PSGR

Physicians & Scientists for Global Responsibility

**December, 2024**

# Report

## The Erosion of Risk Assessment practice at the New Zealand Environmental Protection Authority, and the Australian Pesticides and Veterinary Medicines Authority.

**The case of chlorpyrifos and chlorpyrifos-methyl.**


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**PSGR would welcome response and feedback to this Report**

Physicians and Scientists for Global Responsibility Charitable Trust (PSGR) works to educate the public on issues of science, medicine, technology (SMT). PSGR work to encourage scientists and physicians to engage in debate on issues of SMT, particularly involving genetics and public and environmental health.

## INTRODUCTION

Revocations of the insecticide chlorpyrifos and fumigant chlorpyrifos-methyl have followed regulatory assessments of the weight-of-evidence which strongly suggests these substances are development neurotoxins. Uncertainty extends to their potential genotoxicity.

There is strong evidence that the greatest dietary burdens arise from the permitted higher residue levels of chlorpyrifos-methyl on fumigated cereals, and the higher quantities of cereals that are consumed in the diet, particularly by low-income families.

On November 14, 2024, an New Zealand Environmental Protection Authority (NZEPA) press release announced a call for submissions relating to a proposed ban for chlorpyrifos. Submissions close at 11.59 pm on 12 February 2025. NZEPA's assessment of risks and benefits are described in the staff assessment document 'Staff assessment report – the application to reassess chlorpyrifos'. NZEPA claim that a 'quantitative assessment of human health risks has also been undertaken', this is found in the document 'Science memo: APP204694 chlorpyrifos'.

One month before, in September 2024, the Australian Pesticides and Veterinary Medicines Authority (APVMA) removed most agricultural and urban pest control uses of chlorpyrifos (79 of 91 uses). The APVMA has pushed consultation of chlorpyrifos-methyl into the future.

PSGR recommend that:

- An inquiry is held to assess New Zealand risk assessment practices are fit for purpose, including assessment of the role of epidemiological data, publicly available data and dietary burdens.
- The New Zealand government urge Australia to revoke all tolerances on chlorpyrifos-methyl in order to stop the practice fumigation of cereal grains.
- Applications on brassicas cease as other treatments, such as ozone (O3) are safer.

With bans of residential and public use, New Zealand urban exposures will derive from imported fumigated cereals, predominantly from Australia. Neither the NZEPA nor the APVMA have appropriately engaged with the global weight of evidence that strongly suggests that chlorpyrifos-containing substances and chlorpyrifos-methyl drive developmental neurotoxicity.

Some chlorpyrifos-methyl registrations have been voluntarily withdrawn in Australia, but the APVMA have not confirmed if all chlorpyrifos-methyl fumigation of cereal grains has stopped.

This report has two aims. Firstly, PSGR seek to draw attention to the declining quality of regulatory risk assessment and the continued exclusion by the NZEPA of new data and of epidemiological evidence as to risk, and that the New Zealand public are under-served by the continued erosion in risk assessment practice. The NZEPA claim that they do not have to address dietary burdens as a component of risk assessment, PSGR consider that this is incorrect and misleading.

Secondly, we aim to stimulate discussion on NZEPA's failure to assess risk to pregnant women, the developing foetus, infant and child from exposures that may arise from local agricultural spraying and/or dietary exposures. Women who might work in or near, or live in vicinity to chlorpyrifos-sprayed sites will be exposed on a daily basis for days after, as the substance can persist for weeks.

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## SUMMARY

More and more infants, children and adults are diagnosed with developmental delays. Delays are associated with reduced IQ and increased levels of mental illness. People suffering from these problems can expect lower incomes, and a lower quality of life over the life course.

In recent reports, the New Zealand Environmental Protection Authority (NZEPA) and the Australian Pesticides and Veterinary Medicines Authority (APVMA) claim to have conducted risk assessments and to have reviewed the data, but their publications have downplayed the key controversial issue that has prompted other regulatory authorities to revoke authorisations for the crop insecticide chlorpyrifos and the grain storage fumigant chlorpyrifos-methyl. NZEPA's *Staff assessment report* (2024) contains a risk assessment section (pages 13-53). The NZEPA claim to have 'undertaken a weight of evidence approach'. Much of the Risk Assessment section concerns their 2013 'risk assessment', which they note (page 14) is 'found in the Consultation Report and Evaluation and Review Report'. These November 2012 papers, claimed to purport for risk assessment, cannot in any way be described as fit for purpose risk assessments.

The APVMA did not evaluate the weight of evidence on developmental neurotoxicity, and does not discuss the genotoxic uncertainty, and resorts to old acceptable daily intake data (which is used to justify residue levels) in its Final Review Technical Report (2024).

The APVMA and NZEPA have deliberately separated out and failed to disclose the structural similarities of chlorpyrifos and chlorpyrifos-methyl, and the evidence that combined dietary exposures to both organophosphate pesticides enhance risk, particularly pre- and neonatally.

Chlorpyrifos (CPY) chlorpyrifos-methyl (CPY-M) are structurally similar, they have similar toxicity, including by inhibiting the enzyme acetylcholinesterase (AChE). Yet the New Zealand and Australian public will know nothing of chlorpyrifos-methyl, despite high permitted residues in staple grains. The European Food Safety Authority (EFSA) recognises these risks, as does the U.S. Environmental Protection Agency (USEPA).

PSGR asserts that it is misleading to downplay the epidemiological evidence and actions taken by overseas regulators, particularly in Europe relating to developmental neurotoxicity, and that the NZ misleads the public by failing to consider dietary burdens as an additive exposure, particularly to pregnant women living near sprayed areas.

The current controversy relating to the risk of chlorpyrifos and chlorpyrifos-methyl (and their toxic metabolites) revolves around evidence of genotoxicity and developmental neurotoxicity. Chlorpyrifos (CPY) is applied to fruits and vegetables, while chlorpyrifos-methyl (CPY-M) is a common fumigant used in grain storage facilities.

Higher residue levels of CPY-M are permitted on grains, than of CPY on fruits and vegetables. CPY-M is commonly detected in the Australian Total Diet study, in flour-based items such as biscuits and bread. New Zealand's North Island imports flour from Australia. The risk of banning CPY-M would not be to farmers, but to supply chains. If CPY-M was banned, Australia could adopt best-practice treatment processes used in cereal-growing regions such as Spain, Italy and France, to ensure that cereal grains would not be harmed by fungal or insect-based infestations.

The common mechanism of action of both CPY and CPY-M concerns the inhibition of the enzyme acetylcholinesterase (AChE), which is a key enzyme responsible for maintaining healthy levels of the neurotransmitter acetylcholine.

Both chlorpyrifos and chlorpyrifos-methyl degrade to the same primary metabolite 3,5,6-trichloro-2-pyridinol (TCP). Measurement of TCP in urine cannot discriminate CYP or CYP-M. Studies show chlorpyrifos and its primary metabolite 3,5,6-trichloro-2-pyridinol (TCP) in the urine of urban children and record an association of TCP levels with developmental delays and reduced brain size.

With repeated exposures this metabolite can persist in humans. The pesticide triclopyr also degrades to TCP. However, triclopyr is not approved on food and is not assessed in Australian or New Zealand Total Diet studies.

Following bans of residential spraying, the highest exposures are derived from the diet, and during the spray season for farmworkers and their families. Daily dietary exposures from diets high in cereals, would result in chronic exposure throughout the vulnerable stages of pre-conception, through pregnancy and early childhood. Babies and children consume more by body-weight than adults, and have vulnerable developmental windows where they are more at risk from toxic exposures than adults.

For organophosphate pesticides, repeated exposures generally result in more AChE inhibition at a given administered dose compared to acute exposures (USEPA 2020). CYP and CYP-M exert equivalent of toxicity with long-term exposure, likely due to cumulative AChE inhibition over time (EFSA 2019b).

The European Food Safety Authority (EFSA) published the outcomes of the human health assessment of chlorpyrifos in July 2019. This was followed by an updated statement on chlorpyrifos-methyl in November 2019. EFSA acknowledges that chlorpyrifos and chlorpyrifos-methyl are structurally similar (EFSA, 2019b).

While there is increasing epidemiological and regulatory evidence that CPY is a developmental neurotoxicant, there is a paucity of studies on the developmental neurotoxicity of CPY-M. Both the US EPA and EFSA have acknowledged that chlorpyrifos bridging studies may be used (a 'read-across' approach).

EFSA have revoked approvals for both CPY and CPY-M, due to genotoxic and developmental risks. EFSA determined that the 'epidemiological evidence supports the developmental neurological outcomes in children for both chlorpyrifos and chlorpyrifos-methyl.' EFSA also concluded that the genotoxic potential of both CPY and CPY-M could not be ruled out (unclarified). Because of this potential risk, no dietary reference values could be established, effectively resulting in a ban for CPY and CPY-M (2019b).

The USEPA (2015) in their assessment of CPY-M have also recognised that the fumigant is an AChE inhibitor. This typically was the most sensitive observed effect, following exposure across all animal species evaluated.

To protect and sustain optimum brain metabolism, the body will triage essential nutrients and hormones to the brain. It is not surprising AChE levels in red blood cells are more sensitive following exposure to CPY, CPY-M and TCP. The AChE enzyme catalyzes the breakdown of the key

neurotransmitter acetylcholine, the body would prioritise brain levels in order to maintain homeostasis and prevent toxic buildup of acetylcholine in the brain.

Depleted levels of these hormones elsewhere in the body may be predictive of longer-term risk to the brain. AChE or ChE will be directed preferentially to protect the brain. A more than 10% drop in AChE or ChE in red blood cell levels may infer that the brain is potentially at risk if current toxic exposure levels, which drive the inhibition, persist.

AChE inhibition may not be the only risk pathway. Chlorpyrifos, chlorpyrifos-methyl and other OPs may affect a variety of neuronal targets and processes that are not directly related to the enzyme acetylcholinesterase (AChE) and which are developmentally neurotoxic. Therefore, this represents an additional concern to be taken into consideration for the risk assessment.

Pervasive uncertainty remains regarding how doses *below* those driving cholinesterase inhibition may drive neurodevelopmental effects, and how metabolites might bioaccumulate and exert toxic effects, as a consequence of ongoing lifetime exposures in infancy and childhood.

When red blood cell inhibition is driven by exposures, when do levels sufficiently drop that brain cells are impacted?

PSGR recommends that chlorpyrifos (CPY) chlorpyrifos-methyl (CPY-M) must be considered concordantly, and that the public, experts and lay, must be granted ample opportunity to consider CPY and CPY-M over the same time period.

## CHLORYPRIFOS & CHLORPYRIFOS-METHYL: STRUCTURAL SIMILARITIES

The U.S. and European Commission have recognised structural similarities at different time periods. This is often a consequence of chlorpyrifos-methyl being a relatively unstudied fumigant, despite being used extensively in grain storage. Europe's recent action to recognise the similarities between chlorpyrifos (CPY) chlorpyrifos-methyl (CPY-M) resulted in approvals for both being revoked. It is likely that there will be political pressure from CYP and CYP-M importers and producers, on regulators to not publicly draw attention to the similarities.

The USEPA (2004) concluded that:

> 'given the structural similarities between the two chemicals, toxicity data using chlorpyrifos-ethyl could be used to address data gaps for chlorpyrifos-methyl'.

However, later the USEPA (2015) chlorpyrifos-methyl evaluation, moved away from using bridging data (particularly when the data for CYP-M was missing), stating:

> 'because of the differences in potency of the two chemicals, and the potential differences in pharmacokinetic and pharmacodynamics properties, a recent decision was made that this was not scientifically defensible, and that chemical-specific data for chlorpyrifos-methyl is required.'

In contrast, Europe's explicitly recognised the similar toxikinetics, considering that here were more similarities than differences between chlorpyrifos-ethyl and chlorpyrifos-methyl. For Europe's (2019b) CYP-M review, the experts:

> ‘discussed the structural similarity between chlorpyrifos and chlorpyrifos-methyl and the similar toxicokinetics of the two molecules and agreed to read across between chlorpyrifos and chlorpyrifos-methyl. Since concerns were raised for chlorpyrifos with regard to chromosome aberration, DNA damage (oxidative stress and topoisomerase II inhibition), the experts concluded that a data gap is present for chlorpyrifos-methyl with regard to DNA damage. All the experts agreed that these uncertainties should be considered in the risk assessment of chlorpyrifos-methyl as well, i.e. it cannot be excluded that chlorpyrifos-methyl may have DNA damaging potential.’

The ‘read-across’ approach where experts considered CYP data relevant for CYP-M was In a September 2019 meeting (2019, page 7):

> ‘In particular, the experts took into consideration the differences/similarities in chemical structure between the two molecules, their interaction with serine hydrolases and the mammalian toxicological endpoints in acute, short- and long-term studies. Regarding the molecular structure, the experts considered that the differences between chlorpyrifos and chlorpyrifos-methyl (the presence of the ethyl group instead of the methyl) would not justify a difference in the genotoxicity potential between the two molecules. However, this minor structural difference may contribute to quantitative differences in the acetylcholinesterase (AChE)-inhibitory effect (and likely other serine- hydrolases).’

EFSA acknowledged that public literature studies for CYP-M, that assessments could regard the ‘evidence along the same line as those considered for chlorpyrifos’ and extrapolate risk for both substances.

## PERSISTENCE

Regulatory agencies review how long it takes for chemicals to be eliminated following exposures. Chlorpyrifos is moderately to extensively metabolised by oxidation and hydrolysis and eliminated mostly through urine within 48 h. CYP-M is widely distributed, extensively metabolised through de-methylation, hydrolysis and conjugation, and eliminated mostly through urine within 72 h (2019a, 2019b).

But the elimination period must be considered in tandem with repeated exposures for pregnant women, the developing foetus and children.

The persistence of chlorpyrifos and its metabolites in work environments to pre-conception and pregnant women must be considered. Slow degradation of CPY and  and repeated exposures to workers re-entering premises on a daily basis after spraying, and families living near sprayed fields was downplayed.

> ‘the half-life of chlorpyrifos in soil ranges from 20 to 120 days, with the formation of 3,5,6-trichloro-2-pyridinol (3,5,6-TCP) as the main degradation product. Other data indicate that the half-life can range from 2 weeks to more than 1 year [17]. This high interchangeability of the half-life is related to the soil properties, which include the soil type, pH, moisture, temperature, organic matter and organic carbon content, and the microbial metabolism of CPF. The degradation of CPF is increased by higher soil temperatures with lower organic matter contents and lower acidity. Another important factor is the characteristics of the

> chlorpyrifos-based plant protection product (e.g., its composition, surfactant content, and other auxiliary compounds) and its method of application'. (Wolejko et al. 2022)

As Dr Meriel Watts discussed in the book *Poisoning our Future: Children and Pesticides*:

> 'One study, which quantified exposure estimates for a population of young farmworker children in the USA, found that 95% of 115,000 different exposure scenarios and dose estimates posed a risk to children's health from chlorpyrifos exposure (Beamer et al 2012).'

Watts drew attention to ambient exposures:

> 'not just those rural children living on farms or near fields that are affected: ambient community (i.e. away from the fields) air monitoring data from agricultural regions of California showed that short- term chlorpyrifos exposure estimates exceeded the 'acute reference dose' (another way of saying an 'acceptable dose') for 50% of children; and non-cancer risks were higher for children than adults (Lee et al 2002).'

## GENOTOXICITY

Neither the NZEPA (Staff Assessment Report, 2024; Science memo, 2024) nor the APVMA (Technical Report, 2024) reviewed the available literature regarding the genotoxicity of chlorpyrifos or chlorpyrifos-methyl.

The EFSA experts acknowledged (page 8) that while the genotoxicity data supplied by industry applicants is complete and negative (no evidence of genotoxicity), evidence in the published literature:

> 'should be considered in a weight-of-evidence approach and raised concerns over the potential for DNA damage for chlorpyrifos-methyl, by adopting a conservative approach.'

