PANEL DISCUSSION

R. L. ZIELHUIS

The organizers asked me to be Chairman of this Panel Discussion with the topic, »Research Needs for the Future«, and then to present the Overview. I think we had better combine these functions into one since we have two hours' time. There is no need to present to you the members of the panel; they have already been presented and you know everybody. My task is to guide the discussion, not only the discussion within the panel, but also the discussion within this whole room. However, I think we have to be efficient because two hours looks long but can be very short. So please, everyone on the panel and participants, please put your remarks in statements and not in long presentations. The objective of this panel is discussion, not reading papers or giving enumerations of experimental data, but just discussion and making remarks. The topic is »Research Needs«. Is it the need for the research worker to keep him employed and to induce the flow of money to research institutes? I must warn you, I may belong to this group. Is it the need for industry, for protection of a general population or workers? Is it the need of governments, at national and international levels, to take appropriate steps for safeguarding health of the general population by making air, food, water quality standards, and so on? As you know, research workers never stop asking questions. But I ask the panel and the participants to consider, when discussing subtopics, this point: Is further research needed because research workers like to know more *or* because governments and industry need more data for protection of human health? There is no metal that has been so extensively and intensively studied as lead. There is always the risk of positive feedback, with each study automatically inducing another study. But, you know, positive feedback causes instability. I ask you to consider whether manpower and funds used for research on lead possibly could be used to more advantage for other environmental or occupational health problems. About two or three years ago, I participated in a small meeting in the Common Market discussing lead, especially lead in petrol. I said if you start running cars

on water, you still have the same noise and the same accidents. They said, yes, but we don't talk about accidents, we talk about lead in petrol, and it was outside the discussion. But, I just want to indicate to you that our traffic has more important aspects than only lead in the petrol.

I take the liberty of grouping the subtopics in the discussion which has already taken place into four subheadings, and I plan to organize the panel session along these subheadings. We have about 120 minutes; this allows 20 to 25 minutes for each of the four subheadings, and about another 20 minutes for conclusions and maybe for the discussion, so 20—25 minutes for each topic first. Please, members of panel and the participants, please remember that I kindly asked you to give your opinion in straight statements and not in long exposés. Now, first I'll mention the four subheadings, and introduce this again when we start to discuss them subsequently. The first topic is, *Problems Regarding the Relation between External Exposures and Internal Exposure*, that is, between total external exposure and body burden; second, *Relation between Internal Exposure, Body Burden and Effects;* third, *Monitoring of the Human Population;* and fourth, *Problems of Occupational Health.* Let's start now with the first topic, *Relation between External Exposure and Internal Exposure*, I mean the total external exposure and internal exposure. I particularly recall the papers of Drs. Willoughby, Barltrop, Griffin and Tepper, and also on the negative side, the question of under exposure by Dr. Schwarz. Some questions have been raised. I only mention interaction between metals, nutritional factors affecting absorption, the chemical compound of lead, particle size and shape, specific sources, as wine and soil, the essentiality of lead as a vitamin, and the relation between air lead and intestinal lead and blood lead. Please start to discuss the research needs for the future, keeping in mind the general framework I mentioned. I should like to ask the panel members who would like to start to discuss this problem of the relation between external exposure and internal exposure.

L. B. TEPPER

I'd like to make one of the forbidden orations. Perhaps it would be useful if, in the course of our discussions, we distinguish between 1) the measurements which are made; 2) the health implications which the measurements reflect; and 3) the societal judgment as to what degree these negative health effects will be assumed. This particular separation was just mentioned by the Chairman. Dr. Hernberg mentioned yesterday the matter that assumption of risk by a society is not, in particular, a scientific question. It is the duty of the scientist to develop an estimate of health risk. It is a social judgment as to whether the benefit is worth the risk. The matter of automobile traffic was raised by the Chairman just a few moments ago, in that we operate automobiles and in so doing, incur a risk in the United States which amounts to one in four-thousand;

the risk of death per annum is approximately one in four thousand. We never look at that very closely. We incur that risk for a lifetime, a lifetime risk of dying in the United States by auto accidents is a fantastic risk. I simply want to urge the panel members and the discussants in the audience to separate in their questions the measurement of physiologic phenomena, the implications of those phenomena in a measurelement of health risk, and the matter of a social judgment as to whether it is good for you to have these things happen to you.

R. L. ZIELHUIS

I think this is one of the things we should hold until the end. I deliberately left some 20 to 25 minutes just for this kind of thing. I think we first should start with facts and then we certainly have to talk about permissible exposure. When I was in the WHO a week ago, it was forbidden to talk about permissible limits and I am glad that we are not now in the WHO but are allowed to talk about that. Now we start with the first topic. Who wants to?

J. F. COLE

Well, since the microphone is here I think I will start off by just asking the question concerning what is and what is not a normal blood lead concentration, because that does reflect the internal dose or the internal exposure that you are referring to. I think first of all that we must somehow decide, either through research or interpretation of research results that we already have, what we regard as either an upper acceptable limit of normal or a limit of normal. I think there has been a consensus growing that, perhaps, 40 micrograms of lead per hundred grams of blood is the upper limit of normal, but I note that there is some tendency on the part of some organizations and researchers, perhaps, to lower this level somewhat in the United States. Recently, the Department of Health, Education and Welfare changed the level from 40 to 30 μg/100 ml. I don't know whether that reflects anything of importance or whether it is an attempt to narrow the range of normal, but we have on the panel someone who may know something about that, and perhaps we should start with Dr. Chisolm.

