FAO SPECIFICATIONS AND EVALUATIONS
FOR AGRICULTURAL PESTICIDES

CLOFENETZINE

3,6-bis(2-chlorophenyl)-1,2,4,5-tetrazine

2007

Food and Agriculture Organization of the United Nations
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DISCLAIMER

FAO specifications are developed with the basic objective of promoting, as far as practicable, the manufacture, distribution and use of pesticides that meet basic quality requirements.

Compliance with the specifications does not constitute an endorsement or warranty of the fitness of a particular pesticide for a particular purpose, including its suitability for the control of any given pest, or its suitability for use in a particular area. Owing to the complexity of the problems involved, the suitability of pesticides for a particular purpose and the content of the labelling instructions must be decided at the national or provincial level.

Furthermore, pesticides which are manufactured to comply with these specifications are not exempted from any safety regulation or other legal or administrative provision applicable to their manufacture, sale, transportation, storage, handling, preparation and/or use.

FAO disclaims any and all liability for any injury, death, loss, damage or other prejudice of any kind that may arise as a result of, or in connection with, the manufacture, sale, transportation, storage, handling, preparation and/or use of pesticides which are found, or are claimed, to have been manufactured to comply with these specifications.

Additionally, FAO wishes to alert users to the fact that improper storage, handling, preparation and/or use of pesticides can result in either a lowering or complete loss of safety and/or efficacy.

FAO is not responsible, and does not accept any liability, for the testing of pesticides for compliance with the specifications, nor for any methods recommended and/or used for testing compliance. As a result, FAO does not in any way warrant or represent that any pesticide claimed to comply with a FAO specification actually does so.

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1 This disclaimer applies to all specifications published by FAO.
INTRODUCTION

FAO establishes and publishes specifications* for technical material and related formulations of agricultural pesticides, with the objective that these specifications may be used to provide an international point of reference against which products can be judged either for regulatory purposes or in commercial dealings.

From 2002, the development of WHO specifications follows the New Procedure, described in the 1st edition of “Manual for Development and Use of FAO and WHO Specifications for Pesticides” (2002) and amended with the supplement of this manual (2006), which is available only on the internet through the FAO and WHO web sites. This New Procedure follows a formal and transparent evaluation process. It describes the minimum data package, the procedure and evaluation applied by FAO and the Experts of the FAO/WHO Joint Meeting on Pesticide Specifications (JMPS). [Note: prior to 2002, the Experts were of the FAO Panel of Experts on Pesticide Specifications, Registration Requirements, Application Standards and Prior Informed Consent, which now forms part of the JMPS, rather than the JMPS.]

FAO Specifications now only apply to products for which the technical materials have been evaluated. Consequently from the year 2000 onwards the publication of FAO specifications under the New Procedure has changed. Every specification consists now of two parts namely the specifications and the evaluation report(s):

**PART ONE: The Specification** of the technical material and the related formulations of the plant protection product in accordance with chapter 4, 5 and 6 of the 5th edition of the “Manual on the development and use of FAO specifications for plant protection products”.

**PART TWO: The Evaluation Report(s)** of the plant protection product reflecting the evaluation of the data package carried out by FAO and the JMPS. The data are to be provided by the manufacturer(s) according to the requirements of Appendix A, annex 1 or 2 of the “Manual on the development and use of FAO specifications for plant protection products” and supported by other information sources. The Evaluation Report includes the name(s) of the manufacturer(s) whose technical material has been evaluated. Evaluation reports on specifications developed subsequently to the original set of specifications are added in a chronological order to this report.

FAO specifications under the New Procedure do not necessarily apply to nominally similar products of other manufacturer(s), nor to those where the active ingredient is produced by other routes of manufacture. FAO has the possibility to extend the scope of the specifications to similar products but only when the JMPS has been satisfied that the additional products are equivalent to that which formed the basis of the reference specification.

Specifications bear the date (month and year) of publication of the current version. Dates of publication of the earlier versions, if any, are identified in a footnote. Evaluations bear the date (year) of the meeting at which the recommendations were made by the JMPS.

PART ONE

SPECIFICATIONS

CLOFENTEZINE

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INFORMATION

ISO common names
Clofentezine (ANSI, BSI, E-ISO, F-ISO)

Synonyms
None

Chemical names
- IUPAC: 3,6-bis(2-chlorophenyl)-1,2,4,5-tetrazine
- CA: 3,6-bis(2-chlorophenyl)-1,2,4,5-tetrazine

Structural formula

Empirical formula
\( \text{C}_{14}\text{H}_8\text{Cl}_2\text{N}_4 \)

Relative molecular mass
303.1

CAS Registry number
74115-24-5

CIPAC number
418

EEC Number
277-728-2

Identity tests
HPLC-UV (235 nm) retention time; IR spectrum
1 Description

The material shall consist of clofentezine, together with related manufacturing impurities, and shall be a magenta crystalline solid, free from visible extraneous matter and added modifying agents or stabilizers.

2 Active ingredient

2.1 Identity tests (418/TC/M/2, CIPAC Handbook G, p.18, 1995)

The active ingredient shall comply with an identity test and, where the identity remains in doubt, shall comply with at least one additional test.

2.2 Clofentezine content (418/TC/M/3, CIPAC Handbook G, p.18, 1995)

The clofentezine content shall be declared (not less than 980 g/kg) and, when determined, the average measured content shall not be lower than the declared minimum content.

