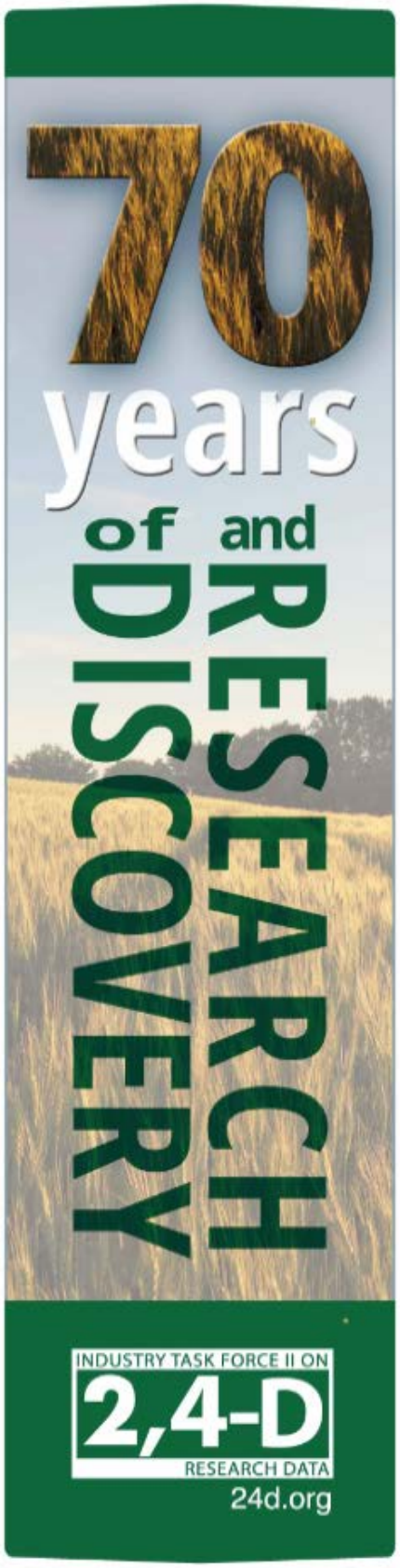

2,4-D - 70 years of Scientific Data Development and Understanding

Carol Burns[1], James Bus[2], Julie Goodman[3], Reza Rasoulpour[4], Steve McMaster[5]*

1 The Dow Chemical Company, Epidemiology, 1803 Building, Midland, MI 48674, USA;
2 E[x]ponent® ,5806 Woodberry Drive, Midland, MI 48640
3 Gradient, 20 University Road, Cambridge, MA 02138, USA
4 Dow AgroSciences LLC, 9330 Zionsville Rd., Indianapolis, IN 46268 USA
5 Industry Task Force II on 2,4-D Research Data, 101 Northway Court, Raleigh, NC 27615
* Author to whom correspondence should be addressed; E-Mail: samcmaster@dow.com

2,4-D – 70 years of Scientific Data Development and Understanding

1. Overview

The herbicide 2,4-dichlorophenoxyacetic acid (2,4-D), has been commercially available for 70 years and is used worldwide. As a pesticide, it is subject to significant regulatory oversight. During the decades of 2,4-D use, the scope and quality of the data being required by these authorities to support the chemical have expanded and improved. In addition, the scientific community have often selected 2,4-D to be the subject of scientific inquires and continual assessments. The results of these combined efforts is a very large and complex scientific assessment of 2,4-D, including analyses relevant to oncogenicity.

This submission to the IARC Working Group reviewing 2,4-D has been prepared by The Industry Task Force II on 2,4-D Research Data ("Task Force"). The Task Force is composed of the companies who manufacture the active ingredient of 2,4-D herbicide and which provide funding for the research studies required for pesticide re-evaluation/re-registration programs on the active ingredient 2,4-D in the United States and Canada. Task Force member companies are Dow AgroSciences LLC (U.S.), Nufarm, Ltd. (Australia) and Agro-Gor Corp., a U.S. corporation jointly owned by Albaugh, Inc. (U.S.) and PBI/Gordon Corp. (U.S). In the European Union, ADAMA Agricultural Solutions Ltd, (Israel) joins Dow AgroSciences and Nufarm in a related consortium. This Task Force was originally organized in 1980 to jointly develop 34 studies required by the U.S. Environmental Protection Agency ("EPA"), including chronic rat and mouse oncogenicity studies. Upon review of these studies, the EPA required a repeat of these oncogenicity studies on the grounds that the first studies did not test a maximum tolerated dose.

The Industry Task Force II on 2,4-D Research Data supports the position that **2,4-D is *not classifiable as to its carcinogenicity to humans* (Group 3).**

As expressed in this document **there is e*vidence demonstrating lack of carcinogenicity in experimental animals.*** There are adequate studies available involving at least two species. These studies show that 2,4-D is not carcinogenic.

Also, **there is *inadequate evidence of carcinogenicity in humans*:** The available studies on humans are of insufficient quality, consistency or statistical power to permit a conclusion regarding the presence or absence of a causal association between exposure to 2,4-D and cancer in humans.

Moreover, there are **no mechanistic data that would support** evidence of 2,4-D carcinogenic modes-of-action.

2. Historical IARC Classifications of Chlorophenoxy Herbicides and 2,4-D

The International Agency for Research on Cancer (IARC) has prepared monographs with information about the chlorophenoxy herbicides, including 2,4-D, on several occasions (IARC 1977, 1982,1986, 1987). In 1977, the Monograph stated that "no evaluation of the carcinogenicity of this compound (2,4-D) could be made" regarding animals. With respect to human data, the Monograph states, "The results of the single cohort study of a small number of workers exposed to various herbicides, including 2,4-D, 2,4,5-T and 3-amino-1,2,4-triazole (amitrole), are not sufficient to evaluate the carcinogenicity of 2,4-D to man" (IARC 1977).

In 1982, summary evaluations of carcinogenic risk to humans from chemicals lists 2,4-D and esters having inadequate evidence for carcinogenicity in humans, inadequate evidence of carcinogenicity in animals and inadequate evidence for activity in short-term tests (Supplement 4, Table 1). The summary evaluation of carcinogenic risk to humans is listed in category 3 (IARC 1982.