R. L. ZIELHUIS

You don't make it easy for me because I've put this down as topic 2. First we must know how we get lead in the blood. This morning I raised the point of the relation between lead in air and lead in blood and lead in gastrointestinal tract and lead in blood, and then I was silenced because this was something for the panel discussion. I will just repeat my question again to the people here.

K. SCHWARZ

From my experience in the trace element field I am convinced that it is not permissible to plot back from low intake figures to zero levels in blood or tissues. For carefully investigated trace elements the dose response, i. e., the relation which one obtaines with respect to body and blood levels from very low intakes to high intakes is biphasic. Over a wide margin of increasing concentrations of a trace element in the diet, for instance, one sees a physiological plateau which goes from very low intakes over several orders of magnitude to a certain upper threshold level. At that point apparently the resistance mechanisms, the adaptive capability of the organism to further intake, is broken down. A breakthrough occurs and suddenly toxic effects become manifest. Below the threshold level the organism is in a steady state where intake is in balance with excretion and deposition in the storage areas. Typical examples for this situation are copper and also selenium. A dynamic steady state situation also appears to exist for lead where the breakthrough point apparently is at an intake which leads to blood lead levels in excess of 40 μg/100 ml. I am questioning the permissibility of saying that we would get to zero blood lead levels if we take all the lead out of air and nutrition. Instead of getting to zero, you get to a low level plateau. It is highly noteworthy in this connection that the blood lead levels, shown by Dr. Tepper, for people from very different geochemical and geophysical environments in the U.S.A. are practically identical. Similar figures were reported from Japan, they were previously found for aborigines in New Guinea and for many other countries throughout the world.

You may recall the chart in my paper where I gave the »concentration window« in which life is possible for selenium: In the environmentalistic approach we keep on talking about the toxic side only, without giving consideration to the fact that supplying the needed amounts of an essential element is just as important; it is also an environmental problem.

D. BARLTROP

Just one small point on this question of comparing blood lead values from different countries. We are making a big assumption when we say that the nutritional status of a New Guinea native is the same as a resident of your home town, even though his blood lead may be the same. It may be that this reflects an enhanced or impaired absorption of lead because of his very different way of life. Certainly, the animal studies that we have reported so far and, I think, some of the interactions which Dr. Willoughby reported earlier, would suggest that there is at least this posibility. We need a great deal more information before we can really say what a background level is.

K. SCHWARZ

In spite of different backgrounds, we find very similar levels in very different geochemical environments in very different races of people living under vastly different nutritional and environmental conditions. That is just the point I want to make.

J. CHISOLM

In response to the comments of Dr. Schwarz about the possibility of regulatory mechanisms for lead in blood and possibly other soft tissues, I should like to add a comment about the »lead lines« seen at the metaphases of the growing bones in children. We customarily think of this »line« in terms of the deposition of lead. We sometimes forget that microscopic studies show that these lines are produced, in part, by interference in the deposition of bone salts and the formation of bone. It is of interest that such changes are rarely seen by x-ray unless blood lead concentration exceeds 50 to 60 μg percent. One could speculate that the appearance of these lines signifies interference in the body's response to increasing lead absorption. It is also of interest from the clinical viewpoint that interference in heme synthesis accelerates sharply as blood lead concentration rises above the 50 to 60 μg level. Other abnormalities also increase in frequency as blood lead concentration rises above this general level.

R. L. ZIELHUIS

Yes, that would be the threshold level, the upper threshold level.

J. CHISOLM

I would agree that the 50 to 60 μg Pb level is the upper threshold level. Our data and that of Cramér and others indicate curvilinear relationships between blood lead and various indicators of effect, as blood lead rises from the »lower threshold« of 30 μg percent to 50 to 60 μg percent.

K. SCHWARZ

I have looked at some of your older data just recently, for instance the chart relating urinary ALA excretion and blood lead levels (Scientific American, *224*, (1971) 18). What strikes me is that if you go to the lower levels, you could actually draw a straight line which establishes a *plateau* below 40 μg/100 ml. Only beyond that threshold do elevated amounts of ALA occur.

J. CHISOLM

Yes, I think so. On the basis of regression analysis, we find essentially no slope between blood lead and indicators of metabolic effect at blood lead concentrations $<$ 30 to 35 μg percent. However, we do not have children with very low blood lead concentrations available for study in my area. I would like to make one other comment. I do not agree completely with Jerry Cole on the interpretation of blood lead concentrations in individuals when it falls in the 50 to 80 μg range. I have presented data on this particular point which indicated to me that chelatable lead and posibly urinary lead are better indicators of the internal dose of lead in the tissue than blood lead in this particular circumstance. Perhaps I am something of a maverick on this point.

J. F. COLE

You don't agree that blood lead in this range is a good reflection of internal dose, buty believe that the U.S. Dept. of HEW has recommended a combination of blood lead and FEP. The difficulty that I have and I think many of these researchers would have, is how do we relate blood lead and FEP and why do we reduce the allowable blood lead, let's say from 40 to 30. What is the use of blood lead, or should we just throw it out? Is this what you are suggesting?

J. CHISOLM

No, I certainly am not suggesting that blood lead measurements be discarded. For fuller evaluation of an individual, I believe that both blood lead and some indicator of lead effect are needed. Only in this way can we indentify reactors and non-reactors. This is particularly important in the threshold zone for blood lead between 30 and 60 μg percent. The only significance that I attach to a blood lead measurement in the 30 to 60 μg range by itself is that that particular individual has probably had some recent intake of lead from some non-dietary source.

