WHO/HSE/AMR/08.03/11
English only

Novaluron in Drinking-water:
Use for Vector Control in Drinking-water Sources and Containers

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

Novaluron in Drinking-water: Use for Vector Control in Drinking-water Sources and Containers
Background document for development of WHO Guidelines for Drinking-water Quality

Printed by the WHO Document Production Services, Geneva, Switzerland

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 on selected chemicals in 1998 and on microbial aspects in 2002. The third edition of the GDWQ was published in 2004, the first addendum to the third edition was published in 2005, and the second addendum to the third edition was published in 2008.

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 and 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 of potential health concern in drinking-water. In the first and second editions, these constituted Volume 2 of the GDWQ. Since publication of the third edition, they comprise a series of free-standing monographs, including this one.

For each chemical contaminant or substance considered, a lead institution prepared a background 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 (USA) prepared the documents for the third edition and addenda.

Under the oversight of a group of coordinators, each of whom was responsible for a group of chemicals considered in the GDWQ, 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. The draft documents were also released to the public domain for comment and submitted for final evaluation by expert meetings.

During the preparation of background documents and at expert 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 Meeting 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

The first draft of Novaluron in Drinking-water: Use for Vector Control in Drinking-water Sources and Containers, Background document for development of WHO *Guidelines for Drinking-water Quality*, was prepared by Mr J.K. Fawell, 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 contributing to the second addendum to the third edition:

Dr J. Cotruvo, Joseph Cotruvo & Associates, USA (*Materials and chemicals*)
Mr J.K. Fawell, United Kingdom (*Naturally occurring and industrial contaminants*)
Ms M. Giddings, Health Canada (*Disinfectants and disinfection by-products*)
Mr P. Jackson, WRc-NSF, United Kingdom (*Chemicals – practical aspects*)
Professor Y. Magara, Hokkaido University, Japan (*Analytical achievability*)
Dr A.V. Festo Ngowi, Tropical Pesticides Research Institute, United Republic of Tanzania (*Pesticides*)
Dr E. Ohanian, Environmental Protection Agency, USA (*Disinfectants and disinfection by-products*)

The draft text was discussed at the Working Group Meeting for the second addendum to the third edition of the GDWQ, held on 15–19 May 2006. The final version of the document takes into consideration comments from both peer reviewers and the public. The input of those who provided comments and of participants in the meeting is gratefully acknowledged.

The WHO coordinators were Dr J. Bartram and Mr B. Gordon, WHO Headquarters. Ms C. Vickers provided a liaison with the Programme on Chemical Safety, WHO Headquarters. Mr R. Bos, Assessing and Managing Environmental Risks to Health, WHO Headquarters, provided input on pesticides added to drinking-water for public health purposes.

Ms Penny Ward provided invaluable administrative support at the Working Group Meeting and throughout the review and publication process. 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

ADI	acceptable daily intake
ai	active ingredient
CAS	Chemical Abstracts Service
DT_{50}	time at which 50% of the parent compound has disappeared from soil or water by transformation or degradation
FAO	Food and Agriculture Organization of the United Nations
GDWQ	*Guidelines for Drinking-water Quality*
IUPAC	International Union of Pure and Applied Chemistry
JMPR	Joint FAO/WHO Meeting on Pesticide Residues
K_{ow}	octanol–water partition coefficient
LC_{50}	median lethal concentration
LD_{50}	median lethal dose
LOAEL	lowest-observed-adverse-effect level
NOAEL	no-observed-adverse-effect level
3-TFA	3-chloro-4-(1,1,2-trifluoro-2-trifluoromethoxyethoxy)aniline
WHO	World Health Organization

Table of contents

This document is based on the JMPR evaluation of novaluron (FAO/WHO, 2005).

1. GENERAL DESCRIPTION

1.1 Identity

CAS No.: 116714-46-6

Molecular formula: $C_{17}H_9ClF_8N_2O_4$

The IUPAC name for novaluron is (*RS*)-1-[3-chloro-4-(1,1,2-trifluoro-2-trifluoro-methoxyethoxy)phenyl]-3-(2,6-difluorobenzoyl)urea.

