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ORIGINAL REPORT

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.

KEY WORDS — succimer; lead poisoning; mineral supplements; children; clinical trials

INTRODUCTION

The Treatment of Lead-exposed Children (TLC) trial was a four-centre, double-blind, randomized, placebo-controlled trial to determine whether succimer, a drug that lowers blood lead, reduces lead-associated developmental delay. Children were eligible for TLC if they were between 12 and 33 months of age and had blood lead levels of 20–44 μg/dL (0.96–2.11 μmol/L; to convert μg/dL to μmol/L, multiply by 0.048) just below the $\geqslant$45 μg/dL labelled indication for succimer. The primary outcome of TLC was developmental status three years after randomization. Besides the randomized intervention, TLC cleaned the lead dust from all of the families' homes and provided chewable vitamin and mineral tablets as dietary supplements. Dietary deficiencies of zinc, iron, calcium or copper were expected in these relatively disadvantaged children, and succimer might deplete these minerals further.

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TLC randomized 780 children between August 1994 and January 1997 at four clinical sites: Baltimore, Cincinnati/Columbus, Newark and Philadelphia. By July 1997, almost all the children had finished taking succimer or placebo and should have been taking the supplement. On Monday 7 July 1997, the TLC Pharmacist (TS) notified the Project Officer (WR) that NutroPharmaceuticals, the manufacturer, was recalling the supplement. (Figure 1 provides a timeline for the recall effort.) Nutro had been notified on 3 July that the iron-wax particles supplied by Particle Dynamics for use in compounding the supplement were contaminated with 250–600 parts per million lead. Particle Dynamics was recalling the lot. Nutro was recalling the supplements to the retail level. This paper describes the response of the TLC research team to this incident.

METHODS

Decision making

If the iron contained 250–600 parts per million lead, we could estimate that the supplements would have 20–48 μg of lead per tablet. Children begin to accumulate lead at approximately 5 μg/kg of lead intake per day. For context, the median daily intake of lead in 2-year-old children in the USA in the 1990s is about 2 μg/day total. As recently as the early 1980s, the median daily intake was 30 μg/day.[1] The mean weight of enrolled children at the time of randomization was about 12 ± 2 (SD) kg. Hence, the estimated daily dose from the supplements would likely not be more than 5 μg/kg for even the smallest children. By definition, however, all TLC children had recent excess exposure to lead from other sources. While it was unlikely that any child would be acutely poisoned, the dose of lead from the supplements came too close to the total dose at which the child's blood lead would be expected to increase.

On 7 July, the Project Officer telephoned the Data Center and the TLC clinicians. All those contacted agreed that TLC should attempt to prevent any further ingestion of the supplements, but that there was time to proceed in an orderly fashion. Accordingly, the Data Center sent a fax to the clinical sites advising them to cease distributing the supplements immediately and arranging a conference call for 8 July.

At the conference call, the TLC Pharmacy reported that Nutro's analyses of the supplements showed about 32μg Pb per supplement tablet, the middle of TLC's estimate. The US Food and Drug Administration (FDA) told us that, since the supplements were contaminated at a level that was unlikely to produce irreversible harm, FDA could only encourage voluntary recall. FDA also told us that the contaminated iron had been traced to a new iron supplier and so likely was a new problem. TLC viewed itself to be in a special situation and its participants particularly vulnerable, and so not recalling at the individual level was never seriously considered.

The TLC Pharmacy had repackaged and distributed 984 bottles of 100 supplement tablets each to the TLC clinical sites. The distribution of the contaminated lot had begun in April 1997. TLC children were on a 3-month visit schedule, and so all should have been scheduled between April and July. TLC decided to contact every family individually and attempt to retrieve the contaminated supplements from them.

