TR 11/2010

Technical report:

HENVINET

Evaluation questionnaire - Causal chain for chlorpyrifos

Aileen Yang[1)] and Alena Bartonova[1)], Editors

Authors:
Brooke L. Magnanti[2)], Sara C. Carreira[2)], Margaret S. Saunders[2)] and Janna G. Koppe[3)]

[1)] Norwegian Institute for Air Research, Kjeller, Norway
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Contents

HENVINET
HEALTH AND ENVIRONMENT NETWORK

Evaluation questionnaire – Causal chain for chlorpyrifos

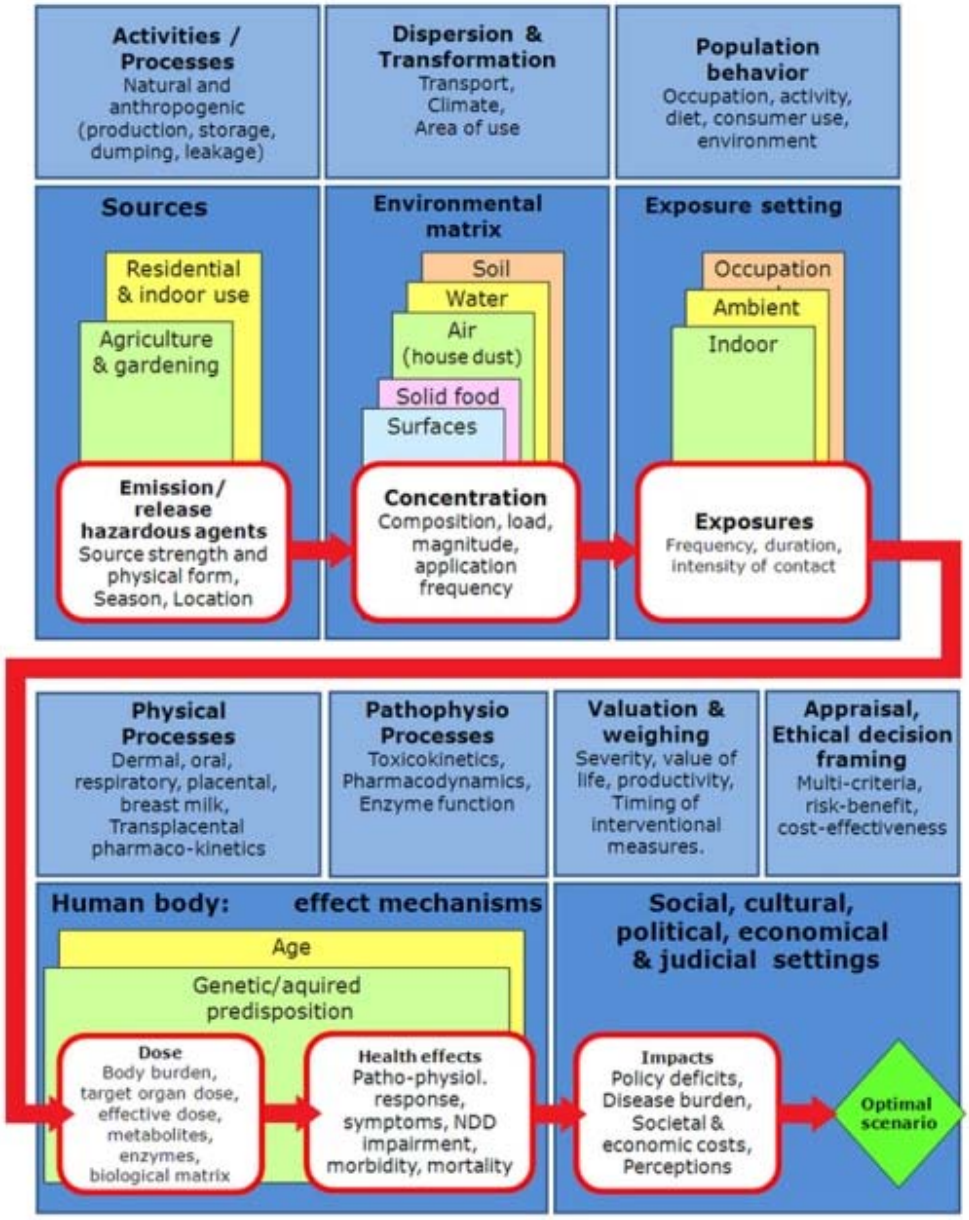
Prelude

Please tell us about your research background and current institutional affiliation. These data will be confidential.

- Name:_____
- Email address: _____
- Institutional affiliation: _____
- 5 keywords describing your area of expertise:

1._____2. _____3. _____ 4._____ 5._____

Introduction



Thank you for participating in this expert evaluation.

With your help we will evaluate the state of scientific knowledge of the cause-effect relationship between Chlorpyrifos and the potential impact on neurodevelopment. Above is a causal chain diagram, illustrating the routes of exposure to CPF and its potential health impact.

The goal is to identify knowledge gaps and potential agreement or disagreement on this between colleagues in the field. Ultimately, the aim is to discuss the implications for policy and research.

The evaluation consists of two separate parts. In the first you will be asked to look at parts of the causal chain diagram and answer questions about your confidence in the ability of science to predict various aspects of health risk. In the second you will comment on the completeness and structure of the causal diagram. We expect the exercise will take 40 minutes to complete.

We ask for your considered opinion based on the quality of your scientific work and trust your broad experience in the field will help achieve an understanding of the issues discussed here.