A. NEUBERGER

I wonder to what extent the blood level of lead is constant in an individual over a period of time, in particular how far it changes from day to day? Has this been looked at to any extent? Is there also some accurate information as to the relationship between the level of lead in the blood and the amount of lead stored in bone; in particular it would be important to know whether the lead in bone is completely inert or can it be mobilised under certain conditions? It would also be interesting to know whether the total amount of lead in the body can be easily assessed?

D. BARLTROP

The question of lead in relation to bone needs to be reiterated once more. Of course, lead is transferred from soft tissues to hard tissues and the rate of turnover from bone is very, very slow. I have yet to meet anybody who claims to have seen clinically significant releases of lead from the skeleton occurring in any situation.

J. CHISOLM

We have had some experience regarding the possibility of release of lead from the skeleton in relation to acute infection. Unfortunately, the number of cases is insufficient for statistical analysis. I have, however, seen some children who, during the first six months or so following recovery from acute lead encephalopathy, have contracted intercurrent infections. We have done simultaneous blood lead, urinary coporporphyrin and EDTA mobilization tests in 10 or 12 such instances. In these cases, we found that urinary coproporphyrin and chelatable lead increased together, but that this increase was not reflected by any change in the blood lead concentration. I have interpreted these data to indicate some redistribution of lead, perhaps from the mobile portion of the bony lead into the soft tissues. I have not, however, seen any recurrence of acute symptoms in relation to infection, as reported in the older literature prior to the days of chelation therapy.

K. SCHWARZ

Are you suggesting, then, that what we read in textbooks about lead poisoning, namely that lead in bone is activated by fever, stress, menstruation, etc., is really untrue?

D. BARLTROP

Yes. What I am saying is that I have yet to meet a worker in this field who has recognized clinically significant release of lead from bone. This is in conflict with what is in the textbooks and the concept should be challenged very seriously.

R. L. ZIELHUIS

Wait a minute. I look like a police agent forbidding you to talk, but I would like to ask you to mention what are the research needs for the future in this area of effects of external exposure on lead in blood or other measures of internal exposure, because that is what we are here to put forward. If we have no research needs, okay; but still, I just would like some research needs.

K. TSUCHIYA

I want to talk about the relationship between external exposure and internal exposure. First of all, it is very difficult to get exact, or accurate information about external exposure. This is very difficult, but still, we may have some measures to cope with this problem. We have been interested in external exposures which are not via food but via the respiratory route and blood lead internal dose. However, we have very little data on the relationships between food exposure and internal exposure. It is very urgent, therefore to do some work concerning this relationship between food exposure and blood lead or internal exposure. Secondly, in Japan, we are very much concerned with lead in the general environment and some possible health effects on population. We have, however, shown no evidence of health effects due to lead in ambient air. But, I think that we should pay more attention to the accumulation of lead in the environment which may alter or destroy the ecosystem. We know very little about the effect on the total ecosystem due to accumulation of lead which had already been emitted by automobiles or from industries and which will continue for some time. It is very urgent to know what will or has happened in the ecosystem.

R. L. ZIELHUIS

I think we must come to a conclusion of this first part. I think what you were summing up – this problem of ecological effects – very few people are talking about it, but a lot of people are asking about it. Dr. Cole, does your organization have anything to do with this type of work?

J. F. COLE

Well, our organization has sponsored some work and is sponsoring some work on the effects of various heavy metals, including lead, on aquatic life. Perhaps, what Dr. Tsuchiya might be suggesting is that someone should look into the eventual sinks of lead in the environment. I don't think we thoroughly understand what happens from point of dispersal through the environment. I don't know if that is a particularly productive area of research, but if I am interpreting your suggestion correctly, this is something you suggest as being worthwhile.

R. L. ZIELHUIS

I think we can provisionally conclude this first topic. I think what is important is that we should not try to reach a very minimum, to go to zero, because there is always the possibility that lead is essential, though

I do not see that this will come in the near future, that we will have an underexposure to lead. The second point is that very little is known all over the world on the oral intake of lead from food, water, wine. Furthermore, we must not forget the factors which determine the oral intake, the nutritional factors and chemical compounds. The third point is that we could probably say that more research should be done on the ecological effects, on the ecological accumulation. I never hear anything about it; we ask, but nobody knows anything about it.

The second topic is »*Internal Exposure and Effects*«, in particular, the papers by Drs. McNeil, Fugaš, Neuberger and Cooper. Specific questions which can be put to them are: What do we still need to know about the effects on the normal hemoglobin heme synthesis, on no effect levels, on heme synthesis, nervous system function, etc., about dose-response relationships, about specific accessibility of subgroups, inborn errors of metabolism, nutritional state, age. What is the significance for health of slightly raised protoporphyrin, of FEP, ALA, and I should also ask, is there any real risk of French wine to brains of Frenchmen? (Laugh from audience). These are some specific questions, because we must know something about no effect levels, about dose-response relationships before we can start to discuss what is permissible. I should like to ask you, not only the panel, but also the audience, can you make some statements or some suggestions?

What are the real things we do not know, and what should we really know before we can go home and sleep very quietly?

L. B. TEPPER

One of areas which seems to be most promising is the general area of inorganic biochemistry, which, I believe, Dr. Willoughby discussed yesterday. There are a number of organizations which are proceeding to study zinc, molybdenum, copper, cadmium and lead. Perhaps one of the research needs might be to emphasize some sort of integrating effort which would cause these parallel paths to seek some coming together which would make sense out of many of these relationships. It had been thought for many years that these things went along separately: lead metabolism was here and copper was here and molybdenum was here. That fancy chart that Dr. Willoughby had with all these criss-crossing lines simply emphasized the point that these things are actually interrelated. A second point which might be made, which Dr. Zielhuis called dose-response, is the examination of organ functions at various levels of lead exposure, examination of the response, of a large number of organs, not just heme. Dr. Neuberger pointed out that heme in hemoglobin might be of lesser significance than heme in the central nervous system.

