



## Limitations of the Columbia University Study of Birth Weight and Childhood Development

### Introduction

Researchers at Columbia University reported that exposure to chlorpyrifos prior to birth can be linked to decreased body length and weight at birth and to later childhood developmental issues. The study measured exposure to chlorpyrifos in terms of its presence in umbilical cord blood at birth. No samples were taken at gestational periods that would have the greatest developmental interest.<sup>2,3</sup>

These researchers also reported that the children that they classified as having had relatively “high” exposures to chlorpyrifos, based on a one-time measurement of umbilical cord blood at birth, had greater problems with attention and increased potential for attention deficit/ hyperactivity disorder at age three. These children also scored lower on standardized tests designed to measure psychomotor and mental development.

Chlorpyrifos opponents have used this study to fuel arguments against the use and re-registration of chlorpyrifos.

At face value, the Columbia University research raises serious questions, and further research into this area will most certainly be conducted. There are compelling reasons, however, why the reported outcomes of these papers are not likely to have been caused by chlorpyrifos:

- Inconsistency with other similar studies
- Exposures reported are well below the no effect level in numerous other studies.
- Exposure was only estimated at one point in time.
- Internal evidence within the research raises concerns about the validity of the reported findings.
- The weight of the evidence from other studies does not support claims of risks to child development from authorized uses of chlorpyrifos.

### Inconsistency with similar studies

Researchers at Mount Sinai Hospital and the University of California at Berkeley conducted similar research on developmental effects and prenatal exposures to chlorpyrifos. But the results of their research are inconsistent with the findings of the Columbia University researchers. (See tables below.) Taken together, the findings from these three groups of researchers do not show a clear link between chlorpyrifos exposure and child health.

The reported outcomes of these evaluations are summarized as follows:

INCREASING MEASURE OF CHLORPYRIFOS EXPOSURE RESULTS			
	Head Size	Body Weight	Body Length
<b>Columbia University</b>	No Effect	Decreased	Decreased
<b>Mount Sinai Hospital</b>	No Effect	No Effect*	No Effect
<b>University of California at Berkeley</b>	No Effect	No Effect*	No Effect

*\*Note: By contrast with the findings reported by Columbia University researchers, those from Mount Sinai and Berkeley actually noted a slight (but not statistically significant) increase in birth weight associated with exposures to the chlorpyrifos breakdown product TCPy.<sup>2, 3, 4, 5, 6</sup>*

INCREASING MEASURE OF CHLORPYRIFOS EXPOSURE RESULTS		
	Psychomotor Development	Mental Development
<b>Columbia University</b>	Decreased test scores	Decreased test scores
<b>University of California at Berkeley</b>	No Chlorpyrifos-Specific Effect	No Chlorpyrifos-Specific Effect
<b>Mount Sinai Hospital**</b>	Chlorpyrifos-Specific Exposures Not Evaluated	N/A

*\*\*Note: Mount Sinai did not evaluate chlorpyrifos-specific measurements of exposure in assessing neurological development. 2, 3, 4, 5, 6*

## Exposure Level Disparities

For children born in 1999, Mount Sinai researchers reported links between levels of chlorpyrifos in umbilical cord blood and reduced body weight, reduced body length and, when the children reached three years of age, reduced scores on various standardized psychological tests.

If the effects reported by Columbia University researchers were actually caused by chlorpyrifos, they would have to be caused at a level of exposure more than 4,000 times below the dose shown to cause no effect in rats, the most sensitive species of laboratory animal. (See table below.) For a product that has been extensively studied throughout the 40-year history of its use, newly reported effects at doses this low would seem to be highly unlikely.

For a product that has been extensively studied over the 40-year history of its use, newly reported effects at doses this low seem highly implausible.

