

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)

References¹

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.

Albanito L, Lappano R, Madeo A, Chimento A, Prossnitz ER, Cappelo AR, Dolce V, Abonante S, Pezzi V, Maggiolini M (2008). G-protein-coupled receptor 30 and estrogen receptor- α are involved in the proliferative effects induced by atrazine in ovarian cancer cells. *Environ Health Perspect* **116**:1648-1655.

Alavanja MC, Samanic C, Dosemeci M, Lubin J, Tarone R, Lynch CF, Knott C, Thomas K, Hoppin JA, Barker J, Coble J, Sandler DP, Blair A (2003). Use of agricultural pesticides and prostate cancer risk in the Agricultural Health Study cohort. *Am J Epidemiol* **157**:800-814.

Brown LM, Blair A, Gibson R, Everett GD, Cantor KP, Schuman LM, Burmeister LF, Van Lier SF, Dick F (1990). Pesticide exposures and other agricultural risk factors for leukemia among men in Iowa and Minnesota. *Cancer Res* **50**:6585-6591.

Brown LM, Burmeister LF, Everett GD, Blair A (1993). Pesticide exposures and multiple myeloma in Iowa men. *Cancer Causes Control* **4**:153-156.

Burmeister LF (1990). Cancer in Iowa farmers: recent results. *Am J Ind Med* **18**:295-301.

Cantor KP, Blair A, Everett G, Gibson R, Burmeister LF, Brown LM, Schuman L, Dick FR (1992). Pesticides and other agricultural risk factors for non-Hodgkin's lymphoma among men in Iowa and Minnesota. *Cancer Res* **52**:2447-2455.

Cooper LR, Laws SC, Das PC, Narotsky MG, Goldman JM, Tyrey EL, Stoker TE (2007). Atrazine and reproductive function: Mode and mechanism of action studies. *Birth Defects Res (Part B)* **80**:98-112.

De Roos AJ, Zahm SH, Cantor KP, Weisenburger DD, Holmes FF, Burmeister LF, Blair A (2003). Integrative assessment of multiple pesticides as risk factors for non-Hodgkin's lymphoma among men. *Occup Environ Med* **60**:E11.

Donna A, Crosignani P, Robutti F, Betta PG, Bocca R, Mariani N, Ferrario F, Fissi R, Berrino F (1989). Triazine herbicides and ovarian epithelial neoplasms. *Scand J Work Environ Health* **15**:47-53.

Enoch RR, Stanko JP, Greiner SN, Youngblood GL, Rayner JL, Fenton SE (2007). Mammary gland development as a sensitive end point after acute prenatal exposure to an atrazine metabolite mixture in female Long-Evans rats. *Environ Health Perspect* **115**:541-7.

Fan WQ, Yanase T, Morinaga H, Gondo S, Okabe T, Normura M, Komatsu T, Morohashi K-I, Hayes TB, Takayanagi R, Nawata H (2007). Atrazine-induced aromatase expression is SF-1 dependent: Implications for endocrine disruption

in wildlife and reproductive cancers in humans. *Environ Health Perspect* **115**:720-727.

Fournier M, Friberg J, Girard D, Mansour S, Krzystyniak K (1992). Limited immunotoxic potential of technical formulation of the herbicide atrazine (AAtrex) in mice. *Toxicol Lett* **60**(3):263-74.

Hessel PA, Kalmes R, Smith TJ, Lau E, Mink PJ, Mandel J (2004). A nested case-control study of prostate cancer and atrazine exposure. *J Occup Environ Med* **46**:379-385.

Hoar SK, Blair A, Holmes FF, Boysen C, Robel RJ (1985). Herbicides and colon cancer. *Lancet* **1**:1277-1278.

Hoar SK, Blair A, Holmes FF, Boysen CD, Robel RJ, Hoover R, Fraumeni JF, Jr. (1986). Agricultural herbicide use and risk of lymphoma and soft-tissue sarcoma. *JAMA* **256**:1141-1147.

Hoar Zahm S, Weisenburger DD, Cantor KP, Holmes FF, Blair A (1993). Role of the herbicide atrazine in the development of non-Hodgkin's lymphoma. *Scand J Work Environ Health* **19**:108-114.

Holloway AC, Anger DA, Crankshaw DJ, Wu M, Foster WG (2007). Atrazine induced changes in aromatase activity in estrogen sensitive tissues. *J Appl Toxicol* **28**: 260-270.

Hopenhayn-Rich C, Stump ML, Browning SR (2002). Regional assessment of atrazine exposure and incidence of breast and ovarian cancers in Kentucky. *Arch Environ Contam Toxicol* **42**:127-136.

International Agency for Research on Cancer (IARC, 1999). IARC Monograph on the Evaluation of Carcinogenic Risk to Humans: Some chemicals that cause tumors of the kidney or urinary bladder in rodents and some other substances. Volume 73. IARC, Lyon, France.

Karrow NA, McCay JA, Brown RD, Musgrove DL, Guo TL, Germolec DR, White KL Jr (2005). Oral exposure to atrazine modulates cell-mediated immune function and decreases host resistance to B16F10 tumor model in female B6C3F₁ mice. *Toxicology* **209**:15-28.

Kettles MA, Browning SR, Prince TS, Horstman SW (1997). Triazine herbicide exposure and breast cancer incidence: An ecological study of Kentucky counties. *Environ Health Perspect* **105**:1222-1227.

MacLennan PA, Delzell E, Sathiakumar N, Myers SL (2003). Mortality among triazine herbicide manufacturing workers. *J Toxicol Environ Health A* **66**:501-517.

