DATA SHEET ON PESTICIDES

No. 63

NICLOSAMIDE

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CLASSIFICATION:
Primary use: Molluscicide
Secondary use: Anthelmintic, lampricide
Chemical group: Chloronitrophenol derivative
Date issued: March 1988

1.0 GENERAL INFORMATION

1.1 COMMON NAME: niclosamide (BSI, ISO and BPC - exception Germany, niclosamid and clonitralid).

1.1.1 Identity: The active ingredient may be niclosamide (I), or its ethanolamine salt (II), or piperazine salt (III), or niclosamide monohydrate (IV).

IUPAC: (I) 2'5-dichloro-4'-nitrosalicylanilide
      (II) 5-chloro-salicyl-(2-chloro-4-nitro) anilide 2-aminoethanol salt
      (III) 5-chloro-salicyl-(2-chloro-4-nitro) anilide piperazine salt
      (IV) 5-chloro-salicyl-(2-chloro-4-nitro) anilide monohydrate

CAS: (I) 5-chloro-N-(2-chloro-4-nitrophenyl)-2-hydroxybenzamide
     (II) 5-chloro-N-(2-chloro-4-nitrophenyl)-2-hydroxybenzamide with 2-aminoethanol (1:1)
     (III) 5-chloro-N-(2-chloro-4-nitrophenyl)-2-hydroxybenzamide with piperazine (2:1)
     (IV) 5-chloro-N-(2-chloro-4-nitrophenyl)-2-hydroxybenzamide with monohydrate (1:1)

CAS Reg. No.: (I) 50-65-7
              (II) 1420-04-8
              (III) 34892-17-6
              (IV) 7336-56-2

Molecular formula: (I) C_{13}H_8Cl_2N_2O_4
                  (II) C_{15}H_{15}Cl_2N_3O_5
                  (III) C_{30}H_{26}Cl_4N_6O_8
                  (IV) C_{13}H_8Cl_2N_2O_4 \cdot H_2O
Relative molecular mass:

(I) 327.1
(II) 388.2
(III) 740.4
(IV) 345.1

Structural formula:

\[
\begin{align*}
(I) & \quad \text{OH} & \quad \text{C} & \quad \text{NH} & \quad \text{C} & \quad \text{NO}_2 \\
& \quad \text{Cl} & \quad \text{Cl} & \quad \text{Cl} & \quad \text{Cl}
\end{align*}
\]

\[
\begin{align*}
(II) & \quad \text{OH} & \quad \text{C} & \quad \text{NH} & \quad \text{NO}_2 \cdot \text{H}_2\text{N} - (\text{CH}_2)_2 - \text{OH} \\
& \quad \text{Cl} & \quad \text{Cl} & \quad \text{Cl} & \quad \text{Cl}
\end{align*}
\]

\[
\begin{align*}
(III) & \quad \text{OH} & \quad \text{C} & \quad \text{NH} & \quad \text{NO}_2 \cdot \text{HN} & \quad \text{NH} \\
& \quad \text{Cl} & \quad \text{Cl} & \quad \text{Cl} & \quad \text{Cl}
\end{align*}
\]

\[
\begin{align*}
(IV) & \quad \text{OH} & \quad \text{C} & \quad \text{NH} & \quad \text{NO}_2 \cdot \text{H}_2\text{O} \\
& \quad \text{Cl} & \quad \text{Cl} & \quad \text{Cl} & \quad \text{Cl}
\end{align*}
\]

1.1.2 Synonyms: Bayer 73R; Bayer 2353R; Bayer 25 648R; BayluscidR; BayluscideR; CestocidR; Clonitralid; DichlosalR; FenosalR; HL 2447R; IomesanR, IomezanR; LintexR; ManosilR; NasemoR; NiclosamidR; Niclosamide, PhenosalR; TredemineR; SulquirR; VermitidR; VermitinR; YomesanR.

