

**Spinosad DT in Drinking-water:
Use for Vector Control in Drinking-water Sources and Containers**

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

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Preface

One of the primary goals of the World Health Organization (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 third edition of the GDWQ was published in 2004, the first addendum to the third edition was published in 2006 and the second addendum to the third edition was published in 2008. The fourth edition will be published in 2011.

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, Japan, the United Kingdom and the United States of America (USA) prepared the documents for the fourth edition.

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 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.

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The first draft of Spinosad 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 fourth edition:

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The draft text was discussed at the Expert Consultation for the fourth edition of the GDWQ, held on 19–23 June 2008. 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 at the meeting is gratefully acknowledged.

The WHO coordinators were Mr R. Bos and Mr B. Gordon, WHO Headquarters. Ms C. Vickers provided a liaison with the International Programme on Chemical Safety, WHO Headquarters. Mr M. Zaim, Public Health and the Environment Programme, WHO Headquarters, provided input on pesticides added to drinking-water for public health purposes.

Ms P. Ward provided invaluable administrative support at the Expert Consultation and throughout the review and publication process. Ms M. 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 comments are greatly appreciated.

Acronyms and abbreviations used in the text

ADI	acceptable daily intake
FAO	Food and Agriculture Organization of the United Nations
GDWQ	<i>Guidelines for Drinking-water Quality</i>
IUPAC	International Union of Pure and Applied Chemistry
K_{ow}	octanol–water partition coefficient
LD ₅₀	median lethal dose
LOAEL	lowest-observed-adverse-effect level
NOAEL	no-observed-adverse-effect level
WHO	World Health Organization
WHOPES	World Health Organization Pesticide Evaluation Scheme

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1. GENERAL DESCRIPTION

1.1 Identity

	Empirical formula	Chemical Abstracts Service Registry No.	Relative molecular mass
Spinosyn A	C ₄₁ H ₆₅ NO ₁₀	131929-60-7	732.0
Spinosyn D	C ₄₂ H ₆₇ NO ₁₀	131929-63-0	746.0

Spinosad is the International Organization for Standardization–approved name for a mixture of spinosyns A and D, with A:D proportions in the range 50:50 to 95:5 (WHO, 2008).

The International Union for Pure and Applied Chemistry (IUPAC) name for spinosyn A is (2*R*,3*aS*,5*aR*,5*bS*,9*S*,13*S*,14*R*,16*aS*,16*bR*)-2-(6-deoxy-2,3,4-tri-*O*-methyl- α -L-mannopyranosyloxy)-13-(4-dimethylamino-2,3,4,6-tetra-deoxy- β -D-erythro-pyranosyloxy)-9-ethyl-2,3,3*a*,5*a*,6,7,9,10,11,12,13,14,15,16*a*,16*b*-hexadecahydro-14-methyl-1*H*-8-oxacyclododeca[*b*]as-indacene-7,15-dione.

The IUPAC name for spinosyn D is (2*R*,3*aS*,5*aR*,5*bS*,9*S*,13*S*,14*R*,16*aS*,16*bR*)-2-(6-deoxy-2,3,4-tri-*O*-methyl- α -L-mannopyranosyloxy)-13-(4-dimethylamino-2,3,4,6-tetra-deoxy- β -D-erythro-pyranosyloxy)-9-ethyl-2,3,3*a*,5*a*,6,7,9,10,11,12,13,14,15,16*a*,16*b*-hexadecahydro-4,14-dimethyl-1*H*-8-oxacyclododeca[*b*]as-indacene-7,15-dione.

1.2 Physicochemical properties

Some important physical and chemical properties of spinosad are summarized in Table 1.

Table 1: Physicochemical properties of spinosad (WHO, 2008)

Property	Value
Melting point	110–123 °C for spinosyns A + D
Water solubility	235 mg/l at pH 7 for spinosyn A 0.332 mg/l at pH 7 for spinosyn D
Log octanol–water partition coefficient (log K_{ow})	4.01 at 23 °C and pH 7 for spinosyn A 4.53 at 23 °C and pH 7 for spinosyn D
Vapour pressure	Negligible at 25 °C

1.3 Major uses and sources in drinking-water

Spinosad is a natural product derived from the bacterium *Saccharopolyspora spinosa*. Spinosad DT is a mixture of spinosyn A and spinosyn D. Each tablet consists of two homogenous horizontal layers of technical spinosad. An upper layer consists of technical spinosad in an effervescent system providing fast release of active ingredient upon application to water, whereas the lower layer is formulated to dissolve in water gradually over time. It is used for mosquito control in potable water in containers. Spinosad DT 7.48% is specified for use as a vector control agent in drinking-water sources against *Aedes aegypti* by the World Health Organization

(WHO) under the WHO Pesticide Evaluation Scheme (WHOPES). Formulations for control of vectors are specified by WHO (2008) at a dose of 0.25–0.5 mg/l. The expected duration of efficacy under field conditions is 4–6 weeks.

