UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

**CONTAINS CONFIDENTIAL BUSINESS INFORMATION**

**DATE:** October 18, 2004

**MEMORANDUM**

Subject: Abamectin: Potential Impact of Proposed New Technical Grade Active Ingredient from Nations Ag II on Human Exposure and Risk
EPA PC Code: 122804
HED TRX#: 0051899

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Registration Division (RD) of OPP and the Office of General Council (OGC) has asked the Health Effects Division (HED) to comment on the relevance of differences between the proposed technical grade active ingredient (TGAI) of abamectin from Nations Ag II, LLC and the registered TGAI belonging to Syngenta Crop Protection, Inc. on exposure to humans and the associated risk. Specifically, HED has been asked to address issues on product chemistry (density, pH, nominal concentration, impurity profile), nature of degradates and residues, and the need for additional toxicological testing.

As background material, it should be noted that abamectin is the common name for a mixture that consists mostly of avermectin B1a and avermectin B1b as the claimed active ingredients. The B1a component is present at much higher concentrations than the B1b analog (minimum ratio of 80/20). Related avermectins are also found as impurities in the TGAI's, generally at lower levels than the B1b component.

## PRODUCT CHEMISTRY

With respect to the issues on product chemistry, the following conclusion was drawn in the 1/13/2004 review of the Nations Ag II technical by Shyam Mathur, Technical Review Branch/RD:

> "The proposed technical/MP was determined not to be substantially similar to the registered product with Reg. No. 100-895 from the product chemistry view point."

The review further states that there are significant differences in the density and pH for the two products. The proposed Nations Ag product has pH and density of 7.2 and 36.52 lbs/cu ft, respectively, while the Syngenta TGAI (Reg. No. 100-895) has values of 8-9 and 73.70 lbs/cu ft for the same properties. In addition, the review concludes that the nominal concentration and the impurity profile for the registered and proposed technical are not the same.

### pH

HED is not concerned with the different pH's (7.2 versus 8-9) from a risk perspective for two reasons. These pH's are sufficiently close to neutral (pH 7) such that they would not constitute a significant hazard by themselves (i.e., not caustic). In addition, when one takes into account the dilution which occurs upon formulating the end use products and preparing the final solution for application in the field, the pH's of the materials to which workers will be exposed and which will be applied to crops will be governed by the added components, not the TGAI's. Therefore, these differences in TGAI pH per se will not result in different exposure of workers and dietary exposure of consumers to avermectin residues.

### Density

Although there is roughly a two-fold difference in the density between the two TGAI's (36.5 and 73.7 lb per cubic foot), this is very likely due to the differing levels of solvent impurities (i.e., moisture) in the TGAI's. The technical with the [redacted] level of remaining solvent (Syngenta 1/22/02 Confidential Statement of Formula [CSF] shows [redacted] has the higher density. The Nation Ag product is [redacted] From a risk perspective, HED is not aware of any impact that differing densities would have on risk. Even if there were a risk component due to density, using a similar argument as above for the pH issue (i.e., the densities of the materials to which exposure occurs will be controlled by the components added during the formulation and/or application processes rather than by the TGAI per se), the differences in density will be essentially eliminated upon the further dilutions which occur in the formulation and application processes.

### Nominal Concentration and Impurity Profile

The different moisture levels of the two TGAI's also affect the conclusions which HED needs to make on (1) the significance from a risk perspective of the nominal concentrations and the impurity profiles for the registered and proposed technical not being the same (as concluded in the 1/13/2004 RD review) and (2) the need for additional toxicological testing (discussed in later section) of the Nations Ag material. Due to the absence of toxicological concern over the presence

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of moisture or residual solvent impurities in the products, it is more appropriate to compare the compositions of the TGAI's on a dry weight basis when considering these two issues. Therefore, the levels of the two major components of the TGAI's (avermectin B1a and B1b) and the related avermectin impurities (i.e., avermectins other than B1a and B1b) have been recalculated by excluding the nominal amounts of the moisture/solvent impurities. [redacted] The amount of moisture in the Nations Ag product is [redacted] (11/5/01 CSF) with the various avermectins comprising the remaining [redacted] On a dry weight basis the concentration of the B1a plus B1b avermectins would be [redacted] while the remaining related avermectins comprise [redacted] The results of these calculations are summarized in the table below.

