data, pendimethalin appears to be devoid of significant mutagenic or genotoxic activity.

IARC has not evaluated pendimethalin. Long-term carcinogenicity studies in mice and rats do not provide evidence of pendimethalin carcinogenicity; however, these studies have some methodological limitations. In the long-term rat feeding study, evidence of slight liver toxicity was noted even at the lowest dose tested; a NOEL for this finding was not established. The dose of 5 mg/kg/day was therefore determined.
to be the LOEL. Applying a safety factor of 1000 to this value, an ADI of 0.005 mg/kg/day was established.

A guideline value of 17 ug/l was calculated.

**Propanil**

Propanil is a compound with high mobility and affinity for the water compartment. This herbicide, however, is not persistent, being easily transformed under natural conditions to several metabolites. Two of these metabolites, 3,4-dichloroaniline (DCA) and 3,3',4,4'-tetrachloroazobenzene (TCAB), are more toxic and more persistent than the parent compound. Although used in a number of countries, propanil has only occasionally been detected in ground or well water.

Propanil is considered to be devoid of mutagenic activity. However, at least one of propanil’s environmental metabolites (TCAB) may present a genotoxic hazard.

IARC has not evaluated propanil. Data from a limited study in mice and an acceptable study in rats do not provide evidence of carcinogenicity in either species.

Under conditions of chronic exposure, propanil is toxic, mainly to red blood cells and the liver. Methaemoglobinemia, caused by one or more propanil metabolites, is responsible for the damage to erythrocytes. The mechanism of liver toxicity is unclear. An ADI of 0.05 mg/kg/day was established, based on the NOEL of 5 mg/kg/day from the 2-year mouse feeding study and a safety factor of 100.

A guideline value of 175 ug/l was calculated.

**Pyridate**

Pyridate is a compound with very low water solubility and relatively low mobility. It is not persistent and is rapidly hydrolyzed, photodegraded and biodegraded. Its primary environmental metabolite (chlorohydroxyphenylpyridazine) is also not persistent but is more mobile. Under favorable conditions, the environmental half-life is on the order of a few days. This compound has been monitored in only a few countries and has only rarely been found.

Pyridate is without mutagenic activity.

IARC has not evaluated pyridate. Pyridate has been tested in long-term feeding studies in rats and mice; no evidence of carcinogenicity was noted in either species. The only treatment-related finding in chronic toxicity studies is alteration of some organ weights. The most sensitive species for this effect is the dog, and a NOEL of 1.7 mg/kg/day was derived from a 1-year feeding study in this species. Using a safety factor of 100, an ADI of 0.017 mg/kg/day was determined.
A guideline value of 60. ug/l was calculated.

**Simazine**

Simazine is a persistent herbicide that is slowly photodegraded and biodegraded. Its mobility in soil is not particularly high; however, this compound has been frequently detected in ground and surface water.

Simazine appears to be devoid of significant mutagenic or genotoxic activity.

IARC has not evaluated simazine. Available evidence, although inadequate for full evaluation, suggests that simazine is not carcinogenic.

Based on available chronic toxicity data from a 2-year feeding study in dogs, a NOEL of 5 mg/kg/day was established. Based on this value and a safety factor of 1000, an ADI of 0.005 mg/kg/day was determined.

A guideline value of 17 ug/l was calculated.

**Trifluralin**

Trifluralin has low water solubility and a high affinity for soil. However, biodegradation and photodegradation processes may give rise to polar metabolites which may contaminate drinking-water sources. Although this compound is used in many countries, relatively little data are available concerning contamination of drinking water. Trifluralin was not detected in the small number of samples analysed.

Although trifluralin of high purity does not possess mutagenic properties, technical trifluralin may contain nitroso contaminants and has been found to be mutagenic.

IARC has not evaluated trifluralin. A number of long-term carcinogenicity/chronic toxicity studies with pure (>99%) test material have not demonstrated evidence of carcinogenicity.