Questionnaire replies will be considered alongside a thorough review of the literature on this issue. These will be used to provide recommendations to policy makers. Content of the literature review can be found in **'Click Here for More Information'** links on each page.

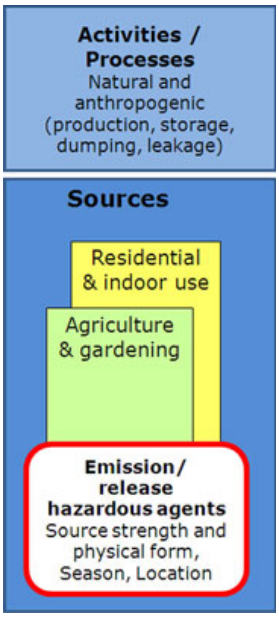
If you have any concerns or questions, please contact Martin Krayer Von Krauss (MAK@euro.who.int) or Margaret Saunders (M.Saunders@bristol.ac.uk).

We appreciate your participation and, on behalf of the WHO Euro and the HENVINET consortium, thank you for your time.

Part A. Evaluation of individual models or associations

CPF Sources

It is important that you consider each question independently from the others. For example, when you answer a question on routes of exposure, do not take into consideration your confidence in our ability to predict levels of exposure.



Where questions ask for your confidence level, please use these guidelines:

Very high confidence - **At least** a 9 out of 10 chance of being correct.
High confidence - **At least** an 8 out of 10 chance of being correct.
Medium confidence - **At least** a 5 out of 10 chance of being correct.
Low confidence - **At least** a 2 out of 10 chance of being correct.
Very low confidence - **Less** than a 2 out of 10 chance of being correct.

1.What is your level of confidence in available data on the production volumes of CPF?*

Very High	High	Medium	Low	Very Low

2. What is your level of confidence in the ability to predict the magnitude of CPF release during production and use?*

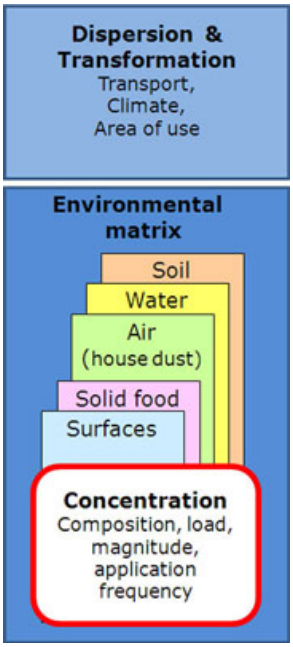
Very high	High	Medium	Low	Very low

3. What is your level of confidence in the available knowledge of different applications of CPF?*

Very high	High	Medium	Low	Very low

Do you have any comments on sources?