By comparison, the USEPA (2015) did not discuss the applicant-supplied genotoxicity studies, but rather noted that

> 'Acceptable carcinogenicity studies in both rats and mice produced no treatment-related increase in tumor incidence; furthermore, no genotoxicity was noted in the mutagenicity battery' (page 28).

There is no available knowledge concerning the quality and suitability of the genotoxicity studies reviewed by the USEPA. For example, the genotoxicity studies in use by the JMPR are 1980's Dow studies.

## BIOLOGICAL MECHANISMS DRIVING DEVELOPMENTAL NEUROTOXICITY (DNT)

CPY and CPY-M are synthetic organophosphate acetylcholinesterase inhibitors.

Acetylcholinesterase (AChE) is a cholinergic enzyme, it catalyses the breakdown of acetylcholine and other choline esters, which function as neurotransmitters. Cholinergic neurons release acetylcholine, and acetylcholine binds to cholinergic receptors. AChE is predominantly detected at

postsynaptic neuromuscular junctions, especially in muscles and nerves. The effect is to stop cholinergic synaptic transmission.

However not all of the effect of exposures to low-dose CPY and CPY-M may be due to cholinesterase inhibition. A 2023 literature review identified the following possible mechanisms:

- Neuroinflammation: Promote inflammatory responses in cultured astrocytes and upregulation of inflammatory cytokines, which significantly impairs spatial memory.
- Mitochondrial dysfunction following CPF-induced neuro-apoptosis.
- Extracellular increases in the level of glutamates.
- Covalent binding of CPF to tubulin.
- CPY may inhibit hydrolases and lipases and produce alterations in novel free fatty acid levels, influencing gene transcription.

EFSA (2019b) noted that:

> 'In addition to inhibition of the nervous system and RBC AChE, observed after administration of both chlorpyrifos and chlorpyrifos-methyl, chlorpyrifos-methyl presented additional critical effects in short-term and long-term toxicity studies on the adrenals.'

Regulatory agencies often struggle to take into account the greater vulnerability of a developing foetus, a young infant, children and adolescents.

> 'Children (from the prenatal period through adolescence) often react differently to chemicals than do adults because, compared to adults, they have different exposures, different vulnerabilities determined by critical windows of development, and a longer life ahead of them. "To protect children's environmental health (especially for the foetus and the small child), it is important to understand when and how they can be particularly vulnerable to chemical exposures. Understanding the rapidly changing nature of the child is essential to understanding vulnerability to chemicals" (IFCS 2003).' (Watts 2013)

In 2014, Philippe Grandjean and Philip J Landrigan, in the paper Neurobehavioural effects of developmental toxicity, noted that:

> 'Neurodevelopmental disabilities, including autism, attention-deficit hyperactivity disorder, dyslexia, and other cognitive impairments, affect millions of children worldwide, and some diagnoses seem to be increasing in frequency. Industrial chemicals that injure the developing brain are among the known causes for this rise in prevalence.'

Grandjean and Landrigan drew attention to an increasing array of chlorpyrifos studies that demonstrated the relationship between exposures and developmental neurotoxicity:

- Campbell CG, Seidler FJ, Slotkin TA. 1997. Chlorpyrifos interferes with cell development in rat brain regions. Brain Res Bull 43:179–189.
- Chanda SM, Pope CN. 1996. Neurochemical and neurobehavioral effects of repeated gestational exposure to chlorpyrifos in maternal and developing rats. Pharmacol Biochem Behav 53:771–776

- Rauh V, Arunajadai S, Horton M, et al. 7-year neurodevelopmental scores and prenatal exposure to chlorpyrifos, a common agricultural pesticide. Environ Health Perspect. 2011; 119:1196–201. [PubMed: 21507777]. Chlorpyrifos levels were tested in umbilical cord blood plasma in inner-city low-income women and children. 535 active participants and 265 children reached 7 years of age with complete data. For each standard deviation increase in CPF exposure (4.61 pg/g), Full-Scale intelligence quotient (IQ) declined by 1.4% and Working Memory declined by 2.8%
- Bouchard MF, Chevrier J, Harley KG, et al. Prenatal exposure to organophosphate pesticides and IQ in 7-year old children. Environ Health Perspect. 2011; 119:1189–95. [PubMed: 21507776] Study measured urinary dialkyl phosphate metabolites in (mostly latino) women during pregnancy in predominantly farmworker families, and found that levels in pregnancy were associated with poorer cognitive abilities in children at 7 years of age. Initial cohort of 601 women, with 329 children in the final cohort.
- Rauh VA, Perera FP, Horton MK, et al. Brain anomalies in children exposed prenatally to a common organophosphate pesticide. Proc Natl Acad Sci USA. 2012; 109:7871–76. [PubMed: 22547821]. Study compared association between chlorpyrifos exposure and brain morphology in 40 children, 20 high exposure, and 20 low exposure children. The findings, alterations in the brain regions and an IQ response, were consistent with the effects of early developmental exposure to chlorpyrifos in animal models.

Developmental delays are a problem in New Zealand infants and children (Moton et al 2023). One-in-four New Zealand children were recently classified as having suboptimal developmental health 18 and special education needs has substantially grown over time (Bourke et al 2021).

More recently in an extensive review of human and animal, in vitro and in vivo studies Ubaid ur Rahman and colleagues (2021) considered several streams of potential pathways of impact which include chlorpyrifos potential role in endocrine disruption, neurotoxicity, reproductive carcinogenesis, and disruptive mammary gland functionality.

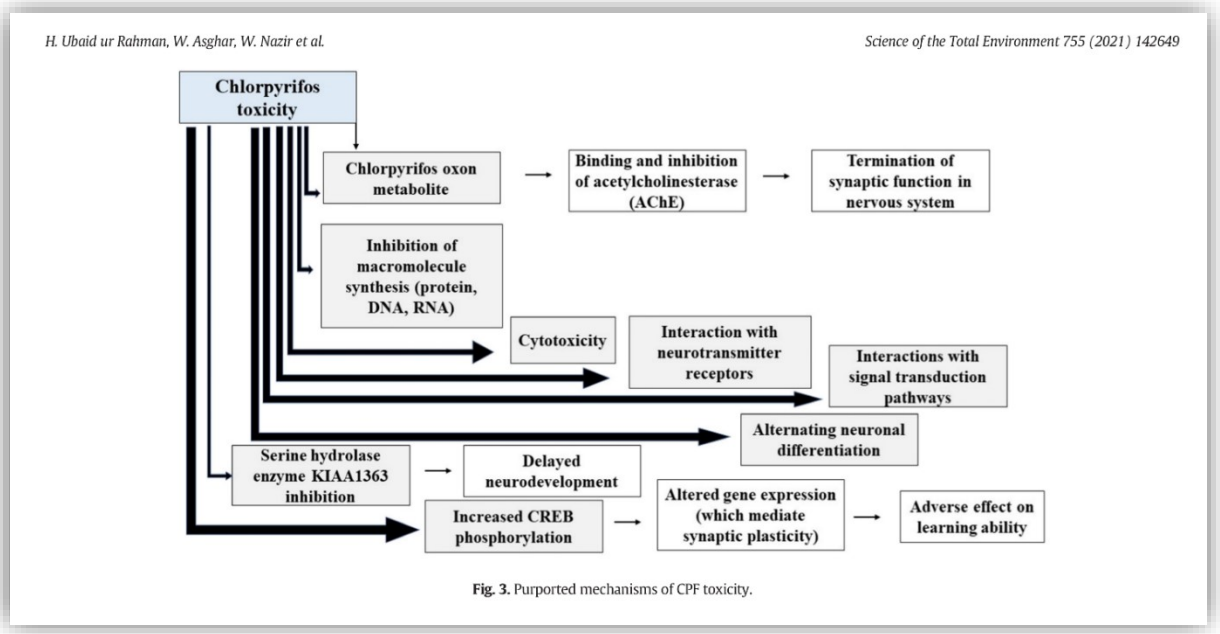


Fig. 3. Purported mechanisms of CPF toxicity.

Even though much of the underlying data is well established, and has been reviewed by other regulatory agencies, neither the NZEPA nor the APVMA reviews or assesses either industry data or the epidemiological evidence concerning developmental neurotoxicity in the 2024 release of information. (Staff Assessment Report, 2024; Science memo, 2024; Technical Report, 2024).

Epidemiological studies tend to be excluded by the NZEPA, when reassessing toxic chemicals. Neil Pearce's easy-to-read book, Pesticides and Health How New Zealand Fails in Environmental Protection, outlines this persistent regulatory deficit.

The NZEPA's Science memo, 2024 notes (page 10 and page 17):

> 'While there has been some suggestion of neurodevelopmental or other effects occurring below the threshold for ChE inhibition, these have yet to be substantiated among recognised international regulators.'

A brief look at considerations by the U.S. and European authorities helps to put the New Zealand notes in perspective.

PSGR believes that neither the NZEPA nor the APVMA have appropriately represented, in their assessments and communications to the public, the extent of regulatory information and discussion on developmental neurotoxicity, the relationship to AChE inhibition and the potential for CPY and CPY-M to exert neurotoxic harm through other pathways.

Many of the industry studies were looking for inhibition of AChE in the brain, but found that brain levels remained stable. The USEPA (2020, page 83) describes how research studies assess AChE or ChE inhibition:

> 'AChE inhibition can be inhibited in the central or peripheral nervous tissue. Measurements of AChE or cholinesterase (ChE) inhibition in peripheral tissues (e.g., liver, diaphragm, heart, lung etc) are rare. As such, experimental laboratory studies generally measure brain (central) and blood (plasma and red blood cell, RBC) ChE. Blood measures do not represent the target tissue, per se, but are instead used as surrogate measures for peripheral toxicity in studies with laboratory animals or for peripheral and/or central toxicity in humans. In addition, RBC measures represent AChE, whereas plasma measures are predominately BuChE. Thus, RBC AChE data may provide a better representation of the inhibition in target tissues. As part of the dose response assessment, evaluations of neurobehavior and clinical signs are performed to consider the dose response linkage between AChE inhibition and apical outcomes.'

The USEPA found that Red blood cell (RBC) AChE was generally more sensitive than the brain AChE to chlorpyrifos-methyl-induced inhibition (2015) EFSA observed that erythrocyte (red blood cell (RBC)) AChE inhibition was the critical effect in all studies conducted with rats, mice and dogs. Additionally, the adrenals (increased weight, hypertrophy and vacuolation of cells of the zona fasciculata) were identified as target organ of chlorpyrifos-methyl in rats (EFSA 2019).

The USEPA considered, as a benchmark, that a 10% or greater red blood cell inhibition is a cause for concern (2015; 2020), however that level is difficult to verify.

The extent of AChE or ChE inhibition in red blood cell levels acts as a surrogate marker, indicating that inhibition is a risk. As the brain is a scavenger, i.e. AChE or ChE will be directed preferentially

to protect the brain, a more than 10% drop in AChE or ChE in red blood cell levels may infer that the brain is potentially at risk if current toxic exposure levels, which drive the inhibition, persist.

## A LITTLE REGULATORY HISTORY

The information prompting the revoking of approvals revolves around the concern that chlorpyrifos (CPY) and chlorpyrifos-methyl (CPY-M) exert neurotoxic effects, harming the development and IQ of the developing foetus and children. The evidence from epidemiological data is accruing, forming a 'weight-of-evidence'.

Steady-state exposures have been an increasing focus by regulatory agencies. The NZEPA concerns itself with re-entry modelling data, but not from steady-state exposures, as, for example, a staff member may return to a sprayed greenhouse and be daily exposed to the recently sprayed pesticide, but as that pesticide degrades, more persistent metabolites. A youth may return to a sports field to kick a ball around, daily after school.

A major shift occurred in April 2014, when EFSA experts agreed to use evidence of red blood cell (RBC) acetyl cholinesterase (AChE) inhibition to derive the reference values. This had not been the standard approach (2014).

Major shifts occurred when the U.S. Environmental Agency conducted a Chlorpyrifos Revised Human Health Risk Assessment (2016) (HHRA 2016) and integrated more epidemiological data into their assessment and took into account AChE inhibition of red blood cells.

Peer review in 2013 had agreed the data in the epidemiological studies were of high quality. Each of the cohorts evaluated the association between prenatal chlorpyrifos and/or OP exposure with adverse neurodevelopmental outcomes in children through age 7-11 years.

*1.* ***The Mothers and Newborn Study of North Manhattan and South Bronx performed by the CCCEH at Columbia University*** *(U.S. EPA, 2016);*

*a. Whyatt RM, Rauh V, Barr DB, Camann DE, Andrews HF, Garfinkel R, et al. 2004. Prenatal insecticide exposures and birth weight and length among an urban minority cohort. Environ Health Perspect 112:1125–1132, doi:10.1289/ehp.6641*

*b. Whyatt RM, Camann D, Perera FP, Rauh VA, Tang D, Kinney PL, et al. 2005. Biomarkers in assessing residential insecticide exposures during pregnancy and effects on fetal growth. Toxicol Appl Pharmacol 206(2):246–254.*

*c. Whyatt RM, Rauh V, Barr DB, Cam Rauh VA, Perera FP, Horton MK, et al. Brain anomalies in children exposed prenatally to a common organophosphate pesticide. Proc Natl Acad Sci USA. 2012; 109:7871–76. [PubMed: 22547821]. Study compared association between chlorpyrifos exposure and brain morphology in 40 children, 20 high exposure, and 20 low exposure children. The findings, alterations in the brain regions and an IQ response, were consistent with the effects of early developmental exposure to chlorpyrifos in animal models.*

*2. Sebe A, Satar S, Alpay R, Kozaci N and Hilal A, 2005. **Organophosphate poisoning associated with fetal death**. Mount Sinai Journal of Medicine, 72, 354–356.*

***3. The Center for Health Assessment of Mothers and Children of Salinas Valley (CHAMACOS)***

*a. Castorina R, Bradman A, Fenster L, Barr DB, Bravo R, Vedar MG, Harnly ME, McKone TE, Eisen EA and Eskenazi B, 2010. Comparison of current-use pesticide and other toxicant urinary metabolite levels among pregnant women in the CHAMACOS cohort and NHANES. Environmental Health Perspectives, 118, 856–863*

*b. Marks AR, Harley K, Bradman A, Kogut K, Barr DB, Johnson C, Calderon N and Eskenazi B, 2010. Organophosphate pesticide exposure and attention in young Mexican-American children: the CHAMACOS study. Environmental Health Perspectives, 118, 1768–1774.*

The HHRA (2016) took into account risks from dietary exposure and drinking water. The HHRA also noted that, following a preliminary (2011) and a revised (2014) risk assessment the human health risk assessment (HHRA) for chlorpyrifos incorporated the following:

> (1) a physiologically-based pharmacokinetic-pharmacodynamic (PBPK-PD) model for deriving toxicological points of departure (PoDs) based on 10% red blood cell (RBC) acetyl cholinesterase (AChE) inhibition; and
>
> (2) evidence on neurodevelopmental effects in fetuses and children resulting from chlorpyrifos exposure as reported in epidemiological studies, particularly the results from the Columbia Center for Children's Environmental Health (CCCEH) study on pregnant women which reported an association between fetal cord blood levels of chlorpyrifos and neurodevelopmental outcomes. The 2014 revised HHRA retained the 10X Food Quality Protection Act (FQPA) Safety Factor (SF) because of the uncertainties that neurodevelopmental effects may be occurring at doses lower than those that cause 10% RBC AChE inhibition and used for the PoD.

Following these findings, a proposed rule (PR) for revoking all tolerances of chlorpyrifos was published in the Federal Register on November 6, 2015 (80 FR 69079).

Implicit in the 2016 considerations was risk from steady state, repeated exposures. Children ages 1-2 years old were the highest exposed population subgroup.

