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READ THE ENTIRE LABEL BEFORE USING THIS PRODUCT.

USE ONLY IN ACCORDANCE WITH INSTRUCTIONS.

KEEP OUT OF REACH OF CHILDREN

## CONTAZOLE 5 EC



### INGREDIENTS

Hexaconazole .....5%  
Other ingredients .....95%

CONTAZOLE 5 EC is a broad-spectrum, systemic fungicide with eradicant and protectant activity against a wide range of plant pathogens, in particular effective for use in grapes.

Trade Names Of Other Firms: Trade names for products containing Hexaconazole include Anvil, Amizol, Conazol, Deviconazole, Canil and Bullet.

### What is Hexaconazole 5 EC and how does it work?

Hexaconazole is a systemic fungicide used for the control of many fungi particularly Ascomycetes and Basidiomycetes.

### Key Benefits of CONTAZOLE 5 EC:

### PRECAUTIONS

Harmful if swallowed, inhaled or absorbed through skin. Causes eye irritation. Avoid contact with skin, eyes or clothing. Avoid breathing dust or vapor. Wash thoroughly with soap and water

after handling. Remove contaminated clothing and wash before reuse. Keep children or pets away from treated area until dry.

### SYMPTOMS OF POISONING

Irritation on skin or eyes.

### MEDICAL TREATMENT

Treatment is symptomatic.

### FIRST AID

If swallowed, call a physician or Poison Control Center. Drink one or two glasses of water and induce vomiting by touching back of throat with finger or if available, by administering syrup of ipecac. Administer 1 tablespoon (15 ml) of syrup of ipecac followed by 1 to 2 glasses of water. If vomiting does not occur within 20 minutes, repeat the dose once. Do not induce vomiting or give anything by mouth to an unconscious person. If on skin, wash thoroughly with soap and water. Get medical attention if irritation occurs. If in eyes, hold eyelids open and flush with plenty of water.

### DIRECTIONS OF USE

Crop	Pests	oz ai/acre
Grape	Mealybugs	0.7 – 1.0

Leafhoppers

Do not apply more than 2.0 oz of AXAPRID 70 WP per year.

### DISPOSAL METHODS

Do not dispose of undiluted chemicals on site. If recycling, replace cap and return clean containers to recycler or designated collection point. If not recycling, break, crush, or puncture and bury empty containers in a local authority landfill. If no landfill is available, bury the containers below 500 mm in a disposal pit specifically marked and set up for this purpose clear of waterways, desirable vegetation and tree roots. Empty containers and product should not be burnt.

### STORAGE CONDITION

Store in the closed, original container in a cool, well-ventilated area. Do not store for prolonged periods in direct sunlight. Store in a locked room or place away from children, animals, food, feedstuffs, seed and fertilizers. Triple or preferably pressure rinse containers before disposal. Add rinsing to spray tank.

For More Details including effects on environment

email [contact@ivorychem.com](mailto:contact@ivorychem.com) with Subject "CONTAZOLE 5 EC DETAILS"

More Details:

#### Human Health: Toxicology and Food Residues

1. It is possible that hexaconazole, like its contaminants the dioxins, are endocrine-disrupting chemicals. These are most toxic to the fetus: fetotoxicity was observed in studies of rats and rabbits in the absence of maternal toxicity. Dioxins and endocrine-disrupting chemicals interfere with hormonal systems and cause disorders of the reproductive system. The signs of abnormal gonadotrophic stimulation (i.e., increased testicular atrophy and increased incidence of Leydig cell tumours observed in the high-dose rats) and the abnormalities of reproductive organ development observed in teratology study could be due to endocrine disruption from this chemical.
2. It is puzzling why the teratology columns contain the highlighted words "No Teratogenic Effects At Any Dose Tested" when teratogenic effects were clearly observed and noted.
3. The toxicology database did include a teratology study, but as usual no functional end points were assessed in the offspring. In addition, there was no immunotoxicity study, nor a developmental neurotoxicity study.
4. Under the provisions of the 1996 Food Quality Protection Act (FQPA), "an additional tenfold margin of safety for the chemical residue and other sources of exposure shall be applied for infants and children to take into account potential pre- and post-natal toxicity and completeness of the data with respect to exposure and toxicity to infants and children." Given that increased sensitivity to the fetus was shown in the reproductive toxicity tests, an additional safety factor, or a least a data base uncertainty factor, would have been applied under FQPA reevaluations. Since important developmental toxicity tests are unavailable, and because one of the prime effects of dioxins is on the immune system, this could be a factor of 10 which would change the allowable daily dose (ADI) to 0.0005 mg/kg bw.
5. As noted in the toxicology summary, hexaconazole is a member of the azole class of chemicals which are known to induce liver toxicity and to inhibit

cytochrome P450 monooxygenase and subsequent hydroxylation of steroids and fatty acids. The nature and sequence of effects observed in animal toxicity studies are consistent with what is known about this class of chemicals. It is believed that liver toxicity plays an important role in the effects observed in the testes. In the study of chronic toxicity in rats, as the severity of the observed liver toxicity increased, adverse effects were observed on lipid metabolism. At progressively higher doses, the alterations in lipid metabolism lead to changes in testicular function (possibly mediated through alterations in steroid levels), ultimately leading to the observation of Leydig cell tumours. Hence, these signs of abnormal gonadotrophic stimulation observed at the high dose of the rat chronic toxicity study are the result of a cascade of effects initially triggered by effects on the liver at much lower dose levels. One principle that is inherent in the hazard assessment is consideration of the dose-response relationship. In performing a risk assessment, appropriate safety factors are applied to the relevant no observed effect level (NOEL) from the toxicology data base. In the case of hexaconazole, the application of safety factors against the NOEL for the liver effects provides an extra level of protection or "buffer" to the testicular effects observed at higher doses. This approach provides reasonable assurance that anticipated exposure levels resulting from the use of hexaconazole would be orders of magnitude below those which that elicited any adverse effects on the endocrine system. As a point of clarification, there were no abnormalities of reproductive organ development observed in the teratology or reproductive toxicology studies.