In 1986, IARC evaluated some halogenated hydrocarbons and pesticide exposures. Table 16 of this monograph indicates for 2,4-D that there is inadequate evidence of carcinogenicity in animals and inadequate evidence for genetic activity in short term tests. This monograph concludes "there is limited evidence that occupational exposures to chlorophenoxy herbicides are carcinogenic to humans" (IARC 1986).

In 1987, IARC published Supplement 7 to Monographs 1 to 42. The evidence for carcinogenicity of chlorophenoxy herbicides to humans remained limited and the evidence for carcinogenicity of 2,4-D to animals remained inadequate (IARC 1987).

Dr. Robert Baan confirmed in 2002, "At the time of the evaluation, the epidemiological data on 2,4-D as a separate compound were inadequate to evaluate its carcinogenicity to humans, because no data on human exposure to the single compound were available. The animal carcinogenicity data for 2,4-D were inadequate. The chlorophenoxy herbicides showed limited epidemiological evidence for increased occupational cancer risk in pesticide applicators, and were evaluated as possibly carcinogenic to humans, Group 2B. Because 2,4-D belongs to this group of substances, the compound has been given the same classification, in the absence of data that would make a full evaluation of 2,4-D possible (Baan 2002)."

3. Cancer in Humans

3.1 Epidemiology Studies

There is inadequate evidence of carcinogenicity in humans: The available epidemiological studies on humans are of insufficient quality, consistency, or statistical power to permit a conclusion regarding the presence or absence of a causal association between exposure to 2,4-D and cancer in humans.

Early case-control studies linked lymphomas to phenoxy herbicide exposure in Australia and Sweden and the U.S. (Kansas) (Hardell et al. 1994; Hoar et al. 1986; Smith and Christophers 1992). Subsequent case-control studies sponsored by the U.S. National Cancer Institute (NCI) collected information specific to 2,4-D and non-Hodgkin lymphoma (NHL). These studies conducted in Nebraska (Zahm et al. 1990) and Iowa and Minnesota (Cantor et al. 1992) reported differing results if the data were self reported or by proxy (Johnson et al. 1993). A pooled analyses of the Kansas, Nebraska and Iowa, Minnesota case control studies reported no increased risk of NHL and 2,4-D use (Odds Ratio 0.9, 95% Confidence Interval, CI 0.6 – 1.2) (De Roos et al. 2003). The increasing dose response of 2,4-D exposure and canine malignant lymphoma (Hayes et al. 1991) was not confirmed in an independent reanalysis of the underlying data (Kaneene and Miller 1999). In order to reduce the methodological weaknesses of case control studies, namely recall bias, the NCI launched the prospective Agricultural Health Study in 1993 (Alavanja et al. 1996). To date, the AHS has more than 100 publications. No significant adverse association has been reported for 2,4-D use among approximately 80,000 participants in studies of children (Flower et al. 2004), breast cancer (Engel et al. 2005), prostate cancer (Alavanja et al. 2003) and melanoma (Dennis et al. 2010). A peer reviewed analysis of 2,4-D and NHL in the AHS has not been published. A poster presented at the 2013 Epidemiology and Occupational Health meeting by Dr. Beane Freeman of the NCI reported “no association with cancer risk overall (p-trend=0.68), NHL overall (p-trend=0.84), or any sub-type of NHL with intensity-weighted lifetime days” (Beane Freeman et al., 2013, and personal communication); however, they observed an association with gastric cancer.

There are many published epidemiology reviews pertinent to 2,4-D. An early review of more than 90 epidemiology studies reported that many of the studies are limited by speculative or indirect indices of exposures. Further, not all of the phenoxy herbicide exposures were specific to 2,4-D (Munro et al., 1992).

A review by the World Health Organization (1996) concluded that the epidemiology data were inconsistent. A decade later, Garabrant and Philbert (2002) concluded the evidence was inadequate among cohort studies to conclude that 2,4-D exposure was associated with soft tissue sarcoma (STS), non-Hodgkin Lymphoma (NHL), Hodgkin’s Disease, or any other cancer. Garabrant and Philbert observed that the case control studies of these cancers were confounded by dioxin, inconclusive, and not reliable. In contrast, Hardell (2008) stated that pesticide exposure, which included 2,4-D, is an established risk factor for NHL. Another review of the case-control studies suggested that NHL may be associated with phenoxy herbicides, but the assessment for 2,4-D exposure was inconclusive (Gandi et al., 2000). Gandi et al., concluded

that overall the results for cancer and 2,4-D were inconsistent. Von Stackelberg (2013) described the epidemiology data as "mixed," whereas Burns and Swaen (2012) characterized the data as "inconsistent."

In their recent meta-analysis of 2,4-D exposure and three cancer endpoints, Goodman et al., (2015) systematically reviewed 24 epidemiology studies that specifically evaluated exposure to 2,4-D. In general, study quality was undermined by several methodological limitations, such as exposure measurement error, information bias, and confounding. Results of individual studies were meta-analyzed for NHL (n = 9 studies), prostate cancer (n = 2 studies) and gastric cancer (n = 3 studies). Results indicated no associations between 2,4-D exposure and any of these cancers. In addition, Goodman et al. (2015) observed evidence of publication bias in epidemiology studies of 2,4-D and NHL indicating small studies presenting positive associations were more likely to be published. Another meta-analyses by Schinasi and Leon (2014) observed a slight elevation of NHL risk associated with 2,4-D exposure (RR=1.4, 95% CI: 1.0-1.9). Interpretation of these results is limited by the substantial heterogeneity in the collected results (I-squared = 61.5%). The scope of Schnasi and Leon (2014) was restricted to agricultural exposures to 2,4-D and included only five studies. This very small sample size of original studies in the meta-analysis precluded an assessment of publication bias or extensive sensitivity analyses to test robustness of results to variations on study exclusion.