Notification

Most TLC families were economically disadvantaged, and many did not have working telephones. TLC decided to mail a letter to all the families explaining that the supplements were lead-contaminated and that the children should stop taking them. Families were assured that the amount of lead was small and unlikely to affect the child. They were asked to bring the child and the supplements in to the TLC clinic. At that visit, blood could be drawn for a measurement of blood lead concentration ('blood lead'). Given the number of people involved and the plan to send a letter, the public information staff from NIEHS and all the sites were invited for the second 8 July call.

TLC had an independent Data and Safety Monitoring Committee. On 8 July, the Chair of the Committee was travelling; the Project Officer notified the Deputy Chair by telephone, and the remainder of the committee by e-mail or telephone. The letters to the families, instructing them to call the TLC clinics, were mailed on 9 and 10 July, and TLC arranged to answer phone calls and accept visits over the weekend. TLC established a telephone tree to manage any press inquiries, but none was received.

All the sites began consulting with the chairs of their Institutional Review Boards (IRBs). In general, the IRBs would view the need to measure blood lead on a child enrolled in TLC as a minor

Friday, April 4:	TLC pharmacy begins shipping repackaged supplements from lot # 23198.
Thursday, July 3:	Particle Dynamics informs Nutro Pharmaceuticals of recall of iron-wax particles for lead contamination
Friday, July 4:	Holiday
Monday, July 7:	Nutro notifies TLC pharmacy of recall of supplements. TLC investigators notified of supplement contamination. NIEHS Project Officer has TLC clinical sites notified to stop distributing supplements.
Tuesday, July 8:	Recall of all TLC supplements initiated. Decision to send letter to all TLC parents and primary care physicians. Decision to schedule clinic visit for all TLC children to return supplements and to obtain blood sample. Oversight organizations notified of supplement contamination: • TLC Data and Safety Monitoring Committee • Food and Drug Administration • IRBs at each participating institution Conference calls of TLC investigators scheduled each workday until further notice
Wednesday, July 9:	Materials prepared for supplement recall • Letter to TLC families • Press release and list of questions and answers • Procedures for documenting retrieval of supplements Letters to parents mailed from three TLC Clinical sites Phone contact of TLC families begins
Thursday, July 10:	Letters mailed from fourth TLC clinical site Home visits of TLC families without phones begins
Friday, July 11:	Phone tree established for response over weekend. 350 of 780 families in study contacted directly.
Friday, July 18:	581 of 628 families with potentially exposed child directly contacted.
Friday, July 25:	Last special investigators conference call.
Monday, July 28:	NIEHS and CDC IRBs approve blood draw of sibs of TLC children. New Jersey lab reports 32 μg lead per tablet from unopened bottles of contaminated supplements.
Monday, Sept. 15:	NTP contractor reports 36 ± 2 μg lead per tablet.
Monday, Oct. 13:	TLC recall effort completed.
Thursday, Dec. 4:	Data and Safety Monitoring Committee reviews response.

Fig. 1. — Timeline of TLC Supplement Recall, 1997

addition to an approved protocol. Only the IRB at the Centers for Disease Control and Prevention (CDC) (the Nutritional Biochemistry Branch at CDC was the TLC lead analysis laboratory) believed that separate consent for an additional blood lead was necessary for children already enrolled in TLC. Consent forms can be approved only at a regular meeting of an IRB. While consent for venipuncture in adults can be approved by an expedited process when the IRB chair declares an activity to pose minimal risk, there is no expedited review process for research involving children. IRBs are not allowed to meet by conference call, and can have several requirements for a quorum beyond a majority, such as the presence of both sexes, more than one race, and a non-scientist

member. While the IRBs at the clinical sites often had scheduled weekly meetings, the NIEHS IRB was not scheduled to meet until 28 July, and could not form a quorum before then. The CDC IRB wanted the results of the NIEHS meeting before it would act. The CDC laboratory continued to analyse blood samples from the main study. Operationally, it had no means of distinguishing blood samples drawn specifically because of the contamination.

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.