CPF Environmental



4.What is your level of confidence in the ability to predict the concentration of CPF in:

Soil:

Very High	High	Medium	Low	Very Low

Water:

Very High	High	Medium	Low	Very Low

Air:

Very High	High	Medium	Low	Very Low

Food:

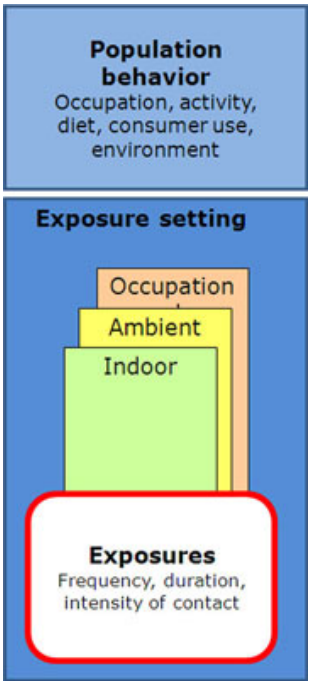
Very High	High	Medium	Low	Very Low

Surfaces:

Very High	High	Medium	Low	Very Low

Do you have any comments on this section?

CPF Exposure



5. What is your level of confidence in scientists' ability to predict the levels of CPF from different routes of exposures:

Oral exposure:

Very High	High	Medium	Low	Very Low

Inhalational exposure:

Very High	High	Medium	Low	Very Low

Dermal exposure:

Very High	High	Medium	Low	Very Low

6. What is your level of confidence in scientists' ability to predict the levels of exposure to CPF in:
General populations:

Very High	High	Medium	Low	Very Low

Occupational exposed groups:

Very High	High	Medium	Low	Very Low

7. What is your level of confidence in scientists' ability to predict the main sources of exposure for:

The general population:

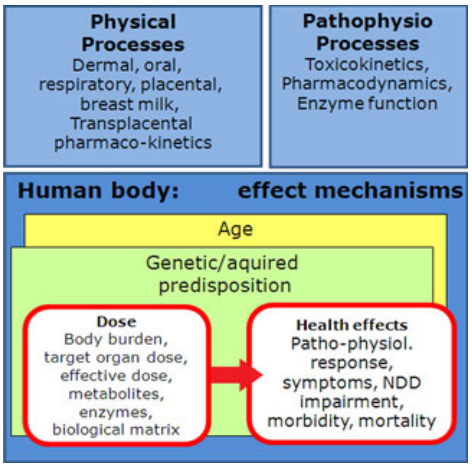
Very High	High	Medium	Low	Very Low

Occupational exposed groups:

Very High	High	Medium	Low	Very Low

Comments about exposures:

CPF Human



Toxicokinetics

8. What is your level of confidence in scientists' ability to identify appropriate biomarkers for CPF exposure?*

Very High	High	Medium	Very Low	Low

9. What is your level of confidence in scientists' ability to predict differences in toxicokinetics among sensitive groups (age, sex, etc.)?

Very High	High	Medium	Low	Very Low

Toxicology/Health Effects

10. What is your level of confidence in scientists' ability to predict that CPF has the potential to cause detrimental health effects?*

Very High	High	Medium	Low	Very Low

11. What is your level of confidence in scientists' ability to predict sex-specific health effects in experimental animals?*

Very High	High	Medium	Low	Very Low

12. What is your level of confidence in scientists' ability to predict neurodevelopmental disorders in humans due to prenatal exposure?*

Very High	High	Medium	Low	Very Low

13. What is your level of confidence in scientists' knowledge of the mechanism(s) of action of CPF and their metabolites?*

Very High	High	Medium	Low	Very Low

14. What is your level of confidence in the validity of the claim that CPF and its metabolites exert adverse effects on:

Foetal growth?

