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Human health risk assessments for three neuropharmaceutical compounds in surface waters

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Abstract

Enhanced sensitivity of analytical chemistry methods has enabled the detection of low-levels of pharmaceuticals in the environment, resulting in questions about the safety of surface waters used for drinking supplies. Human health risk assessments were performed to evaluate the risks from residues of atomoxetine, duloxetine, and olanzapine, which might be found in surface waters. Preclinical safety studies and human clinical data were used to determine an acceptable daily intake (ADI) for each compound: atomoxetine, 1.4 μg/kg/day; duloxetine, 1.8 μg/kg/day; and olanzapine, 1.4 μg/kg/day. The calculated predicted no-effect concentrations (PNECs) for children were 25.7, 19.1, and 35.9 μg/L for atomoxetine, duloxetine, and olanzapine, respectively. Estimated exposure concentrations determined using United States Food and Drug Administration guidelines and predicted exposure concentrations from the P*h*ATE™ model were compared with each PNEC to determine margins of safety, which ranged from 147 to 642. Based on currently available data used in this assessment, no appreciable human health risks exist from exposure to the highest 99th percentile of predicted residue levels of atomoxetine, duloxetine or olanzapine in surface waters under low-flow conditions.

Keywords: Pharmaceuticals; Human health; P*h*ATE™; Water; Risk assessment; Fish consumption; PNEC; CSAF

1. Introduction

Active pharmaceutical ingredients (API) and associated metabolites can enter surface waters after medicines are consumed and excreted by humans. Sensitive analytical chemistry methods have recently been used to detect the low-levels of pharmaceuticals and metabolites that might be present in surface waters (Kolpin et al., 2002). These detections have led to questions about the safety of humans exposed to pharmaceuticals via water supplies (Jones et al., 2005). Human health risk assessments have already addressed these concerns for many pharmaceutical compounds (Schwab et al., 2005; Schulman et al., 2002; Webb et al., 2003; Christensen, 1998). There are, however, no published human health risk assessments for the neuropharmaceutical compounds atomoxetine, duloxetine, or olanzapine. This paper provides human health risk assessments for possible exposure to residues of these compounds that might occur in surface waters of the United States.

2. Methods

2.1. Overview of risk assessment process

Atomoxetine, duloxetine, and olanzapine have diverse chemical structures (Fig. 1) with pharmacological activity effective in a variety of indications. Atomoxetine is a selective norepinephrine reuptake inhibitor indicated for the oral treatment of attention-deficit/hyperactivity disorder (ADHD) (Eli Lilly and Company, 2006b). Duloxetine HCl is a selective serotonin and norepinephrine reuptake inhibitor approved in the United States for the oral treatment of major depressive disorder, diabetic peripheral neuropathic pain, and generalized anxiety disorder (Eli Lilly

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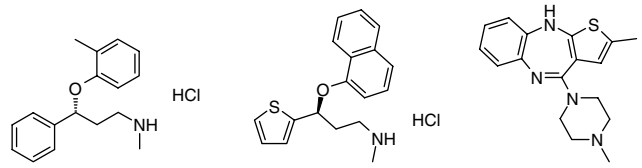

Atomoxetine hydrochloride
CAS # 82248-59-7
MW 291.82

Duloxetine hydrochloride
CAS # 136434-34-9
MW 333.88

Olanzapine
CAS # 132539-06-1
MW 312.44

Fig. 1. Chemical structures.

and Company, 2007). Olanzapine is a dopamine and serotonin antagonist approved for oral and intramuscular treatment of patients with schizophrenia and bipolar disorder (Eli Lilly and Company, 2006a). Potential risks to human health, were evaluated by (1) using hazard characterization and efficacy data from available preclinical and clinical studies to determine the lowest relevant effect dose, (2) using the lowest effect or no-effect dose to derive an acceptable daily intake (ADI) value and (3) calculating the predicted no-effect concentration (PNEC) in water, assuming the ADI could be delivered through drinking water and by eating fish. Calculated concentrations in surface waters were estimated for each chemical using methods recommended by USFDA (1998) and with a chemical fate model for United States surface waters called P*h*ATE™ (Pharmaceutical Assessment and Transport Evaluation). The PNEC was then compared to the highest calculated concentrations in surface waters to determine the PEC/PNEC ratios and margin of safety for each compound.

