Regulatory Toxicology and Pharmacology 71 (2015) 235–243

Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

journal homepage: www.elsevier.com/locate/yrtph

Derivation of human Biomonitoring Guidance Values for chlorpyrifos using a physiologically based pharmacokinetic and pharmacodynamic model of cholinesterase inhibition

Scott M. Arnold [a,*], Alistair Morriss [b], Joseph Velovitch [c], Daland Juberg [c], Carol J. Burns [a], Michael Bartels [a], Manoj Aggarwal [b], Torka Poet [d], Sean Hays [e], Paul Price [a]

[a] The Dow Chemical Company, Midland, MI, United States
[b] Dow AgroSciences Ltd., Milton Park, Abingdon, United Kingdom
[c] Dow AgroSciences, Indianapolis, IN, United States
[d] Summit Toxicology, LLP, Richland, WA, United States
[e] Summit Toxicology, LLP, Lyons, CO, United States

ARTICLE INFO

Article history:
Received 21 August 2014
Available online 25 December 2014

Keywords:
Chlorpyrifos
Biomonitoring Guidance Value
Biomonitoring
Physiologically based pharmacokinetic/pharmacodynamic model
Acetylcholinesterase inhibition
Risk assessment

ABSTRACT

A number of biomonitoring surveys have been performed for chlorpyrifos (CPF) and its metabolite (3,5,6-trichloro-2-pyridinol, TCPy); however, there is no available guidance on how to interpret these data in a health risk assessment context. To address this gap, Biomonitoring Guidance Values (BGVs) are developed using a physiologically based pharmacokinetic and pharmacodynamic (PBPK/PD) model. The PBPK/PD model is used to predict the impact of age and human variability on the relationship between an early marker of cholinesterase (ChE) inhibition in the peripheral and central nervous systems [10% red blood cell (RBC) ChE inhibition] and levels of systemic biomarkers. Since the PBPK/PD model characterizes variation of sensitivity to CPF in humans, interspecies and intraspecies uncertainty factors are not needed. Derived BGVs represent the concentration of blood CPF and urinary TCPy associated with 95% of the population having less than or equal to 10% RBC ChE inhibition. Blood BGV values for CPF in adults and infants are 6100 ng/L and 4200 ng/L, respectively. Urinary TCPy BGVs for adults and infants are 2100 μg/L and 520 μg/L, respectively. The reported biomonitoring data are more than 150-fold lower than the BGVs suggesting that current US population exposures to CPF are well below levels associated with any adverse health effect.

1. Introduction

Chlorpyrifos (CPF) (*O*,*O*-diethyl *O*-(3,5,6-trichloro-2-pyridyl) phosphorothioate) is an insecticide used to control a broad-spectrum of insect pests. CPF is not persistent in the environment and does not bioaccumulate. The compound is metabolized in both insects and mammals (USEPA, 2011). CPF was first registered in the United States (US) in 1965 and it is used in over 100 countries to protect more than 50 different crop types against insect pests. Registered uses of CPF in the US include food crops such as fruit and nut trees and many fruits, vegetables, and grains. Non-food crop applications include forage, golf course turf, industrial sites, greenhouse and nursery production, sod farms, and wood products (USEPA, 2011). Because CPF was withdrawn from residential use in the US in 2001, the primary route of chlorpyrifos exposure to the general population is via dietary residues (USEPA, 2011).

Human exposure to CPF has been investigated in multiple biomonitoring studies of the general population and occupationally exposed subpopulations. These studies generally employed measurements of the parent CPF in blood or its major metabolite, 3,5,6-trichloro-2-pyridinol (TCPy), in urine (Alexander et al., 2006; Barr et al., 2005; Centers for Disease Control and Prevention (CDC), 2009; Farahat et al., 2011; Garabrant et al.,

Abbreviations: BE, Biomonitoring Equivalent; BGV, Biomonitoring Guidance Value; CDC, Centers for Disease Control and Prevention; ChE, cholinesterase; CPF, chlorpyrifos; CYP, cytochrome P450; DEP, diethylphosphate; LOD, limit of detection; MOS, margin of safety; PBPK/PD, physiologically based pharmacokinetic/pharmacodynamic; RBC, red blood cell; TCPy, 3,5,6-trichloro-2-pyridinol; US, United States; USEPA, US Environmental Protection Agency.

* Corresponding author at: The Dow Chemical Company, Toxicology and Environmental Research & Consulting, 1803 Building, Midland, MI 48674, USA. Fax: +1 989 636 1875.

E-mail address: smarnold@dow.com (S.M. Arnold).

http://dx.doi.org/10.1016/j.yrtph.2014.12.013
0273-2300/

2009; Thomas et al., 2010). However, methods for relating measurements of blood CPF and urinary TCPy to levels associated with potential health effects have been lacking.

This manuscript describes a novel methodology that uses a physiologically based pharmacokinetic and pharmacodynamic (PBPK/PD) model to derive Biomonitoring Guidance Values (BGVs) for measurements of blood CPF and urinary TCPy. The BGVs represent the blood CPF and urinary TCPy levels predicted to occur in sensitive individuals exposed to an oral acute dose that results in 10% red blood cell (RBC) cholinesterase (ChE) inhibition (the early marker of ChE inhibition in the peripheral and central nervous systems). The BGVs are then compared to actual CPF biomonitoring data from a number of studies and margins of safety (MOSs) are generated. The MOSs can then be used to inform whether populations are at potential risk.

