

Type I Pyrethroids

Type I pyrethroids are synthetic insecticides that are similar in structure but more toxic to insects and mammals than naturally occurring pyrethrin (pyrethrum) insecticides. Pyrethroids are widely used on agricultural crops. Other uses include home and garden pest control products, treatment of mosquito nets, control of human lice (in shampoos and body lotions), structural pest control, and landscape maintenance. Exposure may occur via inhalation, dermal contact, and through consumption of foods containing residues. Type I pyrethroids include: allethrin, bifenthrin, permethrin, phenothrin, resmethrin, tefluthrin, tetramethrin, metofluthrin, and transfluthrin. Resmethrin was added to the Proposition 65 list of carcinogens in 2008.

Type I pyrethroids as a group passed the human and animal data screens, underwent a preliminary toxicological evaluation, and are being brought to the Carcinogen Identification Committee (CIC) for consultation. This is a compilation of the relevant studies identified during the preliminary toxicological evaluation. The CIC is being asked to advise OEHHA on whether Type I pyrethroids as a group, or specific individual compounds within the group (that are not currently listed) should be considered for listing at a future CIC meeting.

Epidemiological data

Allethrin

- Case-control studies
 - Hospital-based case control study of leukemia in children < 2 years old in Brazil (exposure characterized based on reported maternal exposure via occupational, residential, or unintentional contact 3 months prior to conception, during pregnancy, and 3 months postpartum): Ferreira *et al.* (2013)
 - *In children 0-11 months old, increased risk of acute myeloid leukemia (AML) (adjusted Odds Ratio (OR) = 6.19 [Confidence Interval (CI): 2.07-18.56]) associated with in utero allethrin exposure*

Permethrin

- Cohort studies
 - Prospective study of 49,093 pesticide applicators in the Agricultural Health Study (AHS) in Iowa and North Carolina (1993-1997)
 - *Increased risk of all lymphohematopoietic cancers in the top tertile of permethrin lifetime exposure-days (Relative Risk (RR) = 1.64 [CI: 1.07-2.52]). Increased risk of multiple myeloma in the top tertile of permethrin lifetime exposure-days (RR = 5.72 [CI: 2.76–11.87]) and intensity-weighted lifetime exposure-days (RR = 5.01 [CI: 2.41–10.42]),*

with significant dose-response trends by both exposure metrics: Rusiecki et al. (2009)

- *Increased risk of multiple myeloma associated with ever permethrin use (RR = 2.2 [CI: 1.4–3.5]), and with high use (RR = 3.1 [CI: 1.5–6.2]) with significant dose-response trend: Alavanja et al. (2014)*
- Case-control studies
 - Nested case-control study of the interaction between permethrin use, 8q24 chromosomal variants, and prostate cancer risk in the AHS study: Koutros et al. (2010)
 - *Permethrin exposure increased the risk for prostate cancer in individuals with 8q24 chromosome variants (ORs associated with three different variants: OR = 2.67 [CI: 1.26-5.64]; OR = 2.73 [CI: 1.31-5.69]; OR = 3.37 [CI: 1.40-8.07]), with significant dose-response trends*
 - Hospital-based case control study of leukemia in children < 2 years old in Brazil (exposure characterized based on reported maternal exposure via occupational, residential, or unintentional contact 3 months prior to conception, during pregnancy, and 3 months postpartum): Ferreira et al. (2013)
 - *In children 0-11 months old, increased risk of acute lymphoid leukemia (ALL) (adjusted OR = 2.47 [CI: 1.17-5.25]) and AML (adjusted OR = 7.28 [CI: 2.60-20.38]) associated with in utero permethrin exposure*

Phenothrin

- Case-control studies
 - Hospital-based case control study of leukemia in children < 2 years old in Brazil (exposure characterized based on reported maternal exposure via occupational, residential, or unintentional contact 3 months prior to conception, during pregnancy, and 3 months postpartum): Ferreira et al. (2013)
 - *In children 0-11 months old, increased risk of ALL (crude OR = 7.58 [CI: 1.91-30.08]; adjusted OR = 4.16 [CI: 0.85-20.29]) associated with in utero phenothrin exposure*
 - *In children 12-23 months old, increased risk of AML (adjusted OR = 8.43 [CI: 1.59-44.75]) associated with in utero phenothrin exposure*

Tetramethrin

- Case-control studies
 - Hospital-based case control study of leukemia in children < 2 years old in Brazil (exposure characterized based on reported maternal exposure via occupational, residential, or unintentional contact 3 months prior to conception, during pregnancy, and 3 months postpartum): Ferreira et al. (2013)
 - *In children 0-11 months old, increased risk of AML (adjusted OR = 6.19 [CI: 2.07-18.56]) associated with in utero tetramethrin exposure*

