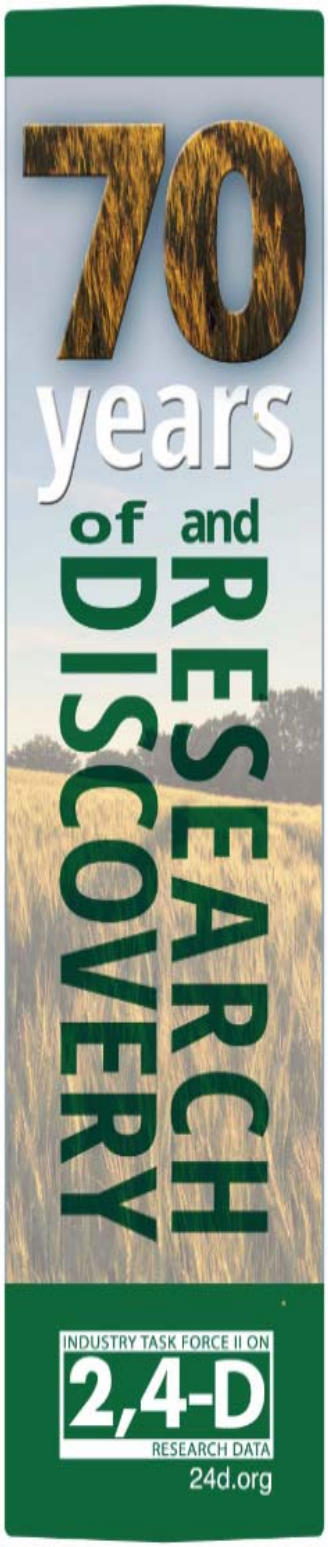


Toxicology of 2,4-D

The 2,4-D toxicology research studies required by United States Environmental Protection Agency (US EPA) and Health Canada's Pest Management Regulatory Agency (PMRA) guidelines have incorporated both state-of-the-art and previously unavailable technologies. These methods of analysis are increasingly more sophisticated than earlier testing techniques, and thus permit development of an improved understanding of 2,4-D toxicology.

The extensive data package of more than 121 new toxicology studies on 2,4-D provide 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 Apart from the hundreds of unpublished studies required by regulatory agencies around the world, there are more than 4,000 peer-reviewed, published studies on 2,4-D in the scientific literature.

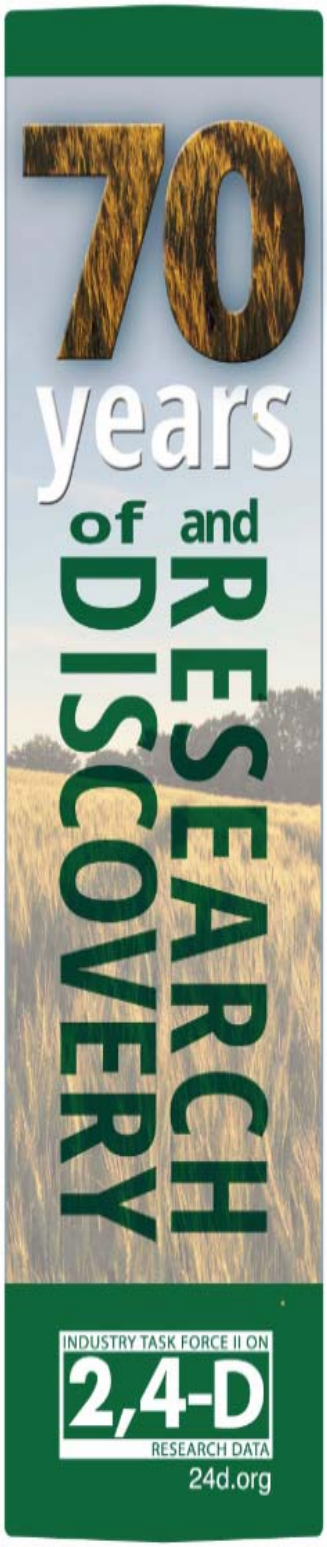
The EPA has recently evaluated the 2,4-dichlorophenoxyacetic acid (2,4-D) F1 Extended one-generation reproduction study which includes assessment of reproduction toxicity, developmental neurotoxicity and developmental immunotoxicity as well as endocrine and thyroid endpoint effects. Toxicokinetics were also evaluated.