> 'Organophosphates (OPs), including chlorpyrifos, exhibit a phenomenon known as steady state AChE inhibition. After repeated dosing at the same level, the degree of inhibition comes into equilibrium with the production of new, uninhibited enzyme. At this point, the amount of AChE at a given dose remains relatively consistent across duration. In general, OPs reach steady state within 2-3 weeks. Therefore, for OPs it is appropriate to assess steady state exposure durations (up to 21 days) instead of longer term exposures. The steady state point of departure is protective of any longer exposure duration, including chronic exposure.' (page 4)
>
> HED has used this exposure value to compare to the ssPAD for children ages 1-2 years old. For the FSE uses alone, the children ages 1-2 years old steady state dietary (food only) exposures for chlorpyrifos are of concern, with an estimated risk of 530% of the ssPAD. (page 24)

Risk to handlers was not limited to application of CPY, but post application, and the risks varied over time, not only arising from CPY exposures but from exposures to the metabolite chlorpyrifos-oxon (CPO).

The U.S.'s shift (as this article explains) occurred when the USEPA deviated from evidence supplied by Dow contracted researchers (Li et al 2012) to broadly review the epidemiological evidence.

As we discussed earlier, following the election of President Trump the USEPA pivoted to downplay the epidemiological evidence in the Third Revised Human Health Risk Assessment for Registration Review, (HHRA 2020) which 'updated' the 2016 Review. The 2020 paper acknowledged that the science addressing neurodevelopmental effects remained unresolved but elected to downplay the epidemiological data and question the underlying data.

Questioning the underlying data, is something that is not done for the old unpublished Dow studies which continue to uphold e.g. acceptable daily intake, ADI estimates, and which use now out-of-date guidelines for Australia (see below).

Following the political about-turn, in April 2021 the U.S. Ninth Circuit Court of Appeals ordered the Environmental Protection Agency (EPA) to ban all food uses of chlorpyrifos. Then in November 2023 the U.S. Court of Appeals for the Eighth Circuit

> 'issued a ruling vacating EPA's final rule revoking all food tolerances of chlorpyrifos and remanding the matter to EPA for further proceedings… all food tolerances for chlorpyrifos that existed prior to the issuance of the final rule revoking these tolerances were reinstated'.

The reinstatement of tolerances rule was published February 2024.

Tolerances for the United States are currently limited to the following 11 crops: alfalfa, apple, asparagus, cherry (tart), citrus, cotton, peach, soybean, strawberry, sugar beet, wheat (spring and winter).

**CANADA**

In December 2020 Canada - PMRA made the decision to cancel most uses of chlorpyrifos (RVD2020-14, see also Environmental Risk Assessment) and then later decided to cancel all remaining uses of chlorpyrifos, with all permissions ceasing at the end of 2023.

**EUROPE: EFSA**

In 2018, Axel Mie, Christina Rudén & Philippe Grandjean demonstrated how industry claims about safety did not necessarily reflect the evidence in the raw data:

> We noted treatment-related changes in a brain dimension measure for chlorpyrifos at all dose levels tested, although not been reported in the original test summary. We further found issues which inappropriately decrease the ability of the studies to reveal true effects, including a dosage regimen that resulted in too low exposure of the nursing pups for chlorpyrifos and possibly for chlorpyrifos-methyl, and a failure to detect any neurobehavioral effects of lead nitrate used as positive control in the chlorpyrifos study. Our observations thus suggest that

> conclusions in test reports submitted by the producer may be misleading. This discrepancy affects the ability of regulatory authorities to perform a valid and safe evaluation of these pesticides. The difference between raw data and conclusions in the test reports indicates a potential existence of bias that would require regulatory attention and possible resolution.

One year later – the European Food Safety Authority (EFSA) finding, released July 2019 that chlorpyrifos does not meet the criteria for reapproval. Their considerations 'particular attention was given to the re-evaluation of the study provided by Mie et al. (2018)' with EFSA stating

'It is well known that morphometry of brain regions is a valuable data for regulatory authorities (Tsuji and Crofton, 2012): the decrease in cerebellum height corrected by brain weight was considered an adverse effect indicating a damage of the architecture of the developing brain.'

The three main birth cohort studies considered by EFSA, included the pre-2013 data considered by the U.S. that should have been available to the NZEPA: The work by Raugh, Whyatt, Perera and colleagues (2004;2005;2012), Sebe et al (2005), Castorina et al (2010) and Marks et al (2010.

EFSA went onto conclude:

- the genotoxicity potential remains unclarified (positive findings from an in vitro chromosome aberration study and two in vitro unscheduled DNA synthesis assays; in vivo positive findings from open literature on chromosome aberration and on DNA damage caused through oxidative stress or by topoisomerase II inhibition which was considered a MIE for infant leukaemia);
- the effects recorded in the DNT study (decrease in cerebellum height corrected by brain weight already at the lowest dose tested, which is a relevant endpoint for hazard characterisation)indicate a concern;
- the epidemiological evidence supports the developmental neurological outcomes in children for chlorpyrifos

EFSA also stated: In addition, the recorded toxicological effects meet the criteria for classification as toxic for reproduction category 1B (regarding developmental toxicity).

Europe effectively banned chlorpyrifos and chlorpyrifos-methyl in February 2020:

> 'On 6 December 2019, at the meeting of the Standing Committee on Plants, Animals, Food and Feed (PAFF Committee) the Member States voted on two draft Implementing Regulations proposing **to not renew the approvals of chlorpyrifos and chlorpyrifos-methyl**.
>
> **For both substances, a qualified majority was reached.**
>
> The European Commission formally adopted the Regulations on 10 January 2020, meaning that Member States must, within one month, withdraw all authorisations for plant protection products containing the active substances.'
>
> On 18 February 2020, Member States endorsed a proposal by the Commission to lower the Maximum Residue Levels (MRLs) of chlorpyrifos and chlorpyrifos-methyl in food and feed to the **lowest level that can be measured by analytical laboratories**.

In 2021 the European Union proposed that chlorpyrifos would be listed on the Stockholm Convention on Persistent Organic Pollutants (UNEP/POPS/POPRC.17/5). New Zealander Dr Meriel Watts had proposed that chlorpyrifos met the criteria for listing as a persistent organic pollutant (Watts 2012).

**AUSTRALIA**

The Australian Pesticides and Veterinary Medicines Authority have released several papers, an Chlorpyrifos interim review report: Toxicology assessment, and the Reconsideration of chlorpyrifos: Toxicology update. These provided the rationale for the APVMAs Gazette notice: Chlorpyrifos reconsideration (No. APVMA 25, 12 December 2023).

There are no mentions of chlorpyrifos-methyl.

Trade was the major consideration, with the APVMA proposing to vary instructions as risk to trade or commerce could not be adequately mitigated:

> The APVMA is not satisfied that the instructions for use entered in the Register for chemical products containing chlorpyrifos, approved for use on cereal grains, canola, cotton, pulses, citrus, grapes, pome fruit, stone fruit, cattle and crops that may fed to animals, will not unduly prejudice trade or commerce between Australia and places outside Australia.

In September 2024 a APVMA Final Review Technical report was released, followed by an October 2024 Chlorpyrifos uses – summary of assessment outcomes in the final regulatory decision.

In September 2024, Australia removed most agricultural and urban pest control uses of chlorpyrifos, releasing the paper: Chlorpyrifos uses – summary of assessment outcomes in the final regulatory decision (October 2024). Seventy-nine of ninety-one uses were revoked. A 12-month phase-out period has now begun, where products bearing the previously approved labels may continue to be sold and used. Use in home and domestic garden products had been revoked in 2019.

A search on the APVMA website does not bring up an assessment of chlorpyrifos-methyl, but acknowledges that it is a 'risk area identified for reassessment'. Corteva voluntarily pulled their registration of chlorpyrifos-methyl in February, however four products remain registered with the APVMA.

There has been no discussion of the cumulative burden of chlorpyrifos plus chlorpyrifos-methyl.

**Uses that remain approved in Australia, but with rate and timing restrictions, are:**

- Cole (brassica) crops (broccoli, brussels sprouts, cabbage, cauliflower).
- Clover seed crops.
- Forage crops
- Lucerne
- Lucerne seed crops
- Medics
- Agricultural, commercial and industrial areas (not publicly accessible).

- Container plants in soil or other growing media (commercial)
- Hides/skins
- Potted ornamentals (commercial)
- Treatment of termite nest or colony (in wall cavities)
- Turf (commercial)

## DEVELOPMENTAL NEUROTOXICITY: CHLORPYRIFOS-METHYL

The data for developmental neurotoxicity (DNT) for CYP-M is scarce. These globally relevant assessments demonstrate the paucity of risk assessment data to support the safety of the grain storage fumigant, CPY-M and risk to pregnant mothers, infants and children.

- JMPR (1991)(1992)
- USEPA (2015)
- EFSA (2019b)

In the paper: A comprehensive review on chlorpyrifos toxicity with special reference to endocrine disruption (Ubaid ur Rahman et al. 2021), the Pakistan-based scientists noted:

> 'Although CPF has low persistence in the body, its active metabolites, 3,5,6-trichloro-2-pyridinol (TCP), and chlorpyrifos-oxon (CPO) are comparatively more persistent, albeit equally toxic, and thus produce serious health complications. … CPM as an insecticide is a structural analog of CPF and is extensively used for the treatment of stored grains, and rather more commonly persists in food staples.'

**DNT: U.S. - USEPA**

While acknowledging data-gaps the USEPA *Chlorpyrifos Methyl Human Health Draft Risk Assessment* (2015) still was able to confirm that AChE inhibition was the primary risk pathway:

> 'AChE inhibition is the most sensitive endpoint in the chlorpyrifos-methyl toxicology database in multiple species, durations, and life stages and is the endpoint used for selection of toxicological points of departure (PODs). The PODs for all routes and durations of exposure for chlorpyrifos- methyl are based on red blood cell (RBC) ChE from oral animal studies.'

Section 4.0 Hazard Characterization and Dose-Response Assessment of the draft risk assessment demonstrated the importance of recognising the accumulation of acetylcholine as a risk-factor for neurotoxicity (2015; page 15):

**4.0 Hazard Characterization and Dose-Response Assessment**

Chlorpyrifos-methyl is a member of the OP class of pesticides. Like other OPs, the initiating event in the AOP/MOA for chlorpyrifos-methyl involves inhibition of the enzyme acetylcholinesterase (AChE) via phosphorylation of the serine residue at the active site of the enzyme. This inhibition leads to accumulation of acetylcholine and ultimately to neurotoxicity in the central and/or peripheral nervous system (see Figure 1). For chlorpyrifos-methyl, AChE inhibition (ChEI) is typically the most sensitive endpoint in the toxicology database in multiple species, durations, life stages, and routes, thus ChEI is the focus of this hazard characterization. The availability of reliable ChEI dose response data is one of the key determinants in evaluating the toxicology database.

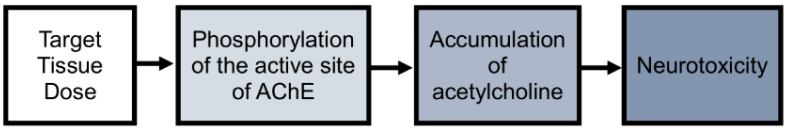


**Figure 1. AOP for OPs.**

**4.1 Toxicology Studies Available for Analysis**

It should be noted that in the past HED has relied on bridging of toxicity data from chlorpyrifos-ethyl to chlorpyrifos-methyl to satisfy the data requirements for the latter. However, because of the differences in potency of the two chemicals, and the potential differences in pharmacokinetic

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The USEPA noted that the toxicology database for chlorpyrifos-methyl is incomplete.

> 'There is no developmental neurotoxicity study for chlorpyrifos-methyl (and the study is not required).'

Regarding the sole developmental toxicity study, a rat prenatal study (MRID 44680603, 1992):

> 'there were no treatment-related effects on survival, maternal body weight, or food consumption. RBC ChEI was seen in dams at the 12.5 mg/kg/day (33%) and at 50 mg/kg/day (47%) dose groups. Brain ChEI was seen only at the high dose. For maternal toxicity, the NOAEL was 1.0 mg/kg/day, and the LOAEL was 12.5 mg/kg/day based on RBC ChEI. No developmental toxicity was seen, and there were no treatment-related increases in external, visceral or skeletal malformations or anomalies.'

For developmental toxicity, the NOAEL was 50 mg/kg/day, the highest dose tested (HDT). The point of departure for the acute dietary (all populations) exposure scenario was derived from the results in the rat developmental study (MRID 44680603) based on RBC ChE inhibition at the LOAEL of 12.5 mg/kg/day (NOAEL is 1.0 mg/kg/day).

The study isn't available for public scrutiny.

**DNT: EUROPE - EFSA**

As rapporteur Member State, Spain was responsible for compiling Europe's Revised Renewal Assessment Report (RAR), that would then be considered by EFSA, and this occurred between 2017-2019.

In considering DNT, European experts reviewed (2019b):

a) a developmental neurotoxicity (DNT) study in rats from 2015.;
b) public literature presented in the systematic review provided by the applicants;
c) additional literature provided by the experts or during the commenting period.

The two-week 2015 DNT study in pregnant rats (days 6-21, equivalent to the second and third trimesters) observed statistically significant lower RBC AChE and brain AChE activity values compared to the control group in maternal generation at 10 and 50 mg/kg bw per day. EFSA (2019, page 9) stated that there was a:

> 'significant decrease in the height of cerebral hemisphere on post-natal day (PND) 72 was observed in males at the top dose. In addition, a statistically significant inhibition of RBC AChE was observed in males at 50 mg/kg bw per day on PND 21. At the experts' meeting in April 2019, all the experts agreed to set a maternal NOAEL at 2 mg/kg bw per day based on decreased RBC AChE and brain AChE activity. The experts noted that, despite the study was performed according to current OECD 426 guideline (OECD, 2007), the cerebellum height in pups (considered the most sensitive endpoint in the DNT study performed with chlorpyrifos) could not be evaluated since just three control samples in females were available on PND 72. Therefore, considering the low statistical power, no reliable analysis could be performed, representing a major deviation from the study protocol. No changes in cerebellum height were reported for males and females at PND 21 and for males at PND 72, but the measurement was only available at the highest dose. In addition, it should be noted that cerebellum height was not corrected by brain weight' (page 9).

All experts (except one) agreed that because the developmental neurotoxicity data was inconclusive,

> 'DNT NOAEL could not be set and the LOAEL of 0.3 mg/kg bw per day derived from the data on chlorpyrifos (study from 1998; Spain 2019b) could be conservatively applied to chlorpyrifos-methyl.'

> 'The experts agreed that particularly the insufficient number of data related to cerebellum height should be regarded as an important deficiency, since the measurement of cerebellum height was considered a critical parameter to assess developmental neurotoxicity for chlorpyrifos.'

The EFSA experts took into account the data on DNT risk from organophosphates, chlorpyrifos research and the studies on the common metabolite CYP in concluding that, based on the available data-set chlorpyrifos-methyl 'may be expected to meet the criteria for classification as toxic for the reproduction'. The comments are reproduced below (2019b, page 10):

> 'The experts discussed the epidemiological evidence showing associations between chlorpyrifos and chlorpyrifos-methyl exposure during neurodevelopment and adverse health effects (attention deficit/ hyperactivity disorders, decrease in intelligent quotient and working memory, etc.). In particular, three main birth cohort studies were considered: the Columbia Center for Children's Environmental Health (CCCEH) study (US EPA, 2016), the Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS) (Castorina et al., 2010; Marks et al., 2010) and Mt. Sinai study (Sebe et al., 2005). Using different biomarkers of exposure, these studies show that prenatal exposure to organophosphates (OPs) produces a consistent pattern of early cognitive and behavioural deficits (Rauh et al., 2012). The experts discussed also other epidemiological evidence from the public literature. The majority of the experts considered that the results from some of these studies (mainly from CCCEH study, Rauh et al., 2012; Engel et al., 2011; Silver et al., 2017) contribute to the evidence of DNT

effects in humans due to the exposure to chlorpyrifos and chlorpyrifos-methyl and occurring at doses lower than that causing 20% inhibition of AChE. Therefore, this would represent a concern to be taken into consideration for the risk assessment.

