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INTRODUCTION

The CDC definition for lead toxicity has been progressively lowered over the past 50 years to reflect evidence that harm exists at the lowest detectable levels. Despite increased screening and an evolving awareness surrounding lead exposure, the development of treatments and guidelines for exposed patients has slowed dramatically since the early 2000s. Most guidelines recommend against using chelation treatment for BLLs <45 µg/dL, yet the current reference level is 3.5 µg/dL, leaving a substantial treatment gap for patients with BLLs between 3.5 and 45 µg/dL.

The treatment guidelines rely on findings from the Treatment of Lead-Exposed Children (TLC) randomized controlled trial. The TLC trial studied the effects of succimer (DMSA) chelation on IQ in children with BLLs 20-44 µg/dL. The investigators showed that although DMSA lowered BLLs short-term, this effect was not sustained, and no cognitive benefit was detected after 3 years.

The investigators concluded that chelation therapy was not indicated for children with BLLs <45 µg/dL and suggested that further efforts should shift towards primary prevention and away from finding and treating patients. In the years that followed, these suggestions were fundamental in shaping U.S. environmental health policy, redirecting responsibilities away from treatment by physicians and towards housing and environmental efforts by federal agencies.

While this shift has been beneficial in some ways, efforts have largely failed at preventing children from being exposed to lead hazards. As a result, many children continue to be exposed to lead and are left without medical options. Finding and treating children who have been exposed to lead is necessary until lead hazards have been fully addressed.

TLC was conducted prior to widespread adherence to CONSORT and ICMJE standards. Given its continued influence on treatment guidelines, and the fact that key investigators of the TLC also subsequently served in key committee positions responsible for incorporating evidence from the TLC trial into policy, believed a re-examination of the TLC trial was warranted. We re-examined the trial's background, methodology, limitations and impact on shaping current U.S. environmental health policy and clinical treatment guidelines over the last twenty-five years.

We found the following limitations:

Environmental Exposure Uncontrolled. Most notably, the trial failed to prevent ongoing environmental exposure in participants. Chelating children while they continue to be exposed to lead has always been contraindicated. TLC provided a home cleaning pre-randomization but lead dust levels remained above federal standards. The house cleaning was designed to suppress lead dust in children's homes for roughly six months during therapy. The primary principle behind chelation, and lead interventions in general, is removing long-term sources of exposure. It's ironic that the trial has been used to steer policy away from medical treatment and towards primary prevention, when it failed to prevent ongoing exposure in its own participants.

Mineral Status Unmonitored. The TLC children were at high baseline risk for mineral deficiency given that most of them lived in poverty. The treatment group was at greater risk of depletion due to succimer's ability to chelate other minerals during treatment. To address this possibility, children were given multivitamins prophylactically but were not monitored for mineral deficiency beyond ferritin values at randomization. This lack of monitoring introduced the potential for effect modification and confounding on the primary neurodevelopmental and secondary growth outcomes. While succimer is less likely than EDTA to cause mineral depletion, the preclinical trials that showed this were done over 5-day courses, not 26 days. It's plausible that zinc, iron, or copper deficiency may have played a role in the reduced linear growth noted in the treatment group. Identifying and addressing mineral deficiencies, if present, is generally always included in a comprehensive treatment plan when treating children with lead exposure.

Limitations

Ferritin Reporting. The trial measured baseline ferritin in its participants but did not report baseline ferritin status of randomized groups among lab values in all but one publication—describing the effect of chelation on growth—published in 2006. In that instance, they reported ferritin as the arithmetic mean. To explain their handling of mineral status (iron in particular) they published a paper which included analysis on a convenience sample of enrolled (but not necessarily randomized) participants, comparing arithmetic mean ferritin with that of NHANES III subjects. They concluded that TLC children with high BLLs had no difference in iron status compared to NHANES III children with lower BLLs, and thus, there was no need to treat or test for iron deficiency with BLLs 20-44 µg/dL.

Arithmetic vs. Geometric Mean Ferritin. Using the arithmetic mean value for ferritin distribution is generally not the best measure of central tendency for skewed distributions. Ferritin, especially in children, is characteristically right skewed and should be analyzed by geometric mean as the best measure of central tendency. Our analyses of NHANES 1998-2002 revealed an arithmetic mean of 28.14 ng/mL for children ages 1-5 across all races, and a median of 22 ng/mL—leaving half of all children in a range considered physiologically deficient (~20 ng/mL). Ferritin analyses should be adjusted with CRP values, since inflammation can increase ferritin levels even in iron deficient states. The analyses we performed are consistent with TLC's, showing little difference in ferritin among different BLL quartiles. However, our interpretation differs in that we believe on average most children are at risk of iron deficiency. Iron deficiency increases lead exposure and absorption, so all children who are at risk of exposure should be screened (using CRP & ferritin) and treated for iron deficiency.

Limitations

Lead-Contaminated Vitamins. Toward the end of the trial, a batch of multivitamins given to participants was found to be contaminated with lead, with 628 of 780 participants potentially exposed. The recall was discussed separately, noting that adherence was variable; of the exposed, 571 were analyzed for BLLs to assess the incident. The authors note that 149 siblings were also exposed, and all but one trial site encouraged sharing of multivitamins with siblings and family. Their interpretation was that no dose-response effect was found, so nothing more was done. The primary NEJM publication mentions the incident in one sentence, citing the ancillary article; the five-year follow-up does not mention it. While the incident likely had little effect on the primary outcome, the lack of rigor and candor in reporting and analysis raises questions about overall trial conduct.

Treatment Endpoint and Power. Our opinion contrasts with the TLC's interpretation that another treatment protocol would unlikely yield different results. The treatment endpoint of 15 µg/dL was insufficient given current understanding of relationships between IQ and BLL. Chelating to lower levels, ideally less than 10 µg/dL, would have been much more likely to result in a detectable IQ increase.

Post-treatment Protocol Changes.

Reporting Issues

Ethical Concerns

BACKGROUND – Chelation therapy

1990—Clinical guidance regarding the management of lead-exposed children was largely based on guidance from the CDC (1985) and the American Academy of Pediatrics (1987). These statements recommended initiating chelation therapy in children with BLLs >55 µg/dL and clinical discretion between 25 and 55 µg/dL—a range which directly reflected the CDC's definition of an elevated BLL (≥25 µg/dL). However, by 1990, new research showed IQ loss occurred as low as 10 µg/dL, raising concerns among clinicians as to whether the current recommended thresholds for intervention were sufficiently protective.

Another controversial recommendation was that prior to chelating children with BLLs below 55 µg/dL, clinicians should use EDTA provocation tests—in which a single intravenous (IV) dose of chelator is followed by urinary lead measurement to estimate 'chelatable lead'. Despite their widespread use, these tests had limited diagnostic value, and animal studies suggested single EDTA doses might paradoxically increase brain lead concentrations, intensifying safety concerns and confusion among clinicians.

The three primary pharmacological agents in use at the time included dimercaprol (BAL)—administered via a painful intramuscular injection in peanut oil solution; calcium disodium EDTA–administered by IV; and D-penicillamine—an orally administered off-label drug approved for Wilson Disease but found to be somewhat effective at increasing urinary lead excretion. Each of the drugs in use carried unique risks, which were gradually coming to light through emerging studies and clinical experience. The 1985 CDC statement identified succimer (DMSA; dimercaptosuccinic acid) as a promising new, but unapproved, oral chelator.

In light of the disarray and lack of consensus among clinicians, in 1990, the Health Resources and Services Administration funded a national survey to determine current chelation practices being used at U.S. academic hospitals. The survey revealed widespread variability in treatment thresholds at levels as low as 20 µg/dL. Succimer, the oral compound mentioned in the 1985 CDC statement, was utilized by only one clinic participating in a special project as it awaited FDA approval.

Bock Pharma had submitted succimer for orphan drug designation in 1984, under the recently passed Orphan Drug Act (1983), and by 1990 preliminary studies suggested succimer was safer, more effective, and easier to administer than the other chelators in clinical use.

1991–Starting January 1st, 1991, the Medicaid Drug Rebate Program (MDRP) came into effect. This meant that if a manufacturer wanted Medicaid to cover its outpatient drugs, the manufacturer would later "true up" the price by sending Medicaid a rebate check tied to how much Medicaid used the drug. Under the new law, state Medicaid programs were legally required to cover any FDA-approved drug if a manufacturer signed a rebate agreement. Most importantly, the law mandated coverage for all "medically accepted indications," which included off-label uses supported by major medical compendia.

On January 30th, 1991, the FDA granted final marketing approval of succimer as an orphan drug for treatment of lead poisoning in children, specifically children with BLLs >45 µg/dL. McNeil Pharmaceuticals, who would market the drug, was given seven years of market exclusivity. Orphan drugs carried numerous incentives and benefits for pharmaceutical companies, and succimer's development was largely subsidized by federal grants. To qualify as an orphan, the drug must be indicated for less than 200,000 patients. It remains unclear how the 45 µg/dL cutoff was selected. Clinical trials submitted to the FDA included children with BLLs as low as 30 µg/dL. However, ensuring the treated population included no more than 200,000 patients would have been a requirement for final FDA approval as an orphan drug. Regardless, succimer was expected to be used off-label to chelate children at much lower BLLs.

Later that year, in October 1991, the CDC released their long overdue guidance update: "Preventing Lead Poisoning in Young Children." The statement included three conflicting recommendations that:

i. lowered the hard line for chelation from 55 to 45 µg/dL, aligning clinical guidance with the FDA-approved indication for succimer. Critically, the guideline allowed clinicians discretion on chelating patients with BLLs 20–45 µg/dL.

ii. lowered the BLL of concern to 10 µg/dL (a level shared by an estimated 1.7 million children), aligning it with evidence of neurotoxicity and creating new cases by definition.

iii. recommended universal lead screening for every 1- and 2-year-old child, substantially increasing the detection of these newly defined cases.

By late 1991, the federal government was caught in a fiscal trap. The CDC had mandated screening to find a massive new population of poisoned children, most of whom were low-income Medicaid patients. The MDRP had created a legal mandate for Medicaid to pay for their treatment, even if off-label. And McNeil Pharmaceuticals held a monopoly on the only safe, oral drug that made mass treatment feasible.

The only plausible way for the government to escape this ongoing fiscal obligation was to change the definition of "medical necessity." If it could be demonstrated that chelating children in the 10–44 µg/dL range provided no long-term benefit, the state could legally justify denial of off-label treatment.

The NIEHS TLC official website acknowledged that succimer's orphan-drug label (≥45 µg/dL) might not constrain real-world use. The archived TLC trial website states:

"NIEHS and its advisors, especially the American Academy of Pediatrics Committee on Environmental Health, believed that many children would be treated with this drug at blood leads below the labelled level, despite the fact that there was relatively little evidence of safety and no evidence of efficacy for prevention of the latent effects of lead, including developmental delay. Lowering of blood lead per se at these levels is without known clinical benefit."

It also foregrounded cost, without explicitly acknowledging that these costs would be borne primarily by Medicaid and other federal programs rather than by patients.

"NIEHS believed that a formal trial of succimer for the prevention of developmental delay in children was warranted. Drug therapy is costly (Chemet® costs about $300/course, most children need multiple courses over months), potentially hazardous, and would be given to asymptomatic children. Effective, simple intervention to regain lost IQ points, however, would be useful in these children and be very cost-effective in the long run. Primary prevention, i.e., prevention of exposure, is perhaps another generation away for millions of children. Good data on which to base therapy were necessary. McNeil (the pharmaceuticals company) was interested only in further studies showing that Chemet reduced blood lead, and had no plans to test the ability of the drug to prevent developmental delay."

“For more than twenty years, NIEHS has sponsored much of the research showing that lead at these levels was harmful to children's brain function, and that succimer lowered blood lead. We had hopes that the treatment would prevent or reduce lead-induced damage in these children, who are mostly poor, African-American, and living in deteriorated housing in big cities. The results of the trial show clearly that treatment after the fact does not undo the damage among 5 year olds. We must prevent these children from being exposed in the first place.”

—NIEHS Director Kenneth Olden, Ph.D. (NIEHS Newsroom — May 9, 2001)

2016 Dr. Rogan’s NIEHS oral history described the TLC trial as a success:
“*We went to where you might imagine we went. Where was the other centers? Philly, Newark, Baltimore, and Cincinnati. We followed 780 kids, half of whom had gotten Succimer, half of whom got placebo... We lowered their blood leads pretty dramatically, and we changed their IQs not at all.”*

“That study ended drug treatment, which had been being promoted as something that you ought to do to these kids. It also stopped the idea of what we call secondary prevention... and moved the attention back to primary prevention, not letting them get exposed to lead in the first place.”

This wasn't framed as a disappointment— it was framed as a contribution. It moved the attention back to primary prevention.

But primary prevention (removing lead from housing, environment) requires massive public investment, and is contingent on funding, and local cooperation from cities and from homeowners. What actually happened was that the TLC result provided legal and medical justification for not providing treatment, while also not funding prevention at scale, essentially shifting the responsibility of prevention to parents and allowing states and cities to decide what to do.

Rogan further reflected on his government career:

“Nothing I've done would have been possible outside of a government agency, either NIH or CDC or EPA... My career has been very much a government scientist career.”

And Dr. Rogan was right. As lawsuits were filed throughout the 2000s against Kennedy Krieger Institute and John Hopkins investigators, NIEHS and Dr. Rogan got away with no repercussions. NIEHS appears to have been effectively litigation-proof due to federal sovereign immunity, FTCA procedural requirements, contract structures that offloaded liability to grantees, and a steering committee structure that made federal control appear "collaborative" rather than directive.

1987

- AAP updates their statement on lead poisoning.

- *Proceedings of the National Conference, Childhood Lead Poisoning: Current perspectives* takes place.

The top people in lead research all present—most of whom are tied in some way to TLC. Herbert Needleman[1], Julian Chrisholm[2], and David Bellinger[3] all present findings from their studies. John Graef (AAP Committee Member on Environmental Hazards)[4] presents on the recent AAP update.

- Routt Reigart[5] is the MC of the event, he closes the event with coments on each presenter, and calls our the AAP and Graef for the recent statement.

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1. **Needleman is** often credited as being responsible for the phase out of leaded gas and linking IQ-loss to lead exposure.
2. **Chrisholm,** of Kennedy Krieger Institute, was very well-known researcher, responsible for most of the clinical research on chelators and treatment. He was also the lead Investigator at the Baltimore TLC. He, and Dr. Joseph Graziano were the Pis that studied succimer prior to its 1991 approval. starting to get into

3
4

micrograms/dl of whole blood. By contrast, infants residing in dilapidated pre-World War II housing show a steady increase between six and eighteen months of age during which geometric mean blood lead concentration increases to 25 micrograms/dl where it stabilizes at least until thirty months of age. In other words, one half of the children residing in old poorly maintained pre-World War II housing have unacceptable elevations in blood lead concentration.

For the past fifteen years, the management of childhood lead toxicity has been based on screening to identify the child with an elevated blood lead concentration, referral for medical evaluation and, in certain cases, chelation therapy. This approach has its limitations. To have any effect at all, it must be coupled with rapid identification and abatement of lead hazards in the child's environment.

An important principle of chelation therapy, as stated by Aaseth,[11] is as follows:

> "Enhanced excretion induced by a drug is meaningless from a therapeutic point of view if it is not paralleled by a decrease of the metal concentration in the critical organ."

In the case of lead, recent human and experimental studies indicate that the brain is the critical organ in the fetus and infant. With these points in mind, new and important experimental data on the use of calcium disodium ethylenediamine tetraacetate ($CaNa_2$ EDTA) raise serious questions particularly in regard to the $CaNa_2$ EDTA Mobilization Test. Cory-Slechta et al have just reported a detailed study on the mobilization and redistribution of lead during the course of $CaNa_2$ EDTA therapy.[12] These workers chronically poisoned rats at a low level, producing pre-treatment blood lead concentrations of 25-40 ug Pb/dl of whole blood. Although the dosages of $CaNa_2$ EDTA used are not directly transferable from rats to humans, the dosages used were considered comparable to those used in children. Following a single dose of $CaNa_2$ EDTA, blood lead concentration decreased and urinary lead output increased sharply, as observed in humans. She also measured the changes in the concentrations of lead after a single dose of $CaNa_2$ EDTA in bone, kidney, liver and brain. Her data showed that the greatest decrease occurred in bone lead and that some decrease in kidney lead also occurred. The studies of others have indicated that approximately 85% of the lead mobilized by $CaNa_2$ EDTA is derived from bone. By contrast a modest increase in the lead content of liver and a marked increase in the lead content of brain occurred indicating substantial redistribution of the lead during the mobilization. In the various experiments, brain lead was increased anywhere from 33-100%. After five days, there was no net loss of lead from either brain or liver, despite the fact that blood lead levels declined and that there was a marked increase in urinary lead output. Other recent studies have also shown, as observed in children, that the excretion of delta-aminolevulinic acid, a marker of lead's inhibitory effect on heme

synthesis, also decreases during chelation therapy. These data, as well as other considerations, raise serious concern about the use of $CaNa_2$ EDTA Mobilization Test in routine clinical practice.[13] Indeed, the animal data call for a re-evaluation of the use of chelating agents in the management of lead toxicity.

New drugs are needed and, perhaps, are on the horizon. Perhaps the most promising drug is 2,3-dimercaptosuccinic acid (DMSA), which in experimental animals has been shown to reduce the concentrations of lead in various soft tissues, including the brain. However, DMSA appears to have little effect in the rat on the lead content of bone. DMSA has also been shown to cause a sharp decrease in blood lead concentration and a marked enhancement of urinary output in lead poisoned adults. As with $CaNA_2$ EDTA, internal redistribution occurs following therapy even without further exposure, so that the soft tissue concentrations of lead after therapy rise toward the pretreatment levels. I know of only one experimental study in which DMSA and $CaNa_2$ EDTA have been administered chronically to the rat.[14] In this study, both drugs, when administered intermittantly over a six week period, reduced the concentration of lead in the brain significantly, but not to control levels.

Between 1978 and 1984, I studied a group of 184 children admitted to the hospital with blood lead $\geq$ 50 ug/dl for long-term chelation therapy.[15] They were then followed as outpatients for up to 2½ years thereafter. Among the 184 children, only 20 could be relocated to either modern public housing in good condition or totally gutted and renovated houses. Only in these 20, was there sustained improvement. Among the remaining 164 children who were returned to old houses abated in the traditional manner, 75 or 46% had a total of 127 recurrences of blood lead levels in excess of 50 ug/dl. These data clearly reveal still further the limitations in chelation therapy and call for a primary preventive approach based on reduction in exposure.

Traditionally, lead-based paints have been removed from woodwork primarily by burning, sanding and scraping. In Baltimore—and I suspect in many other cities—no professional cleanup of the debris has been required. A common practice has been to give an unemployed man a propane torch with which to burn and soften the paint, so that it could be scraped off down to the bare wood. Such workers generally wear no protection and are totally unsupervised. Such an approach fills the house with fine lead-bearing particulates, some of which have been shown to fall within the respirable range. How many "torch men" develop acute lead poisoning, I do not know. However, poisoning in workers removing lead paint in this manner is well known.[16,17]

In 1984 we had an opportunity in Baltimore to compare this traditional approach, with deleading carried out by city crews according to the principles outlined in the 1985 CDC Statement.[7] These city crews removed lead-based paint with heat guns and scrapers, cleaned extensively with ordinary vacuum cleaners and high phosphate detergents

Julian Chrisholm. Proceedings of the National Conference, Childhood Lead Poisoning: Current Perspectives. In: 1987.

TABLE 1
Summary of Household Dust Lead (PbD) Values (mcg/sq ft) over Time by Surface and by Abatement Group

Surface	Pre-Abate GM	Post-Abate GM	6 Mos. Post GM
Floors			
Traditional	234	1,282	307
City Crew	400	687	339
	p <.01	p <.01	ns
Window Sills			
Traditional	1,212	3,444	1,644
City Crew	2,284	907	1,936
	p <.01	p <.001	ns
Window Wells			
Traditional	12,016	12,570	12,815
City Crew	21,313	9,740	26,013
	ns	ns	p <.05

GM=geometric mean p values for t tests

and repainted the deleaded areas. This work was carried out by Mark Farfel, then a doctoral student at the Johns Hopkins University School of Public Health and Hygiene in collaboration with Evan Charney and myself.[18] The deleading process was monitored by obtaining household dust lead samples by the wipe technique from floors, windowsills and window wells. Table 1 shows geometric mean dust lead values as micrograms per square foot pre-treatment, post-abatement and six months later. There were 53 homes in the traditional group and 18 homes in the city crew group. Studies by others have shown that the floors in modern suburban homes and public housing units without lead hazards show mean values of 20 ug of lead per square foot with an upper limit of approximately 150 ug of lead per square foot. Pre-abatement, all surfaces were grossly contaminated and the degree of contamination increases if one moves from floors to windowsills to window wells. In the case of floors and windowsills, the abatement procedures significantly increase dust lead levels in the traditional group. The traditional wisdom has held that a child must bite on and chew discrete chips of paint. Since window wells do not present a biting surface, they were not treated by either group and remained a very rich source of lead-bearing particulates relatively unchanged even after six months. The window wells, indeed, often contained visible particles of paint. Perhaps, the most discouraging finding was the observation that no significant reduction in lead dust levels occurred even after six months.

In the vast majority of cases, blood lead concentrations in the children clearly increased in relation to the abatement. Indeed, among the 27 children residing in the homes abated in the traditional manner, 48% showed an increase in blood lead concentration greater than 5 ug/dl, including nine who were hospitalized for chelation therapy as a result of the abatement. Two, or 10.5%, of the nineteen children in the city crew group showed an increase in blood lead concentration to greater than 50 ug Pb/dl of whole blood and were hospitalized for chelation therapy.

Clearly, past procedures have been based on faulty concepts in that they have not taken into account the importance of particulate lead. That is not to say that children, particularly those with higher levels of lead absorption, do not ingest flakes of paint. Even so, the data of Bornschein et al,[19] indicate that lead in both paint and surface soil contribute to the lead content of household dust which in turn is significantly related to hand lead level, which in turn is related to blood lead level. Their data, in agreement with others, indicate that the major route of lead into the body of children with low level lead toxicity is via the hand to mouth route. Other studies have indicated that the lead in surface soil, particularly that adjacent to houses, is also derived from paint.

The considerations provide the scientific rationale for a new approach. Although experimental data show that dietary deficiencies of calcium, iron, zinc and excesses of dietary fat increase lead absorption, other factors may be equally if not more important. In human adult volunteers lead is far better absorbed when ingested in the fasting state than it is when administered with food.[20] Lead in street dust, while relatively insoluble of neutral pH, is highly solubilized and present in ionic form in 1.5 normal hydrochloric acid.[21] This may be taken as a model for the effect of gastric juice in solubilizing the lead salts in the dust. With regard to dusts, particle size may be even more important. In experiments in rats, Barltrop and Meek[22] fed identical quantities of lead to rats, varying only the particle size between 6 and 180 microns in diameter. Their data clearly showed an inverse relationship between absorption and retention of lead and particle size. The concentration of lead in the kidney was approximately seven times greater when lead was ingested in the smallest particles than it was when lead was ingested in particles of 180 microns in diameter. Particles <100 microns in diameter were the most efficiently absorbed. Que Hee et al[23] studied the distribution of lead according to particle size in household dust. Approximately 80% of the lead was found in particles less than 150 microns in diameter. Indeed, 21% of the lead was found in particles less than 44 microns in diameter. Such small particles cannot be trapped efficiently by the standard household vacuum cleaner. These data indicate that a high efficiency particle accumulator vacuum or HEPA vacuum is required for adequate decontamination. Indeed, all of our experience to date indicates that an effective approach to the

reduction of lead paint hazards in old housing must be similar to the approach used to reduce hazards due to asbestos.

During the past two years, we have undertaken experimental studies on lead abatement in vacant old houses in Baltimore.[24] In many of the old houses in which children with lead poisoning live, the floors are often splintered, pitted or have gaps between the floor boards, making it virtually impossible for the housewife to reduce the dust lead levels effectively through the ordinary means of cleaning. We have observed that dust lead levels are much lower on floors covered with vinyl or smooth linoleum. The effect of floor treatments on residual dust lead levels was studied in three vacant houses in which wooden floors in some of the rooms were treated, while those in other rooms were not. Table 2 shows the results. The target value for floors

TABLE 2

Effect of Floor Treatments on Residual Dust Lead Levels
Baltimore—1986

Group (N)	Residual Dust Lead (PhD) on Floors <150 mcg/ft²	≥ 150 mcg/ft²
Treated† (22)	19	3
Untreated‡ (13)	2	11
		$X^2=14.32$
		p <0.001

†Treated=polyurethane, deck enamel then scrub and HEPA
Pbd: median, 78; range 24-360 mcg Pb/ft²
‡Untreated=scrub and HEPA only
PbD: median, 480; range 84-1620 mcg Pb/ft²

post-abatement has been less than 150 micrograms/ft.² Clearly, treatment of wooden floors with polyurethane or deck enamel results in significantly better results than simply scrubbing the floors and vacuuming them with a HEPA vacuum.

In our more recent studies, we have been using replacement windows, off-site dipping of woodwork that can be easily removed and caustic stripping of woodwork not easily removed from the dwelling. Walls have been treated by encapsulation. If flooring is not in satisfactory condition, new flooring covered with vinyl or linoleum is put down. Table 3 shows the results in a dwelling in which these techniques have been used. This dwelling was unoccupied at the time of abatement, but was occupied immediately after the cleanup. Since we are interested in determining whether the occupant could maintain low dust lead levels, samples were taken two months following occupancy. Comparison of pre-abatement with three months post-abatement dust lead levels on floors and window sills show substantial improvement. However, window wells still remain a problem. Studies in this and

The adequacy of abatement and cleanup will be keyed to achieving the following dust lead levels: Floors < 200 mg/ft.², windowsills < 500 mg/ft.² and window wells < 800 mg/ft.²

In summary, with the removal of lead additives from gasoline and the reduction of lead contamination of food, we have come full circle back to the ancient sources of lead and lead poisoning—those that have been with man for at least 5000-6000 years. There is little doubt that the major remaining public health problem with regard to lead exposure of children is the millions of tons of lead-based paints on the old housing stock. There are limitations to chelation therapy. It is doubtful that anyone has ever been "cured." At best, it is of little value unless the sources of lead in the child's environment are identified and effectively abated or removed. It is time to move toward primary prevention. This will require new approaches and new technology for the identification and abatement of lead paint hazards in housing. Abatement can no longer be left to the unsupervised torch man; rather, training and certification in the newer techniques will be needed. Proper disposal of wastes must be followed rather than dumping of the debris in the backyard or down the storm drain or sending it to the incinerator. Since particulate lead is a most important aspect of the hazard, the approaches that have been applied to asbestos, including the use of HEPA vacuums, will almost certainly be required for adequate cleanup after lead paint removal and/or encapsulation. Far more emphasis in the future must be placed on primary preventive approaches.

Finally, it has been 83 years since J. Lockhart Gibson first recognized the importance of particulate lead and hand-to-mouth activity in young children when he wrote as follows:

> "I . . . advance a very strong plea for painted walls and railings as the source of lead, and for the biting of fingernails or sucking of fingers, as . . . the means of conveyance of the lead to the patient." From J.L. Gibson, Australasian Med. Gazette (1904) 23:149-153.

This in turn leads me to cite a quotation from Benjamin Franklin over 200 years ago:

> "The opinion of this mischievous effect from lead, is at least above sixty years old; and you will observe . . . how long a useful truth may be known . . . before it is generally receiv'd and practis'd on." Letter from B. Franklin to B. Vaughan, Philadelphia, July 31, 1786.

Let us hope that the rate of progress will now accelerate. Thank you.

Let’s examine who was ultimately responsible for the TLC trial— Dr. Kenneth Olden, director of the NIEHS.

Perhaps the most telling quote of his came during a House appropriations committee in 1995.

“The costs for regulatory compliance as well as for health care costs are enormous, and it seems to me that it would be a wise policy to make the investment to do the science. And as soon as that could be done, with a fraction of the resources that it would take to enforce regulations that may or may not be required, we could rehabilitate or treat humans who have disabilities or diseases as a consequence of these exposures.”

***—Dr. Kenneth Olden, NIEHS Director* 1991–2005, NCEA director 2012–2016**

U.S. House of Representatives Committee on Appropriations. **National Institutes of Health.** Hearings before a Subcommittee of the Committee on Appropriations, House of Representatives, One Hundred Fourth Congress, First Session. Part 4. Washington, DC: U.S. Government Printing Office; 1995:418.

Olden has been criticized as NCEA director (in charge of EPA’s Integrated Risk Information System (IRIS), for approving new chemicals) for deferring to industry demands to slow the process that would ban chemicals deemed harmful to humans or the environment. Often the only non-EPA witnesses at some IRIS hearings were chemical industry spokesmen. Michael Walls, a lobbyist for the American Chemistry Council, testified at a House hearing, “You can count me among the fans of Ken Olden.”

Critiques of Kenneth Olden's Tenure in Environmental Health Leadership: NIEHS Directorship (1991–2005)

Critiques During Olden's Prioritizing Research over Regulation: As director of the National Institute of Environmental Health Sciences (NIEHS), Olden often stressed obtaining definitive scientific data *before* regulatory action. For example, in a 1999 report to Congress on the health risks of electromagnetic fields (EMF), Olden concluded the evidence of an EMF–cancer link was "weak" and "not sufficient to warrant aggressive regulatory action". He argued it would be more cost-effective to invest in research first, rather than impose costly regulations that "may or may not be required" without solid science – a stance some saw as favoring economic considerations over precautionary public health measures.