The findings of this study satisfy the 2007 Data Call-In (DCI) requirements for the US EPA and PMRA, establishing a no-observed-adverse-effect-level (NOAEL) based on systemic toxicity. In other words, the toxicological threshold established by the regulatory agencies was achieved. Based on the results of the study and review, the EPA concluded that 2,4-D does not present toxicity of concern for developmental neurotoxicity, developmental immunotoxicity, reproductive toxicity, endocrine or thyroid effects.

Systemic toxicity

A principle to bear in mind when reading this backgrounder is that mammalian toxicity study designs require an adequate dose of the test compound that will cause effects. Margins of exposure to humans are calculated from the next lower NOAEL dose in the study.

Systemic effects on the test animal occur when the kidney's ability to clear 2,4-D from the blood is overwhelmed (in technical terms, renal saturation).
The study confirmed that the kidneys are the limiting organ for 2,4-D toxicity. There were no effects on hematology, clinical chemistry or urinalysis. The same



limiting factor was also found in offspring, meaning there is no enhanced sensitivity in the young relative to the adult.

Across life stages and compared to the extended one-generation reproduction and systemic toxicity study, the male NOAEL is >13,000-times higher than 2,4-D exposures reported in human biomonitoring studies. The female NOAEL is >48,000-times higher than exposure reported from human biomonitoring studies.

Acute Toxicity

The most likely human or animal exposure to 2,4-D is 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 neither 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."

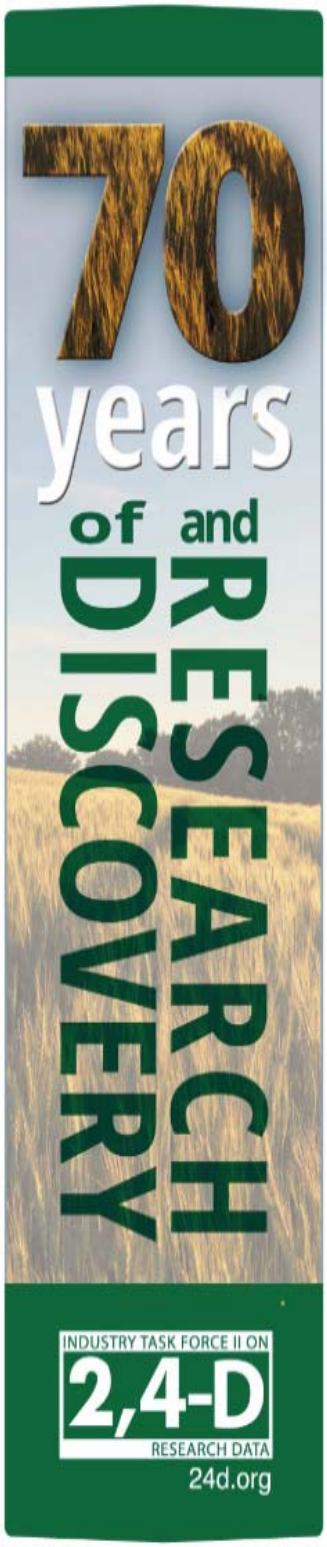
Table 1 – Acute Toxicology Profile as Published by the EPA

Acute Toxicological Profile (technical acid)		Toxicity Classification	
Oral LD50	Low toxicity	Category III	699 mg/kg
Dermal LD50	Low toxicity	Category III	>2000 mg/kg
Inhalation LC50	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)

Carcinogenicity

2,4-D is not a carcinogen. 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 NCI 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, 1986; Zahm, 1990; Cantor, 1992).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) 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.

The carcinogenicity of 2,4-D has been reviewed by numerous scientific and regulatory groups including the US EPA, Health Canada PMRA, the World Health Organization, New Zealand Environmental Risk Management Authority and the European Commission.

