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OFFICE OF CHEMICAL SAFETY AND POLLUTION PREVENTION

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MEMORANDUM

Date: June 2, 2010

SUBJECT: Review of Triple Pack Dermal Absorption Studies for Maxim Quattro

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I. Conclusions

The Registrant (Syngenta) has submitted a position paper evaluating a Triple Pack of dermal absorption studies with thiabendazole formulated as TECTO 500 SC. The Registrant proposed a refined Dermal Absorption Factor (DAF) of 0.15%. OPP has reviewed the data and calculated a DAF of 0.5%. This DAF of 0.5% for TECTO 500 SC is also appropriate for thiabendazole formulated as Maxim Quattro.

II. BACKGROUND

There were no dermal absorption studies for thiabendazole in any formulation. The current DAF used for thiabendazole of 60% is based on a ratio of LOAELs in short-term toxicity studies. The registrant (Syngenta) submitted a Triple Pack of dermal absorption studies (rat skin *in vivo* (MRID 47705131), rat skin *in vitro* (MRID 47705102), human skin *in vitro* (MRID 47705101) with thiabendazole formulated as TECTO 500 SC, as well as an assessment of these studies that calculated a DAF (MRID 47705106). TECTO 500 SC is not sold in the US, but is sold internationally. The registrant's assessment proposes a refined DAF of 0.15% for TECTO 500 SC and argues that this DAF can be bridged to Maxim Quattro, a different formulation of thiabendazole which is sold in the US. This refined DAF for Maxim Quattro may allow room for more uses in the thiabendazole risk cup.

The *in vitro* and *in vivo* dermal absorption studies with TECTO 500 SC were previously reviewed as part of a joint review with PMRA (in which PMRA had the lead) during July of 2009. These joint reviews have not yet been released from PMRA, but should be available at a later date. The registrant's assessment of the Triple Pack studies (MRID 47705106) and proposal of a refined DAF of 0.15% for both the TECTO 500 SC and Maxim Quattro formulations had not been evaluated previously, but is evaluated herein.

III. RESULTS/DISCUSSION

1) Evaluation of Triple Pack studies with the TECTO 500 SC formulation

The term "Triple Pack" refers to the use of three types of dermal absorption data from: 1.) *in vivo* rat; 2.) *in vitro* rat; and 3.) *in vitro* human dermal absorption studies. This approach permits refinement of *in vitro* results using rat skin by correcting for any differences between *in vitro* and *in vivo* absorption rates in that species as well as for species differences seen between rat and humans. This refinement in dermal absorption is important since absorption by human skin is usually lower than that by rat skin. Accordingly, the combined use of data from the three studies and two testing systems offers greater precision in estimating human dermal absorption which strengthens the reliability of the dermal risk assessment.

The Triple Pack approach presumes that if *in vitro* techniques performed using animal skin is shown to be a good predictor of animal *in vivo* dermal absorption for a chemical, that is, if the ratio of animal *in vitro*/animal *in vivo* ≈ 1, then the identical technique performed *in vitro* with human skin may be useful in extrapolating human dermal absorption. Consequently, when

identical protocols are used in both the *in vivo* and *in vitro* studies, these data can then be used in the Triple Pack approach to derive a refined dermal absorption factor for human health risk assessments.[1]

OPP evaluated the Triple Pack of dermal absorption studies with TECTO 500 SC and agrees that these studies are suitable for deriving a refined DAF. Critical parameters that were the same in the *in vivo* rat study and the *in vitro* rat skin and *in vitro* human skin studies were the use of the same test material, the same doses, the same times, and the same treatment of the skin (e.g. when it was washed). Also critical was that the concentrations of the test material and durations of exposure were relevant to occupational exposures.

The Agency has calculated a refined DAF of 0.5%, which is higher than the DAF calculated by the registrant of 0.15%. In calculating the DAF, the Agency utilized the highest percentage absorption observed from an occupationally relevant time and concentration. The Agency first considered if skin-bound residue (the amount of the dose remaining after washing) was available for systemic absorption. This was addressed in the rat *in vivo* study, in which absorption of thiabendazole after skin washing at 6 h was measured. The percentage of the applied dose remaining in the stratum corneum and the application site skin (after normalizing for recovery) declined from 6 hours to 120 hours, indicating that bioavilable skin-bound residues were absorbed. Most of this absorption occurred within 72 hours. The Agency calculated the percentage of bioavailable skin-bound residues as 0.71±0.43% (Table 1).

Table 1: Percentage of Bioavailable Skin-Bound Residues Over Time (MRID 47705131)

Percentage absorbed	6 hours	24 hours	72 hours	120 hours
Stratum corneum Difference from 6 h	0.72±0.20 **0.00±0.20**	0.49±0.17 **0.23±0.26**	0.42±0.12 **0.30±0.23**	0.48±0.20 **0.24±0.28**
Application site Difference from 6 h	0.62±0.39 **0.00±0.39**	0.44±0.36 **0.18±0.53**	0.19±0.20 **0.43±0.44**	0.15±0.13 **0.47±0.41**
Total bioavailable (after 6 h)	**0.00±0.44**	**0.41±0.59**	**0.73±0.50**	**0.71±0.50**

The Agency then considered whether or not the *in vitro* study with rat skin was predictive. The Agency considers this necessary because *in vitro* dermal absorption studies have not been extensively validated[1]. The predictivity of the *in vitro* study was assessed by comparing the rat *in vitro* and rat *in vivo* studies as follows:

If animal *in vitro*/animal *in vivo* ≈ 1, then the in vitro study is considered predictive[1].

[1] NAFTA Dermal Absorption Group Position Paper on the Use of In Vitro Dermal Absorption Data in Risk Assessment, August, 2009.

