APPENDIX 5
# Table of contents

1. BACKGROUND
2. DISCOVERY AND MODE OF ACTION
3. PHYSICAL/CHEMICAL PROPERTIES OF FLUTRIAFOL
4. TOXICOLOGICAL PROFILE
5. ECOTOXICOLOGICAL PROPERTIES OF FLUTRIAFOL
6. METABOLISM IN PLANTS
7. ANALYTICAL METHODS FOR RESIDUES
8. FATE IN SOIL
9. BIOLOGICAL PROPERTIES
10. CONCLUSION ON SYSTEMICITY
11. DISEASES CONTROLLED
12. CROP-WISE USAGE IN VARIOUS COUNTRIES
13. SELECTIVITY
14. ANTI-RESISTANCE STRATEGY
15. MIXTURES
ICI introduced Flutriafol in 1981. Since its introduction the compound has attained an important position in the global fungicide market, where Flutriafol products have proved effective in controlling a vast number of diseases affecting a wide range of crops.

In April 2001, Cheminova acquired the global Flutriafol business from Syngenta, including all of the rights, know-how, registrations and trade marks (or the product). Today, Cheminova sells the product throughout the world as a foliar application product for cereals and other amble crops, as a microgranule product for use in coffee and maize and as a seed treatment product for the control of major seed-borne and soil-borne diseases in cereals. The foliar products are mainly marketed under the well-known trade name Impact® whereas the seed treatment products are sold under the trade name Vinci®.

Flutriafol is an important product in Cheminova's product portfolio and consequently Cheminova will devote considerable effort into supporting the compound in the market.

The aim of this technical bulletin is to describe the background to Flutriafol's success and also to inform our partners about the properties and capabilities of the product.

It will help you to understand the mode of operation, effectiveness and results achieved when using Flutriafol-based products.
In 1981, scientists at ICI’s Jealott’s Hill Research Station used computers to model the active binding site on the cytochrome and were able to determine the shape of a fungicide molecule that would best fit. Flutriafol was selected for commercial development as its chemical structure appeared to best suit the modelled binding site.

All azole fungicides act by blocking the formation of a specific chemical by the fungal pathogen, ergosterol. This blockage occurs in a process called demethylation. Hence azoles are known as Demethylation Inhibitors or DMIs.

In the demethylation process a protein called Cytochrome P-450 is utilised to bring chemicals together, to be changed and prepared for further demethylation. Flutriafol and other azoles bind to this cytochrome, preventing it from binding to and reacting with the natural chemicals within the fungus.
Flutriafol, in common with all other DMIs, has a nitrogen atom that attaches to the centre of an iron group within the cytochrome, and this prevents the formation of the next intermediate product in ergosterol production.

The stronger the binding of the fungicide to the cytochrome protein, the better the inhibition of ergosterol production and hence fungicidal activity.

**CONCLUSION**

Flutriafol was found to bind particularly with the reduced haem iron across the cytochrome.
(RS)-2,4'-difluoro-α-(1H-1,2,4-triazol-1-ylmethyl)-benzhydryl alcohol

**Empirical formula** \( C_{16}H_{13}F_2N_3O \)

**Molecular weight** 301.3

**Physical state** Solid (crystalline powder)

**Colour** Off-white/light brown

**Odour** Odourless

**Melting point** 130°C

**Boiling point** Decomposes

**Density** 1.41 g/ml at 20°C

**Vapour pressure** \( 5.3 \times 10^{-11} \text{ mm Hg} \) at 20°C

**Solubility in water** 130 mg/l at 20°C and pH 7-9

**Solubility in organic solvent** Soluble in acetone, methanol, dichloromethane; slightly soluble in xylene

**\( \text{N-octanol/water} \) partition coefficient** \( \log K_{ow} = 2.29 \)

**Flammability** Not highly flammable

**Surface tension** 68.7 mN/m at 20 ± 2°C (69.7 mg/l flutriafol)

**Explosiveness** Not explosive

**Oxidising properties** Not oxidising

**Storage stability** Stable for at least 5 years at ambient temperature (15-25°C)
The acute and chronic toxicity of Flutriafol has been examined in a large number of tests. The major findings are listed below.

