Figure 2.1b. DATA-BASED INVESTIGATING: Cadmium Levels in Human Blood

Cadmium is a metallic element used in a number of industries – for example, in anti-corrosion coatings, in pigments, and in nickel-cadmium batteries. Partly as a result of its industrial uses and partly because of natural processes, cadmium is widely distributed throughout the environment, and low levels are found in most plants and animals. As a consequence, essentially all humans are exposed to cadmium on a daily basis – an intake of roughly 50 μg per day, mainly in the diet, is considered to be typical, although most of this is believed to be excreted in the faeces without absorption. Cigarettes contain traces of cadmium so that smokers usually have at least double the exposure of non-smokers – respiratory absorption of cadmium is appreciably more efficient than gastrointestinal absorption.

Cadmium is *toxic*. In the past, some workers in cadmium smelters, who were exposed to high levels of the vapour from molten cadmium, died from *respiratory* failure. In contrast to these respiratory effects of *acute* poisoning by 'high' levels of cadmium, people who have been exposed to 'intermediate' cadmium levels, usually for relatively long periods, may exhibit impaired *kidney* function; a few deaths due to kidney failure in such exposed individuals have been attributed to *chronic* cadmium poisoning.

In view of the known toxicity of cadmium and the long-term low-level exposure of the general population, there have been many investigations of cadmium levels in human tissues starting in the 1950s, to try to determine what is 'normal' and whether there is evidence that this cadmium exposure produces any widespread chronic health effects. One tissue commonly used to assess level of exposure is *blood*, because it is relatively straight-forward to obtain blood samples from people. Unfortunately, normal cadmium levels in blood are so low (1 ng/g or less) that their accurate measurement poses considerable difficulties; many of the data in the older (*e.g.*, 1975 and before) scientific literature are suspect, in that they are now considered to be significantly too high due to inaccuracy in the analytical methods used to measure cadmium level.

One investigation in the mid-1970s in the U.S. analysed blood samples from 1,954 male military recruits aged 18-22 years; these subjects were drawn almost entirely from Chicago and adjacent areas of Illinois and Indiana, and were considered to be a 'representative' group of male adolescents and young adults, both white and non-white, from the areas of recruitment. The summary results of the investigation were that the *average* blood cadmium level was 50 ng/g, the *median* level was 35 ng/g, and the *range* was from 50-300 ng/g. Unfortunately, it was subsequently realized that these high levels were a result of *contamination* of the blood samples by cadmium impurities in the glass containers in which the samples were stored at −23°C prior to analysis. This was a serious matter because, in the mid-1970s when this work was done, these analyses represented nearly *half* of all blood cadmium analyses carried out world-wide over about a 20-year period. Even by the *end* of the 1970s, blood cadmium analyses had been published for only a *total* of between 6,000 and 7,000 subjects.

1. What were the *data* in this investigation?

2. What was the main *answer* being sought?
   - Explain briefly why *three* (rather than just one) numerical summaries of the data were given.

3. Were the data *accurate*?
   - Whose *responsibility* was the accuracy of the data?
   - What are the *consequences* of *in*accurate data?

4. *If* the data had been accurate, explain briefly what *other* factor(s) would affect their usefulness.

5. If a *histogram* of Creason *et al.*'s 1,954 observations of blood cadmium levels were to be constructed, suggest a likely model for its *shape*; give reasons briefly for your answer.

6. What condition(s) in the investigation might have made it possible to extract from the *individual* data on blood cadmium levels the *true* values which existed before the contamination took place?
   - Are these condition(s) likely to have occurred in practice? Explain briefly.

REFERENCE: Creason, J.P., Hammer, D.I., Colucci, A.V., Priester, L. and Davies, J. Blood Trace Metals in Military Recruits. *Southern Medical Journal* **69**(3): 289-293 (1976).

