Biomonitoring Data for 2,4-Dichlorophenoxyacetic Acid in the US and Canada: Interpretation in a Public Health Risk Assessment Context Using Biomonitoring Equivalents

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Abbreviations:

2,4-D:	2,4-Dichlorophenoxyacetic acid
BE:	Biomonitoring Equivalent
CDC:	Centers for Disease Control and Prevention
cr:	creatinine
CTEPP:	Children's Total Exposure to Persistent Pesticides and Other Persistent Organic Pollutants
LOD:	Limit of detection
MCPA:	(4-chloro-2-methylphenoxy) acetic acid
NHANES:	National Health and Nutrition Examination Survey
NOAEL:	No observed adverse effect level
POD:	Point of departure
RfD:	Reference dose
PMRA:	Pest Management Regulatory Agency
UF:	Uncertainty factor
USEPA:	United States Environmental Protection Agency

Manuscript Outline:

Abstract

Background: Several extensive studies of exposure to 2,4-dichlorophenoxyacetic acid using urinary 2,4-D concentrations in samples from the general population, farm applicators and farm family members are now available. Reference doses (RfDs) exist for 2,4-D, and Biomonitoring Equivalents (BEs; concentrations in urine or plasma that are consistent with those RfDs) for 2,4-D have recently been derived and published. **Objective:** Review the available biomonitoring data for 2,4-D from the United States and Canada. The available biomonitoring data are compared to BE values to draw conclusions regarding the margin of safety for 2,4-D exposures within each population group. **Data Sources:** Data on urinary 2,4-D excretion in general and target populations from recent published studies are tabulated. The derivation of BE values for 2,4-D is summarized. **Data Synthesis:** The biomonitoring data indicate margins of safety (ratio of BE value to biomarker concentration) of approximately 200 at the central tendency and 50 at the extremes in the general population. Median exposures for applicators and their family members during periods of use appear to be well within acute exposure guidance values. **Conclusions:** Biomonitoring data from these studies indicate that current exposures to 2,4-D are below applicable exposure guidance values. This case study demonstrates the value of biomonitoring data in assessing population exposures in the context of existing risk assessments using the BE approach. Risk managers can use this approach to integrate the available biomonitoring data into an overall assessment of current risk management practices for 2,4-D.

Introduction

Biomonitoring data for 2,4-dichlorophenoxyacetic acid (2,4-D) in urine samples are now available from a number of studies of both the general population (including preschool aged children) and farm applicators and their family members (Alexander et al. 2007; Arbuckle and Ritter 2005; Arbuckle et al. 2002, 2004, 2006; CDC 2005; Morgan et al. 2008). Such data provide an integrated measure of absorbed dose from all pathways and routes of exposure. The hazards of 2,4-D were recently assessed by the United States Environmental Protection Agency (USEPA 2004) and the Canadian Pest Management Regulatory Agency (PMRA 2007) . The USEPA-derived reference doses (RfDs) for acute and chronic exposure to 2,4-D are based on external exposure metrics (administered dose), which are not directly useful for evaluating biomonitoring data. However, Biomonitoring Equivalent (BE) values corresponding to RfDs for acute and chronic exposure scenarios are now available (Aylward and Hays 2008) and can be used as a tool for assessing the biomonitoring data directly in a public health risk assessment context, without requiring calculation of corresponding external dose, as has previously been done (Mage et al. 2004). This paper reviews urinary biomonitoring data for 2,4-D from several studies in the general population and in farmers and farm family members and evaluates the data in the context of the BE values for 2,4-D presented in Aylward and Hays (2008) to assess the current margin of safety (ratio of exposure guidance value such as an RfD to exposure measures) for population exposures to 2,4-D in the United States and Canada.