Scientific Pragmatism and Delays in Action: Olden developed a reputation as a *scientific pragmatist* who was cautious about triggering new regulations in the absence of clear data. In congressional testimony during the 1990s, he repeatedly emphasized the need for the "best and most complete science possible" as the basis for environmental rules. Critics contended that this philosophy, while sound in principle, sometimes translated into using uncertainty as a reason to delay or forego protective regulations. For instance, during a mid-1990s appropriations hearing, Olden suggested that investing in further research would cost only "a fraction of the resources" compared to enforcing potentially unwarranted regulations – implying that robust science could prevent unnecessary rules. Environmental advocates argued that this cautious approach could slow responses to emerging hazards, effectively placing a higher priority on cost-effectiveness than on preventive safety.

Collaboration with Industry – Conflict of Interest Concerns: Olden's close cooperation with the chemical industry drew scrutiny. In 2001, NIEHS (under Olden's leadership) accepted a $1 million donation from the American Chemistry Council (ACC) – the chemical manufacturers' trade association – to fund research grants on developmental toxicants. The *memorandum of understanding* gave ACC an advisory role in reviewing grant applications and project selection. This unprecedented public–private partnership raised eyebrows among lawmakers and public interest groups, who feared it could bias NIEHS's scientific agenda. Congressional Democrats on the House Science Committee (Reps. Bart Gordon, Mark Udall, and Eddie Bernice Johnson) formally questioned the arrangement, prompting a review by the Government Accountability Office. GAO concluded NIEHS had legal authority to accept the conditional gift, but pointedly *urged the institute to adopt safeguards* "to avoid any appearance of a conflict of interest" in future donor partnerships. The incident was cited by critics as evidence that Olden's collaborative style with industry – however well-intentioned – risked blurring the line between independent science and industry influence.

Critiques of Kenneth Olden's Tenure in Environmental Health Leadership: NCEA Directorship (1991–2016)

Slowing Chemical Risk Assessments (IRIS Program): In July 2012, Olden was appointed director of EPA's National Center for Environmental Assessment (NCEA), overseeing the Integrated Risk Information System (IRIS) – the program that assesses health risks of chemicals. Under Olden, IRIS's productivity plummeted, drawing sharp critiques from Congress and watchdogs. By early 2015 (after 2½ years of Olden's leadership), EPA had completed only four chemical risk assessments – an anemic output given the backlog of chemicals awaiting evaluation. The Government Accountability Office had flagged EPA's toxics review program as "high risk" in 2009 due to insufficient assessments, and by 2015 GAO reported very little progress had been made. Democratic lawmakers and environmental groups blasted this sluggish pace as "crippling IRIS" and failing to protect public health. For example, Rep. Suzanne Bonamici (D–OR) warned at a 2014 hearing that Olden's focus on building relationships with industry had "the effect of crippling IRIS rather than… streamlin[ing]" it. In other words, time spent accommodating industry input was coming at the expense of timely health protections.

Deference to Industry and "Regulatory Capture" Concerns: Perhaps the most pointed critiques have centered on Olden's open-door policy toward industry stakeholders in the IRIS process. Olden dramatically increased opportunities for industry and other stakeholders to comment on draft assessments – touting this as improving transparency and scientific quality. *In practice, however, observers say it gave industry unprecedented leverage to slow or dilute chemical reviews.* House Republicans and the chemical industry openly praised Olden's approach: at a 2014 House Science Committee hearing, noted EPA critic Rep. Paul Broun (R–GA) lauded Olden as "a refreshing ambassador for the IRIS program" who brought "increased opportunities for meaningful stakeholder input". Michael Walls, a lobbyist for the American Chemistry Council, went so far as to testify, *"You can count me among the fans of Ken Olden."* Such accolades from industry and anti-regulation politicians raised red flags for public health advocates. Rena Steinzor, a law professor who served as the lone Democratic witness at that hearing, translated Olden's "open and transparent" mantra this way: "a program suffused in … endless peer review, reconsideration of every assessment in the face of chemical company micro-criticisms, workshops, coffee klatches, and reviews." She warned that IRIS under Olden had become *"the clearest case of old-fashioned regulatory capture"* in recent memory. In Steinzor's view (shared by many environmental health experts), Olden's deference to industry input allowed constant second-guessing and nitpicking of EPA science – effectively giving regulated companies power to stall risk assessments they deemed unfavorable.

Imbalanced Hearings and Industry-Dominated Input: Both Congress and independent analysts noted that Olden's changes skewed the IRIS process toward industry voices. He instituted bi-monthly public meetings on draft assessments and invited "all stakeholders" to participate. In reality, these forums have been dominated by industry-paid experts. A Center for Public Integrity analysis found 85% of speakers at IRIS public meetings were funded by industry interests. Jennifer Sass, a scientist with the Natural Resources Defense Council, attested that at many sessions she has been *"the only scientist there not paid by industry"*, leading to one-sided debates. Even some EPA officials acknowledged the imbalance. Olden himself admitted the external input was "not balanced," and by late 2014 he promised to recruit more independent scientists to participate. Yet problems persisted: at one IRIS hearing on a carcinogenic chemical (hexavalent chromium), every single non-EPA speaker on the agenda was industry-funded. Lawmakers took note of this tilt. The House Science Committee's 2014 oversight hearing on IRIS (billed as a review of program reforms) featured a witness panel dominated by industry representatives who largely echoed Olden's emphasis on process improvements, while voices critical of EPA's slow pace were marginalized. Such scenarios led critics to argue that Olden had *"made friends with the chemical industry"* at the expense of public health progress. Indeed, one Democrat at that hearing quipped that EPA's new "early communication" approach was yielding *"input … imbalanced and badly skewed toward the regulated community."*

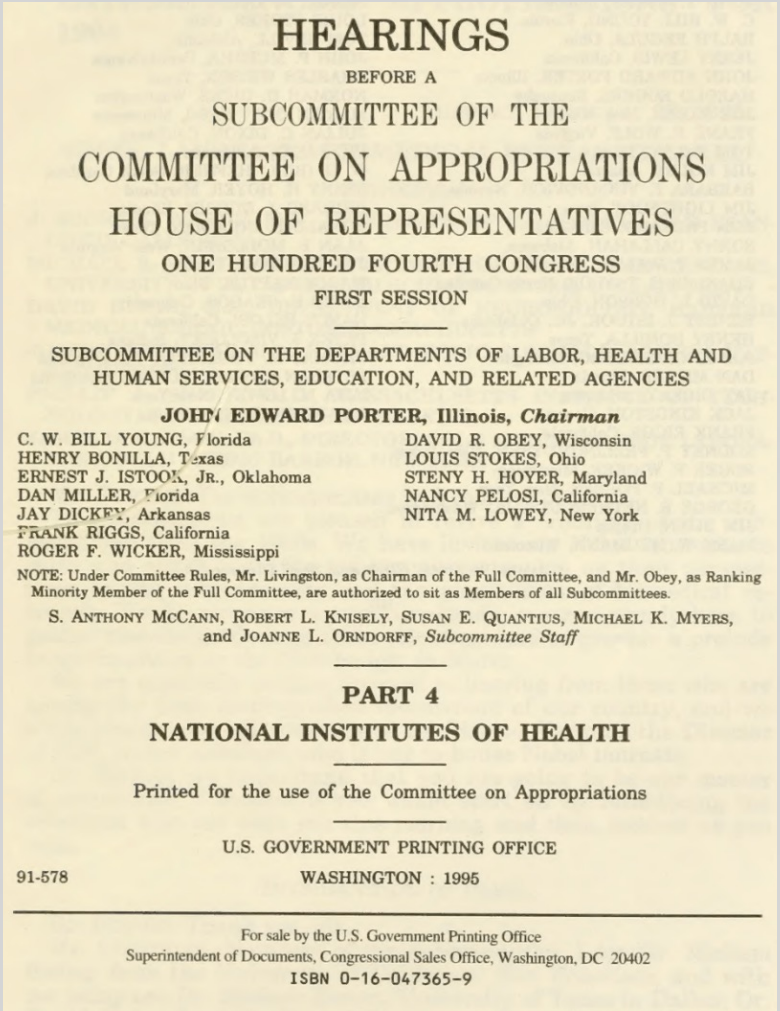
Critiques of Kenneth Olden's Tenure in Environmental Health Leadership: NCEA Directorship (1991–2016)

Using Data Gaps to Avoid Regulation: Olden's detractors characterize his philosophy as "science-forging" that conveniently delays regulation. They point to instances where lack of perfect data was used to justify inaction – benefiting industries facing potential bans or stricter limits. As NIEHS director, for example, Olden often argued that research hadn't yet proven causation strongly enough to support regulatory moves (as seen in the EMF case above). At EPA, he embraced National Academy of Sciences recommendations to overhaul IRIS methods *mid-stream*, a move that forced EPA to pause and redo ongoing chemical assessments. Former EPA Administrator William Ruckelshaus (a Republican who led the agency under Nixon and Reagan) blasted these delay tactics, frequently employed by industry, as "really unconscionable" when they stall warnings about known toxic chemical. By welcoming continuous re-analysis and outside "peer review" of IRIS drafts, Olden arguably gave industry lawyers and consultants more opportunities to contest EPA's findings and demand additional data. Public health advocates argue this endless call for more data effectively *postpones regulatory action* on dangerous substances – a result that chemical manufacturers certainly appreciate. As Ruckelshaus put it, critical health risk findings "ought to be immediately published… To the extent that that's delayed or stalled…it's really unconscionable – particularly if it's done on behalf of the industry".

Institutional Assessments: Various oversight bodies and analysts have effectively seconded these critiques. The GAO, as noted, kept EPA's chemical risk program on its "High Risk" failure list throughout Olden's tenure due to lack of results. And investigative reporting by the *Center for Public Integrity* concluded that the Obama EPA (with Olden at NCEA) **"never fulfilled its campaign promise to divorce science from politics"** in chemical assessments. Instead, political and industry interference continued to derail or delay EPA's scientific conclusions on toxins like formaldehyde and arsenic. By 2014, **EPA's IRIS produced just one new assessment for the entire year** , a pace even worse than under the openly industry-friendly Bush Administration. This led environmental scholars to lambaste Olden's leadership as *"nauseating"* – a **Democratic administration doing "worse than [the] Republican" one on chemical safety**, in the words of Rena Steinzor. Such critiques underscore a broader view that under Olden's risk-assessment framework, **regulatory science became bogged down in process**, to the delight of regulated industries and the dismay of public health champions

Dr. Kenneth Olden's stance

More here



HEARINGS

BEFORE A

SUBCOMMITTEE OF THE

COMMITTEE ON APPROPRIATIONS

HOUSE OF REPRESENTATIVES

ONE HUNDRED FOURTH CONGRESS

FIRST SESSION

SUBCOMMITTEE ON THE DEPARTMENTS OF LABOR, HEALTH AND HUMAN SERVICES, EDUCATION, AND RELATED AGENCIES

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NANCY PELOSI, California
NITA M. LOWEY, New York

NOTE: Under Committee Rules, Mr. Livingston, as Chairman of the Full Committee, and Mr. Obey, as Ranking Minority Member of the Full Committee, are authorized to sit as Members of all Subcommittees.

S. ANTHONY MCCANN, ROBERT L. KNISELY, SUSAN E. QUANTIUS, MICHAEL K. MYERS, and JOANNE L. ORNDORFF, *Subcommittee Staff*

PART 4

NATIONAL INSTITUTES OF HEALTH

Printed for the use of the Committee on Appropriations

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Dr. Kenneth Olden's stance

populations may explain, at least in part, why chemicals or physical agents found to be carcinogenic or toxic in some individuals are less or more active in others. Thus, understanding the DNA repair process could lead to an environmental health policy that takes into account differences in capacity to repair damaged DNA. Furthermore, these studies may lead to the development of diagnostic tests for defective DNA repair genes which could save lives by limiting exposure to known DNA damaging agents or through early detection and treatment.

Scientists at the NIEHS recently discovered a previously unknown DNA repair process in human cells and are now searching for the genes required for this repair process. Defective DNA repair is implicated in a broad spectrum of cancers including a common form of colon cancer. Institute scientists are particularly interested in studies to determine the likelihood of a person being preconditioned for environmentally-induced diseases by inheriting one good copy and one defective copy of a critical repair gene. If such "genetically susceptible" persons knew they had greater than average risk, they could employ prevention strategies and avoid high-risk behavior. They could also be screened for disease more frequently, thus permitting earlier detection and treatment.

Finally, a public health success story made possible by the research supported by the NIEHS and other federal agencies. In July of 1994, the Centers for Disease Control and Prevention reported that in children ages one through five the mean blood lead levels had declined by 76 percent, from 15 to 3.6 micrograms per deciliter of blood, between 1978 and 1991. The percent of children with blood lead levels of 10 micrograms per deciliter of blood decreased from 88 percent to 9 percent. These are tremendous improvements in our children's health because NIEHS-supported research has shown that at blood lead levels higher than 10 micrograms per deciliter, children experience measurable decreases in intelligence and increases in neurobehavioral problems. Unfortunately, socioeconomically disadvantaged children living in urban environments have not experienced a significant decrease in the incidence of lead poisoning.

The identification of lead as a hazard and increased public awareness of the neurotoxic nature of lead has resulted in the phase-out of its use in gasoline and paint over the past 25 years.

Anticipated "Breakthroughs" in the Immediate Future

The Institute will continue exploring the role of estrogens in the development of cancers and other diseases and dysfunctions. In the coming year the NIEHS will focus on the following areas: (1) Defining the relationship of interactions between BRCA1, the breast cancer susceptibility gene, and environmental agents to the development of breast cancer. (2) Exploring links between estrogens and the world-wide increase in testicular cancer. Testicular cancer, typically a disease of young men rather than the elderly, has increased by 2-4 fold in industrialized countries over the past 50 years. Estrogens are a suspected risk factor based on the increased incidence of testicular cancer observed in male offspring of pregnant mice exposed to high doses of estrogens. Also, wildlife exposed to high levels of chemicals with estrogen-like activity develop mammary and testicular cancers. (3) Defining the relationship between exposure to estrogenic substances and the development of endometriosis, and endometrial, vaginal and ovarian cancers. (4) Understanding the relationship between exposure to estrogenic substances and the decrease (30 to 50 percent) in sperm counts, development of anomalies of the male reproductive organs, and the decline in birth rate.

Prevention of environmentally induced diseases remain a major focus of NIEHS research. In support of this goal, a molecular intervention study of aflatoxin B_1-induced liver cancer will start

soon. NIEHS is supporting an intervention study to see if prophylactic use of the drug, oltipraz, prevents aflatoxin-induced liver cancer. This study is part of a series of complementary efforts by the NIEHS and the NCI examining the molecular basis of aflatoxin-induced cancer and the possibility of using oltipraz to intervene in development of this cancer.

The development and validation of alternative models and test systems for detecting environmental carcinogens and toxins will continue. The goal is to develop and validate new models and test systems to reduce the current dependency on the costly rodent bioassay. Preliminary results suggest that models can be developed that are less costly and can be performed more rapidly. Such test systems will allow for screening of dozens of chemicals annually.

The area of lead poisoning treatment and prevention is of special interest. NIEHS and the NIH Office of Minority Health Research are collaborating on research on the most vulnerable targets of lead toxicity, children. Clinical trials on the chelating agent, Succimer, are examining this compound's ability to prevent the neurobehavioral deficits observed from low lead exposures. Other projects explore the role of what might be a child's most important source of environmental lead--its mother. During pregnancy and lactation, the lead stored in a woman's bones might be mobilized and absorbed by her child. Two studies examine the distribution of lead during these critical periods, one in humans and one in primates. Results of these studies will help clinicians decide how best to treat pregnant women and protect developing fetuses from lead exposure.

Partnerships with Other Federal Agencies

The NIEHS manages and provides scientific oversight to approximately $80 million worth of environmental research programs developed through collaborative arrangements with other agencies, including DOE, EPA, and other HHS agencies.

Summary

The programs supported by the NIEHS are consistent with the goal of prevention of human disease and disability, and aid in the formation of economic growth and promotion of public/private partnerships. The Institute's compelling mission, high quality research and efficient management make it a wise investment at this time. The President's request for FY 1996 is $278,832,000. I would be happy to answer any questions.

Dr. Kenneth Olden's stance

Dr. OLDEN. Yes. Well, first of all, I think the National Center for Environmental Health does very little research, especially not laboratory research or toxicological testing. And the Environmental Protection Agency does mission-oriented research, short-term research, that is directed towards some immediate goal. At NIEHS, we do basic research that is long-term. It is not mission-oriented. In other words, there is not a project that we are trying to find an answer to. It is peer-reviewed. It is mainly university-based, whereas the EPA research is mainly in-house and on contracts.

We develop a lot of new methodologies and technologies, whereas the EPA is less interested in that because the standard they have to regulate uses the rodent bioassay. So they are less interested in developing new methodologies of the kind I just described to you. I would say that those are probably the main differences.

Now, with NCI, we are more interested in the role of environmental agents in the etiology of disease. We are concerned about genes only as they relate to gene environment interactions. When we have similar interests as the National Cancer Institute we will collaborate, and occasionally, they will also be interested in some aspect of an environmental agent and we do collaborate on a number of issues.

Mr. PORTER. Thank you, Dr. Olden.

Mrs. Lowey.

COST-BENEFIT REQUIREMENTS

Mrs. LOWEY. Thank you, Mr. Chairman.

Thank you very much for your testimony. In your statement, Dr. Olden, you make reference to NIEHS research that contributed to one of the greatest public health success stories in recent years, the tremendous drop in the levels of lead in our blood. Specifically, since the EPA began to phase down the levels of lead in gasoline and paint 25 years ago, we have seen a 76 percent decline in the mean lead blood levels in children. While no dollar figure can be easily assessed on the value of that decline, we know that countless children have been spared the subtle erosion of mental and psychological functions caused by elevated lead levels in people of all ages, particularly in children.

Had the risk assessment and cost-benefit requirements contained in legislation that recently passed the House been in effect in the mid-1970s, it is my understanding that the EPA's actions back then, which were vehemently opposed by the lead industry, would have been delayed significantly, perhaps by many years.

In reading from this report, I note that the NIEHS and NTP hosted a special workshop on January 11 through 13 and this was important to that dialogue, and it specifically says that recommendations from this workshop will provide a framework for developing risk assessment schemes and prevention programs that will enhance our ability to protect the public health from environmentally caused diseases while maintaining economic vitality.

Given that, would you please comment on the ramifications these new risk assessments and cost-benefit requirements will have on the work of NIEHS?

Dr. OLDEN. Well, the Administration has already articulated its position on that legislation. Let me say my concern is this, the

science, to underscore, to underpin the decisions, is simply not in place to make the kind of decisions that I think need to be made. I am concerned about the quality of the science that goes into the regulatory decisions. And as I said earlier, in my opinion, in most cases, we have to make the decisions at a point where we have very little evidence to make those kinds of decisions.

I am concerned about birth defects, cancers, infant mortality, and not so much about cost benefits. I think those are value judgments that policymakers have to decide. But my concern is that we do not have good scientific bases for making decisions. For example, we do not understand differences in susceptibility. In most cases we do not know what the effects are at low doses. In most cases we are extrapolating from an animal to a human. These are the concerns that I have, not so much about cost benefits.

I think you as a policymaker must be concerned about those, but as the director of a health agency I am concerned about the quality of the decision and the quality of the science that goes into those decisions.

Mrs. LOWEY. I appreciate that, because it would seem to me that with the opposition to this work from the lead industry, I wonder, if this legislation had been in place, whether we would have been able to protect the public. The decisions we make, if this legislation goes through the other body, will not really be adequate because we will not have all the information we need. That is my real concern. I cannot help but believe, due to the pace at which this legislation went through, that many Members were not really thinking of the specifics, such as the lead implications and in a whole range of public health issues.

Dr. OLDEN. The costs for regulatory compliance as well as for health care costs are enormous, and it seems to me that it would be a wise policy to make the investment to do the science. And as soon as that could be done, with a fraction of the resources that it would take to enforce regulations that may or may not be required, we could rehabilitate or treat humans who have disabilities or diseases as a consequence of these exposures.

RISK ASSESSMENT

Mrs. LOWEY. So you share my concern that it may be very difficult to protect the public because hard data will not be available at the time decisions will have to be made?

Dr. OLDEN. Well, risk assessment is not an exact science, so in most cases we will never have all the data to eliminate all the uncertainties. However, I think with a different kind of orientation, the way we do the science, that we can have much of the data in hand when the decision must be made.

For example, it takes four to five years to complete a rodent carcinogenicity bioassay. It takes another year and a half or so to have that data peer reviewed and reported out. So we are talking anywhere from five to six years from beginning to end. During that time, one could conduct some limited epidemiological studies in human populations, so you would have that additional data. You could also do some mechanistic studies.

Olden walks a political tightrope, masterfully, as he responds in front of Congress Appropriations in 1995 to Rep. Lowey (D). She tries to get him to criticize HR 1022, a Republican bill recently passed through the House which gutted environmental regulations.

He declines her bait, emphasizing the need for good science (i.e.: more NIEHS funding) to underpin regulatory decisions…*these are concerns that I have, not so much about cost benefits.*

But towards the end of their back and forth, he appears to shift on his stance.

January 1, 1990 – Early and Periodic Screening, Diagnostic, and Treatment (EPSDT)[1] of the Omnibus Reconciliation Act (OBRA) of 1989 mandated that states must pay for *any* service that is "medically necessary" to correct a condition in children. This included off-label medications.

January 1, 1991 – OBRA 1990 expanded EPSDT with the **Medicaid Drug Rebate Program (MDRP)**[2] which mandated state Medicaid programs to shelve their FDA-approved drug on their formularies if the manufacturer signed up for the rebate program. They could not simply reject an expensive drug (like succimer) if a manufacturer (like McNeil) signed a rebate agreement.

Jan 30, 1991 – FDA approved **succimer (Chemet®)** for BLLs ≥45 µg/dL

Oct 1991 – CDC updates:

1. "level of concern" from 25 to **10 µg/dL**
2. recommended **universal screening** for ages 1 and 2
3. **Treatment thresholds:**

   45 µg/dL → chelate;
   25–44 µg/dL → clinical discretion with a positive provocation test
   <20 µg/dL → not recommended

Medicaid now potentially liable for succimer prescriptions for all children 25−44 µg/dL

July 31st 1992 – NIH Guide first lists TLC Clinical Site and Coordinating Center grant proposals

Succimer (DMSA) Approved for Severe Lead Poisoning: The FDA has approved succimer (Chemet, McNeil Consumer Products Co, Fort Washington, Pa) for the treatment of lead poisoning in children with blood lead levels above 45µg/dL (2.17µmol/L). This is the first approval of an oral medication to treat severe lead poisoning in children. Physician labeling for succimer contains a pediatric dosing chart for an initial 19-day treatment course. Elevated blood lead levels and associated symptoms may return rapidly after discontinuation of therapy because of redistribution of lead from bone stores to soft tissues and blood. After therapy, patients should be monitored for rebound rise of blood lead levels, by measuring blood lead levels at least once weekly until stable. The severity of lead intoxication (as measured by the initial blood lead level and the rate and degree of rebound) should be used as a guide for more frequent monitoring. A minimum of 2 weeks between courses of therapy is recommended. Therapy should always be accompanied by identification and removal of the source of the lead exposure, because the drug cannot prevent lead poisoning in a lead-containing environment.

Nightingale SL. From the Food and Drug Administration. JAMA: The Journal of the American Medical Association. 1991;265(14):1802.doi:10.1001/JAMA.1991.03460140028006

[1] Omnibus Budget Reconciliation Act of 1989, Pub. L. No. 101-239, § 6403, 103 Stat. 2106, 2263–65 (1989) (effective January 1, 1990).
[2] Omnibus Budget Reconciliation Act of 1990, Pub. L. No. 101-508, § 4401, 104 Stat. 1388, 1388-143 to 1388-155 (1990) (effective January 1, 1991).

Orphan Drug Act (1983)

FDA makes administrative determination that a specific drug–indication qualifies as an "orphan" (rare disease/condition in the **U.S. affecting <200,000 people**, or no reasonable expectation of cost recovery). Designation is an incentive tag, not a marketing authorization.

1. The sponsor (Bock Pharmaca) submits an "Orphan Drug Designation Request" to OOPD. The request names: the drug (DMSA). The single 'rare' indication: lead poisoning.
2. The drug company provides a prevalence estimate, a plausible scientific rationale for benefit (animal or human data) and discloses development status.
3. OOPD issues a designation letter tied to that drug–indication. Designation can be obtained at virtually any time before approval (including for an already-approved drug pursuing a new rare indication). **Orphan-drug designation of succimer (05-09-1984)**

Designation provides: Financial and regulatory incentives during development (clinical-trial tax credit, FDA user-fee waiver, eligibility for grants/protocol assistance). In this case, it appears that clinical development for succimer appears to be completely subsidized by grants to clinically test succimer were awarded to **Dr. Julian Chisholm (KKI, TLC investigator)** and **Dr. Joseph Graziano (NIEHS).**

4. Only after FDA approves the product for the designated indication, the sponsor receives 7-year marketing exclusivity for that indication (subject to narrow exceptions such as clinical superiority by a competitor). Pre-approval use while "waiting": designation does not relax restrictions. Any clinical use before approval must occur under an IND (clinical trial or FDA-authorized expanded access/treatment IND) with IRB oversight, informed consent, and FDA manufacturing controls. This is case-by-case permission, not market access.

Marketing approval (**1-30-1991; exclusivity—>01-30-1998**): FDA may permit commercial distribution only after it approves a New Drug Application (NDA) or Biologics License Application (BLA) showing safety and effectiveness for the intended use(s). Approval, not designation, allows routine prescribing and sales. Off-label use exists only after approval; manufacturers still may not promote off-label uses.

Putting succimer (DMSA) into this frame

- 1984: DMSA received orphan designation for pediatric lead poisoning.
- 1991: FDA approved DMSA (Chemet). Only at this point did marketing begin and the 7-year orphan exclusivity attach.
- 1984–1991: Use was confined to IND pathways (research or treatment-IND), not routine clinical distribution.'
- TLC (Dr. Rogan) needed additional IND to test succimer since it was being tested off-label

TOXICITY OF LEAD IN CHILDREN TRIAL: COORDINATING CENTER

NIH GUIDE, Volume 21, Number 27, July 31, 1992

RFP AVAILABLE: NIH-ES-92-32

P.T. 34; K.W. 0755015, 1007009, 0755018

National Institute of Environmental Health Sciences

The National Institute of Environmental Health Sciences seeks a Coordinating Center for a clinical trial, the Toxicity of Lead in Children Trial. The objective of the trial is to test the use of the drug succimer in preventing lead-induced developmental delay. Children eligible for the trial will be about two years old and will be followed until they are at least four. The trial will be double blind to the extent possible. The target lead levels will be between about 20 ^g/dl to 45 ^g/dl. All children thought to be eligible will be treated for iron deficiency, be given vitamin and mineral supplementation, and have dust control measures instituted in their homes.

It is anticipated that there will be three Clinical Centers (Request for Proposals NIH-ES-92-31) and one Coordinating Center. The Coordinating Center will cooperate with the three Clinical Centers in developing, testing, and refining the overall program and in writing the final protocol, Manual of Operations, and training materials before recruitment commences. The Coordinating Center will plan randomization of study subjects. Optimally, no more than three Clinical Centers will randomize to drug or placebo on the order of 1000 total children during a 1-year enrollment and treatment phase.

The Government estimates that an average of five professional FTEs, two technical FTEs, one clerical FTE, and one other FTE will be required on an annual basis. The estimated period of performance is six years. Release of the RFP will be on or about August 6 with proposals due November 4, 1992. All responsible sources may submit a proposal that will be considered by the agency.

Requests for the RFP must reference RFP NIH-ES-92-32 and must be forwarded to:

National Institute of Environmental Health Sciences
Contracts and Procurement Management Branch
ATTN: Thomas M. Hardee, Contracting Officer
79 T.W. Alexander Drive, 4401 Building
P.O. Box 12874
Research Triangle Park, NC 27709
Telephone: (919) 541-7893
FAX: (919) 541-2712

TOXICITY OF LEAD IN CHILDREN TRIAL: CLINICAL CENTER

NIH GUIDE, Volume 21, Number 27, July 31, 1992

RFP AVAILABLE: NIH-ES-92-31

P.T. 34; K.W. 0755015, 1007009, 0740018

National Institute of Environmental Health Sciences

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The Government estimates that an average of five professional FTEs, two technical FTEs, one clerical FTE, and one other FTE will be required on an annual basis per Clinical Center. The estimated period of performance is five years. Release date of the RFP will be on or about August 6, 1992 with proposals due November 4, 1992. All responsible sources may submit a proposal that will be considered by the agency.

Requests for the RFP must reference RFP NIH-ES-92-31 and must be forwarded to:

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Research Triangle Park, NC 27709
Telephone: (919) 541-7893
FAX: (919) 541-2712

On August 27, 1992, NIEHS began soliciting proposals for what would become TLC. It requested proposals "for the planning, conduct, analysis, and reporting of a randomized, multi-center, placebo controlled trial of succimer in the prevention of lead-

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[5]The study initially was known as the "Toxicity of Lead in Children Trial." See Toxicity of Lead in Children Trial - Clinical Center Contract.