Overall, the NOEL for chronic toxicity was 4.8 mg/kg/day, based on a 1-year feeding study in dogs. This species is the most sensitive for the mild hepatic effects on which the NOEL was based. Using this NOEL and a safety factor of 100, and ADI of 0.048 mg/kg/day was determined.

A guideline value of 170 ug/l was calculated.

**RECOMMENDATIONS**

**General**

1. To avoid the long-term contamination of drinking water by herbicides, emphasis should lie on preventive measures.
2. Agricultural and industrial practices should be examined with a view to their improvement to minimize environmental contamination with herbicides which may enter drinking water via ground and/or surface water.

3. In the evaluation of herbicides for registration purposes more attention should be paid to the potential for drinking-water contamination via ground and/or surface water. Such evaluations should take into account the herbicides themselves, possible impurities and environmental metabolites.

4. The concept of good agricultural practice should be extended to incorporate minimization of contamination of ground water.

5. The development of guidelines for predicting and verifying environmental fate and distribution of herbicides with regard to contamination of drinking water via ground and surface water is strongly recommended. Such guidelines should also indicate how herbicides should be managed to prevent drinking-water contamination.

6. More attention should be given to monitoring the trends in the concentration levels of herbicides in ground and surface water over time.

7. Few epidemiological data are available on occupational exposure to herbicides during production, formulation or application. This is a matter for concern, since workers may be exposed to considerably higher levels than the general population, and data gathered from this source could be used in assessing the overall health risk of these chemicals. In particular, no information is available on exposure levels, body concentration and biotransformation.

Specific

Alachlor

A guideline value of 0.3 μg/l is recommended if an excess lifetime cancer risk no greater than 1 in 10^5 is considered to be acceptable.

This herbicide should not be used in areas where it may contaminate drinking water via ground and surface water.

Agricultural workers should take appropriate measures to minimize exposure to this compound.
Atrazine

A tentative guideline value of 2 ug/l is recommended. Improvement of agricultural practices to reduce the use of atrazine should be encouraged. The use of atrazine should be carefully controlled, particularly in ground-water catchment areas.

Bentazon

A guideline value of 25 ug/l is recommended. This herbicide should not be used in areas where it may contaminate drinking water via ground and surface water. Because the ADI and guideline value for bentazon are derived from a subchronic feeding study in dogs, these values should be re-evaluated at such time as chronic toxicity data for this species become available.

MCPA

A guideline value of 0.5 ug/l is recommended.

Metolachlor

A guideline value of 5 ug/l is recommended. The application of metolachlor in areas where it may eventually contaminate drinking water via ground and surface water should be considered with some care.

Molinate

A guideline value of 7 ug/l is recommended. Improvement of agricultural practices to decrease the use of molinate should be encouraged. The local hydrological regime should be considered when formulating permits and restrictions on use.

Pendimethalin

A guideline value of 17 ug/l is recommended. During water treatment with granulated activated charcoal, pendimethalin in the presence of intermediary nitrite might give rise to the formation of N-nitroso compounds which could be carcinogenic.

Propanil

A guideline value of 175 ug/l is recommended.
This guideline value is recommended for the parent compound only. This value may not be protective if some propanil metabolites, in particular 3,3',4,4'-tetrachloroazobenzene (TCAB), are present in drinking water. The monitoring of drinking water for TCAB and 3,4-dichloroaniline in addition to propanil is strongly recommended.

Because of health effects observed as a consequence of occupational exposure, epidemiological surveys should be performed on workers exposed to propanil.

**Pyridate**

A guideline value of 60 ug/l is recommended.

**Simazine**

A guideline value of 17 ug/l is recommended. However, the toxicology data base for this chemical is weak. Because of the potential hazard posed by this chemical to drinking-water supplies, WHO should continue to review this chemical, and the proposed guideline value should be reassessed when chronic toxicity studies currently in progress are available for consideration.

The application of simazine in areas where it may eventually contaminate drinking water via ground and surface water should be considered with some care.

During water treatment with granulated activated charcoal, simazine in the presence of intermediary nitrite might give rise to the formation of N-nitroso compounds which could be carcinogenic.