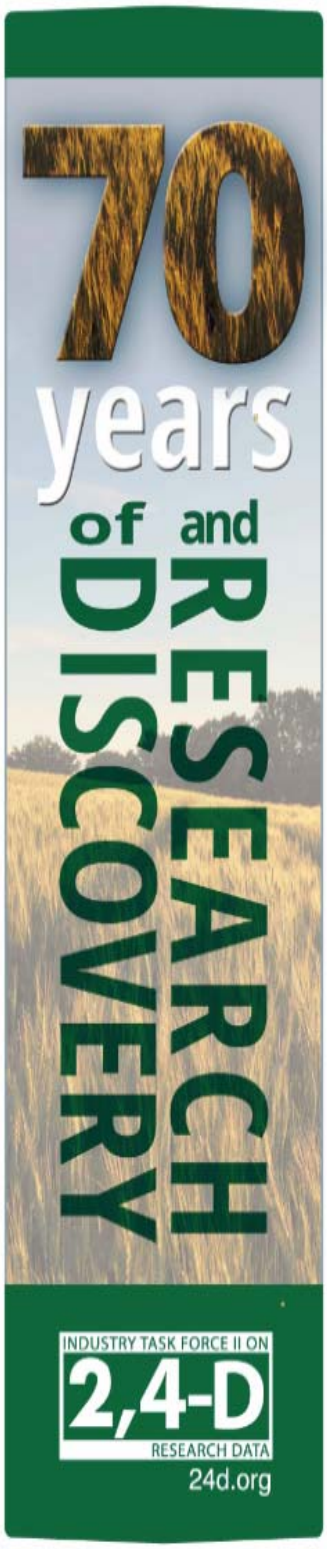
The US EPA in 2007 finalized their 2,4-D Special Review and concluded for human carcinogenicity, "[t]he Agency has determined that the existing data do not support a conclusion that links human cancer to 2,4-D exposure." Further EPA stated: "Based on extensive scientific review of many epidemiology and animal [toxicology] studies, the Agency finds that the weight of the evidence does not support a conclusion that 2,4-D, 2,4-DB and 2,4-DP are likely human carcinogens".

In 2014, the European Food Safety Authority concluded their peer review of 2,4-D. They concluded that 2,4-D is unlikely to have a genotoxic potential or pose a carcinogenic risk to humans. No conclusive association can be established between exposure to phenoxy-herbicides (including 2,4-D acid) and human carcinogenicity. No conclusive evidence in the open literature that 2,4-D may exhibit toxicological properties other than those concluded already based on the toxicity studies conducted with the technical active substance.

In 2015, Goodman et. al., conducted a meta-analysis of the published epidemiological literature for 2,4-D and concluded, "The epidemiology evidence does not support an association between 2,4-D and NHL, gastric cancer, or prostate cancer risk." In its 2015 evaluation, while voting to classify 2,4-D as a '2B – Possible' carcinogen, the IARC review panel concluded, "there is inadequate evidence in humans for the carcinogenicity of 2,4-D" as epidemiological studies did not find strong or consistent increases in risk of NHL or other cancers in relation to 2,4-D exposure.

Neurotoxicity

2,4-D is not neurotoxic. In GLP research sponsored by the Task Force, acute and chronic neurotoxicity effects were limited to high doses only (Mattsson et. al., 1997). For the acute neurotoxicity 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., 1987; Hardwick), and thus their relevance to human exposures is not biologically plausible. Effects noted in the 1-



year chronic neurotoxicity test also were only high-dose related (150 mg/kg/day), 3X above renal clearance.

Mutagenicity

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

"Overall, the pattern of responses observed in both in vivo and in vitro tests indicated that 2,4-D was not mutagenic."

