

## Atrazine

Atrazine is a selective chlorotriazine pre-and post-emergence herbicide used on agricultural crops such as corn and sorghum, and on rights-of-way. Atrazine and its degradation products deethylatrazine, deisopropylatrazine, and diaminochlorotriazine (DACT) are often detected in surface and ground waters. Occupational exposure may occur during manufacture and agricultural use. Exposure of the general population may occur as a result of pesticide drift and consumption of residues in food and water.

Atrazine passed the human and animal data screens, 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

- Cohort studies of triazine manufacturing workers
  - *Increased risks of prostate cancer and non-Hodgkin lymphoma:* MacLennan *et al.* (2002); MacLennan *et al.* (2003)
- Prospective cohort study of Iowa and North Carolina pesticide applicators in the Agricultural Health Study cohort
  - *No association between atrazine exposure and prostate cancer.* Alavanja *et al.* (2003)
  - *No association between atrazine exposure and cancer incidence:* Rusiecki *et al.* (2004)
- Case-control studies
  - *Increased risk of non-Hodgkin lymphoma:* Cantor *et al.* (1992); Hoar *et al.* (1986); Hoar *et al.* (1993); Zahm *et al.* (1993); De Roos *et al.* (2003)
  - *Increased risk of ovarian epithelial cancer.* Donna *et al.* (1989)
  - *No association between atrazine or triazine use and leukemia* (Brown *et al.*, 1990), *multiple myeloma* (Burmeister, 1990; Brown *et al.*, 1993), *colon cancer* (Hoar *et al.*, 1985), *Hodgkin disease or soft tissue sarcoma* (Hoar *et al.*, 1986), *ovarian cancer* (Young *et al.*, 2005), *prostate cancer* (Hessel *et al.*, 2004)
- Ecologic studies
  - *Increased risk of stomach cancer, leukemia* (Van Leeuwen *et al.*, 1999), *prostate cancer, brain cancer, testicular cancer* (Mills, 1998), *and breast cancer* (Kettles *et al.*, 1997), *and potential association of bone, brain, leukemia and lymphoma* (Thorpe and Shirmohammadi, 2005)

- *No association with colon cancer (Van Leeuwen et al., 1999) or breast cancer (Hopenhayn-Rich et al., 2002; Muir et al., 2004; McElroy et al., 2007; Mills and Yang, 2006)*
- Review of epidemiology studies: IARC (1999)

### **Animal carcinogenicity data**

- Long-term feeding studies in rats
  - Two-year studies in male and female Sprague-Dawley rats: Mayhew *et al.* (1986), as reviewed in U.S. EPA (2002b, pp. 15-34)
    - *Increase in malignant mammary tumors in females (by pairwise comparison and trend)*
    - *Increase in interstitial cell tumors of the testes in males (by pairwise comparison and trend)*
  - Two-year studies in intact and ovariectomized (OVX) female Sprague-Dawley rats: Morseth (1998), as reviewed in U.S. EPA (2002b, pp. 15-34); IARC (1999, p. 812)
    - *Increase in mammary carcinoma (by pairwise comparison and trend) and fibroadenoma (by pairwise comparison) in intact females*
    - *No treatment-related tumor findings in OVX females*
  - 104-week feeding study in female Sprague-Dawley rats: Stevens *et al.* (1994)
    - *Increase in mammary gland fibroadenoma (by pairwise comparison)*
  - 104-week feeding study in female Sprague-Dawley rats after exposure *in utero*: Stevens *et al.* (1994)
    - *No increase in mammary tumors*
  - Two-year study in female Sprague-Dawley rats: Thakur (1992a), as reviewed in U.S. EPA (2002b, pp. 15-34)
    - *No treatment-related tumor findings*
  - One-year study in female Sprague-Dawley rats: Pettersen and Turnier (1995), as reviewed in U.S. EPA (2002b, pp. 15-34)
    - *Increase in mammary tumors (by pairwise comparison and trend)*
  - Lifetime studies in male and female Fischer rats: Pintér *et al.* (1990), as reviewed in U.S. EPA (2002b, pp. 15-34; IARC (1999, p. 81)
    - *Increase in benign mammary tumors in males (by pairwise comparison). Treated animals survived longer as compared to controls.*
    - *Increase in leukemia and lymphoma combined in females (by pairwise comparison)*

- Two-year studies in male and female F344 rats: Thakur (1992b), as reviewed in U.S. EPA (2002b, pp. 15-34)
  - *No treatment-related tumor findings*
- Long-term feeding studies in mice
  - 91-week studies in male and female CD-1 mice: Hazelette and Green (1987), as reviewed in U.S. EPA (2002b, pp. 15-34)
    - *No treatment-related tumor findings*
- Intraperitoneal injection study in mice
  - 375-day study in male Swiss albino mice (injected once every three days, for a total of 13 injections): Donna *et al.* (1986), as reviewed by IARC (1999, p. 83)
    - *Increase in lymphoma (by pairwise comparison)*
- Promotion study in rats
  - Female Sprague-Dawley rats were given a single initiating gavage dose of 7,12-dimethylbenz[a]anthracene, ovariectomized 19 weeks later, and then fed diet containing atrazine for 34-weeks: Ueda *et al.* (2005)
    - *Increased incidence and volume of mammary tumors*