In addition, it should be noted that in the CHAMACOS study measurement of trichloro-pyridinol (TCP) in urine,5 common metabolite of both chlorpyrifos and chlorpyrifos-methyl contributed to the evidence of DNT effects in humans due to the exposure to chlorpyrifos and/or chlorpyrifos-methyl. The applicant Ascenza Agro S.A. indicated that no epidemiological studies are available for chlorpyrifos-methyl; however, as indicated above, the measurement of TCP in urine cannot discriminate between the selective exposure to chlorpyrifos or chlorpyrifos-methyl. Taking into consideration the DNT study outcome (reduction in cerebellum height for chlorpyrifos – that could not be explained by the maternal AChE inhibition), the epidemiological evidence showing an association between chlorpyrifos/chlorpyrifos-methyl exposure during development and neurodevelopmental outcomes, and the overall analysis of the published literature (in vivo, in vitro and human data), the experts indicated that chlorpyrifos-methyl, based on the available toxicological data set, may be expected to meet the criteria for classification as toxic for the reproduction, REPRO 1B, H360D 'May damage the unborn child' in accordance with the criteria set out in Regulation (EC) No 1272/2008. EFSA expresses some reservations on this approach, as based on the current experience the criteria for classification would normally be based on the specific effects recorded in good quality data. However, the European Chemicals Agency (ECHA) will be responsible for the final decision.'

## NEW ZEALAND AND CHLORPYRIFOS 'RISK ASSESSMENTS'

NZEPA moved swiftly in June 2020 to start the reassessment process, which entails establishing the grounds for the reassessment, in this particular case, for chlorpyrifos, and all chlorpyrifos-containing substances, chlorpyrifos-methyl, and all chlorpyrifos-methyl-containing substances.

NZEPA then made an Application for Reassessment in October 2024. This application explicitly removed chlorpyrifos-methyl. The assessment of risks and benefits are described in the staff assessment document 'Staff assessment report – the application to reassess chlorpyrifos'. NZEPA claim that a 'quantitative assessment of human health risks has also been undertaken', this is found in the document 'Science memo: APP204694 chlorpyrifos'.

On November 14, 2024 when a press release announced a call for submissions relating to a proposed ban.

The *Staff assessment report* (2024) contains a Risk assessment section (pages 13-53). The NZEPA claim to have 'undertaken a weight of evidence approach'. Much of the Risk Assessment section concerns their 2013 'risk assessment', which they note (page 14) is 'found in the Consultation Report and Evaluation and Review Report'.

The risk assessment claims of worker risk being negligible or low a decade ago, were not based on an assessment of the toxicological literature, and excluded major concerns that were at the same time being considered by the USEPA – primarily the risk of neurotoxicity to children, and the risk from repeat worker re-entry.

It is difficult to understand why worker re-entry risk for pre-conception and pregnant women has not been reviewed, either in 2012 or in 2024, when the primary risk identified globally is to pregnant women, the foetus and young children. NZEPA's dismissive and simplistic discussion on developmental neurotoxic risk suggests that officials may not have the skill-set for this work, but also results in misleading information being communicated to the public.

**NZEPA – THE 2013 'RISK ASSESSMENT'**

These two November 2012 papers cannot in any way, be described as fit for purpose risk assessments, yet the NZEPA claims on page 14 of the *Staff assessment report* (2024) that the 'human health risk assessment conducted for the 2013 reassessment concluded that the risks associated with exposure to chlorpyrifos range from negligible to low.'

In November 2012 the NZEPA released an Application for the Reassessment of a Group of Hazardous Substances APP201045 – Organophosphate and carbamate plant protection insecticides. Group reassessments are a win-win for the industry applicants – they average out risks without a focussed risk assessment – while the regulatory agency fails to consider that pregnant women, children and families are exposed to that class of substance as a dietary burden.

Who knows when the NZEPA last conducted a comprehensive risk assessment that analysed toxicological data independently of other regulators. NZEPA expect their decisions to carry the full force of risk assessment, without undertaking them.

The content in the November 2012 Consultation Report could not be described as a risk assessment. The so-called 'Risk Assessment' on the Effects on human health of OPCs (pages 21-24) failed to review the literature and assess risk.

The Consultation report (2012) acknowledged the U.S. FIFRA work but did not review the findings.

As part of Group Reassessment process, NZEPA contracted an 'Epidemiology Review – A Client Report by Epi Interactive ' (literature review) which 'involved no systematic literature review process and is based on a limited number of epidemiological studies'.

> Muellner P and Wilson N. (February 24, 2013). Client Report. Critical evaluation of selected epidemiological evidence on the association of exposure to low-level organophosphate and carbamate plant protection insecticides with adverse human health effects. Prepared for the Environmental Protection Authority (EPA), New Zealand by Epi-interactive.

Despite this limitation and a limited timeline, the report (which included the Raugh and Whyatt, and Marks studies noted above) concluded:

> Nevertheless, this evaluation found that the evidence for a causal association between OPC exposure and impaired neurodevelopment and between OPC exposure and neurobehavioural/neurophysiological/neurological effects was "probable". The evidence provided for an association between OPC exposure and cancer was graded as "possible".

An Evaluation and Review Report (APP201045) – Organophosphate and carbamate plant protection insecticides, released in February 2013, summarised submitter comments. This report did not include a mention of their own contracted Epidemiology Review.

The final Decision in June 2013, shows how the acceptable daily intake levels were adopted directly from the Australian Pesticides and Veterinary Medicines Authority (APVMA), while acknowledging that 'a complete review of the toxicological and epidemiological information for these active ingredients was not undertaken by EPA staff prior to the selection of the ADIs' (page 33).

The Decision acknowledged Muellner and Wilsons review 'systematic review of 14 occupational studies involving more than 1600 workers which shows neurobehavioural effects 12 and three US children's cohort studies which independently show associations between prenatal OP exposures and neurodevelopmental effects in early childhood' (page 50).

The recommendations from Muellner and Wilson were not published in the Decision.

The NZEPA failed to disclose the Reviews findings in any of their published scientific assessment documents. The NZEPA also failed to disclose and then dismissed it in final Decision, to all appearances, inferring that neurotoxicity risk to the under seven age group would disappear with restrictions on retail use.

Perhaps the committee solely attributed risk to exposures following exposure to home garden use, a problem that would be hypothetically solved by revoking retail use. The U.S. children's cohort studies did not come to any conclusion that the exposures were derived from home garden use.

The Evaluation and Review Report (2012) republished concerns raised by submitters and staff responses (pages 8-121). The balance of the paper discusses classifications and controls. It is not a risk assessment.

The Consultation Report (2012) did not assess the developmental neurotoxic risk of chlorpyrifos, noting merely the EFSA (2005) review where EFSA established an AOEL of 0.01 mg/kg bw/day.

Poisoning incidents to New Zealand children were discussed, but there was no analysis of the scientific literature pointing to developmental neurotoxicity.

The Consultation Report (2012; page 21) briefly alluded to international data on AChE and neurotoxic risk:

A number of studies in laboratory animals and in human populations have shown an association between prenatal and/or early postnatal organophosphate exposure and adverse effects on the development of the nervous system for the foetus or in early childhood[4,5,6,7]. In addition, studies have indicated potential associations between exposure to some OPCs and immunotoxicity, cancer, obesity and diabetes[8]. This research has primarily focused on organophosphates rather than carbamates. Feedback received in response to calls for information on OPCs by the EPA cited reports of these health effects as issues of concern. A potential for the poisoning of domestic pets due to exposure was also raised as a concern during consultation.

To date, however, international regulatory bodies have considered the critical effects of OPCs to be neurotoxicity mediated by inhibition of the acetylcholinesterase enzyme, and their risk assessments have been based on this endpoint. The EPA staff have taken the same approach and used the values set by international regulators in this evaluation. EPA staff are aware that there are more recent studies which it has been unable to incorporate into its assessment because of the timing and number of substances in this Application. A full list of the values set by international regulators that EPA staff have relied on in its assessment is provided in Appendix D.

But this is not a risk assessment. NZEPA then pointed to values set by international regulators in Appendix D. Appendix D contained no reference values set by international regulators on dietary exposures.

Risk from unintentional poisoning was considered, but while risk to bystanders was considered and poisoning incidents. Specific risk to children in agricultural communities, and workers, or from dietary exposures was not considered.

The 2014 ‘risk assessment’ arising from these two reports does not evaluate long-term chronic exposure to workers from re-entry and sustained, steady-state exposures to both chlorpyrifos and the metabolite chlorpyrifos-oxon (CPO). The lack of review or caution for worker safety, is evident in the brevity of information relayed for worker risks.

## 10.3. Chlorpyrifos

### Risks

The risks presented in Tables 14 and 15 are those with the default controls and the following additional controls in place:

**R-4** Buffer zones (excluding granular products) as specified in New Zealand Standard NZS:8409 Management of Agrichemicals

**R-9** Label warning of effects on bees

**R-10** Use of personal protective equipment (PPE and RPE) required, with minimum standards prescribed

**R-12** Restricted entry interval (REI) of 24 hours

Table 14 Risks associated with modelled uses of chlorpyrifos – human health

| Overall risk | Number of use scenarios | | |
|---|---|---|---|
| | **Operator risks** | **Re-entry worker risks** | **Bystander risks** |
| Negligible | 110 | 110 | 104 |
| Low | - | | 6 |
| Medium | - | - | - |
| High | - | - | - |
| **Total** | **110** | **110** | **110** |

The human health risks for the chlorpyrifos use scenarios modelled are almost all negligible. A small proportion carry low risks for bystanders.

Table 15 Risks associated with modelled uses of chlorpyrifos – environment

| Overall risk | Number of use scenarios | | |
|---|---|---|---|
| | **Aquatic risks** | **Bird risks** | **Bee risks** |
| Negligible | 37 | 9 | All[a] |
| Low | 63 | 29 | - |
| Medium | 10 | 70 | - |
| High | - | 2 | - |
| **Total** | **110** | **110** | **110** |

[a] All risks to bees are considered negligible as bees are only expected to be killed when they are directly exposed to the spray solution. Controls are assumed to be effective in restricting application to times when bees are not present.

The majority of chlorpyrifos use scenarios modelled are associated with environmental risks. There are many low risks for aquatic organisms, with a few uses posing medium risks. The majority of uses

Over the same period, 2011-2012, the USEPA was seriously considering the risk from exposure to chlorpyrifos and AChE inhibition, cholinergic and non-cholinergic adverse outcomes, including developmental neurotoxicity studies on behaviour and cognition effects.

Then in December 2014 the agency released Chlorpyrifos: Revised Human Health Risk Assessment for Registration Review. (See (FIFRA SAP 2011; FIFRA SAP 2012 noted in the 2016 paper, page 9).

The lack of focus by NZEPA can be demonstrated by comparing their actions with the USEPA and EFSA.

**NZEPA 2024: FAILURE TO SERIOUSLY CONSIDER DEVELOPMENTAL NEUROTOXICITY**

The Staff assessment report (2024) Risk assessment section (pages 13-53) contains a section 'Assessment of risks identified by international regulatory authorities'. In these 40 pages, developmental risk is mentioned once, in discussion of Europe's 2019 assessment.

The NZEPA did not mention that the revoking from the market of chlorpyrifos and chlorpyrifos-methyl was based on the epidemiological and regulatory data held by the EFSA, and that the revokation was clearly associated with developmental neurotoxicity and genotoxic risk.

At section 4.125:

> 4.125 In 2019, EFSA published an updated human health assessment. In this document EFSA considered that the genotoxic potential of chlorpyrifos was unclear and that there were also significant uncertainties regarding neurodevelopmental toxicity. As a result, EFSA considered that they could not establish toxicological reference values, such that a risk assessment for human health could not be conducted. EFSA concluded that the requirements for approval were not satisfied, and the substance was no longer approved for use in the European Union.

Why hasn't the NZEPA clearly articulated the European Commission's February 2020 ban, which lowered permitted residues of chlorpyrifos and chlorpyrifos-methyl to the lowest level that can be measured by analytical laboratories.

In addition, the NZEPA's Science memo (2024) briefly noted:

> **'**While there has been some suggestion of neurodevelopmental or other effects occurring below the threshold for ChE inhibition, these have yet to be substantiated among recognised international regulators'

**NZEPA 2024: IGNORING DIETARY RISK TO CHILDREN**

The NZEPA state that they will ban the chlorpyrifos by revoking its approvals.

> The EPA considers that all chlorpyrifos use patterns results in risks which cannot be mitigated to human health and/or the environment, with the majority of use patterns presenting risks to both.

NZEPA are not considering all chlorpyrifos *exposure* patterns.

The NZEPA October 2024 Staff assessment report – the application to reassess chlorpyrifos does not consider risk to children in any detail. An assessment of recently sprayed turf that might be transplanted in public amenity spaces is discussed. Dietary risk to birds and bees is discussed, but not children.

This is because, as the assessment report notes:

> Dietary exposure is not under the regulatory remit of the EPA or the HSNO Act. While aspects of a human health assessment undertaken by the US EPA can be used to inform our risk assessment, dietary exposure would not be incorporated into consideration of the risks associated with an approval under the HSNO Act.'

The NZEPA has avoided considering the toxicity of farmworker families who are exposed chronically in the days following sprays (including through household use such as washing work wear) and reviewing dietary exposures in association with proximity risk.

The NZEPA merely considers the toxicity of a child walking near or onto a recently sprayed field (the bystander effect), and acknowledges the risk if sprayed in public places.

Residues of New Zealand children are higher than European children.

The NZ EPA are not clear on how pregnant mothers and babies are exposed – we know, from a 2022 New Zealand study (discussed below in the section on dietary exposures) that New Zealand children have higher levels of this pesticides metabolites in their urine – and there is no discretion between chlorpyrifos-methyl (CPY-M) and chlorpyrifos (CPY).

There is no known level of exposure that is safe for pregnant women and the developing foetus.

> 'One US study found that as little as 4.6 parts per trillion of chlorpyrifos in umbilical cord blood during gestation was associated with a drop of 1.4 percent in a child's IQ, and 2.8 percent of its working memory.' (Panuwet et al 2012)(Watts & Williamson 2015)

This 2022 paper has not been considered by the NZEPA.

## DIETARY EXPOSURES

Dietary intake may be the greatest driver of AChE inhibition by the insecticide chlorpyrifos and the fumigant chlorpyrifos-methyl. Exposures to young children appear to be predominantly derived from either living on and near farms – children of farmworkers are at high risk; or from consuming diets high in cereals.

However, the highest levels, and the most common detections, are from the fumigant, which is applied to staple foods, the cereal group, including wheat, which is consumed in high quantities by babies and children.

The *25th Australian Total Diet Study* (ATDS) (2019) identified that chlorpyrifos and chlorpyrifos-methyl were among the most frequently detected pesticides.

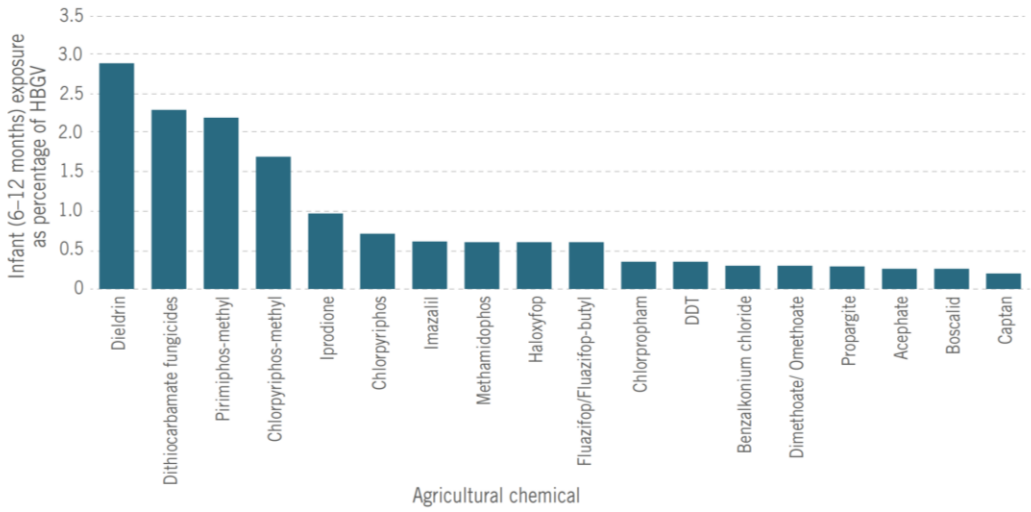
The *25th Australian Total Diet Study* Appendices revealed that it was more common than not to detect chlopyrifos-methyl in biscuits and bread, while chlorpyrifos was commonly found in sultanas.