Three formulations of spinosad have been evaluated by WHOPES for mosquito larviciding (WHO, 2008). WHO specifications for quality control and international trade have been published for the three formulations: i.e. spinosad granules (636/GR), aqueous suspension concentrate (636/SC) and tablets for direct application (636/DT) (WHO, 2008). Only the tablet formulation is used for mosquito larviciding in potable water at the dosage of 0.25–0.5 mg/l of the active ingredient.

WHO specifications for formulations, unless otherwise stated, encompass the products of all formulators legitimately able to certify that their products contain only active ingredient sourced from a manufacturer to whom the WHO specification for technical material/technical concentration applies. Buyers and/or regulatory authorities should demand such certification and ensure both that it is valid and that the products fully comply with the physical and chemical requirements of the WHO specifications. The safety of the formulators used in making the final product should be considered by national authorities for products intended for use in potable water.

1.4 Environmental fate

Spinosad has a relatively high log K_{ow} of 4.0 and would be expected to adsorb to particles, sediment and the sides of containers. In a study by the manufacturers of the formulation developed for use in potable water designed to simulate normal product usage, the maximum concentration observed was 51.7 µg/l after 3 days (Clarke Mosquito Control, 2006).

2. HUMAN EXPOSURE

It is expected that exposure of the public through either food or drinking-water would be low. However, there is a potential for direct exposure through drinking-water when spinosad is directly applied to drinking-water storage containers.

3. TOXICOLOGICAL SUMMARY¹

The pharmacokinetics and metabolism of the two principal constituents of spinosad, spinosyn A and D, are very similar. Oral administration of spinosyn A or D to rats resulted in rapid but incomplete absorption of >70% of the dose. Peak blood concentrations of radiolabel were achieved 1 h after administration of 10 mg/kg body weight and 2–6 h after administration of 100 mg/kg body weight. This delay in achieving peak blood concentrations is likely to reflect saturation of absorption at higher doses. Elimination occurs primarily in the faeces (70–90%) via the bile, and <10% was recovered from urine. Most of the administered radiolabel was recovered within 24 h. The half-times for spinosyn A and D radiolabel were 25–42 h and 29–33 h, respectively. A large proportion of the material excreted in the faeces had been absorbed and eliminated in the bile, primarily as glutathione conjugates of N- and O-

¹ After FAO/WHO (2002). The interested reader should consult this reference for more detailed information and primary references.

demethylated spinosyns A and D. Excretion as exhaled $^{14}\text{CO}_2$ was negligible. The highest concentrations of tissue residues were identified in fat, liver, kidneys and lymph nodes. Although the concentrations in the thyroid were not high in comparison with those in many other tissues shortly after administration of spinosyn A or D, the rate of decline was slow and ultimately resulted in higher concentrations in the thyroid than in other tissues, where the decline was more rapid. Absorbed spinosyn A and D were extensively biotransformed, with glutathione conjugates of *N*- or *O*-demethylated spinosyn A or D as the predominant metabolites.

Technical-grade spinosad had little acute toxicity after oral or dermal administration or inhalation; the median lethal dose (LD_{50}) values after oral administration were consistently >2000 mg/kg body weight and generally ≥ 5000 mg/kg body weight in rats and mice. In one study, however, four of five male rats died after administration of 5000 mg/kg body weight by gavage. The LD_{50} in rabbits treated dermally was >5000 mg/kg body weight, and the median lethal concentration (LC_{50}) after inhalation in rats was >5.2 mg/l.

Spinosad was not irritating to the skin of rabbits and not sensitizing to the skin of guinea-pigs. It caused slight eye irritation in rabbits, which resolved within 48 h.

An extensive range of effects was observed in both short-term and long-term studies with repeated doses, and the effects were similar in mice, rats and dogs. In short-term studies in mice, rats and dogs, tissue vacuolation was a consistent observation at the lowest-observed-adverse-effect level (LOAEL). In mice, the overall no-observed-adverse-effect level (NOAEL) in the 90-day study was 6 mg/kg body weight per day, and increased liver weight was also observed at the LOAEL. In rats, the overall NOAEL was 8.6 mg/kg body weight per day in three 90-day studies and 21 mg/kg body weight per day in two 28-day studies, with increased liver weights again observed at the LOAEL in the 90-day studies. In dogs, the LOAEL in a 28-day study was the lowest dose tested, 6.5 mg/kg body weight per day; the NOAEL in a 90-day study was 4.9 mg/kg body weight per day; and the NOAEL in a 12-month study was 2.7 mg/kg body weight per day. Increased thyroid weights were observed in the 28- and 90-day studies in dogs at doses at and above the LOAEL, in addition to tissue vacuolation. In dogs, however, the lymphatic system was more sensitive to vacuolation than the thyroid, the lymphatic lesions occurring at the LOAEL in both the 90-day and 12-month studies.