[6]NIEHS is a subsidiary of the NIH. NIH is a branch of the United States Department of Health and Human Services (DHHS).

associated cognitive delay in young children." RFP at C.1. In response to the RFP, on November 24, 1992, KKI submitted a Technical Proposal to NIEHS. On June 29, 1993, NIEHS awarded a contract (the Contract) to KKI to operate one of the four CCs.

Under the Contract, NIEHS would provide funding for 5 years, with a total anticipated cost of $5,765,029.00. Contract at §

Source: **Featherstone vs Kennedy Krieger et al**

Tracing the Origins of the TLC

- Who came up with the idea for TLC? Why would NIEHS fund such an expensive trial? Was there pressure from a particular institution? Or did NIEHS feel, since they had funded the clinical trials used in succimer's FDA approval process, that they had a responsibility to investigate it now that it was being used at lower BLLs?

Tracing the Origins of the TLC

- The Project Officer and primary author on most of TLC's publications, was Walter J. Rogan, MD. He was one of the first epidemiologists at NIEHS in the mid-70s, working there until his retirement in 2014.

From Rogan's own 2016 Oral History:

> "The institute had supported the development of a drug that lowered blood lead called Succimer. **We proposed to Dr. Olden that we do a clinical trial,** because lowering blood lead might be a good thing, but it might not be a good thing in the sense of reversing any effect that lead had already had, and it exposed you to the side effects of drug, which you might or might not need. The only thing wrong with you from these low levels of lead that we were going to treat was you'd lost some IQ points, two or three per every 10 micrograms per deciliter of blood lead."

Walter Rogan, MD (AAP Liaison and Chair of the IRB at NIEHS)

- From the 1999 TLC NIEHS Archived Website:

***"*NIEHS and its advisors, especially the American Academy of Pediatrics Committee on Environmental Health, believed that many children would be treated with this drug at blood leads below the labelled level**, despite the fact that there was relatively little evidence of safety and no evidence of efficacy for prevention of the latent effects of lead, including developmental delay. Lowering of blood lead per se at these levels is without known clinical benefit."

Walter Rogan, Chair of the IRB at NIEHS

According to his 1997 CV, Walter Rogan became **Acting Clinical Director** in 1993. His CV also lists him as the **Founding Chair of the NIEHS IRB** and **IRB Chair from 1992–1993:**

1980-1993 – NIEHS Institute Clinical Review Subpanel (now Institutional Review Board)
1980-1983 – **Founding chair of the IRB**
1983-1993 – **Member of the IRB**
1992-1993 – **Chair of the IRB**
1993-1997 – **Acting Clinical Director,** Division of Intramural Research
1991-1993 – **Associate Director for Prevention**, Division of Biometry and Risk Assessment

Walter Rogan, MD (AAP Liaison and Chair of the IRB at NIEHS)

~1991-1992: Rogan proposes the idea of TLC to Ken Olden
1992–1993: Rogan is Chair of the IRB at NIEHS

July 31, 1992: RFP NIH-ES-92-31, is published in NIH Guide.

October 8, 1992: Preproposal conference discussing ethical concerns/questions

October 22, 1992: Memo from NIEHS on conference questions

November 23, 1992: Kennedy Krieger Institute submits Technical Plan to NIEHS.

February 9, 1992: Johns Hopkins IRB approves protocol, sends letter of approval to Chisolm (PI of Baltimore TLC clinical site and PI of R&M studies)

February – June 1993: NIEHS IRB rejects KKI consent form due to ”too high of reading level”’; KKI resubmits to JHU IRB, NIEHS IRB approves revised forms.

June 25, 1993 Rogan appointed Project Officer (memo date); NIEHS Award/Contract for TLC study to KKI.

Conflict of Interest

This overlap of duties, during the planning phase of TLC, appears to have been a possible conflict of interest. This is concerning, given the numerous ethical lapses that occurred during the TLC, and alleged harms to participants, ultimately leading to being classified as nontherapeutic by the U.S. District Court for the District of Maryland.

Who oversaw the NIEHS IRB from 1992–1993, when TLC was being planned and proposals were being screened? Did Rogan know he would be appointed as Project Officer (PO) of the TLC, a project he takes credit for having proposed to Ken Olden? If he didn't know he'd be appointed as PO, what requirements would he have had to recuse himself from IRB proceedings discussing the TLC, given that the idea for the trial allegedly came from him? While we don't know the answers to these questions, we can look at what was addressed by NIEHS and what they communicated in their RFP.

Walter Rogan, MD (AAP Liaison and Chair of the IRB at NIEHS)

So, Walter Rogan himself frames the TLC as something he was involved in proposing to Ken Olden, to make happen. The emphasis "*especially the American Academy of Pediatrics Committee on Environmental Health"* is interesting.

The current NIEHS website's emeritus profile on Rogan:

"**Rogan was NIEHS Liaison to the Committee on Environmental Health at the American Academy of Pediatrics (AAP) for 36 years.** AAP has many technical committees that write policy statements guiding the thousands of pediatricians who are members of the Academy. Rogan was primary author on several such statements, and he participated in the drafting and editing of the many statements produced by the Committee on Environmental Health in his time there. He was also an Ex Officio member of the U.S. Department of Health and Human Services Advisory Committee on Childhood Lead Poisoning Prevention for 16 years. These two committees provided much of the influential policy about children's environmental health in the U.S."

The American Academy of Pediatrics (AAP)

Now, the AAP had apparently harbored some sentiment against universal screening since at least 1987, when the Committee on Environmental Health (of which Rogan was a member), published its guideline update.

The American Academy of Pediatrics (AAP)

In a 1987 conference, Dr. Routt Reigart criticized the AAP's most recent guideline update:

> *"My interpretation of what happened is that the AAP said, 'It is not our problem, it is the government's problem.' Rather than coming out for universal screening, it told pediatricians that if they made a prudent decision to not screen a child they did not have to."*

"What the AAP in effect told pediatricians is, 'This is an important problem but you don't have to be a leader and you don't really have to worry about it unless you are in a 'high risk environment.'"

"The impression we are left with is that the AAP is saying, 'It's not our problem, it's the government's problem, let the government handle it.' Frankly, I find this to be an appalling position for a group that should be at the forefront of child health advocacy."

The Promise and Abandonment of Primary Prevention

In 1998, Dr. Herbert Needleman published an opinion paper titled: Childhood Lead Poisoning: The Promise and Abandonment of Primary Prevention.[5] In it, he writes, "*the attempt to achieve primary prevention of lead paint exposure is a clear failure, and it can claim at least 8 foster fathers. Some are the traditional enemies of lead poisoning control, but significant opposition also emerged from surprising quarters*". One of the "opponents" he describes, was the American Academy of Pediatrics:

"The general decrease in blood lead levels that followed the removal of lead from gasoline was interpreted to mean that the threat had ended. Lead poisoning was once again portrayed as a disease of the ghetto. In fact, between 1988 and 1991 about 8.9% of White children from families above the poverty level had blood lead levels higher than 10 µg/dL, the value currently accepted as toxic. A long-standing tension between medical practice and public health theory became more pronounced. Pediatricians in many middle-class areas believed that testing children's blood for lead was an unnecessary bother and expense and were reluctant to screen children even when asked to do so by parents."

The Promise and Abandonment of Primary Prevention

He goes on to write, that “while the organization's official 1993 statement took a "progressive position" supporting screening as part of routine health supervision, other forces within AAP were moving in the opposite direction. Resolutions against universal screening began appearing on local AAP chapter agendas and were "passed up the ladder." In March 1993, AAP's executive director publicly stated that ‘*there is a good deal of question about whether or not universal testing should be carried out throughout the country.*’”

“An organized campaign against universal screening emerged from California, with commentaries - acknowledging "editorial assistance of the medical editing department of the Kaiser Permanente Foundation Hospitals" - appearing in letters to journal editors, newspapers, and "throwaway" medical journals. These commentaries argued that the prevalence of elevated blood lead levels was questionable, that health effects at these levels were dubious, and that spending on screening and treatment would “‘starve more worthy public health efforts.’”

The Promise and Abandonment of Primary Prevention

The same arguments were circulated to AAP chapter heads and eventually picked up by a former AAP president, Dr. Birt Harvey, who wrote a lengthy attack in 1994,[6] questioning the value of identifying and treating children with BLLs under 20 µg/dL.

In 2002, Dr. Birt Harvey go on to would become the main editor of the ACCLPP's lengthy 200 page recommendation, *Managing Elevated Blood Lead Levels Among Young Children.*[7] Harvey served as **AAP President 1989-1990,** and was based in Palo Alto, California- the same state where Needleman documented the "organized campaign against universal screening" occurred, with Kaiser Permanente's editorial assistance.

In 1994, President Bill Clinton signed Executive Order 12898, a landmark directive requiring all federal agencies to integrate environmental justice into their core missions. The Order mandated that agencies identify and address disproportionately high and adverse health or environmental effects on minority and low-income populations. This directive was pivotal for the EPA, serving to formalize and expand the mission of the Office of Environmental Justice (originally established as the Office of Environmental Equity) to coordinate agency-wide efforts in protecting vulnerable communities from unequal environmental burdens.

Exec. Order No. 12,898, 59 Fed. Reg. 7629 (Feb. 11, 1994).

Office of Research on Minority Health Initiatives

NIEHS Inks New Agreement With Minority Health Office

By Thomas Hawkins

Treatment of lead toxicity, environmental justice, and environmental health sciences centers in areas beset by environmental concerns are several of the minority health programs that are addressed through a major agreement between NIH's Office of Research on Minority Health and NIEHS.

A memorandum of agreement between the two provides NIEHS with $5 million a year for 5 years through 1997 to address minority health concerns related to environmental health. Dr. John Ruffin, ORMH director, and Dr. Kenneth Olden, NIEHS director, recently signed the agreement.

The agreement is part of ORMH's Minority Health Initiative, which has a first-year budget

(See MINORITY, Page 5)

MINORITY

(Continued from Page 1)

of $40 million, to address health problems suffered disproportionately by minorities at every stage of life. Funds provided through the agreement will be apportioned between research programs relating to environmental justice—pollution and environmental health risks distributed across socioeconomic classes and racial groups.

Four major efforts are covered under the agreement:

◆ Three to 4 million children in the U.S. have elevated blood lead levels; NIEHS will support a clinical trial to establish the effectiveness of a drug (chelating agent) that will remove lead from the body. Succimer is a new drug that holds promise for this purpose but has not been adequately tested clinically for this purpose. Succimer is the first newly available chelating agent since 1950.

◆ The agreement will fund research on lead in pregnant women, to learn whether the release of lead stored in bone is increased during pregnancy. This may help scientists understand how the developing fetus may be exposed to lead via exposure of the mother years prior to pregnancy. The research will focus on women from Eastern Europe who have been heavily exposed to lead and who then have migrated to Australia. This provides a unique population for study because of recognizable differences between bone-lead exposure in Europe and blood-lead exposure in Australia. In most other populations, the many kinds of lead in bone and blood make such a study impossible.

Dr. John Ruffin (l), director of NIH's Office of Research on Minority Health, and Dr. Kenneth Olden, NIEHS director, sign a memorandum of agreement giving NIEHS $5 million a year for 5 years to address minority health concerns.

◆ NIEHS will fund developmental centers located at universities near areas of special environmental concern. The first center has been established jointly at Tulane and Xavier universities in New Orleans to address environmental concerns associated with the petrochemical industry there.

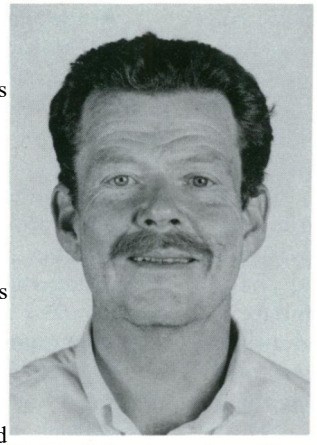
◆ This agreement will also allow NIEHS to sponsor a national meeting July 28-29 in Washington, D.C., that will address environmental justice. ❑

July 20, 1993- The NIH Record. Vol. XLC No. 15

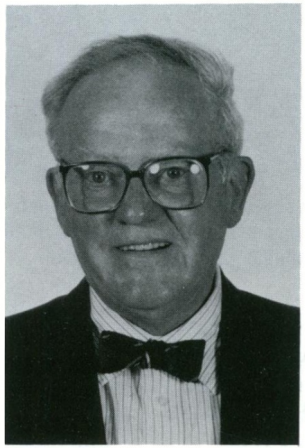
Succimer Gets TLC

Kenneth Olden, director of NIEHS, and John Ruffin, director of NIH's Office of Minority Health Research, have announced the signing of five contracts for a 5-year clinical trial of succimer, a drug that reduces blood lead levels in children.

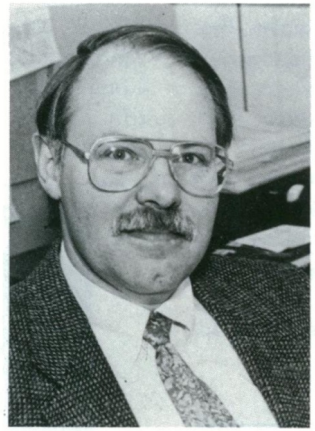
The purpose of the trial is to determine whether treating children with relatively low blood-lead levels prevents or reduces associated developmental delay and whether the drug is safe.



Walter J. Rogan, project officer for the TLC Trial



J. Julian Chisolm, Kennedy-Kreiger Research Institute



James H. Ware, Harvard University

Walter J. Rogan is the project officer for the trial, and the coordinating center will be at Harvard University, with James Ware as principal investigator. The other principal investigators and clinical centers are: 1) **Frances M. Gill** of Joseph Stokes, Jr. Research Institute, Children's Hospital of Philadelphia, 2) **Julian Chisolm of Kennedy-Krieger Research Institute, Inc.**, in consortium with Johns Hopkins University and University of Maryland at Baltimore, 3) **Richard P. Wedeen** of the University of Medicine and Dentistry of New Jersey, and 4) **Robert L. Bornschein** of the University of Cincinnati.

Each of the centers will treat about 250 children 18-24 months of age and follow them for up to 4 years. All children will have the lead dust and paint in their homes cleaned up and will receive vitamin and mineral supplements so they meet current recommended daily allowances, especially for zinc and calcium. **The Toxicity of Lead in Children** (TLC) clinical trial will cost approximately James H. Ware, Harvard University $30 million over the next 5 years. Recent studies of lead-exposed children show that blood-lead levels once thought to be harmless cause significant delays in motor control and intellectual development. These developmental delays may impede social development and readiness for school. The TLC trial will determine if succimer reduces or eliminates such developmental delays.

Succimer is a relatively new drug that has not been adequately tested clinically. It is the first available drug of its type (a chelating agent) since 1950, and it can be orally administered at home. Succimer appears to be relatively safe and may not cause as much loss of elements needed by the body, such as zinc and iron, as do other drugs. The TLC trial is made possible through an agreement between NIEHS and the Office of Research on Minority Health, which allocates $5 million per year for five years to address minority health concerns related to the environment. **The agreement was signed in March** by Olden and Ruffin.

"This clinical trial could have tremendous impact on the health of minority children. Lead poisoning is just one health concern that disproportionately affects minorities. **By joining forces on this issue and others, the ORMH and the NIEHS are working to reduce the burden of illness shouldered by minority Americans**," said Ruffin. In a recent article in Preventive Medicine, Olden noted **"Children ingest their environment. When that environment is contaminated by lead, they ingest lead**. They absorb and transport lead across their gastrointestinal tracts and into their bloodstreams about six times more efficiently than adults do. **A major environmental health issue for children today is the extremely high prevalence of unacceptable exposure to lead, especially in inner cities, but occurring throughout the country. This clinical trial will address the terrible toll lead takes on our children's futures."**

September 1, 1993. *EHP*. Vol. 101, Issue 4, P. 284

NIEHS Minority Health Funding Expanded Through ORMH Deal

Funding for minority health programs at NIEHS has been increased $2.4 million through an expansion of the intra-agency agreement with the Office of Research on Minority Health signed in July. This brings the total funding to $7.4 million for fiscal year 1994, to address minority health concerns related to environmental health. Dr. John Ruffin, director of ORMH, and Dr. Kenneth Olden, director of NIEHS, signed the agreement.

A primary effort under the agreement addresses the determination, evaluation and treatment of lead-exposed children and pregnant women. Learning deficits have been identified in young children exposed *in utero* and postnatally through environmental dust, paints and vapors. Evaluation programs are both planned and ongoing. A clinical trial recently began on the chelating agent succimer for children exposed to environmental lead, to determine if learning deficits can be corrected in individuals with moderate body burdens of lead. Major university medical research centers are conducting the trial that is being coordinated at Harvard University.

Also under the agreement is a program of research grants addressing issues of environmental justice defined through a national environmental justice conference held in Alexandria last February. ❑

September 13, 1994- The NIH Record. Vol. XLVI, No. 19

Was the TLC designed around genuine clinical equipoise or on the basis of saving billions of Medicaid dollars by disproving long-term neurodevelopmental benefits?

Currently, chelation is indicated for BLLs >45 µg/dL. However, no RCTs have shown long–term neurodevelopmental benefits from lowering BLLs, at any level. We chelate children >70 µg/dL, because they are at risk of encephalopathy and we know, empirically, that lowering BLLs mitigates the lead that can interact with their brain.

BLLs are used as a surrogate marker for acute lead exposure. By the time TLC was funded, succimer was already FDA approved and proven to be safe and effective in lowering BLLs. Why spend $30 million to test the drug again at lower BLLs?

Lead has a long half-life (up to 30 years in bone). Lowering bodily lead via chelation, whether it reverses brain damage or not, is removing a source of exposure to the child.

Should we require evidence that preventing ongoing exposure to children reverses neurodevelopmental delays? Or is common sense sufficient that this is generally a good idea?

> Lead poisoning is a preventable illness, but its disappearance is probably another generation away. Meanwhile, if a simple oral treatment regimen in the context of inexpensive but effective residential lead hazard reduction or relocation of the family could prevent lead-associated developmental delay, it would be a useful adjunct to primary prevention until all children live in lead-safe housing. If lowering blood lead levels after they have been found to be high does not prevent the latent consequences of lead poisoning, then it has little to recommend it at levels below 45 µg/dL. Because cognitive impairment can have life-long consequences and many children will continue to be exposed to lead, information about the efficacy and safety of chelation therapy is necessary both for clinicians caring for the lead-exposed child and for policy makers.

Treatment of Lead-Exposed Children Trial Group. The Treatment of Lead-Exposed Children trial: design and recruitment for a study of the effect of oral chelation on growth and development in toddlers. Paediatr Perinat Epidemiol. 1998;12(3):313-333. PMID: 9690266; DOI: 10.1046/j.1365-3016.1998.00122.x

Prevention of Lead-induced Developmental Delay with Oral Chelation: the Treatment of Lead-exposed Children (TLC) trial

Background Prospective, observational studies have shown that lead produces a dose- (or blood level-) related reduction in developmental test scores *(Needleman and Gatsonis, 1990; Pocock et al., 1994).* **The clearest relationship is between peak blood lead,** which occurs at 20 to 30+ months of age, and test scores beginning at age 48-57 months and thereafter. There is no demonstrated threshold for this effect; **it occurs at levels achieved by one million or more children in the US** *(Pirkle et al., 1994),* and at levels that produce no symptoms or laboratory abnormalities. Although childhood lead exposure may also affect growth, hearing, behavior, and blood pressure, the best quantified effect at low levels is on developmental test scores; an increase in blood lead of **10 µg/dl is associated with a decrease in IQ of 2-3 points. If lead causes developmental delay, that effect can be prevented by preventing lead exposure. However, since the mechanism of the effect is unknown, it is unclear whether it can be reversed or attenuated once exposure has occurred**. **It is this question of reversibility which underlies the TLC project.**

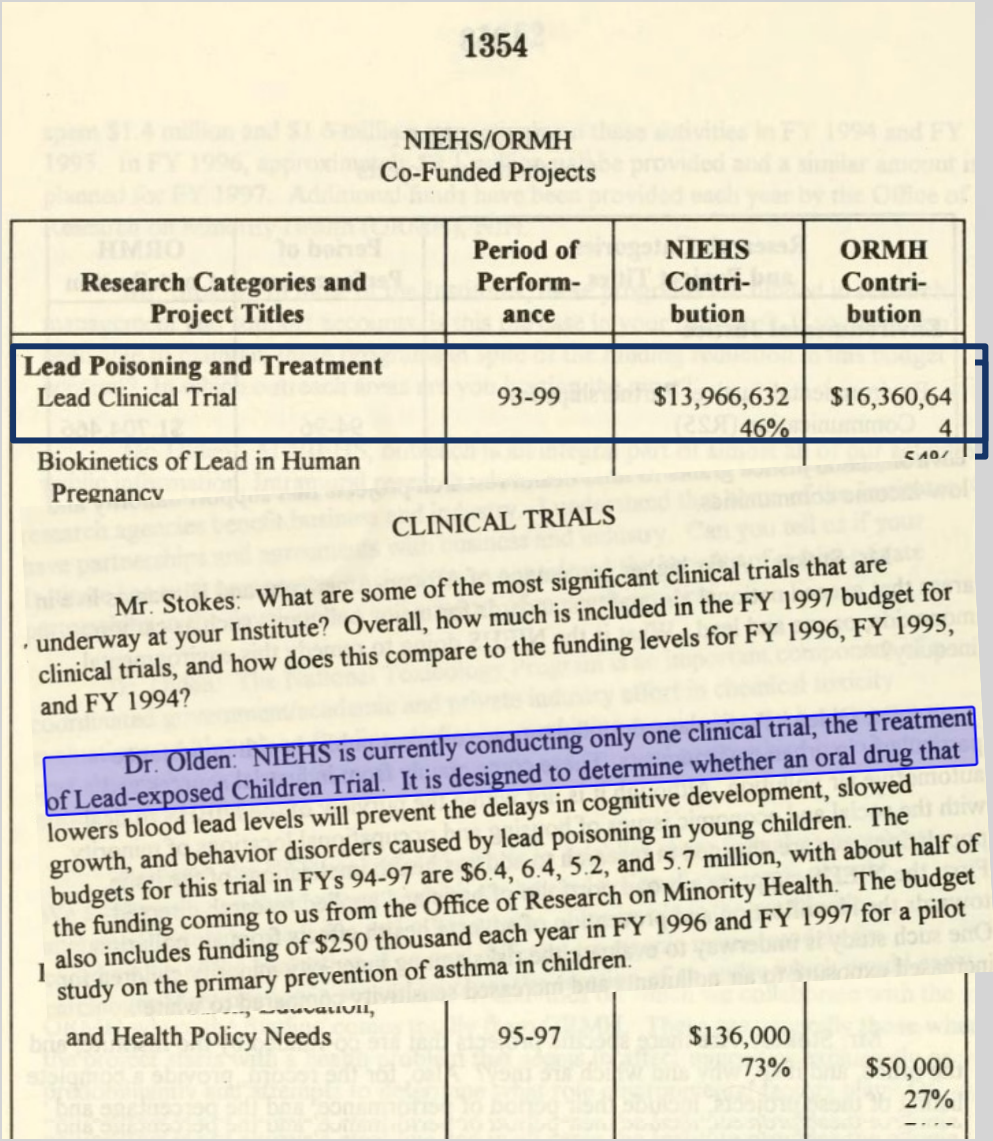
In 1991, the Centers for Disease Control recommended universal screening of children for elevated blood lead *(Centers for Disease Control, 1991)*. They recommended medical therapy, *i.e.*, chelation, for children with blood leads greater than 45 µg/dl. They recommended against medical therapy for children whose blood leads were less than 20 µg/dl, and left the option of therapy, no therapy, or participation in trials of therapy for children between 20 and 45 µg/dl. Until 1991, chelation of lead-poisoned children had been done in specialized centers, which admitted children and treated them parenterally (usually intravenously). However, also in 1991, the orally active chelating drug Chemet® (succimer, McNeil) was licensed (as an Orphan Drug) for treatment of young children with blood levels of 45 µg/dl.

NIEHS and its advisors, **especially the American Academy of Pediatrics Committee on Environmental Health**, believed that many children would be treated with this drug at blood leads below the labelled level, despite the fact that there was relatively little evidence of safety and no evidence of efficacy for prevention of the latent effects of lead, including developmental delay. ***Lowering of blood lead per se at these levels is without known clinical benefit.***

NIEHS believed that a formal trial of succimer for the prevention of developmental delay in children was warranted. **Drug therapy is costly (Chemet® costs about $300/course, most children need multiple courses over months), potentially hazardous, and would be given to asymptomatic children**. Effective, simple intervention to regain lost IQ points, however, would be useful in these children and be very cost-effective in the long run. Primary prevention, *i.e.*, prevention of exposure, is perhaps another generation away for millions of children. Good data on which to base therapy were necessary. **McNeil (the pharmaceuticals company) was interested only in further studies showing that Chemet reduced blood lead, and had no plans to test the ability of the drug to prevent developmental delay.**

This slide is from the TLC website, reformatted for this presentation

Funding



1354

NIEHS/ORMH
Co-Funded Projects

Research Categories and Project Titles	Period of Perform-ance	NIEHS Contri-bution	ORMH Contri-bution
Lead Poisoning and Treatment			
Lead Clinical Trial	93-99	$13,966,632 46%	$16,360,64 4
Biokinetics of Lead in Human Pregnancy			
and Health Policy Needs	95-97	$136,000 73%	$50,000 27%

CLINICAL TRIALS

Mr. Stokes: What are some of the most significant clinical trials that are underway at your Institute? Overall, how much is included in the FY 1997 budget for clinical trials, and how does this compare to the funding levels for FY 1996, FY 1995, and FY 1994?

Dr. Olden: NIEHS is currently conducting only one clinical trial, the Treatment of Lead-exposed Children Trial. It is designed to determine whether an oral drug that lowers blood lead levels will prevent the delays in cognitive development, slowed growth, and behavior disorders caused by lead poisoning in young children. The budgets for this trial in FYs 94-97 are $6.4, 6.4, 5.2, and 5.7 million, with about half of the funding coming to us from the Office of Research on Minority Health. The budget also includes funding of $250 thousand each year in FY 1996 and FY 1997 for a pilot study on the primary prevention of asthma in children.

https://docs.google.com/spreadsheets/d/1uNKh4kOauke12nsyvin18SJEgoUOOBFcjFkML7AAidg/edit?gid=1021367851#gid=1021367851

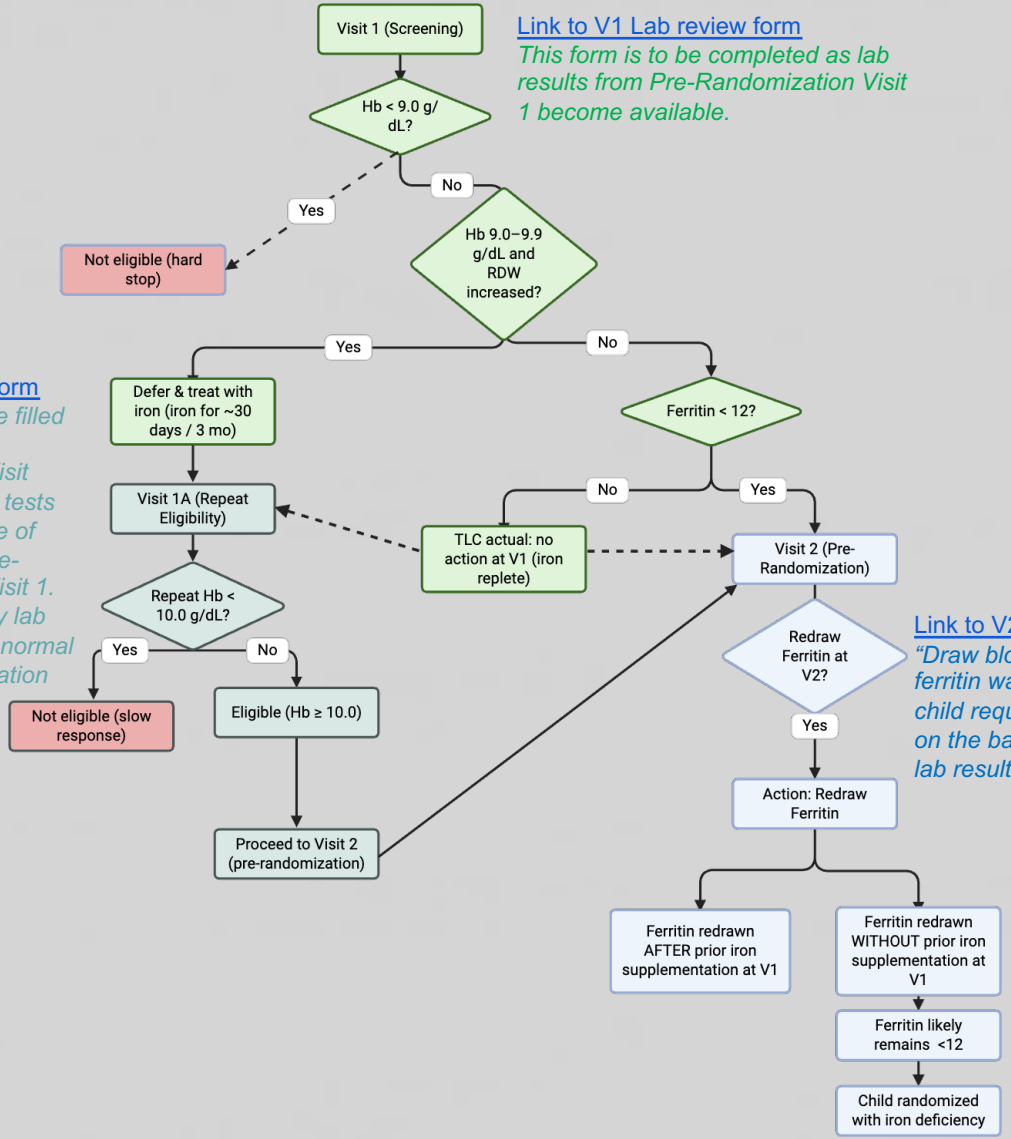
Ferritin reporting. The trial measured baseline ferritin in its participants but did not report baseline ferritin status of randomized groups among lab values, in all but one publication (**see Table 1**) describing the effect of chelation on growth, published in 2004. In that instance, they reported ferritin as the arithmetic mean.