New Zealand's Total Diet Study (2016) showed that chlopyrifos-methyl detections had increased significantly from the 2009 study, becoming one of the ten most detected residues (37 detections).

The two most commonly detected organophosphate insecticides are used as fumigants in grain silos. These are pirimiphos-methyl, a relatively unstudied (but potentially genotoxic) chemical, the most commonly detected (89 detections); and chlorpyrifos-methyl ( 37 detections).

Worryingly, for infants 6-12 months, chlorpyrifos factored in the top 18 dietary exposures.

**Figure 7:** Top 18 dietary exposures for infants (6–12 months), as a proportion of the health based guidance value, for agricultural chemicals analysed in the 2016 NZTDS




24 ∴ New Zealand Food Safety

**New Zealand's Total Diet Study (2016; page 24).**

Chlorpyrifos-methyl may be contributing towards the highest exposure levels because of its use as a grain fumigant in Australia. (Less toxic fumigant processes can be substituted). Cereals

consumed in New Zealand's North Island are predominantly imported from Australia. It does not appear that chlorpyrifos-methyl

PSGR consider that it is important to recognise that the NZEPA, in 2020, was going to consider chlorpyrifos-methyl in tandem with chlorpyrifos, as Europe had done. However by October 2024 *Application for a Reassessment* noted

> 'The grounds for reassessment in this request were approved for both chlorpyrifos and chlorpyrifos-methyl. The current reassessment application is for chlorpyrifos only.'

The Australian reassessment doesn't appear to include chlorpyrifos-methyl either. Chlorpyrifos-methyl is not approved for use in Canada.

**PESTICIDE EXPOSURE IN NEW ZEALAND SCHOOL-AGED CHILDREN.**

In 2022, a group of scientists studied pesticide exposure and neuropsychological effects in New Zealand children. Urban, rural and farm children (aged 5–14 years) were recruited from the lower half of the North Island (the greater Wellington area, the Manawatu, the Wairarapa, and the Hawkes Bay) and the upper half of the South Island of New Zealand.

Urine levels were analysed for 20 pesticide biomarkers, including the metabolite 3,5,6-Trichloro-2-pyridinol (TCPy). This metabolite is common to chlorpyrifos and chlopyrifos-methyl and triclopyr. Triclopyr is a broadleaf herbicide, and is not permitted on food crops.

> Li Y, Wang X, Feary McKenzie J, 't Mannetje A, Cheng S, He C, Leathem J, Pearce N, Sunyer J, Eskenazi B, Yeh R, Aylward LL, Donovan G, Mueller JF, Douwes J. Pesticide exposure in New Zealand school-aged children: Urinary concentrations of biomarkers and assessment of determinants. Environ Int. 2022 May;163:107206. doi: 10.1016/j.envint.2022.107206. Epub 2022 Apr 5. PMID: 35395578.

There were 501 participants. Higher levels in urban children appear to reflect chlorpyrifos-methyl's use as a fumigant in cereal grains (due to the interesting finding that organic food other than fruit and vegetables was a predictor), and may reflect the use of triclopyr as a broadleaf weedkiller in urban parks and gardens.

- Urine concentrations did not differ between children living on a farm and children living in urban areas, with the exception of TCPy, for which concentrations were 40% higher in farm children during the high spray season.
- urine levels of DMTP, TCPy, 3-PBA, DCCA and 2,4-D were significantly higher in the low spray season
- Consumption of organic food other than fruit or vegetables was associated with lower concentration of TCPy in the high spray season.
- chlorpyrifos-methyl is not registered as an active ingredient for any current pesticide products in New Zealand
- The concentration of TCPy in New Zealand children was lower than that in Australian children of similar ages, but 2.2–7.3 times higher than other countries such as the US, Spain and Thailand.

- when we excluded farm children who had the highest levels (Table 6), the TCPy concentration in New Zealand children was still higher than those observed in other countries except for Australia, which also reported higher TCPy levels.
- The post-harvest use of pesticides for transportation and storage is another potential contributor to the concentration of pesticides on fruit/vegetable products, and therefore urinary levels of pesticide metabolites.

The researchers found that compared to other countries, levels of TCPy and pyrethroid metabolites were generally higher than in other countries.

This study showed that New Zealand children had higher levels of a metabolite than children in US, Spain and Thailand.

The US moved to ban chlorpyrifos use in 2021. Spain as a member of the European Union has likely responded to their 2019 decision to ban chlopyrifos, while Thailand banned its use from June 2020.

**NEW ZEALAND'S PERMISSIVE LEVELS.**

The maximum residue level (MRL) for CPY and CPY-M in Europe is 0.01 mg/kg, the lowest level that can be measured by analytical laboratories.

High residue levels in meat and animal and dairy fat is derived from feed that has been treated with CPY and CPY-M. In New Zealand this may be either domestically grown feed, or imported feed, predominantly from Australia. As an exporter of meat and dairy products into Europe (with MRLs at 0.01 mg/kg), and other countries that have restricted CPY and CPY-M, New Zealand must recognise that there is a trade-related risk, if CPY and CPY-M contaminated feed is fed to livestock.

A second trade-related risk comes from food exporters who use food ingredients from Australia, who may be unaware that Australian tolerances for CPY and CPY-M are orders of magnitude higher than European limits.

New Zealand's maximum residue levels, established by the Ministry of Primary Industries in the Food Notice: Maximum Residue Levels for Agricultural Compounds (September 2024):

Food Notice: Maximum Residue Levels for Agricultural Compounds 30 September 2024

| Compound Common Name | Chemical Abstracts Service (CAS) # | Residue to which the maximum residue level applies | Food | Maximum Residue Level (mg/kg) |
|---|---|---|---|---|
| Chlorpyrifos | 2921-88-2 | Chlorpyrifos | Bananas | 2 |
| | | | Fruits (except bananas, grapes, kiwifruit and stone fruits) | 0.2 |
| | | | Grapes | 1 |
| | | | Kiwifruit | 2 |
| | | | Maize | 0.02 |
| | | | Onions | 0.1 |
| | | | Potatoes | 0.01(*) |
| | | | Sheep fat | 1.5 |
| | | | Stone fruits | 1 |
| | | | Tomatoes | 0.2 |

There is no maximum residue level for chlorpyrifos-methyl as it is not approved for use on foods in New Zealand. Foods imported in New Zealand can have high residue levels of CPY-M.

Consider Europe's far lower levels in 2016, before the 2020 ban.

| | | |
|---|---|---|
| 0130000 | **Pome fruits** | |
| 0130010 | Apples | **0,01** (*) |
| 0130020 | Pears | **0,01** (*) |
| 0130030 | Quinces | 0,5 |
| 0130040 | Medlars | (**) |
| 0130050 | Loquats/Japanese medlars | (**) |
| 0130990 | Others | 0,5 |



| (1) | (2) | (3) |
|---|---|---|
| 0140000 | **Stone fruits** | |
| 0140010 | Apricots | 0,05 |
| 0140020 | Cherries (sweet) | 0,3 |
| 0140030 | Peaches | **0,01** (*) |
| 0140040 | Plums | 0,2 |
| 0140990 | Others | 0,05 (*) |
| 0150000 | **Berries and small fruits** | |
| 0151000 | (a) *grapes* | |
| 0151010 | Table grapes | **0,01** (*) |
| 0151020 | Wine grapes | 0,5 |
| 0152000 | (b) *strawberries* | 0,2 |
| 0153000 | (c) *cane fruits* | |
| 0153010 | Blackberries | **0,01** (*) |
| 0153020 | Dewberries | 0,05 (*) |
| 0153030 | Raspberries (red and yellow) | **0,01** (*) |
| 0153990 | Others | 0,05 (*) |

**REGULATIONS COMMISSION REGULATION (EU) 2016/60 of 19 January 2016 amending Annexes II and III to Regulation (EC) No 396/2005 of the European Parliament and of the Council as regards maximum residue levels for chlorpyrifos in or on certain products. Official Journal of the European Union (2016).**

**AUSTRALIA**

In September 2024, the Australian Pesticides and Veterinary Medicines Authority (APVMA) removed 79 of agricultural and urban pest control uses of chlorpyrifos, citing trade-related concerns. Australia has retained approval for Cole (brassica) crops (broccoli, brussels sprouts, cabbage, cauliflower), Clover seed crops, Forage crops, Lucerne, Lucerne seed crops, Medics, Agricultural, commercial and industrial areas (not publicly accessible), Container plants in soil or other growing media (commercial), Hides/skins, Potted ornamentals (commercial), Treatment of termite nest or colony (in wall cavities), Turf (commercial).

Australian maximum residue levels for brassica crops are .05 mg/kg.

**Australian Pesticides and Veterinary Medicines Authority (APVMA) residue levels for chlorpyrifos and chlorpyrifos-methyl.**
Agricultural and Veterinary Chemicals (MRL Standard for Residues of Chemical Products) Instrument 2023 made under section 7A of the Agricultural and Veterinary Chemicals (Administration) Act 1992. Compilation No. 6 Compilation date: 9 November 2024 Includes amendments: F2024L01413

**Chlorpyrifos**

| | | |
|---|---|---|
| VS 0621 | Asparagus | T0.5 |
| FI 0326 | Avocado | 0.5 |
| FI 0327 | Banana | T0.5 |
| FB 0020 | Blueberries | *0.01 |
| VB 0040 | Brassica (cole or cabbage) vegetables, head cabbages, flowerhead brassicas | T0.5 |
| FB 2005 | Cane berries | T*0.01 |
| VR 0463 | Cassava | T*0.02 |
| VS 0624 | Celery | T5 |
| GC 0080 | Cereal grains {except Sorghum} | T0.1 |
| FC 0001 | Citrus fruits | T0.5 |
| SB 0716 | Coffee beans | T0.5 |
| SO 0691 | Cotton seed | 0.05 |
| OC 0691 | Cotton seed oil, crude | 0.2 |
| DF 0167 | Dried fruits | T2 |
| MO 0105 | Edible offal (mammalian) | T0.1 |
| PE 0112 | Eggs | T*0.01 |
| HS 0784 | Ginger, root | *0.02 |
| FB 0269 | Grapes | T1 |
| FI 0341 | Kiwifruit | 2 |
| VA 0384 | Leek | T5 |

Australia will permit CPY to be sprayed on a wide range of animal forage crops. As a consequence of their diet, milk fat levels of CPY are permitted to be as high as 0.2 mg/kg and CPY-M 0.5 mg/kg, and meat fat CPY and CPY-M levels can be as high as 0.5 mg/kg. Cereal grain levels for CPY remain at 0.1 mg/kg.

| COMPOUND | FOOD | MRL (mg/kg) |
|---|---|---|
| FI 0345 | Mango | *0.05 |
| MM 0095 | Meat (mammalian) [in the fat] | T0.5 |
| ML 0106 | Milks [in the fat] | T0.2 |
| SO 0088 | Oilseed {except Peanut} | T0.01 |
| FT 0305 | Olives | T*0.05 |
| HH 0740 | Parsley | 0.05 |
| FI 0351 | Passion fruit | *0.05 |
| SO 0697 | Peanut | T*0.01 |
| VO 0445 | Peppers, sweet [capsicum] | T1 |
| FI 0352 | Persimmon, American | T1 |
| FP 0307 | Persimmon, Japanese | T1 |
| FI 0353 | Pineapple | T0.5 |
| FP 0009 | Pome fruits {except Persimmon, Japanese} | T0.5 |
| VR 0589 | Potato | 0.05 |
| PM 0110 | Poultry meat [in the fat] | T0.1 |
| PO 0111 | Poultry, edible offal of | T0.1 |
| GC 0651 | Sorghum | T3 |
| FI 0367 | Star apple | T*0.05 |
| FS 0012 | Stone fruits | T1 |
| FB 0275 | Strawberry | 0.05 |
| GS 0659 | Sugar cane | T0.1 |
| VR 0497 | Swede | T0.3 |
| VR 0508 | Sweet Potato | T0.05 |
| VR 0505 | Taro | 0.05 |
| VO 0448 | Tomato | T0.5 |
| TN 0085 | Tree nuts | T0.05 |
| | Vegetables {except Asparagus; Brassica vegetables; Cassava; Celery; Leek; Peppers, sweet [capsicum]; Potato; Swede; Sweet potato; Taro; Tomato} | T*0.01 |

The highest levels are from grain storage fumigant CPY-M on cereal grains 10 mg/kg, lupins 10 mg/kg, wheat bran 20 mg/kg and wheat germ 30 mg/kg.

**Chlorpyrifos-methyl**

| | | |
|---|---|---|
| GC 0080 | Cereal grains {except Rice} | 10 |
| SO 0691 | Cotton seed | *0.01 |
| MO 0105 | Edible offal (mammalian) | *0.05 |



| COMPOUND | FOOD | MRL (mg/kg) |
|---|---|---|
| PE 0112 | Eggs | *0.05 |
| VD 0545 | Lupin (dry) | 10 |
| MM 0095 | Meat (mammalian) [in the fat] | *0.05 |
| ML 0106 | Milks [in the fat] | *0.05 |
| SO 0088 | Oilseed {except Cotton seed} | 0.15 |
| PM 0110 | Poultry meat [in the fat] | *0.05 |
| PO 0111 | Poultry, edible offal of | *0.05 |
| VD 0070 | Pulses {except Lupin (dry)} | 0.15 |
| CM 0654 | Wheat bran, unprocessed | 20 |
| CF 1210 | Wheat germ | 30 |

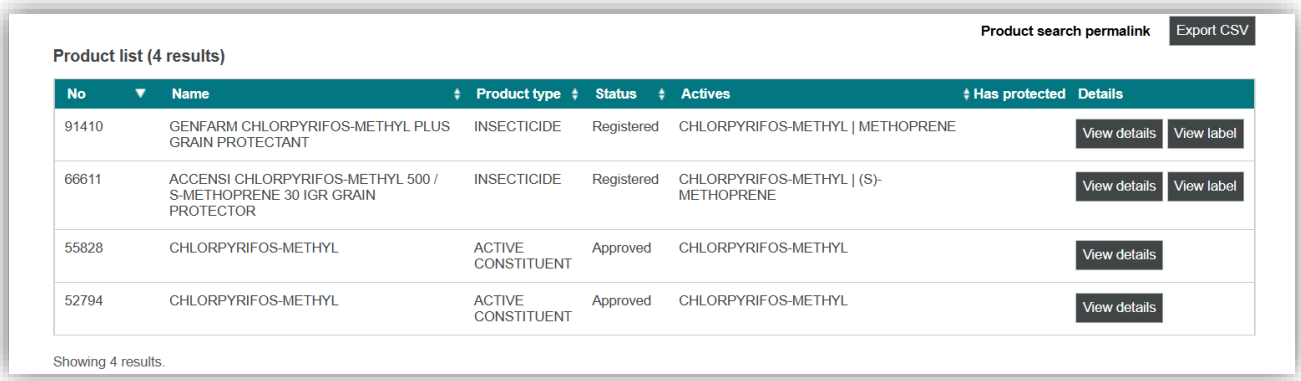
As noted earlier, in February 2024 a bundle of voluntary cancellations for chlorpyrifos-methyl were registered with the APVMA.

- Corteva Agriscience Australia. Approval or registration number 44035.
- Corteva Agriscience Australia. Approval or registration number 84724.
- Corteva Agriscience Australia. Approval or registration number 85030.