At present the evidence is interpreted differently by investigators and reviewers. Recent published reviews and governmental regulatory decisions support the position that epidemiology data are inadequate to establish a causal association between 2,4-D exposure and cancer (von Stackelberg 2013; Burns and Swaen, 2012; EFSA, 2015; USEPA, 2012; European Commission, 2001; EU 2014a; EU 2014b; EU 2014c; Health Canada PMRA, 2008; USEPA, 2005; New Zealand Environmental Risk Management Authority, 2003). Many reviewers point out insufficient quality with respect to exposure and a lack of consistency across multiple studies. Furthermore, the number of exposed cases often precludes sufficient statistical power to robustly evaluate a dose response.

The available studies are of insufficient quality, consistency or statistical power to permit a conclusion regarding the presence or absence of a causal association between exposure to 2,4-D and cancer in humans.

3.2 Biomonitoring

Numerous high-quality biomonitoring studies exist for 2,4-D since it is not metabolized and is rapidly excreted in the urine. Analyses of 2,4-D urine concentrations, and particularly those in which total urine is collected over 24 hour periods, provide direct evidence of aggregate 2,4-D exposures from all sources (occupational, diet, water, air, etc.). Studies of the general population and rural bystanders have demonstrated that exposure to 2,4-D is low to not detectable (Alexander et al., 2007; Centers for Disease Control and Prevention (CDC) 2005; Morgan et al. 2008). Importantly, 2,4-D doses estimated from urine biomonitoring are well below reference doses established as health protective, including cancer, by regulatory agencies (Aylward et al., 2010, Hays et al., 2012).

Further biomonitoring has confirmed low exposures to 2,4-D following applications of either spray or granulated formulations for lawn and garden weed control (Harris and Solomon, 1992) In occupational settings, exposure occurs primarily through mixing, loading and applying and without use of protective clothing or gloves (Alexander et al. 2007; Thomas et al. 2010). In their review, Burns and Swaen (2012) noted that biomonitoring data provide important information about the plausibility and validity of exposure estimates in the epidemiology literature, and offer direct evidence that occupational and general population exposures including those to children are low and well below regulatory reference doses (RfDs) established as health protective.

3.3 Conclusions

With respect to human studies, there is inadequate evidence of carcinogenicity.

4. Cancer in Animals

As expressed in this document, there is evidence demonstrating lack of carcinogenicity in experimental animals. There are adequate studies available involving at least two species. These studies indicate that 2,4-D is not carcinogenic.

4.1 Rodent Cancer Bioassays

Rat and mouse oncogenicity studies (cancer bioassays) on 2,4-D were initially conducted in the 1980s, submitted to the US EPA in 1986, and subsequently summarized in a peer-review publication (Munro et al., 1992). The evaluations of the studies by the EPA questioned if the dose levels utilized in the studies were sufficiently high. In addition, the EPA requested additional follow-up on possible increased incidence in astrocytomas in the high dose male rats (45 mg/kg/day), which was deemed spurious and unrelated to treatment (Munro et al., 1992).

To address both of these concerns, additional oncogenicity studies (cancer bioassays) in rats and mice were conducted under the new GLP guidance, completed in 1995, and published in peer-reviewed literature (Charles et al., 1996). In these dietary studies, dose levels in rats were 0, 5, 75, and 150 mg/kg/day and in mice were 0, 5, 150, and 300 mg/kg/day for females and 0, 5, 62.5, and 125 mg/kg/day for males. No evidence of carcinogenicity was observed in either of these studies, despite the higher dose levels and increased pathology brain sectioning compared to the previous studies.

4.2 Weight of Evidence - Astrocytomas

Regarding the previous apparent increase in astrocytomas in male rats in the 1986 study, (Munro et al., 1992), the incidence in males (out of 50 rats/group) was 1, 0, 0, 2, and 6 in the 0, 1, 5, 15, and 45 mg/kg/day groups, respectively. There was no increased incidence in females (0, 1, 2, 1, and 1 for the same dose groups, respectively). The incidence of astrocytomas in rats in the subsequent dietary study (Charles et al., 1996) in males was 0 and 1 and in females 1 and 1 for the control and high-dose groups (150 mg/kg/day), respectively. No astrocytomas were observed in either sex in the low- and mid-dose levels of the repeat study. The repeat study at doses up to 150 mg/kg/day found no evidence of an oncogenic response in rats in any organ (including brain) for 2,4-D. Importantly, both the mid- and top-dose levels used in the repeat rat bioassays were above dose levels exhibiting non-linear plasma toxicokinetics due to saturation of 2,4-D renal clearance, indicating that rodent tissues experienced disproportionately higher systemic doses relative to lower non-saturating doses (see Section 5). Thus, no evidence of tumorigenicity was observed in the repeat bioassays even though toxicokinetic studies confirmed systemic 2,4-D doses resulting in maximum systemic dose stress to the test animals (2,4-D brain concentrations are disproportionately increased at under conditions of Maximum Tolerated Dose testing).

Analysis of the strength- and weight-of-evidence of the astrocytoma responses across the two rat carcinogenicity bioassays indicates the increase in astrocytomas noted in the initial study (Munro et al., 1992) was not related to 2,4-D treatment. A fundamental scientific principle for

addressing the significance of a finding is replication, and in the case of 2,4-D, the astrocytoma response was not replicated in a second study despite a high-dose approximately 3.3-fold higher than the top dose of 45 mg/kg/day in the initial study. As noted above and detailed in Section 5 below, 2,4-D exhibits non-linear toxicokinetics due to saturation of renal clearance mediated through an active transporter, and 2,4-D doses above saturation result in disproportionate increases in brain concentrations in rats relative to non-saturating doses (reviewed in Munro et al., 1992). Data describing 2,4-D dose-dependent non-linear toxicokinetic behavior affirms the conclusion that the top levels 150 mg/kg/day in the second bioassay (Charles et al., 1996) robustly challenged the potential for 2,4-D to induce astrocytomas. A recent evaluation of 2,4-D toxicokinetics after dietary administration in rats found that 2,4-D renal clearance was saturated at 63 mg/kg/day in males and 25 mg/kg/day in females (Saghir et al., 2013), positioning both the mid- and high-bioassay doses of the replicate study well above the inflection point of toxicokinetic saturation. Since 2,4-D is not metabolized in rats (Munro et al., 1992), these high-dose conditions represent an artificial exposure of the rat brain to 2,4-D that is not relevant to humans (i.e., impossible to be reached in humans under normal use conditions); yet, an increased incidence of astrocytomas was not seen in the second rat study, which reached higher dose levels.