The Modern Regulatory Database

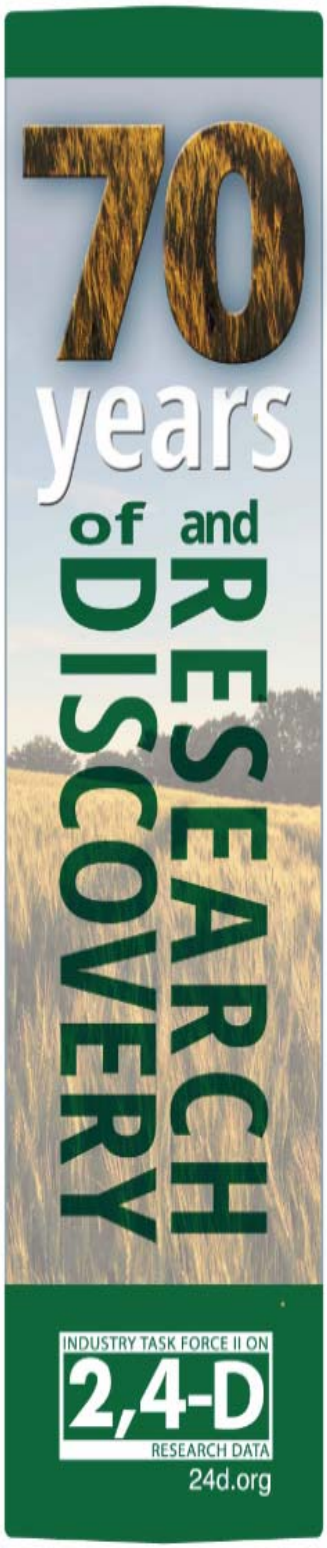
The extended one-generation study adds to the modern regulatory database in presenting a new experimental design to examine systemic toxicity, developmental neurotoxicity, developmental immunotoxicity, reproductive toxicity, endocrine modulation and thyroid effects in a single study. The study design is based on the work of Cooper et. al. who advocate for a tiered approach to life stage testing for agricultural chemical safety assessments.

The goal of this test design is to ensure that studies are scientifically appropriate and necessary, and that tests emphasize toxicological endpoints and exposure durations that are relevant for risk assessment. The advantages of this study design include the opportunity to examine patterns of effects across the parental generation and multiple cohorts of offspring, which facilitates data interpretation. Additionally, significantly fewer animals are sacrificed in the process, a policy objective of the regulatory agencies in Europe and North America.

The findings of this study are consistent with and reaffirm GLP and other published studies on the health and safety of 2,4-D from around the world.

Developmental and Reproductive toxicity

2,4-D is not a developmental or reproductive toxicant. Potential fetal and early life effects, as well as multigenerational reproductive effects of 2,4-D have been assessed by numerous 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.



Based on the US EPA 2,4-D RED, it is not "biologically plausible" that 2,4-D and related compounds are associated with adverse effects on development or reproduction in humans. In animals, developmental toxicity was not observed except at dose levels at or above the threshold limit of saturation of renal clearance. In other words, the dose is so large, that it exceeds the capacity of the kidneys to excrete 2,4-D. Humans are not exposed to 2,4-D under the extreme conditions that would be needed to cause renal saturation.

Critical evaluation of the recent extended one-generation reproduction study by EPA confirmed there is no indication of reproductive toxicity by 2,4-D. 2,4-D had no effects on estrous cyclicity or reproductive indices, including mating, fertility, time to mating, gestation length, pre- and post-implantation loss and corpora lutea number. Litter sizes, pup survival, sperm parameters, ovarian follicle counts and reproductive organ histopathology were unaffected by 2,4-D.

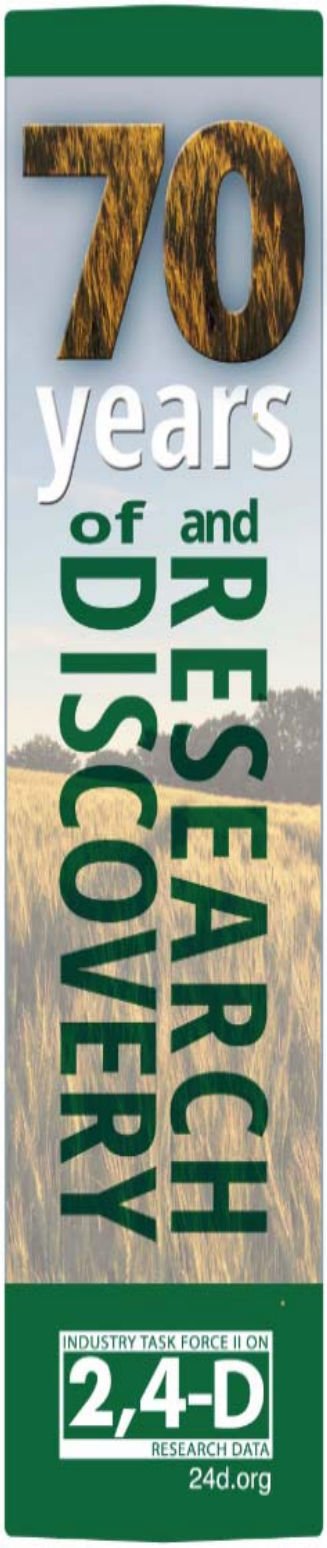
Developmental Neurotoxicity (DNT)

