Bayer CropScience

Monheim, March 21, 2014

Comment of Bayer CropScience Regulatory Toxicology on the proposed classification and labelling of thiacloprid as Carc. Cat.3; R40 / Carc. 2; H351

Triggered by a seminar offered by the Hannover Graduate School for Veterinary Pathobiology, Neuroinfectiology and Translational Medicine, the Department of Pathology at the University of Veterinary Medicine in Hannover, Germany, and the European Society of Toxicologic Pathology on February 21 and 22, 2014 on "Prolactin and tumour patterns – Relevance for man", Bayer CropScience became aware that the findings in the 2 year rat study on thiacloprid (including the increased incidence of uterine adenocarcinoma) reflect very well the pattern of changes occurring in cases of hypoprolactinaemia. In the case of Thiacloprid, the increased incidences of uterine adenocarcinomas in rats, as well as ovarian luteomas in mice, could potentially be attributed to this mode of action, which is non-relevant in humans (Ben-Jonathan et al, 2008, Hargreaves and Harleman, 2011). Therefore, Bayer CropScience asked Professor J. H. Harleman, who gave the lecture at the seminar, to review the data on thiacloprid.

In his expert opinion, Professor Harleman concluded that the findings in the longterm study (2 year) in rats indicate sustained reduced levels of prolactin as the mode of action for uterine adenocarcinoma in rat, and potentially for the ovarian luteoma in mouse.

<u>The following findings were noted in the thiacloprid 2-year rat study</u> and are consistent with the sequelae of chronic hypoprolactinaemia in rat carcinogenicity studies (Hargreaves and Harleman, 2011):

- an increased incidence of uterine neoplasia,
- a reduced incidence of pituitary tumours,
- a reduced incidence of tumours, galactoceles and lacteal cysts in the mammary gland,
- an increased incidence of ovarian cysts and
- a lower incidence and severity of chronic progressive nephropathy in females.
- Furthermore, there was also an increased incidence of Leydig cell hypertrophy and
- a reduction of adrenal tumours in male rats, which are also known to appear in the context of this MOA.

The Mode of Action hypothesis for the thiacloprid induced uterine adenocarcinomas is as follows:

1. Some cholinergic agonists have been reported to inhibit prolactin release (Muraki, 1979)
2. Prolactin is luteotrophic in rats, but not in humans;
3. Inhibition of prolactin release results in an increased Estrogen:Progesterone (E:P) ratio in rats;
4. An increased E:P ratio lengthens the duration of reproductive viability and cyclicity in the ageing rat leading to continued estrogenic stimulation of uterine growth;
5. Thus, reduced levels of prolactin could lead to uterine adenocarcinomas in rats
6. The proposed mode of action for the observed increase in uterine tumors is: thiacloprid-induced reduction in prolactin secretion, thereby suppressing its luteotrophic effect in the rat. This mode of action is not relevant to humans (Ben-Jonathan et al, 2008, Hargreaves and Harleman, 2011).

In order to investigate the presumed Thiacloprid-induced hypoprolactinemia in rodents Bayer CropScience will conduct several mechanistic studies in a tiered approach, including the assessment of cholinergic and dopaminergic pathways.

In addition, Bayer CropScience will ask an endocrine expert to assess the thiacloprid data on sex hormones and steroidogenesis in consideration of the proposed MoA.

Bayer CropScience requests to review the MoA against the offered background of scientific knowledge and thus the justification of the applied classification as Carc. Cat.3; R40 / Carc. 2; H351.