| PRODUCT | % B1a + B1b wet basis | % B1a + B1b dry basis | % related avermectins wet basis | % related avermectins dry basis |
|---|---|---|---|---|
| Syngenta | 90.0 | [redacted] | | |
| Nations Ag | 97.6 | | | |

Based on the results in the table, HED concludes that there is no significant difference in the nominal concentrations of the active ingredients in the two TGAI's on a dry weight basis. Since the dry weight basis is the more appropriate basis for risk comparison purposes as explained above, HED has no concerns over the issue of nominal concentration of the active ingredient. With respect to the related avermectin impurities, the levels on a dry weight basis are also very close. Although there are some differences between the two TGAI's in the identities of these impurities, HED concludes that a significant difference in hazard or risk will not result from the different impurity profiles based on the rationale described in the section on additional toxicological testing.

## DIFFERENT DEGRADATES AND RESIDUE PROFILES

Syngenta has contended that the Nations Ag product could produce different degradates and residues on treated food crops. With respect to the impact of the active ingredients (avermectin B1a and B1b) per se in the two TGAI's, HED does not agree that different degradates and/or residues will be observed in crops since both technicals contain the exact same active components from a chemical structure perspective. Although it is possible in some instances that other components (e.g., impurities) in the TGAI could influence how the active ingredient degrades, the impurities in the two products are present at similar levels and, while not chemically identical, are sufficiently similar to each other and to the active components such that we do not anticipate any significant differences in such an influence from the impurities, if any such impact does exist at all in this case.

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In addition, taking into account the low application rates and tolerances for residues of abamectin, any residues formed from this phenomenon would occur at very low levels. Considering the resulting low levels in conjunction with the earlier discussion on minimal toxicological impact of low level impurities, HED believes it would be very unlikely but that there would be a significant risk concern from any possible unique degradates relative to that resulting from residues of the active ingredient and its known metabolite/degradate, the delta-8,9 isomer. HED would expect comparable amounts of delta-8,9 isomer to be formed from the active ingredient contained in either the Syngenta or the Nations Ag II technical.

## NEED FOR ADDITIONAL TOXICOLOGICAL TESTING

As stated in the HED memos of Sept. 5, 2002 and Apr. 22, 2004, the toxicity of various mectins can differ in both a qualitative manner (different target organs) and quantitative manner (different potencies). However, it is doubtful that any such differences would be seen in the Part 158 animal testing when these other mectins are present only as minor impurities (e.g., totaling about [redacted] dry basis in technical abamectin, which contains very high amounts [greater than [redacted] dry basis] of the active B1a and B1b isomers).

For that reason, the HED Hazard Policy Council (Sept. 2, 2004) determined that, even though the related avermectin impurities in the abamectin technicals may have different toxicities, the overriding reason for not being concerned about the lack of additional toxicological bridging data was that these other impurities were present in relatively small amounts compared to the well-characterized and quite toxic isomers B1a and B1b. Based on the revised calculation on a dry weight basis as outlined above, both TGAI's contain very high levels of these active isomers [redacted] for Syngenta, [redacted] for Nations Ag II) and very similar low percentages of the avermectin related impurities [redacted] versus [redacted]. Although we previously thought that there was about a [redacted] difference in the levels of impurities, the reconsideration on a dry weight basis has led HED to conclude that the differences are minimal and that there is no issue on the different levels of the impurities from a risk perspective.

In addition to the above conclusions on the very similar levels of components in the two products, new information (July, 2004) from Syngenta provided the composition of the technical abamectin tested in key toxicity studies. Our review of this submission indicated that the purity of the test material contained about 95 to 97% B1a and B1b isomers on a dry weight basis. Since this value is very similar to those values for B1a and B1b in the Syngenta and Nations Ag II technicals, this was also used by the Council to determine that further toxicological bridging studies would not be needed from a risk perspective.

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