5 February 2016

Comments of Endura S.p.A. on: 10.9 Carcinogenicity

CLH report on

tetramethrin (ISO); (1,3-dioxo-1,3,4,5,6,7-hexahydro-2H-isoindol-2-yl)methyl 2,2-dimethyl-3-(2-methylprop-1-en-1-yl)cyclopropanecarboxylate

CLH proposal:	Carcinogenicity, category 2, H351
Endura S.p.A. proposal:	No classification
Comment of Endura S.p.A.:	Tetramethrin (TTM) produced Leydig cell tumours (LCTs) in the rat in several carcinogenicity studies in various rat strains. Since these LCTs were only observed in rats and this finding has a high baseline incidence in the rat, a classification as Carc 2 was proposed by the RMS. However, if it can be demonstrated that the mechanism of LCT formation in the rat is not relevant for humans, TTM should not be classified for carcinogenicity. LCTs in rats arise from a wide range of physiological and or endocrine perturbations, generally involving sustained stimulation of testicular interstitial cells by luteinizing hormone (LH). To focus systematically on the most probable mechanism for such an effect it is valuable to assess the existing available data such as organ weights, pathological change in endocrine tissues and hormonal response from general and reproductive toxicology, relevant acute assays, and the outcome of investigative studies in rats treated with TTM. *Endura has a letter of access to refer to most of these studies for the review of TTM under the Biocidal Products Regulation, but does not have the right to see the full study reports. Despite this, from available evidence Endura proposes to eliminate certain putative mechanisms of action.* Notwithstanding, the relevance of LCTs in rats for human health is a matter of debate due to its high background incidence in rats. An EU Commission Working Group of Specialised Experts has concluded the following (ECBI/08/04 Rev.2):

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Substances causing ***Leydig cell tumours in rats by perturbating*** [sic!] ***the HPT axis should be classified in Carc. Cat. 3*** [= Carc 2 in CLP], ***unless the mechanism*** *of perturbation of this axis* ***can be proven not to be relevant*** *for human Leydig cell carcinogenesis.* ***Currently identified mechanisms considered not relevant for humans are dopamine agonists and GnRH agonists****.* [emphasis added].

On these two mechanisms, no information is available for TTM.

Instead, two other mechanisms that are potential causes of LCTs can be excluded for TTM based on the negative Hershberger assay:

- Androgen receptor agonism
- 5-alpha reductase inhibition

In addition, an uterotrophic assay in rats demonstrated absence of oestrogenic activity of TTM, thus excluding a third potential MoA:

- Oestrogen agonism

Two further mechanisms that are potential causes of LCTs might be excluded based on the two-generation reproduction toxicity and/or based on repeated dose toxicity studies. As explained above, Endura cannot review the full study reports, but only the respective study summaries:

- Inhibition of testicular testosterone synthesis: Verify male fertility, weight/appearance of prostate gland and/or seminal vesicle. Judging from the information available in Doc IIIA, there were no effects on these tissues in the chronic dog study, the carcinogenicity studies in rodents, or the two-generation study in rats.
- Aromatase inhibition: Verify weight/appearance of mammary gland, uterus, and/or ovary. This might be the MoA behind the weak anti-oestrogenic activity seen in the uterotrophic assay. Judging from the information available in Doc IIIA, there were no effects on these tissues in the chronic dog study, the carcinogenicity studies in rodents, or the two-generation study in rats.

Consequently, the above mentioned five mechanisms can be excluded based on the information available to Endura. Dopamine and GnRH agonism remain as possible mechanisms. These two are not relevant for humans.

There is also a realistic possibility that increased testosterone excretion secondary to induced hepatic phase-II metabolism at high dose levels leads to Leydig cell (LC) stimulation. This is similar to the well-known situation with thyroid hormone 'wasteage'. Steroid hormones in the rat are thought to be more susceptible to conjugation and subsequent urinary excretion than in humans. This is due to the lack of expression of the steroid-hormone-binding globulin (SHBG) in adult rats. TTM causes early and marked liver enlargement and cellular hypertrophy (30%-increase in

relative liver weight after 28-day treatment with 369 mg TTM/kg bw/day) which is suggestive of a stimulation of hepatic xenobiotic metabolism. This only occurs at very high dose levels in rats which exceed by greater than 60,000-fold the typical exposure to TTM for man from its use in household insecticides (Doc II, Section 7.2.3). So a clear threshold would exist for man indicating that this putative mechanism in the rat would not be relevant for man. This is suggestive of a stimulation of hepatic xenobiotic metabolism.

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