1.2 SYNOPSIS: Niclosamide is a relatively selective, non-cumulative chlorinated aromatic amide pesticide; principally used against aquatic snails but also as an antiparasitic drug in human and veterinary medicine. It is of very low toxicity to mammals (WHO Hazard Class III, table 5), can be toxic to aquatic vertebrates (e.g. fish and amphibians) and crustaceans. Niclosamide is non-persistent in the aquatic environment, has a slight effect on aquatic plants and zooplankton but is not generally phytotoxic at field concentrations.
1.3 SELECTED PROPERTIES

1.3.1 Physical characteristics: Niclosamide is a yellowish grey odourless crystalline solid which melts between 224-229 °C. The piperazine salt melts above 240 °C with decomposition. The ethanolamine salt form is a yellow solid melting at minimum 191 °C.

1.3.2 Solubility: Niclosamide is not very water soluble, 5-8 mg/L at 20 °C, sparingly soluble in ether, ethanol and chloroform, and soluble in acetone; the ethanolamine salt dissolves in distilled water 180-280 mg/L at 20 °C.

1.3.3 Stability: In tablets niclosamide undergoes a biodegradation in moist environments but niclosamide itself is stable in an aqueous solution for several months. The ethanolamine salt is stable to heat, hydrolysed by concentrated acid or alkali, and stable in aquatic environments.

1.3.4 Vapour pressure: <1 mPa at 20 °C

1.4 AGRICULTURE, HORTICULTURE AND FORESTRY

1.4.1 Common formulations: These include an emulsifiable concentrate at 250 g a.i./L, a wettable powder at 700 g a.i. (of ethanolamine salt)/kg, and tablets of various dosages up to 1 105 mg of a.i. These tablets are available only on a restricted basis in many countries.

1.4.2 Pests controlled: Niclosamide is used effectively against molluscs (especially fresh water snails), and cestode and trematode infestations of humans, livestock, and pets.

1.4.3 Unintended effects: Niclosamide is toxic to all fish species at 0.5 mg/L (48 hours), and to zooplankton and aquatic vegetation at high concentrations.

1.5 PUBLIC HEALTH

1.5.1 Common formulations: As in 1.4.1 above.

1.5.2 Pests controlled: Niclosamide is used effectively against fresh water snails that are intermediate hosts for schistosomiasis and fascioliasis. It has also been used in the control of cestodes infecting man.

1.5.3 Use pattern - For environmental applications against snails 0.6-1.0 mg/L is effective. In humans over the age of eight, two oral doses of 1 g each, one hour apart for five successive days are usually effective against dwarf tapeworm in individuals six years old and over, and 500 mg for younger children. In veterinary medicine single doses ranging from 83-500 mg/kg are recommended.

1.5.4 Unintended effects: Occasional gastrointestinal upset is the only side effect reported.
2.0 TOXICOLOGY AND RISKS

2.1 TOXICOLOGY - MAMMALS

2.1.1 Absorption: Niclosamide is slowly absorbed from the gastrointestinal tract, and through the skin or mucous membranes.

2.1.2 Mode of action: In in vitro studies, niclosamide inhibited rat liver mitochondrial synthesis of ATP.

2.1.3 Excretion products: When oral doses of niclosamide ethanolamine salt were given to male rats, one third of the applied dose was absorbed from the gastrointestinal tract. Excretion of this portion occurred within 24 hours via urine (T 1/2 was six hours). The remaining two thirds of the administered dose was excreted in the faeces. The major excretion product was 2,5'-dichloro-4'-amino-salicylanilide. In vitro studies showed that mouse and sheep liver enzyme systems could reduce but not hydroxylate niclosamide. Studies done on pregnant rats have shown that foetuses are unable to metabolize niclosamide until more than 13 days old.

2.1.4 Toxicity, single dose

Oral LD50:

Niclosamide:

<table>
<thead>
<tr>
<th>Species</th>
<th>LD50 (mg/kg b.w.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rat (M,F)</td>
<td>5 000</td>
</tr>
<tr>
<td>Mouse (F)</td>
<td>&gt;1 500</td>
</tr>
<tr>
<td>Rabbit</td>
<td>5 000</td>
</tr>
<tr>
<td>Cat</td>
<td>&gt;1 000</td>
</tr>
</tbody>
</table>

Ethanolamine salt:

<table>
<thead>
<tr>
<th>Species</th>
<th>LD50 (mg/kg b.w.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rat (M,F)</td>
<td>10 000</td>
</tr>
<tr>
<td>Rat (M)</td>
<td>5 000</td>
</tr>
<tr>
<td>Rabbit (M,F)</td>
<td>4 000</td>
</tr>
<tr>
<td>Cat (M,F)</td>
<td>500</td>
</tr>
</tbody>
</table>

