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Comments from:
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The Minnesota and South Dakota Departments of Agriculture have requested a quarantine exemption for the use of flusilazole (Punch 3.3EC) and a flusilazole + famoxadone premix (Charisma 1.7 EC) on soybeans to control Asian soybean rust.

1. EPA should have presented information in the docket on the available animal studies conducted with flusilazole for this exemption request. It should have also included known effects on humans. Without this information, the public is left uninformed of the potential consequences of using flusilazole.

2. Flusilazole, a triazole (or azole) fungicide, presents too many risks for it to be used for this exemption request. It may be an endocrine disruptor, a teratogen, and a carcinogen. It is also persistent in soil.

3. Flutriafol, another triazole (or azole) pesticide, has been requested for exemption use on soybean - please see my comments submitted to Docket OPP-2005-0243. Can the public expect adverse effects from flutriafol and flusilazole to be additive when both are applied to soybean? Will the risks be additive when other foods treated with triazole pesticides are consumed?

4. Flusilazole MAY BE AN ENDOCRINE DISRUPTOR.

According to Appendix One, "Summary of data compiled in support of a Section 18 Emergency Exemption" by DuPont: "In the final two-year feeding study in the rat, flusilazole was found to induce testicular adenomas in males... Flusilazole caused reduction in both serum and testicular testosterone and estradiol... Flusilazole was found to be oncogenic at the higher doses, causing bladder transitional cell neoplasia in both sexes and testicular Leydig cell adenoma in males (pages 28 and 29)." Available at http://www.fluorideaction.org/pesticides/flusilazole.appendix1.pdf

According to Trosken et al. (2004), in vitro data on flusilazole indicate it may be a potent inhibitor of aromatase.
Reference: Comparative assessment of the inhibition of recombinant human CYP19 (aromatase) by azoles used in agricultre and as drugs for humans. Endocrine Research, August; 30(3):387-94. Abstract at: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15554355&query_hl=15

According to a 2002 European Commission report, "Although fish early life-stage tests provide useful information on sensitive life stages of fish, for flusilazole in particular the risk assessment has explicitly identified fish and other aquatic species to be at risk from agricultural use of this a.s., and there is evidence that flusilazole may have specific effects on the reproductive process. Therefore the SCP cannot conclude that a NOEC based on a fish early life-stage test for a single species is necessarily adequate in this particular case to ensure sufficient protection of fish populations from adverse effects on reproduction.
-- The monograph (volume 3, pp. 230-233) identified aquatic species, and fish in particular, as possibly at risk from flusilazole. In addition, a dose-dependent decrease in serum estradiol levels by flusilazole, considered to be indicative of aromatase inhibition, was observed in studies with rats

(volume 3, p. 73). Aromatase inhibition is significant for reproduction since aromatization of testosterone is the process by which oestrogen is formed in vertebrates (Trant et al. 1997). This reaction is mediated by the cytochrome P450 aromatase. It has been shown that oestrogen (i.e., oestradiol) plays a major role in the reproductive physiology of all vertebrates, including gamete development and maturation, and induces the hepatic synthesis of the yolk precursor, vitellogenin. Studies in which fish have been exposed to aromatase inhibitors suggest that aromatase activity, specificity or expression levels vary with maturation stage and among species (Bl‡zquez et al. 2001, Zerulla et al. 2002). ... Neither of the above tests was designed to investigate possible effects on reproductive output or mating behaviour of adult fish. Given that there is evidence that flusilazole is an aromatase inhibitor, there are specific concerns that reproduction could be adversely affected by this substance. Therefore potential effects on mating behaviour, time to sexual maturity, reproductive output and timing, fertilisation success, and sex ratio of offspring are also of concern and should be explicitly addressed by a test designed for this purpose. Reference: July 2002 - Opinion of the Scientific Committee on Plants on specific questions from the Commission concerning the evaluation of flusilazole in the Council Directive 91/414/EEC. European Commission. Health & Consumer Protection Directorate-General. Available at http://www.fluorideaction.org/pesticides/flusilazole.eu.july.2002.pdf

5. Flusilazole MAY BE A TERATOGEN.

Menegola et al. reported in 2005: Triazole-derivatives alter the pharyngeal apparatus morphogenesis of rodent embryos cultured in vitro. The hindbrain segmentation and the rhombencephalic neural crest cell (NCCs) migration are altered by Fluconazole exposure in vitro. The aim of the present work is to identify if a common pathogenic pathway is detectable also for other molecules of this class of compounds. 9.5 days post coitum (d.p.c.) old rat embryos were exposed in vitro to the teratogenic concentrations of Flusilazole, Triadimefon and Triadimenol and cultured for 24, 48 or 60 h. The expression and localisation of Hox-b1 and Krox-20 proteins (used as markers for hindbrain segmentation) were evaluated after 24 h of culture. The localisation and distribution of NCC was evaluated after 24, 30 and 48 h of culture. The morphology of the embryos was analysed after 48 h, while the branchial nerve structures were evaluated after 60 h of culture. Hindbrain segmentation and NCC migration alteration as well as pharyngeal arch and cranial nerve abnormalities were detected after exposure of the tested molecules. A common severe teratogenic intrinsic property for the tested molecules of this chemical class has been found, acting through alteration of the normal hindbrain developmental pattern.
Reference: Menegola E, Broccia ML, Di Renzo F, Massa V, Giavini E (2005). Study on the common teratogenic pathway elicited by the fungicides triazole-derivatives. Toxicol In Vitro. Sep;19(6):737-48.
Abstract available at:
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15913947&query_hl=19