Methods

Biomonitoring data

Urinary biomonitoring data for 2,4-D are available from several studies of both general population adults and children and from studies of farmers and farm family members:

- The National Center for Environmental Health of the Centers for Disease Control and Prevention (CDC) measured 2,4-D in urine samples collected from a complex, stratified random sample of the civilian, non-institutionalized population of the U.S., ages 6 to 59, during 2001-2002, as part of the National Health and Nutrition Examination Survey (NHANES) (CDC 2005).
- Morgan et al. (2004, 2008) recently examined the exposures of 135 preschool children and their adult caregivers to 2,4-D at their homes in North Carolina and Ohio from the Children's Total Exposure to Persistent Pesticides and Other Persistent Organic Pollutants (CTEPP) study. Participants were randomly recruited from homes in six North Carolina and six Ohio counties. Participants were recruited by field staff from homes between February 2000 and February 2001 in NC and January 2001 and November 2001 in Ohio. Monitoring was performed over a 48-hour period at the participants' homes. Spot urine samples and environmental samples including air, soil, dust, hand wipes and food were collected and analyzed for 2,4-D.
- Alexander et al. (2007) reported urinary 2,4-D data from the Farm Family Exposure Study. Participants in the study included 34 farmers in Minnesota and South Carolina who were licensed applicators and their spouses and children (n=53) living on the farm property. Participants collected 24-hour urine samples the day prior to, the day

of, and for 3 days following application of 2,4-D on their farms during the 2000 or 2001 growing season.

- Curwin et al. (2005) measured urinary 2,4-D concentrations in 16 farmers 1 to 5 days following their application of 2,4-D on the farm during the spring and summer of 2001. Samples were composited from urine samples collected in the evening and the following first morning sample.
- The Pesticide Exposure Assessment Study measured the extent to which agricultural pesticide applicators and their families in Ontario, Canada are exposed to pesticides during normal handling practices (Arbuckle et al. 2002, 2004; Arbuckle and Ritter 2005). Farmers from the previously conducted Ontario Farm Family Health Study (Arbuckle et al. 1999), who had reported using phenoxyacetic acid herbicides were telephoned in early 1996 to determine their eligibility for the current study. To be eligible, the farmer had to: 1) be planning to use 2,4-D or (4-chloro-2-methylphenoxy) acetic acid (MCPA) in the coming growing season, 2) be the individual who would be handling the herbicides on the farm, 3) have his or her home on the farm property, and 4) be currently living with his or her spouse. A total of 126 families provided a spot urine sample prior to handling either 2,4-D or MCPA and then provided two consecutive 24-hour samples following use of the herbicide. All samples were collected in 1996.
- The Agricultural Health Study/Pesticide Exposure Study (AHS/PES) was designed to evaluate exposure to 2,4-D and chlorpyrifos in a subset of individuals enrolled in the Agricultural Health Study, which is a large, prospective epidemiological study of pesticide applicators and their spouses in Iowa and North Carolina to study the

relationships between agricultural exposures and disease. Participants in the AHS were contacted randomly and surveyed to ascertain their planned use of the 2,4-D and chlorpyrifos, and then a subset of participants were enrolled in the Pesticide Exposure Study (Thomas et al. 2009). Urinary samples were collected during 2001 and 2002, and included a preapplication first morning void sample, as well as a 24-hour sample starting the day of application ("Day 1") and, optionally, for days 2 through 5 as well.

Descriptions of the Institutional Review Board (IRB) approvals and informed consent information for each of these studies are presented in the underlying publications.

Reference Doses and Biomonitoring Equivalents

The USEPA recently conducted a review of 2,4-D and adopted both a chronic oral RfD as well as acute RfDs (applicable to single day exposures) for this herbicide (USEPA 2004). The derivations of the BE values associated with the RfD values are summarized in Table 1. BEs are defined as the concentration of a chemical or its metabolite in a human biological medium (usually blood or urine) that is consistent with existing exposure guidance values. BE values are screening values corresponding to existing risk assessments and not intended for use as definitive measures of risk for individuals. A full description of the BE approach and application is beyond the scope of this review, but is presented elsewhere (see Hays and Aylward, 2009; Hays et al. 2007, 2008).

