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

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BACKGROUND: Several extensive studies of exposure to 2,4-dichlorophenoxyacetic acid (2,4-D) using urinary 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: We reviewed the available biomonitoring data for 2,4-D from the United States and Canada and compared them with 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 and the derivation of BE values for 2,4-D 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 review 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.

KEYWORDS: 2,4-dichlorophenoxyacetic acid, biomonitoring, exposure biomarkers, exposure monitoring, risk assessment. Environ Health Perspect 118:177–181 (2010). doi:10.1289/ehp.0900970 available via http://dx.doi.org/ [Online 12 August 2009]

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-age children) and farm applicators and their family members [Alexander BH, et al. 2007; Arbuckle and Ritter 2005; Arbuckle et al. 2002, 2004, 2006; Centers for Disease Control and Prevention (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 U.S. EPA through the U.S. Environmental Protection Agency (U.S. EPA) law to provide funding for new research studies required to respond to the Canadian and U.S. pesticide reevaluation task registration program. The 2,4-D Task Force is made up of those companies owning the technical Canadian and U.S. registrations on the active ingredient in 2,4-D herbicides. They are Dow AgroSciences LLC (USA), Nufarm, Ltd. (Australia) and Agro-Gor Corp., a U.S. corporation jointly owned by Anator, S.A. (Argentina) and PBI-Gordon Corp. (U.S.). The U.S. Environmental Protection Agency (EPA) through its Office of Research and Development funded and managed some of the research described here. This research has been subjected to U.S. EPA administrative review and approved for publication. The findings and conclusions in this report are those of the authors and do not necessarily represent the views of Health Canada, the U.S. EPA, or the Centers for Disease Control and Prevention.

Methods

Biomonitoring data. We used urinary biomonitoring data for 2,4-D from several studies of both general population adults and children and from studies of farmers and farm family members, as follows.

The National Center for Environmental Health of the Centers for Disease Control and Prevention (CDC 2005) measured 2,4-D in urine samples collected from a complex, stratified random sample of the civilian, non-institutionalized population of the United States, 6–59 years of age, during 2001–2002, as part of the National Health and Nutrition Examination Survey (NHANES).

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 North Carolina and January 2001 and November 2001 in Ohio. Monitoring was performed over a 48-hr 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.

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Alexander BH, 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-hr urine samples the day before, the day of, and for 3 days after 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 1–5 days after their application of 2,4-D on the farm during the spring and summer of 2001. The evening and the following first morning urine samples were composited.

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 and Ritter 2005; Arbuckle et al. 2002, 2004). Farmers from the previously conducted Ontario Farm Family Health Study (Arbuckle et al. 1999) that had reported using phenoxyacetic acid herbicides were telephoned in early 1996 to determine their eligibility for the Pesticide Exposure Assessment Study. To be eligible, the farmer had to a) be planning to use 2,4-D or (4-chloro-2-methylphenoxy)acetic acid (MCPA) in the coming growing season, b) be the individual who would be handling the herbicides on the farm, c) have his or her home on the farm property, and d) be currently living with his or her spouse. A total of 126 families provided a spot urine sample before handling either 2,4-D or MCPA and then provided two consecutive 24-hr samples after use of the herbicide. All samples were collected in 1996.

The Agricultural Health Study (AHS)/Pesticide Exposure Study (PE) was designed to evaluate exposure to 2,4-D and chlorpyrifos in a subset of individuals enrolled in the AHS, which is a large, prospective epidemiologic study of pesticide applicators and their spouses in Iowa and North Carolina designed to assess 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 PES (Thomas et al. 2009). Urinary samples were collected during 2001 and 2002 and included a preaplication first morning void sample, as well as a 24-hr sample starting the day of application (day 1) and, optionally, for days 2–5 as well.

Table of RfDs and biomonitoring equivalents. The U.S. EPA 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 (U.S. EPA 2004). Table 1 summarizes the derivations of the BE values associated with the RfD values. 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 (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 studies 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 (CDC 2005; Knopp 1994; Knopp and Glass 1991), although a few kinetic studies have also examined plasma concentrations of 2,4-D in humans and animals (Kohli et al. 1974; Saghiri et al. 2006; Sauerhoff et al. 1977; van Ravenswaay et al. 2003). The relative ease of collection of urine samples compared with blood samples contributes to this choice. From a toxicologic point of view, plasma concentrations of 2,4-D are probably more informative for predicting target tissue concentrations and responses (e.g., neurotoxic responses). This would be particularly true under conditions of episodic, high-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, e.g., the definition of RfD provided under the U.S. EPA Integrated Risk Information System program (U.S. EPA 2000)], 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 suggest 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 BEPOD and BERID values for 2,4-D is detailed by Aylward and Hays (2008) and summarized below and in Table 1.

The point of departure (POD) for the U.S. EPA chronic RfD is a no observed adverse effect level (NOAEL) of 5 mg/kg-day 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-day. 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 BEPOD. 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 by Aylward and Hays (2008)]. The average of median estimated creatinine-adjusted 2,4-D concentration consistent with chronic exposure at the human-equivalent POD (BEPOD) 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 BEPOD, which reflects the interspecies UF of 10, by the UF of 10 for intraspecies variation and the UF of 10 applied by U.S. EPA for database uncertainties (for a total composite UF from the animal POD of 1,000 applied to the animal NOAEL POD). BE values corresponding to the acute RfD were derived in a similar fashion, except (for a total composite UF from the animal POD). BE values corresponding to the acute POD of 1,000 applied to the animal NOAEL POD. BE values corresponding to the acute POD were estimated for a variety of child and adults from two states; bars extend to the 95th percentile for all tested participants (median values in farmers involved in application of 2,4-D fell below the applicable acute BE values. Figure 2 presents measured urinary concentrations in farmers involved in application of 2,4-D in the context of BE values corresponding to the U.S. EPA occupational RfD, with median and upper bound measured concentrations more than 100- and 50-fold below the BEPOD.