Additional weight-of-evidence examination of the astrocytoma data and ancillary supporting information further indicates the tumor response was not treatment-related. Several detailed reviews of clear and suspect chemical neurocarcinogens revealed a series of biologic and toxicologic benchmarks useful for identifying chemicals of concern for astrocytoma and other brain tumor formation (Ward and Rice, 1982; Koestner, 1986; Sills et al., 1999). The rat 2,4-D astrocytoma data are not consistent with the biological characteristics of chemically-induced brain tumors identified in these reviews, as summarized below:

- The incidence of astrocytomas in the 45 mg/kg/day group of the Munro et al., 1992 study was not significantly different from concurrent controls and only marginally exceeded the historical control range of 0-4% reported for F344 rats from the US National Toxicology Program (NTP) database during the approximate period of the 2,4-D bioassay. Importantly, Solleveld and coworkers (1984) have also observed that astrocytomas in male rats exhibited significant intergroup variability in an analysis of five historical control lifespan groups, with astrocytoma incidence ranging from 0 to 5.9%.

- A survey of 500 NTP studies identified only 10 studies (chemicals) which may have resulted in brain tumors (Sills et al., 1999). However, almost all of these substances were capable of metabolic generation of reactive intermediates and were mutagenic. 2,4-D is not metabolized to such intermediates and is not genotoxic and or mutagenic (Munro et al., 1992; Charles et al., 1999a,b; Gollapudi et al., 1999).

- The series of chemicals identified as possible brain tumorigens also exhibited tumor multiplicity in individual animals as well as being carcinogenic at multiple sites and across both sexes and species (Sills et al., 1999). The 2,4-D rat and mouse bioassays

fulfilled none of these criteria.

- Chemically-induced brain tumors exhibit a trend towards anaplasia and result in earlier tumor onset and/or decreased lifespan, neither of which was present in the 2,4-D bioassays (in contrast, the single astrocytoma in the Study 1 male rat control group was highly anaplastic; Table 1). In addition, neurocarcinogenic chemicals also show evidence of preneoplastic lesions in the brain which were not seen in interim one-year or terminal sacrifices in either 2,4-D rat bioassays (Munro et al., 1992; Charles et al., 1996).

- Several of the potential brain carcinogens identified in the NTP database are structurally related. 2,4-D does not share any of those structural relationships. In contrast, a close structural analog of 2,4-D, 2-methyl-4-chlorophenoxyacetic acid (MCPA), shares a lack of genotoxicity/mutagenicity, a common renal clearance mechanism, and similar chronic toxicity target organs with 2,4-D. MCPA also is not a rat or mouse carcinogen (EPA, 2004; FAO/WHO, 2012).

- Potential alternative modes of action for brain tumors such as endocrine disruption are not plausible in that 2,4-D is negative in EPA Endocrine Disruptor Screening Program (EDSP) in vitro estrogen and androgen assays (Coady et al., 2014), in vivo short-term fish and amphibian assays (Coady et al., 2013), and in an apical in vivo extended one-generation reproduction study specifically examining estrogen, androgen and thyroid sensitive endpoints (Marty et al., 2013). 2,4-D also is not immunotoxic or immunosuppressive in rat and mouse bioassays, and thus likely does not alter immune surveillance and control of chemically-induced tumors (Blakley and Blakley, 1986; Marty et al., 2013).

- As detailed in Section 3 above, epidemiological studies have not revealed a causative association of 2,4-D exposure and any human cancer outcomes (Munro et al., 1992; Garabrant and Philbert, 2002; Burns and Swaen, 2012; von Stackelberg, 2013). Further diminishing the plausibility of potential human cancer outcomes, 2,4-D systemic exposures resulting from a variety of agricultural and residential uses are well below the overall animal No Observed Effect Level (NOEL) dose of 5 mg/kg/day identified in the Charles et al. (1996) chronic rat and mouse bioassays and generally below systemic doses expected to result from exposures to the chronic Reference Dose (RfD) of 0.21 mg/kg/day established by the EPA (Aylward et al., 2010; 2012; EPA, 2013).

Taken together, the two mouse and two rat oncogenicity studies (Munro et al., 1992; Charles et al., 1996) cover a wide range of dose levels of 2,4-D that clearly establish NOAELs and MTDs for chronic toxicity. Although there was some initial concern over a non-statistically significant increase in male rat astrocytomas at 45 mg/kg/day in the earlier rat oncogenicity study, this finding was not replicated in a subsequent study conducted at 75 and 150 mg/kg/day and affirms the conclusion that this was a spurious finding bearing no relationship to treatment.

4.3 Conclusions

The weight of evidence for data on cancer in animals supports a lack of carcinogenicity. This conclusion has also been supported by government and regulatory agencies in their independent, public documents. For example the EPA concluded ‘‘2,4-D acid was not carcinogenic in male or female Fischer 344 rats…(and) was not carcinogenic in male and female B6C3F1 mice.’’ (EPA,1996), which has been a consistent position across three decades of reviews and assessments (EFSA, 2015; European Commission, 2001; USEPA, 1996 [pg 4]; USEPA, 1997 [pg 3]; USEPA, 2004a [pg 1]; USEPA, 2005 [pg 18]; EPA 2013 [pg. 13-14]). In addition, the World Health Organization (WHO) has come to the conclusion of no evidence of carcinogenicity in mice and rats (WHO, 1996 [pg 33]; WHO, 2003).

With respect to animal studies, there are adequate studies available that address the carcinogenic potential of 2,4-D in animals. The evidence from these studies demonstrate a lack of carcinogenicity in experimental animals, including use of doses resulting in non-linear toxicokinetics and dose-disproportionate increases in tissue 2,4-D concentrations.