* Specifications may be revised and/or additional evaluations may be undertaken. Ensure the use of current versions by checking at: http://www.fao.org/pest-and-pesticide-management/en/
CLOFENTEZINE AQUEOUS SUSPENSION CONCENTRATE

FAO specification 418/SC (April 2007*)

This specification, which is PART ONE of this publication, is based on an evaluation of data submitted by the manufacturer whose name is listed in the evaluation report (418/2006). It should be applicable to relevant products of this manufacturer, and those of any other formulators who use only TC from the evaluated source. The specification is not an endorsement of those products, nor a guarantee that they comply with the specification. The specification may not be appropriate for the products of other manufacturers who use TC from other sources. The evaluation report (418/2006), as PART TWO, forms an integral part of this publication.

1 Description

The material shall consist of a suspension of fine particles of technical clofentezine, complying with the requirements of FAO specification 418/TC (April 2007), in an aqueous phase together with suitable formulants. After gentle agitation the material shall be homogeneous (Note 1) and suitable for further dilution in water.

2 Active ingredient

2.1 Identity tests (418/SC/M/2, CIPAC Handbook G, p.18, 1995)

The active ingredient shall comply with an identity test and, where the identity remains in doubt, shall comply with at least one additional test.

2.2 Clofentezine content (418/SC/M/3, CIPAC Handbook G, p.18, 1995)

The clofentezine content shall be declared (g/kg or g/l at 20 ± 2°C, Note 2) and, when determined, the average content measured shall not differ from that declared by more than the following tolerances:

<table>
<thead>
<tr>
<th>Declared content in g/kg or g/l at 20 ± 2°C</th>
<th>Tolerance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Above 100 up to 250</td>
<td>± 6% of the declared content</td>
</tr>
<tr>
<td>Above 250 up to 500</td>
<td>± 5% of the declared content</td>
</tr>
</tbody>
</table>

Note: the upper limit is included in each range.

3 Physical properties

3.1 pH range (MT 75.3, CIPAC Handbook J, p.131, 2000)

The pH shall be in the range 6.0 to 7.5.


Maximum “residue”: 2%.

* Specifications may be revised and/or additional evaluations may be undertaken. Ensure the use of current versions by checking at: http://www.fao.org/pest-and-pesticide-management/en/
3.3 **Spontaneity of dispersion** (MT 160, CIPAC Handbook F, p.391, 1995) (Note 3)
A minimum of 85% of the clofentezine content found under 2.2 shall be in suspension after 5 min in CIPAC standard water D at 30 ± 2°C.

3.4 **Suspen sibility** (MT 184, CIPAC Handbook K, p.142, 2003) (Note 3)
A minimum of 90% of the clofentezine content found under 2.2 shall be in suspension after 30 min in CIPAC standard water D at 30 ± 2°C.

3.5 **Wet sieve test** (MT 185, CIPAC Handbook K, p.148, 2003) (Note 4)
Maximum: 0.1% of the formulation shall be retained on a 75 µm test sieve.

3.6 **Persistent foam** (MT 47.2, CIPAC Handbook F, p.152, 1995) (Note 5)
Maximum: 20 ml after 1 min.

4 **Storage stability**

After storage at 0 ± 2°C for 7 days, the formulation shall continue to comply with the clauses for:
- suspensibility (3.4),
- wet sieve test (3.5).

After storage at 54 ± 2°C for 14 days, the determined average active ingredient content must not be lower than 98%, relative to the determined average content found before storage (Note 6) and the formulation shall continue to comply with the clauses for:
- pH range (3.1),
- pourability (3.2),
- spontaneity of dispersion (3.3),
- suspensibility (3.4),
- wet sieve test (3.5).

---

**Note 1** Before sampling to verify the formulation quality, inspect the commercial container carefully. On standing, suspension concentrates usually develop a concentration gradient from the top to the bottom of the container. This may even result in the appearance of a clear liquid on the top and/or of sediment on the bottom. Therefore, before sampling, homogenize the formulation according to the instructions given by the manufacturer or, in the absence of such instructions, by gentle shaking of the commercial container (for example by inverting the closed container several times). Large containers must be opened and stirred adequately. After this procedure, the container should not contain a sticky layer of non-dispersed matter at the bottom. A suitable and simple method of checking for a non-dispersed sticky layer "cake" is by probing with a glass rod or similar device adapted to the size and shape of the container. All the physical and chemical tests must be carried out on a laboratory sample taken after the recommended homogenization procedure.

**Note 2** Unless homogenization is carried out carefully, it is possible for the sample to become aerated. This can lead to errors in the determination of the mass per millilitre and in calculation of the active ingredient content (in g/l) if methods other than MT 3.3 are used. If
the buyer requires both g/kg and g/l at 20°C, then in case of dispute the analytical results shall be calculated as g/kg.

**Note 3** Chemical assay is the only fully reliable method to measure the mass of active ingredient still in suspension. However, simpler methods such as gravimetric and solvent extraction determination may be used on a routine basis provided that these methods have been shown to give equal results to those of the chemical assay method. In case of dispute, the chemical method shall be the referee method.

**Note 4** This test detects coarse particles (e.g. caused by crystal growth) or agglomerates (crust formation) or extraneous materials which could cause blockage of spray nozzles or filters in the spray tank.

**Note 5** The test should be carried out at the highest application concentration. The test is to be conducted in CIPAC standard water D.

