BASF Corporation

BASF

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To: U.S. EPA Public Docket

Re: Document ID: OPP-2003-0205-0003; Response to Public Comments from the Fluoride Action Network Pesticide Project Regarding the Notice of Filing of a Tolerance Petition for Chlorfenapyr on all Food Items in Food Handling Establishments where Food Products are Held, Processed and/or Prepared

BASF submits the following response to public comments posted on EDOCKET from the Fluoride Action Network Pesticide Project regarding the NOF of a tolerance petition for Chlorfenapyr on all food items in food handling establishments when used for general pest control

Regarding Points 1.5, 2.1 and 2.2: "Prion Diseases"

These comments compare the effect seen with Chlorphenapyr with effects observed with transmissible spongiform encephalopathies (TSE). Is Chlorfenapyr a chemical that induces prion diseases?

In fact, the effect seen with Chlorphenapyr and the effects observed with TSE differ substantially:

- Importantly, the intramyelinic vacuolation induced by Chlorfenapyr, appears to be a morphological effect, without direct, degenerative damage to myelin or axons. There is no apparent collapse or rupture of myelin sheaths leading to the process of demyelination. Furthermore, there is no evidence of neuronal (axonal) Wallerian degeneration. The vacuolar myelinopathy has not associated with any clinical behavioral effects in rats or mice.
  Whereas TSE cause severe and fatal neurological signs and symptoms.
- Subchronic and chronic dietary administration of Chlorfenapyr to rodents induces translucent vacuoles in the central nervous system's white matter of the brain, spinal cord, and/or spinal nerve roots. This translucent vacuolar alteration probably represents edema accumulation, containing a high proportion of water, between the myelin sheaths. Whereas TSE are characterized by bilaterally symmetrical, non-inflammatory vacuolation of neuronal perikarya and grey matter neuropil.
- The translucent myelopathic alterations induced by Chlorfenapyr were completely reversible following a 4-month recovery period after 12 months of Chlorfenapyr treatment to Sprague-Dawley rats in the one-year neurotoxicity study.
  Whereas TSE are a slowly progressive, degenerative, inevitably fatal diseases.
- No reactive cellular changes occurred following subchronic or chronic Chlorfenapyr treatment, which would indicate specific responses to minor or major injuries to cell targets, including myelinated axons. Also, there is no morphological evidence of any proliferative responses, such as gliosis or hyperplasia of oligodendrocytes in the central nervous system to indicate production of new myelin following cellular injury. Whereas TSE are characterized by neuronal loss and astrocyte proliferation.

Since there is no indication that chlorphenapyr causes a transmittable spongiform disease, there is neither a reason nor a justification to perform additional animal studies with intracerebral injection of brain homogenates from animals treated with chlorphenapyr.

Regarding Points 2.3, 2.4 and 2.5: Role of Bromine and Fluorine

These comments suggest the testing of compounds derived from chlorphenapyr by removing bromine and fluorine from the molecule.

The testing of compounds derived from Chlorfenapyr by removing bromine and fluorine from the molecule is not a Federal Insecticide Fungicide Rodenticide Act registration requirement. Because these derived compounds do not occur (i.e. not metabolites, break-down products nor by-products) the results would not be applicable for an assessment of the safety of Chlorfenapyr relative to this registration decision.

Regarding Points 3.2, 6, 7, 8: Effects of Other Substances

The comments 3.2, 6, 7 and 8 address effects of other pesticides, which contain fluorine, on the brain.

Neither the effects, nor the modes of action (as far as known) of Sulfurylfluoride, Fluazinam, Flufenacet, Sodiumfluoride, Tefluthrin, Acifluorfen and Diisopropylfluorphosphate are the same as seen with Chlorfenapyr. Most importantly, Chlorphenapyr is not "highly toxic" to the brain (as stated in paragraph six, third line of the public comment). There is no reason to assume a common effect or mode of action due to fact that the compounds contain fluorine atoms.
Two forms of myelinopathies (vacuolation), which are disruptions of the axonal myelin sheaths, can occur following exposure to certain neuroactive agents. In the first type, swelling and bubbling of the myelin sheaths occur without demyelination, and the axons are usually spared from damage. In this form of myelinopathy, peripheral nerves are generally less susceptible to insult than white matter of the central nervous system. Such agents, which cause this effect on myelin, are usually associated with clinical and morphological recovery. In contrast, the other type of myelinopathy is concomitant with Wallerian degeneration, which results from injury to myelinating cells or axons. This type of myelinopathy is more severe than the first type and is irreversible. Microscopic characteristics of the second type of myelinopathy include myelin segments which collapse and fold around the cavity originally occupied by the axon (ovoid formation) and demyelination.

Regarding Point 3.3: Industrial Hygiene

Issues associated with the health and safety of people in the workplace is reported under OSHA and to EPA under 6(a)2 .

Regarding Point 3.4

The Federal Insecticide Fungicide Rodenticide Act does not apply to accidental release of chemicals. Appropriate procedures for dealing with spills, leaks, waste disposal and container disposal are listed on the Material Safety Data Sheet.