In long-term studies in mice and rats, tissue vacuolation and other histological alterations were again observed at doses at and above the LOAEL. In mice, the lungs, lymph nodes, stomach and tongue were the main organs affected at doses above the NOAEL of 11 mg/kg body weight per day. The main histological findings were chronic inflammation, hyperplasia and hyperkeratosis of the stomach, vacuolation of the parathyroid, pancreas, ovaries and epididymal epithelial cells, and myopathy of the tongue. In rats, the NOAEL in the 2-year study was 2.4 mg/kg body weight per day. The primary organ affected at the LOAEL of 9.5 mg/kg body weight per day was the thyroid; the lungs, liver, larynx and bone marrow were affected at higher doses. Vacuolation was limited to the epithelial cells of the thyroid gland, and inflammation was observed in the thyroid, lung and larynx. Bone marrow hyperplasia and slight dilatation of liver sinusoids were also observed.

Strong similarities in other toxic effects were found between species and in the short- and the long-term studies. At the higher doses used, spinosad was toxic in multiple organs of mice, rats and dogs, resulting in increased serum activity of liver, muscle and cardiac enzymes (alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase and creatinine phosphokinase), microcytic hypochromic anaemia and increased spleen, thyroid and liver weights. The histological alterations in a wide range of organs were similar in all species tested, the predominant lesions being cellular vacuolation, inflammatory changes (including necrosis), histiocytosis, regenerative and degenerative changes, increased haematopoiesis and skeletal myopathy. In the long-term study in rats, the thyroid was the most sensitive organ overall, effects occurring at lower doses than in other organs and resolving more slowly after withdrawal of treatment.

Vacuolation in the thyroid, the most sensitive toxicological end-point overall, was seen in both short- and long-term studies in rats and was reversible in two studies: a 28-day study in males fed diets containing concentrations equal to doses of 120 mg/kg body weight per day and a 13-week study in rats of each sex fed diets containing concentrations of 40–50 mg/kg body weight per day.

Selected tissues from rats and mice in the short-term studies of toxicity were examined by electron microscopy, and the vacuolation was found to be associated with cytoplasmic lamellar inclusion bodies, reflecting a lysosomal storage disorder. While such disorders may arise through a variety of mechanisms that prevent degradation of cell constituents that are usually processed in the lysosomes, spinosad probably acts mainly through a physicochemical mechanism associated with its cationic amphiphilic structure (having both lipophilic and hydrophilic properties in one molecule).

A comparison of spinosad, spinosyn A and spinosyn D in a 28-day study in rats treated in the diet revealed notable differences in the toxicological profiles of spinosyn A and D. The toxicological effects of spinosyn A were closely similar to those of spinosad, but spinosyn D failed to produce most of the haematological and clinical chemical alterations seen with spinosad or spinosyn A. Consequently, minor variations in the relative proportions of spinosyn A and D in the technical-grade active ingredient are unlikely to alter its toxicological profile significantly.

In long-term studies in mice and rats treated in the diet at doses up to 51 and 49 mg/kg body weight per day, respectively, there was no evidence that spinosad is carcinogenic.

Spinosad gave negative results in an adequate range of assays for genotoxicity in vivo and in vitro. The Meeting concluded that spinosad is not genotoxic.

Given the absence of both genotoxicity in appropriate short-term tests and carcinogenicity in long-term studies in rats and mice, the Meeting concluded that spinosad is unlikely to pose a carcinogenic risk to humans.

The reproductive toxicity of spinosad was investigated in a two-generation study in rats. The reproductive effects, a reduced number of pups per litter and clinical alterations in F_{1a} and F₂ pups, reported only at a dietary concentration adjusted to

deliver a constant dose of 100 mg/kg body weight per day, the highest dose tested, were attributed to nonspecific parental toxicity rather than to a specific toxic effect on the reproductive system. A reduction in the number of pups per litter was observed in each of three generations of pups at 100 mg/kg body weight per day. As a similar finding was not observed at 200 mg/kg body weight per day in the study of developmental toxicity in rats, the reduction in pup number per litter may reflect preimplantation losses. The NOAEL for reproductive toxicity was 10 mg/kg body weight per day.