**Trifluralin**

A guideline value of 170 ug/l is recommended.

Pure trifluralin (>99%) is relatively free of toxic effects. However, the technical product can be contaminated with N-nitroso-dipropylamine, a known carcinogen. As the material tested in chronic toxicity studies did not contain this contaminant (i.e. was ultra-pure), this concern has not been addressed by available studies. Therefore, it is imperative that agricultural workers employ appropriate measures to reduce their exposure to trifluralin which may be contaminated with nitrosamines.

**Mixtures of chemical substances in drinking water**

The problem of exposure to any mixture of two or more of
the herbicides in question cannot be handled in isolation. The quality of raw water which is used for the production of drinking water varies according to its origin and will therefore vary in purity and pattern of contaminants. Therefore, drinking water may contain chemical residues of different types, including pesticides, other environmental contaminants, or micropollutants, many of which may as yet be unidentified.

In addition, people are exposed to chemical substances by many other routes, which may also give rise to possible interactions. The complexity of the problem precludes simple answers. Therefore, the one clear target in ground and surface water management should be, as stated in the Introduction, to minimize contamination. If, however, contamination of drinking water has occurred and the water is found to contain a mixture of herbicides or other micropollutants, the possible toxicological implications of such contamination should be assessed on a case-by-case basis. For such an ad hoc assessment, some general guidance can be provided.

First, the nature of the mixture and the concentrations of the individual components in that mixture must be defined as precisely as possible. If possible, the time-related trend of the contamination should be characterized.

Then all available information on the toxicological properties of the individual substances must be collected in order to assess the hazard of each substance. If only one component of the mixture clearly poses a major hazard, a risk assessment based solely on this substance may be possible.

Otherwise, no general guidance can be given.

Systems used for the treatment of water to purify it for drinking-water purposes may in some cases convert contaminants to derivatives which should be assessed separately.

Further guidance on possible approaches to cope with the problem of mixtures may be found in publications of WHO [4] and the US Environmental Protection Agency [5].

REFERENCES


### Annex 1

**DRINKING-WATER QUALITY: GUIDELINE VALUES FOR SELECTED HERBICIDES**

<table>
<thead>
<tr>
<th>Herbicide</th>
<th>ug/l</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alachlor</td>
<td>0.3&quot;</td>
<td></td>
</tr>
<tr>
<td>Atrazine</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Bentazon</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>MCPA</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>Metolachlor</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Molinate</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Pedimethalin</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Propanil</td>
<td>175</td>
<td></td>
</tr>
<tr>
<td>Pyridate</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>Simazine</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Trifluralin</td>
<td>170</td>
<td></td>
</tr>
</tbody>
</table>

* if cancer risk is >1/10⁵.
The criteria for evaluation described below cannot encompass all of the factors that may be relevant to an evaluation of the carcinogenicity of an agent. When considering all of relevant data, the agent may be assigned to a higher or lower category than a strict interpretation of these criteria would indicate.

1. Degrees of evidence for carcinogenicity to humans and experimental animals and supporting evidence

These categories refer only to the strength of the evidence that these agents are carcinogenic and not to the extent of their carcinogenic activity (potency) or to the mechanism involved. Some agents may be reclassified as new information becomes available.

**Human carcinogenicity data**

The evidence relevant to carcinogenicity from studies in humans is classified into one of the following categories.

**Sufficient evidence of carcinogenicity**: A causal relationship has been established between exposure to the agent and human cancer. That is, a positive relationship has been observed between exposure to the agent and cancer in studies in which chance, bias and confounding could be ruled out with reasonable confidence.

**Limited evidence of carcinogenicity**: A positive association has been observed between exposure to the agent and cancer for which a causal interpretation is considered to be credible, but chance, bias or confounding could not be ruled out with reasonable confidence.

