Vitenskapskomiteen for mattrygghet
Norwegian Scientific Committee for Food Safety

Risk assessment of the growth inhibitor Bonzi with the active substance paclobutrazol

Opinion of the Panel on Plant Protection Products of the Norwegian Scientific Committee for Food Safety

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Persons working for VKM, either as appointed members of the Committee or as ad hoc experts, do this by virtue of their scientific expertise, not as representatives for their employers. The Civil Services Act instructions on legal competence apply for all work prepared by VKM.

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Summary

Bonzi is a new plant growth regulator containing the active ingredient paclobutrazol of the triazole chemical class. Bonzi is for use on ornamental plants, such as Chrysanthemum, Perennial Plants, Bedding Plants, Foliage Plants, Geraniums, Hibiscus and Azaleas, in nurseries and greenhouses.

VKM was requested by the Norwegian Food Safety Authority to consider the potential of Bonzi and paclobutrazol to induce reproductive effects in humans; in particular the relative sensitivity and relation between maternal effects and the effects on the offspring; and to what extent cleft palate observed in developmental studies in rat can be regarded as a specific teratogenic effect of relevance for humans. The risk assessment was finalized in a meeting in VKM's Scientific Panel on Plant Protection Products on May 24. 2013.

VKM's conclusions are as follows:

No adverse effect on fertility or reproductive performance was seen in rats. VKM concluded that the incidences of twisted snout observed in the F1 and F2 offspring of paclobutrazol treated rats are not likely to represent a developmental alteration, but rather an unspecific toxic effect.

Marked maternal toxicity was seen in rats above 250 mg/kg bw/day, while partially ossified 7th cervical transverse processes and supernumerary 14th ribs were found in the offspring at 10 - 40 mg/kg/day. VKM concluded that the latter should be regarded as a direct teratogenic effect of paclobutrazol.

Furthermore, VKM concluded that the data from the developmental toxicity studies are inconclusive regarding the effect on cleft palate development in rat foetuses.

VKM proposes a NOAEL of 2.5 mg/kg bw/day for paclobutrazol based on a developmental toxicity study in rats.

Background

VKM performs risk assessments in the context of pesticide registration cf. Regulation on Pesticides § 4. The Norwegian Food Safety Authority, National Registration Section, is responsible for reviewing and evaluating the documentation submitted by the pesticide notifier. The Norwegian Food Safety Authority takes the final regulatory action regarding registration or deregistration of pesticides based on VKMs risk assessment, along with a comparative assessment of risk and benefits and the availability of alternatives (the principle of substitution).

The Norwegian Food Safety Authority submitted a request on April 18, 2013 for VKM to perform a risk assessment on use of the plant growth regulator Bonzi, containing the active ingredient paclobutrazol, on ornamental plants. The risk assessment was finalized in June, 2013.

Terms of reference

Paclobutrazol is the active ingredient in the plant growth regulator Bonzi. The Norwegian Food Safety Authority would like an assessment of the following:

- The potency of paclobutrazol to induce reproductive effects in humans. The Panel is in particular asked to look at the following:
    - The relative sensitivity of the maternal effects and the effects on the offspring.
    - The cleft palate seen in developmental studies in the rat and if this can be regarded as a specific teratogenic effect.

1 Background documentation

VKM's risk assessment is based on the Norwegian Food Safety Authority's evaluation of the documentation submitted by the applicant. The Norwegian Food Safety Authority publishes both their evaluation of Bonzi and their final regulatory action on the registration of the pesticide product at their homepage www.Mattilsynet.no.

2 Procedure

The first three steps of the risk assessment (hazard identification, hazard characterization and assessment of exposure) are performed by the Norwegian Food Safety Authority and involve an assessment of the documentation submitted by the pesticide notifier. The resulting report on hazard identification, hazard characterization and assessment of exposure, from which the summary is included in the present document, is then reviewed by VKM. This review may result in some amendments in the original documents of both the summary and the full report issued by the Norwegian Food Safety Authority (2011). The fourth step (risk characterization) is based on the three first steps and is VKM's conclusions or risk assessment.