In a study of developmental toxicity in rats, dams were given doses up to 200 mg/kg body weight per day. Slightly reduced maternal body weight gain was observed at the highest dose. Unilateral microphthalmia was found at external examination in two fetuses in separate litters at 200 mg/kg body weight per day and in one at 50 mg/kg body weight per day. Although this is a rare spontaneous malformation in rats, it was discounted as a cluster effect incidental to treatment, for two reasons. First, a similar incidence of this malformation occurred randomly in control and other groups in studies conducted in the same laboratory with the same strain of rat over a number of years; second, it occurred in the absence of the other developmental effects that normally accompany a treatment-related increase in the incidence of malformation. The absence of ocular malformations in the study of reproductive toxicity at doses up to 100 mg/kg body weight per day provides further support for this conclusion. On this basis, the NOAEL for maternal toxicity in rats was 50 mg/kg body weight per day, and that for developmental toxicity was 200 mg/kg body weight per day, the highest dose tested. In a study of developmental toxicity in rabbits, the does were given spinosad on days 7–19 of gestation at doses of 50 mg/kg body weight per day, with no evidence of embryo or fetal effects, despite maternal toxicity, consisting of weight loss, abortion and clinical signs at the highest dose. The NOAEL for maternal toxicity was 10 mg/kg body weight per day, and that for embryo and fetal toxicity was 50 mg/kg body weight per day, the highest dose tested.

Neurotoxicity was investigated in rats by giving them a single dose of 2000 mg/kg body weight, doses of 43 mg/kg body weight per day for 3 months, or doses of 49 mg/kg body weight per day for 12 months. Comprehensive behavioural and histopathological investigations revealed no evidence of neurotoxicity.

JMPR concluded that the existing database was adequate to characterize the potential hazards of spinosad to fetuses, infants and children.

The most sensitive overall toxicological end-point was thyroid vacuolation in rats treated in the diet in the 2-year study of toxicity and carcinogenicity. The Meeting established an acceptable daily intake (ADI) of 0–0.02 mg/kg body weight on the basis of the NOAEL of 2.4 mg/kg body weight per day in this study and a 100-fold safety factor.

Spinosad has little acute toxicity. In studies with repeated doses, no acute toxicological alerts were observed that might indicate the need for establishing an acute reference dose.

4. USE FOR VECTOR CONTROL IN DRINKING-WATER SOURCES

Spinosad DT 7.48% has been approved for use as a larvicide under WHOPES at 0.25–0.5 mg/l active ingredient for the control of *Aedes aegypti* in drinking-water containers. The formulation approved for this purpose is a slow-release tableted formulation designed to provide an expected duration of efficacy under field conditions of 4–6 weeks.

A study was conducted by the manufacturer in which a single tablet was added to a 200-litre container of water and this container was replenished with 10% of water each day of the study, which lasted 14 days. The concentration of spinosad was found to be in the range 26.5–51.7 µg/l (Clarke Mosquito Control, 2006).

5. CONCLUSIONS

It is not appropriate to set a formal guideline value for spinosad DT for use to control vectors breeding in drinking-water containers; however, it is appropriate to determine the probable intakes with the ADI. Spinosad DT 7.48% has been approved for use as a larvicide under WHOPES with an application rate of 0.25–0.5 mg/l active ingredient for the control of *Aedes aegypti* in drinking-water containers with an expected duration of efficacy under field conditions of 4–6 weeks.

The ADI for spinosad is 0.02 mg/kg body weight (20 µg/kg body weight) (FAO/WHO, 2002), with no acute reference dose set because of its low acute toxicity. Although spinosad at the approved application rate could apparently exceed the ADI for children and infants, the use of a slow-release tablet formulation means that this would not be possible. The maximum concentration actually achieved with the slow-release formulation was approximately 52 µg/l. The intake would therefore be:

- 39 µg for a 5 kg bottle-fed infant assuming consumption of 0.75 litre = 7.8 µg/kg body weight
- 52 µg/l for a 10 kg child assuming consumption of 1 litre = 5.2 µg/kg body weight
- 104 µg for a 60 kg adult assuming consumption of 2 litres = 1.7 µg/kg body weight. However, this could be higher if drinking-water consumption is also higher.

This means that the exposure is well below the ADI for all sectors of the population. Even the application of a double dose would result in exposure below the ADI.

The ADI is, of course, set for lifetime, and the average exposure over time will be lower than the exposures indicated above.

6. RECOMMENDATIONS

WHO specifications for formulations, unless otherwise stated, encompass the products of all formulators legitimately able to certify that their products contain only active ingredient sourced from a manufacturer to whom the WHO specification for technical material/technical concentrate applies. Buyers and/or regulatory authorities

should demand such certification and ensure both that it is valid and that the products fully comply with the physical and chemical requirements of the WHO specifications. The safety of the formulants used in making the final product should be considered by national authorities for products intended for use in potable water.

National authorities, in approving products for use in drinking-water in containers, should ensure that any slow-release formulations are appropriate to deliver concentrations of active ingredient below the ADI, taking into account possible exposure from other sources, such as food, and are maintained for the expected duration to be consistent with efficacy.

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, the ADI is unlikely to be exceeded by any group, and, in the event of an exceedance, this does not necessarily mean that adverse effects will result. 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.

7. REFERENCES

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