A request to the APVMA to understand whether use of the fumigant chlorpyrifos-methyl is still permitted in Australia for cereal grain storage returned this response:

> The expert area within the APVMA advised the following:
>
> *Chlorpyrifos-methyl products and actives were not included in the chlorpyrifos review, so there has been no change to the currently approved uses of chlorpyrifos-methyl products. The list of chlorpyrifos products and actives that were affirmed or cancelled in the review was published in the Special Gazette, 3 October 2024.*
>
> *Active constituents prioritised for future reconsiderations (including chlorpyrifos-methyl) are listed on our website.*

Four products remain registered with the APVMA. APVMA PubCRIS database search:



Product search permalink Export CSV

Product list (4 results)

| No | Name | Product type | Status | Actives | Has protected | Details |
|---|---|---|---|---|---|---|
| 91410 | GENFARM CHLORPYRIFOS-METHYL PLUS GRAIN PROTECTANT | INSECTICIDE | Registered | CHLORPYRIFOS-METHYL \| METHOPRENE | | View details View label |
| 66611 | ACCENSI CHLORPYRIFOS-METHYL 500 / S-METHOPRENE 30 IGR GRAIN PROTECTOR | INSECTICIDE | Registered | CHLORPYRIFOS-METHYL \| (S)-METHOPRENE | | View details View label |
| 55828 | CHLORPYRIFOS-METHYL | ACTIVE CONSTITUENT | Approved | CHLORPYRIFOS-METHYL | | View details |
| 52794 | CHLORPYRIFOS-METHYL | ACTIVE CONSTITUENT | Approved | CHLORPYRIFOS-METHYL | | View details |

Showing 4 results.

PSGR have reached out to GrainCorp and to the Grain Industry Association of Western Australia to confirm whether grain-storage operators continue to fumigate with chlorpyrifos-methyl, or whether they fumigate with a substitute product. As at publication time, PSGR are yet to receive a response.

**U.S.**

The maximum residue levels for wheat fumigated with chlorpyrifos-methyl is far higher than for wheat which is exposed to in-field weed spraying, using the insecticide chlorpyrifos.

As an example, in the U.S. the tolerance for chlorpyrifos (§ 180.342) *per se* (*O,O*-diethyl-*O*-(3,5,6-trichloro-2-pyridyl) phosphorothioate) in wheat grain is 0.5 parts per million.

By comparison, the tolerance is established for the combined residues of the fumigant (§ 180.419) [*O,-O,*-dimethyl *O*-(3,5,6-trichloro-2-pyridyl)] phosphorothioate and its metabolite (3,5,6-trichloro-2-pyridinol) – Table 2.2.3 below, is far higher for stored grains. Residues on wheat and rice residues can go up to 30 parts per million, while barley and sorghum can go to 90 parts per million.

PSGR could not confirm whether the fumigant chlorpyrifos-methyl which was last assessed by the USEPA in 2015 will be withdrawn. The USEPA did not include data on cereal levels post fumigation and the additive potential, following use, for example, in wheat crops. Chlorpyrifos-methyl and its

metabolite are commonly detected at high levels by the U.S. Department of Agriculture Pesticide Data Program (PDP).

| Table 2.2.3. Tolerance Summary for Chlorpyrifos-Methyl | | | |
|---|---|---|---|
| Commodity | Established Tolerance (ppm) | HED-Recommended Tolerance (ppm) | Comments *(correct commodity definition)* |
| Sorghum, grain | 6.0 | 10 | Increase tolerance level to harmonize with CODEX proposed MRL |
| Wheat, grain | 6.0 | 10 | Increase tolerance level to harmonize with CODEX proposed MRL |
| Barley, bran | 90 | 20 | 1999 tolerance recommendation (residue and processing data) * |
| Barley, pearled barley | 90 | 20 | 1999 tolerance recommendation (residue and processing data)* |
| Rice, bran | 30 | 13 | 1999 tolerance recommendation (residue and processing data)* |
| Rice, hulls | 30 | Revoke | No longer considered a significant feedstuff |
| Rice, polished rice | 30 | Revoke | Residue data indicate a separate tolerance for this rice processed commodity is not required. Residues of chlorpyrifos-methyl do not concentrate in polished/milled rice. |
| Sorghum, grain, bran | 90 | Revoke | Sorghum bran is not a sorghum processed commodity |
| Wheat, bran | 30 | 20 | 1999 tolerance recommendation (residue and processing data)* (CODEX currently at 20 ppm with proposed MRL of 6 ppm) |
| Wheat, germ | 30 | 20 | 1999 tolerance recommendation (residue and processing data)* |
| Wheat, middlings | 30 | 20 | 1999 tolerance recommendation (residue and processing data)* |
| Wheat, shorts | 30 | 20 | 1999 tolerance recommendation (residue and processing data)* |
| Aspirated grain fractions | --- | 330 | Based on residue and processing data, a tolerance should be established on *aspirated grain fractions*. |
| **Tolerances listed under 40 CFR §185 and §186.1050:** | | | |
| Barley milling fractions (except flour) | 90.0 | Revoke | Tolerance should be revoked concomitant with establishing a 20 ppm tolerance on *barley, bran*. |
| Oats milling fractions (except flour) | 130.0 | | Tolerance should be revoked concomitant with establishing a 10 ppm tolerance for *oat, grain*. |
| Rice milling fractions (except flour) | 30.0 | | Tolerance should be revoked concomitant with establishing a 13 ppm tolerance on *rice, bran*. |
| Sorghum milling fractions (except flour) | 90.0 | | Tolerance should be revoked. There are no longer any processed commodities of grain sorghum |

## OUT-DATED DATA DERIVES ACCEPTABLE DAILY INTAKE

The acceptable daily intake (ADI) is considered the safe dose, or level of exposures that a person can be exposed to without acute or chronic health conditions arising. The ADI is frequently derived from industry supplied and selected studies. Dow company have paid for, selected and supplied the majority of studies used by regulators to arrive at the claimed safe level of exposures.

New guidelines can be published, but the old study, using the out-dated guidelines, can be held as the justification for high residue levels on foods.

Unfortunately, the selected ADI can be 'locked in' for decades. Calculations of total exposures following the workplace exposures and dietary intakes forms the daily allowance or burden, these must, by milligram per kilogram of bodyweight, come under the ADI level.

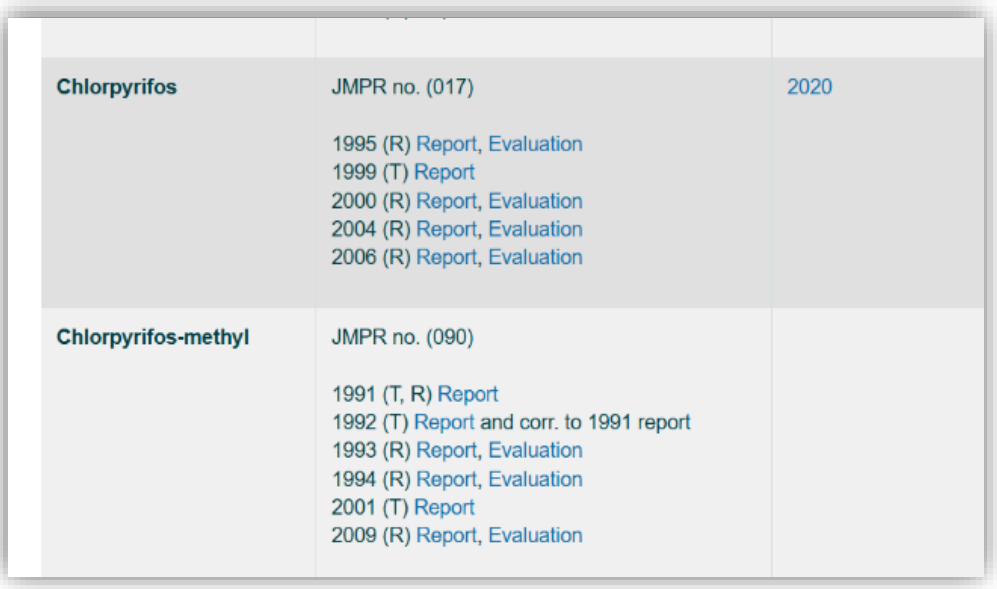
Because the ADI level is usually derived from one to three studies (primarily on rodents and dogs), they are largely speculative, and a safety factor can be built in, of 10 or even 100, to allow for inter-species differences. It must be noted that the industry applicant does not register all studies prior to undertaking them, and is not required to disclose the results of all studies that are undertaken for regulatory risk assessment.

The uncertainty around whether people are protected can be alleviated by the production of well-designed epidemiological studies. This is particularly important for assessing risks to infants and children. It is important that regulators do not exclusively rely on old ADI studies.

### JOINT MEETING ON PESTICIDES RESIDUES (U.N. AFFILIATED AGENCIES)

New Zealand and Australia often cite findings and studies used in the Joint Meeting on Pesticide Residues (JMPR), an expert ad hoc body administered jointly by Food and Agriculture Organization and the World Health Organization toxicological evaluations.

The current evaluations as this screenshot reveals, shows that both CPY and CYP-M are not regularly assessed. When the links are found, the main toxicological studies and assessments were conducted in the 1990s. These evaluations are used by Codex Alimentarius to set maximum residue levels.



| | | |
|---|---|---|
| **Chlorpyrifos** | JMPR no. (017)<br><br>1995 (R) Report, Evaluation<br>1999 (T) Report<br>2000 (R) Report, Evaluation<br>2004 (R) Report, Evaluation<br>2006 (R) Report, Evaluation | 2020 |
| **Chlorpyrifos-methyl** | JMPR no. (090)<br><br>1991 (T, R) Report<br>1992 (T) Report and corr. to 1991 report<br>1993 (R) Report, Evaluation<br>1994 (R) Report, Evaluation<br>2001 (T) Report<br>2009 (R) Report, Evaluation | |

**JMPR: CHLORPYRIFOS (017)**

1990 Report: 'toxicology of chlorpyrifos were reviewed by the 1982 Joint Meeting and the ADI was increased to 0-0.01 mg/kg bw, based on a NOAEL of 0.1 mg/kg bw per day in humans exposed to chlorpyrifos for 9 days and using a 10-fold safety factor. This ADI was supported by findings in rats and dogs.'

**JMPR: CHLORPYRIFOS-METHYL (090)**

The ADI was established in 1992, and little work has been undertaken to update this. Most data can be found on the INCHEM website. The 2009 Evaluation and 2009 Toxicology papers contain limited toxicological assessment:

> 'The Meeting established an ADI of 0–0.01 mg/kg bw based on the NOAEL of 1 mg/kg bw per day identified on the basis of inhibition of brain acetylcholinesterase activity and adrenal vacuolation in the 2-year study of toxicity and carcinogenicity in rats and with a safety factor of 100. This value is supported by the NOAEL of 1 mg/kg bw per day for inhibition of parental brain acetylcholinesterase activity in the multigeneration study of reproductive toxicity in rats and by the NOAEL of 1 mg/kg bw per day for inhibition of maternal brain acetylcholinesterase activity in the study of developmental toxicity in rats.'

**AUSTRALIA APVMA: CHLORPYRIFOS**

The APVMA publication *Acceptable daily intakes for agricultural and veterinary chemicals* (2024) lists the Australian ADI for chlorpyrifos and chlorpyrifos-methyl (page 34).

Chlorpyrifos: 0.001 mg/kg bw/day. The NOAEL is 0.1 mg/kg bw/day[1]

Chlorpyrifos-methyl: 0.001 mg/kg bw/day and a NOAEL of 0.4 mg/kg bw/day.

The APVMA Technical Report states that the ADI is derived from two studies, (page 15), Young and Grandjean 1988, and Breslin et al 1991. This APVMA acceptable daily intake (ADI) is drawn from studies supplied to the Joint Meeting on Pesticides Residues (JMPR), toxicological evaluation which have evaluated both CPY-M and CPY.

The acceptable daily intake for Australia is based on a series of studies in young adult rats, and the two cited studies are Dow Chemical Company studies.

These studies (reproduced in the Appendix [I]) were supplied to the 1999 JMPR toxicological evaluations, to the Joint meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Core Assessment Group Rome, (20-29 September 1999).

- Young, J.T. & Grandjean, M. (1988) Chlorpyrifos: 2 year dietary chronic toxicity-oncogenicity study in Fischer 344 rats. Unpublished report No. K-044793-079 from Lake Jackson Research

[1] NOAEL: no observable adverse effect level.

Center, Dow Chemical Co., Freeport, Texas, USA. Submitted to WHO by Dow AgroSciences, Indianapolis, Indiana, USA.

- Breslin, W.J., Liberacki, A.B., Dittenber, D.A., Brzak, K.A. & Quast, J.F. (1991) Chlorpyrifos: Two-generation dietary reproduction study in Sprague-Dawley rats. Unpublished report No. K-044793-088 from the Toxicology Research Laboratory, Dow Chemical Co., Midland, Michigan, USA. Submitted to WHO by Dow AgroSciences, Indianapolis, Indiana, USA.

Young, J.T. & Grandjean, M. (1988) observed alterations at the low dose but went onto claim only treatment-related effects at the high dose. Erythrocyte cholinesterase activity was 0.1 mg/kg bw per day. Data was unaccounted for.

Breslin et al (1991) identified a NOAEL for developmental effects was 1 mg/kg bw per day. The study is extremely out of date and does not consider many endocrinological end-points that were implemented from 2000 onwards (eg. in OECD TG 443). This study by Breslin did not comment on effects to the developing nervous system such as locomotion. Reduction in plasma cholinesterase was observed at the lowest dose. Reduction in plasma cholinesterase levels while brain levels remain stable following administration (Ubaid ur Rahman et al 2021) should be expected following dosing by CPY, as the body will preferentially direct resources to the brain. Three of the five litters in the F2 generation died, this was blamed on the mothers, rather than being considered a treatment associated effect. The F2 generation was not biopsied and their cholinesterase levels not tested, as per study protocols.

**AUSTRALIA APVMA: CHLORPYRIFOS-METHYL**

APVMA has assigned a 0.4 NOAEL for CPY-M is based on a (page 34):

> '78-week oral carcinogenicity and toxicology study in mice; a NOEL of 0.4 mg/kg bw/d was based on the inhibition of erythrocyte cholinesterase and brain cholinesterase at the next higher dose.' And a 'A total uncertainty factor of 300 was applied (10 for interspecies, 10 for intraspecies and 3 for database deficiencies due to a lack of neurotoxicity and developmental neurotoxicity studies).'

Often, due to commercial in confidence agreements with the corporate industry applicants, even the summary of a study is unavailable. The raw data is never available.

There is no record of this study in the JMPR files.

The study may have been considered by the USEPA (2015) who stated: The chronic mouse study had an RBC ChE LOAEL of 3.9 mg/kg/day in females and a NOAEL of 0.4 mg/kg/day. Considering the reproducibility of rat studies, the similarity in magnitude of the NOAELs of 0.4 mg/kg/day in mice compared to 1.0 mg/kg/day in rats, the NOAEL of 1.0 mg/kg/day from the rat studies is considered protective for steady state RBC cholinesterase inhibition and was chosen as the POD for this assessment.

It is unclear how old this study is, whether it conformed to guidelines, and how many rodents were studied, yet it is the key study deriving the ADI for Australia.

It's also noteworthy that the Australian ADI for Triclopyr, which breaks down to the same metabolite CPY is 0.005, based on a NOAEL of 0.5, based on a 5 November 1986 1-year dietary dog study. The NOAEL of 0.5 mg/kg bw/d was based on reduced phenolsulfonphthalein excretion, increased plasma BUN and creatinine at the next higher dose.

**EFSA: CHLORPYRIFOS**

EFSA 2015: ADI 0.001 mg/kg bw/day

The new available toxicological data lead to the decrease of the reference values established in 2005: the Pesticides Peer Review meeting agreed on a new ADI and AOEL of 0.001 mg/kg bw per day, and an ARfD of 0.005 mg/kg bw, based on significant decrease of RBC ChE in rats, using an uncertainty factor of 100.

- EFSA (European Food Safety Authority), 2014. Conclusion on the peer review of the pesticide human health risk assessment of the active substance chlorpyrifos. EFSA Journal 2014;12(4):3640, 34 pp.