**Acute toxicity of Flutriafol**

<table>
<thead>
<tr>
<th>Species</th>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rat (M)</td>
<td>Acute oral</td>
<td>LD$_{50}$: 1140 mg/kg</td>
</tr>
<tr>
<td>Rat (F)</td>
<td>Acute oral</td>
<td>LD$_{50}$: 1480 mg/kg</td>
</tr>
<tr>
<td>Rat</td>
<td>Acute dermal</td>
<td>LD$_{50}$ &gt;1000 mg/kg</td>
</tr>
<tr>
<td>Rat</td>
<td>Inhalation (4h)</td>
<td>LC$_{50}$: 65 mg/l air</td>
</tr>
<tr>
<td>Rabbit</td>
<td>Eye irritation</td>
<td>Mildly irritating</td>
</tr>
<tr>
<td>Rat/Rabbit</td>
<td>Skin irritation</td>
<td>Non-irritant</td>
</tr>
<tr>
<td>Guinea pig</td>
<td>Sensitisation</td>
<td>Non-sensitiser</td>
</tr>
</tbody>
</table>

**Medium and long-term toxicity of Flutriafol**

- **Rat**
  3 months feeding study: No Effect Level 20 ppm in diet (approx. 1.5 mg/kg bw/day)
  2-year feeding study: No Effect Level 20 ppm in diet

- **Dog**
  3 months feeding study: No Effect Level
  1-year feeding study: No Effect Level 1 mg/kg bw/day

**Mutagenicity**

Flutriafol is not mutagenic. There was no evidence of mutagenicity in a battery of in vivo and in vitro assays (Ames test, mouse lymphoma mutation assay, rat cytogenic study, unscheduled DNA synthesis, a dominant lethal and a micronucleus study in mice).

**Teratogenicity**

No teratogenic effects in rats at doses up to 10 mg/kg bw/day and in rabbits in doses up to 7.5 mg/kg bw/day.

**Reproduction**

In a two-generation reproduction study with rats the reproductive no-effect level was established as 240 ppm.
Ecotoxicological properties of Flutriafol

The toxicity of Flutriafol to the fauna has been tested in a range of tests.

<table>
<thead>
<tr>
<th>Species</th>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Birds</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mallard duck</td>
<td>Acute oral</td>
<td>LD$_{50}$: &gt;5000 mg/kg</td>
</tr>
<tr>
<td>Red-legged partridge</td>
<td>Acute oral</td>
<td>LD$_{50}$: 616 mg/kg</td>
</tr>
<tr>
<td><strong>Aquatic organisms</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rainbow trout</td>
<td>96 h</td>
<td>LC$_{50}$: 61 mg/l</td>
</tr>
<tr>
<td>Mirror carp</td>
<td>96 h</td>
<td>LC$_{50}$: 77 mg/l</td>
</tr>
<tr>
<td>Daphnia</td>
<td>48 h</td>
<td>EC$_{50}$: 78 mg/l</td>
</tr>
<tr>
<td>Algae</td>
<td>96 h</td>
<td>EC$_{50}$ (growth inhibition): 12 mg/l</td>
</tr>
<tr>
<td><strong>Other non-target organisms</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eisenia fetida</td>
<td>14 days</td>
<td>LC$_{50}$: &gt;1000 mg/kg</td>
</tr>
<tr>
<td>Bees</td>
<td>48 h</td>
<td>LD$_{50}$ (oral and contact): &gt;50 mg/bee</td>
</tr>
</tbody>
</table>

CONCLUSION ON ECOTOXICITY

The ecotoxicological profile of Flutriafol demonstrates that Flutriafol presents a low risk to the environment when handled according to label recommendations. Flutriafol has low toxicity to most wildlife species tested. Flutriafol is classified as harmful to aquatic organisms (EU classification), for which regular releases into the environment should be avoided.
In plants the main metabolites identified are derivatives of triazole.
The main metabolites identified as triazolealanine (2) and triazolelactic acid (3) and a small amount of 4-hydroxyflutriafol (4) were present in wheat straw.

Analytical methods for residues

Residues can be analysed by various methods, including extraction using acetonitrile and water, and qualitatively and quantitatively determined by GLC.

Fate in soil

Flutriafol degrades slowly in soil with a half life of more than one year. No significant degradation products have been identified. It has been demonstrated in field studies that residues in soil do not interfere with phytotoxicity effects on following crops. Flutriafol is moderately mobile in soil. Field studies have indicated that there is no particular concern for leaching to ground water under practical use conditions.
Many factors can influence the activity of Flutriafol. Systemic fungicides (like Flutriafol) differ from protectants. The latter have to form a protective layer on the plant surfaces.

Systemic fungicides have to overcome extra barriers before coming into contact with the target organism.