**Note 6** Samples of the formulation taken before and after the storage stability test should be analyzed concurrently after the test in order to reduce the analytical error.
## CLOFENETIZINE

### 2006

<table>
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<th>FAO/WHO evaluation report based on submission of data from Makhteshim Agan Industries Group (TC, SC)</th>
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<tr>
<td>Annex 2: References</td>
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</table>
Recommendation

The Meeting recommended that specifications proposed by Makhteshim Agan Industries Group for clofentezine TC and SC, as amended, should be adopted by FAO.

Appraisal

The meeting considered data on clofentezine, submitted by Makhteshim Agan Industries Group, in support of proposed new FAO specifications for clofentezine TC and SC.

Clofentezine is a magenta-coloured crystalline solid. It has very low solubility in water but is slightly to moderately soluble in organic solvents. It undergoes hydrolysis, the rate of which increases with pH (over the range 4-9). It is susceptible to fairly rapid photolysis. Clofentezine has no acidic or basic properties of practical significance (it is an extremely weak base of estimated pKa = -1.68 but the very low water solubility prevents experimental observation of its protonation).

The meeting was provided with confidential information on the manufacturing process and manufacturing specifications for purity and impurities, which were supported by 5 batch analysis data. Mass balances were 98.9-100.5% and no unidentified impurities were detected. The Meeting questioned whether or not an additional impurity could occur but the manufacturer stated that its absence was ensured through control of the starting materials. A statement was provided by the UK Pesticides Safety Directorate confirming that the confidential data on the manufacturing process and declaration of composition submitted to the FAO were the same as those submitted to the national regulatory authority.

The Meeting agreed that none of the impurities should be designated as relevant.

A full CIPAC analytical method is available for determination of the clofentezine content of the TC and SC.

The proposed specifications for TC and SC were essentially in accordance with the requirements of the manual (FAO/WHO 2006). However, the Meeting questioned the proposed upper limit for the pH range of the SC formulation (7.5), because the supporting data indicated that rapid hydrolysis occurs at pH 8. The company stated that, although hydrolysis is rapid in water, in the SC formulation the active ingredient is stable throughout the proposed range. The Meeting therefore accepted the proposed limits for pH in the SC.
SUPPORTING INFORMATION
FOR
EVALUATION REPORT 418/2006
Uses

Clofentezine is an acaricide, which interferes with cell growth and differentiation during the final stages of embryonic and early larval development. It is used in agriculture for the protection of ornamentals, food and non-food crops in the field, orchards or under glass, against spider mites.

Identity

ISO common names

Clofentezine (ANSI, BSI, E-ISO, F-ISO)

Synonyms

None

Chemical names

IUPAC 3,6-bis(2-chlorophenyl)-1,2,4,5-tetrazine

CA 3,6-bis(2-chlorophenyl)-1,2,4,5-tetrazine

Structural formula

\[
\begin{array}{c}
\text{Cl} \\
\text{Cl}
\end{array}
\]

Empirical formula

\(C_{14}H_8Cl_2N_4\)

Relative molecular mass

303.1

CAS Registry number

74115-24-5

CIPAC number

418

EEC Number

277-728-2

Identity tests

HPLC-UV (235 nm) retention time; IR spectrum
## Physical and chemical properties

### Table 1. Physicochemical properties of pure clofentezine

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
<th>Purity, %</th>
<th>Method</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vapour pressure</td>
<td>6.0 x 10^{-7} Pa at 20°C</td>
<td>99.3</td>
<td>EC Directive 92/69 A4</td>
<td>R-13285</td>
</tr>
<tr>
<td>Melting point</td>
<td>183.4°C (1); 182.1°C (2)</td>
<td>99.3</td>
<td>EC Directive 92/69 A1 Method (1): Differential Scanning Calorimetry (DSC) (2)</td>
<td>R-13283</td>
</tr>
<tr>
<td>Boiling point</td>
<td>Decomposes before boiling</td>
<td>99.3</td>
<td>EC Directive 92/69 A2</td>
<td>R-13283</td>
</tr>
<tr>
<td>Solubility in water at 22°C</td>
<td>2.52 µg/l at pH 5 &lt;2.0 µg/l at pH 7 &lt;2.0 µg/l at pH 9</td>
<td>98.2, radio-purity</td>
<td>Batch equilibration with clofentezine/acetone (99:1)</td>
<td>R-12523</td>
</tr>
<tr>
<td>Octanol:water partition coefficient</td>
<td>Log $P_{ow}$ = 4.1 at 40°C at pH 2, 7 and 9</td>
<td>99.7</td>
<td>EC Directive 92/69 A8, OECD 11 EC Method A8, L251 (1984), OECD 107, shake-flask method Shake-flask method</td>
<td>R-12519</td>
</tr>
<tr>
<td></td>
<td>Log $P_{ow}$ = 4.09 at 25°C</td>
<td>99.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Log $P_{ow}$ = 3.1 at 20°C</td>
<td>Not stated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydrolysis characteristics, half-life, days</td>
<td>10.3 at 22°C at pH 4.95 2.08 at 38°C at pH 4.95 1.43 at 22°C at pH 6.98 0.21 at 38°C at pH 6.98 0.70 at 10°C at pH 9.18 0.18 at 22°C at pH 9.18 1.1 at 25°C at pH 7 0.6 at 35°C at pH 7</td>
<td>&gt;98.4</td>
<td>US EPA Subdiv N Ref. PB83-153973 Sec. 161-1 (1982)</td>
<td>R-12520, R-13318</td>
</tr>
<tr>
<td></td>
<td></td>
<td>99.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Photolysis characteristics, half-life, days, at pH 5.05</td>
<td>Natural sunlight: &lt;7 d Dark control: &gt;31 d Calculated values for 12/12h light/dark cycles:</td>
<td>97.5, 14C-radiopurity</td>
<td>In-house method similar to SETAC except natural light used; Calculation using GCSOLAR program</td>
<td>R-12521, R-13286</td>
</tr>
<tr>
<td></td>
<td>Lat. Spring Summer Fall</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>30°N 0.74 0.71 0.89</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>40°N 0.81 0.74 1.1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>50°N 0.93 0.80 1.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dissociation characteristics</td>
<td>Non-acidic. Very weakly basic, with theoretically calculated pKa of -1.68 (Scifinder Registry), not experimentally measurable due to very low water solubility</td>
<td>-</td>
<td></td>
<td>R-16523</td>
</tr>
</tbody>
</table>
Table 2. Chemical composition and properties of clofentezine technical material (TC)