**EFSA: CHLORPYRIFOS-METHYL**

Previously set toxicological reference values of chlorpyrifos-methyl (European Commission, 2005, 2015): ADI 0.01 mg/kg bw per day, ARfD 0.1 mg/kg bw, AOEL 0.01 mg/kg bw per day

- European Commission, 2015. Review report for the active substance chlorpyrifos-methyl finalised in the Standing Committee on the Food Chain and Animal Health at its meeting on 3 June 2005 in view of the inclusion of chlorpyrifos-methyl in Annex I of Directive 91/414/EEC. SANCO/3061/99 – rev. 2, 20 March 2015.

## NEW ZEALAND – DIETARY BURDENS IGNORED

The New Zealand Environmental Protection Authority (NZEPA) have just released a statement (APP204964):

> 'We'd like feedback on our proposal to ban chlorpyrifos. We're reassessing this insecticide because new information suggests its risks outweigh its benefits.'

Old information suggests chlorpyrifos' risks outweigh its benefits. Thirty years ago, scientists recognised that low-dose chlorpyrifos (CPY) presents the highest risk to the developing brain.

New Zealand's recent decision has nothing to do with recognising risk following domestic efforts to highlight the risk from chlorpyrifos. The NZEPA are simply following the pattern set by other jurisdictions.

The NZEPA's decision is a consequence of 2016-2020 determinations by the USEPA and 2019 determinations by the European Commission and the European Food Safety Authority, EFSA. The majority of the information considered by USEPA and EFSA was publicly available when NZEPA last considered chlorpyrifos, in 2012-2013 (see below).

The NZEPA have never conducted a comprehensive risk assessment of chlorpyrifos or chlorpyrifos-methyl. Residential use has been phased out in New Zealand, but the NZEPA states 'may conceivably be used in similar public amenity spaces. There is potential for dermal exposure where the chlorpyrifos containing substances are applied as a spray rather than via infill drilling. There is particular concern when the application area is accessible to members of the public, including children, who are likely to have moderate to high levels of dermal exposure when using these spaces.'

Public amenity spaces include sports grounds and parks. When broadleaf herbicides are boom-sprayed on these grounds there is generally not a public notice, while localised spraying will be notified. The same may occur if chlorpyrifos is boom-sprayed.

Authorities are not testing to analyse the risk to pregnant women and children who live near chlorpyrifos-sprayed crops, or families who live in urban environments. Nor have the NZEPA or MPI tested to assess dietary burdens despite the long association of CPY risk from these pathways.

There is a plurality of regulatory jurisdictions at play. Some jurisdictions may be considered best practice, such as Europe, they more swiftly ban substances as the evidence accrues, or industry aligned, and elect to pivot to reasoning that resembles industry-based interests. Australia and New Zealand are more like the latter. The USEPA was taking steps to ban chlorpyrifos, until Donald Trump won the U.S. election in 2017. The Centre for Biological Diversity stated:

> Over the past six years, Dow has donated $11 million to congressional campaigns and political action committees, and has spent an additional $75 million lobbying Congress. In January 2017 Dow was one of three companies that donated $1 million to the Trump inauguration. President Trump named Dow Chemical CEO Andrew Liveris as the head of the American Manufacturing Council in his administration. Liveris praised Trump by stating that Trump is making the United States "not a red-tape country, but a red-carpet country for America's businesses."

The U.S. about-turn was a consequence of political influence.

However, countries with large funding pots for scientists to monitor and assess harm from hazardous substances and technologies can also produce data, from laboratory studies and from population-wide epidemiological studies, that provides important information for regulators and can shift regulatory thinking on the safety and risk of hazardous substances.

The European Union sets aside funding for this research, for the benefit of European citizens, and the U.S. grants funding for large epidemiological studies.

Funding for this sort of work is negligible in New Zealand, and there are no established funding mechanisms for long term research. This explains why New Zealand doesn't have scientists who are experts who can speak publicly about environmental toxicity and pollution and risk. The funding grants are not there, these are politically controversial subjects, and most scientists do not wish to be tainted by association, and risk career opportunities.

Neither the NZEPA or the Ministry for Primary Industries, nor ESR have reached out – in our small island nation – to request funding for serum testing to assess exposures from the Ministry for Business, Innovation and Employment, who control science funding. The Centre for Public Health

Research receives small funding parcels, but cannot undertake strategic long-term planning at scale.

NZEPA and MPI operate in a siloed manner. NZEPA strangely claim that they do not assess dietary risk, which makes the NZEPA an outlier in comparison to the USEPA and EFSA.:

> 'Dietary exposure is not under the regulatory remit of the EPA or the HSNO Act. While aspects of a human health assessment undertaken by the US EPA can be used to inform our risk assessment, dietary exposure would not be incorporated into consideration of the risks associated with an approval under the HSNO Act. Any risk concerns associated with exposure to residues in food products which have been treated with chlorpyrifos are regulated under the ACVM Act, as appropriate.'(NZEPA, 2024a, page 29).

Risk assessment cannot be fit for purpose if dietary burdens are not assessed in tandem with worker exposures and exposures from spraying in public areas. New Zealand has never conducted a risk assessment to review the literature on CPY and CPY-M's neurodevelopmental toxicity, despite having large areas of land dedicated to horticultural and arable crops where chlorpyrifos could be used.

The problem of higher residue levels on cereals and the potential to increase exposure levels and promote developmental neurotoxicity must be addressed from an ethics-based, socio-economic and equity perspective. Poorer populations are likely to consume more cereals as a proportion of their diets. Many of the epidemiological studies have involved low-income minority communities, for example, latino communities in North America.

Despite an obligation to Māori to protect health, there is no cross-talk between the NZEPA and the authorities and agencies that could fund and set in motion, the research capacity to assess whether higher levels of cereal intake might be associated with higher urinary metabolites and developmental delays, and the NZEPA are pretending that human health risk assessment is not part of their obligations in law.

NZEPA have in recent years stepped away, or been directed away from conventional obligations. PSGR have observed that the NZEPA have, for example, failed to risk assess fluoride, which is emitted in urban waste streams. Regulators may step away from politically controversial chemicals and activities. In the U.S. a recent judgement following a decision found against the USEPA, involved the judge, in the decision, procedurally going through the USEPA's own risk assessment process, which includes health-based risk assessment, including the consideration of dietary burdens.

The NZEPA's risk assessment framework may have been watered down in recent years, following the publication of a modelling-based Risk Assessment Methodology document, which fails to require the authority to consider the epidemiological literature, take seriously published literature supplied by the public, and fails to provide directions and reasoning for officials to support a precautionary approach when the data is uncertain but potentially demonstrates risk and/or hazard.

NZEPA to have crafted lower order regulations so as to infer that they are not required to assess dietary burdens and human health risk in the context of a formal risk assessment.

The purpose of the Hazardous Substances and New Organisms Act 1996 includes to 'health and safety of people and communities, by preventing or managing the adverse effects of hazardous substances and new organisms', and that the NZEPA must consider public health. Yet somehow the NZEPA does not believe it should undertake a human health assessment from dietary exposures, which may be additive for people operating in environments where they are exposed to hazardous substances, of the hazardous substances it stewards.

The NZEPA mention the ACVM Act. The Agricultural Compounds and Veterinary Medicines Act 1997 mentions risks to public health and the role of preventing or managing risks from agricultural compounds (such as pesticides formulations) but it does not specify that dietary burdens should be analysed.

The NZEPA does not know whether pregnant women, babies and children remain exposed to chlorpyrifos. Their proxy risk-assessments solely revolve around re-entry risk to a sprayed agricultural crop. The risk that arises from the persistence and toxicity of CPY metabolites in the body 3,5,6-trichloro-2-pyridinol (TCP) and chlorpyrifos-oxon (CPO), has been ignored by regulatory authorities.

PSGR suspects that the major route of exposure in New Zealanders arises from dietary burdens from Australia – because chlorpyrifos-methyl (CAS no 5598-13-0, European Community No. 227-011-5) is a common fumigant in cereals, particularly wheat, and our North Island wheat is shipped in from Australia. But NZEPA's proxy risk-assessment has chosen not to include this risk.

Strikingly, the epidemiological studies considered by the USEPA and EFSA show that risk is not limited to exposures to agricultural communities, and workers. Urban populations an association between CPY and reduced birth weight and birth length was identified – in urban populations.

For NZEPA to 'protect' – NZEPA must not pretend that dietary burdens are outside its scope.

Writing in 2017 of the Trump administrations reneging on a promise to ban chlorpyrifos, Professor Leonardo Trasande noted that the CPY case study was 'emblematic of a broader dismissal of scientific evidence and attacks on scientific norms.' Trasande (2017) went on to state:

> 'Let us for a moment assume that there are no alternatives to chlorpyrifos and that it is needed to sustain the global food supply. At the very least, there are serious tradeoffs to consider in such a decision: is keeping children well fed worth their being less smart and able to contribute to the future of the global economy?'

PSGR's comments in response to a 2019 consultation demonstrate how the NZEPA documents and decisions reflect the decisions made in weaker jurisdictions, while ignoring decisions taken in Europe where standards are consistently safer.

When one regulator has the political will to look more deeply into data that they previously ignored or dismissed, it can set off a domino effect. It's not a scientific decision – but a social and political decision. The incremental change of not conducting formal, process-based toxicological and epidemiological risk assessments which may then be debated and discussed, of failing to engage with outside experts, have resulted in a regulatory drift, a movement away from normative socio-regulatory convention – and public law conventions. The erosion of due process often remains unrecognised by the courts, and by civil society.

There is a double movement – at the same time, the authorities do not update their own rules and guidelines to incorporate new knowledge on risk (such as the toxicity of the full formulation), and new technologies (for example, that may show risk biomarkers) that may demonstrate risk into their own guidelines.

## GLOSSARY AND ABBREVIATIONS

**AChE acetylcholinesterase:** A cholinergic enzyme primarily found at postsynaptic neuromuscular junctions, especially in muscles and nerves. This enzyme catalyzes the breakdown of key neurotransmitter acetylcholine and some other choline esters that function as neurotransmitters. Higher concentration of acetylcholine can become toxic to the cell.

With no breakdown enzyme, acetylcholine can accumulate in the synapses and neuromuscular joints (nicotinic and muscarinic toxicity). Symptoms include increased salivation, cramps, diarrhea, blurry vision, paralysis, and muscle twitches. Too much acetylcholine may prompt a cholinergic crisis.

**ADI** acceptable daily intake

**AOEL** acceptable operator exposure level

**Bw/day** body weight per day, as in a dose of miligrams per kilogram body weight per day.

**CCCEH** Columbia Center for Children's Environmental Health

**CHAMACOS** Center for the Health Assessment of Mothers and Children of Salinas

**Cholinesterases** Group of enzymes that hydrolise esters of choline. AChE is a well-known example.

**CNS** central nervous system

**DNT** developmental neurotoxicity

**JMPR** Joint Meeting on Pesticides Residues. Expert ad hoc body administered jointly by FAO and WHO in the purpose of harmonizing the requirement and the risk assessment on the pesticide residues, and provides independent scientific expert advice to the Codex Alimentarius Commission (CAC) and its specialist Committee on Pesticide Residues as well as to FAO, WHO and member countries.

**LOAEL** lowest observable adverse effect level

**NOAEL** no observed adverse effect level

**OECD** Organisation for Economic Co-operation and Development

**OP** organophosphate

**PND** post-natal day

**PoD** point of departure

**Mg/kg** Milligrams per kilogram, equivalent to 1 part per million.

**PPR** panel EFSA's Panel on Plant Protection Products and their Residues

**RAR** Renewal Assessment Report

**RBC** red blood cells

**RMS** rapporteur Member State

**US EPA** United States Environmental Protection Agency

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# APPENDIX

## [I] STUDIES WHICH UPHOLD THE AUSTRALIAN ADI

**Acceptable daily intakes (ADI) for agricultural and veterinary chemicals used in food producing crops or animals Edition 3/2024 Current as of 30 September 2024**. (Page 34)

https://www.apvma.gov.au/sites/default/files/2024-10/Acceptable%20daily%20intakes%20%28ADI%29%20for%20agricultural%20and%20veterinary%20chemicals%20%E2%80%93%20Edition%203%2C%20September%202024.pdf

| | | | | | |
|---|---|---|---|---|---|
| Chlorpyrifos | 0.001 | 0.1 | June 2019 | Based on the no observed effect level for inhibition of blood cholinesterases in rats following repeated daily exposure from post-natal day 11 to adulthood. | Selected points of departure is protective against inhibition of brain cholinesterases and other known effects of chlorpyrifos.(APVMA Reconsideration of chlorpyrifos - Toxicology update - June 2019) |
| Chlorpyrifos-methyl | 0.001 | 0.4 | 13 July 2023 | 78-week oral carcinogenicity and toxicology study in mice; a NOEL of 0.4 mg/kg bw/d was based on the inhibition of erythrocyte cholinesterase and brain | A total uncertainty factor of 300 was applied (10 for interspecies, 10 for intraspecies and 3 for database deficiencies due to a lack of neurotoxicity and developmental neurotoxicity studies). |

**CHLORPYRIFOS**

**Chlorpyrifos Final Review Technical Report September 2024**. (Page 15)

https://www.apvma.gov.au/sites/default/files/2024-10/Chlorpyrifos%20Final%20Review%20Technical%20Report.pdf



| Reference | Study type | No observed adverse effect level (NOAEL) | Comments |
|---|---|---|---|
| Young and Grandjean 1988 | 2 year repeat daily oral (dietary) carcinogenicity study (OECD Test Guideline No. 451) in F344 rats | 0.1 mg/kg bw/day based on inhibition of erythrocyte and plasma cholinesterases at higher doses | NOEL for inhibition of brain cholinesterase was 1 mg/kg bw/day based on consistent, statistically significant ($p < 0.05$) inhibition at 10 mg/kg bw/day |
| Breslin et al 1991 | 2 generation reproductive toxicity study in SD rats | 0.1 mg/kg bw/d based on inhibition of blood cholinesterases at higher doses | NOAEL for inhibition of brain cholinesterase and maternal toxicity was 1 mg/kg bw/day. The NOAEL for developmental effects was 1 mg/kg bw/day, and the NOAEL for effects on fertility and reproductive effects was 5 mg/kg bw/day |

The ADI of 0.001 mg/kg bw/day is based on the NOEL of 0.1 mg/kg bw/day for inhibition of blood cholinesterases (blood acetyl- and butyrylcholinesterases) in rats in a repeat oral dose study, with a total intra- and inter-species uncertainty factor of 100 applied.

**Young, J.T. & Grandjean, M. (1988) Chlorpyrifos: 2 year dietary chronic toxicity-oncogenicity study in Fischer 344 rats. Unpublished report No. K-044793-079 from Lake Jackson Research Center, Dow Chemical Co., Freeport, Texas, USA. Submitted to WHO by Dow AgroSciences, Indianapolis, Indiana, USA.**

https://www.inchem.org/documents/jmpr/jmpmono/v99pr03.htm

In a study conducted in compliance with GLP standards, groups of 60 Fischer 344 rats of each sex received diets containing chlorpyrifos (purity, 98.5%) at concentrations that provided doses of 0 (control), 0.05, 0.1, 1, or 10 mg/kg bw per day for 24 months. Ten rats of each sex at each dose were randomly designated at the start of the study for interim sacrifice at 12 months. Blood was collected for haematology, clinical chemistry, and measurement of plasma and erythrocyte cholinesterase activity at 6, 12, and 18 months as well as at the 24-month terminal sacrifice. The groups were observed daily for deaths and signs of toxicity. All rats were examined clinically at least once a week from after the sixth month. All animals were palpated for externally detectable masses before treatment, before the 12-month kill, and monthly thereafter. Body weights and feed consumption were determined weekly for the first 3 months and monthly thereafter. All rats were weighed, but feed consumption was determined for only 20 rats of each sex per group.