This leads us to Jerry Cole's preliminary question as to what is normal; normal really seems to be two things. One, normal is simply a

statement of what exists. You take the mean and put a couple of standard deviations to each side and that's normal. That's one judgement of normal. The other definition of normal is what is good for you. They may or may not be what exists in the ambient population. That brings us back to the actual organ system function under certain circumstances of lead stress. That is the dose-response relationship in a wide number of systems.

R. L. ZIELHUIS

I completely agree with what you have said because what is health is ultimately not a significant thing, but just a »political« concept, that is, what we want to call health. Therefore, we again run into this permissibility, what we want to regard normal or what we want to regard as an effect. In any case, a permissible response has to do with our subjective decision as to what is health. One of the troubles is that scientists usually discuss health of other people and go on to decide what they call acceptable in *other* people.

W. M. PALLIES

There are people who are not sick in any way clinically that anyone seems to be able to determine. It occurs to me, then, that what is going on here, and which a couple of people have referred to, is that whole blood lead really doesn't mean anything. It would seem that active part of the lead would be just that in the serum. I wonder if we couldn't develop some methods to measure this, rather than measure blood lead. I am not a physiologist, but I don't see how cell bound lead leaves the body through the kidneys because the cells don't go through. So you have to take lead out of the serum, remove lead from cells, re-establish an equilibrium in the serum. I suppose this lead in the serum to be the active part that is acting heme synthesis. Certainly nothing is happening to heme synthesis in the red cells.

R. L. ZIELHUIS

Who is determining lead and who wants to talk about lead in serum?

J. CHISOLM

There are very few studies of lead in plasma. The numbers of subjects studied is extraordinarily small. You may recall that Clarkson and Kench, in *in vitro* studies, showed no increase in plasma lead as total blood lead increased from 15 to about 150 μg percent. Rosen has reported similar findings in children. While there may be theoretically

significant changes in plasma lead concentration, they appear to be so small that they are beyond our means of measurement today, unless possibly one uses the stable isotope dilution mass spectroscopy technique. This situation is somewhat similar to the bilirubin situation in newborn infants in which changes in plasma bilirubin are of theoretical importance, but cannot be demonstrated with present methodology.

K. SCHWARZ

I have discussed this with Dr. Rabinowitz who has worked with the stable isotope. It appeared to me that if lead is essential, there should be a steady plasma level. Such homeostatic levels are ridigly maintained for most of the other essential elements. They are usually at a very low plateau. Dr. Rabinowitz indicated, after looking over his data, that the lead level in the plasma is really quite stable as far as he could determine, I think, as Dr. Chisolm does, that this is of great importance even though it is technically very difficult to pursue at present.

V. STANKOVIĆ

I am an immunologist and I know that there are enough data showing that excess of lead has quite measurable immuno-suppressive effects before clinical signs are present. I don't really know why this observation is not more used in evaluation of lead toxicity by toxicologists. It seems that immuno-suppression reduces resistance not only against infection, but also against malignancy. Therefore some of clinical and post mortem data which I saw here for the lead exposed people could be due to an immuno-suppressive effect of lead. So, I think that future programmes on lead research should include an immuno-toxic investigation of lead, too. That is my proposal.

J. L. McNEIL

The smoke screen that is being raised about lead in air and dirt has contributed to our knowledge concerning the effects of subclinical increased lead absorption. We must not allow it to obscure the primary problem or to deter our efforts to correct the primary problem of availability and ingestion of high content lead paint by children. I don't think anybody can get too much information, basic research is always necessary. However, we are inappropriate in the application of our knowledge and regulations when we quadruple the number of children under observation by lowering the range of normal when we have not yet established a level of increased lead absorption, short of encephalopathy, that is permanently deleterious.

D. BARLTROP

Dr. McNeil expressed my views much more succinctly than I could have done myself. I wonder if there is any immuno-suppressive action of lead, whether there is any clinician who has seen any evidence of this in real life? I would look particularly to the representatives from industry at this meeting today, who, surely, must have the greatest collective experience of exposure to lead. Can they not tell us what is the health experience of their workers?

M. R. ZAVON

The experience with organic lead is that the health of the workers is certainly not affected significantly by exposure to inorganic lead. I know of no evidence in workers, with whom I have had a fair amount of experience, that there is any greater incidence of infectious disease among workers exposed to inorganic lead. In my experience with children and lead exposure, which goes back some twenty years, I see no evidence, and I think Dr. Chisolm and Dr. Barltrop might comment, that this has been a practical factor. So that although, theoretically, lead may have been shown to interfere with the immunological system, in the practical sense, I think this is completely irrelevant, and, in terms of toxicology, has never been shown to be of any meaning at all.