<table>
<thead>
<tr>
<th>Manufacturing process, maximum limits for impurities ≥ 1 g/kg, 5 batch analysis data.</th>
<th>Confidential information supplied and held on file by FAO. Mass balances were 98.9–100.5%. No unidentified impurities were detected.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Declared minimum clofentezine content:</td>
<td>980 g/kg</td>
</tr>
<tr>
<td>Relevant impurities ≥ 1 g/kg and maximum limits for them:</td>
<td>None</td>
</tr>
<tr>
<td>Relevant impurities &lt; 1 g/kg and maximum limits for them:</td>
<td>None</td>
</tr>
<tr>
<td>Stabilizers or other additives and maximum limits for them:</td>
<td>None</td>
</tr>
<tr>
<td>Melting or boiling temperature range</td>
<td>180-195°C, followed by decomposition in the temperature range 190-250°C</td>
</tr>
</tbody>
</table>

Hazard summary

Clofentezine has been evaluated by the FAO/WHO JMPR for toxicology (JMPR 1986b, 2005) and residues (JMPR 1986a, 1987, 1989, 1990 & 1992). It was scheduled for periodic re-evaluation by FAO/WHO JMPR (toxicology in 2005, residues in 2007). The 1986 JMPR estimated an ADI of 0-0.02 mg/kg bw/d, which was confirmed in 2005 (JMPR 2005). The 2005 JMPR concluded that it was unnecessary to estimate an ARfD, as “clofentezine has low acute toxicity and does not cause developmental toxicity or any other toxicological effect that would be elicited by a single exposure”.

The WHO hazard classification of clofentezine is: U, “unlikely to present acute hazard in normal use” (WHO 2006).

Clofentezine is currently under EU review, according to Council Directive 91/414/EEC (list 3a, UK as Rapporteur Member State). The review has thus far concluded (EU 2005), with respect to a tested formulation, that clofentezine should be classified as follows.

- Human health effects: none.
- Ecotoxicological effects: R52, harmful to aquatic organisms; R53, may cause long-term adverse effects in the aquatic environment.

Clofentezine was evaluated by the US EPA (USEPA 1999) and classified (Makhteshim 2005) as follows.

- Acute oral, dermal and inhalation toxicity: Category III
- Acute eye and skin irritation: Category IV
- Dermal sensitization hazard: Not applicable

With respect to potential carcinogenicity, the US EPA concluded that clofentezine is in Category C (possible human carcinogen) with Q1 as $4.31 \times 10^{-7}$ (well below the level of concern of $1 \times 10^{-5}$).
Formulations and co-formulated active ingredients

The main formulation type available is SC. These formulations are registered and sold in many countries throughout the world, as either 200 or 500 g/l. Clofentezine may be co-formulated with bifenthrin (Torant CL, Percut, containing 200 g/l clofentezine + 40 g/l bifenthrin).

Methods of analysis and testing

The analytical method for determination of the active ingredient (including identity tests), in TC and SC, is a full CIPAC method (CIPAC G). Clofentezine is determined by HPLC, using UV detection at 235 nm and internal standardization.

The methods for determination of impurities are based on HPLC, using UV detection and internal standardization, following calibration with authentic standards.

Test methods for determination of physico-chemical properties of the technical active ingredient were OECD, EPA, EC while those for the SC formulation were CIPAC, as indicated in the specification.

Physical properties

The physical properties, the methods for testing them and the limits proposed for the SC formulation, comply with the requirements of the FAO/WHO manual (FAO/WHO 2006).

Containers and packaging

No special requirements for containers and packaging have been identified.

Expression of the active ingredient

The active ingredient is expressed as clofentezine, in g/kg or g/l in the SC.
ANNEX 1

HAZARD SUMMARY PROVIDED BY THE PROPOSER

Note: Makhteshim Agan Industries Group provided written confirmation that the toxicological and ecotoxicological data included in the following summary were derived from clofentezine having impurity profiles similar to those referred to in Table 2, above.
### Table A. Toxicology profile of clofentezine technical material, based on acute toxicity, irritation and sensitization.