To explain their handling of mineral status (iron in particular) they published a paper which included analysis on a convenience sample of enrolled (but not necessarily randomized) participants, comparing arithmetic mean ferritin with that of NHANES III subjects. They concluded that TLC children with high BLLs had no difference in iron status compared to NHANES III children with lower BLLs, and thus, there was no need to treat or test for iron deficiency with BLLs 20-44 µg/dL.

"Your child will have a blood test and check up today. You will get another appointment to come back to the clinic in about one month for a second check up and blood test. We will look for several things with the blood tests. We will measure the amount of lead. We will make sure that there is not something about the way that your child's liver or kidneys work that would keep us from giving succimer to them.

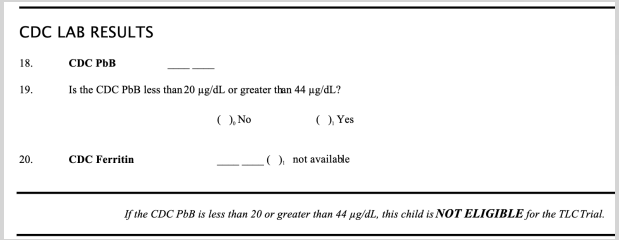
We will make sure that the cells in their blood are normal and that they have enough iron. If your child has so little iron that he or she is anemic or has low blood, then we will give you iron for him or her and check him or her again after taking it to see if he or she is eligible."

Protocol Version 10, APPENDIX 2: Core Consent Forms: p. 44



[Link to V1 Lab review form]

This form is to be completed as lab results from Pre-Randomization Visit 1 become available.



CDC LAB RESULTS

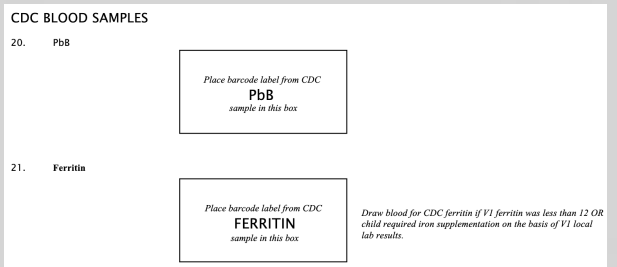
18. **CDC PbB** ___ ___

19. Is the CDC PbB less than 20 µg/dL or greater than 44 µg/dL?

( ), No ( ), Yes

20. **CDC Ferritin** ___ ___ ( ), not available

*If the CDC PbB is less than 20 or greater than 44 µg/dL, this child is **NOT ELIGIBLE** for the TLC Trial.*



CDC BLOOD SAMPLES

20. PbB

Place barcode label from CDC PbB *sample in this box*

21. **Ferritin**

Place barcode label from CDC FERRITIN *sample in this box*

Draw blood for CDC ferritin if V1 ferritin was less than 12 OR child required iron supplementation on the basis of V1 local lab results.

[Link to V1A trial form]

"This form is to be filled out at Pre-Randomization Visit V1A, for local lab tests repeated because of abnormality at Pre-Randomization Visit 1. Do not repeat any lab tests which were normal at Pre-Randomization Visit 1.lab"

[Link to V2 trial form]

"Draw blood for CDC ferritin if V1 ferritin was less than 12 OR child required iron supplementation on the basis of V1 local lab results."

The design paper states that:
"If the child qualified but was iron deficient, a 30-day course of oral iron was prescribed and the child was scheduled to return in 1 month".

This implies that any child with iron deficiency (typically defined by low Ferritin, which the protocol notes was measured at Visit 1) should be identified, treated, and deferred.

The Visit 1 Review Form determines eligibility and deferral solely based on Hemoglobin (Hb) and Red Cell Distribution Width (RDW) from the local lab.
Item 12 asks: "Is the hemoglobin greater than or equal to 9.0 but less than 10.0 AND is the RDW increased?".
Answering "Yes" triggers a "Defer" status.

Item 20 records "CDC Ferritin" but provides an option for "not available" and, crucially, does not link Ferritin results to the deferral or eligibility decision.

The forms fail to capture children who are iron deficient but not anemic (e.g., Normal Hb > 10.0, but Low Ferritin < 12). According to the forms, these children would be marked "Eligible" at Visit 1 and would not receive the 30-day iron run-in treatment described in the protocol. This contradicts the protocol's implication that "iron deficient" children (broadly) would be treated before randomization.

Inconsistent Ferritin Monitoring
Visit 1: Ferritin is measured but effectively ignored for clinical decision-making (Screening Form items 10-17 do not reference it).

Visit 2: The form suddenly re-introduces Ferritin as a critical value.

"Draw blood for CDC ferritin if V1 ferritin was less than 12 OR child required iron supplementation on the basis of V1 local lab results". (Item 21)

The study did consider Ferritin < 12 to be the threshold for concern. However, because the Visit 1 form did not use this value to trigger the "30-day iron course" (deferral), a child with Ferritin < 12 (but Hb > 10) would arrive at Visit 2 untreated. Redrawing their ferritin at Visit 2 seems inconsistent if no intervention occurred to change it. Form 1 Form 1A Form 2

The Protocol's Conflicting Definitions

While the Design Paper suggests a broad "identify and treat" approach for iron deficiency, the Protocol explicitly narrows this definition for enrollment purposes, creating a conflict with its own scientific acknowledgment of ferritin's value.

In Section 8.3, the protocol explicitly states that ferritin is the correct tool for identifying iron deficiency:
"Serum ferritin provides a much more sensitive indicator of iron body stores than a traditional serum iron assay.... Serum ferritin is reduced in iron deficiency."

Despite the above admission, Section 7.1.2 ("Management of Iron Status") defines the "iron deficiency" used for study eligibility solely by Hemoglobin and Red Cell Distribution Width (RDW), effectively rendering the "sensitive" ferritin data irrelevant for clinical decision-making:

"Children who are not iron deficient on the basis of the RDW or whose hemoglobin is greater than or equal to 10 g/dL will be enrolled." The protocol contradicts the Design Paper's "30-day course" description.

Instead, Section 7.1.2 dictates a longer prescription but a similar re-test window, which implies that "iron deficient" children (by the narrow Hb/RDW definition) are deferred:

> "...be provided with three months of supplemental iron therapy and will undergo repeat testing at their next visit (approximately one month)."

This evidence suggests that while the study collected ferritin and knew it was the "sensitive indicator" (Section 8.3), it deliberately designed the Management of Iron Status (Section 7.1.2) and the Visit 1 Forms to ignore low ferritin levels. A child with normal hemoglobin but critically low ferritin, a clear case of "iron deficiency" by the protocol's own definition in Section 8.3—would be enrolled without treatment under Section 7.1.2.

TLC Investigators knew that testing for ferritin and treating ID was the standard of care, and explicitly stated it throughout the protocol, but their actions and the trial design did not reflect that

Ferritin, like hemoglobin, is a major iron storage protein. Circulating plasma ferritin is most like the L-isoferritin. **Serum ferritin provides a much more sensitive indicator of iron body stores than a traditional serum iron assay**. **Serum ferritin is increased in iron overload, aging, infection, inflammation, liver disease, juvenile rheumatoid arthritis, leukemia, and Hodgkin's disease. Serum ferritin is reduced in iron deficiency**.

Ferritin will be measured by using the Bio-Rad Laboratories "Quantimmune Ferritin IRMA" kit which is a single-incubation two-site ^{125}I-immunoradiometric assay (IRMA) based on the general principles of assays as described by Addison *et al*.(35) and Miles(36) and modified by Jeong *et al*(37). Protocol 10: 8.3. Ferritin Analysis

IRON STATUS AND SPECIAL TESTS

Tests for Iron Deficiency

Because iron deficiency can enhance lead absorption and toxicity and often coexists with it, all children with blood lead level 20 ug/dL should be tested for iron deficiency.

Measurements of hemoglobin, hematocrit, and reticulocytes are not adequately sensitive, and erythrocyte protoporphyrin (EP) is not specific enough to diagnose iron deficiency (although EP can be used to screen for iron deficiency).

Serum iron and iron binding capacity (transferrin saturation) and ferritin are the most sensitive indicators of iron status. An abnormally low ratio of serum iron to iron binding capacity (transferrin saturation) of 0.2 is consistent with iron deficiency. The serum ferritin level, however, is the most definitive and accurate indication of overall iron status, although it is an acute phase reactant and may be falsely elevated in sick children; a value 12 g/dL [sic] indicates iron deficiency. Although all iron deficient children should receive treatment for this condition, the treatment should not be started until after chelation is completed in children receiving dimercaprol (BAL).

Protocol 10: Appendix 3: Regulation of Environmental Lead- CDC 1991 Guidelines

No difference in iron status between children with low and moderate lead exposure

Janet R. Serwint, MD, Andrew I. Damokosh, PhD, Omer G. Berger, MD, J. Julian Chisolm, Jr, MD, Elaine W. Gunter, BS, MT, Robert L. Jones, PhD, George G. Rhoads, MD, and Walter Rogan, MD, MPH, the Treatment of Lead-Exposed Children Trial

We compared the iron status between children 11 to 33 months old with confirmed blood lead levels of 20 to 44 µg/dL and demographically similar children with blood lead levels of <10 µg/dL. There were no differences. Laboratory investigation or empirical treatment for iron deficiency is not justified on the basis of moderately elevated blood lead levels alone. (J Pediatr 1999;135:108-10)

For children with elevated lead levels, guidelines from the Centers for Disease Control and Prevention state that iron status should be evaluated and iron intake encouraged.[1] It is not clear whether there is a physiologic association between lead exposure or absorption and iron depletion[2,3] or whether some other common factor, perhaps poverty, leads to both.[1] It is important to identify and treat iron deficiency anemia in lead-exposed toddlers because both conditions are thought to contribute to abnormal cognition and development.[4] In this study we explore whether moderately elevated lead levels are associated with measures of iron status, adjusting for other relevant social variables.

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0022-3476/99/$8.00 + 0 9/22/99258

METHODS

We compared iron status between 2 groups of children. The children with moderate lead exposure came from among those recruited for a clinical trial, the Treatment of Lead-Exposed Children Trial, which used oral chelation to attempt to prevent lead-associated developmental delay.[5] These children had blood lead levels of 20 to 44 µg/dL. We compared them with children selected from the third National Health and Nutrition Evaluation Survey who were demographically similar but had low lead levels (<10 µg/dL).

Recruitment for TLC is described elsewhere.[5] Briefly, children were recruited from lead referral and primary care sites in 4 urban centers between August 1994 and October 1996. Eligible children were between 11 and 33 months old and had lead levels of 20 to 44 µg/dL confirmed by the CDC laboratory. At their first visit to a TLC clinic, children had venipuncture for complete blood count and determination of ferritin and blood lead levels. Although TLC excluded children with hemoglobin concentrations of <9 g/dL from further participation, we included those children in this analysis. Because of over 70% of subjects in the TLC were African American and because hemoglobin concentration is lower in black children, we confined the analysis to them.[6]

CDC	Centers for Disease Control and Prevention
FER	Serum ferritin
MCV	Mean corpuscular volume
NHANES III	Third National Health and Nutrition Evaluation Survey
RDW	Red cell distribution width
TLC	Treatment of Lead-Exposed Children Trial

NHANES III was conducted from 1988 to 1994.[7] This survey collected nationally representative data from household interviews, direct standardized physical examinations, and phlebotomy. A total of 24,894 persons aged 1 year and older were examined, of whom 12% were (self-reported) African American and 15% (of the total) were 5 years old or younger. Laboratory data included complete blood count and ferritin and blood lead levels. We selected all African Ameri-

Convenience sample; arithmetic mean ferritin. Not sure if correctly weighted due to lack of reporting.

DISCUSSION

Because fewer parents in the TLC group had completed high school, fewer were employed, and more received medical assistance, one might expect that they would have higher levels of iron deficiency based on these issues alone. This is not what the data demonstrated. This study had a power of 80% to detect a 10.3% difference in iron deficiency or iron deficiency anemia between the 2 groups.

Venipuncture is painful, laboratory work is expensive, and iron may be toxic and is a common pediatric ingestion. Thus laboratory workup or empirical treatment with iron should be reserved for children whose risk derives from factors other than a moderately increased blood lead level.

Tables of same study from previous slide

Table I. Characteristics of TLC and NHANES III patients

		TLC	NHANES III	*P* value for group comparison
Sample size		787	222	
Age (mo)				
	Mean	22.9	23.1	.585
	SD	5.6	6.2	
	N	787	222	
Female				
	%	43.4	49.1	.131
	N	786	222	
Either parent finished high school	%	60.2	77.2	.000
	N	777	219	
Either parent employed	%	36.0	61.2	.000
	N	774	214	
Medicaid assistance received by family	%	85.5	67.2	.000
	N	761	186	
Blood lead level (μg/dL)				
	Mean	26.8	5.0	.000
	SD	5.6	2.1	
	N	787	222	
Ferritin level (μg/L)				
	Mean	27.2	27.0	.904
	SD	18.4	20.4	
	N	756	211	
Hemoglobin (g/dL)				
	Mean	11.6	11.8	.002
	SD	0.9	0.8	
	N	784	212	
RDW (%)				
	Mean	14.3	13.5	.000
	SD	1.8	1.5	
	N	778	212	
MCV (fL)				
	Mean	75.4	78.0	.000
	SD	5.9	5.4	
	N	761	212	

Table II. Prevalence (sample size) of iron depletion, iron deficiency, and iron deficiency anemia in the TLC and NHANES III patients

	TLC	NHANES III	*P* value
Iron depletion			
FER <10 mg/L	11% (756)	13% (212)	.46
Iron deficiency			
FER <10 μg/L and RDW >14.5%	7% (748)	5% (204)	.27
FER <10 μg/L and MCV <70 fL	4% (730)	3% (204)	.99
Iron deficiency anemia			
FER <10 μg/L and hemoglobin <11 g/dL	3% (753)	4% (204)	.52
FER <10 μg/L, RDW >14.5%, and hemoglobin <11 g/dL	3% (748)	3% (204)	.65
FER <10 μg/L, MCV <70 fL, and hemoglobin <11 g/dL	2% (727)	2% (204)	.99

Senwint JR, Damokosh AI, Berger OG, et al. No difference in iron status between children with low and moderate lead exposure. Journal of Pediatrics. 1999;135:108-110. doi:10.1016/s0022-3476(99)70338-0

Table 3. *Children with abnormal laboratory values at clinical centers' local laboratories by treatment group*

Laboratory test	Criteria	Placebo (n = 374) No.	Placebo (n = 374) Proportion (95% CI)	Succimer (n = 383) No.	Succimer (n = 383) Proportion (95% CI)	Difference in proportion (succimer − placebo) Difference (95% CI)
Heme/lymphatic						
Platelet count	<150,000/mm^3	12	3.2 (1.8, 5.5)	19	5.0 (3.0,7.6)	1.8 (−1.7,6.4)
	Confirmed	1	0.3 (0.0, 1.4)	0	0.0 (0.0,0.9)	−0.3 (−2.6,1.4)
Absolute neutrophil count	<800/mm^3	36	9.6 (6.8, 13.0)	43	11.2 (8.2,14.8)	1.6 (−3.3,7.4)
	Confirmed	5	1.3 (0.5, 3.1)	3	0.8 (0.2,2.2)	−0.6 (−4.0,1.8)
Metabolic						
Alkaline phosphatase	>local upper limit of normal*	146	39.0 (34.2, 44.0)	148	38.6 (33.7,43.7)	−0.4 (−7.9,6.7)
	>5× local upper limit of normal	7	1.9 (0.9, 3.7)	9	2.4 (1.2,4.3)	0.5 (−2.3,4.5)
	Confirmed > 5× local upper limit of normal	2	0.5 (0.1, 1.9)	2	0.5 (0.1,1.8)	0.0 (−3.2,2.1)
Aspartate aminotransferase	> local upper limit of normal†	157	42.0 (36.9, 46.9)	163	42.6 (37.6,47.6)	0.6 (−6.6,8.0)
	> 2× local upper limit of normal	12	3.2 (1.8, 5.5)	9	2.4 (1.2,4.3)	−0.9 (−5.1,2.3)
	Confirmed > 2× local upper limit of normal	0	0.0 (0.0, 0.9)	1	0.3 (0.0,1.4)	0.3 (−1.3,2.6)
Alanine aminotransferase	> local upper limit of normal‡	15	4.0 (2.3, 6.4)	27	7.0 (4.7,10.1)	3.0 (−0.8,8.0)
	> 2× local upper limit of normal	4	1.1 (0.4, 2.7)	3	0.8 (0.2,2.2)	−0.3 (−3.7,2.0)
	Confirmed > 2× local upper limit of normal	0	0.0 (0.0, 0.9)	1	0.3 (0.0,1.4)	0.3 (−1.3,2.6)

* Alkaline phosphate local upper limit of normal (U/L): Baltimore, 320 (Hopkins/U Maryland), 490 (University Hospital); Newark, 270 (0–2 y) and 415 (>2 y); Philadelphia, 131; Ohio, 400 (Columbus), 305 (♂) and 390 (♀) (Cincinnati).

† Aspartate aminotransferase local upper limit of normal (U/L): Baltimore, 35 (Hopkins/U Maryland), 40 (University Hospital); Newark, 42 (0–2 y) and 65 (>2 y); Philadelphia, 30; Ohio, 75 (Columbus), 35 (Cincinnati).

‡ Alanine aminotransferase local upper limit of normal (U/L): Baltimore, 30 (Hopkins/U Maryland), 45 (University Hospital); Newark, 60 (0–2 y) and 50 (>2 y); Philadelphia, 35; Ohio, 150 (Columbus), 30 (Cincinnati).

Safety and Efficacy paper, No baseline ferritin reported.

Rogan W, Bornschein RL, Chisolm J, et al. Safety and efficacy of succimer in toddlers with blood lead levels of 20-44 µg/dL. *Pediatric Research*. 2000;48:593-599. doi:10.1203/00006450-200011000-00007

therapy) and the child was examined. If no disqualifying condition was noted from the history and physical examination, blood was drawn for measurement of blood lead, ferritin, complete blood count, and other indices were selected either

Table 1. Laboratory results before treatment in randomised children

	Placebo			Active drug		
	n	Mean	SD	*n*	Mean	SD
Haemoglobin (g/dL)	384	11.7	0.9	393	11.7	0.9
Red cell distribution width (%)	384	14.4	1.9	390	14.3	2.0
Serum creatinine (mg/dL)	381	0.4	0.1	392	0.4	0.1
Platelets (count/mm^3)	384	358	91	392	354	85
Alkaline phosphatase (IU/L)	383	270	111	393	277	136
Alanine aminotransferase (IU/L)	383	18	9	394	19	10
Aspartate aminotransferase (IU/L)	383	38	10	393	38	13
Absolute neutrophil count (count/mm^3)	377	2770	1576	389	2733	1489

SD, standard deviation.

Design and recruitment paper. No baseline ferritin reported

Rogan WJ. The Treatment of Lead-exposed Children (TLC) trial: Design and recruitment for a study of the effect of oral chelation on growth and development in toddlers. *Paediatr Perinat Epidemiol*. 1998;12:313-333. doi:10.1046/j.1365-3016.1998.00122.x

TABLE 1. BASE-LINE CHARACTERISTICS OF ENROLLED CHILDREN ACCORDING TO TREATMENT GROUP FROM 1994 THROUGH 1997.*

CHARACTERISTIC	PLACEBO GROUP (N=384)	SUCCIMER GROUP (N=396)
Age — mo	24±6	24±6
Blood lead level — μg/dl	26±5	26±5
Weight — kg	12.3±1.9	12.3±2.0
Body-surface area — m^2	0.53±0.1	0.52±0.1
Reported birth weight — g†	3169±620	3136±551
Bayley Scales of Infant Development		
Mental Development Index‡	82±14	84±14
Psychomotor Development Index§	93±13	93±15
IQ of the caregiver¶	80±11	81±11
Female sex — no. (%)	165 (43)	178 (45)
Ethnic group or race — no. (%)		
Hispanic	19 (5)	20 (5)
Black	292 (76)	309 (78)
Single parent — no. (%)	277 (72)	281 (71)
Parent with less than a high-school education — no. (%)	153 (40)	162 (41)
At least one employed parent — no. (%)	165 (43)	162 (41)
Annual family income — no. (%)		
<$10,000	137 (36)	152 (38)
≥$10,000	102 (27)	107 (27)
Unknown	145 (38)	137 (35)
Parent receiving public assistance — no. (%)	371 (97)	376 (95)

*Plus–minus values are means ±SD.

†These data were available for 361 children in the placebo group and 380 children in the succimer group.

‡These data were available for 375 children in the placebo group and 390 children in the succimer group.

§These data were available for 335 children in the placebo group and 348 children in the succimer group.

¶These data were available for 370 children in the placebo group and 375 children in the succimer group.

Primary outcome. No baseline ferritin reported.

Rogan WJ, Dietrich KN, Ware JH, et al. The Effect of Chelation Therapy with Succimer on Neuropsychological Development in Children Exposed to Lead. New England Journal of Medicine. 2001;344(19):1421-1426. doi:10.1056/nejm200105103441902

TABLE 2. Baseline Characteristics of Enrolled Children Followed to Seven Years of Age According to Treatment Group

Characteristic	Placebo Group (N = 322; Mean [SD])	Succimer Group (N = 325; Mean [SD])
Age, mo	25 (5)	25 (6)
Blood lead level, μg/dL	26 (5)	27 (5)
Weight, kg	12.4 (1.9)	12.3 (2.0)
Body surface area (m^2)	0.50 (0.1)	0.50 (0.1)
Reported birth weight†	3171 (624)	3140 (552)
Bayley Scales of Infant Development		
Mental Development Index‡	82 (13)	84 (13)
Psychomotor Development Index§	92 (13)	93 (14)
Caregiver's IQ‖	79 (11)	81 (11)
Female	44%	47%
Ethnicity		
Hispanic	8%	6%
Black	75%	79%
Single parent	71%	71%
Parent with less than a high school education	40%	39%
At least 1 employed parent	44%	40%
Annual family income		
<$10 000	38%	38%
≥$10 000	26%	28%
Unknown	37%	35%
Parent on public assistance	96%	95%

* Convert to μmol/L ([μg/dL] × 0.04826).
† These data were available for 302 children in the placebo group and 311 children in the succimer group.
‡ These data were available for 313 children in the placebo group and 320 children in the succimer group.
§ These data were available for 275 children in the placebo group and 283 children in the succimer group.
‖ These data were available for 318 children in the placebo group and 315 children in the succimer group.

5-year follow-up. No baseline ferritin.

Dietrich KN, Ware JH, Salganik M, et al. Effect of chelation therapy on the neuropsychological and behavioral development of lead-exposed children after school entry. Pediatrics. 2004;114:19-26. doi:10.1542/peds.114.1.19

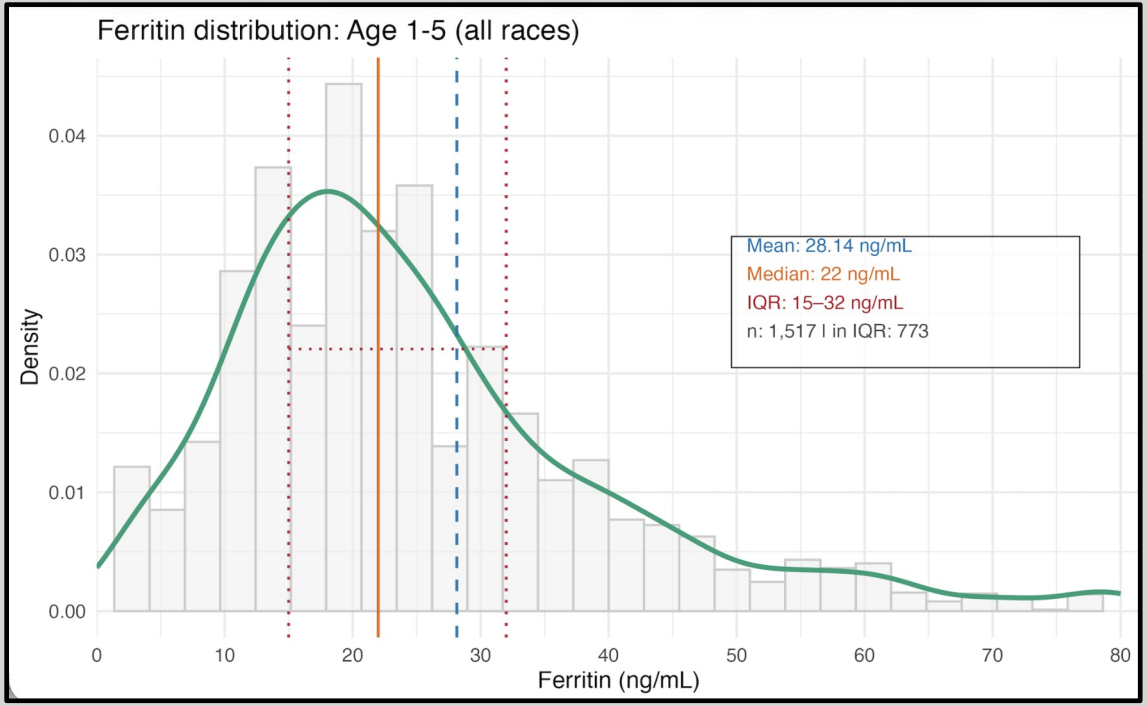
First time baseline ferritin is reported. Note how large the SD, which is why arithmetic mean is a poor metric of central tendency for ferritin.

Table 1. Baseline health status characteristics of randomized subjects by treatment group: TLC trial.

	Placebo		Succimer	
	No.	Mean ± SD	No.	Mean ± SD
Age (months)	384	24.5 ± 5.5	396	24.4 ± 5.7
Blood lead (μg/dL)	384	25.9 ± 4.8	396	26.5 ± 5.4
Hemoglobin (g/dL)	384	11.7 ± 0.9	393	11.7 ± 0.9
Ferritin (μg/dL)	380	28.5 ± 19.6	393	28.1 ± 17.6
Birth weight (g)	361	3,169 ± 620	380	3,136 ± 551
Height (cm)	380	85.5 ± 5.7	388	85.3 ± 6.0
Height-for-age *Z*-score	380	–0.11 ± 1.01	388	–0.12 ± 1.01
Weight (kg)	374	12.3 ± 1.9	389	12.3 ± 2.0
Weight-for-age *Z*-score	374	–0.02 ± 1.18	389	0.01 ± 1.25
Body surface area (m^2)	384	0.5 ± 0.1	396	0.5 ± 0.1

Peterson KE, Salganik M, Campbell C, et al. Effect of succimer on growth of preschool children with moderate blood lead levels. *Environmental Health Perspectives*. 2004;112(2):233-237. doi:10.1289/ehp.6331

Arithmetic vs geometric mean ferritin. Using the arithmetic mean value for ferritin distribution is generally not the best measure of central tendency for skewed distributions. Ferritin, especially in children, is characteristically right skewed and should be analyzed by geometric mean as the best measure of central tendency.



Our analyses of NHANES 1998-2002 revealed an arithmetic mean of 28.14 ng/mL for children ages 1-5 all races, and a median of 22 ng/mL—leaving half of all children in a range considered physiologically deficient (~20 ng/mL). Additionally, ferritin analyses should always be adjusted with CRP values, since inflammation can increase ferritin levels even in iron deficient states. The analyses we performed are consistent with TLCs, showing little difference in ferritin among different BLL quartiles. However, our interpretation differs in that we believe on average most children are at risk of iron deficiency. Iron deficiency increases lead exposure and absorption, and so all children who are at risk of exposure should be screened (using CRP & ferritin) and treated for iron deficiency.