Piperazine salt:

<table>
<thead>
<tr>
<th>Species</th>
<th>LD50 (mg/kg b.w.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rat</td>
<td>5 000</td>
</tr>
<tr>
<td>Mouse (M)</td>
<td>1 000</td>
</tr>
<tr>
<td>Cat</td>
<td>1 000</td>
</tr>
<tr>
<td>Dog</td>
<td>1 000</td>
</tr>
</tbody>
</table>

Niclosamide monohydrate:

<table>
<thead>
<tr>
<th>Species</th>
<th>LD50 (mg/kg b.w.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rat (M)</td>
<td>5 000</td>
</tr>
<tr>
<td>Mouse (M,F)</td>
<td>10 000</td>
</tr>
</tbody>
</table>
**Dermal LD$_{50}$:**

Rat (F) $2000$ mg/kg b.w. (700 g/kg w.p.)

**Intraperitoneal LD$_{50}$:**

Rat (M) $44-250$ mg/kg b.w. (ethanolamine salt)

**Intravenous LD$_{50}$:**

Rat (M) $7$ mg/kg b.w. (ethanolamine salt)

In studies on dogs and cats given niclosamide intraperitoneally or intravenously, animals were seen to vomit as a result of niclosamide poisoning.

**Inhalation LD$_{50}$:**

Rat (M,F) $2270$ mg/m$^3$/hr (ethanolamine salt)

Rat (M,F) $>260$ mg/m$^3$/4 hr (700 g/kg w.p.)

Symptoms of poisoning were non-specific, and consisted of behavioural disturbances, hypopnea and convulsions.

**Ocular irritation:** Testing in rabbits revealed that the ethanolamine salt, $700$ g/kg w.p. and $250$ g/kg emulsion concentrate had strong irritative effects upon the mucous membranes of the eye. They were also found to be corrosive to the cornea.

**Toxicity, repeated doses**

**Oral:** A marginal decrease in haemoglobin concentration and erythrocyte count occurred when male and female rats were given niclosamide at $5000$ mg/kg/day for four weeks. The no-effect level was $2000$ mg/kg/day. No effects were seen on cats in two studies for up to four weeks with dose levels of niclosamide up to $900$ mg/kg/day.

Male and female dogs treated with niclosamide showed no toxic effects at doses up to $4500$ and $6000$ mg/day for four weeks.

**Dermal:** No evidence of toxicity was seen in rats treated with niclosamide at $200$ mg/kg/day for three weeks.

**Dietary Studies**

**Short term:** No effects were seen in rats fed on a diet containing $5$ or $15$ ppm niclosamide ethanolamine salt for $90$ days. Reduction in weight was seen in male rats fed on a diet containing $10000$ or $25000$ ppm of niclosamide for $326$ or $319$ days. No effects were seen in female rats similarly dosed. Rats fed on a diet containing $2000-20000$ ppm of niclosamide for $14$ weeks showed no effects at any dose level. Male rats given niclosamide $1000$ or $2500$ mg/kg/day for $55$ or $64$ days, followed by feeding on a diet containing $10000$ or $25000$ ppm niclosamide for the remainder of $365-381$ days, had reduced body weights in the high dose group. No other damage was observed at either dose.
No effects were seen in dogs fed niclosamide or niclosamide ethanolamine salt 100 mg/kg/day for one year.

**Long term**: No published information available.

### 2.1.7 Supplementary studies of toxicity

**Carcinogenicity**: Male and female rats and female mice developed no carcinomas when administered the niclosamide ethanolamine salt in feed at dose levels of 14 216-28 433 ppm and 274-549 ppm respectively. Poor survival of male mice did not permit evaluation of carcinogenic potential of niclosamide in these animals.

**Teratogenicity**: No embryotoxic or teratogenic effects were seen after doses of 1 000 mg/kg/day on gestation days 7-10, 10-12, or 13-16. Likewise, no teratogenic or embryotoxic effects were seen in rats treated orally with a dose of 1 000 mg/kg/day on days 4-6, 7-9, or 10-12.