<table>
<thead>
<tr>
<th>Species</th>
<th>Test</th>
<th>Duration, conditions, guideline adopted, purity</th>
<th>Result</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rat (m,f)</td>
<td>Oral</td>
<td>Single oral dose (14-d), in-house method equivalent to 92/69/EEC B.1. Dose levels 0, 800, 1131, 1600, 2261, 3200 mg/kg. Purity 99.0%</td>
<td>LD$_{50}$ &gt;3200 mg/kg bw</td>
<td>R-12815</td>
</tr>
<tr>
<td>Rat (m,f)</td>
<td>Dermal</td>
<td>Single dermal dose (14-d), in-house method equivalent to 92/69/EEC B.3. Dose levels 0, 2100 mg/kg. Purity 99.3%</td>
<td>LD$_{50}$ &gt;2100 mg/kg bw</td>
<td>R-12631</td>
</tr>
<tr>
<td>Rat (m,f)</td>
<td>Inhalation</td>
<td>Single inhalation dose (14-d). US EPA (1978) 43, (163), 37336-37402 equivalent to 92/69/EEC B.2. Dose level 1.51 mg a.i./litre. Purity: 80 WP (77.6-82.4% w/w clofentezine)</td>
<td>LC$_{50}$ &gt;1.51 mg/l</td>
<td>R-12606</td>
</tr>
<tr>
<td>Guinea pig (f)</td>
<td>Skin irritation</td>
<td>Dosing for 24 h, in-house method equivalent to 92/69/EEC B.4. Dose 33.3 mg. Purity 99.1%</td>
<td>Not irritant</td>
<td>R-12600</td>
</tr>
<tr>
<td>Guinea pig (f)</td>
<td>Skin sensitization</td>
<td>In-house method equivalent to 92/69/EEC B.6, M &amp; K. Purity not stated</td>
<td>Not a skin sensitizer</td>
<td>R-12612</td>
</tr>
</tbody>
</table>

### Table B. Toxicology profile of clofentezine technical material based on repeated administration (sub-acute to chronic)

<table>
<thead>
<tr>
<th>Species</th>
<th>Test</th>
<th>Duration, conditions, guideline adopted, purity</th>
<th>Result</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rat (m,f)</td>
<td>Oral</td>
<td>17-d, in-house method equivalent to guideline 92/69/EEC B.7, range finding study. Purity &gt;99%, dose levels 0, 5, 20,80, 320,1280 mg/kg</td>
<td>NOEL = 5 mg/kg bw/d LOEL = no adverse effects at any dose.</td>
<td>R-12565</td>
</tr>
<tr>
<td>Rat (m,f)</td>
<td>Oral dietary</td>
<td>90-day, In-house method equivalent to guideline 2001/59/EC B.26. Purity &gt;99.1%, dose levels 0, 40, 400, 4000 ppm (m: 0, 2.65, 26.2, 265; f: 0, 2.91, 29.3, 292 mg/kg)</td>
<td>NOEL = 40 ppm (2.81 mg/kg bw/d) LOEL = 400 ppm (27.8 mg/kg bw/d)</td>
<td>R-12605</td>
</tr>
<tr>
<td>Mouse (m,f)</td>
<td>Oral dietary</td>
<td>90-day, In-house method equivalent to guideline 2001/59/EC B.26. Purity &gt;99.0%, dose levels 0, 200, 1000, 5000 ppm (m: 0, 30.3, 151.4, 757.1; m: 0, 35.2, 176.5, 884.9 mg/kg)</td>
<td>NOEL = 200 ppm (30.3 mg/kg bw/d) LOEL = 1000 ppm (151.4 mg/kg bw/d)</td>
<td>R-12609A</td>
</tr>
</tbody>
</table>
### Table B. Toxicology profile of clofentezine technical material based on repeated administration (sub-acute to chronic)

<table>
<thead>
<tr>
<th>Species</th>
<th>Test</th>
<th>Duration, conditions, guideline adopted, purity</th>
<th>Result</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dog (m,f)</td>
<td>Oral dietary</td>
<td>90-day, In-house method equivalent to guideline 2001/59/EC B.26. Purity &gt;99.7%, dose levels 0, 3200, 8000, 20000 ppm</td>
<td>NOEL = none defined&lt;br&gt;LOEL = 3200 ppm (123.8 mg/kg bw/d)</td>
<td>R-12603</td>
</tr>
<tr>
<td>Dog (m,f)</td>
<td>Oral dietary</td>
<td>1-year, In-house method equivalent to guideline 2001/59/EC B.27. Purity 98.2%, dose levels 0, 50, 1000, 20000 ppm (m: 0, 1.75, 33.2, 692.6; f: 0, 1.70, 38.8, 719.1 mg/kg)</td>
<td>NOEL = 50 ppm (1.72 mg/kg bw/d)&lt;br&gt;LOEL = 1000 ppm (35 mg/kg bw/d)</td>
<td>R-12621A</td>
</tr>
<tr>
<td>Rat (m,f)</td>
<td>Feeding, carcinogenicity</td>
<td>2-year, in-house method according to US EPA proposed guidelines, subpart F, 40 CFR, part 163 (1978 &amp; 1982) and OECD, section 4 (May 1981). Purity 97.2%, dose levels 0, 10, 40, 400 ppm (m: 0, 0.43, 1.72, 17.3; m: 0, 0.55, 2.18, 22.1 mg/kg)</td>
<td>NOAEL (toxicity) = 40 ppm (1.95 mg/kg bw/d)&lt;br&gt;NOAEL (carcinogenicity) = 400 ppm (19.7 mg/kg bw/d)&lt;br&gt;No evidence of carcinogenicity</td>
<td>R-12623A</td>
</tr>
<tr>
<td>Mouse (m,f)</td>
<td>Feeding, carcinogenicity</td>
<td>2-year, in-house method according to guidelines EPA/FIFRA (1978) equivalent to method 87/302/EEC B.32. Purity 98.7%, dose levels 0, 50, 500, 5000 ppm (m: 0, 5.0, 50.7, 543.4; m: 0, 5.3, 56.9, 557.1 mg/kg)</td>
<td>NOAEL (toxicity) = 50 ppm (5 mg/kg bw/d)&lt;br&gt;NOAEL (carcinogenicity) = 5000 ppm (550 mg/kg bw/d)&lt;br&gt;No evidence of carcinogenicity</td>
<td>R-12624A</td>
</tr>
<tr>
<td>Rat (m,f)</td>
<td>Feeding, 2 generation reproduction</td>
<td>In-life phase: 1-year, in-house method equivalent to method 87/302/EEC B.35. Purity 97.9-99.3%, dose levels 0, 4, 40, 400 ppm (ca. 0, 0.4, 4, 40 mg/kg)</td>
<td>NOAEL (reproductive) = 400 ppm (40 mg/kg bw/d)&lt;br&gt;NOAEL (developmental) = 40 ppm (4 mg/kg bw/d)&lt;br&gt;No evidence of reproductive toxicity at any dose level</td>
<td>R-12620A</td>
</tr>
<tr>
<td>Rat (m,f)</td>
<td>Teratogenicity and developmental toxicity</td>
<td>Dosing phase: about 1 month, in-house method equivalent to method 87/302/EEC B.31. Purity 100%, dose levels 0, 320, 1280, 3200 mg/kg</td>
<td>NOAEL (reproductive) = 3200 mg/kg bw/d&lt;br&gt;NOAEL (developmental) = 3200 mg/kg bw/d&lt;br&gt;No evidence of teratogenicity at any dose level</td>
<td>R-12610A</td>
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<tr>
<td>Rabbit</td>
<td>Teratogenicity and developmental toxicity</td>
<td>In-life phase: about 2 months, in-house method equivalent to method 87/302/EEC B.31. Purity 98.5%, dose levels 0, 250, 1000, 3000 mg/kg</td>
<td>NOAEL (reproductive) = 3000 mg/kg bw/d&lt;br&gt;NOAEL (developmental) = 1000 mg/kg bw/d&lt;br&gt;No evidence of teratogenicity at any dose level</td>
<td>R-12613A</td>
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</tbody>
</table>
Table C. Mutagenicity profile of clofentezine technical material based on *in vitro* and *in vivo* tests