Very High	High	Medium	Low	Very Low

Somatic growth of exposed children?

Very High	High	Medium	Low	Very Low

Central nervous system?

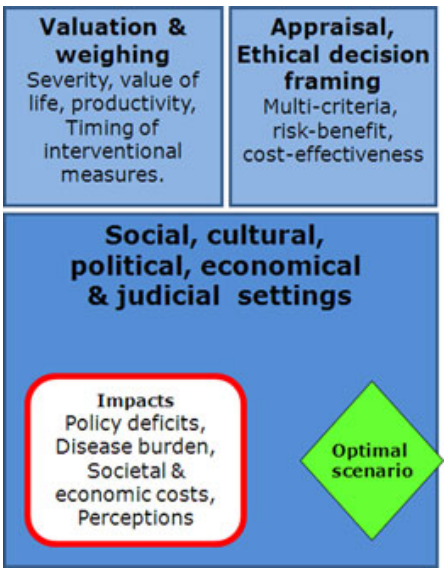
Very High	High	Medium	Low	Very Low

Behavioural end points?

Very High	High	Medium	Low	Very Low

Do you have any comments on physical processes and effect mechanisms?

CPF Social



15. What is your overall level of confidence in the ability to predict harmful effects of CPF in the environment and on human health?

Very High	High	Medium	Low	Very Low

What is your level of confidence in the ability to predict the effects of CPF on neurodevelopment?*

Very High	High	Medium	Low	Very Low

16. Should CPFs be banned from home use due to any factors

Yes, and there is sufficient evidence
Yes, but more evidence is needed
Neither Yes nor No
No, but more evidence is needed
No, and there is sufficient evidence

