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Comparative evaluation of SDHI fungicide toxicity with special emphasis on their carcinogenic potential

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Succinate dehydrogenase inhibitors, fungicides, carcinogenicity, mode of action, toxicity, risk assessment

Aim of the study
Animal studies show that many SDHIs, when administered orally at high doses, lead to the formation of adenomas and carcinomas (mainly in the liver, uterus and thyroid) in rodents. The Federal Food Safety and Veterinary Office (FSVO) has identified a need to evaluate the carcinogenic potential of substances of the SDHI fungicide class. The FSVO has therefore requested a comparative assessment of available animal data on SDHI carcinogenicity and other potentially relevant endpoints. The aim is to compare tumorigenicity and establish whether effect patterns and modes of action (MOAs) can be recognized across the group of SDHIs.

Material and methods
All publicly available data, including both peer-reviewed literature and reports from government and international bodies were used to gain an overview about the subject and select relevant SDHIs. Available non-public individual study data from dossiers submitted to competent authorities for marketing authorization were used to analyze specific SDHIs in detail with consultation from external histopathologist and statisticians to clear open questions and to be able to compare the SDHI outcomes. Modes of action were identified which were used to explain tumor occurrences.

Results and significance
A mode of action was identified for increased uterine tumors combined with reduced mammary gland tumors, as already described by EFSA. This mode of action proposes that reduced body fat leads to suppression of the age-related increase in prolactin, which leads to reduced mammary gland proliferation and delayed reproductive senescence, maintaining uterine and vaginal mucosal cyclicity, resulting in increased incidence of uterine adenocarcinoma. A major uncertainty about the MoA for uterine tumors involving reduced body fat is that the high dose in carcinogenicity studies normally produces reduced body weight (so called maximum tolerated dose, MTD), but not all substances induce uterine tumors. In addition to reduced body fat, there must therefore be some specific (maybe metabolic) effect of SDHIs which leads to uterine tumors, but this has not been adequately characterized. In view of data gaps such as missing body fat and leptin measurements, and apparent discrepancies in effects on food utilization and vaginal mucification, considerable uncertainty remains about the proposed MoA for uterine tumors. Implications concerning 3R, including access to non-public study data, are discussed.

Publications, posters and presentations
Review to be submitted for publication in Frontiers in Regulatory Toxicology

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