MacLennan PA, Delzell E, Sathiakumar N, Myers SL, Cheng H, Grizzle W, Chen VW, Wu XC (2002). Cancer incidence among triazine herbicide manufacturing workers. *J Occup Environ Med* **44**:1048-1058.

McElroy JA, Gangnon RE, Newcomb PA, Kanarek MS, Anderson HA, Brook JV, Trentham-Dietz A, Remington PL (2007). Risk of breast cancer for women living in rural areas from adult exposure to atrazine from well water in Wisconsin. *J Expo Sci Environ Epidemiol* **17**:207-214.

Mills PK (1998). Correlation analysis of pesticide use data and cancer incidence rates in California counties. *Arch Environ Health* **53**:410-3.

Mills PK, Yang R (2006). Regression analysis of pesticide use and breast cancer incidence in California Latinas. *J Environ Health* **68**:15-22.

Modic WM (2004). The role of testicular aromatase in the atrazine mediated changes of estrone and estradiol in the male Wistar rat. Available at <http://www.lib.ncsu.edu/thesis/available/ets-08052004-132003/>. Accessed 2010.

Muir K, Rattanamongkolgul S, Smallman-Raynor M, Thomas M, Downer S, Jenkinson C (2004). Breast cancer incidence and its possible spatial association with pesticide application in two counties of England. *Public Health* **118**:513-520.

Pogrmic K, Fa S, Dakic V, Kaisarevic S, Kovacevic R (2009). Atrazine oral exposure of peripubertal male rats downregulates steroidogenesis gene expression in leydig cells. *Toxicol Sci* **111**:189-197.

Pruett SB, Fan R, Zheng Q, Myers LP, Herbert P (2003). Modeling and predicting immunological effects of chemical stressors: characterization of a quantitative biomarker for immunological changes caused by atrazine and ethanol. *Toxicol Sci* **75**:343-353.

Rooney AA, Matulka RA, Luebke RW (2003). Developmental atrazine exposure suppresses immune function in male, but not female Sprague-Dawley rats. *Toxicol Sci* **76**:366-75.

Rusiecki JA, De Roos A, Lee WJ, Dosemeci M, Lubin JH, Hoppin JA, Blair A, Alavanja MCR (2004). Cancer incidence among pesticide applicators exposed to atrazine in the agricultural health study. *J Natl Cancer Institut* **96**(18):1375-82.

Stevens JT, Breckenridge CB, Wetzel LT, Gillis JH, Luempert LG, 3rd, Eldridge JC (1994). Hypothesis for mammary tumorigenesis in Sprague-Dawley rats exposed to certain triazine herbicides. *J Toxicol Environ Health* **43**:139-153.

Stoker TE, Laws SC, Guidici DL, Cooper RL (2000). The effect of atrazine on puberty in male wistar rats: an evaluation in the protocol for the assessment of pubertal development and thyroid function. *Toxicol Sci* **58**:50-59.

Stoker TE, Robinette CL, Cooper RL (1999). Maternal exposure to atrazine during lactation suppresses suckling-induced prolactin release and results in prostatitis in the adult offspring. *Toxicol Sci* **52**:68-79.

Thorpe N, Shirmohammadi A (2005). Herbicides and nitrates in groundwater of Maryland and childhood cancers: a geographic information systems approach. *J Environ Sci Health C Environ Carcinog Ecotoxicol Rev* **23**:261-278.

Ueda M, Imai T, Takizawa T, Onodera H, Mitsumori K, Matsui T, Hirose M (2005). Possible enhancing effects of atrazine on growth of 7,12-dimethylbenz(a) anthracene-induced mammary tumors in ovariectomized Sprague-Dawley rats. *Cancer Sci* **96**:19-25.

U.S. Environmental Protection Agency (U.S. EPA, 1990). Memorandum from Joseph A. Cotruvo to Penelope Fenner-Crisp on structure –activity relationship (SAR) analysis of S-triazine pesticides and related compounds. pp 1-10.

U.S. Environmental Protection Agency (U.S. EPA, 2002a). Atrazine: Revised Human Health Risk Assessment. Office of Prevention, Pesticides and Toxic Substances, Health Effects Division.

U.S. Environmental Protection Agency (U.S. EPA, 2002b). Atrazine: Toxicology chapter of the revised registration eligibility decision. Second Revision. Office of Prevention, Pesticides and Toxic Substances. TXR No. 0050644. April 11, 2002. 83 p. Accessed at:
www.epa.gov/oppsrrd1/reregistration/atrazine/hed_toxchap_11apr02.pdf.

U.S. Environmental Protection Agency (U.S. EPA, 2010). Atrazine update. Office of Prevention, Pesticides and Toxic Substances.
http://www.epa.gov/opp00001/reregistration/atrazine/atrazine_update.htm.
accessed June 2010.

Van Leeuwen JA, Waltner-Toews D, Abernathy T, Smit B, Shoukri M (1999). Associations between stomach cancer incidence and drinking water contamination with atrazine and nitrate in Ontario (Canada) agroecosystems, 1987-1991. *Int J Epidemiol* **28**:836-840.

Young HA, Mills PK, Riordan DG, Cress RD (2005). Triazine herbicides and epithelial ovarian cancer risk in central California. *J Occup Environ Med* **47**:1148-1156.

Zahm SH, Weisenburger DD, Saal RC, Vaught JB, Babbitt PA, Blair A (1993).

The role of agricultural pesticide use in the development of non-Hodgkin's lymphoma in women. *Arch Environ Health* **48**:353-358.