#### Other relevant data

- Endocrine system effects
  - *Induction of aromatase (CYP19A1) expression (aromatase converts androgens to estrogens):* Fan *et al.* (2007); Holloway *et al.* (2007)
  - *Expression of estrogen target genes via G-protein coupled receptor 30 (GPR30):* Albanito *et al.* (2008)
    - GPR30s are found in numerous tissues, including the hypothalamus, and other regions of the brain, the pituitary, adrenal medulla, renal pelvis, and ovary
  - *Increased serum estrone and estradiol in male rats:* Modic *et al.* (2004); Stoker *et al.* (2000)
  - *Increased serum estrone in ovariectomized female rats:* Cooper *et al.* (2007)
  - *Increased adrenal corticosterone secretion in mice :* Pruett *et al.* (2003)
  - *Delayed mammary gland development in female Long-Evans rats exposed prenatally:* Enoch *et al.* (2007)
  - *Increased pituitary prolactin concentrations in 60-day old female Long-Evans rats exposed prenatally:* Enoch *et al.* (2007)

- *Decreased suckling-induced release of prolactin in rat dams, with subsequent increase in incidence of prostatitis in 120-day old male offspring: Stoker et al. (1999)*
- *Suppression of conversion of testosterone to dihydrotestosterone (DHT) in hypothalamus, anterior pituitary and prostate; reduced binding of DHT to androgen receptor in prostate; reduced pituitary, prostate and seminal vesicle weights in rats: as reviewed in Pogrmic et al. (2009)*
- *Reduced testis, seminal vesicle and ventral prostate weights in rats: Pogrmic et al. (2009)*
- *Reduced steroidogenesis gene expression in male rats: Pogrmic et al. (2009)*
- **Genotoxicity**
  - Review: U.S. EPA (2002b, pp. 35-45, Appendix Table 5)
    - Mutagenicity in *Salmonella* (negative)
    - Mutagenicity in *Escherichia coli* (negative)
    - Mutagenicity in *Saccharomyces cerevisiae* (positive and negative)
    - Mutagenicity in *Schizosaccharomyces pombe* (positive)
    - Mutagenicity in *Aspergillus nidulans* (positive)
    - DNA damage in *Escherichia coli* (negative)
    - Gene conversion in *Saccharomyces cerevisiae* (positive and negative)
    - Gene conversion in *Aspergillus nidulans* (negative)
    - Mitotic recombination in *Saccharomyces cerevisiae* (negative)
    - Mitotic recombination in *Aspergillus nidulans* (positive and negative)
    - Aneuploidy in *Aspergillus nidulans* (positive)
    - Aneuploidy in *Neurospora crassa* (positive)
    - *Drosophila melanogaster* somatic mutations (positive)
    - *Drosophila melanogaster* sex-linked recessive lethal mutations (positive and negative)
    - *Drosophila melanogaster* dominant lethal mutation (positive) aneuploidy (positive)
    - Aneuploidy in *Drosophila melanogaster* (positive)
    - Chromosome aberrations (CA) in Chinese hamster ovary (CHO) cells (negative)
    - Sister chromatid exchange (SCE) in CHO cells (negative)
    - Sister chromatid exchange (SCE) in human lymphocytes *in vitro* (positive and negative)
    - CA in human lymphocytes *in vitro* (positive and negative)
    - Unscheduled DNA synthesis (UDS) in rat primary hepatocytes *in vitro* (negative)
    - UDS in human EUE cells *in vitro* (negative)

- DNA damage in human lymphocytes *in vitro* (positive)
  - Mouse *in vivo* bone marrow micronuclei (MN) assay (positive and negative)
  - Mouse *in vivo* bone marrow CA assay (negative)
  - Mouse dominant lethal effects in spermatids (positive)
  - DNA strand breaks in rat stomach, liver, kidney and lung *in vivo* (positive)
  - DNA damage in *Rana catesbeiana* tadpoles (positive)
  - Mutations and chromosomal damage to plants (positive and negative)
- Immune system effects
    - Acute exposure in C57Bl/6 mice: Fournier *et al.* (1992)
      - *Transient suppression of IgM production and T cell proliferation in response to challenge*
    - 14-day gavage study in female B6C3F1 mice: Karrow *et al.* (2005)
      - *Increased splenic CD8+ T cell count, increased cytotoxic T cell and mixed leukocyte responses*
      - *Reduced host resistance to B16F10 melanoma, reduced thymus and spleen weights, total splenic cell counts, and fixed macrophage function*
    - Early exposure (gestation day 10 - postnatal day 23) in male and female Sprague-Dawley rats: Rooney *et al.* (2003)
      - *Decreased IgM and delayed hypersensitivity responses in males*
- Structure activity considerations: U.S. EPA (1990, Table 1)
    - Similarity with other 2-chloro-4,6-bis-(alkylamino)-s-triazine compounds (i.e., simazine, cyanazine, propazine) that each induce mammary tumors in Sprague-Dawley rats
    - Similarity with terbutryn, a 2-alkylthio-4,6-bis-(alkylamino)-s-triazine, which also induces mammary tumors in Sprague-Dawley rats.

## Reviews

- IARC (1999)
- U.S. EPA (2002a)
  - Status update: U.S. EPA (2010)

## References<sup>1</sup>

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<sup>1</sup> 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.

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