**Inadequate evidence of carcinogenicity**: The available studies are of insufficient quality, consistency or statistical

---

1 Taken from IARC [3].
power to permit a conclusion regarding the presence or absence of a causal association.

Evidence suggesting lack of carcinogenicity: Several adequate studies covering the full range of doses to which humans are known to be exposed are mutually consistent in not showing a positive association between exposure to the agent and any studied cancer at any observed level of exposure. A conclusion of evidence suggesting lack of carcinogenicity is inevitably limited to the cancer sites, circumstances and doses of exposure and length of observation covered by the available studies. In addition, the possibility of a very small risk at the levels of exposure studied can never be excluded.

In some instances, the above categories may be used to classify the degree of evidence for the carcinogenicity of the agent for specific organs or tissues.

Experimental carcinogenicity data

The evidence relevant to carcinogenicity in experimental animals is classified into one of the following categories.

Sufficient evidence of carcinogenicity: A causal relationship has been established between the agent and an increased incidence of malignant neoplasms or of an appropriate combination of benign and malignant neoplasms in (a) two or more species or (b) in two or more independent studies in one species carried out at different times or in different laboratories or under different protocols.

Exceptionally, a single study in one species might be considered to provide sufficient evidence of carcinogenicity when malignant neoplasms occur to an unusual degree with regard to incidence, site, type of tumour or age at onset.

In the absence of adequate data on humans, it is biologically plausible and prudent to regard agents for which sufficient evidence of carcinogenicity has been found in experimental animals as if they presented a carcinogenic risk to humans.

Limited evidence of carcinogenicity: The data suggest a carcinogenic effect but are limited for making a definitive evaluation because, for example, (a) the evidence of carcinogenicity is restricted to a single experiment; (b) unresolved questions remain regarding the adequacy of the design, conduct or interpretation of the study; or (c) the agent increases the incidence only of benign neoplasms or lesions of uncertain neoplastic potential, or of certain
neoplasms which may occur spontaneously in high incidences in certain strains.

Inadequate evidence of carcinogenicity: The studies cannot be interpreted as showing either the presence or absence of a carcinogenic effect because of major qualitative or quantitative limitations.

Evidence suggesting lack of carcinogenicity: Adequate studies involving at least two species are available which show that, within the limits of the tests used, the agent is not carcinogenic. A conclusion of evidence suggesting lack of carcinogenicity is inevitably limited to the species, tumour sites and doses of exposure studies.

Supporting evidence of carcinogenicity

The other relevant data judged to be of sufficient importance to affect the making of the overall evaluation are indicated.

2. Overall evaluation

Finally, the total body of evidence is taken into account: the agent is described according to the wording of one of the following categories, and the designated group is given. The categorization of an agent is a matter of scientific judgement, reflecting the strength of the evidence derived from studies in humans and experimental animals and from other relevant data.

Group 1 - The agent is carcinogenic to humans

This category is used only when sufficient evidence of carcinogenicity in humans is found.

Group 2 - The agent is probably/possibly carcinogenic to humans

This category includes agents for which, at one extreme, the degree of evidence of carcinogenicity in humans is almost sufficient, as well as agents for which, at the other extreme, no human data are available but for which experimental evidence of carcinogenicity exists. Agents are assigned to either Group 2A (probably carcinogenic) or Group 2B (possibly carcinogenic) on the basis of epidemiological, experimental and other relevant data.
Group 2A - The agent is probably carcinogenic to humans

This category is used when limited evidence of carcinogenicity in humans and sufficient evidence of carcinogenicity in experimental animals has been found. Exceptionally, an agent may be classified into this category solely on the basis of limited evidence of carcinogenicity in humans or of sufficient evidence of carcinogenicity in experimental animals strengthened by supporting evidence from other relevant data.

Group 2B - The agent is possibly carcinogenic to humans

This category is generally used when limited evidence of carcinogenicity in humans and insufficient evidence of carcinogenicity in experimental animals have been found. It may also be used when an agent gives inadequate evidence of carcinogenicity in humans or when human data are nonexistent but sufficient evidence of carcinogenicity in experimental animals exists. In some instances, an agent for which evidence is inadequate or no data in humans are available but for which limited evidence of carcinogenicity in experimental animals together with supporting evidence from other relevant data may be placed in this group.