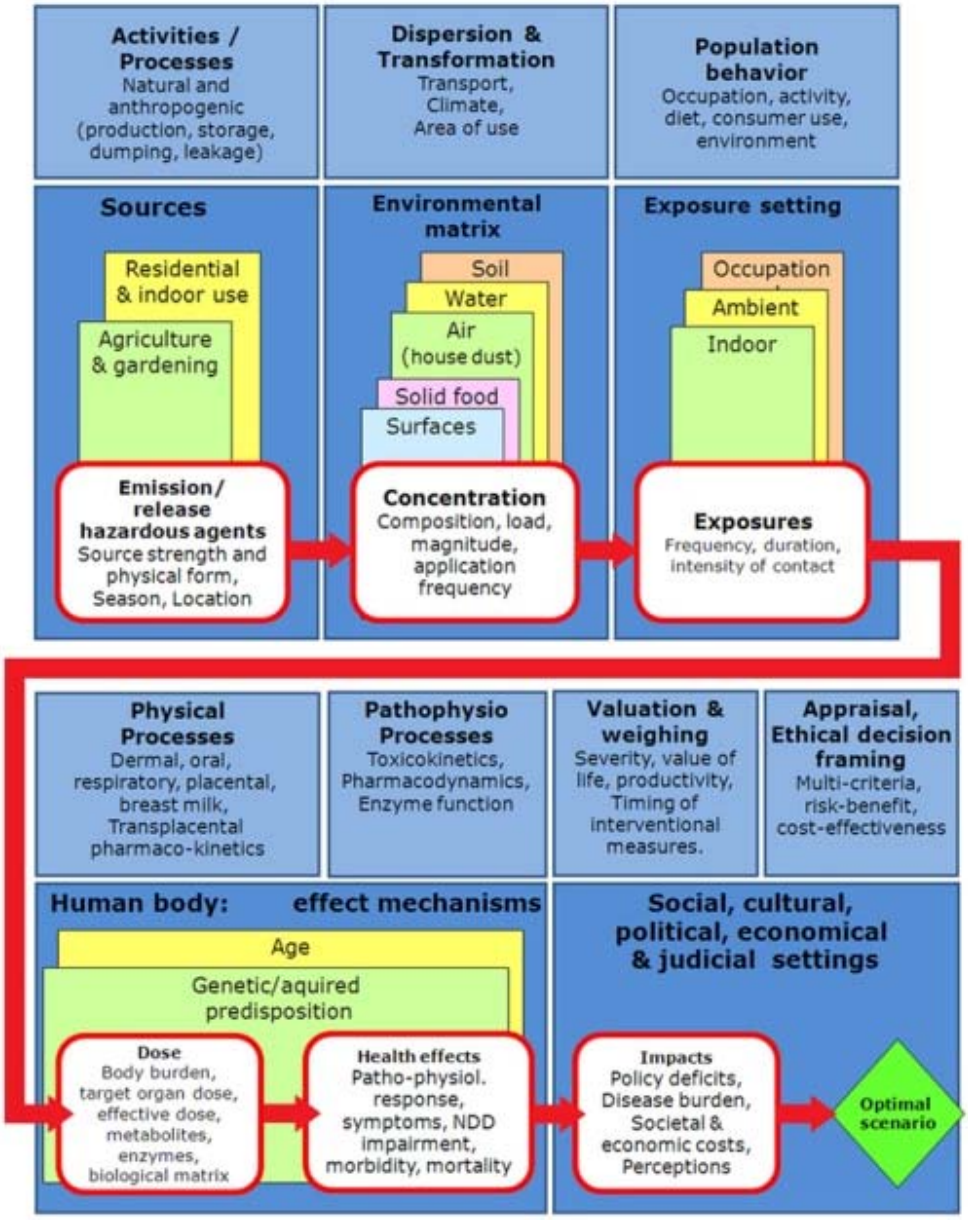
17. Should CPFs be banned for home use due specifically to neurodevelopmental effects?*

Yes, and there is sufficient evidence
Yes, but more evidence is needed
Neither Yes nor No
No, but more evidence is needed
No, and there is sufficient evidence

Do you feel there are other regulatory interventions justified by our current level of knowledge?

Do you have any comments for this page?

Part B. Evaluation of structure and completeness of the causal diagram



The complete diagram is designed to illustrate the cause/effect relationship between production and usage of CPF and health effects. For a summary explanation of the scientific basis of the diagram, please see Annex 1. Now that you have considered the different causal relationships on their own, please comment on the comprehensiveness and structure of the diagram as a whole.

18. Does the diagram take into account all of the important parameters when evaluating the risks related to production, use and discharge of Chlorpyrifos? * YES/NO

If the previous answer was No, Please explain:

19. Are the different causal relationships adequately structured? * YES/NO

If the previous answer was No, Please explain:

20. Are there any unnecessary parameters shown in the diagram that could be deleted? * YES/NO

If the previous answer was Yes, please explain:

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ANNEX 1 Summary explanation of the causal diagram.

Sources

Organophosphate (OP) compounds are used worldwide in agriculture and gardening to control insect pests. They also have residential and indoor applications for pest control especially for cockroaches and termites (Van den Hazel & Zuurbier 2005, Gurunathan et al 1998, Aprea et al 2000, Morgan et al 2005, Becker et al 2006, Whyatt & Barr 2001). OPs act by inhibiting acetylcholinesterase, thus affecting nerve function in insects, humans and other animals. Most of the animal and human studies published between 2000 and 2007 refer to the OP **chlorpyrifos (CPF)**.

OPs are used frequently in Europe for pest control due to their low price and broad spectrum of activity. In 2003 they accounted for over 59% (4645 tonnes) of insecticide sales in the EU, with CPF the top selling insecticide (15.6%, 1226 tonnes) (Eurostat 2007). CPF was also one of the most widely used OPs in the US for pest control (Gurunathan et al 1998), but the US Environmental Protection Agency (EPA) imposed a ban on the sale of CPF for residential use in December 2001 (US EPA 2000).