The pharmacokinetics of 2,4-D have been studied in two sets of human volunteers (Kohli et al. 1974; Sauerhoff et al. 1977). Both found that 2,4-D is eliminated in urine either as

the unchanged parent compound (80-95%) or as a conjugate, with urinary half-lives on the order of 1 day. There was no evidence of oxidative metabolism, consistent with data from other mammalian species (Timchalk 2004). Based on these pharmacokinetic data, continuing exposure for more than 1 week of exposure would result in a steady-state in which the amount excreted daily in urine would be approximately equivalent to the amount absorbed each day.

Because 2,4-D is excreted as the parent compound in urine, most biomonitoring evaluations of exposure to 2,4-D have relied on measurements (quantifying both free and conjugated parent compound) in urine samples (Knopp and Glass 1991; Knopp 1994; CDC 2005), although a few kinetic studies have examined plasma concentrations of 2,4-D in humans and animals as well (Kohli et al. 1974; Saghir et al. 2006; Sauerhoff et al. 1977; van Ravenzwaay et al. 2003). The relative ease of collection of urine samples compared to blood samples contributes to this choice. From a toxicological point of view, plasma concentrations of 2,4-D are probably more informative for predicting target tissue concentrations and responses (for example, neurotoxic responses). This would be particularly true under conditions of episodic, higher-level exposures. However, under conditions of chronic, low-level exposures, urinary excretion rates of 2,4-D should be specific and quantitatively relevant in a framework of a mass-balance assessment. That is, under exposure conditions that approximate steady-state conditions (consistent with the definition of chronic RfDs and related exposure guidance values; see, for example, the definition of reference dose provided under the USEPA IRIS program at

http://www.epa.gov/IRIS/help_gloss.htm#r), daily urinary excretion of 2,4-D should equal daily intake.

The straightforward elimination kinetics of 2,4-D (as parent compound or conjugate in urine with essentially no oxidative metabolism) and the lack of direct relationship between urinary concentration and critical internal dose metrics suggests a simple mass-balance approach for derivation of BE values for urinary 2,4-D consistent with chronic exposure at the chronic RfD. The process of deriving the BE_{POD} and BE_{RfD} values for 2,4-D is detailed in Aylward and Hays (2008) and summarized below and in Table 1.

The point of departure (POD) for the USEPA chronic RfD is a no-observed-adverse-effect-level (NOAEL) of 5 mg/kg-d in rats fed 2,4-D chronically in the diet. Applying an uncertainty factor (UF) of 10 for interspecies variation, the human equivalent POD is 0.5 mg/kg-d. Calculating the average concentration of 2,4-D in urine in humans associated with this chronic daily dose (after application of the interspecies UF) yields the BE_{POD}. The daily mass intake at the human equivalent POD was estimated for a variety of child and adult body weights. Estimated distributions of daily creatinine excretion or urinary volume as a function of sex, age, and body size were used in a Monte Carlo analysis to estimate a distribution of creatinine-adjusted urinary 2,4-D concentrations for various age and sex categories (methods are described in detail in Aylward and Hays, 2008). The average of median estimated creatinine-adjusted 2,4-D concentration consistent with chronic exposure at the human equivalent POD (the BE_{POD}) for 2,4-D for adults (males and females) is approximately 20,000 µg/L or 30,000 µg/g creatinine. These values were

consistent with the range of median values identified in the simulations for children of various ages. Concentrations at the 95th percentiles of the estimated distributions were generally within a factor of 2 of the median values.

