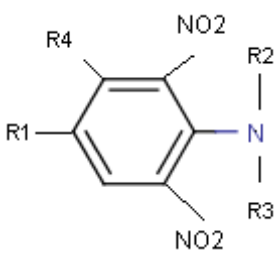
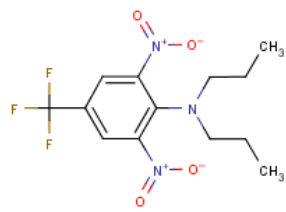
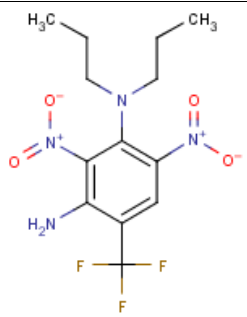
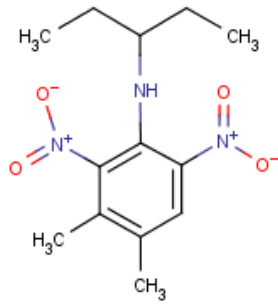
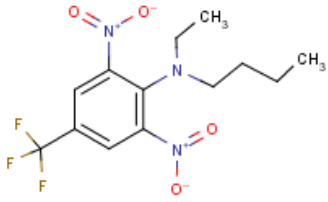
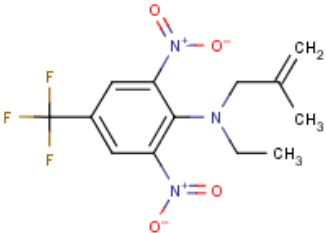
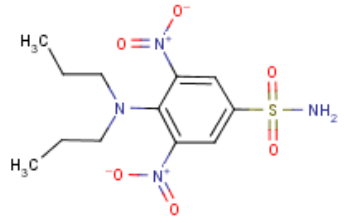


Dinitroaniline Pesticides and Prodiamine and Trifluralin

Dinitroaniline pesticides are herbicides that prevent weeds from emerging through the soil surface. This group includes oryzalin, prodiamine, trifluralin, pendimethalin, ethalfluralin, and benfluralin. One dinitroaniline pesticide, oryzalin, is currently listed as a carcinogen under Proposition 65. The basic chemical structure of dinitroaniline and the structure of several individual dinitroaniline pesticides are shown in Table 1. In 2009, dinitroaniline pesticide use in California was 1,796,365 pounds for pendimethalin, 530,491 pounds for trifluralin, 522,825 pounds for oryzalin, 43,130 pounds for ethalfluralin, and 28,562 pounds for prodiamine. In 2009, no use of benfluralin was reported in California. Tolerance levels have been established by the U.S. EPA for some dinitroaniline pesticides in some foods (*e.g.*, carrots, asparagus). Exposures may occur to workers and consumers that use dinitroaniline pesticides. The general population may be exposed through pesticide drift, and consumption of foods containing residues.

Dinitroaniline pesticides as a chemical 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. In addition, two individual compounds in the group (*i.e.*, prodiamine and trifluralin) passed the human (trifluralin) and/or animal (prodiamine and trifluralin) data screens, underwent a preliminary toxicological evaluation, and are also 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 dinitroaniline pesticides as a group, or prodiamine alone, or trifluralin alone, or some combination of these compounds should be considered for listing at a future CIC meeting.

Table 1. Chemical structures of dinitroaniline pesticides

 <p>basic dinitroaniline structure</p>	
 <p>Trifluralin</p>	 <p>Prodiamine</p>
 <p>Pendimethalin</p>	 <p>Benfluralin</p>
 <p>Ethalfluralin</p>	 <p>Oryzalin (Proposition 65 carcinogen)</p>

Epidemiological data

Trifluralin

- Case-control studies as reviewed in IARC (1991, p. 521)
 - *Population-based study of soft-tissue sarcoma, Hodgkin's disease, and non-Hodgkin's lymphoma in Kansas (increased risk for non-Hodgkin's lymphoma): Hoar et al. (1986)*
 - *Population-based study of ovarian epithelial cancer in northern Italy (no association): Donna et al. (1989)*
 - *Population-based study of leukemia in male farmers in Iowa and Minnesota (no association): Brown et al. (1990)*