E. KING

Returning to serum lead, I have made a few hundred estimations in the past two or three years, and normally find 1 to 3 μg Pb/100 mls. The most impressive evidence is some work by Dr. W. McRoberts, of Bradford, who received the Rene Barthe International Prize for it in 1972. (Fractionated Blood Lead Concentrations in Lead Poisoning). We were following a series of men. One in particular started with a blood lead of about 500 μg Pb/100 mls, asymptomatic except for a slight tremor. Dr. McRoberts decided to chelate him, and we followed him before, during and after treatment with both plasma and red cell lead. However, before the treatment started the plasma Pb started rising to a level of about 70 μg Pb/100 mls, and about simultaneously with the start of treatment, he went into what Dr. McRober thought was an encephalopathic episode and then into cardiac arrest, with a whole blood of about 50 μg Pb/100 mls. The treatment was, of course, stopped, and the man recovered. We followed this with some other people, again with minor symptoms, and found plasma leads of about 6 to 8 μg Pb/100 mls, as opposed to the normal 2 to 3 μg Pb/100 mls. This is certainly something to be investigated in more detail.

V. STANKOVIĆ

It was very impressive to hear that people who have looked at toxic signs didn't notice immuno-suppression, but my question is how did they find out if immuno-suppresive effect was present. It is known that malignancy and lower immuno-activity are going together. It is after all my impression that it should be known more about the possibilities of lead to induce different effects which were shown here.

M. WAGNER

The research needs that we are speaking of normally concern new data, the finding of new data. I am concerned about interpretation of data that we already have. For example, FEP. Several speakers spoke about the necessity of determining FEP, due to several points where FEP is of special significance. It is very easy to determine in the field; it is good as a screening test; finger prick samples are stable over weeks.

We conducted such research. We found that with children who had elevated lead levels above 28, sometimes a 40 and 50 microgram percent lead in blood, we had a level of about 500 percent raise of the normal median FEP level. We presented these results and we found out that, for the individual case, there was no clinician able to give us any advice as to what to do with these children.

In other words, we have data, but these data just lie there and there are not consequences for the individual case being made. I think before we want new data, a more theoretical thing, what do we do with the facts we have? It is a bone marrow reaction. It is a very good test which could be employed universally. It shows chronic exposure a long time after the blood level and ALAD have normalized. The quantitative contribution of iron deficiency, for instance, is one question which we would like to know, because we have children with 28 micrograms lead in blood per one-hundred milliliters, and that is below the acceptable and tolerable level, of 30 or even 39.9 from the pediatric society, the old tolerable level, much below. Yet they have strongly elevated FEP's in some cases. What is the meaning of these things?

What can we, as workers in the field, do with it? Where are the clinicians to tell us what to do with the kids? Otherwise, we can stop getting this information.

D. BARLTROP

It is just possible, of course that there may be no significant health effects. This is, perhaps, why Dr. Wagner's clinicians were unable to assist him. Because we find a demonstrable biochemical change, it does

not necessarily mean that it has untoward significance. This is something that we ought to bear in mind when we are setting stardards.

I would like to come back to the question of plasma lead in individuals undergoing treatment. Chelated lead would be in the plasma phase and not in the cells.

W. C. COOPER

I wish to make some observations in regard to the relation of exposure and effects, which will also bear upon our later topic, »Occupational Health«. Before I do that, I would like to comment on two things that have been brought up which, in view of our mortality study, should be put on the record. First, we did look at mortality from infectious diseases in our entire population and saw no outstanding deviation from what we expected. This is a difficult thing to be sure of, because people at work may have better experiences. Still, there was no outstanding difference. Second, the point was made that we had demonstrated that there were no excess malignancies in our study. I would not go quite so far as Dr. Zielhuis went in his summary. We have made the point very strongly that we were not studying lead exposures *per se*. We were studying smelter workers and battery plant workers in whom we were unable, retrospectively, to establish the full range of exposures. We are certain that many had exposures to arsenic and cadmium, and certainly to zinc. Probably there were other exposures in this group. We found slight excesses in certain types of cancer and, as I said, they were somewhat bothersome to us. We are not prepared to say that in the working conditions that had prevailed in these industries there were not some factors that had caused a ten to fifteen percent increase, but we feel there is no justification for saying that this was lead. This is a clarification of the summation.

An epidemiologic study, such as we carried out, is a very blunt instrument in terms of defining exposures and effects, because of the inability to define exposures retrospectively, the uncertainities as to diagnoses from death certificates coming from a variety of sources, and our insecurity in selection of the populations with whom our group should be compared. Nevertheless, they gave us data to show that people very heavily exposed to lead do not have a disastrous life expectancy; and, in fact, helped counter the argument that people are being killed and dying off early because of uncontrolled exposures. That definitely is not happening.

In response to the question about various types of lead exposure and occupational health, the issues before us lie in the range of exposures that lead to absorption associated with blood leads of 50, 60, 70 and 80 μg/100 ml. I think this is the frontier. I do not think that we can learn very much more by depending on studies of veteran workers who have

gone through the era of much higher exposures. I think we have to think in terms of individuals who have entered these industries in a more modern era.

We have to think in terms of the posibility of hyper-susceptibles in this population. We have mentioned such things as metabolic abnormalities, G6PD defficiences, the abnormal hemoglobins, which create constant problems for us in occupational health. You almost hate to know. You feel you would rather not study a worker sometimes because after you find out that he has an abnormal hemoglobin or he has sickle cell trait or has a G6PD deficiency, then the questions arise as to his employment. Should you handle this individual differently when we don't know whether he is really at undue risk?

An even more important question, to answer which research is urgently needed, is whether women should work in environments where their blood leads would be in the range 40, 50, 60 or 70 μg/100 ml.