In addition to the intrinsic toxicity of Flutriafol to the target pathogen, its pattern of uptake and movement within the plant is critical.

**Biological properties**

**Technical influences**
- Formulation
- Drop velocity
- Formulation
- Active ingredient
- Formulation
- Active ingredient
- Formulation
- Active ingredient
- Active ingredient

**Atmospheric influences**
- Influence of crop
- Angle of plant surface
- Movement of plant
- Wax layer
- Wax cuticula
- Membrane structure
- Fungal cell wall
- Site of action

**Flutriafol**

**Diagram:**
- Drop deposition
- Penetration in the plant
- Systemic transport
- Penetration in the fungal cells
- Fungicidal activity
The ease with which fungicides enter and move within the plant is largely determined by their physical and chemical properties.

One measure of this is the ability of the fungicide to distribute itself between alcohol (octanol) and water when shaken up in a mixture of the two substances. This is called its Partition Coefficient or \( \log K_{\text{ow}} \) value.

Fungicides with a value of 3.2 or less all move fast within cereal plants. Those with higher values do not move very rapidly, although they penetrate the plant.

**\( \log K_{\text{ow}} \) values of different products**

<table>
<thead>
<tr>
<th>Product</th>
<th>( \log K_{\text{ow}} ) Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyproconazole</td>
<td>2.9</td>
</tr>
<tr>
<td>Triadimenol</td>
<td>3.2</td>
</tr>
<tr>
<td>Tebuconazole</td>
<td>3.7</td>
</tr>
<tr>
<td>Propiconazole</td>
<td>3.8</td>
</tr>
<tr>
<td>Hexaconazole</td>
<td>3.9</td>
</tr>
<tr>
<td>Flusilazole</td>
<td>3.9</td>
</tr>
</tbody>
</table>

The low \( \log K_{\text{ow}} \) value of Flutriofol allows it to rapidly penetrate through the waxy outer layer of the cereal leaf (the cuticle).

This is especially so over the first 24 hours after application. In fact, depending on conditions, Flutriofol often penetrates very rapidly even during the first hour.
As the spray droplets dry on the leaf the concentration of the active ingredient increases. Most uptake occurs during the latter part of this drying process.

Generally speaking with natural droplet drying, uptake over the first 24 hours can be around 35-45 per cent of that applied on a leaf.

Radio-chemical studies undertaken at Jealott's Hill Research Station illustrate the uptake of Flutriafol over a seven-day period compared to another manufacturer's (OM) triazole.

Within three days of application about 80% of the applied Flutriafol has been absorbed.
Once inside the plant Flutriafol does not accumulate at the point of entry, but diffuses into the underlying tissues. Some of the Flutriafol will move into the water-filled cell walls and may move up the plant in the transpiration stream in a network of cell wall interconnections.

However, most of the Flutriafol is transported up the plant (acropetal movement) in the main conducting tissue — the xylem. To do this it has to cross another formidable cell boundary called the endodermis. Again, the physical/chemical properties of Flutriafol allows this with relative ease.

There is no evidence of Flutriafol moving in the phloem.

Cross section of cereal leaf

- water-filled cell walls
- cuticle
- conducting vessels (xylem)
- endodermis
Studies by Jecott's Hill scientists using radiolabelled Flutriafol show the movement of the product visually from a leaf base application, with time.

Autoradiographs identify Flutriafol as a highly systemic product. Within 24 hours Flutriafol redistributes throughout the entire leaf several times faster than other triazoles.

Single leaf autoradiographs (C¹⁴ radiolabelled Flutriafol)

Lightened areas indicate distribution of radiolabelled triazoles at times indicated after treatment.
CONCLUSION ON SYSTEMICITY

Flutriafol is clearly one of the most mobile of the modern triazoles.

Flutriafol moves rapidly to protect new leaves not unfurled at time of application – this is particularly important in a fast-growing crop such as wheat.

Flutriafol moves rapidly to sites of established infections for fast curative activity.

Where spray coverage is less than optimal (often with lower volumes at flag leaf) Flutriafol redistribution ensures that vital leaves are not left unprotected.

With products of slower redistribution there is a higher risk of disease establishing in new or unprotected growth. The disease is then more difficult to control once the product finally reaches these areas.

Flutriafol products are therefore effective both before and at the onset of infection.
Diseases controlled

Flutriafol is effective against most pathogens belonging to the asco- and basidiomycetes class of fungi.