The BE associated with the chronic RfD was derived by dividing the BE_{POD} by the UF of 10 for intraspecies variation and the UF of 10 applied by USEPA for database uncertainties (for a total composite UF of 1,000 applied to the animal NOAEL POD). BE values corresponding to the acute RfDs were derived in a similar fashion, except that the assumption of steady-state was not made. Based on the urinary elimination half-life of approximately 1 day, an assumption was made that one-half of the intake doses at the human equivalent POD for the acute RfD values would be eliminated in the first 24 hours following exposures. Average urinary 2,4-D concentrations (both absolute and creatinine-adjusted) corresponding to one-half the human equivalent POD doses were estimated, and the intra-species and database uncertainty factors were then applied to obtain the BE_{RfD_acute} values. These BE values are appropriate for use when the exposure is short term and episodic and the timing of the sample collection compared to exposure is known. The derivation and resulting values are summarized in Table 1.

Results

Urinary 2,4-D concentrations measured in studies of general population groups (CDC, 2005; Morgan et al. 2008) are summarized in Table 2. Exposure pathways for persons in the general population may include ingestion of residues in food products, inhalation, and direct contact with dust (Morgan et al. 2004, 2008). The measured urinary concentrations

are presented in the context of the appropriate BE values based on the USEPA chronic RfD in Figure 1. The urinary levels of 2,4-D observed in the general population samples are far below the BE value corresponding to the USEPA chronic RfD, with median and upper bound measured concentrations more than 100- and 50-fold below the BE_{RfD}.

Corresponding data for farmers and members of their families obtained in the days immediately following application of 2,4-D (Alexander et al. 2007; Arbuckle and Ritter 2005; Arbuckle et al. 2002, 2004; Curwin et al. 2005; Thomas et al. 2009) are summarized in Table 3. Exposure pathways for non-applicators on the farm may include secondary exposure to field, farm machinery, or the applicator, and drift of herbicide during application with resulting inhalation, dermal and oral exposure following contact with residues on surfaces in the home. Urinary concentrations collected from farm family members in the day or days immediately following application of 2,4-D fell below the applicable acute BE values.

Measured urinary concentrations in farmers involved in application of 2,4-D are presented in the context of BE values corresponding to the USEPA occupational exposure guidance values in Figure 2. Again, the data suggest an overall margin of safety, with median or geometric mean levels in farmers involved in application of 2,4-D more than 25-fold below the occupational BE target value. However, some individuals had single spot urinary concentrations that approached the occupational BE target value. The highest urinary level of 2,4-D reported in Thomas et al. (2009) on Day 5 following application was 2500 µg/L, in excess of the occupational BE value of 2000 µg/L (data

not shown). However, all other reported occupational measurements were below the occupational BE.

Discussion

Available biomonitoring data for 2,4-D in both the general and agricultural populations indicate that current uses and practices suggest exposures that are below the acceptable exposures identified by the USEPA. A "margin of safety" is the ratio between the exposure guidance value and measured exposure. In this analysis, the exposure guidance value (RfD) was converted to a BE_{RfD} value for comparison to the measured biomarker concentrations. General population values indicate a margin of safety compared to the BE_{RfD} of approximately 200 at the central tendency and greater than 50 at the upper percentiles of exposure. In turn, the BE_{RfD} is 100-fold below the BE_{POD}, which is the biomarker concentration associated with chronic intake in humans at the animal-to-human extrapolated POD. The conclusion of a substantial margin of safety holds whether comparisons are made using volume or creatinine-adjusted concentrations. Median or average urinary 2,4-D concentrations for applicators are consistently below the BE values associated with occupational exposure targets set by USEPA (2004); however, evidence exists for exceptions near the occupational BE target value in a few individuals from the studied occupationally exposed populations. Biomonitoring data for spouses and children of applicators on the day following use of 2,4-D also fall below the BE values associated with general population acute exposure RfDs set by USEPA (2004).