R. L. ZIELHUIS

I think within topic 2, you had the suggestion that studies should be done not only on lead or cadmium or zinc or copper or something else, but in combination in order to be able to study relationships. Second, the study on organ functions should be promoted especially, and one of the examples is non-hemoglobin heme, and, in connection with that, studies to try to find the real concentration or indicator of the concentration at the organ levels. I know that we not only rely on blood levels, but how can we come to the target organ? Then there was a cry — no, not a cry — let's say a real call for help. I can completely understand, from Dr. Wagner. What do we do with the facts we have? As public health physicians, you have some responsibility for the community, but the clinicians don't answer. We can say that the clinicians may think it is not harmful, but, also, I think most of the clinicians were not especially involved in lead; they just don't know. This is an area in which there should be more information.

Then there is the suggestion of Dr. Cooper to do epidemiologic studies in individuals who have been moderately exposed, not so highly exposed, and also to take into account the hypersusceptibility. I think there is a need for determining more exactly, if possible, no-effect in dose-response levels and that leads us to topic 3, »*Monitoring of the Human Population*«. I think we should distinguish between two approaches; both were present in this symposium. One approach is screening to detect individuals at risk, in the same way that you can screen for carcinoma of lungs. That was more the approach brought forward by Dr. Chisolm. Second, the true biological monitoring in humans to evaluate the total ex-

posure, as brought by Drs Tsuchiya, Boudène, and Tepper. In that case, individual findings are primarily relevant as contributing to the group picture.

There are many questions. What groups are we going to select? Which methods? Lead in blood, ALAD, FEP, lead in hair, lead in teeth? What more? I should like to ask the panel and other people to tell me which method best serves the objective of the programme? I think Dr. Chisolm may have a different objective than Dr. Tepper and Dr. Tsuchiya and that determines the method. Also, not only which method best serves the objective, but also, which method can be performed effectively and efficiently, with as little input of manpower as possible, and not to forget with as little inconvenience for the subject as possible. We can also ask how are these parameters affected by other factors, as diseases, as discussed by Professor Neuberger.

Then we come to not only what we find in groups, but what is the permissible limit of lead in blood or FEP in these groups. I should like to ask what is the permissible distribution of the levels of FEP, ALAD or lead in blood or lead in hair, and so on, in groups of the population. So I should like to ask the panel members and, secondly, the other people to think of these points and try to get the answer or suggestions.

J. CHISOLM

You ask about the interpretation of FEP measurements in children. One must arrive at a decision in children as to whether iron deficiency or increased lead absorption is the more important factor. In general, if the FEP measurement is <500 μg/100 ml erythrocytes or less than 10 times the average normal value, we would give first consideration to nutritional iron status. If the FEP value is greater than this, one would consider that significantly increased lead absorption, with or without concurrent iron deficiency, is probably present and would undertake ancillary tests to arrive at a decision. From the practical viewpoint, these two conditions occur in the same child with such frequency that both frequently require therapeutic intervention.

K. TSUCHIYA

One of the reasons why lead in the environment became of so much concern to public health people, I think, is that in the United States and in England, you have a serious health problem in children due to lead. As we already discussed, in Japan or in other European countries, we have very few reports on the health effects of children. I think in other countries, including Japan, monitoring of children is very important. Maybe someone would say we haven't looked at it, and that's the reason we don't find any health hazard in children. Maybe this is so, but maybe not. We would like to have conclusive information very urgently.

M. FUGAŠ

I would like to say something in connection with the assessment of exposure to lead in air. Various measurements have been made all around the world, but the question is how well these figures represent the real exposure. It has been shown that in a smelting environment, where there is one big chimney emitting a lot of lead, there is a pretty uniform dispersion of lead in air and the measurement of lead in air, I mean in outside air, represents quite well the exposure of people. But in urban areas it depends very much where the instrument is situated. If the source is small, as a car, the concentration decreases very fast with distance from the traffic lane. For instance, we have measured lead in air near busy roads. Twelve meters away the concentration was only 30% of the concentration close to the road. In some cities, e. g. Paris, the measurements are made on the streets and if such measurements are related to the exposure of people who live 20 or 30 meters away, they have nothing in common with the real exposure.

Of course, there is also difference in outdoor and indoor lead concentrations which is not necessarily a steady ratio but depends again on methodological factors and on the source. Again, in the industrial area with a massive source of pollution, there is a pretty steady relationship, but we have observed that in the urban areas the relationship changes with the site. For instance in the environments with very low lead in air, concentrations indoors may be even higher, while for relatively higher concentrations of lead in air there is a sharp decrease from outdoor to indoor lead concentrations. Therefore, I think more attention should be paid to where the monitoring instrument is situated and what data are used for assessment of exposure.

R. L. ZIELHUIS

I think, Dr. Fugaš, you make this a well-known plea and one does not enough take to heart this comparability and uniformity methods of sampling in order to be compared, and also for indoor and outdoor. I know the problem in the Common Market has also been the problem you mention; you have some data on cities and nobody knows how it was done.

I completely agree with Dr. Tsuchiya that this monitoring of children is of big importance. I have questions to ask to this panel. If you examine children and you have a certain distribution with, say, 90—95% below 30, or 50% below 20, can you say: let's not worry anymore about lead; it doesn't matter whether it is from water or air or food, let's go and look for other topics, because all the children are below a certain level? In that case do you still need to sample air or not? That, I think, is an important thing; what is the permissible distribution, and if you have this permissible distribution, can you just say okay, I don't need to worry about air or soil?

K. TSUCHIYA

Yes, if you look at the children of other countries, then I think you may get the permissible limit, in relation to pica, because in the United States or in England, in many areas children are very heavily exposed or contaminated. But, maybe in other countries they may show much lower levels of exposure, so that you can refer to these findings to establish these permissible levels. For this reason, also, I think monitoring of children would be very helpful.