1.2 Physicochemical properties

Property	*Value*
Melting point	176.5–178.0 °C
Water solubility	3 µg/l at 20 °C, neutral pH
Log octanol–water partition coefficient (log K_{ow})	4.3 at 20–25 °C, pH 7.1
Vapour pressure	1.6×10^{-5} Pa at 25 °C

1.3 Major uses and sources in drinking-water

Novaluron has been registered as an insecticide for food crops (including soya, maize, pome fruit, citrus and potato) and ornamentals in a number of countries. It is a member of the benzoyl urea class of insecticides, which incorporates two benzene ring structures, and is a racemate of two enantiomers. The benzoyl ureas are insect growth regulators. Novaluron inhibits the synthesis of chitin (the major structural component of arthropod exoskeletons) during insect development. WHO has assessed novaluron for use as a mosquito larvicide in drinking-water in containers, particularly to control dengue fever. The recommended dosage of novaluron in potable water in containers should not exceed 0.05 mg/l under the WHO Pesticides Evaluation Scheme (WHO, 2004, 2006).

1.4 Environmental fate

The DT_{50} of novaluron in three kinds of soil was reported to be between 5 and 20 days at 20 °C after an application of 0.13 mg/kg. The primary degradation product was 1-[3-chloro-4-(1,1,2-trifluoro-2-trifluoromethoxyethoxy)phenyl]urea, and the DT_{50} for this compound was between 46 and 64 days at 20 °C. A significant proportion of the radioactivity was in the form of carbon dioxide, and all of the material was eventually mineralized. Novaluron was also reported to be photolysed in aqueous solution with a DT_{50} in natural water of 31.1 days under light equivalent to the sunlight at Tokyo (latitude 35°N) in springtime, and the main degradation product was 2,6-difluorobenzamide (Japanese Food Safety Commission, 2003).

The residual levels of novaluron were examined in tomatoes, eggplants, cabbages and Chinese cabbage. The highest residual value of the compound (0.41 mg/kg) was observed in Chinese cabbage cropped 7 days after the third spraying with 85 g ai/ha. Although the size of the experiment was small, no extreme residual value was

observed in any vegetables examined (Japanese Food Safety Commission, 2003). This implies that exposure from food will be limited.

2. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

There are no specific data on exposure to novaluron in drinking-water, but its high soil adsorption coefficient (K_{oc}) and low solubility suggest that it will not be mobile in the environment and is unlikely to be found frequently in treated drinking-water. Where novaluron is directly applied to drinking-water containers, there is a significant probability of some exposure.

3. TOXICOLOGICAL SUMMARY[1]

Following oral administration in rats, [chlorophenyl-^{14}C (U)]-novaluron was poorly absorbed (≤7%) after a single low dose (2 mg/kg of body weight) and about 10-fold less after a single high dose (1000 mg/kg of body weight), with maximum plasma concentrations occurring at 5–8 h or 2–5 h, respectively. Novaluron was widely distributed. The tissue concentrations of radioactivity were highest in fat, liver and kidneys and were about 3- to 5-fold higher after 14 repeated daily doses than after a single dose, with a terminal half-life of 52–56 h in fat after the final dose. Excretion was rapid, primarily via the faeces (>94%; via bile ≤1%) and to a lesser extent via urine (about 5%), with most of the administered dose being excreted within 48 h.

Absorbed novaluron was extensively metabolized, mainly by cleavage of the urea bridge between the chlorophenyl and difluorophenyl moieties. In urine and bile, up to 15 metabolites were detected, and individual metabolites accounted for ≤1% of a low dose of [chlorophenyl-^{14}C (U)]-novaluron. Most of the faecal radioactivity consisted of unchanged novaluron, which was also the major component present in fat, liver and kidneys. The aniline metabolite of novaluron, 3-chloro-4-(1,1,2-trifluoro-2-trifluoromethoxyethoxy)aniline, or 3-TFA, was identified at low levels (≤0.7%) in the urine, bile, liver and kidneys.