Other studies have reported related biomonitoring data. Arcury et al. (2007) studied children from North Carolina farm worker families in 2004. Multiple pesticides (or

metabolites) were measured in urine samples from these children (1 to 6 years of age). The median 2,4-D concentration was below the limit of detection (LOD) of 0.2 µg/L (42% of the 60 sampled children had detectable concentrations of 2,4-D, but the range of detected concentrations was not reported). Garry et al. (2001) measured urinary 2,4-D in small numbers of forestry applicators who used a variety of methods to apply the herbicide. Backpack sprayers had the highest measured urinary concentrations during time periods of use, with a median of 160 µg/L and a range up to 1700 µg/L (n=7). Other modes of application such as use of boom sprayers or aerial applications resulted in lower urinary 2,4-D concentrations, with all measured values below 500 µg/L for boom sprayers and below 100 µg/L for other modes. These values are consistent with the concentrations observed in farm applicators from the Alexander et al. (2007) study, and are also below the occupational BE_{RfD} presented in Table 1.

The evaluation presented here is based on BE values derived from the USEPA risk assessment of 2,4-D (USEPA 2004). However, the Canadian PMRA has also recently estimated acceptable daily exposures to 2,4-D (PMRA 2007). The derived acute and chronic reference doses are based on the same underlying data as used by the USEPA, with similar or identical choices of POD. However, the PMRA assessment generally applied total uncertainty factors approximately 3-fold lower than those applied by USEPA, resulting in exposure estimates that are approximately 3-fold greater than those set by the USEPA. Thus, the BE_{POD} values associated with the PMRA risk assessment would be essentially identical to those for the corresponding USEPA exposure guidance values. Although BE values were not specifically derived based on the PMRA

assessments, corresponding urinary BE values would be approximately 3-fold higher than those derived based on the USEPA RfDs. BE values corresponding to the PMRA Acute RfD (ARfD) values for acute exposure in the general population and in females of reproductive age equal to 1,000 and 4,000 µg/L, respectively (2,000 and 7,000 µg/g creatinine). The BE value corresponding to the PMRA acceptable daily intake (ADI) for chronic exposure would be 700 µg/L (1,000 µg/g creatinine). Thus, reliance on the PMRA risk assessment does not change the overall conclusion of a substantial margin of safety under the various exposure scenarios.

Uncertainties and Limitations.

BE values are derived based on expected average concentrations (either volume based or creatinine-adjusted) in urine under conditions consistent with the underlying exposure guidance value (chronic or acute exposure conditions). Some variability in concentration is expected due to use of spot urine samples, inter-individual variability in creatinine excretion rates, and variability in urinary volume due to hydration status. Morgan et al. (2004, 2008) investigated the variability of 2,4-D concentrations among spot urine samples (i.e., first morning void, after lunch, and before bedtime) collected over the course of 48 hours from 28 adults and 28 children. The maximum measured spot urine value was within a factor of 3 of the mean value in 53 of the 56 individuals, consistent with previous assessments of variability among spot samples (see, for example, Scher et al. 2007).

2,4-D is relatively short-lived, with a urinary half-life on the order of one day, so for an individual in the general population, a single measurement does not characterize long-term exposure. However, the NHANES urinary data for 2,4-D are representative of the United States population and samples were collected at various times through the year. NHANES data would be expected to capture indications of higher exposures if they were occurring with any frequency, unless such variations were highly seasonal and geographically isolated. Urinary concentration data from Morgan et al. (2004, 2008) collected from two different geographical regions of the United States (NC and OH) over the course of a year suggest somewhat higher exposures than reflected in the NHANES dataset, but both sets indicate general population exposures far below health-based exposure guidance values.

A notable deficit in the available data for the general population pertains to residential uses of 2,4-D. Unlike exposures to 2,4-D users in agricultural populations, systematic evaluations of domestic use of the chemical are not available. These episodic exposures would not likely be captured in the NHANES or Morgan et al. (2008) data. To the extent that domestic applications do not result in exposures greater than those resulting from agricultural applications, human exposures should be within the margin of safety demonstrated by these existing study data. More research is needed to understand the domestic usage patterns of 2,4-D in residential settings and the resulting potential human exposures to this herbicide in the United States and Canada.