2. Background

2.1. CPF metabolism

Oral doses of CPF are well absorbed and undergoe extensive first pass metabolism (Bakke et al., 1976; Smith et al., 1967; Nolan et al., 1984, 1987; Timchalk et al., 2006; Griffin et al., 1999). When CPF enters the body it is initially metabolized by cytochrome (CYP) P450s, mainly in the liver, to primarily TCPy or diethylphosphate (DEP) metabolites or to the trace-level, short-lived CPF-oxon metabolite. Minor CYP metabolism also occurs in the intestine, lung, skin, and brain (Poet et al., 2014b), and CPF is known to irreversibly inhibit CYP P450s (Eaton et al., 2008). The low levels of CPF-oxon that are formed are rapidly metabolized to TCPy in both the liver and circulating blood (Fig. 1) by paraoxonase (PON1) and other esterases (Eaton et al., 2008).

In rats, CPF is primarily excreted in the urine as conjugates of TCPy (Bakke et al., 1976; Smith et al., 1967). Nolan et al. (1987) also studied CPF metabolism in the rat and found that it undergoes extensive first-pass metabolism to TCPy, with no parent compound excreted in urine. These authors reported the major urinary metabolite to be TCPy-glucuronide, with lesser amounts of TCPy-sulfate and free TCPy (Nolan et al., 1987). Sunaga et al. (1989) reported similar findings, following intraperitoneal administration of CPF to rats, showing urinary TCPy accounted for more than 85% of the administered dose of CPF, with lower percentages of the diethylphosphate metabolites recovered. A subsequent study was conducted in rats to evaluate the time-course of blood metabolites following oral administration of 0.5–100 mg CPF/kg body weight (Timchalk et al., 2006). The authors determined 99% of blood metabolites were in the form of TCPy with only 1% as parent compound. Trace levels of CPF-oxon levels were found but were generally 100-fold lower than CPF levels. These trace levels of the CPF-oxon metabolite are consistent with the report of high first-pass metabolism of CPF by the liver (Sultatos, 1994).

The metabolism and pharmacokinetics of CPF have been evaluated in several human volunteer studies. Nolan et al. (1984) found at least 70% of a single oral dose of CPF (0.5 mg/kg) was absorbed and excreted in the urine, primarily as acid-labile conjugates of TCPy (Nolan et al., 1984). Trace levels of CPF were found in this study, with no measurements conducted for CPF-oxon (Nolan et al., 1984). Griffin et al. (1999) measured urinary DEP metabolites of CPF following oral or dermal doses, showing 93% of administered dose is excreted in urine as these DEP metabolites. In a later multi-dose level pharmacokinetic study, Kisicki et al. (1999) found that following a single oral dose of either 0.5, 1.0 or 2.0 mg CPF/kg body weight, TCPy was the major metabolite in blood, with CPF levels <1% of TCPy concentrations. No CPF-oxon was detected in blood samples from this study, with the 1 ng/mL limit of quantitation value 3- to 18-fold lower than the highest CPF concentrations observed. These CPF-oxon results are consistent with the rat pharmacokinetic results and indicate that CPF undergoes extensive first-pass metabolism in humans as well as animals.

2.2. CPF mode of action

The mode of action for CPF has been well described (Eaton et al., 2008). CPF is lipophilic with a log K_{ow} value of 4.96 (Sangster, 1994); whereas, the CPF-oxon and hydrolysis metabolites, TCPy and diethylphosphates, are substantially more polar. The parent compound; containing the P=S bond is more chemically stable than the reactive CPF-oxon, due to the P=S bond being less electronegative than

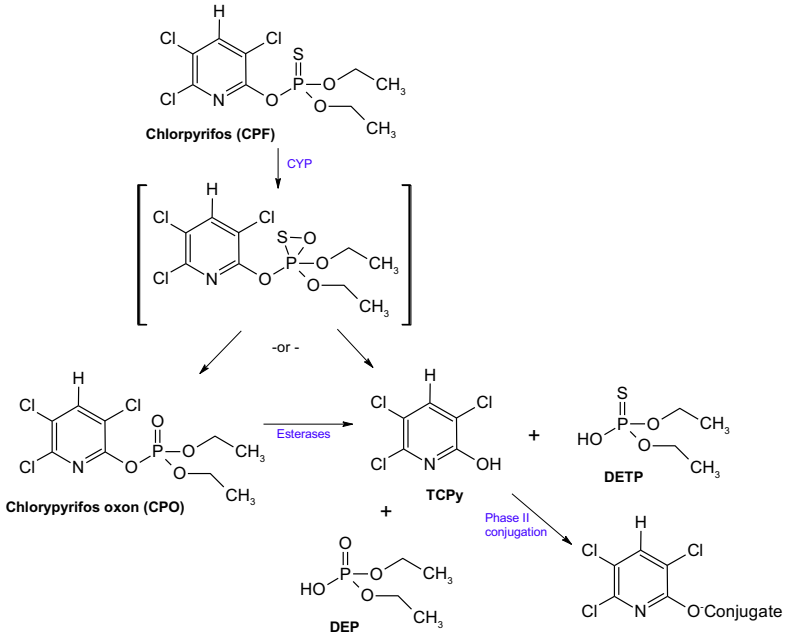

Fig. 1. Metabolic scheme of chlorpyrifos in mammals.