<table>
<thead>
<tr>
<th>Apples</th>
<th>Peanuts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Podosphaera leucotricha</td>
<td>Mycosphaerella arachidis</td>
</tr>
<tr>
<td>Venturia inaequalis</td>
<td>Mycosphaerella berkeleyi</td>
</tr>
<tr>
<td>Mycosphaerella fijicola</td>
<td>Puccinia arachidis</td>
</tr>
<tr>
<td>Mycosphaerella musicola</td>
<td>Oilseed rape</td>
</tr>
<tr>
<td>Cereals</td>
<td>Alternaria spp.</td>
</tr>
<tr>
<td>Erysiphe graminis</td>
<td>Cylindrosporum concentricum</td>
</tr>
<tr>
<td>Helminthosporium spp.,</td>
<td>Phoma lingam</td>
</tr>
<tr>
<td>Puccinia spp.</td>
<td>Potatoes</td>
</tr>
<tr>
<td>Rhynchosporium secalis</td>
<td>Alternaria solani</td>
</tr>
<tr>
<td>Septoria spp.,</td>
<td>Soybeans</td>
</tr>
<tr>
<td>Tilletia spp.,</td>
<td>Cercospora kikuchii</td>
</tr>
<tr>
<td>Ustilago spp.,</td>
<td>Cercospora sojana</td>
</tr>
<tr>
<td>Chicory</td>
<td>Mischphaeaeo diffusa</td>
</tr>
<tr>
<td>Erysiphe cichoracearum</td>
<td>Septoria glycines</td>
</tr>
<tr>
<td>Puccinia cichorii,</td>
<td>Sugar beet</td>
</tr>
<tr>
<td>Coffee</td>
<td>Cercospora beticola</td>
</tr>
<tr>
<td>Hemileia vasatrix</td>
<td>Erysiphe betae</td>
</tr>
<tr>
<td>Corn</td>
<td>Ramularia beticola</td>
</tr>
<tr>
<td>Sphacelotheca reilianca</td>
<td>Uromyces betae</td>
</tr>
<tr>
<td>Flax</td>
<td>Sunflowers</td>
</tr>
<tr>
<td>Colletotrichum lini</td>
<td>Diporth helinthi</td>
</tr>
<tr>
<td>Grapevine</td>
<td>Erysiphe spp.,</td>
</tr>
<tr>
<td>Guignardia bidwelli</td>
<td>Cercospora spp.,</td>
</tr>
<tr>
<td>Uncinula necator</td>
<td></td>
</tr>
<tr>
<td>Peas and beans</td>
<td></td>
</tr>
<tr>
<td>Aschochyla pisi</td>
<td></td>
</tr>
<tr>
<td>Uromyces pisi</td>
<td></td>
</tr>
<tr>
<td>Colletotrichum pisi</td>
<td></td>
</tr>
</tbody>
</table>
Crop-wise usage in various countries

Flutriafol is today registered in more than 50 countries throughout the world as a foliar as well as a seed treatment product.

To illustrate the considerable variation in the use of Flutriafol in different countries, some of its crop outlets are listed below:

Argentina
Cereals, potatoes, peanuts

Australia
Cereals, oilseed rape

Brazil
Cereals, coffee

France
Cereals, chicory, maize, oilseed rape, peas, sugar beet

Germany
Cereals, maize

Italy
Cereals, sugar beet

Russia
Apples, cereals, grapevine, sugar beet, sunflower
Selectivity

All triazoles generally interfere with the synthesis of gibberellins in many crops whereby a growth-regulating effect can be seen.

Compared to other triazoles, the growth-regulating effect of Flutriafol is low.

The growth-regulating effect is particularly critical when triazole fungicides are used for the treatment of seeds.

A large number of trials have been conducted in order to establish that Flutriafol can be used safely as a seed treatment product. The general conclusion of the trials is that Flutriafol delays emergence, but after four weeks, no difference can be observed.

The delay in emergence increases at lower temperatures. Lower dose rates are therefore tolerated in colder climates.

Dosage rates up to 50 ppm in wheat and 150 ppm in barley are generally recommended as safe to use independent of the weather following application.
Anti-resistance strategy

According to the FRAC (Fungicide Resistance Action Committee), the resistance risk of using triazole fungicides is moderate.

It is recommended to either apply Flutriofol in mixture or in sequence with fungicides with another mode of action. The most important are chlorothalonil, benzimidazoles, morpholines and strobilurines.

Mixtures

Flutriofol is today marketed in mixtures with:
- Chlorothalonil
- Carbendazim
- Thiabendazole
- Imazalil

And the insecticide
- Carbuthuron

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