Massa et al reported in 2003: abnormalities at the level of the branchial apparatus; disorganisation and fusions at the level of the cranial nerves; abnormalities in the migration of NCC, not able to form 3 distinct migration stripes from the rhomboencephalon to the branchial apparatus; alteration of the hindbrain segmentation, with reduced and scattered immunolocalised stripes. Reference: Mechanisms Involved In Triazole-Induced Teratogenesis: In Vitro Study. Toxicol Lett 2003 Sep ;144 (Suppl 1):S107

Vergieva reported in 1990: Pregnant Wistar rats were given single oral dosages of flusilazole or bitertanol on days 9, 10, 11 or 13th of gestation (positive vaginal smear=day 1) at levels of 1/5, 1/10 and 1/50 LD50. The dosages were calculated from the reported LD50 values of 1272 mg/kg for flusilazole and 5000 mg/kg for bitertanol. The results of the study demonstrated that both compounds induce congenital anomalies when given on

days 9, 10 or 11th at levels corresponding to 1/5 and 1/10 LD50. The types of the registered malformations after flusilazole treatment were exophthalmus, hypognathia, macroglossia and cleft palate and after bitertanol treatment micro- and acaudia and in rare cases exophthalmus, hypognathia and cleft palate. A clear dose effect relationship was established for both compounds. Reference: Triazoles teratogenicity in rats. Teratology 1990 Aug;42(2):27A-28A.

The Scottish Daily Record & Sunday Mail Ltd. October 15, 2000, reported: "Parents believe that exposure to Flusilazol during pregnancy resulted in severe eye deformities such as microphthalmia (small eyes) and coloboma, a defect in the structure of the eyes." Available at - http://www.fluoridealert.org/pesticides/flusilazole.scot.eye.2000.htm

Flusilazole may be implicated in the rare eye defects found in the Benlate poisoning incidents in Florida. It has been reported by Jan Hollingsworth in a December 18, 1995, Tampa Tribune (Florida) news report that flusilazole was an "undisclosed ingredient in some lots of Benlate 50 DF." Reference: Fungicide studies offer little comfort. Memo: buried secrets pursuing a medical mystery. Page 4.

6. Flusilazole MAY BE A CARCINOGEN.

-- Flusilazole was found to exert a clear systemic toxicity on sub-chronic and chronic administration to rats, mice and dogs. A similar pattern of effects was apparent across the three species, with the liver, urinary system and blood system targeted to varying degrees. It was found to be oncogenic at high dose levels in both mice and rats, inducing bladder transitional cell neoplasia in rats and testicular adenoma in male rats and hepatocellular adenomas and carcinomas in mice. (Page 30)
Reference: DuPont Punch (Active ingredient: Flusilazole) and DuPont Charisma (Active ingredients: Flusilazole and Famoxadone): Summary of data compiled in support of a Section 18 Emergency Exemption request for control of Asian soybean rust on soybeans. By DuPont authors: Cosgrove T, Czochor L, Dinter A, Jemberg K, Klemens A, Marcon A, McInnes B, Mullin L, Russell M, Ryan D, Singles S, Vanderbroeck V. Revision No. 1: February 2, 2005.
Available at:
http://www.fluorideaction.org/pesticides/flusilazole.appendix1.pdf

7. Flusilazole IS PERSISTENT IN SOIL. Its potential to leach into groundwater needs clarification. Flutriafol is another triazole (or azole) pesticide requested for exemption use on soybean. Flutriafol is extremely persistent and water contamination is likely.

(page 51): [Flutriafol] is extremely persistent in soil and will accumulate following repeated annual applications. Soil residues also demonstrate the potential to be mobile. Although the fate and behaviour of flutriafol in water has not been evaluated and no data are available from natural water monitoring, the high spray application rate and the use on cereals, indicated that water contamination is likely.
Reference: Evaluation on: Flutriafol. October 1996. Issue No. 158, UK Department for Environment, Food and Rural Affairs, Pesticides Safety Directorate, Mallard House, Kings Pool, 3 Peasholme Green, York YO1 7PX.
Available at:
http://www.pesticides.gov.uk/PSD_PDFs/Evaluations/158_flutriafol.pdf

Note: This submission is available online at
http://www.fluorideaction.org/pesticides/flusilazole.comments.oct05.html
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