<table>
<thead>
<tr>
<th>Species</th>
<th>Test system</th>
<th>Conditions, purity</th>
<th>Result</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Salmonella typhimurium</em> (TA 1535, TA 1537,</td>
<td></td>
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</tr>
<tr>
<td>TA 1538, TA 98 and TA 100)</td>
<td><em>In vitro</em>, Ames test, reverse mutation assay</td>
<td>10 µg, 33 µg, 100 µg, 330 µg, 1 mg and 3.3 mg per plate ±S-9 mix. Purity not</td>
<td>Negative</td>
<td>R-12564</td>
</tr>
<tr>
<td>Mammalian cell line (CHO)</td>
<td></td>
<td>stated</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>LS1787 cells</em></td>
<td></td>
<td>0.4, 2 and 4 µg/ml ± metabolic S-9 activation. Purity 99.6%</td>
<td>Negative</td>
<td>R-12635</td>
</tr>
<tr>
<td>heterozygous at the thymidine kinase (TK ±)</td>
<td></td>
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<tr>
<td>locus</td>
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<tr>
<td><em>Mouse bone marrow cells</em></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td><em>Mouse bone marrow cells</em></td>
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</tr>
<tr>
<td><em>Yeast, Saccharomyces cerevisiae</em> strain D-7</td>
<td><em>In vitro</em>, mitotic gene conversion &amp; recombination</td>
<td>12.5, 25, 50, 100 and 200 µg/ml ± S-9 mix. Purity 98.4%</td>
<td>Negative</td>
<td>R-12619</td>
</tr>
<tr>
<td><em>Strains H17 (Rec +) and M45 (Rec -)</em> of</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td><em>Bacillus subtilis</em></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td><em>Rats, male CD Sprague-Dawley (30 in total)</em></td>
<td><em>In vivo</em>, dominant lethal mutation test</td>
<td>Diet of 0, 4, 40 or 400 ppm for 10 weeks followed by pairing each with two</td>
<td>Negative</td>
<td>R-12617</td>
</tr>
<tr>
<td></td>
<td></td>
<td>females for 14 days. Purity 98.1%</td>
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</table>

Table D. Ecotoxicology profile of clofentezine technical material

<table>
<thead>
<tr>
<th>Species</th>
<th>Test</th>
<th>Duration and conditions, purity</th>
<th>Result</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Salmo gairdneri</em> (Oncorhynchus mykiss),</td>
<td>Acute toxicity</td>
<td>US EPA-660/3-75-009 (1975) equivalent to method</td>
<td>LC₅₀ &gt;LOS⁺</td>
<td>R-12643</td>
</tr>
<tr>
<td></td>
<td></td>
<td>dose levels 0.039-0.005 mg/l.</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Salmo gairdneri</em> (Oncorhynchus mykiss),</td>
<td>Acute toxicity</td>
<td>In-house method equivalent to method 92/69/EEC</td>
<td>LC₅₀ &gt;LOS⁺</td>
<td>R-12664</td>
</tr>
<tr>
<td>rainbow trout</td>
<td></td>
<td>C.1: 96-h, continuous flow. Purity 98.6%, dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>levels &gt;0.0146 mg/l.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* LOS = limit of solubility, i.e. <0.002-0.00252 mg/l.
Table D. Ecotoxicology profile of clofentezine technical material