Table 1: Overall Summary Statistics for Children Aged 1–5 Years (All Races)
This table outlines the key weighted and unweighted descriptive statistics for the entire cohort aged 1–5 years

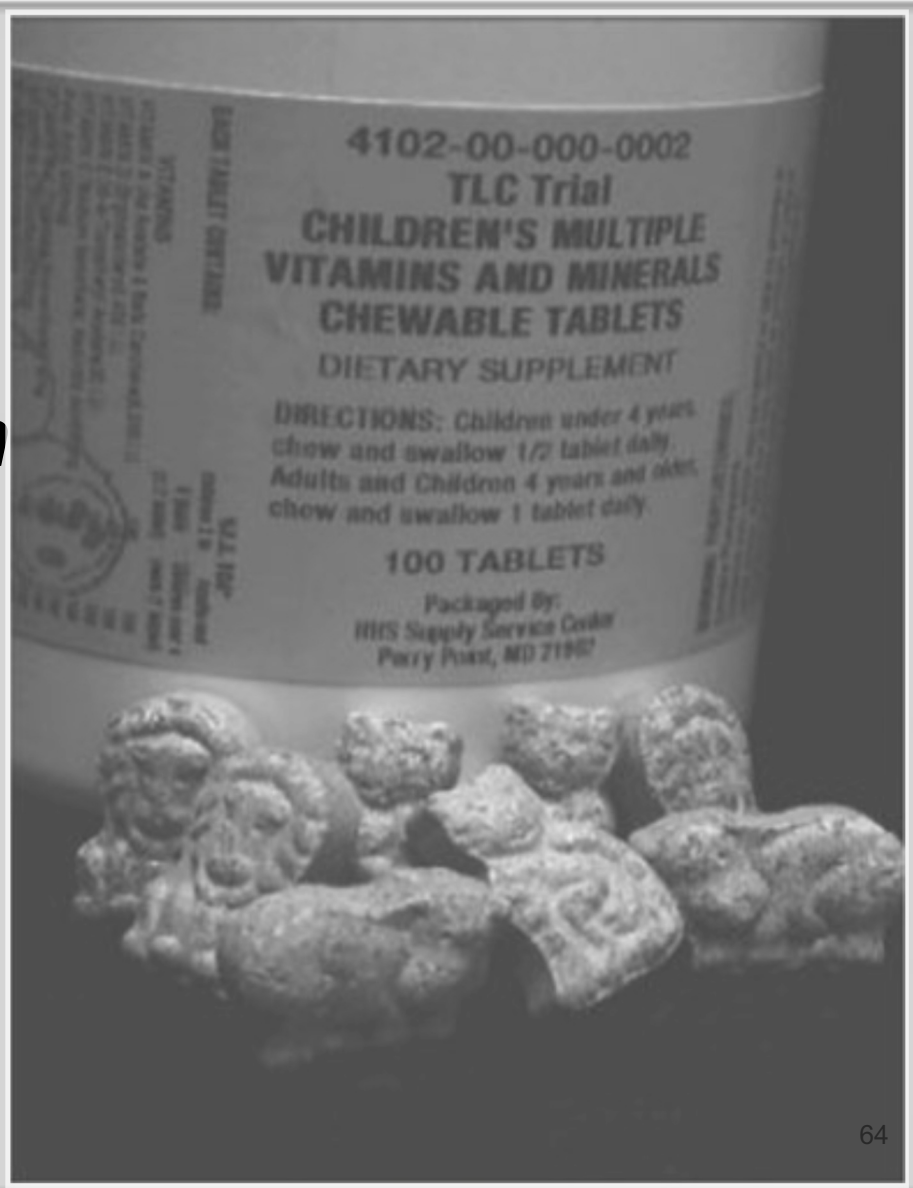
Race	Lead Level Band ()	(unweighted)	Survey design	Geometric Mean Blood Lead (95% CI)	Geometric Mean Ferritin (95% CI)
All	1–5	941	29	1.94 (1.85–2.03)	20.75 (19.46–22.14)
All	5–10	78	10	Suppressed ()	Suppressed ()
All	10–20	18	2	Suppressed ()	Suppressed ()
Non-Hispanic Black	1–5	332	21	2.37 (2.25–2.50)	26.42 (24.11–28.95)
Non-Hispanic Black	5–10	73	7	Suppressed ()	Suppressed ()
Non-Hispanic Black	10–20	12	1	Suppressed ()	Suppressed ()

NHANES 1999-2001

Table 2: Measures of Association (Ages 1–5, All Races)- summarizes the weighted measures quantifying the relationship between ferritin and lead levels.

Statistic	Value
Unweighted Sample Size ()	1,517
Survey Design Degrees of Freedom (df)	29
Weighted Arithmetic Mean Ferritin (95% CI)	28.14 ng/mL (24.86–31.41)
Ferritin Median (IQR)	22 ng/mL (15–32)
Weighted Arithmetic Mean Blood Lead (95% CI)	2.47 (2.28–2.67)
Lead Median (IQR)	1.80 (1.20–2.90)
with Ferritin <10 ng/mL	163 (9.41%; 95% CI 6.99–11.82%)
with Ferritin <15 ng/mL	380 (23.89%; 95% CI 20.38–27.40%)
with Ferritin <20 ng/mL	635 (41.56%; 95% CI 38.24–44.89%)

Recall of a Lead-Contaminated Vitamin



Recall of a Lead-Contaminated Vitamin and Mineral Supplement in A Clinical Trial

Towards the end of the trial, a batch of multivitamins which TLC gave participants were found to be contaminated with lead, with 628 out of 780 participants potentially exposed. They discuss the recall of these vitamins in a separate publication, noting that adherence to supplements was surprisingly variable among participants. Of those 628 exposed, 571 had BLLs to assess the exposure's effect on blood lead.

The authors note that 149 siblings were also exposed to the lead contaminated vitamins.

All but one trial site encouraged sharing of multivitamins with siblings and family members. Their interpretation was that they found no dose response effect from the incident, so nothing more was to be done. The primary publication in NEJM addresses the limitation in one sentence, citing the ancillary article. The five-year follow-up does not mention the incident or cite it as a reference.

Of note, no report of exposure status by treatment group was given.

Recall of a Lead-Contaminated Vitamin and Mineral Supplement in A Clinical Trial

Read this abstract.

How many participants, as you understand it, were exposed to contaminated vitamins?

Recall of a Lead-Contaminated Vitamin and Mineral Supplement in a Clinical Trial

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SUMMARY

Purpose — The Treatment of Lead-exposed Children (TLC) trial tested whether developmental outcome differed between children treated for lead poisoning with succimer or placebo. On 7 July 1997, TLC was informed that the vitamin and mineral supplements it gave to all children were contaminated with about 35 μg of lead per tablet.

Methods — TLC recalled the contaminated supplements and measured the children's exposure.

Results — The families of 96% of the children were contacted with 30 days. Among the 571 children to whom the contaminated supplements were dispensed, the mean increase in blood lead was 0.06 ± 0.01 μmol/L (1.2 ± 0.2 μg/dL); among 78 children to whom they were not, it was 0.09 ± 0.03 μmol/L (1.8 ± 0.7 μg/dL). There was no evidence of a dose-response relation between estimated supplement consumption and increase in blood lead concentration.

Conclusions — The children's blood lead concentrations were not detectably affected by the contamination. Since the association of cognitive delay with lead exposure is best described for blood lead, we believe that the trial's inference about the effect of drug therapy on lead induced cognitive delay should be unaffected.

Recall of a Lead-Contaminated Vitamin: Published Tables are misleading

Table 1. — Results of contact effort by exposure status; 1 July 1997 to 13 October 1997

			n	%
Potentially exposed			628	
	Contacted			
		Had PbB[a]	571	90.9%
		Did not have PbB	52	8.3%
	Not contacted		5	0.8%
Not exposed			152	
	Contacted			
		Had PbB	104	68.4%
		Did not have PbB	5	3.3%
	Not contacted		43	28.3%
Total			780	

[a]Blood lead measurement.

Table 2. — Mean change in blood lead concentrations between receipt of supplements and recall clinic visit by exposure status. Potentially exposed children are further stratified by contents of returned bottles of supplements, April–October 1997

		Mean	Standard error	*N*
Potentially Exposed		1.2	0.2	571
	Returned contaminated bottle(s)	0.8	0.3	234
	Quintiles of missing supplements			
	40–100	0.8	0.5	46
	21–39	0.1	0.6	46
	8–20	1.7	0.6	49
	1–7	0.5	0.7	50
	0	1.0	0.7	43
	Did not return contaminated bottle(s)	1.5	0.3	337
Unexposed		1.8	0.7	78

Recall of a Lead-Contaminated Vitamin: Published Tables are misleading

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Potentially Exposed	1.2	0.2	571
Returned contaminated bottle(s)	0.8	0.3	234
Quintiles of missing supplements			
40–100	0.8	0.5	46
21–39	0.1	0.6	46
8–20	1.7	0.6	49
1–7	0.5	0.7	50
0	1.0	0.7	43
Did not return contaminated bottle(s)	1.5	0.3	337
Unexposed	1.8	0.7	78

“Potentially Exposed: 571”

This is misleading. They were able to measure 571 kids BLLs. 628 were potentially exposed. I reformatted the data in the following slides.

Recall of a Lead-Contaminated Vitamin: Tables Reformatted

Results of contact effort by exposure status

1 July 1997 to 13 October 1997

	n	%
Total	780	100.00%
Potentially exposed	628	80.51%
Contacted	623	79.87%
—Had BLL	571	73.21%
—Did not have BLL	52	6.67%
Not contacted	5	0.64%
Not exposed	152	19.49%
Contacted	109	13.97%
—Had BLL	104	13.33%
—Did not have BLL	5	0.64%
Not contacted	43	5.51%

Recall of a Lead-Contaminated Vitamin: Tables Reformatted

Mean change in blood lead concentrations between receipt of supplements and recall clinic visit by exposure status

Potentially exposed children are further stratified by contents of returned bottles of supplements, April–October 1997

Exposure detail	Mean (µg/dL)	Standard error (µg/dL)	*N*
Potentially Exposed	**1.2**	0.2	571
Returned contaminated bottle(s)	**0.8**	0.3	234
Quintiles of missing supplements			
40–100	0.8	0.5	46
21–39	0.1	0.6	46
8–20	1.7	0.6	49
1–7	0.5	0.7	50
0	1.0	0.7	43
Did not return contaminated bottle(s)	**1.5**	0.3	337
Unexposed	**1.8**	0.7	78

Change reported in µg/dL. Data from recall clinic visits, April–October 1997.

Recall of a Lead-Contaminated Vitamin: Tables Reformatted

Recall of a Lead-Contaminated Multivitamin–reformatted				
Exposure Status	**N=780**	**% of 780**	**Mean (µg/dL)**	**SE (µg/dL)**
Exposed	628	80.5%		
Contacted in recall	623	79.9%		
BLL measured	571	73.2%	**1.2**[a]	**0.2**
Returned contaminated bottle(s)	234	30.0%	**0.8**[b]	**0.3**
Number of missing supplements				
40–100	46	5.9%	0.8	0.5
21–39	46	5.9%	0.1	0.6
8–20	49	6.3%	1.7	0.6
1–7	50	6.4%	0.5	0.7
0	43	5.5%	1	0.7
Did not return contaminated bottle(s)	337	43.2%	**1.5**[b]	**0.3**
No BLL Measured	57	7.3%		
Not contacted in recall	5	0.6%		
Siblings exposed	149			
Not exposed	152	19.5%		
Contacted in recall	109	14.0%		
BLL measured	104	13.3%	?	?
BLL measured and reported[a]	78	10.0%	**1.8**[a]	**0.7**
BLL measured, not reported[c]	26	3.3%	**?**[c]	**?**
No BLL measured	5	0.6%		
Not contacted in recall	43	5.5%		

[a] Investigators compared 571 children who were exposed, to 78 children of the 152 children not exposed, and using quantiles of missing supplements of those who returned bottles, found no evidence of a dose-response relationship.

[b] If we examine the children who returned contaminated bottles, with those who didn't, a clear dose response is evident.

[c] There were apparently 26 "not-exposed" children who had BLLs taken during the recall effort, but were not included in the table. No explanation is given as to why they are ommitted.

All but one of the TLC sites had encouraged families to give the supplements to any other small child in the home ('sibs' hereafter). Because some sibs had been taking contaminated supplements, TLC wanted to offer to measure their blood lead as a clinically indicated test, not as a research procedure. CDC was reluctant to analyse sibs' blood leads without a research protocol and a consent process that covered these children. To resolve this impasse, the Cincinnati clinical centre volunteered its laboratory to measure the sibs' blood leads free of charge, as a clinically indicated, non-research test. Eventually, 149 such sibs were tested. They were managed according to local clinical guidelines; none were thought to have been specifically affected by the supplements.

All but 1 site encouraged families give supplements to other small children at home.

149 siblings were exposed to the contaminated supplements.

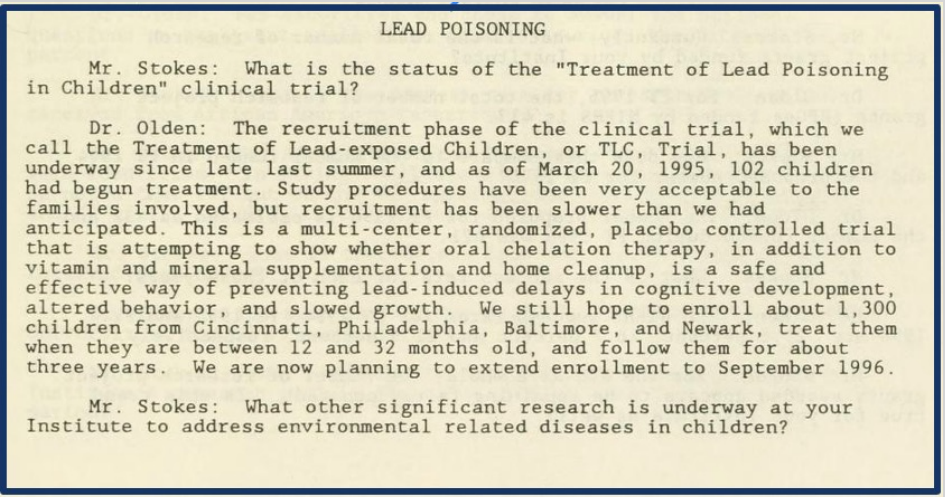
TLC concluded this episode when, on 4 December 1997, TLC staff presented the incident to the Data and Safety Monitoring Committee. The investigators proposed that the supplements had not caused a clinically significant increase in the blood leads of TLC children. Thus, the ability of the trial to assess the effects of succimer treatment on development had not been compromised by the incident. The Committee accepted that conclusion, and had no suggestions for further activity related to the contamination.

Conclusions by DSMC: no further suggestions, no need for a sensitivity analysis

TLC makes intense efforts to achieve adherence to its drug regimen, and so we were surprised to see how much of the supplement came back when we asked the families to bring in all of their bottles. One family in Cincinnati returned 519 tablets from 6 bottles, most of which had been dispensed prior to the contamination. Succimer and placebo were given only for 6 months or so, and the families were reminded of adherence by pill counts and diaries.

Heterogeneous adherence to the multivitamins

Design and Recruitment



LEAD POISONING

Mr. Stokes: What is the status of the "Treatment of Lead Poisoning in Children" clinical trial?

Dr. Olden: The recruitment phase of the clinical trial, which we call the Treatment of Lead-exposed Children, or TLC, Trial, has been underway since late last summer, and as of March 20, 1995, 102 children had begun treatment. Study procedures have been very acceptable to the families involved, but recruitment has been slower than we had anticipated. This is a multi-center, randomized, placebo controlled trial that is attempting to show whether oral chelation therapy, in addition to vitamin and mineral supplementation and home cleanup, is a safe and effective way of preventing lead-induced delays in cognitive development, altered behavior, and slowed growth. We still hope to enroll about 1,300 children from Cincinnati, Philadelphia, Baltimore, and Newark, treat them when they are between 12 and 32 months old, and follow them for about three years. We are now planning to extend enrollment to September 1996.

Mr. Stokes: What other significant research is underway at your Institute to address environmental related diseases in children?

TLC had trouble enrolling enough kids, making it even less likely they'd detect the miniscule 3 IQ points (likely closer to 1 based off current evidence) they would theoretically achieve with a 10 µg/dL BLL difference.

They hoped to enroll 1300 kids based off Olden's 1995 Congressional Appropriations hearing, but had only enrolled 102 by March 1995. The initial call for grants in 1992 puts the number of randomized participants "on the order of 1000", and the August 1994 and 1997 Protocols expected to enroll 1332 (333 from each site) and retain 1040 (78% of those enrolled) to 3-year follow-up.

Design and Recruitment

The abstract of the The Design and Recruitment Paper is very telling:

> ….***The study can detect a three-point difference in full-scale IQ at 3-year follow-up.*** ***Statistical power for the other end points is more difficult to estimate.*** ***A total of 1854 children were evaluated and 780 children were randomised between August 1994 and January 1997****. The mean age of randomised children was 24 months and mean blood lead level 26 µg/dL. Three-quarters were African-American. Most children had poor, single mothers who had completed 12 or fewer years of school and who lived in older, poorly maintained residences.*

So TLC wasn't powered to detect any thing except 3-points on full-scale IQ??

That's not clinically meaningful, and within the margin of error for IQ tests—especially for 5-year olds….but… okay. Let's see how they calculated that number...

Design and Recruitment

The abstract of the The Design and Recruitment Paper is very telling:

their treatment assignment (an 'intent-to-treat' analysis). Assuming that the 36-month WPPSI-R score will have a standard deviation of 14 in this sample, that 78% of the 780 randomised children will be tested successfully at 36 months and that adjustment for baseline IQ and maternal IQ will explain 16% of the variance of 36-month IQ, the TLC Trial has the power of 0.82 to detect a difference of three IQ points between treatment groups at 36 months. In observational data, a 10 µg/dL difference in blood lead is associated with as much as a three-point IQ difference.[1,2] In the trial, the mean blood lead at the beginning of therapy is 26 µg/dL, and the treatment goal is 15 µg/dL.

1 Pocock SJ, Smith M, Baghurst P. Environmental lead and children's intelligence: a systematic review of the epidemiological evidence. BMJ. 1994;309(6963):1189-1197.doi:10.1136/bmj.309.6963.1189

2 Needleman HL, Gatsonis CA. Low-level lead exposure and the IQ of children: A metaanalysis of modern studies. JAMA 1990; 263: 673±678.

TLC Website

Background Prospective, observational studies have shown that lead produces a dose- (or blood level-) related reduction in developmental test scores *(Needleman and Gatsonis, 1990; Pocock et al., 1994).* **The clearest relationship is between peak blood lead,** which occurs at 20 to 30+ months of age, and test scores beginning at age 48-57 months and thereafter. There is no demonstrated threshold for this effect; **it occurs at levels achieved by one million or more children in the US** *(Pirkle et al., 1994),* and at levels that produce no symptoms or laboratory abnormalities. Although childhood lead exposure may also affect growth, hearing, behavior, and blood pressure, the best quantified effect at low levels is on developmental test scores; an increase in blood lead of **10 µg/dl is associated with a decrease in IQ of 2-3 points. If lead causes developmental delay, that effect can be prevented by preventing lead exposure. However, since the mechanism of the effect is unknown, it is unclear whether it can be reversed or attenuated once exposure has occurred**. **It is this question of reversibility which underlies the TLC project.**

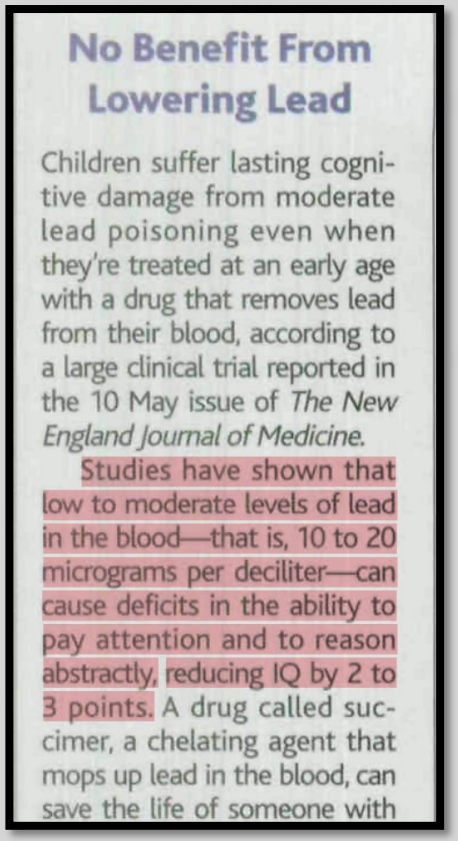
1 Pocock SJ, Smith M, Baghurst P. Environmental lead and children's intelligence: a systematic review of the epidemiological evidence. BMJ. 1994;309(6963):1189-1197.doi:10.1136/bmj.309.6963.1189

2 Needleman HL, Gatsonis CA. Low-level lead exposure and the IQ of children: A metaanalysis of modern studies. JAMA 1990; 263: 673±678.

Design and Recruitment

The five prospective studies with over 1100 children showed no association of cord blood lead or antenatal maternal blood lead with subsequent IQ. Blood lead at around age 2 had a small and significant inverse association with IQ, somewhat greater than that for mean blood lead over the preschool years. The 14 cross sectional studies of blood lead with 3499 children showed a significant inverse association overall but showed more variation in their results and their ability to allow for confounders. The seven cross sectional studies of tooth lead with 2095 children were more consistent in finding an inverse association, although the estimated magnitude was somewhat smaller. Overall synthesis of this evidence, including a meta-analysis, indicates that a typical doubling of body lead burden (from 10 to 20 µg/dL (0.48 to 0.97 µmol/l) blood lead or from 5 to 10 µg/g tooth lead) is associated with a mean deficit in full scale IQ of around **1-2 IQ points.**

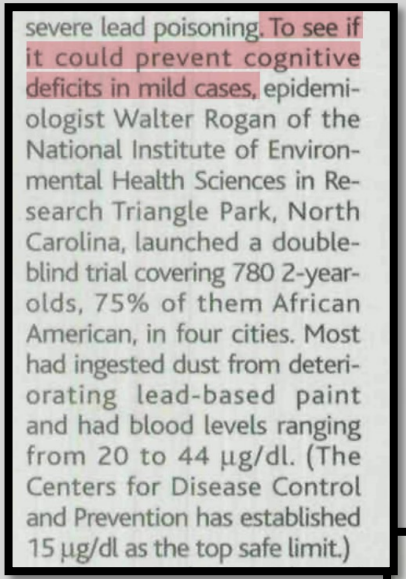
1 Pocock SJ, Smith M, Baghurst P. Environmental lead and children's intelligence: a systematic review of the epidemiological evidence. BMJ. 1994;309(6963):1189-1197.doi:10.1136/bmj.309.6963.1189



No Benefit From Lowering Lead

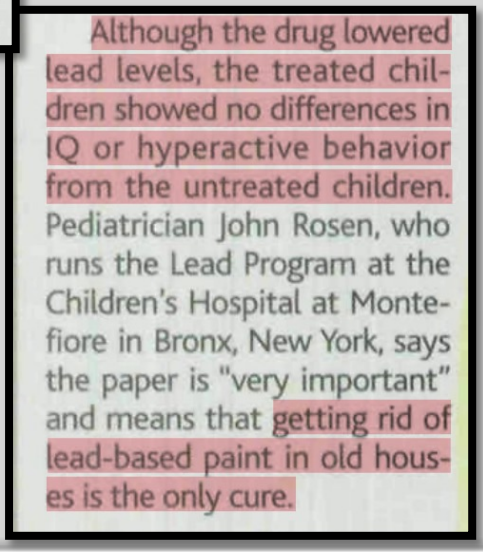
Children suffer lasting cognitive damage from moderate lead poisoning even when they're treated at an early age with a drug that removes lead from their blood, according to a large clinical trial reported in the 10 May issue of *The New England Journal of Medicine*.

Studies have shown that low to moderate levels of lead in the blood—that is, 10 to 20 micrograms per deciliter—can cause deficits in the ability to pay attention and to reason abstractly, reducing IQ by 2 to 3 points. A drug called succimer, a chelating agent that mops up lead in the blood, can save the life of someone with



severe lead poisoning. To see if it could prevent cognitive deficits in mild cases, epidemiologist Walter Rogan of the National Institute of Environmental Health Sciences in Research Triangle Park, North Carolina, launched a double-blind trial covering 780 2-year-olds, 75% of them African American, in four cities. Most had ingested dust from deteriorating lead-based paint and had blood levels ranging from 20 to 44 µg/dl. (The Centers for Disease Control and Prevention has established 15 µg/dl as the top safe limit.)

Here it's described as being tested as *preventative*, which is really what TLC tested since participants had ongoing exposure



Although the drug lowered lead levels, the treated children showed no differences in IQ or hyperactive behavior from the untreated children. Pediatrician John Rosen, who runs the Lead Program at the Children's Hospital at Montefiore in Bronx, New York, says the paper is "very important" and means that getting rid of lead-based paint in old houses is the only cure.

TLC participants didn't have BLLs of 10–20 µg/dL…they had BLLs of 44–20 µg/dL, 20 µg/dL was the exclusion criteria. And the treatment endpoint was 15 µg/dL so TLC never targeted a treatment effect that they were basing the 3-point IQ difference on.

$$\mathrm{IQ}_{20} - \mathrm{IQ}_{10} = \Delta\mathrm{IQ}_{\mathrm{observed}} = -3 \text{ IQ points}$$

$$BLL_{20} - BLL_{10} = 10\ \mu g/dL$$

Assumed design slope

$$\frac{\mathbf{\Delta BLL_{planned}}}{\mathbf{\Delta IQ}_{expected}} = -0.3$$

TLC assumed a linear dose–response: ~1 IQ point per 3 µg/dL change in BLL across the entire exposure range.

TLC Planning inference

$$\mathbf{\Delta BLL_{20-10} = 10\ \mu g/dL \approx -3\ \Delta IQ\ pts} \Longrightarrow \Delta\mathrm{BLL}_{\mathrm{planned}} = 10\ \mu\mathrm{g/dL}$$

This inference treats equal ΔBLLs as cognitively equivalent across exposure ranges.

TLC Expected inference

$$BLL_{26} \Longrightarrow BLL_{15}\ \mathbf{\Delta BLL}\ (-10\ \mu g/d\mathrm{L}) \Longrightarrow +3\mathrm{IQ\ points}$$

Equivalent ΔBLLs at higher exposure levels do not yield equivalent cognitive gains.

$$\Delta AUC \equiv \int_{t_0}^{T} \left(BLL_P(t) - \mathrm{BLL}_S(t)\right) dt$$

$\int_{t_0}^{T}$ Integration over time (t) from randomization ($\mathbf{t_0}$) to the end of follow-up ($\mathbf{t=T}$). This accounts for the fact that exposure effects accumulate over time, not at a single exposure, especially in the case of TLC participants

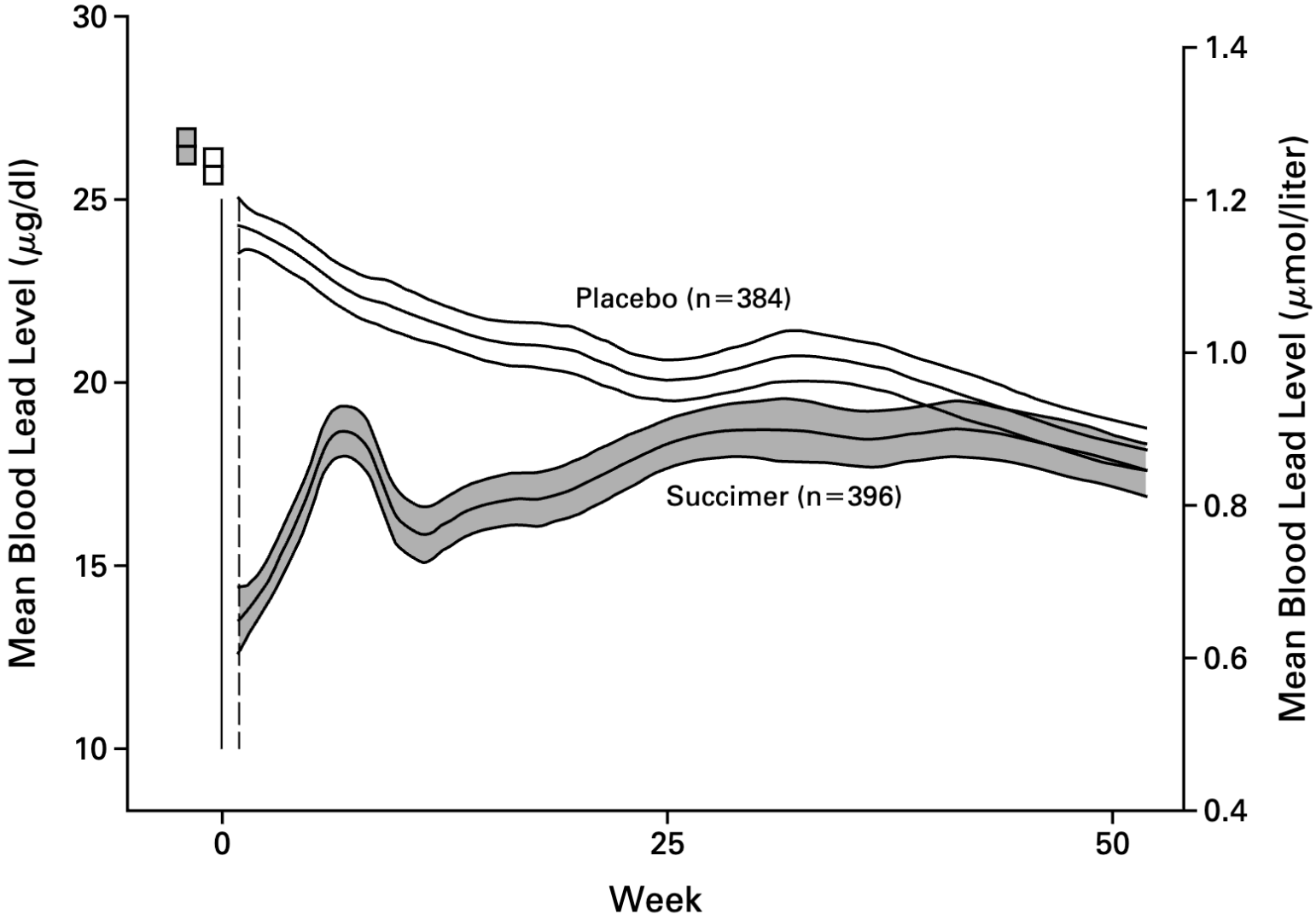
$\mathbf{BLL_P(t)}$**:** mean BLL at time (t) among children randomized to placebo (**P**). This is the expected trajectory under no chelation, including regression to the mean and secular decline.