K. SCHWARZ

I agree that we need blood levels in children from many different countries. Maybe they are not so very low in other countries, as one may conclude from the values found for adults.

D. BARLTROP

I am going to inject a slight note of heresy and ask whether children really constitute a special group from the point of risk. These claims are very often made and, of course, we know that childhood lead poisoning is, one of the most common forms of lead poisoning. But, this might merely reflect the very heavy local exposures which they meet. I am not happy that the child's brain or the developing brain, has been shown to be any more vulnerable to lead than at any later time in life.

Secondly, on the question of monitoring children, I am not going to be rash enough to suggest what the permissible levels should be. However, I would suggest that children should have different standards from adults. Furthermore, such standards ought to be different for different seasons of the year, since we know there is a fluctuating level at different times of the year.

J. L. McNEIL

In line with Dr. Wagner's question and all this comment and your trying to set us on a level, I'd like to mention a little formula that's kind of fun to play with. In the numerator, you put the blood lead which you are talking about, the protoporphyrin, which is measurable. You divide this by SCAN-s for source, C for consumption, A for anemia, and N for nutrition. Then, you have four factors to modify the values above. If you do it on a one-to-four basis of decreasing risk, it makes your denominator bigger. Apply that formula to my smelter children. In the child with 80 and a reasonably high FEP, who is inadvertently taking dirt, who has no anemia, who is well nourished, the risk is rapidly

decreased, despite the high levels that you are measuring here which don't always mean what they say. I think until we apply all these factors we are not going to get an answer in the individual child as to what to do. That's what we need in terms of practice.

K. KOSTIAL

I just want to point out that our data on animals suggest strongly that there are differences in lead metabolism related to age. First of all, young animals have a higher absorption from the intestine and they also retain more of a single parenteral dose and excrete less. They have different kinetics of lead distribution and retention. Not only that their spontaneous elimination of lead is lower, but also if they are treated with chelating agents, chelating agents are less efficient in removing lead from young rats. This all indicates that lead might be bound in a different way in the young and that there might be less of a free fraction or chelatable fraction of lead at this age. I believe that there is good enough reason to look at the young population in a separate way from adults.

D. BARLTROP

I am familiar with Dr. Kostial's work and there are other similar studies reported. The fact remains that this is the young suckling rat. We do not know how far this compares with the human. I am not satified that we have good evidence that the child is uniquely susceptible to this material or differs in any way in his response from the adult. It may be that it is true, but there is no good evidence to support this idea.

J. CHISOLM

Mr. Chairman, most of the work done in the United States in children has been done on children between 3 and 6 years of age simply because there is easy access to this age group. When you consider the possible effects of excess lead on the developing brain, one must consider that the latter growth spurt of the brain begins in the latter half of pregnancy and extends well into the first 18 to 24 months of life. If there is an increased susceptibility to lead, it is likely to lie in this very young age group. To my knowledge, there have been no systematic studies of children less than 12 months of age, even though this is likely to be the age range in which the question of age-related susceptibility is the most important.

D. BARLTROP

I would make the point that although people may not have examined this particular age group as such, they have examined populations who

were living in situations of sustained exposure, which must have passed through a phase of heavy exposure during those early critical stages of development.

J. L. McNEIL

At least in Smeltertown, 43 of the 44 in the serious group have been there since birth, the first three years. Of the 75 of the moderate group, all but nine have been there since birth. At least one woman had delivered 11 of her children in that place, so they had been there from the moment of birth. We still showed nothing with what we can test, as of now.

M. R. ZAVON

I would like to build on what Dr. Chisolm said earlier as to research needs. If we are to protect the central nervous system, I think it is imperative that we have, as soon as possible, normal values and standardized methods developed, both as referred to yesterday, for blood leads, as to whether we correct for hematocrit and hemoglobin, and in a standardized way, normal values and standardized methods for FEP and zinc erythrocyte porphyrin, and for nerve conduction velocity measurements, some interpretation that can be generally accepted as to what differences in nerve conduction velocity mean, the question of whether a difference of 10 meters per second means anything or not. We need the same things for EEG and EMG. There may be others that other members of the panel would like to add, but I think that as long as we go on as we have been, without normal values, without standardized methods, we only perpetuate a type of chaos which leads to all sorts of wild statements that are picked up by the press to the detriment of the very children and adults we are trying to protect.

J. CHISOLM

The point about normal values is well taken. In young children, we have rather severe ethical problems within human research committees in our attempts to get normal values. It is a major stumbling block.

J. F. COLE

I would just like to support Dr. Zavon very strongly and I would add to his list, perhaps, standardized methodologies for evaluating such things as hyperactivity. I think that this also bears on another problem as to what constitutes standards of proof or what constitutes controversy in this effect. We have seen one investigator in humans find some evidence or, at least, indicate some evidence of hyperactivity. Yet there are

five citable studies in which hyperactivity has been searched for and not found. Yet controversy goes on. Therefore, we must have some kind of standardized, agreed-upon methodology eventually to satisfy at least most of the people as to whether these effects do or do not occur.

R. L. ZIELHUIS

I completely agree with what Dr. Zavon said, only I want to change his wording a bit. He is talking about normal values. You never get a normal value for an FEP; you must ask for the normal distribution of values. That doesn't say it is a »normal« (Gaussian) distribution. You must ask what is the normal distribution in a group of levels. As you say, EEG, EMG's; I think they are coming now.