2.2. Hazard characterization

Hazard characterization, by evaluation of preclinical and clinical data, was completed for the three compounds. The preclinical data from animal studies were reviewed for acute, chronic, developmental, reproductive, mutagenic, and carcinogenic endpoints. The clinical data from human studies were reviewed to determine pharmacological and adverse effects. Based on this evaluation, the point of departure (POD) (the lowest observed dose that resulted in an effect of human relevance or caused no effect) was determined for each API (USEPA, 2002a). If the same effect was observed in both humans and animals, the human study was used for the POD in the risk assessment (Dourson et al., 2001). If the same effect was not observed in both animals and humans, the POD was selected from the animal or human study that, in combination with the appropriate uncertainty factors (UFs), gave the lowest ADI.

2.3. Derivation of the ADI

The ADI is an estimated daily chronic dose of the pharmaceutical that is likely to be without any appreciable risk of deleterious effects, including sensitive subpopulations (USEPA, 2002a; Schwab et al., 2005). The ADI for each of the three compounds was determined by dividing the POD by UFs using established methods (USEPA, 2002a). In the absence of sufficient data, default UFs of 10 each were used to account for extrapolation from a low-effect level (LOEL) to a no-effect level (NOEL), to account for extrapolation from animal data to humans, and to account for variability within the human population (IPCS, 1999; USEPA, 2002a). However, where available, clinical trial data replaced default UFs, allowing calculation of chemical specific adjustment factors (CSAFs) (IPCS, 2005; Naumann et al., 2001). In this report, CSAFs provided estimates of the actual variability in human responses, thereby reducing the uncertainty and allowing for adjustments based on actual human data rather than default values. These CSAFs replaced default UFs, where appropriate, to adjust for pharmacokinetic variability in humans, which accounts for a portion of the total inter-individual UF (3.2 for pharmacokinetics and 3.2 for pharmacodynamics) (IPCS, 2005).

2.4. PNEC derivation

The PNEC derivation (Table 1) translates the ADI into an acceptable water concentration by considering possible exposure through daily consumption by humans of water and fish (USEPA, 2000; Schwab et al. 2005). PNEC values were determined for adults and children based on consumption rates listed in Table 1. A relative source contribution factor of one was applied since water and fish were assumed to be the only potential sources of non-therapeutic exposure. The bioconcentration factor (BCF) was calculated (Table 1) from the Log K_{ow} (USEPA, 2000).

2.5. Exposure assessment

The exposure assessment estimates the level of API in surface waters. The estimated environmental concentration (EEC) recommended for environmental assessments of pharmaceuticals by the USFDA was calculated by dividing the annual total mass of API sold in the United States by the volume of water exiting all publicly-owned treatment works (POTWs) annually, and by a dilution

Table 1
Equations

Equations	Source
$\log \mathrm{BCF}\ (\mathrm{L/kg}) = (0.85 \times \log K_{ow}) - 0.7$	USEPA (2000)
$\mathrm{PNEC}\ (\mu\mathrm{g/L}) = \frac{\mathrm{ADI}\times\mathrm{BW}}{\mathrm{DI}+(\mathrm{FI}\times\mathrm{BCF})}$	USEPA (2000); Schwab et al. (2005)
$\mathrm{EEC}\ (\mathrm{mg})/\mathrm{L} = \frac{\text{mass sold/year}}{1.214\times10^{11}\,\mathrm{L}\times10\times365\ \text{days}}$	USFDA (1998)

(1) BW is body weight (kg).
(2) DI is drinking water intake: 2 L/day for adults (70 kg); 1 L/day for children (30 kg) (USEPA 2000).
(3) FI is fish intake: 0.0175 kg/day for adults (70 kg); 0.013 kg/day for children (30 kg) (USEPA 2000, 2002b).