Pendimethalin

- Prospective cohort study. Agricultural Health Study (AHS) in Iowa and North Carolina.
 - *Increased risk for lung cancer in the highest lifetime exposure subgroup (Odds Ratio (OR) = 4.4; 95% CI: 1.2-15.4) with significant dose-response trend: Alavanja et al. (2004, p. 883)*
 - *No clear association of lifetime exposure for overall cancer incidence or for specific cancer sites: Hou et al. (2006)*
 - *Increased risk of pancreatic cancer with pendimethalin use (OR = 3.0; 95% CI: 1.3-7.2) with significant dose-response trend: Andreotti et al. (2009)*

Animal data

Trifluralin

- Long-term feeding studies in rats
 - 78-week exposure and additional 33-week observation in male and female Osborne-Mendel rats: NCI (1978)
 - *No treatment-related tumor findings in males or females*
 - *The trifluralin tested was contaminated with the carcinogen dipropylnitrosamine.*
 - Two-year studies in male and female Sprague-Dawley rats: as reviewed in U.S. EPA (1986, p. 4)
 - *No treatment-related tumor findings in males or females*
 - Two-year studies in male and female Fischer 344 rats: as reviewed in U.S. EPA (1986, pp. 6-10)
 - *Increases in renal pelvis carcinoma (by pairwise comparison and trend) and thyroid follicular cell adenoma and carcinoma (combined) (by pairwise comparison) in males*
 - *Increase in urinary bladder papilloma and combined papilloma and carcinoma (by pairwise comparison and trend) in females*

- 28-month studies in male and female Wistar rats: as reviewed in U.S. EPA (1987a, pp. 2, 29, 55-57, 60)
 - *Increase in benign granular cell meningioma of the brain (by pairwise comparison and trend) and benign liver tumor (by trend) in males*
 - *Increase in thyroid follicular cell adenoma and adenocarcinoma (by trend) in females*
- Long-term feeding studies in mice
 - 78-week exposure and additional 12-week observation in male and female B6C3F₁ mice: NCI (1978)
 - *Increase in hepatocellular carcinoma, and hepatocellular carcinoma and adenoma (combined) in females (by pairwise and trend when compared to matched or pooled controls)*
 - *Increase in alveolar/bronchiolar adenoma, and adenoma and carcinoma (combined)(by pairwise comparison and trend when compared to pooled controls), and squamous-cell carcinoma of the forestomach, an uncommon tumor (by pairwise comparison with pooled controls) in females*
 - *No treatment-related tumor findings in males*
 - *NCI reported the trifluralin tested was contaminated with the carcinogen dipropylnitrosamine, and suggested the possibility that the carcinogenicity observed in these studies may be explained by the presence of this contaminant.*
 - Two-year studies in male and female B6C3F₁ mice: as reviewed in U.S. EPA (1986, p. 4); Francis *et al.* (1991)
 - *No treatment-related findings in males or females*
 - Two-year studies in male and female NMRI mice: as reviewed in U.S. EPA (1987a, pp. 1-2, 22-27)
 - *Increases in hepatocellular carcinoma and hepatocellular adenoma and carcinoma (combined), and in bronchioalveolar tumors in mid-dose males (by pairwise comparison)*
 - *No treatment-related findings in females*

Prodiamine

- Long-term feeding studies in rats
 - 108-week diet studies in male and female Sprague-Dawley rats: Powell *et al.* (1989) as reviewed in U.S. EPA (1989a, pp. 18-19; 1991)
 - *Increase in follicular cell adenoma (by trend), follicular cell adenoma and carcinoma combined (by pairwise comparison and trend) in males*
 - *Increase in follicular cell adenoma (by trend), and combined adenoma and carcinoma (by pairwise comparison and trend),*

mammary gland adenocarcinoma (by pairwise comparison), and pancreatic islet adenoma (by trend) in females

- Long-term feeding studies in mice
 - 99-week studies in male and female CD-1 mice: U.S. EPA (1989b, 1991)
 - *Increase in subcutaneous fibrosarcoma (by pairwise comparison and trend) in males*
 - *No treatment-related findings in females*