The RfD values derived by the USEPA are based on non-cancer endpoints. 2,4-D has also been assessed for potential carcinogenic effects. Non-Hodgkin lymphoma (NHL) was associated with herbicides and 2,4-D in a series of case-control studies initiated more than 20 years ago (Hoar et al. 1986; Zahm et al. 1990). Subsequent case-control and cohort studies have not confirmed these early observations (Burns et al. 2001; DeRoos et al. 2003; Hartge et al. 2005; Pearce et al. 1989; Schroeder et al. 2001; Woods et al. 1987). Recent reviews of NHL (Alexander et al. 2007) and 2,4-D (Garabrant and Philbert 2002) have concluded that the epidemiologic evidence remains "scant" and unsupportive for this association.

BE values are screening values and are not intended for use as definitive measures of risk for individuals. They do not represent a bright line between safe and unsafe levels, but rather allow evaluation of biomonitoring data in a public health risk context consistent with the existing risk assessment for 2,4-D (LaKind et al. 2008). Biomarker concentrations below the BE_{RfD} indicate a low priority for risk assessment follow-up, while concentrations in excess of the BE_{RfD} but below the BE_{POD} indicate a medium priority for risk assessment follow-up. Values in excess of the BE_{POD} indicate a high priority for risk assessment follow-up. Risk assessment follow-up may include examination of the underlying risk assessment, exposure pathway investigations, or other risk management activities (LaKind et al. 2008). Acute RfDs and the corresponding BE values are targeted at isolated, single-day exposures, and are only appropriate for use in evaluating biomonitoring data when there is specific knowledge of a potential acute exposure. The biomonitoring data reviewed here for both members of the general

population and applicators generally falls into the range of low priority for risk assessment follow-up, according to the guidelines for BE communication (LaKind et al. 2008).

Conclusions

Considerable population-level and micro-level data are now available regarding domestic and agricultural exposures to 2,4-D as measured by urinary 2,4-D excretion. These data suggest that current usage patterns and risk management efforts by industry and government are likely keeping average exposure to 2,4-D for the general population and in farm family members, and likely other persons potentially exposed due to proximity during usage of this herbicide, to levels well below current non-cancer reference values established both by the USEPA's Office of Pesticide Programs and by Canada's PMRA.

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Tables

Table 1: Reference doses established by USEPA (2004) for 2,4-D and derivation of corresponding BE values. Details of the derivation are presented in Aylward and Hays (2008).

Reference value:	RfD, chronic	RfD, acute, females of reproductive age	RfD, acute, other general population	Occupational Exposure[a]
Underlying study type:	Rat chronic dietary bioassay	Rat oral gavage, gestational days 6-15	Rat acute gavage	Rat chronic dietary bioassay
Endpoint:	Decreased bodyweight gain and food consumption, alterations in hematology and clinical chemistry parameters, increased thyroid weights, and decreased testes and ovarian weights.	Skeletal variations and malformations	Gait abnormalities	Same as for chronic RfD
POD (NOAEL), mg/kg-d:	5	25	67	5
Interspecies UF:	10	10	10	10
Human equivalent POD, mg/kg-d:	0.5	2.5	6.7	0.5
BE_{POD}, urinary 2,4-D:	20,000 µg/L (30,000 µg/g cr[c])	40,000 µg/L (70,000 µg/g cr)	100,000 µg/L (200,000 µg/g cr)	20,000 µg/L (30,000 µg/g cr)
Intraspecies UF:	10	10	10	10
Database UF:[b]	10	10	10	NA
BE_{RfD}, urinary 2,4-D:	200 µg/L (300 µg/g cr)	400 µg/L (700 µg/g cr)	1000 µg/L (2000 µg/g cr)	2000 µg/L (3000 µg/g cr)

[a] Derivation based on USEPA (2004) memorandum indicating 1) POD same as for general population chronic RfD, and 2) desired margin of exposure (MOE; ratio between POD and exposure level) of 100, based on UFs of 10 each for inter- and intra-species variation.
[b] Uncertainty factor applied to account for the lack of a developmental neurotoxicity study and the need for a repeated 2 generation bioassay with a focus on thyroid and immunotoxicity endpoints.
[c] cr = creatinine

Table 2: Urinary biomonitoring data for samples from the general population in the United States.