Group 3 - The agent is not classifiable as to its carcinogenicity to humans

Agents are placed in this category when they do not fall into any other group.

Group 4 - The agent is probably not carcinogenic to humans

This category is used for agents for which evidence suggests a lack of carcinogenicity in humans together with evidence suggesting a lack of carcinogenicity in experimental animals. In some circumstances, agents with inadequate evidence of or no data on carcinogenicity in humans but with evidence suggesting a lack of carcinogenicity in experimental animals, consistently and strongly supported by a broad range of other relevant data, may be classified in this group.
A subgroup was formed from the members of the July Consultation to consider the carcinogenic potential of alachlor.

Two studies were conducted in the rat. In the first study, doses of 0, 14, 42 and 126 mg/kg were tested for 2 years. The subgroup concluded that this study provided clear evidence of oncogenicity based on the following facts: a statistically significant increase in the incidence of adenoma of the nasal turbinate, statistically significant increases in the incidences of malignant stomach tumours and statistically significant increases in thyroid follicular tumours in high-dose males. This conclusion is also based on the single incidences of adenocarcinoma of the nasal turbinate in mid-dose males and females, and the observation of submucosal hyperplasia in nasal tissues. This conclusion was supported by a repeat study of the highest dose only (126 mg/kg) in which adenoma and adenocarcinomas of the nasal cavity and malignant stomach tumours were found.

The second study tested doses of 0, 0.5, 2.5 and 15 mg/kg for 2 years. A statistically significant increase in the incidence of adenoma of the nasal turbinate was observed at the highest dose tested. Submucosal gland hyperplasia of the nasal turbinate was also noted in this study. The subgroup concluded that this study also provided clear evidence of oncogenicity.

The subgroup considered that the presence of stabilizers in the technical material was unlikely to have influenced the carcinogenic response observed in the rat.

The subgroup was unable to reach a consensus on the significance of the mouse carcinogenicity data but did agree that the data do not provide clear evidence of carcinogenicity in this species.
PARTICIPANTS
Rome, 11-13 February 1987

TEMPORARY ADVISERS

Dr M. Borzsony, National Institute of Hygiene, Budapest, Hungary

Dr E. Funari, Istituto Superiore de Sanità, Rome, Italy

Dr R. Goulding, Keat's House, Guy's Hospital London, United Kingdom (Vice-chairman)

Dr J. Hrubec, Laboratory for Ecotoxicology, Environmental Chemistry and Drinking Water, National Institute of Public Health and Environmental Hygiene, Bilthoven, Netherlands

Professor K. Hurle, Institute of Botany, Stuttgart, Federal Republic of Germany

Dr E.I. Krajnc, National Institute of Public Health and Environmental Hygiene, Bilthoven, Netherlands

Mr W. M. Lewis, Styvechale, Coventry, United Kingdom (Rapporteur)

Dr M. Lotti, University of Padua, Institute of Occupational Health, Padua, Italy

Dr M. Manno, University of Padua, Institute of Occupational Health, Padua, Italy

Professor M. Maroni, Institute of Occupational Health, Clinica del Lavoro L. Devoto, University of Milan, Milan, Italy

Dr R. Plestina, Institute for Medical Research and Occupational Health, Zagreb, Yugoslavia

Professor A. Pocchiari, Istituto Superiore de Sanità, Rome, Italy (Chairman)

Dr A. Rico, National Veterinary School of Toulouse, Toxicology Laboratory, Toulouse, France

Professor A. Sampaolo, Istituto Superiore de Sanità, Rome, Italy
DRINKING-WATER QUALITY: GUIDELINES FOR SELECTED HERBICIDES

Dr J. Sokal, Institute of Occupational Medicine, Lodz, Poland
Dr B. Wahlström, National Chemical Inspectorate, Solna, Sweden
Dr S. Wilbur, Syracuse Research Corporation, Syracuse, USA