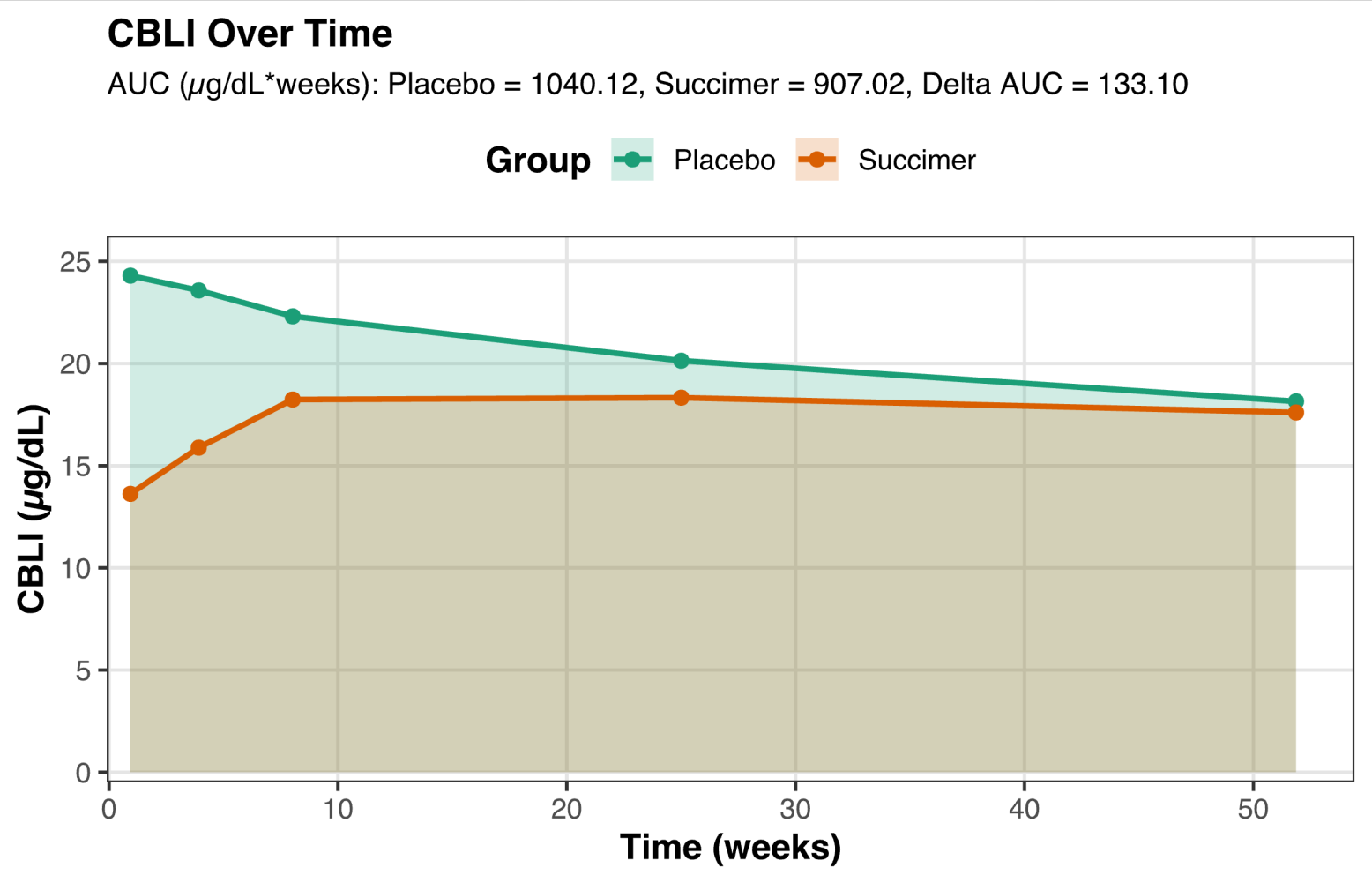
$\mathbf{BLL_S\ (t)}$**:** mean BLL at time (t) among children randomized to succimer (**S**). This reflects both drug effects and the same secular processes affecting placebo.

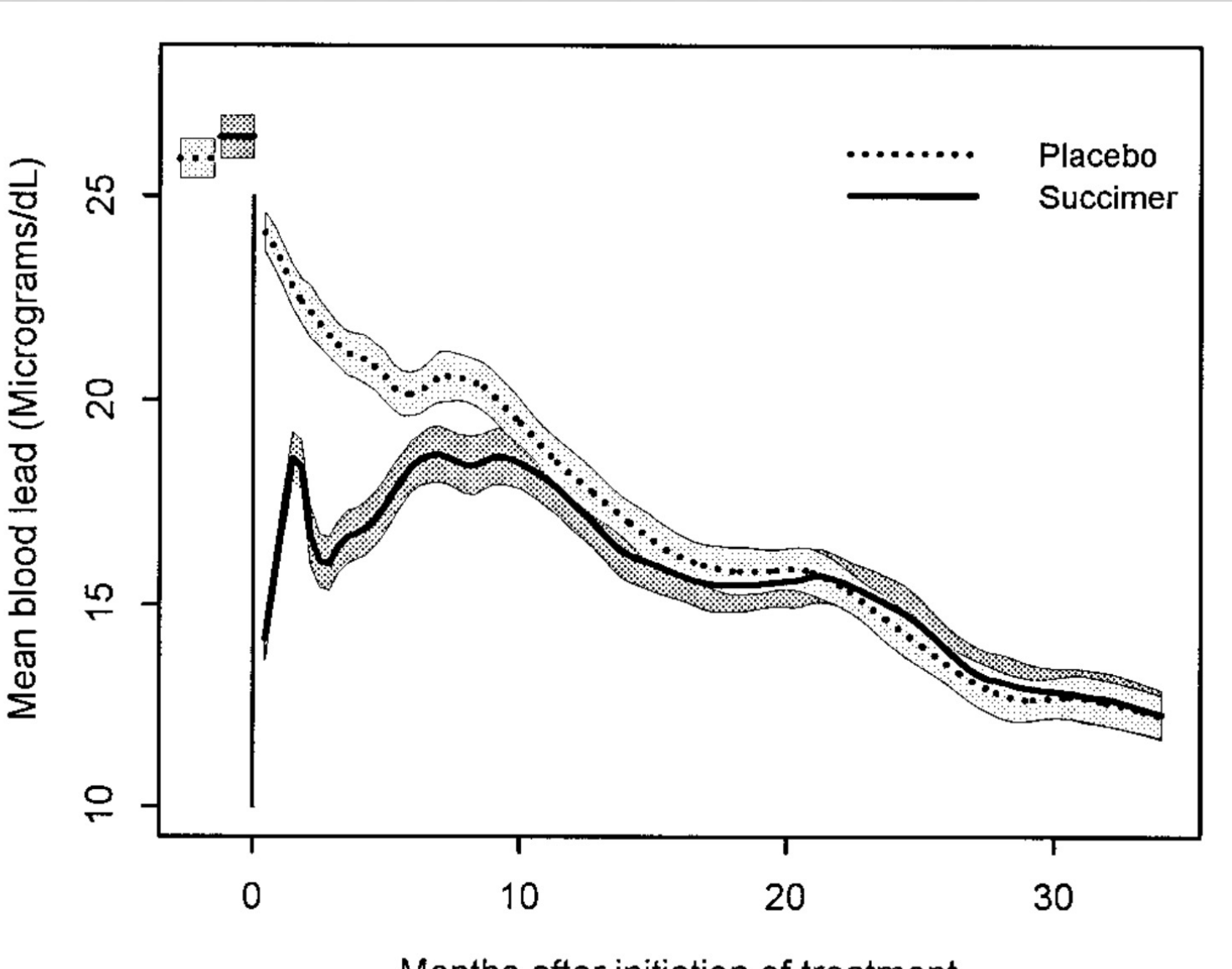
$\mathbf{(BLL_P(t) - BLL_S(t))}$**:** The instantaneous between-group separation in blood lead at time *t*. Positive values mean placebo has higher lead than succimer at that moment.

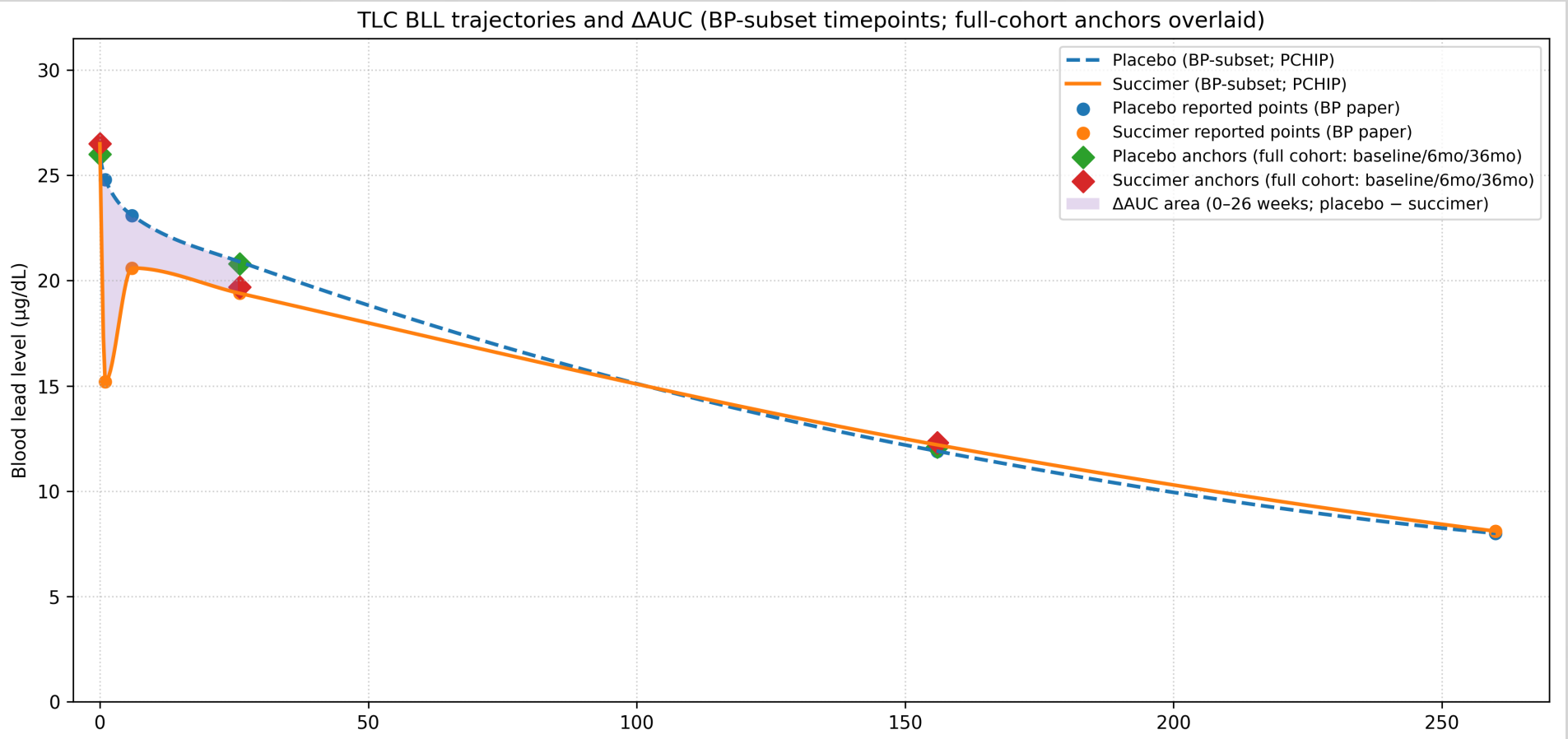
dt: An infinitesimal increment of time; ensures the separation is accumulated continuously rather than compared at isolated visits.

$\mathbf{\Delta AUC}$: The difference in area under the blood-lead–versus–time curves between the placebo and succimer groups over follow-up. The cumulative between-group exposure separation attributable to randomization.


30
25
20
15
10
Mean Blood Lead Level (μg/dl)
1.4
1.2
1.0
0.8
0.6
0.4
Mean Blood Lead Level (μmol/liter)
Placebo (n=384)
Succimer (n=396)
0
25
50
Week


CBLI Over Time
AUC (μg/dL*weeks): Placebo = 1040.12, Succimer = 907.02, Delta AUC = 133.10
Group
Placebo
Succimer
CBLI (μg/dL)
25
20
15
10
5
0
0
10
20
30
40
50
Time (weeks)


Placebo
Succimer
Mean blood lead (Micrograms/dL)
10
15
20
25
0
10
20
30


TLC BLL trajectories and ΔAUC (BP-subset timepoints; full-cohort anchors overlaid)
Blood lead level (µg/dL)
0
5
10
15
20
25
30
0
50
100
150
200
250
Placebo (BP-subset; PCHIP)
Succimer (BP-subset; PCHIP)
Placebo reported points (BP paper)
Succimer reported points (BP paper)
Placebo anchors (full cohort: baseline/6mo/36mo)
Succimer anchors (full cohort: baseline/6mo/36mo)
ΔAUC area (0–26 weeks; placebo − succimer)

Treatment Endpoint insufficient and limited cognitive gains well below SEM for IQ

So how do we quantify lead toxicity in the absence of a k-xrf (bone lead)? BLLs. BLLs are really a poor proxy for total bodily lead burden since most lead is stored in bone tissue.

Two children with BLLs of 25 µg/dL can have very different bodily lead burdens. When those children are removed from their source of exposure, the rate at which their BLLs drop is a good proxy for how much lead they have stored. The longer they've been exposed, the more gradual the decline. The duration and intensity of their exposure determines the level of lead they likely have stored in bone. As they cease exposure, BLLs drop slowly as kidneys are very inefficient at processing lead and excreting it into urine. As they excrete more lead and BLLs decline, bone lead is released into blood to replenish their BLLs.

Kids with higher BLLs get chelated right? Kids with lower levels don't. Why do we chelate the kids with higher BLLs? To lower BLLs. So that suggests that it's general clinical consensus that lower BLLs are better than higher BLLs? Who's to say that lowering BLLs is actually reversing brain damage in non-encephalopathic patients with levels >45ug/dL? What RCTs have been done in these patients?

There is no randomized clinical evidence showing that chelation at 46 µg/dL prevents brain damage better than removal of exposure, yet we do it. Should clinicians chelate a child with BLLs of 46 µg/dL? What treatment endpoint do they chelate to? 44 µg/dL? Is that helping the patient? Once they pass below the 45 µg/dL threshold, we are treating outside of guidelines and against recommendations.

2.3. Study Population

The planned sample size for the TLC Study is 1,332. Each of four Clinical Centers will enroll 333 children. The racial and ethnic composition of the study sample is expected to reflect the composition of the clinic population at each Clinical Center. However, linguistic minorities will be excluded in all centers except Newark, where Hispanic children make up a sizable portion of the population and will be included.

Insufficient Treatment Endpoint

Our opinion contrasts with the TLC's interpretation that another treatment protocol would unlikely yield different results. The treatment endpoint of 15 mg/dL was insufficient given current understanding of relationships between IQ and BLL. Chelating to lower levels, ideally less than 10 mg/dL, would have been much more likely to result in a detectable IQ increase.

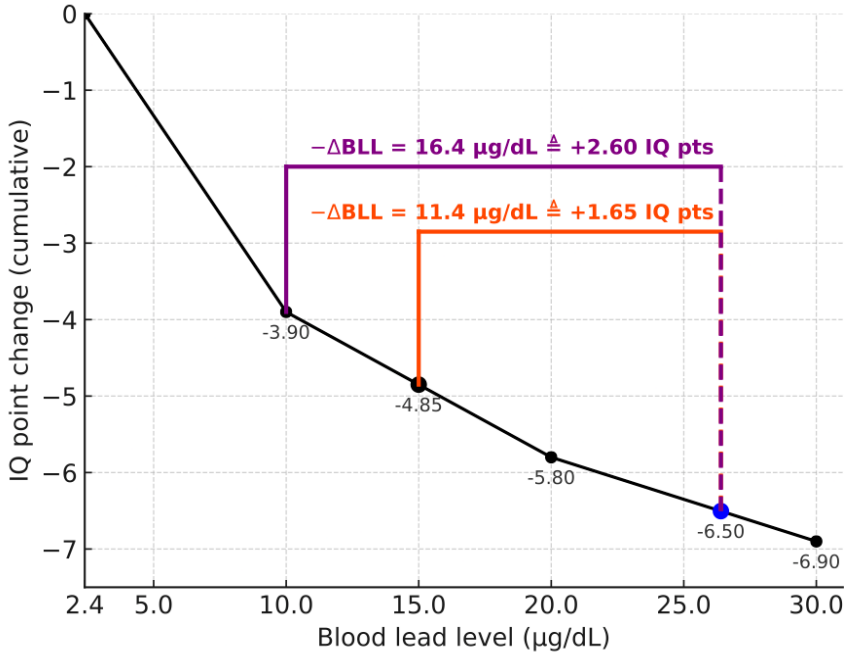


Figure 1. Piecewise regression of IQ loss by concurrent blood lead levels.
Data from Lanphear et al.[29]

Questioning the evidence for current guidelines and treatment endpoint.

At a BLL of 26 µg/dL, epidemiological models estimate a cognitive deficit of roughly 5-7 IQ points compared to unexposed peers.

Based on that evidence, with the 10 µg/dL BLL separation TLC targeted with a 15 µg/dL treatment endpoint, we would expect a difference of 1.65 IQ points (orange line), if the separation was maintained until IQ testing.

Regaining 1 or 2 points isn't "reversing damage"; it's minor fluctuation. Regaining 5 points (1/3 of a standard deviation) effectively restores the child to their unexposed potential.

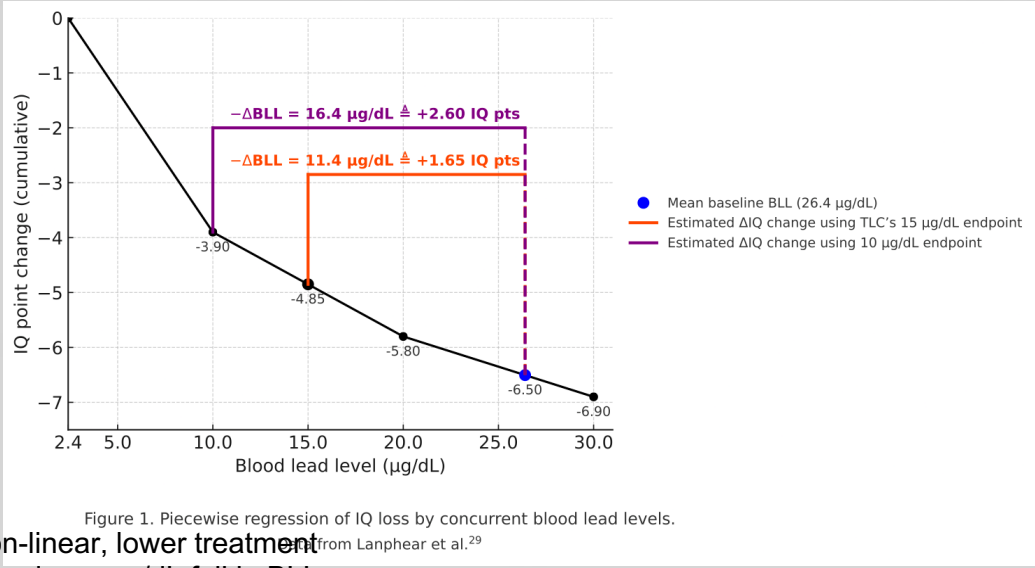


Figure 1. Piecewise regression of IQ loss by concurrent blood lead levels.
Data from Lanphear et al.[29]

Since the relationship between BLLs and IQ decrements is non-linear, lower treatment endpoints can be expected to result in greater IQ points regained, per µg/dL fall in BLL. The majority of recoverable IQ points lie in the 10 µg/dL to 0 µg/dL range.

If I were designing the TLC trial to prove reversal of brain damage (not just statistical significance), I would have set the MCID at 5 IQ points. Here is the rationale:
IQ tests (like the WPPSI-R or WISC-III used in these studies) have a standard deviation of 15. The Standard Error of Measurement (SEM) is typically 3 to 4 points. If a child's score goes up by 2 or 3 points, you don't know if they got smarter or if they just guessed better that day.

The TLC trial was powered to detect a difference of 3 points. They set their expected treatment effect inside the margin of error. To prove reversal, the signal must exceed the noise.

Prospective, observational studies have shown that lead produces a dose- (or blood level-) related reduction in developmental test scores ***(Needleman and Gatsonis, 1990; Pocock et al., 1994).*** The clearest relationship is between peak blood lead, which occurs at 20 to 30+ months of age, and test scores beginning at age 48-57 months and thereafter**[…]**best quantified effect at low levels is on developmental test scores; an increase in blood lead of **10 µg/dl is associated with a decrease in IQ of 2-3 points.** If lead causes developmental delay, that effect can be prevented by preventing lead exposure. However, since the mechanism of the effect is unknown, it is unclear whether it can be reversed or attenuated once exposure has occurred.

TLC Website

the TLC Trial has the power **of 0.82 to detect a difference of three IQ points** between treatment groups at 36 months. **In observational data, a 10 mg/dL difference in blood lead is associated with as much as a three-point IQ differe**nce.[1,2] In the trial, the mean blood lead at the beginning of therapy is 26 mg/dL, and the treatment goal is 15 mg/dL.

Rogan WJ. The Treatment of Lead-exposed Children (TLC) trial: Design and recruitment for a study of the effect of oral chelation on growth and development in toddlers. Paediatric and Perinatal Epidemiology. 1998;12:313-333. doi:10.1046/j.1365-3016.1998.00

For longitudinal studies, the estimate IQ loss was 2.96 IQ points (±1.25 IQ points), and for the cross-sectional studies, the estimated IQ loss was 2.69 IQ points (± 0.51 IQ points). Hence there was little evidence that the two study designs were showing different effects.

For studies in **disadvantaged populations, the estimated IQ loss was 1.85 IQ points (±0.92 IQ points) versus a 2.89 IQ point loss (±0.50 IQ points) in the non-disadvantaged populations**.

Schwartz J. Low-Level Lead Exposure and Children's IQ: A Metaanalysis and Search for a Threshold. *Environmental Research*. 1994;65(1):42-55. doi:10.1006/ENRS.1994.1020

time with IQ tests. These studies also tend to be more rigorously designed, and all included some assessment of the home environment as measured by the HOME scale. Four of the five prospective studies showed a negative coefficient for the lead variable, although in only two was it statistically significant. Pocock et al. concluded, on the basis of all relevant and available studies, that a doubling of blood lead level, from 10 to 20 ug/dl, may cause an IQ deficit of the order of one to two points. Others, such as Needleman and Gatsonis (1990), have suggested that the effect may be in the range of two to three IQ points.

Rogan WJ, Ware JH. Correcting for Omitted-Variables and Measurement-Error Bias in Regression with an Application to the Effect of Lead on IQ: Comment. *Journal of the American Statistical Association*. 1998;93:513. doi:10.2307/2670097

effects of lead on cognition. A previous meta-analysis suggested a 2.6-point decline in IQ for an increase in lead concentration from 10 to 20 µg per deciliter.[2] Bellinger et al.,[3] in a study of children with blood lead concentrations closest to those in the current study, estimated a decline of 5.8 points with an increase in blood lead concentration from 10 to 20 µg per deciliter. Although the remarkable steep-

Rogan W, Ware J. Exposure to Lead in Children — How Low Is Low Enough? *New England Journal of Medicine*. Published online 2003.

Single study (affluent children)

from this meta-a

Here, Drs. Rogan and Ware try to minimize the fact that TLC was underpowered, and cherry pick the Bellinger et al. data, which showed a 5.8 IQ per 10 ug/dL difference in comparison to Schwartz's meta-analysis which showed ~3 IQ per 10 ug/dL. However, Bellinger et al. was actually included in Schwartz's meta-analysis and was the only one to study children with higher socioeconomic families. The TLC participants are more comparable to the **1.85 IQ per 10ug/dL seen in disadvantaged populations**

So far, I've been able to find 2 protocol versions.

Version 9 (v9) and Version 10 (v10)

v9 is dated August 23rd, 1994

v10 is dated November 4th,1997

Protocol 10

- Protocol 10, appears to never have been publicly accessible from the main public TLC pages. I found it under an ‘admin’ url by browsing the domain.

  http://dir.niehs.nih.gov/direb/tlc1/admin/prot_v10.html

- The page was captured by the Wayback Machine twice on: **October 30, 2004.**
- The protocol is dated: **November 4, 1997**. This date is several months after all children were finished with treatment (summer, 1997). Exploring the protocol further for digital evidence is something I intend on doing in the future, to determine *when* the protocol was actually listed online.
- You may access the archived version of Protocol 10 here.
- Reformatted Protocol 10 for easier searching/less spacinghere.
- Protocol 10 includes appendices, but I have no other protocols to compare to assess completeness of the appendices.

Protocol 9

I found part of protocol 9, while doing literature review.

It was listed as an appendix (Appendix 2, p. 176) in a a Ph.D. dissertation from 1999.

The full article can be accessed here.

The author acknowledges advisor **Dr. Paul Lioy** (known for his analysis of 9/11 dust) and co-advisor **Dr. George Rhoads**, (a TLC investigator and future ACCLPP committee chair) who likely had direct access to the most current version of the document.

This version includes 40 of 136 total pages, basically the whole protocol without appendices and supplemental material, which are likely pages 41–136.

In 1999, TLC was near 2 years post-treatment follow-up. The protocol should not have been edited in any way by that time. Assuming Dr. Rhoads provided his mentee with the most up to date protocol for inclusion in the appendix of their 1999 thesis, version 10 being dated November 4, 1997 is suspicious.

Changes between PROTOCOL VERSION 9 vs VERSION 10:

BLINDING METHODOLOGY (Section 4.6)

Version 9: Mucomyst method. A 2 cm² piece of filter paper soaked with Mucomyst 20% solution (acetylcysteine) placed in placebo bottles to mask the sulfur odor. Unsoaked filter paper placed in succimer bottles.

Version 10: Succimer canister method. A vented cylindrical plastic canister, 0.5 inches diameter by 0.6 inches length, filled with 200 mg of succimer added to ALL bottles (both active and placebo). Placebo bottles also receive a canister with 200 mg placebo to ensure identical appearance.

Complete abandonment of the original blinding strategy. The Mucomyst approach was replaced entirely with actual succimer in masking canisters. This confirms the initial blinding method failed during the trial.

DRUG REPACKAGING METHOD (Section 9.1.1)

Version 9: "The Drug Distribution Center will place a two cm² piece of filter paper which has been soaked with Mucomyst 20% solution into each bottle of placebo drug. An unsoaked piece of filter paper will be placed inside each bottle of succimer so that all bottles will appear the same."

Version 10: "In order to provide placebo with an odor comparable to that of succimer, the Drug Distribution Center will place a small canister containing 200 mg of active drug into each bottle of placebo drug. A canister containing 200 mg of placebo will be placed inside each bottle of succimer so that all bottles will appear the same."

Confirms the methodology change described in Section 4.6. The repackaging procedures were completely revised.

Protocol 9 vs Protocol 10

NEUROPSYCHOLOGICAL ASSESSMENT (Section 5.7)

Version 9: "Neurodevelopmental Battery" consisting of 5 individual tests administered separately:

Woodcock-Johnson Memory for Names
Stanford-Binet Bead Memory
Kaufman Assessment Battery for Children (K-ABC) Magic Window
Diamond's Modified Stroop Task
Tower of Hanoi (for children 60 months or older only)
Total administration time: 45-60 minutes, plus 25-30 minutes for Tower of Hanoi in older children.

Version 10: "Developmental Neuropsychological Assessment (NEPSY)" — a single consolidated standardized instrument described as "the first standardized neuropsychological examination developed specifically for pre-school and primary school children." Assesses 5 functional domains: Executive Functions (attention, planning, problem solving), Language and Communication, Sensorimotor Functions, Visuospatial Functions, and Learning and Memory. Core battery administration time: approximately 1 hour. No age restrictions mentioned.

Fundamental change from an ad hoc collection of individual tests to a standardized, validated neuropsychological battery. If this change occurred mid-enrollment, children tested at different times may have received different assessments, creating measurement heterogeneity.

CONNERS' PARENT RATING SCALE (Section 5.6)

Version 9: 48-item scale with 5 subscales: Conduct Problem, Learning Problem, Psychosomatic, Impulsive/Hyperactive, and Anxiety. Includes a 10-item Hyperactivity Index described as containing items "most sensitive to drug effects." Normative data from 578 children.