Novaluron had low acute toxicity in rats, causing no mortality at limit doses after oral (LD_{50} > 5000 mg/kg of body weight), dermal (LD_{50} > 2000 mg/kg of body weight) and inhalation (LC_{50} > 5.15 mg/l air) exposures. Novaluron was not irritating to the skin and eyes of rabbits and not sensitizing to guinea-pig skin.

In short-term and long-term studies of toxicity, the erythrocyte was identified as the primary target of toxicity attributable to novaluron, with secondary effects apparent in the spleen and less commonly in liver and kidneys. The spectrum of effects was essentially similar in mice, rats and dogs, and the underlying mechanism was considered to be the same. Although the mechanism of the effects on erythrocytes has not been elucidated, it was considered to be most likely that the aniline metabolite of novaluron, 3-TFA, caused oxidative damage to the mature erythrocyte, resulting in increased concentrations of methaemoglobin (caused by accelerated oxidation of haemoglobin from the ferrous to the ferric state) and increased numbers of erythrocytes containing Heinz bodies (which are formed when damaged haemoglobin precipitates onto the cell membrane). The presence of Heinz bodies led to early

[1] After FAO/WHO (2005).

destruction of erythrocytes by the spleen, with the consequence of increased erythrocyte turnover, characterized by stimulated erythropoiesis in both normal sites (sternum, femur) and functional reserve sites (spleen, liver) and increased deposition of the products of haemoglobin catabolism (haemosiderin) in the spleen, liver and kidneys. After cessation of treatment, the adverse effects regressed, although incompletely, over a 4-week period after treatment in rats and dogs, and completely within 8 weeks in mice.

In 28-day and 90-day studies of toxicity in mice treated orally, the overall NOAEL was 30 mg/kg (equivalent to 4.2 mg/kg of body weight per day) on the basis of haematological changes (decrease in erythrocyte volume fraction and erythrocyte counts, increase in Heinz bodies and sulfhaemoglobin) at dietary concentrations of 100 mg/kg (equivalent to 12.8 mg/kg of body weight per day) and above, whereas changes in the spleen (increased weight, increased haematopoiesis and haemosiderosis) were evident at 700 mg/kg (equivalent to 114.7 mg/kg of body weight per day) and above.

In 28-day and 90-day studies in rats treated orally, the overall NOAEL was 50 mg/kg (equivalent to 4.2 mg/kg of body weight per day) on the basis of haematological changes (decrease in haemoglobin, erythrocyte volume fraction and erythrocyte counts) and histopathological changes in the spleen and liver (increased haematopoiesis and haemosiderosis) at dietary concentrations of 100 mg/kg (equivalent to 8.3 mg/kg of body weight per day) and above. By week 4 of the reversibility period, there was full recovery for most changes, except for increased concentrations of methaemoglobin, spleen weights and splenic haemosiderosis at dietary concentrations of 20 000 mg/kg (equivalent to 1667 mg/kg of body weight per day).

In 90-day and 1-year studies in dogs treated orally, the overall NOAEL was 10 mg/kg of body weight per day on the basis of haematological changes (decrease in haemoglobin, erythrocyte volume fraction and erythrocyte counts; increase in reticulocytes, Heinz bodies and Howell-Jolly bodies), increased serum concentrations of bilirubin and changes in the spleen and liver (increased weight, increased red pulp congestion, increased haemosiderin in Kupffer cells) at doses of 100 mg/kg of body weight per day or greater, whereas increased concentrations of methaemoglobin were evident at doses of 300 mg/kg of body weight per day or greater. By week 4 of a reversibility period, there was full recovery for most changes, except for increased liver weights in female dogs at 1000 mg/kg of body weight per day.

In a 28-day study in rats treated dermally, the NOAEL for systemic toxicity was 75 mg/kg of body weight per day on the basis of increased concentrations of methaemoglobin at doses of 400 mg/kg of body weight per day or greater.

Novaluron gave negative results in an adequate battery of studies of genotoxicity in vitro and in vivo.

JMPR concluded that novaluron was unlikely to be genotoxic.