TLC believed that it had consent to measure blood lead for TLC children, and that blood lead measurement in sibs was clinical care, not research. TLC also believed that it was very important to act in a timely manner, and that the children needed appropriate clinical management regardless of the research setting in which they had received the supplements. Not offering to do blood leads for either the TLC children or the sibs for weeks until all the IRBs had met was out of the question, and was never seriously discussed by the investigators nor proposed by any IRB. There was, though, at least the appearance of a dilemma about a new consent document, which never was allowed to become an operational problem.

Measurement of the contamination

The National Toxicology Program (NTP), which is run from NIEHS, volunteered to analyse a hundred supplement tablets for lead. The Environmental and Occupational Health Sciences Institute at the University of Medicine and Dentistry of New Jersey/Robert Wood Johnson Medical School (the 'New Jersey lab' hereafter), offered to do a smaller number in a shorter time. Because the TLC Pharmacy bought the supplements in large drums and re-packed them into bottles of 100, there seemed little point in estimating bottle-to-bottle variability. There was a question of tablet-to-tablet variability, and a question of local contamination. Since TLC homes were all contaminated by lead dust, opened bottles that were being returned might contain exogenous lead from the home. The New Jersey clinical site had opened and unopened bottles, both presumed contaminated and presumed clean. We decided to have the New Jersey laboratory analyse 16 composite samples. Battelle Preclinical Drug Development, Northwest Operations, Richland, WA ('Battelle' hereafter) was the NTP contract laboratory, which could do individual tablets. We gave them 100 tablets directly from the TLC Pharmacy, two each from 48 previously unopened, presumed contaminated bottles, and two each from two unopened, presumed clean bottles. All analyses were done blind to source of tablets.

On 28 July, the NIEHS IRB met and agreed with its chair's opinion that children enrolled in TLC required no extra consent for venipuncture, and cleared a consent form for venipuncture on the sibs. The CDC IRB then cleared both activities, but suggested that a script be prepared and read to the families prior to venipuncture on the sibs. This suggestion was passed on to the clinical sites; however, they continued to use the Cincinnati laboratory for blood lead measurement in the sibs and none chose to implement the CDC suggestion.

RESULTS

Follow up

The recall effort began on 8 July. On 13 October, we froze the data in order to prepare for the December Data Safety Monitoring Committee meeting. By 14 July, TLC staff had contacted 375 (48%) of the 780 families. In subsequent weeks, the recall effort was focused on the 628 children who were potentially exposed to the contaminated supplements.

By 21 July, 501 (80%) of the 628 families whose children were potentially exposed had been contacted by clinic visit, home visit, or telephone (Figure 2). By 4 August, 601 families of potentially exposed children (96%) had been contacted. The remaining 27 families either had disconnected telephones or had not been reachable by telephone. TLC staff began visiting the last known address of these families. An additional 22 families were contacted

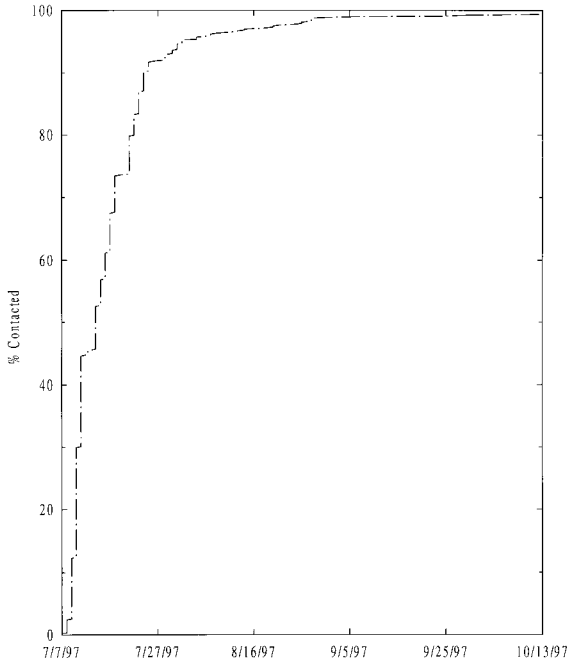

Fig. 2. — Cumulative frequency of contact with children ($n = 628$) potentially exposed to contaminated supplements, July to October, 1997

during the remainder of the recall period, so that 623 (99%) of the families were eventually reached.