There was no evidence of DNT related to 2,4-D exposure. There were no exposure-related effects on brain histopathology at any age. There were no exposure-related effects on functional observational battery (FOB) parameters (hand-held and open-field observations, grip performance, landing foot splay, rectal temperature), motor activity and acoustic startle response (ASR) when assessed in offspring F1 adult animals. In addition, brain weights, gross brain measurements and morphometric measurements were not affected. Habituation (behavioral response to a stimulus) was not affected at any dose of 2,4-D. There was no exposure-related neuropathology, including no effects on brain myelin (assessed by special staining). Thus 2,4-D exposure shows no evidence of DNT.

Endocrine

2,4-D is not an endocrine disruptor. Endocrine-sensitive endpoints included estrous cyclicity, reproductive indices, organ weights/pathology, and sperm parameters. Anogenital distance, nipple retention, and puberty onset were assessed in offspring; quantitative ovarian follicle counts in a subset of offspring. Thyroid assessments are detailed below. 2,4-D did not alter estrogen- or androgen-sensitive endpoints. There were no effects on estrogen-sensitive endpoints including vaginal opening, estrous cyclicity, uterine weights or histopathology, or quantitative ovarian follicle counts.

There were no significant, exposure-related changes in reproductive organ weights in offspring. Other androgen-sensitive endpoints, including anogenital distance (AGD) and nipple retention (which are considered very sensitive endpoints) sperm parameters and testicular and accessory sex gland



histopathology, were not altered. Based on this data and other studies, 2,4-D shows no evidence of being an endocrine disruptor interacting with either estrogen or androgen at doses at or below those resulting in nonlinear renal clearance.

In 2012 the 2,4-D Task Force concluded an EPA Endocrine Disruptor Screening Program (EDSP) "to determine whether certain substances may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen." Eleven in-vitro and in-vivo tests were required including fish and frog in- vivo studies. Adding to the wealth of endocrine data from the extended one-generation reproduction study, the EDSP studies showed that all in-vitro and in-vivo tests were interpreted as "Negative", i.e., no evidence of endocrine disruption potential.

On July 30, 2015, the EPA released its reviews of the Tier 1 screening assay results for the first 52 pesticide chemicals (active and inert ingredients) in the EDSP and found no convincing evidence of potential interaction with the estrogen, androgen or thyroid pathways for 2,4-D.

Thyroid

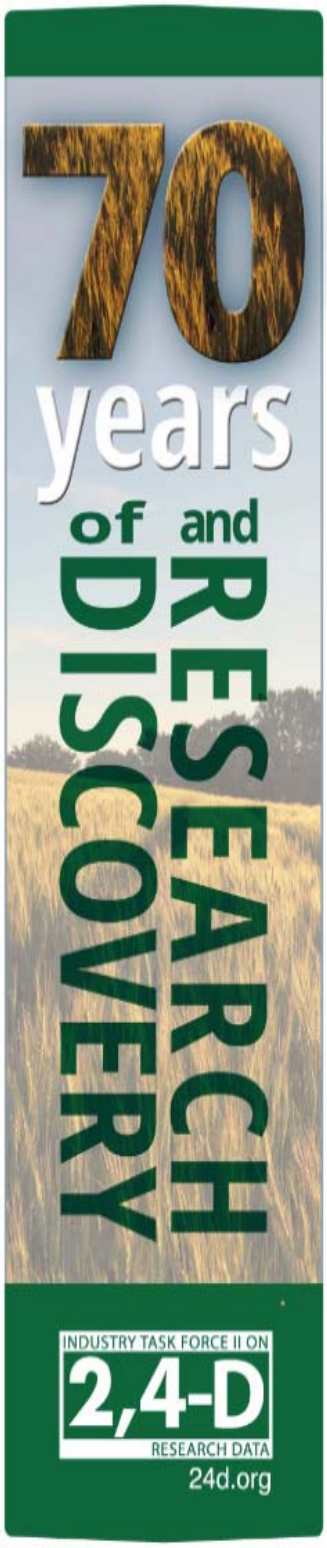
There were no thyroid effects at low- and mid-dose levels and no biologically significant effects on thyroid endpoints at all life stages examined. There were no adverse pathological alterations; although slight thyroid changes seen in a satellite group of pregnant females were considered adaptive non-adverse responses. The only altered thyroid endpoints occurred at an exposure level that clearly resulted in non- linear renal clearance.