2.1 HEALTH RISK ASSESSMENT

The assessment of health risk of pesticides is based on the adverse effects produced by the active substance and product in several experimental test systems including long term animal studies. On the basis of this, limits of exposure which represent no health risk are determined. The limits take account of the uncertainties of extrapolating data from animals to humans and compared to the operator exposure and human exposure to possible residues in the food.

The UKPoem and the German model are used to estimate operator exposure. The models are based on a limited number of studies and are not validated. Thus, the models may not always be sufficiently representative for Norwegian conditions. The limitations of model estimates of exposure are taken into consideration when the calculated level of exposure is close to the threshold limit for acceptable operator exposure (Acceptable Operator Exposure Level; AOEL). VKM uses the 75 percentile of exposure assessment for both UK poem and German model. VKM has to base the assessment on the models whenever exposure data for the product is missing.

VKM makes use of a higher safety factor when calculating AOEL and ADI in cases where the product contains critical active substances with serious adverse inherent properties (toxic to reproduction or carcinogenic).

In order to describe the exceeding of maximum tolerated dose, VKM makes use of a scale. The scale is based on the ratio between the estimated exposure based on models or measured exposure in field studies and the Acceptable Operator Exposure Level (AOEL). In cases where the estimated exposure significantly exceeds AOEL, the use of the products may lead to increased risk for health effects.

The following scale is used:

Very high excess of AOEL	more than 500% of the limit
High excess of AOEL	300 – 500% of the limit
Medium excess of AOEL	150-300% of the limit
Moderate excess of AOEL	100-150% of the limit
The limit is not exceeded	

VKM may also consider co-formulants of the product when the risk is to be determined. Consequently, if a product contains critical co-formulants it may be assessed to represent higher risk than what the inherent properties of active substances imply.

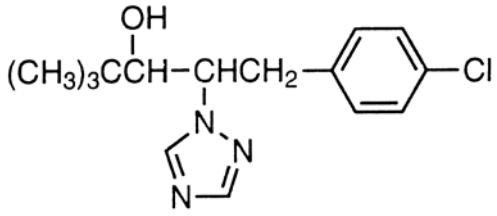
3 Summary by the Norwegian Food Safety Authority (hazard identification, hazard characterization and assessment of exposure)

Bonzi is a plant growth regulator of the triazol group with the active ingredient paclobutrazol.

3.1 IDENTITY AND PHYSICAL/CHEMICAL DATA

Product name:	Bonzi
Active substances:	Paclobutrazol
Formulation:	Soluble liquid concentrate (SL)
Concentration of active substance:	4 g/L
IUPAC-name:	(2RS,3RS-1-(4-klorfenyl)-4,4-dimetyl-2-(1H-1,2,4-triazol-1-yl)-pentan-3-ol
CAS number:	76738-62-0

Structural formula:



Molecular weight:	293.8
Water solubility:	22.9 mg/L at 20 °C in purified water (purity: 99.7 %) 17.2 mg/L at 20 °C (pH 5) 24.8 mg/L at 20 °C (pH 7) 24.1 mg/L at 20 °C (pH 9)
Vapour pressure:	1.9 x 10^{-6} Pa at 20 °C (99.7 %)
Henrys law const.:	2.39 x 10^{-5} Pa m^3 mol^{-1}
log Pow:	3.11 at 23 °C (pH 6.5) (purity: 99.7 %)
pKa:	Structure of molecule is such that dissociation is not expected.

3.2 MAMMALIAN TOXICOLOGY

The absorption of paclobutrazol is rapid and almost complete also at high dose. Excretion is more rapid at low than at high dose probably due to saturation of excretion or metabolic pathways. There are differences in excretion pattern between the sexes and also between males from different strains. There is extensive excretion via bile, more in male than female rats. There is enterohepatic recirculation. Paclobutrazol is almost completely metabolized, apparently only at the tertiary butyl moiety. However, a substantial part of the metabolites is unidentified, especially in female rats at high dose. Paclobutrazol is harmful by inhalation and if swallowed. It is not a skin sensitizer, but is mildly irritating to skin and eyes. Target organ in the repeated dose studies is the liver for rat, mouse and dog. Liver effects found were clinical chemistry changes and increased weight with histopathological alterations (increased incidences of hydropic and fatty changes, including hepatocyte steatosis). In the 2-generation

study there were seen increased incidences of chromodacryorrhea, thickened eyelids, and dental malocclusions/twisted snout. The chromodacryorrhea and thickened eye lids were outside the historical control data, but the toxicological significance is uncertain. In developmental studies in the rat, there were seen incidences of cleft palate and effects on the skeleton at doses that gave some reduction in maternal body weight gain. There were not seen teratogenic effects in studies with rabbit.

