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Developmental neurotoxicity in the progeny after maternal gavage with chlorpyrifos

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ABSTRACT

Today, developmental intellectual disorders affect one out of six children in industrialised countries. Intensively used in agriculture, the neurotoxicant pesticide chlorpyrifos (CPF) is known for its environmental persistence and bioaccumulation. Its role has not yet been established in the aetiology of intellectual impairments. Here we assessed whether maternal ingestion of low CPF dose in rats could impair the cerebral function of their progeny.

Rat dams received daily CPF exposures (1 mg/kg, per os) during gestation and lactation. Behaviours relevant to mental retardation were measured in the surface righting, negative geotaxis and grip strength at post-natal days (PND) 3 and 7. Open field tests were performed at PND 16, 18 and 20. Fear conditioning was assessed at PND 34. Startle inhibition was tested at PND 31 and 60.

According to the results, the progeny of CPF-treated dams showed slower negative geotaxis as neonates, lower novelty exploration as juveniles and faster startle reflex as adolescents and adults.

This data suggests that developmental CPF relevant to human exposure may impair novelty-related activity and sensori-motor functions, thus adaptability to the environment. This data supports the hypothesis that CPF may contribute to behavioural disorders including acquisition retardation and consequences as an adult.

1. Introduction

Today, developmental intellectual disorders affect about one out of six children in industrialised countries. According to the World Health Organization, the international classification of mental and behavioural deficits diagnosed in children includes mental retardation, psychological development deficits, and behaviour and emotional deficits. They all affect adaptability to the environment and have considerable social and life quality consequences with intellectual disabilities and childhood suffering. Their evolution may regress with age with slight deficits persisting in adults or in some cases critically impairing autonomy of adults.

Chlorpyrifos (CPF) is a non-persistent organophosphate largely used in both agricultural and urban communities as a pesticide. Despite having been banned for residential use in 2001 by the US Environmental Protection Agency (EPA), it remains widely used in the world. CPF (or its metabolites) is one of the most detected substances in soil and humans (French Agency for Food, Environmental and Occupational Health & Safety (ANSES, 2013)). Its detection in tap water, fruits, vegetables and cereals (reported by ANSES, 2013) suggests that very low CPF doses are chronically ingested by the general population. CPF and its metabolites were detected in urine samples from a cohort study of pregnant women (Chevrier et al., 2009) and in the umbilical cord blood of a cohort of children (Rauh et al., 2012). CPF is known to elicit overt cholinergic toxicity through the inhibition of acetylcholinesterase (AChE). Its major concern is neurobehavioural consequences in children resulting from chronic, low-level exposure below its insecticide dose (Slotkin et al., 2006). It was originally thought to exert adverse effects on brain development through its insecticide mechanism. Its further non-cholinergic mechanisms of action are now evident (Barone et al., 2000).

Epidemiology studies showed links between residual oral exposure and the intellectual impairment of children. Third pregnancy trimester exposure to organophosphates was negatively associated with perceptual reasoning at 12 months of age and throughout early childhood (Engel et al., 2011). High maternal or umbilical cord plasma CPF exposure was linked to lower psychomotor and mental development index scores in children at 36 months of age (Lovasi et al., 2011; Rauh et al., 2006). The same authors showed that high blood CPF prenatal exposure was linked to anatomical changes in the developing brain using

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Abbreviations

AChE	acetylcholinesterase
ADG	average daily gain
ANOVA	analysis of variance
ANSES	French Agency for Food, Environmental and Occupational Health and Safety
CPF	Chlorpyrifos
dB	decibel
EPA	Environmental Protection Agency
FGR	fractional growth rate
GD	gestational day
PND	post-natal day
PPI	prepulse inhibition
SEM	standard error of the mean

imaging, as well as deficits in Working Memory Index and Full-Scale IQ (including perceptual reasoning and processing speed) around 7 years of age (Rauh et al., 2012).

In a rodent experiment, 5 mg/kg oral exposure (Tanvir et al., 2016) is a dose in the range of the oral repeated No Observed Effect Level, set at 4.5 mg/kg for rats after birth. According to Mattsson and his collaborators' pharmacokinetic study, oral exposure at 1 mg/kg/day in the rat replicated environmental CPF concentration in the milk and blood of pregnant women (Mattsson et al., 2000). A developmental neurotoxicity study designed according to the U.S. EPA 1991 guidelines did not establish any causal relationship between maternal oral low levels CPF (1 mg/kg/day) from gestational day (GD) 6 to lactation day 10 in the rat and developmental deficit on learning in adolescents and adults (Maurissen et al., 2000). However, a more recent study indicated that repeated pre-weaning pups exposure from post-natal day (PND) 10 to PND 16 to oral CPF (0.5, 0.75 and 1.0 mg/kg) decreased anxiety-like behaviour in juvenile rats at PND25 (Carr et al., 2015).