Activities involved in the production, storage, transport and use of CPF may play a role in release as it is transferred from the production site to the final user. Unintentional release through dumping or leakage can lead to unexpected exposure. The uptake of CPF into the environment depends on factors such as the strength at the source and the physical form (dry solid, liquid, etc.). The extent of use will also depend on the time and location. For example, agricultural and gardening use will be influenced by the seasonal growth of crops and plants, whereas residential use is less likely to be specifically influenced by seasons apart from climate effects on pest infestation. There may still be seasonal influence on child exposure (Becker et al 2006)

Environmental matrix

Dispersion and transformation of CPF from the sources affects uptake into the environment and may be influenced by transport, climate and the characteristics of the area where they are being applied. The use of CPF for agricultural and gardening purposes will lead to accumulation in soil, water and on food such as vegetables and fruit as well as atmospheric dispersal (van den Hazel & Zuurbier 2005, Aprea et al 2005, Gurunathan et al 1998, Morgan et al 2005, Becker et al 2006).

However, **residential use is considered to be the main source** for the majority of the population, alongside contaminated food consumption (Becker et al 2006). This can lead to accumulation in indoor air, including house dust, and on surfaces including toys (Gurunathan et al 1998, Morgan et al 2005).

Incorporation of CPF into each environmental matrix will vary according to concentration and is influenced by composition (parent compound/environmental metabolite), how the load is spread (concentrated or dispersed), and the magnitude of the load and the frequency of application.

Exposure setting

Population behaviour influences interaction between the environment/exposure setting and the extent of exposure. For CPF, there are three key exposure settings: **occupational**, **ambient** and **indoor**.

Occupation puts farming and greenhouse workers at risk from sources used in agriculture and gardening. Similarly, manufacturing workers are also at risk, especially if there is an inadvertent leak.

The general public, especially children, are mainly at risk from **ambient** and **indoor** residential exposure. Several physical processes are possible.

Oral exposure can arise particularly from fruit and vegetables consumed as part of the normal diet, but also water, milk and derived products (Morgan et al 2005, Aprea et al 2000). Indirect exposure occurs within the ambient and indoor settings (Morgan et al 2005, Gurunathan et al 1998, Aprea et al 2000, Becker et al 2006). Contact with soil and oral non-dietary exposure are important exposure routes for younger children due to their behaviour patterns with respect to play at floor level and on/with other surfaces and toys. Inhalation of indoor air is another route with house dust a critical component. Dermal exposure is also possible.

Exposure during pregnancy is an area of concern given the high percentage of women using pest control during pregnancy and the vulnerability of the fetus during development. Fetal exposure occurs through transplacental transfer with the placenta failing to act as a barrier to lipophilic OPs (Whyatt & Barr 2001). There is limited data concerning the presence of OP in human breast milk (Sanghi et al 2003), possibly due to partitioning into the water fraction of breast milk. This area requires further investigation as it may present an additional exposure route during the postnatal period (Rauh et al 2006).

The extent of exposure will be affected by the frequency, duration and intensity of contact which can all vary. There may also be transfer between settings. For example, a parent who is an agricultural worker may transfer residue to their offspring within the home.

Toxicokinetics

The dose of pesticides in organs and tissues is determined by the **pharmacokinetics of CPF**: physical absorption, distribution, metabolisms and excretion processes following uptake. An important element in assessing exposure is the biological matrix used for sampling. Levels in humans are determined through **biomarkers** which may be subject to interpretation.