DOSE-RESPONSE: CHRONIC EXPOSURE TO CHLORPYRIFOS	
Outcome	Dose (ng/kg/BW)
Lowest Observed Effect Level (LOEL): Nonadverse Change in Blood Enzymes (ChE inhibition) - Rat	100,000 <sup>8</sup>
No Observed Effect Level (NOEL): No Effect - Rat	30,000 <sup>8</sup>
EPA Safety Factor	1,000
EPA's Maximum Allowable Chronic Exposure - Human	30
Dose at Which Columbia University Researchers Have Reported Effects – Human	7

As demonstrated by the table above, the chronic dose at which no effect was found from exposure to chlorpyrifos in laboratory rats was 30,000 ng/kg/BW (nanograms per kilogram of body weight) per day. By contrast, the Columbia University researchers reported that the median level of chlorpyrifos exposure in umbilical cord blood in 1999 when these associations reportedly occurred was 6.9 picograms (pg) per gram<sup>7</sup>, which, assuming for the moment that the exposure was uniform and constant over time, would be the equivalent of 6.9 ng/kg/BW.

Is it possible that effects such as those reported in the Mount Sinai research actually occurred in prior animal work but were not detected? For the physical measurements (body weight and body length), this is highly unlikely. In numerous guideline laboratory studies, offspring of several animal species exposed during fetal development had measurements taken of their at-birth body weight, body length and other parameters. No effects on these parameters were noted at doses less than 30,000 ng/kg/BW per day.

In terms of neurological development, obviously no direct comparison can be made between laboratory tests of animal response following exposure to chlorpyrifos versus the performance of children on standardized psychological tests. But it should be noted that in prior animal research based on EPA accepted protocols no exposure-related effect was found with chlorpyrifos on measured behavioral parameters (including tests of motor activity, auditory startle, delayed spatial alteration). Additionally, no exposure-related neuropathology was noted, even at doses high enough to cause significant brain cholinesterase inhibition (5,000,000 ng/kg/BW per day).

The enormous discrepancy between the Columbia University findings and those of extensive prior animal research raises serious questions of interpretation. Internal evidence within the Columbia University studies also raises concerns about the validity of their reported findings:

	Animal Research <sup>8</sup>	Columbia University Research
<b>Body weight &amp; Length</b>	No effect found at oral dose of <b>30,000 ng/kg BW/day</b>	Effect reported at <b>7 ng/kg</b> in umbilical cord blood.
<b>Neurological Development</b>	No effect found at oral dose of <b>5,000,000 ng/kgBW/day</b>	Effect reported at <b>7 ng/kg</b> in umbilical cord blood.

## Exposure was Only Estimated at One Point in Time

The authors estimated the exposures that these children had to chlorpyrifos based on levels detected in umbilical cord blood at birth. They then assumed that these levels were similar for each child prenatally. Since the samples were taken from the children at birth, however, the levels of chlorpyrifos detected would not necessarily reveal the extent of their exposures throughout their prenatal period.

## Internal Evidence of Problems with Earlier Columbia University Findings

Given that the findings of the Columbia University researchers are inconsistent with the findings of other, similar human research and that they are in direct conflict with what is known about dose-response from extensive animal research, it is worth evaluating whether the design and execution of these studies may have unintentionally skewed their results. There are many reasons to believe that this may have been the case.

*Exposures Too Low for Accurate Measurement:* Based on the analytical method used, the researchers would have had difficulty accurately categorizing children by their exposures because most of the levels of chlorpyrifos detected in umbilical cord blood were below levels that the test could accurately measure.

*Problems with Dose-Response:* Even assuming that the Columbia University researchers were able to accurately classify the children according to their exposures, the researchers found that children with low exposure to chlorpyrifos had better developmental testing scores than children with no exposure. Reduced scores on developmental tests were only found when children with reportedly “high” exposures were compared with the new, combined group of low and undetectable exposure.

*Inconsistent Trends on Test Scores:* According to Columbia University researchers, children born in 1999 when chlorpyrifos was still authorized in the U.S. for in-home use performed more poorly at age three on standardized developmental tests than three-year-old children born in 2000, when chlorpyrifos was being phased out of residential use in the United States. On its face, this might seem like a fairly convincing demonstration that the reductions in test performance were caused by exposure to chlorpyrifos.

But a closer look at these findings raises significant doubt.

In 2001, the levels of chlorpyrifos detected in umbilical cord blood were even lower than in 2000. If chlorpyrifos exposure was linked with lower test scores, then the children born in 2001 ought to have performed better on these tests than those born the previous year. But in fact, the children born in 2001 (i.e., with lesser exposure) performed worse on the tests than those born in 2000 (i.e., when exposures were higher)<sup>3</sup>.