3.3 DOSSIER QUALITY AND COMPLETENESS

The dossier is complete and is adequate as a basis for an evaluation of the active substance, metabolites and product.

4 Risk characterization

4.1 SUMMARY OF HUMAN TOXICITY/INHERENT PROPERTIES

VKM was requested by the Norwegian Food Safety Authority to consider the potential of Bonzi and paclobutrazol to induce reproductive effects in humans; in particular the relative sensitivity and relation between maternal effects and the effects on the offspring; and to what extent cleft palate observed in developmental studies in the rat can be regarded as a specific teratogenic effect of relevance for humans.

4.1.1 REPRODUCTIVE EFFECTS

In the rat multi-generation reproduction study, no adverse effects on fertility or reproductive performance were seen up to the top dose of 117 mg/kg bw/day paclobutrazol. There were some incidences of twisted snout in both generations. However, it was concluded that the increased incidence of twisted snout observed in the F1 and F2 offspring is unlikely to be a developmental effect of paclobutrazol. Since the same finding was detected in the treated adult animals of the F0 generation, with a similar incidence, it is considered that it more likely represents a general, unspecific toxic effect of paclobutrazol to pups and adult animals.

4.1.2 DEVELOPMENTAL EFFECTS

In the teratogenicity studies in rats, there was marked maternal toxicity at doses ≥ 250 mg/kg bw/day paclobutrazol. The toxicity consisted of enhanced maternal lethality, stained fur in the genital region, reduced body weight and decreased food consumption during the dosing period.

Increases in the incidences of partially ossified 7th cervical transverse processes and supernumerary 14th ribs were found in the offspring at dose levels 10 and 40 mg/kg/day, respectively, in a rat developmental study. The finding of skeletal defects at doses lower than that of maternal toxicity, suggest that the defects are likely to be of direct teratogenic origin.

Cleft palate was noted in one fetus (of 297 examined) at 40 mg/kg bw/day, and in three foetuses (of 234 examined) in two litters at 250 mg/kg bw/day, in a rat developmental study. In a preliminary study, cleft palate was observed in one foetus at 0 and one at 80 mg/kg bw/day, as well as in six foetuses in one litter at 250 mg/kg bw/day. VKM discussed the seriousness and relevance of these findings and concluded that the data from the

developmental toxicity studies are inconclusive regarding the effect on cleft palate development in rat foetuses.

4.1.3 ESTABLISHMENT OF NOAEL

Although the developmental effects (including the supernumerary 14th ribs and partially ossified 7th cervical transverse processes) are not considered serious malformations by EFSA, VKM considers these effects to be relevant for the establishing of a NOAEL, and proposes a NOAEL of 2.5 mg/kg bw/day based on the developmental toxicity study in rats.

5 Conclusion

5.1 HEALTH

No adverse effect on fertility or reproductive performance was observed in rats. VKM concluded that the incidences of twisted snout observed in the F1 and F2 offspring of paclobutrazol treated rats are not likely to represent a developmental alteration, but rather an unspecific toxic effect.

Marked maternal toxicity was seen in rats above 250 mg/kg bw/day, while partially ossified 7th cervical transverse processes and supernumerary 14th ribs were found in the offspring at 10 - 40 mg/kg/day. VKM concludes that the latter should be regarded as a direct teratogenic effect of paclobutrazol.

Furthermore, VKM concluded that the data from the developmental toxicity studies are inconclusive regarding the effect on cleft palate development in rat foetuses.

VKM proposes a NOAEL of 2.5 mg/kg bw/day for paclobutrazol based on a developmental toxicity study in rats.

6 Documentation

The documentation submitted by the applicant in the process of application for registration of Bonzi has been compiled and evaluated by The Norwegian Food Safety Authority (www.mattilsynet.no).

In addition, VKM has performed a combined literature search in PubMed, TOXNET and Embase using the name of the active substance (paclobutrazol). The resulting references has been considered by VKM and used in the risk assessment when relevant.