The 6 hour time point was used for this calculation, since this is the time point at which the DAF will be calculated:

Predictivity of Absorption of Thiabendazole by the *In Vitro* Study (at 6 hours)

3.75%. (rat *in vitro*) ÷ 1.53 (rat *in vivo*) = 2.45*
*Note that this value is greater than 1.

Presently, OPP has no policy on how close to 1 this value has to be to be considered adequately predictive. These studies were considered acceptable for regulatory use because both studies were of high quality and the integrity of the rat skin *in vitro* was verified by electrical conductance. However, the *in vitro* study was not completely predictive (the ratio was >1), and so the ratio method used by the registrant (MRID 47705106) for adjusting the human DAF will not be used by OPP. OPP's rationale is that this is not adequately conservative, since it would effectively result in decreasing the human DAF by three fold compared to a study in which the ratio of rat *in vitro*/rat *in vivo* was 1:

The Ratio Method is not Conservative when *In Vivo*/*In Vitro* >1

rat *in vivo*/rat *in vitro* = human *in vivo*/human *in vitro*
therefore,
rat *in vivo*/rat *in vitro* x human *in vitro* = human *in vivo* (ratio method of registrant)

but
1.53/3.75 x human *in vitro* < 1/1 x human *in vitro* (an ideal study)
therefore
assuming rat in vivo/rat in vitro = 1 is more conservative.

OPP therefore calculated a partial DAF at 6 hours of 0.160±0.022%[2] for the 1/50 dilution (MRID 47705101). This is considered a partial DAF because it does not consider bioavailability of skin-bound residues. It was calculated by using the absorption data for human skin *in vitro* under the following assumptions:

Calculation of a Partial DAF at 6 h (No Skin-Bound Residue)

animal *in vitro*/animal *in vivo* ≈ 1
therefore,
human *in vitro* = human *in vivo*=$DAF_{PARTIAL}$=0.160±0.112[2]% (no skin-bound residues)

The total DAF was calculated by adding in skin-bound residues. This was necessary because the rat *in vivo* data from Table 1 clearly show that skin-bound residues (found in the stratum corneum and remaining epidermis) are bioavailable over time (72 hours). Thus, the total DAF was calculated as follows:

Calculation of a Total DAF at 6 h (With Skin-Bound Residue)

DAF_{TOTAL}= 0.218±0.092%[2] (stratum corneum) + 0.160±0.092%[2] (remaining epidermis) + 0.160±0.112%[2] (receptor fluid) = 0.538±0.172% = 0.5% (rounded)

The rationale assuming that all skin-bound residues from the stratum corneum and epidermis were bioavailable (even though the rat *in vivo* data had indicated that some were not) was that the *in vitro* human data did not allow determination of the percentage of skin-bound residue that were bioavailable over time.

OPP's DAF of 0.5% differs from the registrant's calculated DAF of 0.15%. This difference is due primarily to OPP's inclusion of contributions of skin-bound residue from the stratum corneum and epidermis that *in vivo* studies had shown were bioavailable.

[2] Converted SEM to SD, where SD = (SEM)SQRT(N)= (SEM)SQRT(5)=SEM(2.24)

2) Bridging the DAF for TECTO 500 SC to Maxim Quattro

The registrant wanted to bridge the DAF for TECTO 500 SC to Maxim Quattro. OPP has considered the chemical composition of these formulations as well the acute dermal toxicity profiles and agrees with the registrant that both are sufficiently similar to support bridging the DAF. The rationale in support of this is described in detail below.

Considerations for bridging a DAF between two different formulations include the chemical composition (both the concentration of the a.i. and other components of the formulation that could influence dermal absorption) and whether or not the toxicity profiles are similar. These are described below in the context of bridging the DAF.

- *Concentration of the a.i.* The TECTO 500 SC and Maxim Quattro formulations differ in the concentration of the a.i. TECTO 500 SC has 50.0% a.i. The DAF for TECTO 500 SC is based on a 50-X dilution (a 1% solution). Importantly, the percentage of the absorbed dose for this 1% solution was at least 10-fold higher than the concentrate in all *in vivo* and *in vitro* test systems. This is expected, since the percent absorption usually increases with decreasing concentration. The concentration of thiabendazole in Maxim Quattro is about half that of TECTO 500 SC, at 26.5%. Maxim Quattro can be diluted during seed treatments, but dilution would most likely be in an enclosed system. Therefore, operators would be most likely exposed to the concentrate. Since the DAF is based on a concentration of thiabendazole (1%) that is 26-fold less than that in Maxim Quattro, and since the data with TECTO 500 SC demonstrate that the DAF for thiabendazole increases with increasing dilution, a DAF for Maxim Quattro of 0.5% is conservative. Therefore, the different concentrations of thiabendazole in TECTO 500 SC and Maxim Quattro in the concentrate are not of concern to OPP for bridging the DAF.
- *Formulation composition.* The Agency has reviewed both formulations and has low concern for these formulations to differently impact dermal absorption of the a.i.
- *Dermal toxicity profile.* The registrant noted that the dermal toxicity profiles of TECTO 500 SC and Maxim Quattro are similar, with both causing dermal sensitization. Maxim Quattro causes slight acute dermal irritation in rabbits, whereas TECTO 500 SC does not (MRID 47705106). Severe dermal irritation that compromises the skin barrier would be expected to increase dermal penetration, but OPP considers the slight, reversible erythema caused by Maxim Quattro (MRID 47705128) unlikely to compromise the skin barrier. OPP agrees that the acute dermal toxicity profiles of TECTO 500SC and Maxim Quattro are sufficient to support bridging the DAF.

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