Study	n	Age group, population	Sample description	Percentiles, µg/L 50th	95th	Percentiles, µg/g cr 50th	95th
NHANES, 2001-2002 (CDC 2005)	546	Ages 6-11, US	spot	<LOD[a]	1.55	<LOD	1.40
	797	Ages 12-19	spot	<LOD	1.24	<LOD	0.662
	1070	Ages 20-59	spot	<LOD	1.27	<LOD	1.04
	2413	All, ages 6-59	spot	<LOD	1.27	<LOD	1.08
Morgan et al. 2008	66	Ages 2-5, NC	48-hour composites	0.5	1.9	1.0[b]	3.4[b]
	69	Ages 2-5, OH	48-hour composites	1.2	4.3	1.5[c]	5.1[c]
	66	Ages 20-44, NC	48-hour composites	0.7	2.8	0.6[b]	2.3[b]
	69	Ages 19-49, OH	48-hour composites	0.7	3.3	0.5[c]	3.3[c]

[a] LOD for NHANES 2001-2002 was 0.2 µg/L
[b] n=55
[c] n=59

Table 3: Concentrations of 2,4D measured in urine collected following acute exposure due to agricultural use of 2,4-D. Concentrations reported are 2,4-D in urine samples collected 1 day following application of 2,4-D on farms in applicators (Alexander et al. 2007; Arbuckle et al. 2002; Thomas et al. 2009) and family members (spouses and children; Alexander et al. 2007; Arbuckle et al. 2004) or in applicators 1 to 5 days following application (Curwin et al. 2005).

		µg/L	µg/g cr		
Group	n	Median (range)	Median (range)	Sample type	Study
Applicators	34	73.1 (1.5-1856)	45.8 (1.1-533.8)	24-hour	Alexander et al. 2007
	43	6.0 (0.5-410.0)	NR	24-hour	Arbuckle et al. 2002
	16	13[a] (NR)	NR	Composite of evening and following morning spot samples	Curwin et al. 2005
	28	26[b] (2.2-1000)	NR	24-hour	Thomas et al. 2009
Spouses[c]	34	1.2 (0.5-20)	1.1 (0.2-13.1)	24-hour	Alexander et al. 2007
	43	<LOD[*](<LOD-61)	NR	24-hour	Arbuckle and Ritter 2005
Children ages 4-17	52	2.9 (0.5-640.4)	2.3 (0.3-660.2)	24-hour	Alexander et al. 2007
Children ages 3-18	91	<LOD[*] (<LOD-12)	NR	24-hour	Arbuckle et al. 2004

[a] Geometric mean for farmers who reported spraying 2,4-D themselves in the previous 1 to 5 days.
[b] Geometric mean
[c] All spouses were female and all applicators were male.
[*] LOD = 1 µg/L.
NR= Not reported

Figure Legends

Figure 1: Urinary 2,4-D concentrations (μg/L) in general population studies presented in the context of the BE value corresponding to the USEPA RfD for general population chronic exposures. The NHANES symbol represents the 95th percentile for all tested participants (median values were below the LOD; see Table 2). The symbols for data from Morgan et al. (2008) represent the median values for the children and adults from two states; bars extend to the 95th percentile for each group. The shaded regions represent concentration ranges associated with low, medium, and high priority for risk assessment follow-up based on the criteria described in the BE communications guidelines (LaKind et al. 2008).