**Mutagenicity**: No indication of mutagenic potential was seen in the progeny of mice subjected to a dominant lethal test with niclosamide ethanolamine salt. Likewise no mutagenic potential was seen in an Ames test without metabolic activation while slight mutagenic effects were seen with metabolic activation in *Salmonella typhimurium*. Both of the above studies used the ethanolamine salt.

**Other Studies**: Studies on goats, one heifer and sheep showed no toxic effects of orally applied niclosamide except some temporary diarrhoea in goats. An increased rate of absorption and somewhat decreased rate of excretion was found to occur in the ruminants as compared with laboratory animals, but this had no effect on the toxicity of niclosamide.

### 2.1.8 Modifications of toxicity: No information available.

### 2.2 TOXICOLOGY — MAN

#### 2.2.1 Absorption route: Niclosamide is absorbed from the gastrointestinal tract, through the skin or by Inhalation of fine dust or mist.

#### 2.2.2 Dangerous doses: No information available.

#### 2.2.3 Observations on occupationally exposed workers: Skin reactions have occasionally been reported in field workers applying the 250 g/L emulsion concentrate. Skin reactions were not thought to be caused by niclosamide itself but by other formulation ingredients.

#### 2.2.4 Observations on exposure of the general population: No information available.

#### 2.2.5 Observations on volunteers: Nausea and abdominal pain occurred in about 10% of patients following oral dosage. Single oral doses of 2 000 mg niclosamide (radiolabelled) given to male and female volunteers showed that 2-25% of the compound was excreted in urine over four days, with the rest being eliminated with the faeces. Maximum serum concentrations ranged from 0.25-0.60 μg/ml and metabolites were excreted in the form of glucuronide conjugates. These included...
niclosamide, 2',5-dichloro-4'-aminosalicylanilide, and 2',5-dichloro-4'-acetaminosalicylanilide. No signs of intoxication were noted in adult males or females treated once or twice with niclosamide at 1 000 mg/person, or in children treated with 750-1 000 mg/person. Dermal applications had no sensitizing effects on individuals suffering from a photoallergy to tribromosalicylanilide. No methemoglobin formation was observed in males treated orally with 30 mg niclosamide/kg b.w.

2.2.6 Reported mishaps: No information available.

2.3 TOXICITY TO NON MAMMALIAN SPECIES

2.3.1 Fish: Niclosamide is toxic to fish and zooplankton, LC₅₀ being 0.05 mg/L (during 24-48 hours); carbaryl potentiates its toxicity in rainbow trout.

2.3.2 Birds: Ducklings treated orally with 100 mg niclosamide/bird showed no toxic effects.

Oral LD₅₀ (technical material):
- Red-winged blackbird >60 mg/kg b.w. (in the feed for 18 days)
- Mallard >2000 mg/kg b.w. (single dose)
- Ringbilled duck 500 mg/kg b.w. (single dose)

2.3.3 Others: Niclosamide is toxic to crayfish, frogs, clams, and other aquatic organisms. It is not harmful to bees if applied as recommended.

3.0 FOR REGULATORY AUTHORITIES - RECOMMENDATIONS ON REGULATION OF COMPOUND

3.1 RECOMMENDED RESTRICTIONS ON AVAILABILITY (For definition of categories see Introduction to Data Sheets)

All available formulations, category 5

3.2 TRANSPORT AND STORAGE

Formulations in Category 5: Should be transported and stored in clearly labelled, leakproof containers out of reach of children, away from food and drink.

3.3 HANDLING

Formulations in Category 5: No facilities other than those needed for the handling of any other chemical are required.
3.4 DISPOSAL AND/OR DECONTAMINATION OF CONTAINERS

Formulations in Category 5: Containers may be decontaminated but should never be used for food or water (for method see paragraph 4.3). If to be disposed of, containers should be burned or crushed and buried below topsoil, away from water sources.

3.5 SELECTION, TRAINING AND MEDICAL SUPERVISION OF WORKERS

Formulations in Category 5: No pre-employment or periodic medical examinations are required. Special account should be taken of the workers' ability to comprehend and follow instructions. Training of workers in techniques to avoid contact is essential.

3.6 ADDITIONAL REGULATIONS RECOMMENDED IF DISTRIBUTED BY AIRCRAFT

All formulations: For non-aquatic field applications, pilots and loaders should have special training in application methods. Flagmen should wear overalls and a broad brimmed hat, they should be well away from the dropping zone.