For CPF, the most commonly used biomarkers are found in blood and urine. In blood, exposure is determined by measurement of plasma butyrcholinesterase (BuChe) activity and erythrocyte acetylcholinetserase (AChE) activity (Albers et al 2007). Urine measurements detect excretion of metabolites. This is more widely used for young children compared with taking blood samples. CPF is activated in the liver to **CPF oxon** by cytochrome P450-dependent desulfuration (Needham 2005).

Measurements of CPF or CPF oxon are the most specific marker for exposure (Barr & Angerer 2006). However, organophosphates are rapidly metabolized in the body and almost entirely excreted in the urine (Aprea et al 2000). Some may be stored in adipose tissue (Barr & Angerer 2006), meaning that parent compound levels in blood are very low compared with metabolites.

The specific CPF metabolite **3-5-6 trichloro-2-pyridinol (TCPy)** can be detected in urine (Berkowitz et al 2004, Eskenazi et al 2004) as can the non-specific OP dialkyl phosphate (DAP) metabolites formed from nearly all OP insecticides (Becker et al 2006). For CPF, these DAP metabolites are diethyphosphate (DEP) and diethylthiophosphate (DETP). However, about 75% of OP pesticides are also biotransformed to DETP, DEP or other DAPs measured in the same way and they cannot be distinguished from environmental degradates (Needham 2005). Careful interpretation is needed when measuring DAPs as they cannot necessarily be correlated with specific OP insecticides and the metabolites themselves may be ingested (Becker et al 2006).

Route of exposure will affect the absorption and hence body burden and target organ dose. A case study of CPF and malathion biomonitoring demonstrated that about 70-93% of the oral dose of CPF could be recovered in the urine but only 1-3% of the dermal dose was (Barr & Angerer 2006). Pharmacokinetics also influence organ dose and effective dose through distribution, metabolite production and enzyme function. OP pesticides can be converted to the oxon form which interacts with available cholinesterase. However, the oxon form can also be enzymatically or spontaneously hydrolysed to form a DAP metabolite and an organic metabolite. Unconverted OP can also be hydrolysed to the organic group metabolite and DAP metabolites (Barr & Angerer 2006). These metabolites or their conjugates are excreted in urine.

Health effects

Age and genetic/acquired predisposition may determine health effects from the CPF exposure dose. CPF toxicitiy is due to the inhibition of acetylcholinesterase by the CPF oxon, preventing efficient degradation of acetylcholine and leading to accumulation of transmitter molecules in the nerve synapse. Elevated synaptic acetylcholine levels result in persistent receptor stimulation and the alteration of signalling pathways with functional changes at tissue/organism level (Pope et al 2005).

Health effects following occupational exposure in adults include impaired memory and concentration, disorientation, severe depression, irritability, confusion, headache, speech difficulties, delayed reaction times, nightmares, sleepwalking, insomnia and flu-like symptoms (Barr & Angerer 2006).

Animal and *in vitro* studies suggest that CPF can act by other mechanisms and have clearly shown that CPF exposure at doses below the threshold for systemic toxicity and inhibition of brain cholinesterase exerts disruptive effects on neural cell development, with respect to DNA synthesis, gene transcription, cell differentiation, and synaptogenesis (Crumpton et al 2000).

Several rat studies have indicated that CPF targets neurotransmitter systems further to the cholinergic one, as the monoamines, norepinephrine, dopamine, and serotonin (Aldridge et al., 2004). In addition, glial cells are more sensitive to CPF than neurons and may be preferentially targeted (Colborn 2006). **Interference with brain maturation** is associated with behavioral disturbances in exposed rodents, including hyperactivity, learning impairment and alterations in the social and emotional domain (Aldridge et al 2005, Carr et al 2001, Dam et al 2000, Levin et al 2001, Ricceri et al 2003 & 2006). This suggests vulnerability during fetal and childhood periods (Berkowitz et al 2004).

CPF is considerd moderately toxic and is an EPA class II toxicant i.e. oral dose LD50 is 50-500mg/kg (Barr & Angerer 2006).