Table 2 summarizes the corresponding data for farmers and members of their families obtained in the days immediately after application of 2,4-D. Exposure pathways for non-applicants on the farm may include secondary exposure to treated fields, farm machinery, or the applicator, and drift of herbicide during application with resulting inhalation, dermal, and oral exposure after contact with residues on surfaces in the home. Urinary concentrations collected from farm family members in the day or days immediately after application of 2,4-D fell below the applicable acute BE values. Figure 2 presents measured urinary concentrations in farmers involved in application of 2,4-D in the context of BE values corresponding to the U.S. EPA occupational exposure guidance values. 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 days 1–5 after application was 2,500 µg/L, in excess of the occupational BE of 2,000 µg/L (data not shown). All other reported occupational measurements were below the occupational BE.

Results
Table 2 summarizes urinary 2,4-D concentrations measured in studies of general population groups (CDC 2005; Morgan et al. 2008). 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). Figure 1 presents the measured urinary concentrations in the context of the appropriate BE values based on the U.S. EPA chronic RfD. The urinary levels of 2,4-D observed in the general population samples are far below the BE value corresponding to the U.S. EPA chronic RfD, with median and upper bound measured concentrations more than 100- and 50-fold below the BEPOD.

Figure 2 presents measured urinary concentrations in farmers involved in application of 2,4-D in the context of BE values corresponding to the U.S. EPA occupational exposure guidance values. 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 days 1–5 after application was 2,500 µg/L, in excess of the occupational BE of 2,000 µg/L (data not shown). 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 U.S. EPA. 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 BERID value for comparison with the measured biomarker concentrations. General population values indicate a margin of safety compared with the BERID of approximately 200 at the central tendency and > 50 at the upper percentiles of exposure. In turn, the BEBERID is 100-fold below the BEPOD, which is the biomarker concentration associated with chronic intake in humans at the POD.
extrapolated from animals to humans. 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 the U.S. EPA (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 after use of 2,4-D also are less than the BE values associated with general population acute exposure RfDs set by the U.S. EPA (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 (1–6 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 1,700 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 < 500 µg/L for boom sprayers and < 100 µg/L for other modes. These values are consistent with the concentrations observed in farm applicators from the Alexander BH, et al. (2007) study and are also below the occupational BEPOD presented in Table 1.

The evaluation presented here is based on BE values derived from the U.S. EPA risk assessment of 2,4-D (U.S. EPA 2004). However, the Canadian PMRA has also recently estimated acceptable daily exposures to 2,4-D (PMRA 2007). The derived acute and chronic RfDs are based on the same underlying data as used by the U.S. EPA, with similar or identical choices of POD. However, the PMRA assessment generally applied total UFs approximately 3-fold lower than those derived based on the U.S. EPA RfDs. BE values corresponding to the PMRA acute RfD 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 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 because of use of spot urine samples, interindividual 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 hr 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 (e.g., Scher et al. 2007). 2,4-D is relatively short-lived, with a urinary half-life of the order of 1 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 U.S. 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 (North Carolina and Ohio) over the course of a year suggest somewhat higher exposures than reflected in the NHANES data set, 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

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**Figure 2.** Urinary 2,4-D concentrations (µg/L) in applicators on the day after application of 2,4-D presented in the context of the human-equivalent BEPOD and target BE values associated with the occupational risk assessment (U.S. EPA 2004) (see Table 1). Symbols represent the median (or, in the case of Curwin et al. 2005 and Thomas et al. 2005, the geometric mean), and the bars extend to the maximum measured value in each study (not reported for Curwin et al. 2005). For description of shaded regions, see Figure 1 legend.
evaluations of domestic use of the chemical are not available. These episodic exposures would not likely be captured in the NHANES (CDC 2005) 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 patterns of domestic use 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 U.S. EPA are based on noncancer end points. 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 > 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; De Roos et al. 2003; Hargreaves et al. 2001; Pearce 1989; Schroeder et al. 2001; Woods et al. 1987). Recent reviews of NHL (Alexander DD, et al. 2005; Pearce 1989; Schroeder et al. 2001; Woods et al. 1987). Recent reviews of NHL (Alexander DD, et al. 2005; Pearce 1989; Schroeder et al. 2001; Woods et al. 1987). Recent reviews of NHL (Alexander DD, et al. 2005; Pearce 1989; Schroeder et al. 2001; Woods et al. 1987). Recent reviews of NHL (Alexander DD, et al. 2005; Pearce 1989; Schroeder et al. 2001; Woods et al. 1987). Recent reviews of NHL (Alexander DD, et al. 2005; Pearce 1989; Schroeder et al. 2001; Woods et al. 1987). Recent reviews of NHL (Alexander DD, et al. 2005; Pearce 1989; Schroeder et al. 2001; Woods et al. 1987). Electric microlevel.

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_{24D} indicate a low priority for risk assessment follow-up, whereas concentrations in excess of the BE indicate a medium priority for risk assessment follow-up. Values in excess of the BE 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, episodic exposures greater than those resulting from prolonged exposures that may be captured in the NHANES (LaKind et al. 2009).

Conclusions

Considerable population-level and microlevel 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 use 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 from proximity to use of this herbicide, to levels well below current noncancer reference values established by both the U.S. EPA’s Office of Pesticide Programs and by Canada’s PMRA.

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