5. Mechanistic and Other Data

5.1 Toxicokinetic data

The toxicokinetic data for 2,4-D is important to the understanding of human relevance of the animal toxicity findings, including high-dose specific toxicity findings in rodents as well as findings suggesting elevated 2,4-D toxicity in dogs. Once absorbed, 2,4-D is rapidly and completely excreted in urine by both rats and humans, but not dogs (Van Ravenzwaay et al., 2003; Timchalk, 2004). In rodents and human, renal excretion of 2,4-D is facilitated by a saturable organic anion active transporter located in the renal tubules (Timchalk, 2004). The transporter does not function effectively in dogs, resulting in higher peak and total systemic plasma 2,4-D doses in dogs compared to rodents (Van Ravenzwaay etal, 2003; Timchalk, 2004). Toxicokinetic studies in rats indicate the renal clearance of 2,4-D is clearly saturated at oral dose levels between 25 to 63 mg/kg/day, depending on sex, and that use of gavage or dietary treatments resulting in nonlinear increases in 2,4-D blood concentrations at these dose and above (Gorzinski et al., 1987; Van Ravenzwaay et al., 2003; Saghir et al., 2013). The onset of saturation of 2,4-D renal clearance at doses that are widely disparate from real-world human exposures suggests that animal toxicity findings observed at or above such dose levels overestimate potential human hazards and risks (Foran et al., 1997; Slikker et al., 2004 a,b; Timchalk, 2004; Barton et al., 2006; Carmichael et al., 2006; Doe et al.,2006; OECD, 2011).

As mentioned in the cancer in animals section above (Section 4), data describing 2,4-D dose-dependent non-linear toxicokinetic behavior affirms the conclusion that the top dose level in the second bioassay (Charles et al., 1996) robustly challenged the potential for 2,4-D to induce astrocytomas. A recent evaluation of 2,4-D toxicokinetics after dietary administration in rats (Saghir et al., 2013), confirms that both the mid- and high-dietary bioassay doses of both sexes in the replicate study by Charles et al. (1996) were well above the inflection point of toxicokinetic saturation. These high-dose non-linear toxicokinetic conditions represent an artificial worst case of exposure of the brain to 2,4-D (i.e., impossible to be reached in humans under normal use conditions); yet, an increased incidence of astrocytomas was not seen in the second study.

In the case of dogs, both subchronic and chronic studies indicate this species, with an overall NOAEL of 1 mg/kg/day (Charles et al., 1996c), is more sensitive to 2,4-D-induced toxicity than rodents, with an overall NOAEL of 5 mg/kg/day (Charles et al., 1996b). Consistent with these studies was a two-year study in rats and beagle dogs that demonstrated no evidence of carcinogenicity (Hansen et al., 1971). Because the dog is lacking an effective renal organic anion clearance mechanism, this differential species response has been attributed to an inability of the dog to effectively clear 2,4-D from the body, resulting in significantly higher 2,4-D blood concentrations in dogs relative to rats and humans at an equivalent oral dose of 5 mg/kg (Van Ravenzwaay et al., 2003; Timchalk, 2004). Since both rats and humans both express renal organic anion transporters (Timchalk, 2004; Nozaki et al., 2007), the EPA has concluded that the rat represents a better predictor of potential toxicity in man than the dog (EPA, 2004).

5.2 Mechanisms of carcinogenesis

As stated previously, 2,4-D has been evaluated for carcinogenicity in multiple rat and mouse chronic dietary bioassays (Munro et al., 1992; Charles et al. 1996), and recent in-depth reviews of those studies by the regulatory agencies of Canada and the United States and the EU have concluded that 2,4-D is not an animal carcinogen (EFSA, 2015; European Commission, 2001; EPA, 2005; PMRA, 2007). This conclusion is supported by findings that 2,4-D is non-genotoxic and non-mutagenic in both *in vitro* and *in vivo* assays (Canadian Centre for Toxicology, 1987; Munro et al., 1992; Charles et al., 1999a,b; Gollapudi et al. 1999). The lack of animal tumorigenicity of 2,4-D also is consistent with its lack of metabolism to reactive intermediates in either rodents or humans, and no structural alerts of the parent molecule for genotoxic or mutagenic activity have been identified (Munro et al., 1992).

In addition to the 10 key characteristics of carcinogens presented on Table 1, modes and mechanisms of action of molecules that cause NHL, gastric cancer, and astrocytoma are presented in Tables 2, 3, and 4, respectively. As noted in the previous sections, epidemiology studies have reported possible associations of 2,4-D with NHL and gastric cancer, while animal studies have described a non-replicable increase in astrocytomas. It is important to note that data in the Cancer in Human and Cancer in Animals sections support that 2,4-D is not carcinogenic based on the overall data from epidemiology and animal studies. However, for the sake of completeness, the potential modes of action of three tumor types are described in more detail in order to outline the absence of potential biological plausibility of any association between 2,4-D and these mechanisms.

The subsequent section highlights three common characteristic in IARC's general list (Table 1), NHL (Table 2), gastric cancer (Table 3), and astrocytoma (Table 4). These three common MoA are genotoxicity, immunotoxicity, and endocrine/receptor-mediated effects. The additional MoA are described with references in the appropriate tables, but not discussed in detail here.

Genotoxicity

A common mode-of-action (MoA) to a number of carcinogens, including NHL and astrocytoma, is genotoxicity (Tables 1, 2, and 4). For example, in the case of NHL, benzene and trichloroethylene are genotoxic chemicals, and exposures are associated with increased risk of NHL (Goldstein, 2010; Rusyn et al., 2014). Many NHL cases show chromosomal translocations (von Stackelberg, 2013). The most common translocation is t(14;18) translocation that activates the Bcl-2 oncogene (Martelli et al., 2013). However, NHL development appears to require additional promotion events in addition to genotoxicity, since t(14;18) translocations are seen in humans without NHL (von Stackelberg, 2013). Similarly, in the case of astrocytomas, mutations in tumor suppressor genes have been observed in human gliomas or astrocytomas (Maher, Furnari et al. 2001, Reilly and Jacks 2001, Zhu and Parada 2002, Xiao, Yin et al. 2005, Network 2008, Lim, Llaguno et al. 2011, Cohen and Colman 2015).