(*continued overleaf*)

Figure 2.1c. DATA-BASED INVESTIGATING: Lead Levels in Human Vertebra and Lung

Like cadmium described in Figure 2.1b, lead is another toxic metal widely dispersed throughout the environment, but there are two differences from cadmium. First, the environmental dispersion of lead is largely the result of *human* activities, notably the use, since the 1930s, of organo-lead compounds as anti-knock agents in gasoline and, mainly in the U.S., the former widespread use of lead-based house and building paints; as an example of more localized episodes of lead pollution, secondary lead smelters in Toronto have sometimes been in the news in the last decade or so. Second, whereas cadmium accumulates primarily in the kidney (and secondarily in the liver), lead accumulates mainly in *bone* because of its chemical similarity to calcium. The majority of the human body burden of lead is thus believed to be immobilised in the bone matrix of the skeleton.

Like cadmium, lead is *toxic* – there is the conjecture that the decline of the Roman aristocracy, due to health problems, was brought about by lead poisoning from pewter drinking vessels and other uses of lead such as water pipes, water containers and lead-based ceramic glazes in contact with food and beverages. Investigations prompted by the *modern* concern about possible chronic health effects of environmental lead have produced good evidence that *children* are particularly susceptible to *neurological* damage from lead (*e.g.*, by ingestion of paint flakes in old buildings); there has also been a long-standing search for chronic health effects in *adults* due to the long-term low-level exposure we all experience because of environmental pollution by lead.

As part of a Danish investigation of lead in human tissues from the *past* (using skeletons from archeological discoveries) and the *present*, analyses were carried out of vertebral samples obtained at autopsy from 81 males and 38 females who had died suddenly. The respective *average* lead levels found for the two sexes were about 0.9 and 0.7 $\mu g/g$ wet (*i.e.*, fresh) bone; these values are less than *one-fifth* of the averages of around 5 $\mu g/g$ found in several other investigations in Canada, Japan and the U.S., for example. A question of interest is whether contemporary skeletal lead levels are *really* so much lower in Danes.

It turned out that the Danish vertebral samples had been preserved in *formalin* prior to analysis. This technique is *not* recommended in trace-element investigations; an earlier large American study of lead levels in bone, one of the few to use formalin preservation, had stressed that the formalin *had* to be ashed and analysed with the bone samples. This was *not* done in the Danish work – the formalin was simply discarded after the bones had been removed from it for analysis. It therefore seems likely that the low lead levels in these vertebral samples were caused by *leaching out* of the major part of their lead content by the formalin preservative.

Two matters of interest subsequently arose in connection with these low Danish vertebral lead levels. First, the work was awarded a prize by the University of Copenhagen. Second, the data were cited as evidence that, in Denmark, the current environmental lead levels from anti-knock additives in gasoline were *not* of concern from a public health perspective.

Two years after the Danish work on vertebra was published, a scientific paper reported lead levels in *lung* from a large group (146 males and 98 females) of Norwegian autopsies; this investigation also used formalin preservation of tissue samples prior to analysis. The average lead levels in these lungs were about 15-50 percent of those found in seven earlier studies in other countries. Such decreased levels are reminiscent of the Danish vertebral data and, in view of the use of formalin, they suggest that this may be another instance of loss of lead due to leaching.

1 What were the *data* in the Danish investigation?

2 What was the main *answer* being sought?
- How was the answer expressed in order to convey it to people who read the published report of the investigation?

3 Were the data *accurate*?
- Whose *responsibility* was the accuracy of the data?
- What are the *consequences* of *in*accurate data?

4 *If* the data had been accurate, explain briefly what *other* factor(s) would affect their usefulness.

5 Apart from including the formalin in the analyses, is there a way to recover, from the *individual* data on vertebral lead levels, the *true* values which existed before the leaching took place?

REFERENCES: 1. Grandjean, P. *Lead in Danes. Historical and Toxicological Studies*. In: T.B. Griffin and J.H. Knelson (Eds.), *Lead*. Georg Thieme and Academic Press, Stuttgart and New York (1975).

2. Brown, K.S., Cherry, W.H. and Forbes, W.F. Studies of Trace-Metal Levels in Human Tissues – VI. Concerning the Estimation of Lead Levels in Human Lung and Vertebra, with Particular Reference to Formalin Fixation. *Bull. Environ. Contam. Toxicol.* **22**: 552-560 (1979).