Long-term studies of toxicity and carcinogenicity were conducted in mice and rats. In the study of carcinogenicity in mice, the NOAEL was 30 mg/kg (equivalent to

3.6 mg/kg of body weight per day) on the basis of increased body weight gain (in the first 4 or 26 weeks in males and females, respectively), haematological changes (decrease in haemoglobin, erythrocyte volume fraction and erythrocyte counts; increase in reticulocytes, sulfhaemoglobin and Heinz bodies) and changes in spleen (increased weight, increased incidence of extramedullary haematopoiesis, haemosiderosis and congestion) and kidneys (increase in cortical tubular pigment) at dietary concentrations of 450 mg/kg (equivalent to 53.4 mg/kg of body weight per day) and greater. There was no evidence of carcinogenicity in mice at dietary concentrations of up to 7000 mg/kg (equivalent to 800 mg/kg of body weight per day), the highest dose tested.

In the long-term study of toxicity and carcinogenicity in rats, the NOAEL was 25 mg/kg (equivalent to 1.1 mg/kg of body weight per day) on the basis of haematological changes (decreases in haemoglobin, erythrocyte volume fraction and erythrocyte counts; increases in methaemoglobin formation and reticulocytes) and changes in the spleen (increase in weight, haemosiderosis) and kidneys (increase in cortical tubular pigment) at dietary concentrations of 700 mg/kg (equivalent to 30.6 mg/kg of body weight per day) and greater. There was no evidence of carcinogenicity in rats at dietary concentrations of up to 20 000 mg/kg (equivalent to 884.2 mg/kg of body weight per day), the highest dose tested.

In view of the absence of a carcinogenic potential in rodents and the lack of genotoxic potential in vitro and in vivo, JMPR concluded that novaluron is unlikely to pose a carcinogenic risk to humans.

In a two-generation study of reproductive toxicity in rats, the NOAEL for effects on fertility was 12 000 mg/kg (equivalent to 894.9 mg/kg of body weight per day), the highest dose tested. The NOAEL for systemic toxicity in parental animals and offspring could not be identified, since there were secondary changes in spleen and liver relating to increased erythrocyte damage at all doses tested. The LOAEL for systemic toxicity was 1000 mg/kg (equivalent to 74.2 mg/kg of body weight per day) on the basis of increased spleen weights in adults and increased spleen and liver weights in offspring.

In a study of prenatal developmental toxicity in rats, the NOAEL for maternal and developmental toxicity was 1000 mg/kg of body weight per day, the highest dose tested. The increases in body weight gain and food consumption in all treated groups were not considered to be adverse effects.

In a study of prenatal developmental toxicity in rabbits, the NOAEL for both maternal and developmental toxicity was 1000 mg/kg of body weight per day, the highest dose tested. In the absence of any other evidence for an effect on fetal development, the slight increase in incidence of incompletely ossified fifth sternebrae at 300 mg/kg of body weight per day and 1000 mg/kg of body weight per day was not considered to be adverse. The finding of absent implantation or high rates of pre-implantation loss in two dams at 1000 mg/kg of body weight per day was considered to be incidental and not related to treatment.

JMPR concluded that novaluron is not a developmental toxicant.

In a study of acute neurotoxicity in rats, non-specific clinical signs (fast respiration, piloerection) of minor toxicological relevance were seen in all groups treated at doses of 200 mg/kg of body weight and greater. The NOAEL for neurotoxic effects was 2000 mg/kg of body weight, the highest dose tested.

The manufacturing impurity MCW RI 458 had low acute oral (LD_{50} > 5000 mg/kg of body weight) and dermal toxicity (LD_{50} > 2000 mg/kg of body weight) in rats and was not mutagenic in an assay for gene mutation in bacteria. The manufacturing intermediate MCW I was not mutagenic in an assay for gene mutation in bacteria.

JMPR concluded that the existing database on novaluron was adequate to characterize the potential hazards to fetuses, infants and children and established an ADI of 0–0.01 mg/kg of body weight on the basis of the NOAEL of 1.1 mg/kg of body weight per day for erythrocyte damage and secondary splenic and liver changes in a 2-year dietary study in rats, and a safety factor of 100.