The genotoxic and mutagenic potential of 2,4-D has been examined in numerous studies. Overall, the weight of evidence shows that 2,4-D is not genotoxic in vitro or in vivo (Burns and

Swaen, 2012; Charles et al., 1999a; Charles et al., 1999b; ; USEPA, 2004b; USEPA, 1996 [pg 8]; EFSA, 2015 [pg.7]; EPA 2013 [pg. 13-14]; EUROPEAN COMMISION, 2001 [pg 10]; Gollapudi et al., 1999; Pesticides Board, 2000; PMRA, 1991[pg 5]; PMRA, 2007 [pg 8]; von Stackelberg, 2013; WHO, 1996 [pg 35]).

Immunotoxicity

Another common MoA to a number of molecules, including NHL and astrocytomas, is immunotoxicity (Tables 1, 2 and 4). In the case of NHL, trichloroethylene exposure in humans has been associated with NHL and lower serum immunoglobulin levels (Zhang et al., 2013). Animals exposed to trichloroethylene show suppression of B cell counts and altered levels of anti-inflammatory cytokines (Chiu et al., 2013). Human NHL cases are associated with prior immunosuppressive drug therapy and immunodeficiency from genetic disease or viral infection (Fisher and Fisher, 2004; Whiteside, 2006; Vineis et al., 2007). In addition, NHL is associated with autoimmune disease (Vineis et al., 2007), and there is evidence that animal models of trichloroethylene exposure increases autoimmune disease (Fisher and Fisher, 2004). In the case of astrocytoma, progesterone-induced blocking factor (PIBK) and immunomodulatory protein has been detected in human glioblastoma multiforme (GBM) and has been described as one of the factors suppressing anti-tumor immunity and thereby allowing tumor progression in these astrocytomas (Gonzalez-Aguero, Gutierrez et al. 2007, Kyurkchiev, Naydenov et al. 2014).

In the case of 2,4-D, the data support a lack of immunotoxic effects. Although a transient, short term immunomodulatory effect of 2,4-D in humans was reported in a single "preliminary" study (Faustini 1996), the weight of evidence indicates 2.4-D is not immunotoxic or immunosuppressive (Blakley et al., 1992; Blakley et al., 1998; Carlo et al., 1992; Charles et al., 1996; Garabrant and Philbert, 2002; Kaneene and Miller, 1999; Marty et al., 2013; USEPA, 2012).

Endocrine/Receptor-Mediated Effects

Finally, another common MoA to a number of molecules, including gastric cancer, are receptor-mediated effects (Tables 1 and 3). Receptor-mediated effects can occur through modulation of endocrine receptors such as androgen receptor (AR) and estrogen receptor (ER). In the case of gastric cancer, although not all epidemiological data are supportive, some epidemiology studies suggest a correlation between tamoxifen (an estrogen receptor antagonist) drug therapy and increased incidence of gastric cancer (Chandanos et al., 2008; Chen et al., 2014).

In the case of 2,4-D, numerous studies have been conducted to assess the potential for 2,4-D to interact with the endocrine system including the EPA Endocrine Disruptor Screening Program (EDSP) as well as the extended one-generation reproductive toxicity study, which serves as a Tier II/OECD Level 5 definitive data. These data demonstrate that 2,4-D does not alter estrogen receptor activity in vitro or in vivo (Coady et al., 2014; Marty et al., 2013; Sun et al., 2012).

Oxidative stress

Several studies have reported 2,4-D-induced alterations in various biomarkers of oxidative stress (Bukowska, 2003; Bongiovanni et al., 2007; Celik and Tuluce, 2007; Dinamarca et al., 2007; Ferri et al., 2007; Nakbi et al., 2010; Pochettino et al., 2013; Tayeb et al., 2013). However, the human health hazard relevance of these studies as potential indicators of genotoxic and/or cancer modes of action (Table 1) is highly tempered for a combination of reasons including use of *in vivo* or *in vitro* doses that were above those associated with saturation of renal clearance (Section 5.1), use of inappropriate modes of administration, and evaluation of formulations of unknown composition. Importantly, as noted above, the health hazard significance these observations is further questioned in that 2,4-D is not an *in vitro* or *in vivo* genotoxicant or an animal carcinogen despite use of test doses substantially exceeding saturation of renal clearance.

5.3 Conclusions

The weight of evidence for data on cancer in animals and humans supports a lack of carcinogenicity. Exploration of possible mechanisms associated with carcinogens and specifically with NHL, astrocytoma, and gastric cancer, discussed earlier in this document show no association between these mechanisms and 2,4-D. Therefore, the mechanistic examination supports that **there are no mechanistic data that provide biologically plausible evidence** of 2,4-D carcinogenicity.

6. Dioxins and Furans

The presence of dioxins and furans in chlorophenoxy herbicides has confounded IARC reviews since 1977. (IARC, 1977) Manufacture of the 2,4-DCP intermediate in 2,4-D production has been optimized by controlling processing conditions necessary to drive the chlorination reaction to the preferred two and four carbon positions, thereby limiting the formation of impurities that can lead to dioxin formation. Controlled temperature and residence time during the chlorination reaction, programmed addition of the chlorinating agent, and efficient agitation in the reaction vessel are processing factors that contribute to the purity of 2,4- DCP. Additionally, distillation of 2,4-DCP is a technique that may be employed post-chlorination to increase purity. Moreover, quality control sampling and analytical procedures are also utilized to verify product quality at various steps of the 2,4-DCP process. According to Results of testing of 2,4-DCP, performed in response to the Toxic Substances Control Act (TSCA) Dioxin/Furan Test Rule, showed no detectable concentrations of 2,3,7,8-substituted tetra- through hepta-CDD/CDFs.(EPA,2005)

As a result of changes in the manufacturing processes for 2,4-D over the past 15-20 years, dioxins are no longer found at detectable levels in 2,4-D products sold and used in the United States (EPA, 2014). The EPA has required testing of all 2,4-D products for dioxins and furans using very sensitive methods. Additionally, the Agency conducted an assessment assuming that dioxins were present at the detection limit in all 2,4-D products – an implausible situation, but a very protective assumption. Human health risks assessed with this assumption were insignificant (EPA, 2014). Dioxins and furans were also assessed in the most recent EU reevaluation of 2,4-D. In this review, EFSA (2015) states: “Dioxins and furans, considered as relevant impurities in 2,4-D if formed, were not detected in the batches at a LOQ of 10 μg/kg (ppb).”