<table>
<thead>
<tr>
<th>Species/Mixture</th>
<th>Test Type</th>
<th>Method/Reference</th>
<th>Purity/Dose Level</th>
<th>EC50/NOEC/LC50/LD50</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lepomis macrochirus, bluegill fish</td>
<td>Acute toxicity</td>
<td>In-house method equivalent to method 92/69/EEC C.1: 96-hours, continuous flow.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Purity 99.8%, dose levels &gt;0.25 mg/l.</td>
<td></td>
<td>LC50 &gt; LOS*</td>
<td>R-12649</td>
</tr>
<tr>
<td>Oncorhynchus mykiss, rainbow trout</td>
<td>Early life stage</td>
<td>Method equivalent to OECD 210 (1992); 97-days. Purity 99.5%, dose level 0.007 mg/l.</td>
<td>NOEC ≥ LOS*</td>
<td></td>
<td>R-12681</td>
</tr>
<tr>
<td>Lepomis macrochirus, bluegill fish</td>
<td>Bio-accumulation</td>
<td>US EPA 560/B-82_002 (1982), equivalent to OECD 305E. Purity 99.2%, dose level 0.033 mg/l.</td>
<td>BCF = 248</td>
<td></td>
<td>R-12666, R-12671</td>
</tr>
<tr>
<td>Daphnia magna, water flea</td>
<td>Acute toxicity</td>
<td>US EPA -660/3-75-009 (1975); US EPA draft 43 (132) (1978); 48-h, static. Purity 99.0%, dose level 0.08 mg/l.</td>
<td>EC50 &gt; LOS*</td>
<td></td>
<td>R-15417</td>
</tr>
<tr>
<td>Chironomus riparius</td>
<td>Chronic</td>
<td>BBA part VI, 2-2 (1995) Static+sediment. Purity &gt;98.7%, dose levels 0.0625, 0.125, 0.25, 0.5, 1.0 mg/l.</td>
<td>NOEC = 0.5 mg/l</td>
<td></td>
<td>R-13278</td>
</tr>
<tr>
<td>Mallard duck</td>
<td>Acute toxicity</td>
<td>US EPA No132 § 163-71-1 (1978): single oral gavage. Purity 99 %, dose level 3000 mg/kg.</td>
<td>LD50 &gt;3000 mg/kg</td>
<td></td>
<td>R-12646</td>
</tr>
<tr>
<td>Bobwhite quail</td>
<td>Acute toxicity</td>
<td>US EPA No132 § 163-71-1 (1978): single oral gavage. Purity not stated, dose level 7500 mg/kg.</td>
<td>LD50 &gt;7500 mg/kg</td>
<td></td>
<td>R-12648</td>
</tr>
<tr>
<td>Mallard duck</td>
<td>Sub-acute dietary toxicity</td>
<td>US EPA No132 § 163-71-2 (1978): 3-d pre-treatment, 5-d treatment period, 3-d post-treatment period. Purity 99.3%, dose levels 2353, 3361, 4802, 6860, 9800, 14000, 20000 ppm.</td>
<td>LC50 &gt;20000 ppm, equivalent to 3617 mg/kg bw/day</td>
<td></td>
<td>R-12647</td>
</tr>
<tr>
<td>Species</td>
<td>Test Type</td>
<td>Source</td>
<td>LC₅₀/LD₅₀</td>
<td>Remarks</td>
<td>Code</td>
</tr>
<tr>
<td>-------------------------</td>
<td>----------------------------</td>
<td>------------------------------------------------------------------------</td>
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<td>----------------------------------------------</td>
<td>------</td>
</tr>
<tr>
<td>Bobwhite quail</td>
<td>Sub-acute dietary toxicity</td>
<td>US EPA No132 § 163-71-2 (1978): 3-d pre-treatment, 5-d treatment period, 3-d post-treatment period. Purity 99.3%, dose levels 2353, 3361, 4802, 6860, 9800, 14000, 20000 ppm.</td>
<td>LC₅₀ &gt;20000 ppm, equivalent to 3448 mg/kg bw/day</td>
<td>R-12645</td>
<td></td>
</tr>
<tr>
<td>Mallard duck</td>
<td>Dietary reproduction</td>
<td>US EPA No132 § 163-71-4 (1982): 22 weeks. Purity 98.9%, dose levels 0, 30, 90, 270 ppm.</td>
<td>NOEC = 270 ppm, equivalent to 39.2 mg/kg bw/day</td>
<td>R-12680</td>
<td></td>
</tr>
<tr>
<td>Bobwhite quail</td>
<td>Dietary reproduction</td>
<td>US EPA No132 § 163-71-4 (1982): 22 weeks. Purity 98.9%, dose levels 0, 30, 90, 270 ppm.</td>
<td>NOAEC¹ = 90 ppm, equivalent to 6.6 mg/kg bw/day</td>
<td>R-12682</td>
<td></td>
</tr>
<tr>
<td>Honey bee</td>
<td>Acute contact</td>
<td>EPPO guideline no. 170 (1992). SC 43% a.i., dose levels 0, 98.2, 196.5 µg formulation/bee.</td>
<td>LD₅₀ &gt;196.5 µg product/bee or &gt;84.5 µg a.i./bee</td>
<td>R-13290</td>
<td></td>
</tr>
<tr>
<td>Honey bee</td>
<td>Acute oral</td>
<td>48 h. EPPO guideline no. 170 (1992). SC 43% a.i., dose levels 0, 7.5, 60.3, 587.4 6 µg formulation/bee.</td>
<td>LC₅₀ &gt;587.6 µg product/bee or &gt;252.6 µg a.i./bee</td>
<td>R-13289</td>
<td></td>
</tr>
</tbody>
</table>

