

INDUSTRY TASK FORCE II ON 2,4-D RESEARCH DATA

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Issue Background

TOXICOLOGY

The 2,4-D research studies required by the most recent EPA guidelines have incorporated both state-of-the-art and previously unavailable technologies. These methods of analysis are significantly more sophisticated than earlier testing techniques, and thus permit development of an improved understanding of the toxicology of 2,4-D.

The extensive data package of more than 114 new toxicology studies on 2,4-D provide a valuable new perspectives affirming the minimal potential for the use of 2,4-D to adversely affect the environment, animal or human health. Apart from the hundreds of unpublished studies required by various regulatory agencies around the world, there are more than 4,000 peer-reviewed, published studies on 2,4-D in the scientific literature.

A principle to bear in mind for reading this background is that study designs generally intend and require that high doses of the test compound will cause effects. Margins of exposure to humans are calculated from the no-effect dose in the study.

Acute Toxicity: The most likely human or animal exposure to 2,4-D would be short term or acute. The EPA review of numerous acute toxicological studies has concluded, “2,4-D generally has low acute toxicity via the oral, dermal and inhalation routes of exposure (Toxicity Category III or IV). 2,4-D is not a skin irritant nor a skin sensitizer. Although ester forms are not eye irritants, the acid and salt forms are considered to be eye irritants.”¹

Carcinogenicity: Pesticide opponents often refer to the series of National Cancer Institute (NCI) epidemiology studies on agricultural herbicide use and non-Hodgkin’s lymphoma (NHL) to support their position that 2,4-D is a possible carcinogen. Early studies that purported an association between 2,4-D and NHL (e.g., Kansas, Nebraska) were not validated by later studies (e.g., Iowa, Minnesota). Hoar, 1986²; Zahm, 1990³; Cantor, 1992⁴. The case-control studies were critically weakened by differential exposure perceptions among respondents. And all the studies were critically weakened by undocumented exposure to a specific herbicide. A recent NCI published paper, (De Roos, 2003)⁵, completed a re-analysis of the Kansas and Nebraska farm worker studies and reported, “*This analysis of the pooled data found no association with having ever used 2,4-D.*” The weight of evidence from these NCI studies is that 2,4-D is not a carcinogen.

A 1994 EPA SAB report⁶ concluded that if 2,4-D were to possibly cause cancer, it would have to be an extremely potent carcinogen affecting humans but not animals and acting by a unique mechanism which has yet to be understood. When considered with other available information, the biological plausibility of such a mechanism is very low.

The carcinogenicity of 2,4-D has been reviewed by numerous scientific and regulatory groups including the Environmental Protection Agency¹, Health Canada PMRA⁷, the World Health Organization⁸, New Zealand Environmental Risk Management Authority⁹ and the European Commission¹⁰. All agencies state, “*no evidence of carcinogenicity*”.

Mutagenicity: Although the publications of many anti-pesticide advocacy groups continue to show 2,4-D to be a mutagen, there are now more than 25 recent, state-of-the-art EPA/GLP mutagenicity studies on 2,4-D in the toxicology data package, none of which show any evidence of mutagenicity. The EPA Reregistration Eligibility Decision (2005)¹ confirms 2,4-D is not mutagenic.

Developmental/Reproduction: Potential fetal and early life effects, as well as multi-generational reproductive effects of 2,4-D have been assessed by these studies. At the lower tested doses, no birth defects have been observed related to 2,4-D or its derivatives in 17 reproductive and developmental studies conducted in laboratory animals. Available studies suggest that high dose exposures toxic to the mother may also be toxic to the fetus, with resulting effects on reproduction and development. These effects occur only when the dose is so large as to overwhelm the processing capacity of the mother's kidneys¹¹. No-effect levels in the animal studies showed that the substantially lower exposures potentially encountered by humans could not plausibly result in these effects.

Neurotoxicity: In the GLP research sponsored by the Task Force, acute and chronic neurotoxicity were limited to high doses only (Mattsson et. al., 1997)¹². For the acute studies, findings were only noted at doses above those well known to saturate the renal clearance of 2,4-D in rodents (approximately 50 mg/kg; Gorzinski et. al., 1987¹³; Hardwick¹⁴), and thus their relevance to likely human exposures is very minimal, if any. Effects noted in the 1-year chronic neurotoxicity test also were only high-dose related (150 mg/kg/day); however, the appearance of retinal degeneration may be suggestive of weak neurotoxic potential.

Safety and Database Uncertainty Factors: The Food Quality Protection Act (FQPA) directs the Agency to use an additional tenfold (10X) exposure safety factor to protect for special sensitivity of infants and children to pesticide residues in food, drinking water, in residential settings, or to compensate for a partially incomplete database. FQPA authorizes the Agency to modify the tenfold safety factor only if reliable data demonstrates that another factor would be appropriate.

For 2,4-D the EPA removed the default 10X FQPA special safety factor. The Agency has acceptable data and no residual concerns for the effects seen in the developmental toxicity studies. Therefore, the 10X FQPA special safety factor was reduced to 1X.¹

However, the Agency has determined that a 10X database uncertainty factor is needed to account for a repeat of the rat reproduction study, a subchronic inhalation study, and a new study requirement, developmental neurotoxicity. Therefore, the current risk assessments must meet a much higher level of health protection, 1000X margin of exposure (MOE) or (10X for interspecies variability, 10X for intraspecies variability and 10X uncertainty factor).

In conclusion, toxicology and epidemiology studies often referenced by pesticide opponents do not sufficiently document exposures and are far from adequate to make cause and effect conclusions. In contrast, the extensive regulatory toxicology profile available for 2,4-D provides a robust and reassuring characterization of the compound.

Toxicology Profile:

The comprehensive environmental and health assessment released by the Environmental Protection Agency¹ confirms:

**Acute Tox Profile:
(technical acid)**

Toxicity Classification

Oral LD ₅₀	Low toxicity.	Category III	699 mg/kg
Dermal LD ₅₀	Low toxicity.	Category III	>2000 mg/kg
Inhalation LC ₅₀	Low toxicity.	Category III	> 1.79 mg/l
Eye Irritation	Severe irritation.	Category I	irritation >21 days***
Skin Irritation	Non- irritant.	Category IV	no irritation
Sensitization	Not a skin sensitizer.	N/A	Negative

*** ester formulations are mild or no eye irritation (Category III)

- To put the LD50 data endpoints into perspective, 2,4-D is less toxic than caffeine and slightly more toxic than aspirin.
- Subchronic effects are generally limited to very high doses when compared to the exposure levels humans may face in the environment.
- 2,4-D has low reproductive toxicity.
- 2,4-D does not cause birth defects.
- Chronic effects are limited to long term exposure at high doses.
- 2,4-D has low potential to cause neurotoxicity in short and long term exposures.
- 2,4-D does not cause genetic damage.

About the Task Force

The Industry Task Force II on 2,4-D Research Data is organized to provide funding for more than 300 Good Laboratory Practice (GLP) research studies required to respond to the EPA reregistration and PMRA pesticide re-evaluation programs. The 2,4-D Task Force is comprised of those companies owning the technical registrations on the active ingredient in 2,4-D herbicides. They are Dow AgroSciences (U.S.), Nufarm, Ltd. (Australia) and Agro-Gor Corp., a U.S. corporation jointly owned by Atanor, S.A. (Argentina) and PBI Gordon Corp. (U.S.).

References:

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