7. Pesticide Regulatory Decisions

Recent regulatory reviews include those conducted by the United States Environmental Protection Agency (EPA), Health Canada Pest Management Regulatory Agency (PMRA) and the European Union (EU). These reviews have uniformly concluded there is no conclusive association between 2,4-D exposure and human cancer. Following is a chronological presentation of the conclusions drawn from recent cancer assessments.

In 1996, the World Health Organization (WHO, 1996) concluded that "there was no evidence of carcinogenicity" in all animal feeding studies with 2,4-D. They also agreed that while "Epidemiological studies have suggested an association between the development of soft-tissue sarcoma and non-Hodgkins lymphoma and exposure to chlorophenoxy herbicides, including 2,4-D. The results of these studies are not, however, consistent; the associations found are weak, and conflicting conclusions have been reached by the investigators."

On October 2, 2001, the European Commission Health and Consumer Protection Directorate-General re-registered 2,4-D for all uses within the European Union (European Commission, 2001). In making this determination, the Directorate-General concluded:"…no clear association between cancer development and exposure to phenoxy herbicides (including 2,4-D and 2,4-D 2-EHE) could be established from the available epidemiological studies." The Commission classified 2,4-D as "No evidence of carcinogenicity"

In 2003, the New Zealand Environmental Risk Management Authority (New Zealand, 2003) concluded a consultation process for proposed classification and control of several substances.

The Authority concluded that "there is inadequate evidence of a causal relationship between exposure to chlorophenoxy herbicides and the development of Non Hodgkin's Lymphoma (NHL) and other cancers in humans at this time, and the available data could not be interpreted as showing the presence or absence of a carcinogenic effect".

Health Canada, Pesticide Management Regulatory Authority (PMRA) in 2008, conducted its re-evaluation of 2,4-D (PMRA, 2008) and determined "that 2,4-D meets Canada's strict health and safety standards." PMRA concluded: "No other international regulatory body considers 2,4-D to be a human carcinogen. Based on all available and relevant data, Health Canada agrees with this position…Health Canada found that 2,4-D does not increase the risk of cancer and can be used safely by homeowners, provided label directions are followed."

Beginning in 1988, the EPA conducted a reregistration review of 2,4-D that the Agency completed in June, 2005 with its publication a Reregistration Evaluation Decision on 2,4-D (EPA, 2005). The RED concluded that "none of the more recent epidemiological studies definitively linked cancer causes to 2,4-D." The RED assigned 2,4-D to its category D: Not Classifiable as to Human Carcinogenicity. On August 8, 2007, EPA announced its decision not to initiate a special review of 2,4-D: "Based on extensive scientific review of many epidemiology and animal 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." (U.S. Fed. Reg., 2007).

As recently as 2014, the EPA assessed the carcinogenicity of 2,4-D as part of a new product registration: "Studies in rats and mice showed no statistically significant tumor response in either species; furthermore, 2,4-D is not mutagenic, a flag for potential carcinogenicity. The Agency determined, based on several reviews of epidemiological studies, in addition to the animal studies, that the existing data did not support a conclusion that links human cancer to 2,4-D exposure." (EPA, 2014)

In 2015, the conclusions of the European Food Safety Authority (EFSA) following the peer review of the initial risk assessments carried out by the competent authority of the Rapporteur Member State Greece, for the pesticide active substance 2,4-D were reported. (EFSA, 2015) It concluded "it was therefore agreed that 2,4-D, as currently manufactured, is unlikely to have a genotoxic potential or pose a carcinogenic risk to humans." The report goes on to conclude: "*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*."

8. Conclusions

As presented in this document **there is e*vidence demonstrating lack of carcinogenicity in experimental animals.*** There are adequate studies involving at least two species available which show that, within the limits of the tests used, 2,4-D is not carcinogenic.

Also, **there is *inadequate evidence of carcinogenicity in humans*.** The available studies are of insufficient quality, consistency or statistical power to permit a conclusion regarding the presence or absence of a causal association between exposure and cancer.

Moreover, the mechanistic section supports that there are **no mechanistic data that would support** evidence of 2,4-D carcinogenic modes-of-action.

Taken together, it is the position of the Industry Task Force II on 2,4-D Research Data that **2,4-D is *not classifiable as to its carcinogenicity to humans*.**

Table 1. Key characteristics of carcinogens according to IARC		
Characteristic	**Example of relevant evidence**	**Commonly linked characteristics**
1. Electrophilic or ability to undergo metabolic activation	Parent compound or metabolite with an electrophilic structure (e.g. epoxide, quinone, etc.), formation of DNA and protein adducts	2, 3, 4, 7, 8, 9
2. Genotoxic	DNA damage (DNA strand breaks, DNA–protein crosslinks, unscheduled DNA synthesis), intercalation, gene mutations, cytogenetic changes (e.g. chromosome aberrations, micronucleus formation)	1, 3, 4, 5, 10
3. Alter DNA repair or cause genomic instability	Alterations of DNA replication or repair (e.g. topoisomerase II, base-excision or double-strand break repair)	1, 2, 4, 6, 7, 9, 10
4. Epigenetic alterations	DNA methylation, histone modification, microRNAs	1, 6, 10
5. Oxidative stressor	Oxygen radicals, oxidative stress, oxidative damage to macromolecules (e.g. DNA, lipids)	2, 6, 8, 10
6. Induce chronic inflammation	Elevated white blood cells, myeloperoxidase activity, altered cytokine and/or chemokine production	3, 4, 5, 7, 8, 10
7. Immunosuppressant	Decreased immunosurveillance, immune system dysfunction	1, 3, 6, 8, 9
8. Modulate receptor-mediated effects	Receptor in/activation (e.g. ER, PPAR, AhR) or modulation of exogenous ligands (including hormones)	1, 5, 6, 7, 10
9. Immortalization	Inhibition of senescence, cell transformation	1, 3, 7, 10
10. Alter cell proliferation, cell death and nutrient supply	Increased proliferation, decreased apoptosis, changes in growth factors, energetics and signalling pathways related to cellular replication or cell-cycle control, angiogenesis	2, 3, 4, 5, 6, 8, 9