6. Hexaconazole is not a teratogen. The effects in offspring observed in the teratology studies were considered variations or delays in development and not malformations (terata). In evaluating developmental toxicity studies, the PMRA makes a clear distinction between the variations and malformations for regulatory purposes and regulates chemicals that demonstrate malformations much more aggressively than those which elicit variations. This approach is consistent internationally. Developmental variations or delays occur frequently in untreated

animals. Generally, they are considered reversible, are highly dependent on dose in treated groups, and do not affect fetal survival, development, or function. Malformations are rare, irreversible structural changes that are likely to adversely affect fetal survival, development, or function.

7. In the studies which form a toxicological data base, there are numerous parameters that provide evidence for potential effects on organ systems such as the neurological and immunological systems. For example, chemicals that affect the immune system generally affect immune organ pathology (lymph nodes, spleen, bone marrow), haematology parameters (white blood cell counts, differentials), and the ability to resist infection or neoplastic events. Such parameters are examined in the toxicology data base involving several animal species and including lifetime exposures. Similarly, the toxicology data are closely assessed for effects on the neurological system. If the evidence suggests that these and other organ systems might be affected, additional information is requested to further this investigation. Upon examination of the toxicological data base for hexaconazole, it was concluded that there were no indications of adverse effects on other organ systems and hence further studies and information were not required.
8. PMRA's approach for ensuring safety to infants and children is consistent with that of the U.S. EPA. Like the U.S. EPA, the PMRA applies additional uncertainty factors when warranted by the results observed in the data base. The increased sensitivity of the fetus and the observations suggesting adverse effects on the endocrine system were flagged as warranting additional attention. These issues were addressed in the PRDD. To set the ADI, the PMRA used the lowest no observable adverse effect level (NOAEL) from the study of chronic toxicity in rats rather than a higher NOAEL from the teratology study with the end point of concern. By doing this, a 500-fold safety margin was built into the risk assessment for the observed fetal variations. This also resulted in a 1000-fold safety margin for the observed testicular effects. These are considered acceptable.
9. Hexaconazole has not been assessed for use as a fungicide seed treatment for barley and wheat in the United States.

At the time of making their submission, the company (Zeneca Agro) chose to apply for registration in Canada only.

## OCCUPATIONAL EXPOSURE

1. Although nearly all occupational exposure is expected to be via the dermal route, almost all of the toxicological studies were performed for exposure via the oral route. The dermal absorption data generated in the rat using <sup>14</sup>C-hexaconazole were used to correct for dermal occupational exposure. Differences in rat versus human dermal absorption are not specifically accounted for in occupational risk assessment.
2. Dermal absorption studies where the compound is applied to human skin in vivo provide the most relevant information for human exposure and risk assessment. However, toxicity and ethics preclude the use of humans for such studies. Therefore, animal studies typically are performed to assess dermal absorption. Based on comparative data, rat skin has consistently been shown to be more permeable to topically applied compounds than human skin. Therefore dermal absorption studies with rat skin would overestimate dermal absorption in humans and provide a conservative (i.e., higher) estimate of absorbed dose in humans.

## ENVIRONMENTAL TOXICOLOGY AND FATE

1. There is no mention of the standard reproduction studies conducted with the bobwhite quail and the mallard duck. We believe this issue needs to be addressed because treated seeds represent a high-exposure situation for birds which usually coincides with the timing of reproduction. Given the effects seen with two [previously reviewed] fungicides of the same chemical family, we strongly believe the same attention should be given to the potential reproductive effects on birds of hexaconazole.
2. Statements such as "Proseed may be applied as a seed treatment at very low use rates (1.5 g a.i./100 kg seed)" and "has the advantage of a very low rate of activity, thus potentially reducing pesticide loading" may imply that the use of a substance is safe or safer than a substance used at a higher rate. The important point is that a product is used at a rate that is biologically active, and

- as such it is irrelevant if this rate is “low” or “high.” What matters is the biological activity of the product, not the total loading in and of itself.
3. EC50 is referred to as an “Environmental Concentration 50%,” EC50 is in fact a “median effective concentration.”
  4. At the time of the review of hexaconazole, avian reproduction studies were not part of the data requirements for this use pattern. However, the PMRA has since revised the data requirements and now has included these studies in its list of those required for all outdoor use patterns. Avian reproduction studies on bobwhite quail and mallard duck for hexaconazole were requested from the applicant. The PMRA reviewed these studies and found that if all treated seed was exposed on the soil surface and the birds ate the treated seed at a maximum feeding rate (4.17% of mallard body weight per day and 8.94% of bobwhite body weight per day), there would be adequate margins of safety for reproductive effects. These margins were  $\times 24$  for mallard duck and  $\times 4.3$  for bobwhite quail. It is concluded that the use of hexaconazole as seed treatment for wheat and barley will not be a risk to wild birds such as mallard duck and bobwhite quail.
  5. Relative to other fungicides currently used in Canada for the same purpose, Proseed provides similar disease control using less active ingredient. However, we agree that it is the biological activity of the product that matters.



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