Figure 2: Urinary 2,4-D concentrations (μg/L) in applicators on the day following application of 2,4-D presented in the context of the human-equivalent BE_{POD} and target BE values associated with the occupational risk assessment (USEPA 2004; see Table 1). Symbols represent the median (or, in the case of Curwin et al. 2005 and Thomas et al. 2009, the geometric mean) and the bars extend to the maximum measured value in each study (not reported for Curwin et al. 2005). See the Figure 1 caption for interpretation of the shaded concentration regions.

Figure 1

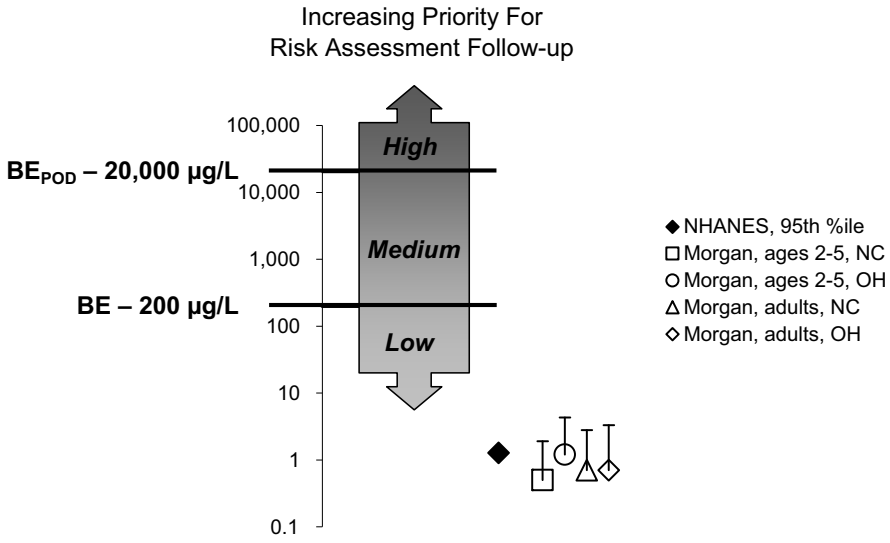
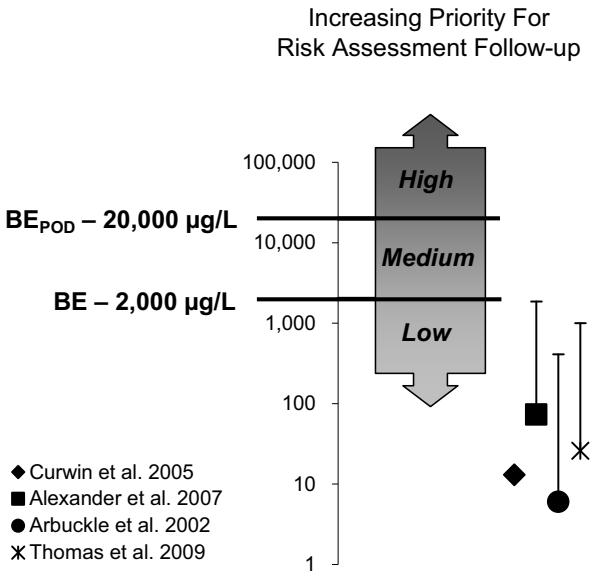

Increasing Priority For
Risk Assessment Follow-up
100,000
10,000
1,000
100
10
1
0.1
High
Medium
Low
BE$_{POD}$ – 20,000 µg/L
BE – 200 µg/L
NHANES, 95th %ile
Morgan, ages 2-5, NC
Morgan, ages 2-5, OH
Morgan, adults, NC
Morgan, adults, OH

Figure 2


Increasing Priority For
Risk Assessment Follow-up
100,000
10,000
1,000
100
10
1
High
Medium
Low
BE$_{POD}$ – 20,000 µg/L
BE – 2,000 µg/L
Curwin et al. 2005
Alexander et al. 2007
Arbuckle et al. 2002
Thomas et al. 2009