Here we aimed to determine the impact of oral CPF administration during gestation and lactation on neonatal, juvenile, adolescent and adult behavioural responses in the rat, according to the Organization for Economic Cooperation and Development (OCDE) 426 guideline for developmental neurotoxicity.

Rat dams received daily oral CPF exposures (1 mg/kg) during the entire gestation and lactation periods. The offsprings' behavioural scores of surface righting, negative geotaxis, grip strength, open field, fear conditioning and prepulse inhibition (PPI) of the startle reflex were assessed between the neonatal and adult periods in both males and females.

2. Materials and methods

2.1. Animals

Twenty-one female (10 weeks old) and ten male Wistar rats were purchased from Janvier (France). Animals were kept in a 12 h light/dark cycle at 22 °C room temperature with food and tap water *ad libitum*. Protocols complied with the decree on vertebrate animal experiments (French State Council, 1987) and were approved by the Regional Ethical Committee N. 96 (CREMEAP).

2.2. Procedures and experimental groups

Oestrus cycle phase was determined using daily vaginal smears. Two females in pro-estrus were housed with one male. After observation of sperm in smear (GD 1), females were housed individually. They were daily force-fed with corn oil (SIGMA, France, 1 mL/kg) containing CPF (Institute of Industrial Organic Chemistry, Poland), 0 (sham group, n = 10 pregnant females) or 1 mg/kg/day (CPF group, n = 11 pregnant females) from GD 1 until the weaning of pups (PND 21).

At birth, litters were adjusted to four male and four female pups by reduction or adoption. After weaning, rats from the same litter were housed three per cage per gender. Two rats per litter (one male and one female) were semi-randomly selected to be sacrificed at PND10, PND35 or PND45. Meanwhile, two rats per litter (one male and one female) were semi-randomly selected to undergo the 6 behavioural tests until adulthood according to the OCDE 426 guideline for neurodevelopment as described in Fig. 1. Physical development was evaluated from birth. Neonatal tests were performed at PND 3 and 7. Open field was performed at PND 16, 18 and 20. Fear conditioning was performed at PND 34. PPI of the startle reflex was performed at PND 31 and 60.

2.3. Physical development

Every four days from birth, body weight and length were measured. Average daily gain (ADG, (body weight$_{x+1}$ − body weight$_x$)/four days) and fractional growth rate (FGR, (body weight$_{x+1}$ − body weight$_x$)/birth weight)) were calculated. The delays (PND) for the opening of eyes, beginning and end of incisor eruption and pinna detachment were reported for each rat. The sum of the four delays was used as the score for sensorial development. Higher scores indicate slower physical development.

2.4. Neonatal reflex tests

Surface righting was assessed by the latency (maximum 60 s) to right from a supine position. Grip strength was assessed using the latency (maximum 60 s) to fall from a wire (1 mm in diameter) grasped by both forepaws. Negative geotaxis was tested using the number of falls and the latency (maximum 60 s) to turn 180° when placed head downward on a 30° inclined plane. The sum of the latencies to right (in the surface righting), the duration of not gripping the bar (grip strength) and the latency to turn 180° determined the score for neonatal

Treatment:														
Gestation	Lactation								*Withdraw*					
CPF Exposure														
Behavioural tests:														
Prenatal	Neonatal			Juvenile				Adolescent					Adult	
GD0	**21**	**PND0**	**3**	**7**	**10**	**16**	**18**	**20**	**21**	**31**	**34**	**35**	**45**	**60**
			Reflex	**Reflex**		**Open field**	**Open field**	**Open field**		**Startle reflex**	**Fear conditioning**			**Startle reflex**

Fig. 1. Experimental design: From GD 1, females were daily force-fed with CPF 0 mg/kg/day (sham rats, n = 10) or 1 mg/kg/day (CPF rats, n = 11) until weaning of pups (PND 21). Physical development was evaluated every 4 days from birth. Neonatal tests were performed at PND 3 and 7. Open field was tested at PND 16, 18 and 20. Fear conditioning was performed at PND 34. PPI of the startle reflex was performed at PND 31 and 60.

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