Animal carcinogenicity data

Bifenthrin

- Long-term feeding studies in mice
 - 20- to 21-month studies in male and female Swiss mice: Geiger (1986), as reviewed in ECHA (2009)
 - *Increase in urinary bladder tumors (by pairwise comparison) in males*
 - *Increases in lymphoblastic leukemia and lung tumors (by pairwise comparisons) in females*
- Long-term feeding studies in rats
 - 104-week studies in male Sprague-Dawley and female Tac (SD) fBR rats: McCarty (1986), as reviewed in ECHA (2009)
 - *No treatment-related tumor findings*

Metofluthrin

- Long-term feeding studies in rats
 - Two-year studies in male and female HanBrl:WIST (SPF) rats: Schmid *et al.* (2005), as reviewed by US EPA (2007) and DPR (2006)
 - *Increase in liver adenomas (by trend), carcinomas (by pairwise comparison and trend), and combined adenomas and carcinomas (by pairwise comparison and trend) in males*
 - *Increase in liver adenomas, carcinomas, and combined adenomas and carcinomas (each by pairwise comparison and trend) in females*
- Long-term feeding studies in mice
 - 78-week studies in male and female CD-1 mice: Schmid *et al.* (2005), as reviewed by US EPA (2007) and DPR (2006)
 - *No treatment-related tumor findings*

Permethrin

- Long-term feeding studies in mice
 - Two-year studies in male and female CD-1 mice: Bio/dynamics (1977), as reviewed by DPR (1997)
 - *No treatment-related tumor findings*
 - Two-year studies in male and female Alderley Park mice: ICI (1977), as reviewed by DPR (1997) and US EPA (2002)
 - *No treatment-related tumor findings*
 - 91-week studies in male and female CFLP mice: Wellcome (1980), as reviewed by DPR (1997)
 - *No treatment-related tumor findings in males*
 - *Increase in lung adenomas (by pairwise comparison and trend), carcinomas (by trend), and combined adenomas and carcinomas (by pairwise comparison and trend) in females*
 - Two-year studies in male and female Swiss mice: ICI (1987), as reviewed by DPR (1997) and US EPA (2002)
 - *No treatment-related tumor findings*

- Two-year studies in male and female CD-1 mice: Bio/dynamics (1979), as reviewed by DPR (1997) and US EPA (2002)
 - *Increase in liver adenomas (by pairwise comparison and trend) and combined adenomas and carcinomas (by pairwise comparison) in males*
 - *Increases in lung adenomas, lung carcinomas, and combined lung adenomas and carcinomas (each by pairwise comparison and trend) and liver adenomas (by pairwise comparison and trend) and combined liver adenomas and carcinomas (by pairwise comparison) in females*
- Long-term feeding studies in rats
 - Two-year studies in male and female Long Evans rats: Bio/dynamics (1977), as reviewed by DPR (1997) and US EPA (2002)
 - *No treatment-related tumor findings*
 - Two-year studies in male and female Wistar rats: ICI (1977), as reviewed by DPR (1997) and US EPA (2002)
 - *No treatment-related tumor findings*
 - Two-year studies in male and female Wistar rats: Wellcome (1980), as reviewed by DPR (1997)
 - *No treatment-related tumor findings*
 - Two-year studies in male and female Alpk:AP Wistar-derived rats: ICI (1987), as reviewed by DPR (1997) and US EPA (2002)
 - *No treatment-related tumor findings*
- Long-term feeding studies in dogs
 - One-year studies in male and female dogs: ICI (1982), as reviewed by DPR (1997)
 - *No treatment-related tumor findings*

Phenothrin

- Long-term feeding studies in rats
 - Two-year studies in male and female Charles River rats: IBT (1980), as reviewed by US EPA (1989b); DPR (1996)
 - *No treatment-related tumor findings*
 - Two-year studies in male and female Fischer 344 rats: Martin (1992), as reviewed by US EPA (1989b); DPR (1996)
 - *No treatment-related tumor findings*
 - Two-year studies in male and female Fischer 344 rats: Aughton (1995), as reviewed by US EPA (1996)
 - *Increase in liver adenomas (by trend), carcinomas (by pairwise comparison and trend), and combined adenomas and carcinomas (by pairwise comparison and trend) in males*
 - *Increase in liver carcinomas, and combined adenomas and carcinomas (each by pairwise comparison and trend) in females*

- Long-term feeding studies in mice
 - Two-year studies in male and female B6C3F1 mice: Amyes (1987), as reviewed by US EPA (1989b); DPR (1996)
 - *No treatment-related tumor findings in males*
 - *Increase in combined liver adenomas and carcinomas (by pairwise comparison) in females*
- Long-term feeding studies in dogs
 - One-year studies in male and female beagle dogs: Cox (1987), as reviewed by DPR (1996)
 - *No treatment-related tumor findings*