Version 10: Conners' Parent Rating Scale - Revised, Short Form. 27-item scale with 3 subscales: Oppositional, Cognitive Problems, and Hyperactivity. No Hyperactivity Index mentioned. Normative data from 2,426 children.

The Hyperactivity Index was explicitly designed to detect drug effects. Its removal from Version 10 raises questions about why a drug-sensitive subscale was dropped from a drug trial.

Protocol 9 vs Protocol 10

SECONDARY OBJECTIVES (Section 1.2.2)

Version 9: Lists individual neuropsychological tests as secondary outcome measures: Woodcock-Johnson Memory for Names, Stanford-Binet Bead Memory, Kaufman's Magic Window, Diamond's Modified Stroop Task, and Tower of Hanoi.

Version 10: Identical language — still lists the same individual tests as secondary outcome measures.

The Secondary Objectives in Version 10 still reference the individual tests, but Section 5.7 describes NEPSY as the neuropsychological assessment. This is an internal inconsistency within Version 10 — the objectives were not updated to match the changed methodology.

RANDOMIZATION STRATIFICATION (Section 4.5)

Version 9: Stratification by city (Baltimore, Newark, Philadelphia, Cincinnati, Columbus), class of body surface area, and most recent CDC blood lead level (20-24 µg/dL and 25-44 µg/dL).

Version 10: Stratification by city, class of body surface area, language (English or Spanish), and most recent CDC blood lead level.

Language was added as a stratification factor, reflecting the Newark site's Spanish-speaking population.

TABLE 5 — SCHEDULE OF PSYCHOMETRIC TESTING

Version 9: At 36-month visit, lists all 5 individual neuropsychological tests.

Version 10: At 36-month visit, lists single "Developmental Neuropsychological Assessment (NEPSY)."

Consistent with the Section 5.7 changes.

QUESTIONS ARISING FROM THESE CHANGES

When exactly was the blinding methodology changed? If Version 10 was not issued until November 1997, were children enrolled from 1994-1996 treated under the failed Mucomyst blinding while later enrollees received the improved succimer-canister method?

When was the neuropsychological assessment changed from the ad hoc battery to NEPSY? Were children assessed with different instruments at different points in the trial? Were data from different instruments pooled in the final analysis?

Why was the Hyperactivity Index dropped? This subscale was specifically designed to detect drug effects. Was it removed because it was detecting treatment effects?

Were these protocol amendments reported to IRBs and the Data Safety Monitoring Board? Changes of this magnitude would require approval.

Were these changes disclosed in publications? The 2001 NEJM paper should have reported any mid-trial protocol changes.

Why do the Secondary Objectives in Version 10 still reference the individual neuropsychological tests when Section 5.7 describes NEPSY? Was this an oversight, or were both assessment approaches used?

Exposure to lead in children—how low is low enough?

In the early 2000s, TLC investigators utilized participant data to take part in a very hot, high impact research conversation at the time—peak BLLs (typically achieved when kids are toddlers and pica behavior is highest) more indicative of IQ later in life? Or are concurrent BLLs, at the time IQ is measured, most indicative of IQ?

Canfield, Lanphear et al. published several landmark analyses in the early 2000s. These papers showed a non-linear IQ/BLL relationship, with greater IQ loss at lower BLLs. They also showed concurrent BLL (at the time IQ was measured) and not peak BLL, was most closely correlated with IQ decrements.

Rogan and Ware published a perspective in *NEJM* to accompany Canfield's paper, where they highlighted their own observational research from TLC participants, who now had BLLs in the range the Canfield papers examined. TLC was only able to observe these "associations" because the children remained poisoned. If the children had been successfully treated or their homes fully abated.

They highlight TLC results, "*A previous report in the Journal indicated that chelation therapy... had no beneficial effects on tests of cognition, behavior, or neuropsychological function*", but completely fail to mention that the TLC treatment protocol capped the treatment endpoint at 15 µg/dL, ensuring participants wouldn't benefit from the steeper IQ gains that might exist below 10 µg/dL.

Instead of taking the opportunity to make a valuable contribution to the scientific body of evidence, they essentially write an epitaph for not only chelation therapy, but treatment of any kind after exposure has occurred, embracing the idea that since IQ loss was not reversed by succimer in TLC, the only solution is prevention.

They entirely miss the implications of Canfield's findings in relation to the TLC instead pushing the agenda that because the damage from lead is irreversible, "*Prevention is thus the only plausible strategy".*

Sources:
Canfield RL, Henderson CR, Cory-Slechta DA, Cox C, Jusko TA, Lanphear BP. Intellectual Impairment in Children with Blood Lead Concentrations below 10 µg per Deciliter. New England Journal Of Medicine. 2003;16:1517-1543.

Rogan W, Ware J. Exposure to Lead in Children — How Low Is Low Enough? New England Journal of Medicine. Published online 2003.

TLC began randomizing children in Fall of 1994 and stopped randomizing children in January 1997. By Summer, 1997, all children had completed their treatment course(s) The 18-month follow up visits, which included the interim psychometric assessments, were complete as of Fall 1998.

Baseline data describing the population and the treatment regimen from TLC were published in *Paediatric & Perinatal Epidemiology's* July 1998 issue. A description of the safety and efficacy of the succimer treatment regimen was published in November 2000 in *Pediatric Research*.

The 36-month follow up visits, which include the WPPSI IQ assessment and NEPSY administration, were completed in April 2000. As investigators started to realize the treatment had failed, the ethical obligation would typically be to find another way to help the children—full abatement of their homes, or plausibly more chelation to bring BLL down significantly.

Instead, they were able to secure more funding, to continue observing the children as they continued to be lead poisoned, until age 7.5 years old, in what was described by investigators (and later by courts) as ***TLC-Plus***.

Further follow up

In 1999, a cooperative agreement, **TLC-Plus**, was awarded to TLC for followup of the cohort children through age 7. Recognizing that the most important effects of early lead exposure are difficult to assess prior to school age, TLC-Plus is designed to assess the long-term developmental benefits of oral chelation therapy with succimer. The study's principal aim is to determine whether succimer is effective in ameliorating the adverse impact of early lead toxicity on neuropsychological functioning behavior and social adjustment. A state of the art, efficient assessment battery will be administered to TLC-Plus subjects at all Clinical Centers in two sessions following their seventh birthday. At this age, a wider and more differentiated range of abilities can be examined, scores on psychometric measures are more precise and reliable, and early academic performance and social functioning outside of the home environment can be evaluated. Assessments of psychometric, psycho educational, social-adaptive, and neurological functioning will be made Instruments tapping these domains will be administered to TLC subjects when they attain 7 and 7.5 years of age. Intent-to-treat data analyses will examine the impact of treatment on these domains using analysis of covariance and repeated measures methods.

Archived TLC Website

The ***TLC–Plus*** extended observation findings were published in 2004 in *Pediatrics.*

Instead of stopping the trial there, Rogan et al. continued to use TLC participant data and blood samples, ultimately publishing 12 new papers over the next 10 years.

Their final paper, published in 2014, examined TLC blood samples from the kids at age 7 years old for relationships between mercury and neurodevelopment. By that time, participants were in their early twenties.

Records show Walter Rogan received roughly $1.8 million dollars in grant funding for the post-hoc TLC analyses between 2007 and 2014.

This supports the argument established in *Grimes v. Kennedy Krieger*, that the TLC study was "*non-therapeutic.*" Clinical trials which which offer no direct benefit to the subject, but instead are intended to generate knowledge to benefit the public or general population, are deemed *non-therapeutic*, and thus constitute a special relationship between investigators and the child.

The studies observing the damage as it happened, or which observed associations between IQ, succimer, and metals like mercury and cadmium—metals which TLC participants were not poisoned from— would all be legally classified as *non-therapeutic* and thus, parental consent could not necessarily be given.

Interview with Dr. Walter Rogan who talks about succimer and mercury

Dietrich KN, Ware JH, Salganik M, Radcliffe J, Rogan WJ, Rhoads GG, et al. Effect of chelation therapy on the neuropsychological and behavioral development of lead-exposed children after school entry. Pediatrics. 2004;114(1):19-26. PMID: 15231903; DOI: 10.1542/peds.114.1.19

Chen A, Dietrich KN, Ware JH, Radcliffe J, Rogan WJ. IQ and blood lead from 2 to 7 years of age: are the effects in older children the residual of high blood lead concentrations in 2-year-olds? Environ Health Perspect. 2005;113(5):597-601. PMID: 15866769; DOI: 10.1289/ehp.7625

Chen A, Rhoads GG, Cai B, Salganik M, Rogan WJ. The effect of chelation on blood pressure in lead-exposed children: a randomized study. Environ Health Perspect. 2006;114(4):579-583. PMID: 16581549; DOI: 10.1289/ehp.8634

Chen A, Schwarz D, Radcliffe J, Rogan WJ. Maternal IQ, child IQ, behavior, and achievement in urban 5-7 year olds. Pediatr Res. 2006;59(3):471-477. PMID: 16492992; DOI: 10.1203/01.pdr.0000199910.16681.f0

Chen A, Cai B, Dietrich KN, Radcliffe J, Rogan WJ. Lead exposure, IQ, and behavior in urban 5-7 year olds: does lead affect behavior only by lowering IQ? Pediatrics. 2007;119(3):e650-e658. PMID: 17332184; DOI: 10.1542/peds.2006-1973

Bhattacharya A, Shukla R, Auyang ED, Dietrich KN, Bornschein RL. Effect of succimer chelation therapy on postural balance and gait outcomes in children with early exposure to environmental lead. Neurotoxicology. 2007;28(3):686-695. PMID: 17499360; DOI: 10.1016/j.neuro.2007.03.007

Cao Y, Chen A, Radcliffe J, Dietrich KN, Jones RL, Caldwell KL, Rogan WJ. Postnatal cadmium exposure, neurodevelopment, and blood pressure in children at 2, 5, and 7 years of age. Environ Health Perspect. 2009;117(10):1580-1586. PMID: 20019909; DOI: 10.1289/ehp.0900765

Cao Y, Chen A, Jones RL, Radcliffe J, Caldwell KL, Dietrich KN, Rogan WJ. Does background postnatal methyl mercury exposure in toddlers affect cognition and behavior? Neurotoxicology. 2010;31(1):1-9. PMID: 19969021; DOI: 10.1016/j.neuro.2009.10.017

Cao Y, Chen A, Jones RL, Radcliffe J, Caldwell KL, Peddada S, Rogan WJ. Efficacy of succimer chelation of mercury at background exposures in toddlers: a randomized trial. J Pediatr. 2011;158(3):480-485.e1. PMID: 20889164; DOI: 10.1016/j.jpeds.2010.08.036

Cao Y, Chen A, Bottai M, Jones RL, Radcliffe J, Rogan WJ. The impact of succimer chelation on blood cadmium in children with background exposures: a randomized trial. J Pediatr. 2013;163(2):598-600. PMID: 23591107; DOI: 10.1016/j.jpeds.2013.03.009

Wang Y, Chen A, Dietrich KN, Radcliffe J, Caldwell KL, Rogan WJ. Postnatal exposure to methyl mercury and neuropsychological development in 7-year-old urban inner-city children exposed to lead in the United States. Child Neuropsychol. 2014;20(5):527-538. PMID: 23971942; DOI: 10.1080/09297049.2013.824955

Visit https://tlctrial.com/ for a full list of publications

In 2007, several of the TLC investigators from the Cincinnati site, published findings that revealed a painful irony: the drug actually improved measures for physical coordination, but this positive finding came long after the policy door had closed.

Unlike the IQ tests, this study found that children treated with succimer had significantly better scores on balance and gait compared to placebo. The treated children showed less "postural sway" and were more stable when crossing obstacles.

The placebo children exhibited a cautious gait, walking slower and with more braking force, indicating they felt unsteady and had poorer neuromuscular control.

The study suggests the drug helped the proprioceptive system (the body's ability to sense its own position) recover from lead damage. However, it did *not* seem to fix the vestibular system (inner ear balance).

Despite finding a clear benefit, the authors admit in the discussion that the CDC's *Advisory Committee for Childhood Lead Poisoning Prevention* had *already* removed the recommendation for chelating these children in 2002. They conclude that their positive findings "do not provide strong support for any changes to current practice" because the IQ (neurocognitive) failure was viewed as the deciding factor.

In its most recent guidelines for the management of lead-exposed children, the CDC has omitted any recommendation for the chelation of children with PbB levels under 45 µg/dL (USCDC, 2002). Succimer is labeled only for children with higher PbB levels. The findings of this study, nor those that involved the entire TLC sample (Dietrich et al., 2004; Rogan et al., 2001) do not provide strong support for any changes to current practice. However, even in the absence of a recommended medical treatment at these levels, high-risk children should still be screened for Pb exposure. This is principally because such screening can trigger environmental controls that can limit further exposure. More effective public health policies to assist parents with such environmental interventions are also needed. The elimination of childhood Pb poisoning by the year 2010 remains a worthwhile goal and progress in this direction can only be assessed if screening continues. Our efforts, however, should go beyond mere screening for cases. Indeed, the first line of defense against this avoidable environmental disease should be the screening of homes with potentially hazardous sources of exposure. By the time a child is identified as Pb poisoned the damage may have already been done with possibly irreversible consequences.

"*For more than twenty years, NIEHS has sponsored much of the research showing that lead at these levels was harmful to children's brain function, and that succimer lowered blood lead. We had hopes that the treatment would prevent or reduce lead-induced damage in these children, who are mostly poor, African-American, and living in deteriorated housing in big cities. The results of the trial show clearly that treatment after the fact does not undo the damage among 5 year olds.* ***We must prevent these children from being exposed in the first place.***"

—NIEHS Director Kenneth Olden, May 9, 2001

https://wayback.archive-it.org/20032/20221213173519/https://www.niehs.nih.gov/news/newsroom/releases/2001/may09/index.cfm

Society, Not Succimer, Must Get the Lead Out

By Rich McManus

Hopes were high 10 years ago as scientists began a study that would determine whether a stinky white powder called succimer—which can leach lead out of the bloodstreams of youngsters—could reverse the IQ deficits they suffered from their lead exposure. But after 7 years of studies on an initial cohort of almost 800 kids—*most of them poor and black—in four* cities, scientists led by Dr. Walter Rogan of the National Institute of Environmental Health Sciences determined that, although it lowered blood lead levels, the drug didn't budge average IQ scores.

"We learned that the only way to prevent lead-associated [intellectual] deficits is to prevent lead exposure in the first place," he told a Clinical Center Grand Rounds audience on June 9.

Dr. Walter Rogan

McManus R. Society, Not Succimer, Must Get the Lead Out. NIH Record. July 6, 2004;56(14):1-2.

About 25 percent of American children under age 6 live in houses contaminated with hazardous levels of lead, a common element in the decaying house paint in many poor neighborhoods in America's Rust Belt cities; about 16 million houses are thought to be affected. As the paint in old homes ages, it chips, flakes and chalks, becoming a kind of dust that is easily ingestible, especially by boys, who tend to put things in their mouths more often than girls, Rogan explained. Although blood lead levels in U.S. children have fallen, mostly due to the removal of lead from gasoline, there are still half a million kids whose levels are at or above what Rogan and CDC call "a level of concern."

Rogan presents a slide showing how oral succimer was delivered in an NIEHS study attempting to prevent IQ deficits due to blood lead exposure.

Back in the mid-1950's, scientists felt that the "level of concern" began at around 60 micrograms per deciliter of blood. But by 1991, new evidence had suggested that a level of 10 indicated a risk of delayed cognitive development, Rogan said. To put quantities in perspective, 1 gram of lead in a child is enough to kill him, Rogan noted. "That's an amount smaller than the nail on your pinky."

Lead poisoning is far from gone, emphasized Rogan, who has been an intramural scientist at NIEHS for 28 years. An individual child's blood lead level typically peaks around age 2, and mental deficits become apparent around age 4. Lead is associated with a 2 to 3 point drop in IQ points for each increase in blood lead of 10 micrograms per deciliter, based on a meta-analysis of many studies, Rogan said.

He described the oral succimer clinical trial, begun shortly after NIEHS director Dr. Kenneth Olden took over the institute in 1991. Earlier studies had shown that intravenous or intramuscular drugs like EDTA and BAL could lower blood lead levels, so there were high hopes for an oral preparation. "Succimer is a white crystalline powder with an unpleasant mercaptan odor," Rogan explained. "It smells like a 16-year-old's gym locker." The chemical binds non-covalently to lead, mercury, zinc, calcium and iron, and can be excreted in urine. Olden okayed the oral succimer trial, whose goal was to prevent cognitive impairment by lowering blood lead concentration.

Rogan and his colleagues lit out to crumbling row houses in Newark, Philadelphia (near where Rogan himself had grown up in a row house), Baltimore and Cincinnati, where they found plenty of old paint, old putty, and windows and radiators flaking away under numerous layers of lead paint (whose main constituents are lead carbonate and linseed oil, Rogan said). They cleaned the homes with HEPA vacuums, patched walls, cleaned windows and generally tried to keep the lead dust down for the 6 months that the study cohort received succimer in the randomized, double-blind, placebo-controlled study. Socioeconomic factors—the homes were all in poorer neighborhoods, virtually all were on public assistance, the parents were all below U.S. norms with respect to income, and the average IQ for children was 81—were undeniably at play in determining risk.

The study retained 90 percent of the original 780 enrollees for 5 years, and 65 percent for the full 7 years, Rogan reported, but the results were unequivocal—succimer lowered blood lead but could not reverse declines in IQ.

Looking ahead to the future, Rogan is encouraged by several new research directions. First, the HHS Healthy People 2010 initiative includes the goal of eliminating lead poisoning (in other words, getting the level below 10 micrograms per deciliter) in children. Rogan said there is increasing attention paid to lead levels in water, as has been heavily reported in the metropolitan Washington, D.C., area this spring, and to prevention of lead exposure by a variety of means. He also said studies are widening to include the effects of exposure in older kids. Future studies will also try to disentangle the confounding nature of lead exposure and socioeconomic status.

But the clear impression from Rogan's talk is that lead poisoning has become less a matter of treatment and more one of prevention; cleanup time has arrived.

NIH RECORD

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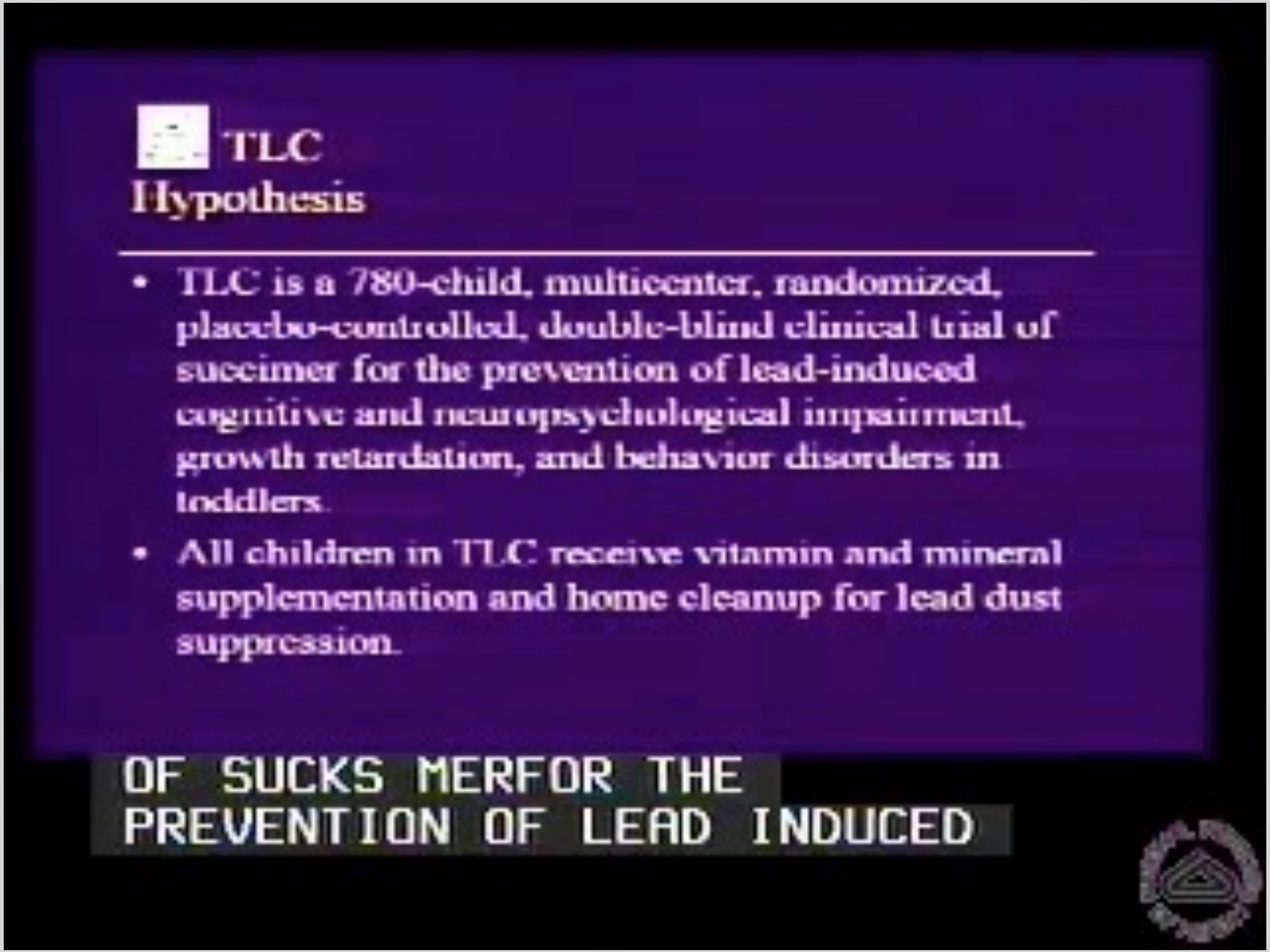
TLC
Hypothesis
• TLC is a 780-child, multicenter, randomized, placebo-controlled, double-blind clinical trial of succimer for the prevention of lead-induced cognitive and neuropsychological impairment, growth retardation, and behavior disorders in toddlers.
• All children in TLC receive vitamin and mineral supplementation and home cleanup for lead dust suppression.
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PREVENTION OF LEAD INDUCED

ACCLPP

Following the publication of the primary TLC results in 2001, investigators served on the Advisory Committee for Childhood Lead Poisoning Prevention (ACCLPP), effectively placing the researchers in charge of interpreting their own evidence for federal policy.

Carla Campbell Clinical Center Investigator (Philadelphia).
ACCLPP Chair: 2002–2006
ACCLPP Liaison (AAP): 2011-2012

George Rhoads Chair, Steering Committee.
ACCLPP Member: October 2004, March 2005, October 2005.
ACCLPP Chair: 2006–2011

Walter Rogan Project Officer (NIEHS).
AAP Committee on Environmental Health Liaison: 2004–2005.
ACCLPP Ex-Officio/Liaison (NIH): 2002–2013*

Kim Dietrich Investigator (University of Cincinnati).
ACCLPP Guest Presenter: March 2006.
ACCLPP Member: 2011-2012

Robert Jones Steering Committee / Central Laboratory.
ACCLPP CDC Representative: October 2006, October 2009, November 2011.

More on ACCLPP

*Dr. Walter Rogan held the longest tenure of any ACCLPP member. He served as *ex-officio,* but all *ex-officio* members were granted voting rights in 2003. He also drafted the 2005 AAP guideline.

ACCLPP

Following the publication of the primary TLC results in 2001, investigators served on the Advisory Committee for Childhood Lead Poisoning Prevention (ACCLPP), effectively placing the researchers in charge of interpreting their own evidence for federal policy.

Customarily, the HHS Secretary would approve any ACCLPP member to the charter that CDC recommended.

But in 2002, the Bush administration was accused of interfering in the ACCLPP, when he rejected several recommended experts (Dr. Bruce Lanphear, Dr. Weitzman) and appointed several members who had worked as expert witnesses in lead industry lawsuits.

Dr. Michael Weitzman was supposed to be Chair, but he was rejected by HHS, and his position was not renewed.

Instead, Dr. Carla Campbell (Philidelphia TLC investigator) became Chair, a position she held until 2006. Dr. George Rhoads (New Jersey TLC investigator and Steering Committee Chair) took over from 2006 to 2011.

ACCLPP began to shift their guidance statements from clinical management and treatment of children exposed to lead, to primary prevention. While treatment of Medicaid patients (who constitute the main portion of lead poisoned children) is federally mandated, primary prevention is not.

Childhood Lead Poisoning Prevention Programs (CLPPPs) are CDC-funded, state/locally lead cooperative agreements that are essentially the core of primary prevention. States can choose whether or not they want to participate, and how much they want to participate. States and cities can choose how much or little they want to engage. In FY 2021, the CDC spent $24 million on CLPPPs.

More on ACCLPP

*Dr. Walter Rogan held the longest tenure of any ACCLPP member. He served as *ex-officio,* but all *ex-officio* members were granted voting rights in 2003. He also drafted the 2005 AAP guideline.

Children's Environmental Health Policy
Rogan was NIEHS Liaison to the Committee on Environmental Health at the American Academy of Pediatrics (AAP) for 36 years. AAP has many technical committees that write policy statements guiding the thousands of pediatricians who are members of the Academy. Rogan was primary author on several such statements, and he participated in the drafting and editing of the many statements produced by the Committee on Environmental Health in his time there. He was also an Ex Officio member of the U.S. Department of Health and Human Services Advisory Committee on Childhood Lead Poisoning Prevention for 16 years. **These two committees provided much of the influential policy about children's environmental health in the U.S.**

Walter Rogan

https://www.niehs.nih.gov/research/atniehs/labs/epi/staff/emeriti/rogan

I've accessed transcripts of reviewed every ACCLPP meeting from 2002-2013, except the following meeting, in which the TLC Trial results were presented.

Record of the proceedings : Advisory Committee on Childhood Lead Poisoning Prevention, Atlanta, Georgia, February 27-28, 2001

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Centers for Disease Control and Prevention

Advisory Committee on Childhood Lead Poisoning Prevention: Meeting

In accordance with section 10(a)(2) the Federal Advisory Committee Act (Pub. L. 92–463), the National Center f Environmental Health (NCEH) of the Centers for Disease Control and Prevention (CDC) announces the following committee meeting.

Name: Advisory Committee on Childhoo Lead Poisoning Prevention.

Times and Dates: 8:30 a.m.—5:15 p.m., February 27, 2001; 8:30 a.m.—12:15 p.m., February 28, 2001.

Place: Swissotel Atlanta Hotel, 3391 Peachtree Road, N.E., Atlanta, Georgia 303 telephone 404/365–0065.

Status: Open to the public, limited only the space available. The meeting room accommodates approximately 90 people.

Purpose: The Committee shall provide advice and guidance to the Secretary; the Assistant Secretary for Health; and the Director, CDC, regarding new scientific knowledge and technological developmen and their practical implications for childhood lead poisoning prevention effor The Committee shall also review and repo regularly on childhood lead poisoning prevention practices and recommend improvements in national childhood lead poisoning prevention efforts.

Matters to be Discussed: Agenda items include: Updates on Medicaid Targeted Screening issues, Case Management issues, EPA, and MMWR Publication Process, Treatment of Lead-Exposed Children Trial Presentation, and discussion of future topics.

Agenda items are subject to change as priorities dictate.

Opportunities will be provided during the meeting for oral comments. Depending on the time available and the number of requests, it may be necessary to limit the time of each presenter.

This notice is published less than 15 days prior to the meeting due to administrative delays.

Contact Person for More Information: Becky Wright, Program Analyst, Lead Poisoning Prevention Branch, Division of Environmental Hazards and Health Effects, NCEH, CDC, 1600 Clifton Road, NE, M/S E–25, Atlanta, Georgia 30333, telephone 404/639–1789, fax 404/639–2570.

The Director, Management Analysis and Services office has been delegated the authority to sign **Federal Register** notices pertaining to announcements of meetings and other committee management activities, for both the Centers for Disease Control and Prevention and the Agency for Toxic Substances and Disease Registry.

Dated: February 13, 2001.

Carolyn J. Russell,

Director, Management Analysis and Services Office, Centers for Disease Control and Prevention.

[FR Doc. 01–4101 Filed 2–16–01; 8:45 am]

BILLING CODE 4163–18–P

Overview of the Treatment of Lead-Exposed Children (TLC) Trial

Dr. Campbell reconvened the ACCLPP meeting at 8:40 a.m. on October 20, 2004 and yielded the floor to the first presenter. Dr. Walter Rogan is ACCLPP's *ex officio* member for NIH/National Institute of Environmental Health Sciences (NIEHS). He provided an overview of the TLC Trial. The study is a formal clinical trial to evaluate the use of succimer as an oral chelating drug in preventing or reducing lead-associated cognitive, behavioral and neuropsychological deficits in toddlers. Nationally representative prevalence data of 16.4 million U.S. homes were reviewed to determine the number of homes and percentage of children ≤6 years of age with a lead hazard based on age of home. The number of homes built in the time periods of pre-1940, 1940-1959, 1960-1977 and 1978-1998 ranged from <58,000-~2 million. Of these homes, the percentage of lead hazards was estimated to range from <1%-81%. Of homes in which children ≤6 years of age resided, 25% had lead hazards in 2000.

ACCLPP Minutes October 19-20, 2004, p. 31

The data showed an extremely small statistical difference in attention/executive function of children seven years of age in the succimer group. The findings also suggested that the attention of the succimer group was a little better than the placebo group. However, TLC did not produce evidence to demonstrate that succimer is beneficial to children. Treatment was not found to lead to better scores on cognitive, neuropsychological or behavioral tests at 36 months of follow-up when the children were five years of age or additional follow-up at seven and 7.5 years of age.