Developmental Immunotoxicity (DIT)

2,4-D exposure had no biologically significant effect on the development of immune function. Potential immune system evaluations included both the sheep red blood and natural killer (NK) cell tests. 2,4-D had no effect on antibody forming cells and the assay showed no effects from 2,4-D exposure. No treatment related immunotoxicity was observed. 2,4-D exposure is not a concern for the developing immune system.

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 developmental toxicity studies. Therefore, the 10X FQPA special safety factor was reduced to 1X.

Following submission and review of the Extended One-generation Reproduction study, EPA determined that the modern database is complete, and removed all database uncertainty factors.

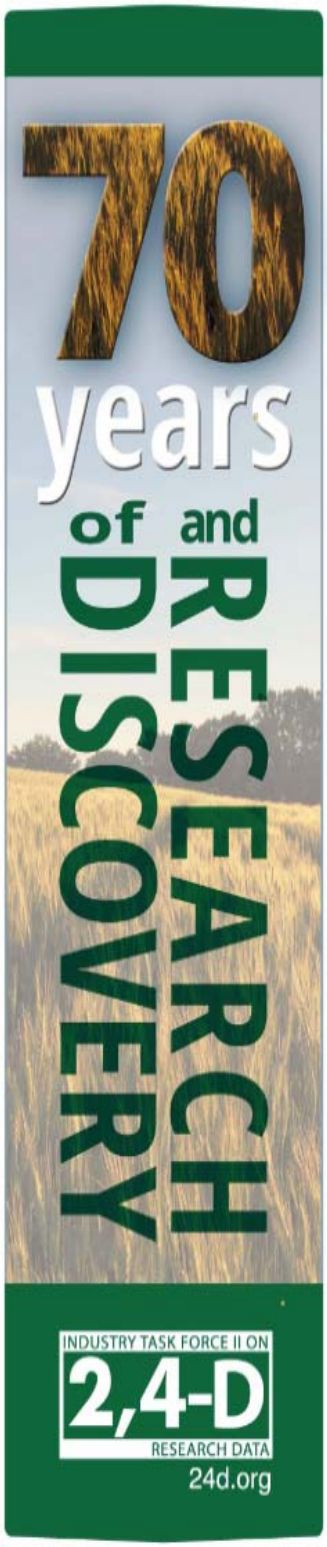
Key Findings from Good Laboratory Practice (GLP) Science:

- No evidence of carcinogenicity
- Not a reproductive toxicant: 2,4-D does not cause birth defects
- Not a developmental neurotoxin: 2,4-D has low potential to cause neurotoxicity
- Not an immunotoxin: No evidence of immune system effects
- Not a mutagen: 2,4-D does not cause genetic damage
- No evidence of endocrine disruption
- Very low potential for dermal toxicity
- Excreted unchanged as 2,4-D acid: does not metabolize or accumulate in the body
- Short half-life in humans (less than 17 hours)
- Biomonitoring studies show very low exposure to applicators/handlers and virtually no exposure to bystanders.

Tolerance reassessment: In the 2,4-D RED, EPA evaluated the human health risks associated with all registered uses of 2,4-D and determined that there is a reasonable certainty that no harm will result from aggregate non-occupational exposure to the pesticide chemical residue.

Risk assessment: “2,4-D toxicity generally occurs at doses above renal saturation, i.e., doses above which the excretory processes could readily eliminate the chemical; the Agency’s risk assessment regulated at doses below this level. Consequently, the Agency had high confidence that the risk assessment does not underestimate risks from exposure to 2,4-D”.