Tefluthrin

- Long-term studies in rats
 - Studies in male and female Alpk:AP rats: Stonard (1986), as reviewed by US EPA (2012)
 - *No treatment-related tumor findings in males*
 - *Increase in uterine adenocarcinomas (by trend) in females*
- Long-term studies in mice
 - Studies in male and female SPF Alk:AP mice: Wickramaratne (1986), as reviewed by US EPA (2012)
 - *Increase in pituitary gland adenomas, and combined adenomas and carcinomas (each by trend) in males*
 - *Increase in pituitary gland pars intermedia adenomas (by trend) and combined adenomas and carcinomas (by pairwise comparison and trend) in females*

Tetramethrin

- Long-term feeding studies in rats
 - Life-time studies (exposed during pre-conception, *in utero*, lactation, and weaning through 104 weeks) in male and female CD-1 Sprague-Dawley rats: Hazleton Laboratories (1974), as reviewed by US EPA (1989a)
 - *Increase in testicular interstitial cell adenomas (by pairwise comparison and trend) in males*
 - *No treatment-related tumor findings in females*
 - Life-time studies (exposed during pre-conception, *in utero*, lactation, and weaning through 104 weeks) in male and female CD-1 Sprague-Dawley and Long Evans Hooded rats: Hazleton Laboratories (1981), as reviewed by US EPA (1989a)
 - *Increase in testicular interstitial cell adenomas (by pairwise comparison and trend) in males of both strains*
 - *No treatment-related tumor findings in females of either strain*
- Long-term feeding studies in mice
 - Two-year studies in male and female B6C3F1 mice: Hazleton Laboratories (1986), as reviewed by US EPA (1989a)
 - *Increase in Harderian gland adenomas (by pairwise comparison) in males*

- *No treatment-related tumor findings in females*
- 78-week studies in male and female CD-1 mice: Moore (1995), as reviewed by DPR (2003)
 - *Increase in hepatocellular carcinomas (incidence/significance not reported in DPR report) in males*

Transfluthrin

- Long-term feeding studies in rats
 - Two-year studies in male and female rats: Bayer (1999), as reviewed by WHO (2006)
 - *Increase in urinary bladder papillomas and carcinomas in females (tumor incidences not given in report)*
- Long-term feeding studies in mice
 - Two-year studies in male and female mice: Bayer (1999), as reviewed by WHO (2006)
 - *Increase in liver adenomas in females (tumor incidence not given in report)*

Resmethrin

Resmethrin, a Proposition 65 carcinogen, induced malignant and combined malignant and benign liver tumors in female rats and male mice when administered in the diet (US EPA, 2005).

Other relevant data

- Genotoxicity

Allethrin

- As reviewed in ATSDR (2003)
 - *Salmonella* reverse mutation assays, strains TA100 (+/-S9)¹, JK3 (-S9), JK947 (-S9), TA97 (+S9), TA104 (+S9) (*positive*)
 - *Salmonella* reverse mutation assays, strains TA97 (-S9), TA98(+/-S9), TA104 (-S9), TA1535(+/-S9), TA1537(+/-S9), TA1538(+/-S9), JK1 (+/-S9) (*negative*)
 - *E. coli* mutation assays in strain WP2 *her* without activation (*negative*)

Bifenthrin

- As reviewed in US EPA (1992)
 - *Salmonella* reverse mutation assays, strains TA98, TA100, TA1535, TA1537, and TA1538 (+/-S9) (*negative*)
 - Hamster hypoxanthine-guanine-phosphoribosyl-transferase (HGPRT) mutation assays in mouse lymphoma cells (*negative*)
 - Forward mutation at the TK locus in mouse lymphoma cells (*negative*)

¹ +S9: with S9 activation; -S9: without S9 activation; +/-S9: with and without S9 activation

- Chromosomal aberration (CA) assays in Chinese hamster ovary (CHO) cells and rat bone marrow cells *in vitro* (negative)
- Unscheduled DNA synthesis (UDS) in rat hepatocytes *in vitro* (negative)
- Sister chromatid exchange (SCE) in CHO cells *in vitro* (negative)
- As reviewed in ECHA (2009)
 - CA in rats *in vivo* (negative)
 - Micronucleus (MN) formation in mouse bone marrow *in vivo* (negative)
 - UDS in rat hepatocytes *in vivo* (negative)

Metofluthrin

- As reviewed in DPR (2006)
 - *Salmonella* reverse mutation assays, strains TA98, TA100, TA1535, and TA1538 and *E. coli* strain WP2uvrA (+/-S9) (negative)
 - CA in Chinese hamster lung cells *in vitro* (negative)
 - MN formation in mice *in vivo* (negative)