TLC did not generate data on the use of succimer, but 41% of families reported difficulties in administering the drug. The succimer group was associated with unexplained, excess trauma based on hospitalization, history and physical examination data. Events reported in the succimer group included a near drowning, asthma attacks and head injury from an iron. Succimer is an expensive drug that is taken for six months and resulted in symptoms in children who were previously asymptomatic. The findings do not support conducting another trial to determine if succimer would be effective in children with BLLs <45 µg/dL. The investigators reasonably inferred that the prevention of lead exposure at the outset is the most effective approach to preventing lead-associated defects.

ACCLPP suggested that the TLC investigators use animal models to identify expression or repression of genes in response to lead, determine pathways and locate small molecules to enhance repair. TLC data should be used to emphasize the importance of improving the environment, particularly housing-based problems that cause lead poisoning. Dr. Brown has learned from one state that Medicaid will not reimburse for succimer if the child's BLL is 44 µg/dL or lower.

ACCLPP Minutes October 19-20, 2004, p. 33

USPSTF 2019 Guidelines on TLC

On the evidence basis for chelation therapy for lead poisoning, 2019 USPSTF: "All trials in table were fair quality except for TLC Trial Group,[31] which was good quality. Quality was assessed using criteria outlined in the US Preventive Services Task Force Procedure Guide.[8]

The Treatment of Lead-Exposed Children (TLC) study, a good-quality RCT(n = 780), evaluated children aged 12 to 33 months with blood lead levels between 20 and 44 µg/dL.[31,34,35,38] All children received nutritional supplements and had home inspections ***with lead abatement***

Curry SJ, Krist AH, Owens DK, et al. Screening for Elevated Blood Lead Levels in Children and Pregnant Women: US Preventive Services Task Force Recommendation Statement. JAMA - Journal of the American Medical Association. 2019;321(15):1502-1509. doi:10.10

Lawsuits

There have been a number of lawsuits by participants against KKI and contractors who carried out remediation on their behalf.

While it's initially easy to blame them, I think that they had good intentions and while there is evidence that the interventions they employed harmed some of the children, KKI *seemed* to be more thorough than other clinical sites and obtained additional funds to implement more intensive interventions (R&M Levels 1 & 2) than the baseline NIEHS cleaning they knew wouldn't work. However, the fact that they likely were also using TLC as a means of testing their R&M environmental interventions, was non-therapeutic. And it appears they likely had dust wipes immediately follow their interventions and knew they had failed, but didn't do anything.

I think the trial's design was fundamentally *non-therapeutic,* and that is due to the NIEHS, so I'm more interested in looking into the NIEHS officers than the people they paid to do TLC.

Therapeutic vs non-therapeutic research

Nontherapeutic research **"generally utilizes subjects who are not known to have the condition the objectives of the research are designed to address... [and] is not designed to directly benefit the subjects utilized in the research, but, rather... the public at large."**

Now Featherstone vs KKI is interesting, because NIEHS almost became involved in the legal trouble KKI was facing, but avoided it. The judge found TLC was *nontherapeutic,* something most other courts never did. (besides Deshields v KKI as I'm aware).

I disagree with their reasoning behind their classification non-therapeutic research however:

> *"Because succimer, the drug tested in the TLC Study, conferred no known, long-term benefit to children with blood lead levels in the range of the subjects, the study was classified as non-therapeutic.*

That is the whole point of why the study was being done, and succimer was already known to be the most effective and safest chelator for lowering BLLs by the time TLC was funded. TLC demonstrated a rapid but un-sustained drop in BLLs among the succimer group, which is a surrogate marker for clinical management of lead toxicity, so it is a poor argument for why the trial was non-therapeutic.

The reason why succimer, was nontherapeutic, was how they delivered it.

Therapeutic vs non-therapeutic research

By 1994 (when TLC was recruiting), the CDC had clearly established 10 µg/dL as the blood lead "level of concern." If lead is sufficiently toxic to justify experimental drug treatment at 26 µg/dL, it is internally inconsistent to argue that 15 µg/dL is an acceptable stopping point. Doing so deliberately leaves the child in a state of known toxicity (See previous discussion on Insufficient Treatment Endpoint)

In clinical medicine, treatment is directed toward a defined target, not an arbitrary midpoint. By capping therapy at 15 µg/dL, the protocol necessarily caps any potential recovery. If the hypothesis is that lead damages the developing brain, then leaving a substantial lead burden in place actively undermines the child's chance of neurological recovery.

The child bears 100% of the drug-related risks, including neutropenia, hepatotoxicity, and mineral depletion. If the protocol is designed to stop short of full detoxification, the child incurs these risks without the possibility of maximal benefit.

The study design therefore appears engineered to produce an ambiguous or negative result. When combined with a weak power calculation predicated on detecting only a 3-point IQ difference, the 15 µg/dL stopping rule effectively ensured that no meaningful cognitive improvement could be detected.

A study that systematically undertreats its subjects is scientifically invalid: it evaluates a compromised implementation of the therapy rather than the therapy's true potential.

Had I been the project officer reviewing this protocol prospectively, I would have had serious reservations about approving it. Endorsing such a design is analogous to asking: "Does half a course of antibiotics cure a complicated infection?" When the answer predictably returns "No," nothing meaningful has been learned about antibiotics, only that half-measures fail.

In clinical practice, antibiotics are not discontinued simply because a fever resolves while pathogenic bacteria remain. Likewise, stopping chelation at 15 µg/dL ensures that the child remains poisoned, merely less so.

If failure to demonstrate an IQ increase is then used as evidence that chelation-based BLL reduction is futile, and that the neurological damage is already "done", the logic collapses further: under that premise, there is no coherent justification for removing the child from ongoing lead exposure at all.

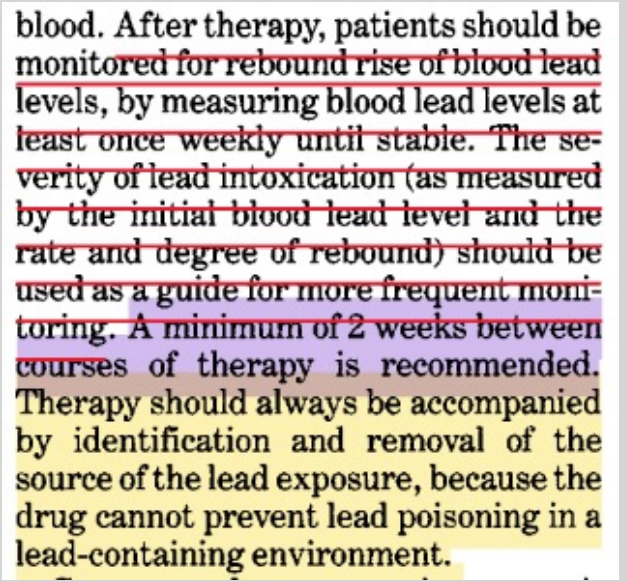
Informed Consent

"We believe that children in the study will get equal or better care than children outside the study, and that their homes will have less lead in them sooner…"

At the time of TLC, standard of care for BLLs 25-44 ug/dL included chelation based on an EDTA challenge test or clinician discretion. A clinician chelating a child with those BLLs would have followed the drug labeling recommendations. Children assigned to placebo were not prevented from the standard of care at the time, and children assigned to succimer did not receive the standard of care that would be expected (weekly monitoring, chelating based on patient response (pragmatically) and not pre-defined endpoints (15 µg/dL) which are still considered lead toxic. Importantly, any reasonable clinician chelating a child at the time would have monitored ferritin, throughout chelation, and would have ensured the child did not become iron deficient due to the treatment they were receiving. I would argue that zinc and copper monitoring should also be a component of standard of care, although there was more clinical equipoise on that versus iron status, especially in the early 1990s.

"We will make sure that the cells in their blood are normal and that they have enough iron. If your child has so little iron that he or she is anemic or has low blood, then we will give you iron for him or her and check him or her again after taking it to see if he or she is eligible."

Protocol Version 10, APPENDIX 2: Core Consent Forms: p. 44



blood. After therapy, patients should be monitored for rebound rise of blood lead levels, by measuring blood lead levels at least once weekly until stable. The severity of lead intoxication (as measured by the initial blood lead level and the rate and degree of rebound) should be used as a guide for more frequent monitoring. A minimum of 2 weeks between courses of therapy is recommended. Therapy should always be accompanied by identification and removal of the source of the lead exposure, because the drug cannot prevent lead poisoning in a lead-containing environment.

Nightingale SL. From the Food and Drug Administration. *JAMA: The Journal of the American Medical Association*. 1991;265(14):1802. doi:10.1001/JAMA.1991.03460140028006

Because iron deficiency can enhance lead absorption and toxicity and often coexists with it, all children with blood lead level 20 g/dL should be tested for iron deficiency. *Measurements of hemoglobin, hematocrit, and reticulocytes are not adequately sensitive, and erythrocyte protoporphyrin (EP) is not specific enough to diagnose iron deficiency (although EP can be used to screen for iron deficiency).*

Protocol 10: Appendix 3: Regulation of Environmental Lead- CDC 1991 Guidelines

- https://www.baltimoresun.com/2001/09/06/kennedy-krieger-sued-over-lead-study/

Featherstone v Kennedy Krieger Institute

link

Defendants KKI and Cecilia Davoli, an employee of KKI and a co-investigator for TLC, removed this action from the Circuit Court for Baltimore City to the Court **[*4]** pursuant to the federal officer removal statute, *28 U.S.C. § 1442(a)(1)*, on the assertion that they were acting under the direction of a federal officer in administering the Baltimore portion of the TLC study.

*Plaintiffs allege, inter alia, that succimer was "**not indicated for prophylaxis of lead poisoning in an environment containing lead hazards**," that **the parents of the children were not informed of this fact**, that Defendants knew or should have known that the interventions performed on the study homes were "**not sufficient to remove lead-based paint hazards,"** and that Plaintiffs received no benefit from participation in TLC, but were in fact harmed by it. Id. at ¶¶ 6-25.*

Defendants KKI and Davoli removed this action on the assertion that, as persons acting under an officer of the United States, they are entitled to removal pursuant to 28 U.S.C. § 1442(a)(1).14 Thereafter, Defendants moved to dismiss the Complaint for failure to join a necessary party or, in the alternative, for joinder of the NIEHS. Plaintiffs opposed the motion, arguing that the NIEHS was neither necessary or indispensable under Rule 19 of the Federal Rules of Civil Procedure in that the challenged aspects of TLC were within the control of the Defendants, not NIEHS.

*In the instant case, KKI and Davoli, while making certain allegations of general control, **clearly single out Dr. Rogan as the key federal officer responsible for administering TLC**.[19]*

Thus, Defendants argue that Dr. Rogan's position on the Steering Committee was such that he "specifically directed each and every facet of the TLC study[.]" Opp'nat 11.

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[12] Plaintiffs use the term "intervention" to refer to activities designed to removed lead dust and lead hazards from the homes. Defendants use the terms "clean" or "clean up."

[13] Plaintiffs allege that, "in order to facilitate recruitment," Defendants offered the parents of the participants, "cash, gift certificates, and other financial rewards for allowing their children to remain in the study." Compl. ¶ 14. Defendants also allegedly promised that they would "look carefully at the children['s] homes to identify lead hazards," that "if their house did not 'qualify'" for the study, the child would be relocated to lead-safe housing, and that they would "clean up the lead" in the homes of children enrolled in the study. Id. ¶¶ 10-12.

Featherstone v Kennedy Krieger Institute

"In order to be eligible to participate in TLC, a child had to reside in a pre-designated area (catchment area) and have a confirmed pre-existing blood lead level in the range of 20-44 micrograms per deciliter. Protocol at § 3. Because succimer was not indicated for children who continued to be exposed to lead, a condition for enrollment in the study was that the child's residence was not "too lead hazardous to be adequately cleaned." Id. Two home visits were conducted prior to a child being deemed eligible for TLC. "

"If deterioration was "extensive," "proper paint abatement" or relocation of the child was required for the child to be clear, however, that TLC was not designed to "oversee comprehensive lead paint abatement," id., and the Contract specifically states that the contractor "shall not expend contract funds for lead abatement." Contract at § B.4.g."

Featherstone v Kennedy Krieger Institute

The court document notes that NIEHS's strict control was "*designed in large part to ensure the relative uniformity of procedures... to promote the validity of the results*". They needed the "placebo" and "treatment" groups to be living in similar conditions. In other words, NIEHS wanted the children to continue to be exposed to lead dust. They explicitly state in multiple publications that the environmental interventions performed were intended to suppress lead dust levels *"…for up to 6-months*".

When the gap between the placebo and treatment groups BLLs began to narrow after 6-months, ultimately becoming equal after a year, it made it seem as if the drug itself was not effective at lowering BLLs, that way there was no wiggle room for saying succimer might be a medical necessity, as the argument could be made that succimer is ineffective at lowering BLLs long-term and not medically necessary and thus coverable by OBRA. However, the reality, is that the factors that gave each treatment group similar BLLs pre-randomization, was once again the same, and since BLLs largely reflect recent exposure, their BLLs reflected that.

Featherstone v Kennedy Krieger Institute

actual control. See Good, 914 F. Supp. at 1129 (noting that a defendant has the burden to "set forth evidence showing that it did, in fact, act under a federal officer"). The Court begins with the affidavits signed by Davoli and Merrill Brophy, KKI's Project Manager for TLC. The affidavits detail the role of the Steering Committee, Dr. Rogan, NIEHS, the CDC, and the FDA in controlling aspects of the study. With regard to Dr. Rogan, both Davoli and Brophy aver that the Steering Committee "was charged with responsibility for virtually all aspects of the study," that "each and every decision of the Steering Committee was reviewed by Dr. Rogan prior to or during the process of its implementation," and that "[n]o decision was final without review by Dr. Rogan and the NIEHS." Aff. of Merrill Brophy ¶¶ 4-5; Aff. of Cecilia Davoli ¶¶ 4-5. With regard to the IC forms, Davoli avers that "the NIEHS directly controlled and approved the information provided to the Study participants and their families

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[19]Defendants also suggest that NIEHS's contracting officer, Thomas Hardee, exercised direct and detailed control over TLC as the "sole agent of NIEHS" for purposes of the study and the only person who could approve funding changes. Opp'n at 5. The Notice of Removal, however, makes only one reference to "NIEHS's contracting officer" with respect to Mr. Hardee's role in approving the Contract after it was signed. Notice of Removal at ¶ 12. The affidavits attached to the Notice of Removal make no mention of Mr. Hardee, either by name or by title. The Court concludes that the Notice of Removal fails to allege any direct and detailed control by Mr. Hardee.

Deshields v Kennedy Krieger Institute

PLAINTIFF'S RESPONSE TO DEFENDANT KENNEDY KRIEGER INSTITUTE, INC.'S MOTION FOR PROTECTIVE ORDER

1. The instant matter is a lead-paint poisoning claim where in it is alleged that the Plaintiff, Shawnta DeShields, suffered severe and permanent injuries as the result of exposure to and ingestion of lead-based paint and lead based paint dust at 910 N. Freemont Avenue, Baltimore, Maryland.

2. The Plaintiff has filed suit against Kennedy Krieger for negligence in regard to the Plaintiff's participation in a research study ***misleadingly entitled 'Treatment of Lead Exposed Children' (TLC).*** *It is alleged that, in the course of that study, otherwise healthy children with documented elevated blood lead levels (including the [*2] Plaintiff) were referred to Kennedy Krieger for treatment, were negligently enrolled into the study and enticed and lulled into living in and/or remaining in lead infested houses for the purpose of perpetuating research for the enrichment and increased prestige of Kennedy Krieger.*

3. That on April 2, 2003 this Honorable Court held a hearing during which the scope of documents to be produced and the rationale behind the production of these documents was specifically addressed. ***This Honorable Court explicitly contemplated the placement of the produced documents in a "document repository" for use in regard to the other cases.*** *(Exhibit 1) Therefore, the Defendant's blanket assertion of privilege, aside from failing to comport with Local Federal Rule 13 requiring "particular designations of confidentiality", is in direct defiance of the intent of this Honorable Court.*

*4. Any argument by Kennedy Krieger that the information requested is confidential is vitiated because Kennedy Krieger has disclaimed obligations to study participants through the waiver of confidentiality in consent forms signed with the study participants, and the Defendants own admissions that the study is a non-therapeutic [*3] study.*

5. The burden is on the Defendant in seeking confidentiality to justify it and the Defendant has not shown the good cause required for the grant of a protective order, and has not shown that there is any privilege attached to any of the documents this Honorable Court ordered to be produced and for that reason, Kennedy Krieger's Motion for Protective Order should be denied.

6. In support of the Plaintiff's response to Kennedy Krieger's Motion for Protective Order, the Plaintiff incorporates by reference the attached Memorandum.

Deshields v Kennedy Krieger Institute

The court documents I've been able to access clearly establish that there was a court-approved, multi-case TLC repository arrangement. The judge agreed it would be a good idea to save time on discovery for future cases since so many lawsuits were coming out against TLC and R&M.

KKI filed a motion of protection out of concern that some of the 6 banker boxes full of documents they had released to the plaintiffs were *deliberative* or *pre-decisional*— meaning they included discussion of the planning phase of TLC, and as a result, *if* they were requested from NIEHS in a FOIA request, NIEHS could technically use Exemption 5 to not release them.

I was unable to locate the actual Motion for Protective Order (Doc 30), only the opposition and replies between council.

I'm not sure of the exact categories of information KKI sought to protect (IRB materials, protocol drafts, agency–contractor communications, DSMB-type records, etc.). The current documents strongly references this but does not reliably provide a clean standalone text of Doc 30.

The plaintiff argues that KKI's request for a protective order is not really about legitimate confidentiality (privacy of participants, trade secrets), but about preventing disclosure of information that would make KKI look bad—"embarrassing" or "unfavorable" facts about how TLC was conducted.

When plaintiffs frame a protective order this way, they are signaling they want to use discovery materials beyond the narrow litigation record, potentially for public accountability. That increases defendants' incentive to argue "deliberative"/FOIA-style protection for agency–contractor communications.

Thus, in the present case, if Plaintiffs sought to obtain directly from the government much of the confidential information already produced by Kennedy Krieger, the NIEHS would be entitled to withhold the documents that reflect the pre-decisional, deliberative process that took place during the development and conduct of the TLC study.

*As set forth more fully in Kennedy Krieger's Motion, the documents designated as "confidential" should be protected from dissemination outside of the course of this litigation for the [*10] following reasons: (1) Kennedy Krieger is obligated by contract to maintain the confidentiality of information or data of a personal nature about an individual, or proprietary information or data submitted by or pertaining to an institution; [9] (2) many of the documents reflect the deliberative process of the NIEHS and its contractors; [10] and (3) Institutional Review Board documents must be treated as confidential based on legislative intent and sound public policy. [11] In sum, open communication and frank discussion among researchers is paramount to the success of scientific and medical research. If researchers believed that their personal notes, observations, internal communications, and critiques would be subject to unfettered disclosure, the chilling effect would hinder the frank and open discussions necessary to conduct valuable and scientifically sound research. See U.S. v. Nixon, 418 U.S. 683, 705 (1974).*

9 See Motion, p. 4 (quoting 48 C.F.R. § 352.224-70).10 See Motion, pp. 5-10 (stating that the purpose of the deliberative process privilege was established to prevent injury to the quality of agency decisions).

10 See Motion, pp. 5-10 (stating that the purpose of the deliberative process privilege was established to prevent injury to the quality of agency decisions).

11 See Motion, pp. 10-11 (explaining that to ensure that research on human subjects is conducted in the best manner possible, members of the IRB must be free to voice opinions and criticisms with candor, without fear that a comment will later be used in litigation.

PLAINTIFF'S RESPONSE TO DEFENDANT KENNEDY KRIEGER INSTITUTE, INC.'S MOTION FOR PROTECTIVE ORDER

I. FACTUAL BACKGROUND

*This suit arises from the minor Plaintiff, Shawnta DeShields' participation in a research study entitled 'Treatment of Lead Exposed Children' (TLC). The study was conducted to research and assess the long term effects of allowing lead to remain in the bloodstream and bodies of children versus removing the lead from the child's bloodstream using a drug called Succimer. Under this research study, children with elevated blood lead levels were recruited and given either Succimer or a placebo on a double blind basis. Kennedy Krieger has conceded that the purpose was not to render treatment to any child enrolled in the study but instead to measure the extent of permanent damage to the cognitive functioning based upon the chronically elevated blood lead levels of children.[1] In this manner, otherwise healthy children with documented elevated blood lead levels were referred to Kennedy Krieger Institute for treatment, and were negligently enrolled into the study and enticed and lulled into living in and/or remaining in lead infested houses for the [*5] purpose of perpetuating research for the enrichment and increased prestige of Kennedy Krieger.*

1 The Court of Appeals has made its dim opinion of such studies very clear in regard to the similar Kennedy Krieger multi-level abatement study which was conducted during the same time period:

Otherwise healthy children, in our view, should not be enticed into living in, or remaining in, potentially lead-tainted housing and intentionally subjected to a research program, which contemplates the probability, or even the possibility, of lead poisoning or even the accumulation of lower levels of lead in blood, in order for the extent of the contamination of the children's blood to be used by scientific researchers to assess the success of lead paint or lead dust abatement measures.

PLAINTIFF'S RESPONSE TO DEFENDANT KENNEDY KRIEGER INSTITUTE, INC.'S MOTION FOR PROTECTIVE ORDER

I. ARGUMENT

Due to these facts, this Court entered an Order in the course of a hearing conducted on April 2, 2003, directing Kennedy Krieger to produce all documents related to the TLC study for Plaintiffs' counsel to make a determination of relevancy.

The Court: *Well, it seems to me, particularly with all these other cases going on in the Circuit Court of Baltimore City, all of the documents ought to be rounded up, collected, there should be a repository, and unless there is a privilege you should be able to see all of them, and make your own determination as to whether they are relevant or*
not. (Exhibit 1)

*Under the Order and Rulings from the bench of this Honorable Court, Kennedy Krieger was to produce all documents pertaining to the TLC study. Any documents in regard to which Kennedy Krieger wished to assert any claim of privilege were to be identified and withheld by Kennedy to be addressed at a later date. Although the Defendant reasons that these documents contain personal information about study participants, and sensitive research data that need the protection of the Court, the Defendant also concedes that those specific documents were not produced anyway. By [*7] the Defendant's own admission, specific information pertaining to other study participants has already been withheld by the Defendant (see footnote 3 of Defendants Memorandum in Support of Motion for Protective Order). In addition, the Defendant has (the Plaintiffs would argue, wrongfully) also redacted information it deemed confidential or proprietary (see footnote 4 of Defendant's Memorandum in Support of Motion or Protective Order). Now, in direct opposition to the common sense directive of this Honorable Court to establish a "document repository" of the TLC study documents for use in the remaining cases, the Defendant seeks to have to gag the Plaintiffs from access to these documents which the court has ordered produced. This would doom the parties and the courts to spending countless months and years of labor re-fighting the same discovery battles over and over and over again to obtain access to the documents which are applicable to all the TLC claims. The Court can establish what documents should be protected, and the scope of that protection. However, courts "could not say that there was an established or well-settled practice of protecting research data in realm of civil [*8]discovery." Burka v. U.S. Dept. Of Health and Human Services 87 F.3d 508. The documents which Kennedy Krieger seeks to protect clearly fall into the realm of research data and as such, merit no claim of absolute privilege. Kennedy Krieger asserted at the hearing of April 2, 2003 that the documents requested were confidential in nature, reflecting data collected by the study, or transmitted to the study, and that they contained proprietary information about Kennedy Krieger that should not be disseminated outside of the present litigation. After considering the arguments the Court ordered the Defendant to produce the documents regarding the TLC program. Additionally, by the Defendants' own admission, this study was a non-therapeutic study in which the study participants waived confidentiality through a proviso in the consent form drafted by Kennedy Krieger. This waiver provided a mechanism whereby study participants allowed Kennedy Krieger to reveal information to outside parties. Clearly the Defendant is trying to hide under the guise of confidentiality only when it is favorable to them to do so.*

Plaintiff opposition is docketed as **Document 33** filed **08/29/2003** (as shown in the stamped footer)
KKI reply appears as **Document 35** filed **09/09/2003** in the same footer sequence
Case ends in a **dismissal with prejudice** (Document 39) filed **07/30/2004**.

Hope to obtain

1. The underlying Motion for Protective Order (Doc 30) (not just the opposition/reply)

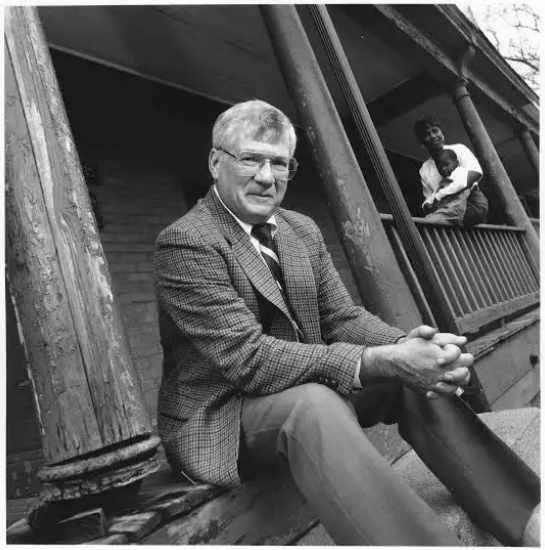
2. Any court order resolving the protective order motion (grant/deny and on what terms).

3. Any exhibit list or confidentiality legend used in production (if it exists).....what KKI/NIH considered “deliberative”

Dr. Herbert Needleman, a University of Pittsburgh scientist known for studies that linked learning deficits to low-level lead poisoning, said he's convinced that [Mark] Farfel [(of the R&M studies)] is an ethical scientist who might have grown distant from community sensitivities.

"*You begin to think of subjects not as individuals but as data points, and they lose their individuality*", Needleman said.

"*It happens to everybody, even to me. That's what happened to Mark*."



* Dr. Needleman was on the TLC Data Safety and Monitoring Committee.

These factors, combined, make interpretation of the TLC trial results difficult. Ultimately, the TLC trial showed that succimer chelation is not a replacement for reducing environmental exposure, nor a magic bullet for lead's persistent cognitive damage.

It illustrated how a single randomized controlled trial can shape national policy for decades, redirecting efforts from identifying and refining clinical treatment toward an almost exclusive emphasis on housing and environmental regulation.

Efforts to reduce lead hazards in housing have been slow—there were an estimated 24 million houses with lead hazards in 1999 and still 21.9 million in 2019. By collapsing the concept of prevention into a single, upstream intervention, a false dichotomy was created: treat the environment or treat the child. While the shift to primary prevention was justified and much needed at the time, our abandonment of a search for treatment was not. Well-designed pragmatic trials are still needed to determine the safest and most effective protocols for lowering lead levels in children. Until then, we must apply the existing guidelines with our best clinical judgement, always keeping in mind the individual context of the child in front of us, and continue to advocate vigorously for primary prevention so that fewer children ever need face this predicament

Outstanding Questions

- Any other TLC lawsuits outside of Maryland?
- Featherstone v KKI affidavits from Merrill Brophy and Cecilia Davoli
- Vitamin Recall: can't find any information on it (FDA, Federal Register), outside of the published paper.
- NIEHS/NTP special workshop on January 11–13, 1995.
- Likely will never see– discovery documents from TLC repository from Deshields case. \

Planning to submit proposal to UA for IRB-exemption for a request to get the following from NIEHS:

- Ferritin levels for each study participant.
- Lead-contaminated vitamin exposure documentation for each study participant.
- IQ scores by study participant.
- Treatment group assignment for each study participant.
- Adherence for each participant to see what how adherence was actually measured and what differences between clinical sites.
- Previous protocol versions in full.

actual control. See Good, 914 F. Supp. at 1129 (noting that a defendant has the burden to "set forth evidence showing that it did, in fact, act under a federal officer"). The Court begins with the affidavits signed by Davoli and Merrill Brophy, KKI's Project Manager for TLC. The affidavits detail the role of the Steering Committee, Dr. Rogan, NIEHS, the CDC, and the FDA in controlling aspects of the study. With regard to Dr. Rogan, both Davoli and Brophy aver that the Steering Committee "was charged with responsibility for virtually all aspects of the study," that "each and every decision of the Steering Committee was reviewed by Dr. Rogan prior to or during the process of its implementation," and that "[n]o decision was final without review by Dr. Rogan and the NIEHS." Aff. of Merrill Brophy ¶¶ 4-5; Aff. of Cecilia Davoli ¶¶ 4-5. With regard to the IC forms, Davoli avers that "the NIEHS directly controlled and approved the information provided to the Study participants and their families

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[19]Defendants also suggest that NIEHS's contracting officer, Thomas Hardee, exercised direct and detailed control over TLC as the "sole agent of NIEHS" for purposes of the study and the only person who could approve funding changes. Opp'n at 5. The Notice of Removal, however, makes only one reference to "NIEHS's contracting officer" with respect to Mr. Hardee's role in approving the Contract after it was signed. Notice of Removal at ¶ 12. The affidavits attached to the Notice of Removal make no mention of Mr. Hardee, either by name or by title. The Court concludes that the Notice of Removal fails to allege any direct and detailed control by Mr. Hardee.