May 30, 2013

BASF Corporation

Comments on final GreenScreen™ assessment of Hexamoll® DINCH®

The conclusions by Tox Services LLC for potential endocrine activity are incorrect and inconsistent with those reached by BASF SE, the European Food Safety Authority (EFSA), the Australian National Industrial Chemicals Notification and Assessment Scheme (NICNAS), and the EU Scientific Committee on Emerging and Newly-identified Health Risks (SCENIHR).

Potential anti-androgenic effects

BASF substantially disagrees with ToxServices LLC and is convinced that the data show no anti-androgenic related endocrine activity for Hexamoll® DINCH®. This conclusion also was reached in the Australian NICNAS assessment:

> *No significant treatment-related effects on ano-genital distance were observed in any of the reproductive toxicity studies, suggesting that the* ***notified chemical does not possess endocrine disrupting effects of the kind seen with phthalate esters, e.g. the anti-androgenic effects*** *observed for dibutyl phthalate . . . (NICNAS 2008, p. 12 of 54).*[1]

In addition, the NICNAS report contained the following discussion about the very detailed pre/peri/post-natal developmental study:

> *There was a marginal (about 7-8% lower than the respective control values), but statistically significant decrease of the anogenital distance (AGD) in the high dose males and of the anogenital index (AGI) in high dose males and females. These were considered to be spurious, with no biological relevance because:*
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> - ***all other corresponding sexual development parameters did not show any substance-related adverse effects***
> - *the female AGI was lowered to the same extent as the male AGI, which is contradictory for the reduction in AGI being an indicator of an impaired androgen-medicated development of the male reproductive tract; and*
> - *the variability in the open literature were considered to be similar to those seen the present study.*
>
> *In addition, any effects on sexual development/reproductive performance were investigated in the follow-up full-scale two-generation study . . .* [NICNAS 2008, p. 41 of 54]

In addition, the European Food Safety Authority concluded that there were no reproductive or developmental effects:

[1] The NICNAS assessment was submitted to ToxServices LLC early in the project; i.e., this and other references to the NICNAS report are not new information.

No evidence of developmental or reproductive toxicity was obtained in prenatal and two-generation toxicity studies in Wistar rats and in rabbits, up to the highest administered dose of 1000 mg/kg bw/day. [this conclusion would have considered any developmental changes to male and female sexual organs]

Our conclusion is further supported by the work of L. E. Gray, US EPA, who has tested Hexamoll® DINCH® in a screening test that showed no indication of anti-androgenic activity based on the absence of any effects on fetal testosterone levels.[2]

Potential thyroid effects

The discussion on Page 15 (Appendix B) around the indirect mechanism of the thyroid effects is irrelevant. We agree that the thyroid effects are not due to peroxisome proliferation and that Hexamoll® DINCH® is not a peroxisome proliferator. As noted in the NICINAS report:

Lack of proliferative effects on peroxisomes

No peroxisome proliferative effects related to activation of the PPARα receptor were observed for the notified chemical (c.f. phthalate esters like DINP). No effects were observed on cyanide-insensitive palmitoyl CoA oxidase in the 90-day study, and no peroxisome accumulation was observed in any of the repeat dose oral toxicity studies. [NICNAS 2008, p. 12 of 54]

On the other hand, NICNAS concluded that the thyroid effects are due to an indirect mechanism:

The proposal that thyroid effects of the notified chemical in rats are associated with an indirect mechanism was supported by the performance of special mechanistic studies. These demonstrated that, at relevant dose rates in rats, hepatic metabolic pathways involved in T4 conjugation are strongly induced, and that T3, T4 and FSH levels are perturbed in a manner consistent with an indirectly acting enzyme inducer (phenobarbital). [NICNAS 2008, p.11 of 54]

EFSA also reached a similar conclusion:

Considering the absence of genotoxic properties, the induction of follicular cell hyperplasia and adenomas in rat thyroid can be attributed to a non-genotoxic, indirect mechanism. As rodents are far more sensitive than humans to chemical disturbance of thyroid function (IARC, 1999), the effects on thyroid observed in 90 days and chronic toxicity/carcinogenicity studies are not appropriate to set a TDI.

The data and these conclusions by competent regulatory bodies do not support a conclusion that the observed thyroid effects are evidence of adverse endocrine activity.

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[2] See http://cfpub.epa.gov/si/si_public_record_report.cfm?dirEntryId=230785 and also the presentation at the CPSC Chronic Hazard Advisory Panel meeting, July 2010 (Slide 8): http://www.cpsc.gov//PageFiles/126385/gray.pdf.