JMPR also concluded that it was not necessary to establish an acute reference dose for novaluron in view of its low acute toxicity, the absence of relevant developmental toxicity in rats and rabbits that could have occurred as a consequence of acute exposure and the absence of any other toxicological effect that would be elicited by a single dose.

4. PRACTICAL ASPECTS

4.1 Analytical methods and analytical achievability

The concentration of novaluron can be determined by high-performance liquid chromatography with ultraviolet detector (detection limit 0.02 mg/l). Novaluron can also be detected by liquid chromatography with electrospray mass spectrometry in both positive and negative ionization modes (Japanese Food Safety Commission, 2004).

4.2 Use for vector control in drinking-water sources

Novaluron is used as a larvicide for control of disease-carrying mosquitoes that breed in drinking-water containers at a dosage not exceeding 0.05 mg/l.

Formulations of pesticides used for vector control in drinking-water should strictly follow the label recommendations and should only be those approved for such a use by national authorities, taking into consideration the ingredients and formulants used in making the final product.

5. CONCLUSIONS

It is not considered appropriate to set a formal guideline value for novaluron as a vector control agent in drinking-water. JMPR established an ADI of 0–0.01 mg/kg of body weight for novaluron in 2005. At the most efficacious dose for water in containers of 0.05 mg/l, the intake of a 60-kg adult drinking 2 litres of water would represent only 17% of the ADI. Similarly, the intake for a 10-kg child drinking 1 litre of water would be 50% of the ADI, whereas a 5-kg bottle-fed infant drinking 0.75

litre of water would receive an intake of 75% of the ADI. However, the high log K_{ow} of 4.3 indicates that novaluron is likely to adsorb to the sides of containers, and so the actual concentration is likely to be less than the recommended dose. Exposure to novaluron through food is not expected to be significant.

National authorities should note that this document refers only to the active ingredient and does not consider the additives in different formulations.

6. RECOMMENDATIONS

In setting local guidelines or standards, health authorities should take into consideration the potential for higher rates of water consumption in the area or region under consideration. However, exceeding the ADI will not necessarily result in adverse effects.

The diseases spread by vectors are significant causes of morbidity and mortality. It is therefore important to achieve an appropriate balance between the intake of the pesticide from drinking-water and the control of disease-carrying insects. Better than establishing guideline values are the formulation and implementation of a comprehensive management plan for household water storage and peridomestic waste management that does not rely exclusively on larviciding by insecticides, but also includes other environmental management measures and social behavioural changes.

7. REFERENCES

FAO/WHO (2005) Novaluron. In: *Pesticide residues in food — 2005.* Rome, Food and Agriculture Organization of the United Nations, Joint FAO/WHO Meeting on Pesticide Residues (FAO Plant Production and Protection Paper 183; http://www.fao.org/ag/AGP/AGPP/Pesticid/JMPR/DOWNLOAD/2005_rep/report2005jmpr.pdf).

Japanese Food Safety Commission (2003) *Novaluron evaluation report*. Tokyo, Japanese Ministry of Health, Labour and Welfare, Japanese Food Safety Commission, Pesticides Expert Committee, 24 December.

WHO (2004) *Novaluron: (±)-1-[3-chloro-4-(1,1,2-trifluoro-2-trifluoromethoxyethoxy)phenyl]-3-(2,6-difluorobenzoyl)urea.* Geneva, World Health Organization (WHO Specifications and Evaluations for Public Health Pesticides; http://www.who.int/whopes/quality/en/Novaluron_evaluation_Dec_2004.pdf).

WHO (2006) *Pesticides and their application for the control of vectors and pests of public health importance*, 6th ed. Geneva, World Health Organization, Department of Control of Neglected Tropical Diseases, Pesticides Evaluation Scheme (WHO/CDS/NTD/WHOPES/GCDPP/2006.1; http://whqlibdoc.who.int/hq/2006/WHO_CDS_NTD_WHOPES_GCDPP_2006.1_eng.pdf).