Lead in the supplements

The New Jersey laboratory provided its analysis of the supplements on 28 July. Unopened bottles of the contaminated lot contained 32 μg/tablet. Lead levels in bottles from previous lots were below the limit of detection. Opened bottles from the contaminated lot that had been distributed to the families contained 34 to 39 μg/tablet, consistent with some dust contamination, and opened bottles from uncontaminated lots had concentrations below detection. On 15 September, Battelle's analysis showed a mean lead concentration of 36 ± 2.2 μg/tablet, with a range of 32 to 47 μg, based on two tablets from each of 48 unopened bottles provided by the TLC Pharmacy. Battelle found 'much less' than 8.3 μg/g, the limit of detection, in tablets from a previous lot.

Children's blood lead

Of the 628 children who were potentially exposed, 571 (91%) were seen in a TLC clinic for blood lead and an additional 52 (8%) were contacted but did not have a blood lead between 7 July and 13 October (Table 1). A valid blood lead was obtained during subsequent follow-up for all but one of these children. In addition, 109 (72%) of the 152 unexposed children had participated in the recall effort.

For the 571 children who had both a blood lead between 4 April and 7 July and a blood lead during the recall period, the mean increase in blood lead from the first to the second measurement was 1.2 ± 0.2 μg/dL (Table 2). Analyses by the number of missing tablets showed no dose-response. In the 78 children who had no clinic visit or did not attend a scheduled visit during the time when the contaminated supplements were distributed, the blood lead increased 1.8 ± 0.7 μg/dL from their last clinic visit to the first visit after 7 July.

DISCUSSION

Contamination of TLC's mineral supplement created a potential hazard to participating children, and a threat to inference from TLC. TLC recalled the contaminated supplements and assessed the children's exposure. Within a month, more than 95% of families had been contacted. Ultimately, all but five of 628 affected families were contacted and the children evaluated. We saw no change in blood lead that we could attribute to the supplements.

While there was no detectable difference between the blood leads of children who received contaminated supplements and those who did not, the visits of the unexposed children were further apart than those of the potentially exposed children. Blood leads tend to increase during the summer, and so the unexposed children may have had a larger change because of a greater opportunity for seasonal change. On the other hand, blood lead declines with age in virtually all TLC children, and so the longer time available for decline may mean that using those children as controls is conservative. The data available to TLC investigators suggest that the contaminated supplements had little or no effect on blood leads. TLC believes that, for this incident to affect inference about the effect of drug treatment on cognitive delay, it would have had to produce some change in blood lead, which it did not.

This experience shows the need for redundancy in the principal investigator (PI) function at

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

participating sites. The 7 July date meant that many people were travelling. Two of the four clinical centre PIs, the Data Centre PI, the Chair of the TLC Steering Committee, the Chair of the Data & Safety Monitoring Committee, and the NIEHS Director could not be reached immediately. TLC had been in existence for almost four years when this incident happened, so other staff were prepared to assume responsibility. That, however, was to some degree a happy accident due to low turnover. Although the Steering Committee usually operated by consensus, the pace of this episode required decisiveness. Thus, having one of the Steering Committee members available who was accustomed to chairing the meetings was valuable. While experienced field staff is much more important in managing such an episode than the PIs, the coordinators do not all go out of the country at the same time, whereas the PIs do.

TLC attempted to contact the families quickly, with relatively little information on the degree of contamination. Unlike a drug company, TLC had no laboratory that could rapidly and defensibly analyse the supplements. We had to rely initially on the results available from the manufacturer. On that basis, we believed that we had to recall the supplements and accepted the possibility that the degree of contamination was insignificant and our reaction unnecessary. On the other hand, we did not mobilize the city health departments, the police, or the press to help recover the supplements, because we thought that acute severe toxicity was unlikely. Given that many of the children had been taking the supplements for three months and that we had seen no such toxicity, we had clinical evidence in addition to the chemical analyses to support this.