*Differences in Test Scores Fell within Test/Retest Variation:* Reported differences in performance between the “high” vs. “low” exposure groups fell well within the expected test/retest variability for the standardized tests in question<sup>9</sup>. Consequently, these findings have no clinical meaning.

*Missing Data:* Maternal IQ has been shown to have significant bearing on the IQs of their offspring, and the authors note that the average IQ score for these women was 86. When IQ scores were missing from 29 women in this research, however, the researchers arbitrarily substituted the sample mean for the missing data. And when cord blood data were missing for 12 percent of the subjects, the researchers substituted data from maternal blood. It is impossible to determine to what extent these decisions influenced the researchers’ final conclusions.

*Unique Developmental Challenges Among Children:* Test scores from the research showed that about one-third of all the children in this inner city cohort had cognitive and developmental delays, regardless of whether or not the researchers considered them exposed to chlorpyrifos<sup>3</sup>. This suggests that chlorpyrifos may be masking a yet-to-be-discovered underlying effect (e.g., socio-social factors that may potentially influence children’s performance on standardized tests).

*No Adjustment for Blood Lipids:* Chlorpyrifos binds to blood lipids, and blood lipid levels were not evaluated by the Columbia University research. Increased levels of certain lipids (e.g., elevated LDL cholesterol) have been associated with adverse birth outcomes in prior research, including reduced head circumference, reduced birth weight and reduced ponderal index (similar to body mass index). Women with higher levels of lipids in their blood would be expected to have higher measurable levels of chlorpyrifos as well. Consequently, these findings may be masking some unhealthy lipid levels operating as an underlying cause.

*Polycyclic Aromatic Hydrocarbons:* With one of the cognitive tests (the MDI or Mental Development Index) used by the Columbia University researchers to assess the developmental outcomes of prenatal chlorpyrifos exposure at age three, nearly identical results were seen in another recent epidemiological study, where the deficits were attributed to polycyclic aromatic hydrocarbons. These compounds were apparently not evaluated in the Columbia University research<sup>10</sup>.

The remarkable similarities in age-versus-cognitive-function profiles reported in Rauh et al., 2006<sup>3</sup> versus Perera et al., 2006<sup>10</sup> suggest alternative explanations for the Columbia University research findings, especially since both chlorpyrifos and PAHs bind to blood lipids.

*Other Exposures:* Other reviewers have noted that there appeared to be a higher prevalence of exposure to alcohol and tobacco in the group of women evaluated by the Columbia University research compared to similar research conducted by researchers at Mount Sinai Hospital and the University of California at Berkeley. While researchers did try to control for potential confounding from ethanol intake and second-hand tobacco smoke, other researchers have noted that there were clear limitations in what was possible.<sup>1</sup>

Also not controlled as potential confounders in the Columbia University research was the potential effect of maternal depression, duration of breast feeding, household income, and father's presence in the home.

All in all, serious questions remain about the validity of these findings. They conflict with other research; there are a number of concerns about the way in which the children were categorized as to exposure; there are questions as to the significance of the three- and seven-point differences in test scores; and there is still plausible reason to suppose, given the complex number of factors affecting childhood development, that unreported variables have confounded the results.

## The Weight of Accumulated Evidence

Finally, the weight of accumulated evidence over decades of study does not support claims of chlorpyrifos-related risk to child development. After evaluating thousands of available studies on chlorpyrifos, including those conducted by Columbia University researchers, an international panel of 13 eminent physicians, medical scientists, toxicologists and epidemiologists concluded in an extensive report published in 2008 that *there is no scientific support for a cause-and-effect connection between current levels of chlorpyrifos exposure and adverse human development.*<sup>1</sup>

The scientists who undertook this comprehensive review spent more than six months evaluating scientific databases from around the world, including Chinese biomedical studies that they had translated for this purpose. While the review was sponsored by Dow AgroSciences, the expert panelists were given full control of their research effort, they had no contact or interaction with the sponsor in the analysis of data or formulation of their opinions and conclusions, and they were given, prior to beginning their research, the right to publish their conclusions regardless of what findings they reached.

Access the peer-reviewed report online:

<http://www.informaworld.com/smpp/content~db=all?content=10.1080/10408440802272158>

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