Pendimethalin

- Long-term feeding studies in rats
 - 24-month diet studies in Sprague-Dawley rats: Weltman (1987) as reviewed in U.S. EPA (1992, p. 6)
 - *Increase in thyroid follicular cell adenoma (by pairwise comparison and trend) in females*
 - *Increase in thyroid follicular cell adenoma and combined adenoma and carcinomas (by pairwise comparison and trend) in males*
- Long-term feeding studies in mice
 - 18-month diet studies in male and female CD-1 mice: Johnson *et al.* (1988) as reviewed in U.S. EPA (1992, p. 8)
 - *No treatment-related findings*

Benfluralin

- Long-term feeding studies in rats
 - 24-month diet studies in male and female Fischer 344 rats: U.S. EPA (2003a, pp. 17-20)
 - *Increase in hepatocellular adenoma, combined hepatocellular adenoma and carcinoma, thyroid follicular cell adenoma, carcinoma, and combined adenoma and carcinoma (all by pairwise comparison and trend) in males*
 - *Increase in thyroid follicular cell adenoma (by trend) and combined adenoma and carcinoma (by pairwise comparison and trend) in females*
- Long-term feeding studies in mice
 - 24-month diet studies in male and female B6C3F₁ mice: as reviewed in U.S. EPA (2003a, pp. 20-22)
 - *Increase in combined hepatocellular adenoma/carcinoma (by pairwise comparison and trend) in females*
 - *No treatment-related findings in males*

Ethalfuralin

- Long-term feeding studies in rats
 - 24-month diet studies in male and female Fischer 344 rats: U.S. EPA (1994, pp. 5-8)
 - *Increase in mammary gland fibroadenoma, and combined mammary gland adenoma and fibroadenoma (by pairwise comparison and trend) in females*
 - *No treatment-related findings in males*
- Long-term feeding studies in mice
 - 24-month diet studies in male and female B6C3F₁ mice: U.S. EPA (1994, pp. 9-11)
 - *No treatment-related findings in males or females*

Oryzalin

Oryzalin, a Proposition 65 carcinogen, induced multiple treatment-related tumors in male and female rats when administered in the diet (U.S. EPA, 2003b). Tumors induced in rats by oryzalin include thyroid follicular cell tumors in males and females, skin fibrous tumors (fibromas and combined fibromas and fibrosarcomas) in males, skin tumors (keratoacanthomas, and combined papillomas, sebaceous gland adenomas, squamous cell carcinomas, basal cell adenomas, and keratoacanthomas) in females, and mammary gland fibroadenomas in females.

Other relevant data

- Genotoxicity as reviewed by U.S. EPA (1980, 1987b, 1991, 1992, 1994, 2003a, 2003b)

Table 3. Genotoxicity of dinitroaniline pesticides

Chemical	Gene mutation		Chromosomal effects		UDS
	<i>Salmonella</i>	Other	MN	Other	
Trifluralin	-	- <i>E. coli</i> +/- Drosophila		+ mitotic crossing-over (Cardoso <i>et al.</i> , 2010) CA + plants - CHO cells +/- bone marrow <i>in vivo</i>	- mammalian cells
Prodiamine	-	- Mouse lymphoma		- CHO cells	-
Pendimethalin	+	- <i>E. coli</i> , CHO, <i>in vivo in rats</i>	- <i>In vivo in mouse</i>	- CHO cells	-
Ethalfuralin	+	- Mouse lymphoma		+ CA in CHO cells	- mammalian cells
Benfluralin	-			- CHO cells	-
Proposition 65 Carcinogen					
Oryzalin	-	-		+/- SCE <i>in vivo</i> (bone marrow cells)	-

CA: chromosome aberration; CHO: Chinese hamster ovary; MN: micronucleus; SCE: sister chromatid exchange; UDS: unscheduled DNA synthesis;

- Structure activity considerations
 - Several dinitroaniline pesticides induce tumors in rats and/or mice, and often in multiple target tissues.
 - Thyroid tumors are induced in rats by several dinitroaniline pesticides (e.g., trifluralin, prodiamine, pendimethalin, benfluralin, oryzalin).
- Mechanistic considerations
 - Proposed involvement of alterations in thyroid hormone levels (T₃, T₄, TSH) in the induction of thyroid tumors by trifluralin in rats: Saghir *et al.* (2008)

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