Permethrin

- As reviewed in ATSDR (2003)
 - *In vitro*
 - *Salmonella* reverse mutation assays, strains TA97, TA98, TA100, TA1535, TA1537, TA1538 (+/-S9) (negative)
 - *E. coli*, strain WP2 *her* (negative)
 - Gene mutation assay in CHO cells (negative)
 - Mitochondrial mutation assay in yeast strains A and HB with activation (positive) and without activation (negative)
 - CA in CHO cells *in vitro* (positive)
 - CA in human lymphocytes *in vitro* without activation (positive) and with activation (negative)
 - SCE in human lymphocytes *in vitro* (weak positive)
 - MN formation in human lymphocytes *in vitro* (positive/negative)
 - MN formation in human whole blood *in vitro* (negative)
 - *In vivo*
 - CA in rat bone marrow *in vivo* (positive)
 - MN formation in rat bone marrow (positive) and mouse bone marrow (negative)
 - Sex linked recessive lethal mutations in *Drosophila* *in vivo* (positive/negative)

Phenothrin

- As reviewed in DPR (1996)
 - *Salmonella* reverse mutation assays, strains TA98, TA100, TA1535, TA1537, TA1538 and *E. coli* strain WP2uvrA (negative)
 - CA in CHO cells *in vitro* (negative)
 - UDS in human HeLa cells *in vitro* (negative)

Tefluthrin

- As reviewed in US EPA (2012) and US EPA (2013)
 - *In vitro*
 - *Salmonella* reverse mutation assays, strains TA1535, TA1537, TA1538, TA98, TA100 (+/-S9) (*negative*)
 - L5178Y/TK forward mutation assay in mammalian cells *in vitro* (+/-S9) (*negative*)
 - UDS in rat hepatocytes *in vitro* (*negative*)
 - *In vitro* mouse lymphoma assay (*negative*)
 - CA in CHO cells *in vitro* (*negative*)
 - *In vivo*
 - CA in rat bone marrow *in vivo* (*negative*)
 - MN formation in mice *in vivo* (*negative*)
 - Dominant lethal assay in mice *in vivo* (*negative*)

Tetramethrin

- As reviewed in DPR (2003)
 - *Salmonella* reverse mutation assays, strains TA97, TA98, TA100, TA1535, TA1538 and *E. coli* strain WP2uvrA (+/-S9) (*negative*)
 - UDS in rat hepatocytes *in vitro* (*negative*)
 - CA in mouse bone marrow *in vivo* (*negative*)

Transfluthrin

- As reviewed in WHO (2006)
 - *In vitro*
 - *Salmonella* reverse mutation assays, strains TA98, TA100, TA1535, and TA1537 (+/-S9) (*negative*)
 - HPRT-test in CHO cells *in vitro* (+/-S9) (*negative*)
 - Mitotic recombination assay in *Saccharomyces cerevisiae* D7 (+/-S9) (*negative*)
 - SCE in CHO cells *in vitro* (+/-S9) (*negative*)
 - UDS in rat hepatocytes *in vitro* (*negative*)
 - CA in human lymphocytes *in vitro* (+/-S9) (*negative*)
 - *In vivo*
 - UDS in mouse hepatocytes *in vivo* (*negative*)
 - MN formation in mouse bone marrow cells *in vivo* (*negative*)
 - Adduct formation in rat hepatocytes and urinary bladder cells *in vivo* (*negative*)

Resmethrin

Resmethrin, a Proposition 65 carcinogen, was negative in *S. typhimurium* assays (strains TA98, TA100, TA1535, TA1538) with and without S9 activation, an *in vitro* chromosome aberration assay in Chinese hamster ovary cells with and without S9

activation, and an unscheduled DNA synthesis assay in rat hepatocytes (US EPA, 2005).

- Mechanistic considerations
 - Endocrine disruption
 - Allethrin is an estrogen agonist: Kim *et al.* (2004)
 - Bifenthrin affects testosterone synthesis in adolescent male mice: Jin *et al.* (2015)
 - Permethrin interacts with hormone receptors
 - Estrogen agonist and antagonist: Kim *et al.* (2004); Du *et al.* (2010)
 - Androgen antagonist: Du *et al.* (2010)
 - Thyroid receptor antagonist: Du *et al.* (2010)
 - Tetramethrin interacts with hormone receptors
 - Thyroid receptor antagonist: Du *et al.* (2010)
 - Estrogen agonist: Kim *et al.* (2004)
 - Gap junction intercellular communication
 - Permethrin inhibited GJIC at non-cytotoxic concentrations in Balb/c3T3 cells: Tateno *et al.* (1993)

Reviews

Permethrin

- IARC (1991)

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