

Metofluthrin

Metofluthrin is a Type I pyrethroid ester pesticide that is used as a mosquito repellent. It can be dispersed into the air from two types of devices: paper strips from which the metofluthrin slowly evaporates, and personal clip-on diffusers from which metofluthrin vaporizes after activation of a battery-powered fan. Consumers will be exposed to metofluthrin through the use of these products.

Metofluthrin passed the animal data screen, underwent a preliminary toxicological evaluation, and is being brought to the Carcinogen Identification Committee for consultation. This is a compilation of the relevant studies identified during the preliminary toxicological evaluation.

Epidemiological data

No cancer epidemiology studies were identified.

Animal carcinogenicity data

- Long-term feeding studies in rats
 - Two-year studies in male and female Wistar rats: U.S. EPA (2007)
 - *Increase in hepatocellular carcinoma, and hepatocellular adenoma and carcinoma (combined) in males (by pairwise comparison and trend)*
 - *Increase in hepatocellular carcinoma, and hepatocellular adenoma and carcinoma (combined) in females (by pairwise comparison and trend)*
- Long-term feeding studies in mice
 - 78-week studies in male and female CD-1 mice: U.S. EPA (2007)
 - *No treatment-related tumor findings in males or females*

Other relevant data

- Genotoxicity
 - As reviewed in U.S. EPA (2007; pp. 20 - 21)
 - *Salmonella typhimurium* reverse mutagen assays (*negative*)
 - *Escherichia coli* WP2uvrA reverse mutation assays (*negative*)
 - *In vitro* chromosomal aberration assay in Chinese hamster lung cells (*negative*)
 - *In vivo* mouse micronucleus assay (*negative*)

- Structure-activity considerations: U.S. EPA (2007; pp. 21 - 22)
 - Structurally similar to other Type I pyrethroid pesticides, several of which induce tumors in rodents (e.g., resmethrin, permethrin, tetramethrin, bifenthrin, transfluthrin)
 - Resmethrin: Classified as “likely to be carcinogenic to humans” by U.S. EPA in 2005; listed under Proposition 65 as a carcinogen
 - Permethrin: Classified as “likely to be carcinogenic to humans” by U.S. EPA in 2002
- Mechanistic considerations
 - Liver tumors and mitogenic proliferative responses: Hirose *et al.* (2009), Yamada *et al.* (2009)

Reviews

- U.S. EPA (2007)

References¹

Hirose Y, Nagahori H, Yamada T, Deguchi Y, Tomigahara Y, Nishioka K, Uwagawa S, Kawamura S, Isobe N, Lake B, Okuno Y (2009). Comparison of the effects of the synthetic pyrethroid metofluthrin and phenobarbital on CYP2B form induction and replicative DNA synthesis in cultured rat and human hepatocytes. *Toxicology* **258**:64-69.

U.S. Environmental Protection Agency (U.S. EPA, 2007). Metofluthrin: Second Report of the Cancer Assessment Review Committee. PC Code: 109709, Memorandum July 26, 2007, from Jessica Kidwell to Kim Harper. Office of Prevention, Pesticides and Toxic Substances.

Yamada T, Uwagawa S, Okuno Y, Cohen SM, Kaneko H (2009). Case study: an evaluation of the human relevance of the synthetic pyrethroid metofluthrin-induced liver tumors in rats based on mode of action. *Toxicol Sci* **108**(1):59-68.

¹ Excerpts or the complete publication have been provided to members of the Carcinogen Identification Committee, in the order in which they are discussed in this document.