All clinical laboratory procedures scheduled for 6 and 12 months were performed on rats designated for the 12-month interim kill, whereas tests scheduled for 18 and 24 months were performed on rats designated for terminal sacrifice. Blood samples were obtained for haematology and clinical chemistry by orbital sinus puncture under

Table 8. Group mean percent inhibition of cholinesterase activity in comparison with vehicle controls in rats given diets containing chlorpyrifos

| Assay time (weeks) | Dose (ppm) | Cholinesterase inhibition (%) | | | | | |
|---|---|---|---|---|---|---|---|
| | | Plasma | | Erythrocytes | | Brain | |
| | | Male | Female | Male | Female | Male | Female |
| 50 | 0 | 0 | 7 | 0* | 31 | 0 | 35 |
| | 0.2 | 1 | 4 | 0 | 42 | 0 | 14 |
| | 5 | 15 | 51 | 0* | 39 | 9 | 10 |
| | 100 | 93 | 98 | 13 | 45 | 57* | 80* |
| 78 | 0 | 0 | 3 | 27 | 0 | | |
| | 0.2 | 4 | 3 | 11 | 0 | | |
| | 5 | 28* | 47* | 0 | 0 | | |
| | 100 | 93* | 97* | 10 | 0 | | |
| 104 | 0 | 8 | 9 | 0 | 0 | 18 | 4 |
| | 0.2 | 13 | 0 | 0 | 0 | 0 | 0 |
| | 5 | 36 | 37* | 17 | 11 | 0 | 0 |
| | 100 | 95* | 96* | 34 | 18 | 58* | 61* |

Values the same as or higher than those of the vehicle control are recorded as 0 inhibition.
* Significantly different from control at $p < 0.01$ or $p < 0.001$

light anaesthesia. The haematological determinations consisted of packed cell volume, haemoglobin concentration, erythrocyte count, total and differential leukocyte counts, and platelet count. The clinical biochemical determinations included blood urea nitrogen, alkaline phosphatase and alanine and aspartate aminotransferase activities, glucose, total protein, albumin, globulin (calculated), creatine phosphokinase, total bilirubin, cholesterol, calcium, phosphorus, sodium, potassium, and chloride. Urine samples were obtained 1-2 weeks before the scheduled sacrifices at 12 and 24 months and at 6 and 18 months from 10 rats of each sex per group. The urinary parameters measured included specific gravity and semi-quantitative estimates of bilirubin, glucose, ketones, occult blood, pH, protein, and urobilinogen. Microscopy of a pooled sample was also conducted.

Plasma and erythrocyte cholinesterase activities were assayed in 10 rats of each sex per group at 6, 12, 18, and 24 months, and acetylcholinesterase activity was measured in half-brain samples obtained at the 12-month and 24-month scheduled necropsies. All animals killed at the interim and terminal sacrifices or which died or were killed when moribund were necropsied and subjected to a complete gross examination. The brain, liver, kidneys, testes, ovaries, and adrenal glands were weighed, and many organs and tissues were removed and preserved in neutral, phosphate-buffered 10% formalin for subsequent histopathological evaluation. Histological sections of the formalin-fixed tissues from all controls and those at the highest dose were prepared, stained with haematoxylin and eosin and examined microscopically. Histopathological examination of tissues from animals at the three lower doses was limited to the liver, kidneys, adrenals, and tissues with gross lesions at both sacrifices. At terminal sacrifice, the lungs, spleen, testes, pituitary, and thyroid/parathyroid were also examined microscopically. Appropriate statistical tests were applied to the data.

Males at the high dose showed a consistent decrease in body-weight gain relative to controls in the absence of reduced food consumption, depression of plasma (56-87%), erythrocyte (20-40%) and brain (56-58%) cholinesterase activities, and an increase in the weight of their adrenal glands which was characterized microscopically by exacerbated fatty vacuolation of the zona fasciculata.

Similar effects were observed in females at this dose, but were generally less pronounced than in males: for example, a transient decrease in body-weight gain relative to controls with no reduction in food consumption, depression of plasma (82-95%), erythrocyte (generally $\geq$ 20%), and brain (57-61%) cholinesterase activities, and an increase in adrenal weight at the terminal sacrifice with no associated histopathological lesions. At 1 mg/kg bw per day, the only effects attributable to treatment were inhibition of plasma cholinesterase activity (39-71% in males and 60-86% in females) and erythrocyte cholinesterase activity (20-40% in males and $\leq$ 22% in females); brain cholinesterase activity was not affected. These results are summarized in Table 9. No treatment-related effects were observed at the two lower doses. There was no increase in the incidence of any type of tumour.

The NOAEL for inhibition of erythrocyte cholinesterase activity was 0.1 mg/kg bw per day, on the basis of toxicologically (> 20%) or statistically significant inhibition at 1 mg/kg bw per day, and the NOAEL for inhibition of brain cholinesterase activity was 1 mg/kg bw per day on the basis of toxicologically and statistically significant inhibition at 10 mg/kg bw per day (Young & Grandjean, 1988).

**Breslin, W.J., Liberacki, A.B., Dittenber, D.A., Brzak, K.A. & Quast, J.F. (1991) Chlorpyrifos: Two-generation dietary reproduction study in Sprague-Dawley rats. Unpublished report No. K-044793-088 from the Toxicology Research Laboratory, Dow Chemical Co., Midland, Michigan, USA. Submitted to WHO by Dow AgroSciences, Indianapolis, Indiana, USA.**

https://www.inchem.org/documents/jmpr/jmpmono/v99pr03.htm

Four groups of Sprague-Dawley rats were used in a two-generation (one litter per generation) study of reproductive toxicity in which diets containing chlorpyrifos (purity, 97.8-98.5%) at doses of 0, 0.1, 1, or 5 mg/kg bw per day were administered. The study was conducted in accordance with FIFRA guideline 83-4, OECD guideline 416, and GLP principles. The $F_0$ parental animals (30 of each sex per dose) were

Table 11. Statistically significant differences in group data for litters of the $F_0$ generation of rats given diets containing chlorpyrifos

| Time | Litter parameter | Dose (ppm) | | | |
|---|---|---|---|---|---|
| | | 0 | 2 | 10 | 50 |
| At birth | Litter size, total | 12 | 13 | 14** | 13 |
| | Litter size, live | 12 | 13 | 14** | 13 |
| | Litter weight (g) | 70 | 72 | 79* | 71 |
| | Pup weight (g) | 6.1 | 5.6*** | 5.7** | 5.7* |
| Day 4 | Litter size, live | 11 | 13* | 14*** | 12 |
| | Litter weight (g) | 100 | 110 | 120* | 110 |
| | Mean pup weight (g) | 9.3 | 8.7 | 8.6* | 9.2 |
| Day 8 | Litter size, live | 11 | 13** | 13*** | 12 |
| | Mean pup weight (g) | 15 | 14* | 14* | 15 |
| Day 12 | Litter size, live | 11 | 13** | 13*** | 12 |
| | Litter weight (g) | 240 | 270 | 280** | 250 |
| | Mean pup weight (g) | 22 | 21 | 21* | 22 |
| Day 21 | Litter size, live | 11 | 13* | 13*** | 12 |
| | Litter weight (g) | 460 | 520 | 530* | 480 |
| | Mean pup weight (g) | 44 | 42 | 40* | 42 |

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

6 weeks of age at the beginning of the study and were mated after 10 weeks of exposure to produce the F1 litters. Groups of 30 rats of each sex per dose were selected from the F1 weanlings and were treated for 12 weeks before breeding to produce the F2 litters.

Pairing in both generations allowed for three periods of 7 days' cohabitation in a 1:1 ratio, the males being changed weekly. Care was taken to avoid sibling pairings. Females were removed from pairing when vaginal lavage showed sperm, and this was considered to be day 0 of gestation.

The F1 and F2 litters were culled if appropriate to a total of eight pups on day 4. Clinical observations were performed daily on all animals; litter size at birth, the numbers of live and dead pups on days 0, 1, 4, 7, 14, and 21 post partum, and the sex and weight of each pup were recorded on days 1, 4, 7, 14, and 21 of lactation. Body weights and food consumption were recorded weekly Before and after breeding. The body weights of dams were recorded on days 0, 7, 14, and 21 of gestation and on days 1, 4, 7, 14, and 21 of lactation, whereas food consumption was recorded once during the first week of lactation, twice during the second week, and every 2-3 days during the third week. Inhibition of cholinesterase activity in plasma, erythrocytes, and brain was measured in 10 F0 and F1 parental animals of each sex at necropsy after 19 and 21 weeks of exposure. Complete necropsies were conducted on all F0 and F1 adults, and included ocular examinations and collection of many tissues. Histopathological examinations were made of the adrenals, brain, gross lesions, and reproductive tissues (cervix, coagulating glands, epididymides, ovaries, oviducts, pituitary, prostate, seminal vesicles, testes, uterus, and vagina) of controls and animals at the high dose. The livers of 10 F1 parental males in the control and high-dose groups were also examined microscopically. Only the adrenals from animals at the intermediate and low doses were examined. Ten F1 and F2 pups of each sex per dose were autopsied grossly. Appropriate statistical tests were applied to all data.

No significant effects of treatment were seen on clinical signs, food intake, or body weight. A slight but not statistically significant decrease in body weight was seen in F1 males at 5 mg/kg bw per day, and F1 females at this dose showed reduced body-weight gain during lactation. Plasma cholinesterase activity was inhibited in parental F0 and F1 rats of each sex at 1 mg/kg bw per day (40-57%) and at 5 mg/kg bw per day (< 72%). Plasma cholinesterase activity was also inhibited in animals of both generations at 0.1 mg/kg bw per day as part of a dose-related trend, although the inhibition was generally not statistically significant at this dose. Erythrocyte cholinesterase activity was strongly inhibited at 1 and 5 mg/kg bw per day, but that of brain was inhibited only at 5 mg/kg bw per day (Table 12).

Gross observation of F0 and F1 parents revealed no significant alterations, and the only significant histopathological change in the parental animals was vacuolation consistent with fatty changes in the adrenal zone fasciculata. Treatment had no effect on fertility, length of gestation, survival during gestation, time to mating, sex ratio, or litter size in either generation. F1 pups at 1 mg/kg bw per day showed slightly decreased body-weight gain during lactation and statistically significantly decreased body-weight gain and survival at 5 mg/kg bw per day. No effect of treatment was seen during gross or daily observation of the F1 weanlings.

F2 pups did not show dose-related decreases in body-weight gain during lactation, but the survival of pups at 0 and 5 mg/kg bw per day was decreased, with total loss of three and five litters, respectively; this effect was stated to be due to maternal neglect, since the stomachs of pups in these litters contained no milk. No effect of treatment was seen during gross or daily observation of the F2 weanlings. The NOAEL for inhibition of erythrocyte cholinesterase in adults was 0.1 mg/kg bw per day and that for inhibition of brain cholinesterase activity and maternal toxicity was 1 mg/kg bw per day. The NOAEL for developmental effects was 1 mg/kg bw per day, and the NOAEL for effects on fertility and reproductive effects was 5 mg/kg bw per day (Breslin et al., 1991).

Table 12. Mean cholinesterase activity in $F_0$ and $F_1$ parent rats at necropsy (percentage inhibition compared with controls)

| Generation | Dose (mg/kg bw per day) | Cholinesterase activity (% inhibition) | | | | | |
|---|---|---|---|---|---|---|---|
| | | Plasma (IU/ml) | | Erythrocytes (IU/ml) | | Brain (IU/g) | |
| | | Male | Female | Male | Female | Male | Female |
| $F_0$ | 0 | 0.54 | 2.0 | 1.1 | 1.0 | 9.3 | 9.0 |
| | 0.1 | 0.46 (15%) | 1.6 (20%) | 1.0 (5%) | 1.0 | 9.2 (1%) | 9.1 |
| | 1 | 0.30[a] (44%) | 0.8[a] (59%) | 0.3[b] (92%) | 0.36[b] (65%) | 8.8 (6%) | 8.7 (3%) |
| | 5 | 0.21[a] (61%) | 0.6[a] (67%) | 0.3[b] (92%) | 0.31[b] (70%) | 4.9[b] (48%) | 4.6[a] (49%) |
| $F_1$ | 0 | 0.53 | 1.8 | 1.1 | 0.96 | 9.7 | 9.4 |
| | 0.1 | 0.43 (19%) | 1.6 (15%) | 0.98[a] (13%) | 0.97 | 9.7 | 9.2 (2.5%) |
| | 1 | 0.30[a] (43%) | 0.93[a] (52%) | 0.37[a] (67%) | 0.32[b] (67%) | 9.4 (3%) | 9.0 (4.5%) |
| | 5 | 0.19[a] (64%) | 0.52[a] (72%) | 0.33[a] (70%) | 0.24[b] (75%) | 4.6[a] (52%) | 4.0[b] (58%) |

[a] Statistically significantly different from control mean by Wilcoxon's test
[b] Statistically significantly different from control mean by Dunnett's test

## [II] STUDIES SHOWING HARM TO THE BRAIN & PRIMARY METABOLITE OF CPY & CPY-M

### HARM TO BRAIN – TWENTY YEARS OLD

Animal models have demonstrated that chlorpyrifos is toxic to both glia and neurons, and the data on this is twenty years old.

- Garcia SJ, Seidler FJ, Qiao D, Slotkin TA (2002) Chlorpyrifos targets developing glia: Effects on glial fibrillary acidic protein. Brain Res Dev Brain Res 133:151–161
- Garcia SJ, Seidler FJ, Crumpton TL, Slotkin TA (2001) Does the developmental neurotoxicity of chlorpyrifos involve glial targets? Macromolecule synthesis, adenylyl cyclase signaling, nuclear transcription factors, and formation of reactive oxygen in C6 glioma cells. Brain Res 891:54–68
- Perera FP, Rauh V, Tsai WY, Kinney P et al (2003) Effects of Transplacental Exposure to Environmental Pollutants on Birth Outcomes in a Multiethnic Population. Environmental Health Perspectives 111;2:201-205
- Roy TS, Seidler FJ, Slotkin TA (2004) Morphologic effects of subtoxic neonatal chlorpyrifos exposure in developing rat brain: regionally selective alterations in neurons and glia. Brain Res Dev Brain Res 148:197–206.
- Roy TS, Sharma V, Seidler FJ, Slotkin TA (2005) Quantitative morphological assessment reveals neuronal and glial deficits in hippocampus after a brief subtoxic exposure to chlorpyrifos in neonatal rats. Brain Res Dev Brain Res 155:71–80. 20.

**PRIMARY METABOLITE OF CPY & CYP-M**

Many epidemiological studies have explored the relationship of the common metabolite 3,5,6-trichloro-2-pyridinol with adverse neurodevelopmental outcomes, including the CHAMACOS study.


- Castorina R, Bradman A, Fenster L, Barr DB, Bravo R, Vedar MG, Harnly ME, McKone TE, Eisen EA and Eskenazi B, 2010. Comparison of current-use pesticide and other toxicant urinary metabolite levels among pregnant women in the CHAMACOS cohort and NHANES. Environmental Health Perspectives, 118, 856–863.
- Fortenberry G Z et al (2014) Urinary 3,5,6-trichloro-2-pyridinol (TCPY) in pregnant women from Mexico City: Distribution, temporal variability, and relationship with child attention and hyperactivity. International Journal of Hygiene and Environmental Health. 217; 2–3:405-412
- Guo J et al (2019) Associations of prenatal and childhood chlorpyrifos exposure with Neurodevelopment of 3-year-old children. Environmental Pollution 251:538-546 https://doi.org/10.1016/j.envpol.2019.05.040. 'Our findings suggest that adverse neurodevelopmental effects were associated with early childhood CPF exposure, but not prenatal exposure.'
- Koch H M et al (2001) Biological monitoring of exposure of the general population to the organophosphorus pesticides chlorpyrifos and chlorpyrifos-methyl by determination of their specific metabolite 3,5,6-trichloro-2-pyridinol. International Journal of Hygiene and Environmental Health. 204, 2–3:175-180
- Marks AR, Harley K, Bradman A, Kogut K, Barr DB, Johnson C, Calderon N and Eskenazi B, 2010. Organophosphate pesticide exposure and attention in young Mexican-American children: the CHAMACOS Study. Environmental Health Perspectives, 118, 1768–1774.