We prepared for press interest but did not have any beyond a nibble. The only other time in the collective experience of the Steering Committee that letters had gone to study participants with

KEY POINTS

- A large paediatric clinical trial evaluating therapy for lead poisoning inadvertently distributed a vitamin and mineral supplement contaminated with lead for about three months
- The level of contamination was sufficiently low that recall was voluntary on the part of the manufacturers
- No change in blood lead occurred in the children attributable to the supplements
- With consumption of supplements now so widespread, such contamination episodes may begin to have clinical importance

unwelcome news, a participant had notified the press. That story played nationally, and consumed the Project Officer for several weeks.[2] Such a story has a face, and is more appealing to the media than interviewing cautious and defensive investigators. TLC would not have released names of participants to a reporter, but, had a story run, some of the participants might have come forward. In any event, there is no chance of keeping such an activity secret, and so involving those whose job it is to deal with the press is best done as early as possible.

It is ironic that a clinical trial involving lead poisoned children would distribute lead contaminated supplements. The TLC investigators, however, were well qualified to deal with such an incident. Because paediatric lead poisoning is so well understood and because most of the TLC investigators specialized in it, TLC could make credible, timely statements about the expected change in lead level and the expected consequences of the contamination. If TLC had to deal with an unfamiliar or less well-characterized contaminant, such as dioxin or aflatoxin, the process might not have moved so quickly. Conversely, had an antibiotic or vaccine trial had a lead problem, they might not have been able to act so quickly.

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. We did not employ such tactics for the supplements once the children were in follow-up, and so adherence was probably much lower. In this case, the relatively low rate of adherence prevented a greater impact of the contamination.

The contamination was discovered because one very large formulator tested its iron supply. Even then, FDA had no authority to require recall, and Particle Dynamics and Nutro Laboratories acted voluntarily. FDA, of course, has nothing approaching the capability to analyse a significant of sample of the huge numbers of supplements sold in the USA. Thus this kind of relatively low-level contamination could be happening frequently and go undetected, or, if detected, not result in recall.

Suppliers of constituents like iron for compounding into supplements are supposed to provide a Certificate of Analysis, which shows, among other things, that the product contains no more than a very small amount of lead. We were told that the company that sold the iron to Particle Dynamics had such a certificate. While it is tempting to call for re-analysis at every step, this is impractical. We at TLC, even in retrospect, do not think that we should have arranged for the analysis of the supplements. If we had done so, we might have been more concerned with tablet-to-tablet variability in iron, which was the most toxic substance that we dispensed, rather than lead. We did arrange for some analyses of our succimer, because we used some of it beyond the date that a commercial preparation would have been labelled to expire. Yet, had the level of lead been two orders of magnitude higher, very vulnerable children could have been made ill and a trial that cost millions to mount could have been invalidated.

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.

CONCLUSION

A large paediatric clinical trial inadvertently distributed a vitamin and mineral supplement

contaminated with lead for about three months. Once the contamination was discovered, the trial staff recalled the supplements from the families, and believe that no child was harmed and that inference from the trial is unaffected, based on the fact that blood lead levels did not change. This incident provides anecdotal evidence that such contaminations occur, and that a rapid and open response to such an event is reasonably acceptable to the participants.

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REFERENCES

1. Pirkle, J. L., Brody, D. J. and Gunter, E. W. *et al*. The decline in blood lead levels in the United States. The National Health and Nutrition Examination Surveys (NHANES). *JAMA* 1994; **272**: 284–291.
2. Rogan, W. J., Gladen, B. C., McKinney, J. D. and Albro, P. W. Chromatographic evidence of polychlorinated biphenyl exposure from a spill. *JAMA* 1983; **249**: 1057–1058.