Regarding Point 3.5: Gender Susceptibility in Mice

An explanation of gender susceptibility in mice is not a Federal Insecticide Fungicide Rodenticide Act registration requirement. Furthermore, the compound is regulated based upon the most sensitive species and gender.

However, the gender dimorphism of the myelinopathy (i.e., vacuolation was only seen in male rats but in both male and female mice) may be related to the metabolism of chlorphenapyr to a potent uncoupler of oxidative phosphorylation (AC 303,268). The rate of formation of this metabolite is higher in males versus females. The neuropathic lesions are likely attributed to the uncoupling of oxidative phosphorylation.
Similarly, mice are generally more sensitive than rats to the toxic effects of chlorphenapyr due to enhanced formation of AC 303,268.
Using LD_{50} values as indicators of the rate and extent of formation of the uncoupler AC 303,268, male and female rats show a greater difference in their LD_{50} values than male and female mice (2.6-fold versus 1.7-fold, respectively). These differences in LD_{50} values and, in turn, the formation of AC 303,268, may partly explain the absence of the vacuolar myelinopathy in female rats and its presence in both male and female mice.

Regarding Point 4: Developmental Neurotoxicity Study (DNT)

BASF has agreed to conduct a DNT to support the establishment of permanent tolerance of Chlorfenapyr on fruiting vegetables.

Regarding Point 5: Endocrine Effects

This comment addresses findings of endometrial stromal polyps and testicular interstitial cell tumours

The occurrence of endometrial stromal polyps in the uterus was slightly increased in high-dose females, as compared to controls. Although the incidence of endometrial stromal polyps in high-dose females (5/65 or 7.7%) is statistically different from the concurrent control females (0/65) by the Fisher Exact Test ($p< 0.05$), the incidences are not statistically different using the exact prevalence method. This is the more appropriate method to compare two groups with heterogeneous survival rates (survival was significantly increased in high-dose females). All five females with stromal polyps were sacrificed at termination. Furthermore, the incidence (0/65) of these benign polyps in the control females was unusually low for this commonly occurring proliferative lesion that may represent an aging, hormonal-type response. Moreover, the incidence in high-dose females is only slightly above the overall total mean historical rate (35/727 or 4.8%), and well below the maximal spontaneous incidence (8/60 or 13.3%). Therefore, the occurrence of this benign proliferative lesion in females of the high-dose group is not considered treatment related.

The occurrence of benign interstitial cell tumors in male rats was 3/65, 1/65, 3/65 and 7/65 (4.6, 1.5, 4.6, 10.8%) in the control and the low-, mid- and high dose, respectively. There was no statistically significant increase in either group when compared to the control group and no clear dose-response relationship. Moreover the incidence of 7/65 was at the upper limit of the historical control range (10.0%). Therefore, the occurrence of this benign proliferative lesion in males of the high-dose group is not considered treatment related.

Overall, there is no indication of an endocrine effect of chlorphenapyr in any of the studies, including the two-generation study in rats and the oncogenicity studies in rats and mice.

Regarding Point 9

BASF is not aware of the existence of the data that would be needed to evaluate exposure to subsets of the population with specific neurodegenerative diseases. However there is no reason to believe that these groups would be any more sensitive that the general population.

Regarding Point 9.1

There is no tolerance established by the US EPA for Chlorfenapyr in tea. Tea imported with residues of Chlorfenapyr would be considered adulterated subject to enforcement action.

Regarding Point 10: Disposal

Instructions for safe disposal of product and containers can be found on the label as well as on the Material Safety Data Sheet for the product. There is no reason for special consideration of the disposal of Chlorfenapyr.

Regarding Point 10.1: Disposal of Exposed Food

Food products containing the 0.01 ppm Chlorfenapyr can be safely composted and/or fed to farm animals. BASF reminds EPA that information to address these issues is found in the Chlorfenapyr residue and metabolism database that explains the fate of residue in food products. Additionally, the eco-toxicology database for chlorfenapyr contains results of studies that demonstrate an insignificant risk to birds if they ate feed treated with 0.01 ppm chlorfenapyr. The lowest LC_{50} for birds is about 8 ppm, so a level of 0.01 ppm affords an 800-fold safety factor. Chlorfenapyr exhibits a steep dose response curve in birds, and the Lowest Lethal Concentration was 5 ppm, so there is a 500-fold safety factor for bird mortality. Considering chronic effects, the lowest No Observable Effect Level for avian reproduction is 0.5 ppm, so there is a 50-fold safety factor for effects on avian reproduction. The actual safety factor would be much greater because it is unlikely that any bird feed item would contain as much as 0.01 ppm.

Regarding Point 10.2: Incineratioin

Transformation products when Chlorfenapyr is incinerated?
This is not a Federal Insecticide Fungicide Rodenticide Act requirement for pesticide registration for these uses. However, the decomposition temperature for technical Chlorfenapyr is 183° C.

Regarding Point 11: Inerts Disclosure

The chlorfenayr product for use with this pending tolerance is registered, EPA Reg. No. 241-392. Information on the composition of formula, including inert ingredients, is confidential business information. All inert ingredients in this product are on the EPA list of approved inert ingredients.

Respectfully submitted,

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