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 modern regulatory toxicology profile available for 2,4-D provides a robust and reassuring characterization of the



compound. In conclusion, "2,4-D can be used safely when label directions are followed".

About the Task Force

The Industry Task Force II on 2,4-D Research Data is organized to provide funding for the on-going Good Laboratory Practice (GLP) research studies required to respond to the US EPA registration review and PMRA pesticide re-evaluation programs. The 2,4-D Task Force is comprised of those companies holding technical 2,4-D registrations: Dow AgroSciences (U.S.), Nufarm, Ltd. (Australia) and Agro-Gor Corp., a U.S. corporation jointly owned by Albaugh, LLC. (U.S.) and PBI-Gordon Corp. (U.S.).

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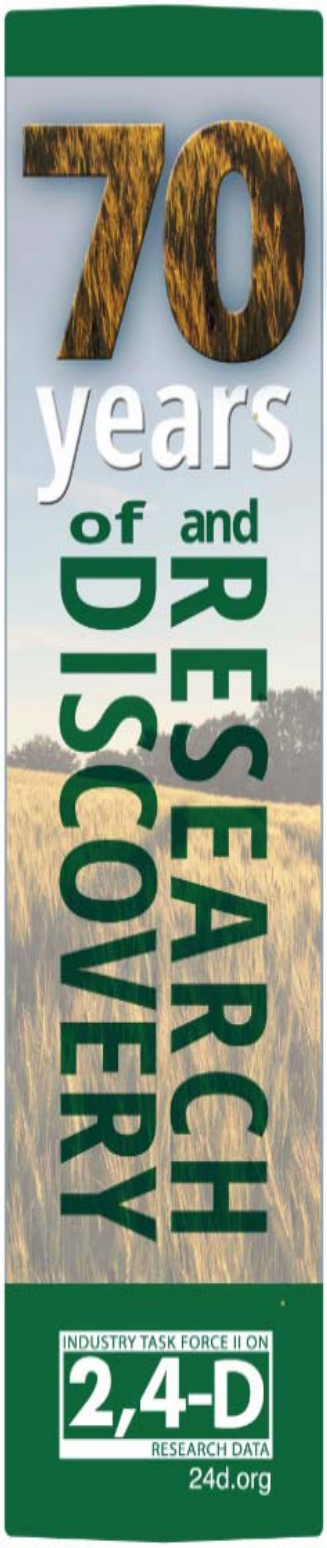

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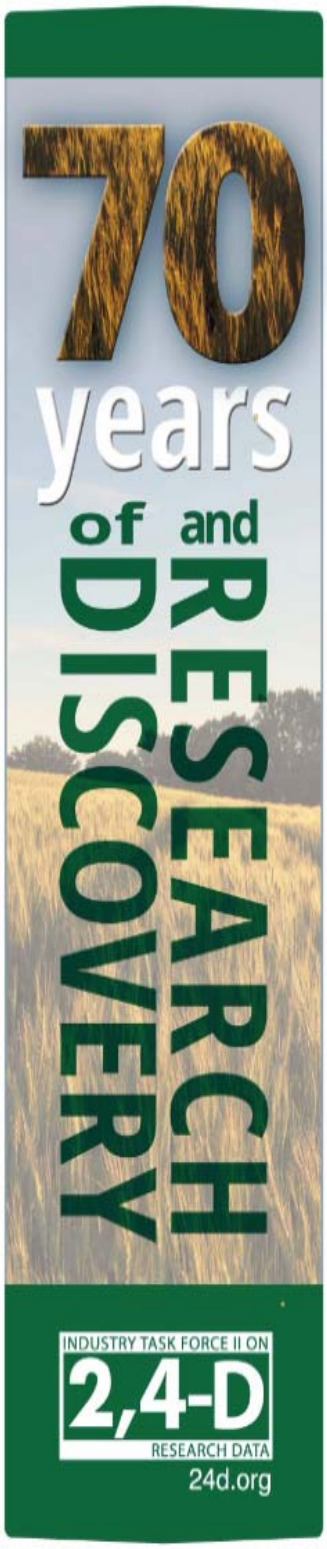

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