OBSERVERS

Dr N. Sarti, Division of Water and Soil, Ministry of Health, Rome, Italy
Professor I. Camoni, Laboratory of Applied Technology, Pesticide Section, Istituto Superiore di Sanità, Rome, Italy
Ing. G.A. Zapponi, Laboratory of Comparative Toxicology and Ecotoxicology, Istituto Superiore di Sanità, Rome, Italy

REPRESENTATIVES OF OTHER ORGANIZATIONS

International Register of Potentially Toxic Chemicals (IRPTC)/United Nations Environment Programme (UNEP)

Ms B. Bender, Regional Office for Europe, Palais des Nations, Geneva, Switzerland

WORLD HEALTH ORGANIZATION

Headquarters

Dr J. Herrman, International Programme on Chemical Safety (IPCS)

Regional Office for Europe

Dr D. Kello, Consultant, Environmental Systems Management
DRINKING-WATER QUALITY: GUIDELINES FOR SELECTED HERBICIDES

Annex 2

PARTICIPANTS
Rome, 13-18 July 1987

TEMPORARY ADVISERS

Dr V. Benes, Institute of Hygiene and Epidemiology, Prague, Czechoslovakia

Professor D. Calamari, Institute of Agricultural Entomology, Faculty of Agriculture, University of Milan, Milan, Italy

Dr Z. Deak, National Institute of Hygiene, Budapest, Hungary

Professor G. Della Porta, National Tumour Institute, Milan, Italy

Dr H. Dieter, Institute for Water, Soil and Air Hygiene of the Federal Health Office, Berlin (West)

Dr R.G. Dortland, Ministry of Housing, Physical Planning and Environmental Management, Directorate for Soil and Groundwater, Water and Chemicals, Leidschendam, Netherlands

Dr E. Funari, Istituto Superiore di Sanità, Rome, Italy

Dr J. Hrubec, Laboratory for Ecotoxicology, Environmental Chemistry and Drinking Water, National Institute of Public Health and Environmental Hygiene, Bilthoven, Netherlands

Mr W. M. Lewis, Styvechale, Coventry, United Kingdom

Dr N. Loprieno, Department of Environmental and Soil Science, Università degli Studi, Pisa, Italy

Dr M. Peraica, Institute for Medical Research and Occupational Health, Zagreb, Yugoslavia

Professor A. Pocchiarl, Istituto Superiore di Sanità, Rome, Italy (Vice-chairman)

Dr A. Rico, National Veterinary School of Toulouse, Toxicology Laboratory, Toulouse, France
DRINKING-WATER QUALITY: GUIDELINES FOR SELECTED HERBICIDES

Dr L. Ritter, Environmental Health Directorate, Health Protection Branch, Department of National Health and Welfare, Ottawa, Canada

Professor A. Sampaolo, Istituto Superiore di Sanità, Roma, Italy

Dr D.S. Saunders, Hazard Evaluation Division, (TS-769C) US Environmental Protection Agency, Washington, DC, USA (Rapporteur)

Dr J. Sokal, Institute of Occupational Medicine, Lodz, Poland (Chairman)

OBSERVERS

Dr N. Sarti, Division of Water and Soil, Ministry of Health, Rome, Italy

Professor I. Camoni, Laboratory of Applied Toxicology, Pesticide Section, Istituto Superiore di Sanità, Rome, Italy

Professor A. Carere, Laboratory of Applied Toxicology, Mutagenesis and Cancerogenesis Section, Istituto Superiore di Sanità, Rome, Italy

Professor G.A. Zapponi, Laboratory of Comparative Toxicology and Ecotoxicology, Istituto Superiore di Sanità, Rome, Italy

WORLD HEALTH ORGANIZATION

International Agency for Research on Cancer (IARC)

Dr J. Wilbourn, Unit of Carcinogen Identification and Evaluation Headquarters

Dr J. Herrman, International Programme on Chemical Safety (IPCS)

Regional Office for Europe

Dr J.H. Duffus, Consultant, Toxicology and Occupational Health

Dr D. Kello, Project Officer, Environmental Epidemiology and Food Safety

23