¹ This value represents the ecotoxicologically relevant NOAEC. Statistically non-significant effects on embryo viability at 90 ppm were counteracted by increased survival of young birds. Effects at LOEC (270 ppm) related to hatching rate, chick bodyweight and survival.
## Annex 2. References

<table>
<thead>
<tr>
<th>Makhteshim document number or other reference</th>
<th>Year and title of report or publication details</th>
</tr>
</thead>
<tbody>
<tr>
<td>R-12519</td>
<td>1990. Clofentezine: Determination of the partition coefficient between N-octanol and water at 25°C.</td>
</tr>
<tr>
<td>R-12520</td>
<td>1985. The kinetics of the hydrolysis of NC 21314 under acid, neutral and basic conditions. Amended report.</td>
</tr>
<tr>
<td>R-12523</td>
<td>1985. Solubility of Clofentezine in aqueous solution under acid, neutral and basic conditions.</td>
</tr>
<tr>
<td>R-12565</td>
<td>1980. The 17 day cumulative oral toxicity of NC21314 (NC21314/4, 99% pure) to male and female rats.</td>
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<tr>
<td>R-12600</td>
<td>1980. The primary skin irritancy of unformulated NC 21314 (CR 20099/5) to the guinea pig.</td>
</tr>
<tr>
<td>R-12603</td>
<td>1981. The 90-day subchronic oral toxicity of technical (CR 20099/8) NC21314 in the diet to the dog.</td>
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<tr>
<td>R-12606</td>
<td>1982. The acute inhalational toxicity of NC21314, 80WP CR 15569, to the rat.</td>
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<tr>
<td>R-12609A</td>
<td>1982. The 90-day subchronic oral toxicity of technical (pilot plant) NC21314 in the diet to the mouse.</td>
</tr>
<tr>
<td>R-12612</td>
<td>1982. Delayed dermal sensitisation study in the guinea pig. NC21314 technical.</td>
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<tr>
<td>R-12613A</td>
<td>1983. Effect of technical NC21314 on pregnancy of the rabbit (teratology study).</td>
</tr>
<tr>
<td>Makhteshim document number or other reference</td>
<td>Year and title of report or publication details</td>
</tr>
<tr>
<td>---------------------------------------------</td>
<td>------------------------------------------------</td>
</tr>
<tr>
<td>R-12621A</td>
<td>1984. NC21314 oral toxicity study in dogs (final report: repeated dietary administration for 52 weeks).</td>
</tr>
<tr>
<td>R-12623A</td>
<td>1985. The oncogenicity and chronic toxicity of technical NC21314 (Clofentezine) in the diet to the rat (final report).</td>
</tr>
<tr>
<td>R-12633</td>
<td>1986. REC-assay with spore method on Clofentezine.</td>
</tr>
<tr>
<td>R-12643</td>
<td>1980. The acute toxicity of technical (unformulated) NC21314 to rainbow trout (Salmo gairdneri).</td>
</tr>
<tr>
<td>R-12645</td>
<td>1981. The subacute dietary toxicity (LC50) of technical NC21314 to the bobwhite quail.</td>
</tr>
<tr>
<td>R-12646</td>
<td>1981. The acute oral toxicity (LD50) of technical (pilot plant, CR 20099/5) NC21314 to the mallard duck.</td>
</tr>
<tr>
<td>R-12647</td>
<td>1981. The subacute dietary toxicity (LC50) of technical NC21314 to the mallard duck.</td>
</tr>
<tr>
<td>R-12648</td>
<td>1981. The acute oral toxicity (LD50) of technical NC21314 to the bobwhite quail.</td>
</tr>
<tr>
<td>R-12649</td>
<td>1981. Determination of the acute toxicity of NC21314 to bluegill sunfish (Lepomis macrochirus).</td>
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<tr>
<td>R-12664</td>
<td>1986. Determination of the acute toxicity of [14C]-Clofentezine to rainbow trout (Salmo gairdneri) using a dynamic test system.</td>
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<tr>
<td>R-12681</td>
<td>1993. The toxicity of Clofentezine technical to early life stages of the rainbow trout Oncorhynchus mykiss, in a flow through system.</td>
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<tr>
<td>R-12815</td>
<td>1980. The acute oral toxicity of unformulated NC21314 to the male and female rat.</td>
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<tr>
<td>R-12824</td>
<td>1980. Determination of NC21314 concentrations in aqueous gum tragacanth suspensions for an acute skin irritation study with guinea pig.</td>
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<td>R-13278</td>
<td>2000. Chronic toxicity to the sediment dwelling chironomid larvae Chironomus riparius. Clofentezine, Apollo 50 SC.</td>
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<td>Year and title of report or publication details</td>
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<tr>
<td>R-13289</td>
<td>2000. Oral toxicity (LD50) to honeybees (Apis mellifera L). Clofentezine water miscible suspension concentrate 500 g/L.</td>
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<tr>
<td>R-13290</td>
<td>2000. Contact toxicity (LD50) to honeybees (Apis mellifera L). Clofentezine water miscible suspension concentrate 500 g/L.</td>
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<td>R-15417</td>
<td>1981. Determination of the acute toxicity of technical NC21314 to the water flea, Daphnia magna.</td>
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<td>R-18737</td>
<td>1982. The micronucleus study in mice using technical NC21314.</td>
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