3.7 LABELLING

Formulations in Category 5 - Minimum cautionary statement:

CAUTION - POISON

This product contains niclosamide, a molluscicide and anthelmintic of low toxicity to mammals but no significant hazard to human health. Very small amounts are absorbed by ingestion. As a drug it should be taken only on the advice of a physician. Avoid excessive skin contact. Wash with soap and water after handling. Store in a tightly closed container out of reach of children and well away from food, animal feed and food utensils. If a large quantity is ingested call a physician. There is no specific antidote, if illness follows exposure, treatment must be symptomatic.

3.8 RESIDUES IN FOOD: Niclosamide has never been evaluated by the FAO/WHO Joint Meeting on Pesticide Residues in Food and no maximum residue limits in food have been determined.

4.0 PREVENTION OF POISONING IN MAN AND EMERGENCY AID

4.1 PRECAUTIONS IN USE

4.1.1 General: Niclosamide is a molluscicide and anthelmintic of low toxicity to mammals. It can be absorbed from the gastrointestinal tract to a very limited extent only. It is a metabolic poison of no known health hazard to man; therapeutically it is useful against cestoda in humans.

4.1.2 Manufacture and formulations: For T.L.V. no information available.

Closed systems and forced ventilation may be required to reduce, as much as possible, the exposure of workers to the chemical, because of its initiative properties.
4.1.3 Mixers and applicators: When opening a container and when mixing, protective impermeable boots, clean overalls, and impermeable gloves should be worn. Mixing, if not mechanical, should always be carried out with a paddle of appropriate length. Avoid contact with mouth, eyes and skin. Before eating, drinking or smoking, hands and other exposed skin should be thoroughly washed.

4.1.4 Other associated workers (including flagmen in aerial operations):

Persons exposed to niclosamide and associated with its application should observe the precautions described above in 4.1.3.

4.1.5 Other populations likely to be affected: Other populations are not likely to be exposed to hazardous amounts of niclosamide.

4.2 ENTRY OF PERSONS INTO TREATED AREAS: No restriction necessary.

4.3 SAFE DISPOSAL OF CONTAINERS AND SPILLAGE: Residues in containers should be emptied in a diluted form into a deep pit taking care to avoid contamination of ground waters. The empty container may be decontaminated by rinsing two or three times with water and detergent and scrubbing the sides. The hands should be protected during this work. Decontaminated containers should not be used for food or drinking water.

4.4 EMERGENCY AID

4.4.1 Early symptoms of poisoning: Niclosamide has apparently not caused human poisoning and has been used in man for therapeutic reasons. Nausea, abdominal pains and vomiting are infrequent side effects in anthelmintic therapy.

4.4.2 Treatment before person is seen by a physician, if symptoms appear following exposure: The person should stop work immediately, remove any contaminated clothing and clean affected skin area. If a large quantity of material was swallowed and signs of toxicity are apparent, induce vomiting if person is conscious avoiding aspiration of vomit.

5.0 FOR MEDICAL AND LABORATORY PERSONNEL

5.1 MEDICAL DIAGNOSIS AND TREATMENTS OF POISONING

5.1.1 General information: Niclosamide is a molluscicide and anthelmintic with no known toxic effect in man. It may be absorbed by ingestion to a limited extent, and is frequently prescribed for cestode infection in humans. (See Review: Andrews, P., Thyssen, J. and Lorke, D., (1983) Pharm. Ther., 19, 245-295.)

5.1.2 Signs and symptoms - No information is available on the acute toxic effects; nausea, abdominal cramps and vomiting are infrequent side effects in anthelmintic therapy.
5.1.3 Laboratory: Methods for determining primary metabolite levels or the native compound in body fluids or urine have been developed (see references).

5.1.4 Treatment: Follow treatment for general poisoning. In case of eye exposure decontaminate with copious amounts of water.

5.1.5 Prognosis: Unknown.

5.1.6 References to previously reported cases: There have been no previously reported cases.

5.2 SURVEILLANCE TESTS - None.

5.3 LABORATORY METHODS

5.3.1 Detection and assay of compound and residues: In water and sediment samples GC or HPLC methods can be used:


5.3.2 Methods for determining the native compound in body fluids or urine


5.3.3 Other tests in case of poisoning: None