Request to the Carcinogen Identification Committee (CIC) / OEHHA -

for Low Prioritization of Dinitroaniline Compound

Pendimethalin under Proposition 65

Frederick Hess, Ph.D.

Mammalian Toxicology

Research Triangle Park, NC
Not Appropriate to Consider Dinitroaniline Herbicides as a Single Class for Carcinogenicity Assessment

**Although dinitroanilines may act similarly in plants** (prevent pre-emergent crabgrass), individual compounds have dissimilar mammalian toxicological profiles. Authoritative Body **U.S. EPA** confirms below:

- **U.S. EPA (2009)** concludes that for carcinogenic potential - dinitroaniline compounds should be considered separately, not cumulatively.
- “Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding as to pendimethalin and any other substances.”

- **Thus BASF requests that pendimethalin be prioritized independently of other dinitroaniline pesticides.**
Pendimethalin’s Mammalian Toxicological Profile

Lack of Genotoxic Potential

- Pendimethalin was “not mutagenic in mammalian somatic cells and germ cells.”

- Pendimethalin has “no genotoxic potential.”

EU Member States / Sweden (2008), Spain (2009), Denmark (2010)
- “Pendimethalin was regarded as a non-genotoxic substance.”
Pendimethalin’s Mammalian Toxicological Profile

Animal Bioassay Data

**Tumor Induction:** Limited to one **benign tumor type in one species.**

- **At Highest Dose Tested** (w/↓BW gain 20-30%) : increased incidence of **benign thyroid follicular cell adenomas** in male and female **rats**.
- **US EPA Cancer Peer Review (1992)** stated: “There is no evidence of progression to malignancy.”
- **Thyroid Tumor induction:** well-known threshold MOA: 2 feedback mechanism - initially involves enzyme induction (↑ glucuronyl transferase in the liver).
- **Rats** have demonstrated to be **much more sensitive** to this MOA than humans. **[EPA: ↓ 10X Uncertainty Factor (Interspecies) to 3X UF]**
- Based on information above, **EPA** classified pendimethalin only as **“possible” human carcinogen.**

**Also - EC (2003). Member States (Sweden/2008; Spain/2009; Denmark/2010):**

- For long-term toxicity studies “in rats increased incidence of thyroid adenomas was noted at MTD (max tolerable dose). **This effect was not relevant for humans.**”
Human Epidemiology Data
Several Papers from Ag Health Survey Indicate
No Clear Association of Lifetime Pendimethalin Exposure with
Overall Cancer Incidence or with Specific Cancer Sites

- **Lung Cancer (2004)** - an increased risk for lung cancer. However, **not observed** in a later report (2006):
  - “Overall cancer incidence did not increase with increasing lifetime pendimethalin use, and there was no clear evidence of an association between pendimethalin use and risks for specific cancers.”

- **Pancreatic Cancer (2009)** – association between pancreatic cancer risk and pendimethalin.
  - However, the **Discussion** of paper indicates that **the association is inconclusive**:
  - “Because we examined several pesticides with biological effects in humans that are unclear …, these findings should be considered hypothesis generating and in need of confirmation.”

- **BASF Comments** regarding **hypothetical association** for increased pancreatic cancer risk:
  - i) There is no evidence from extensive Animal Data to support biological plausibility.
  - ii) The assessment of “estimated exposure” is based on individual recollection of product use and not on direct measurement of exposure.
  - iii) The paper does not clarify how many applicators were moderate-to-heavy cigarette smokers OR how many applicators had long-standing diabetes and/or long-standing obesity.
Overall Conclusion
Why Low Prioritization for Carcinogenicity Identification Is Appropriate for Pendimethalin

Based on Scientific Weight-of-Evidence Presented Above:

- Pendimethalin’s toxicological profile for Genotoxicity Data & Animal Data (incl. Bioassay Results) indicates compound does not represent a chemical that causes invasive cancer in animals or in humans.

- Collective evidence from Human Epidemiology Data (AHS papers) (2004/2006/2009) indicate no clear association of lifetime pendimethalin exposure either with overall cancer incidence or with specific cancer sites.

- Therefore, the CIC should consider Low Prioritization for pendimethalin when identifying compounds for purposes of carcinogenicity under Proposition 65.