Table 2. Non-Hodgkins Lymphoma (NHL) Mode of Action and Mechanism		
Mode of Action	**Mechanism (References)**	**Association with 2,4-D (References)**
1. Genotoxicity	Chromosomal translocations and gene mutations that increase oncogene expression and/or activity (Bulka et al., 2013; Goldstein, 2010; Martelli et al., 2013; Rusyn et al., 2014; von Stackelberg, 2013)	2,4-D is not genotoxic. (Burns and Swaen, 2012; Charles et al., 1999a; Charles et al., 1999b; Gollapudi et al., 1999; von Stackelberg, 2013)
2. Altered lymphocytic cell cycle regulation	AhR activation in lymphocytes. Alterations in expression/activity of genes controlling apoptosis (e.g. Bcl-2 and caspases) (Kelly et al., 2010; Sherr and Monti, 2013; von Stackelberg, 2013)	At environmentally relevant concentrations, 2,4-D does not increase lymphocyte proliferation and is not known to alter lymphocyte apoptosis (Holland et al., 2002; Kaioumova et al., 2001; von Stackelberg, 2013)
3. Immunotoxicity/ Immunosuppression	Suppression of lymphocyte cell counts. Chronic immunosuppression from viral infection. Alteration of cytokine levels. (Chiu et al., 2013; Martelli et al., 2013; Tan and Coussens, 2007; Vineis et al., 2007; von Stackelberg, 2013; Whiteside, 2006; Zhang et al., 2013b)	2,4-D is not immunotoxic or immunosuppressive. (Blakley et al., 1992; Blakley et al., 1998; Carlo et al., 1992; Charles et al., 1996; Faustini et al., 1996; Garabrant and Philbert, 2002; Kaneene and Miller, 1999; Marty et al., 2013; USEPA 2012)

Table 3. Gastric Cancer Mode of Action and Mechanism		
Mode of Action	**Mechanism (References)**	**Association with 2,4-D (References)**
1. Gastric microbiome alteration	Increased levels of Helicobacter pylori in gastric microbiome leading to chronic inflammation, reactive oxygen species generation, and DNA damage (Brawner et al., 2014)	2,4-D is not known to alter the gastric microbiome. (No published data available)
2. Endocrine	Estrogen receptor antagonism (Chandanos et al., 2008 but see Chen et al., 2014 for a dissenting conclusion)	2,4-D does not alter estrogen receptor activity (Coady et al., 2014; Marty et al., 2013; Sun et al., 2012)
3. Nuclear receptor activation	AhR activation (Andersson et al., 2002)	2,4-D does not activate nuclear receptors, including AhR. (Kaioumova et al., 2001; Maloney and Waxman, 1999)
4. Epigenetic	Hypermethylation of tumor suppressor gene promoters (Chen et al., 2011; Liu et al., 2010; Sarbia et al., 2004)	2,4-D is not known to alter hypermethylation of tumor suppressor gene promoters (No published data available)
5. Gastric gland atrophy	Cytotoxicity leading to enterochromaffin-like cell proliferation (Furukawa et al., 2014)	2,4-D is not known to cause gastric gland atrophy. (No published data available)

Table 4. Astrocytomas Mode of Action and Mechanism		
Mode of Action	**Mechanism (Reference)**	**Association with 2,4-D (Reference)**
1. Genotoxicity	Tumor suppressor gene mutations, mutation/induction of oncogenes, mutation in metabolic genes (Cohen et al. 2015; Dang et al. 2009; Fontebasso et al. 2014; Lim et al. 2011; Lu et al. 2012; Network 2008; Noushmehr et al. 2010;; Reilly et al. 2001; Song et al. 2013; Turcan et al. 2012; Vivanco & Sawyers 2002; Wiencke et al. 2007; Xiao et al. 2005; Zhu at al. 2002)	2,4-D is not genotoxic (EFSA 2015; European Commision 2001; Pesticides Board 2000;PMRA, 1991, 2007; USEPA 1996, 2004b, 2013, WHO, 1996)
2. Epigenetic	Epigenetic silencing of tumor suppressor genes, onco-metabolite impairs histone post-translational modifications (Beaza et al. 2003; Fontebasso et al. 2014; Lu et al. 2012; Turcan et al. 2012; Wiencke et al. 2007; Zhang et al. 2013a)	No known association between 2,4-D and an epigenetic MoA
3. Immunotoxicity/ Immunosuppression	Progesterone-induced blocking factor (PIBK) induction, leading to anti-tumor immunosuppression and subsequent cell proliferation (Gonzalez-Aguero et al. 2007; Kyurkchiev et al. 2014)	2,4-D is not immunotoxic or immunosuppressive. (Blakley et al., 1992; Blakley et al., 1998; Carlo et al., 1992; Charles et al., 1996; Faustini et al., 1996; Garabrant and Philbert, 2002; Kaneene and Miller, 1999; Marty et al., 2013; USEPA 2012)
4. Receptor-mediated Effects	P_4 regulates human astrocytomas cell proliferation through the interaction with PR (Brinton et al. 2008; Cabrera-Munoz et al. 2011; Camacho-Arroyo & Montor 2012; German-Castelan et al. 2014; Graham & Clark 1997; Hernandez-Hernandez et al. 2012) E_2 induces cell growth of human astrocytoma cell lines through ERα and its interaction with SRC-1 and SRC-3 (Gonzalez-Arenas et al. 2012)	No known ER-a binding/activation activity (Coady et al. 2014; EFSA 2015; Industry Task Force 2014; Industry Task Force II, 2009; USEPA 2012)

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