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

for Low Prioritization of Dinitroaniline Compound

Pendimethalin under Proposition 65

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Not Appropriate to Consider Dinitroaniline Herbicides as a Single Class for Carcinogenicity Assessment

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- **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

US EPA (1997, 2006, 2009, 2010)

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

European Commission (EC) (2003) and

International Agency for Research on Cancer (IARC) (2003)

- 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

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- **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

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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.