Juvenile and prenatal susceptibility

Animal studies have demonstrated that **juveniles are more susceptible to OP toxicity** than adults (Furlong et al 2005). Animal and *in vitro* studies show low-dose OP exposure in pre- or early post-natal period produces neurochemical and neurobehavioural changes (Berkowitz et al 2004). This is attributed to incomplete metabolic competence during development (Kousba et al 2007) and the susceptibility of the rapidly developing nervous system.

Paraoxonase 1/arylesterase (PON1) is a key OP detoxifying enzyme. Increased sensitivity to OP toxicity in newborns may be due to reduced PON1 levels, which are 3- to 4-fold lower than

in adults. There is considerable PON1 polymorphism and this genetic variability will affect sensitivity alongside a 13-fold variation in adult levels (Furlong et al 2005 & 2006).

Additional noncholinergic mechanisms - such as oxidative stress - may damage the developing brain with exposures occurring below the systemic effects threshold. Thus nonsymptomatic exposure for pregnant women, infants and children and could be linked with increased risk for development of metabolic diseases such as diabetes (Slotkin et al 2005).

Neurodevelopmental toxicity is of concern in prenatal and early postnatal periods. Prenatal residential exposure to CPF of inner city children assessed at age 3 years was **linked with impaired motor skills and impaired mental development**. Highly exposed children more likely to exhibit clinical symptoms of attention problems, ADHD and pervasive developmental disorders (Rauh et al 2006).

In utero exposure of children born in an area of major agricultural production was associated with impaired reflex functioning, particularly in those assessed after 3 days postnatal (Young et al 2005). Organophosphate poisoning in children under the age of 3 was linked with impaired verbal learning and motor inhibition tasks, with higher impulsivity in OP intoxicated children (Kofman et al 2006).

In mother-infant pairs exposed to indoor residential pesticide exposure, a positive trend was found between maternal PON1 activity and head circumference in offspring where maternal CPF metabolite (TCPy) were above the limit of detection (Berkowitz et al 2004). Eskenazi et al (2004) found an association between increased levels of dimethyl phosphate metabolites (coming from malathion) in the urine in later pregnancy and a reduced gestational duration.

Also in that study a reduced length of gestation was found in relation with the cholinesterase levels (ChE) in umbilical cord whole blood. Maternal dialkyl phosphate metabolite levels and ChE levels in later pregnancy were not correlated. Unexpectedly, there was a positive effect of the dialkyl phosphate metabolite levels on head circumference after correction for creatinine levels. In contrast, Whyatt et al (2004) found a significant inverse correlation between cord blood plasma CPF levels and birth weight and length for children born before the 2001 ban. Later follow-up of this group revealed neurodevelopmental abnormalities at the age of 3 in relation to prenatal exposure to CPF parent compound as could be expected considering the intra-uterine growth retardation. (Rauh et al 2006)

Further studies would benefit from careful consideration of the foetal toxicokinetics and exposure time frame.

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TITLE

HENVINET

Evaluation questionnaire - Causal chain for chlorpyrifos

PROJECT LEADER

Alena Bartonova

NILU PROJECT NO.

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A

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Chlorpyrifos	Neurodevelopment disorders	Knowledge evaluation, Cause-effect diagram

ABSTRACT

The HENVINET consortium has developed a questionnaire to identify knowledge gaps in the state of the art in scientific knowledge. Literature reviews covered all elements that compose the causal chain of the different environmental health issues from emissions to exposures, to effects and to health impacts. Ultimately, the aim is to discuss the implications of these for policy and research.

In this evaluation we focus on various aspects of the cause-effect relationship between chlorpyrifos and the potential impact on neurodevelopment . The questionnaire consists of two separate parts. In Part A, you will be asked to look at parts of the causal chain diagram and answer questions about your level of confidence in the ability of science to predict various aspects of health risk. In Part B, you will be asked to comment on the completeness and structure of the causal diagram.

** Classification*
A Unclassified (can be ordered from NILU)
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