I think the recommendations are coming up more fruitfully now. I think Dr. Chisolm started with it, that we do preventive examinations on the assumption that we know something about the central nervous system and about the no-effect levels but we don't know enough yet. It must be studied where is the no-effect level and where can you find early indicators; does FEP, as such, have any meaning for the central nervous system?

Secondly, there is a plea for monitoring, particularly of children. I think it is always a necessity; outside of the U. S. we know very little about children. Still, I was in a meeting not so long ago, and one man from the U. S. was talking about the lead in blood levels of rural children in the U. S. based upon 230 levels in two rural communities. He was talking about rural in the U. S.; therefore, I still think you don't know enough of the U. S. Then there is the comparability and uniformity in methods of sampling air — indor and outdoor air.

Third, there is some doubt in Dr. Barltrop whether children are really more sensitive. I think children, at this moment, still deserve the precaution of accepting at least an increased hypersusceptibility. Fourth, we need to study the normal distribution of values and standardised methods for all kinds of effects. I won't enumerate; they have to be somewhere in a very beautiful paper.

Then we come from this to No. 4 and we start discussing the same problem, I think, again because we come to *occupational health*. That was not a topic, as such, in the programme, but was touched upon again and again in the paper by Cooper and the contribution of Hernberg and I must evaluate this problem, too. Now we come to the same problem as in a population, what are the relevant parameters for early health impairment; conduction velocity, how do you measure that and what is the significance of highly sophisticated, psychological tests, FEP, etc.

I should like to raise my pet topic, and Dr. Cooper already raised it: What about increased susceptibility of women? This is the year of the women. I don't know if it is in the whole world or only in a little part

of it, but still in our country some people say it's only one year. But, still, it is the year of the women, and I think we have to take into account the increased susceptibility of women. I know that women, and probably quite rightly, want to have equal opportunities as males, but taking up these equal opportunities, there is a posibility, for certain jobs, to take up at the same time increased risks, more than the males. I think that is an important problem that has some bearing on the whole problem of occupational health and lead. I also think the International Lead Zinc Research Organization has sponsored a lot of studies on the general population. I should also like to ask ILZRO what they think about further research being needed in the field of occupational health. Let's start talking about occupational health. I don't think we should start a complete discussion on permissible limits in occupational health because, otherwise, I am sure, you won't get out of Dubrovnik in the first two weeks. But the sun is coming out, and I think we would like to stay, and I agree. Who wants to discuss the occupational health problem?

W. C. COOPER

I don't know the answers. This is why I said earlier that the frontier we are working on in occupational health is in the range of 40 to 80 μg/100 g. We can, with some confidence, feel that nearly all to the population of males working in, and honestly staying in, that range, are not going to get into any demonstrable difficulties. I don't believe in sharp demarcation lines, but I do think that when it comes to the problem of whether a women should be placed in that same environment, I feel very uneasy. Even though there is no evidence at all to indicate that this would have any detrimental effects in case she became pregnant or whether it would affect her fertility, there is still enough experimental evidence to make you wonder where the threshold is and whether we are safe in operating in the range of 40, 50, 60 or 70.

So, I, at present, in spite of equal opportunity demands, would tell employers who asked me, that I would not put a female employee in an area where she might absorb lead to get into this range of levels for two reasons. First, I honestly don't know whether there is a possibility of harm. Secondly, I know there is a normal background of abnormalities, so that you are certain to have them occur in the population. But, I think that if the issue were raised by a woman demanding equal opportunity — »what is your evidence for denying me this job?« — one would be hard put to say that you had the evidence. So, I think that this is something that demands that we get more evidence; I don't have it.

R. L. ZIELHUIS

I don't know about Yugoslavia, but I know that in Western Europe, you don't find women working in the lead industry. I know that in

Eastern Europe, you have more women working in industry. Do you have any experience? The only study that I know is a study by Panova from Sophia who found irregularity of the ovary cycles in women; there was also an indication of increased irregularity with increased exposure. This is one of the few things I know, but is there more evidence in other countries? You see, it is forbidden in Western Europe.

M. FUGAŠ

As far as I know women are not employed in the lead indstry in Yugoslavia either, but in the population we observed women had an arithmetic mean of lead in blood of about 50 μg/100 ml, which is rather high. As I have reported, so far, we have observed some difficulties in pregnancies and deliveries and higher abortion rates than in controls. Of course we have to analyse still more data before we can make any conclusions.

J. F. COLE

I believe that your preliminary data did show an increase in abortion rate, but you also showed a higher fertility rate in smelter area, is this not so?

M. FUGAŠ

The proportion of fertile women was higher, but fertility rate, i. e. the number of newborn to a thousand of fertile women, was about the same.

M. R. ZAVON

Two points. There is a recent article in Lancet which hypothesizes, on fairly good grounds, I think, that about half of the conceptuses are aborted spontaneously, so that any studies will have to take into account the very real possibility that about half of the conceptions spontaneously abort. If you are really looking, you are going to find a lot more abortions take place than are normally recorded. With regard to the specific question asked by the Chairman a moment ago, with what we now know, for example, about diethylstilbestrol, I wouldn't put a woman in manufacturing of diethylstilbestrol; but with lead, I think that the greater responsiveness of the female with FEP, as the Chairman showed a couple of years ago, should be called responsiveness to FEP, not, at this time, greater sensitivity. I think there is a very real difference between the responsiveness of a particular biochemical measurement and the significance of this responsiveness. I think that at

this time we do not know what the greater responsiveness of the female population with free erythrocyte porphyrin or with zinc, perhaps with zinc erythrocyte porphyrin, than with the male, we do not know the significance of this in terms of the homeostatic mechanism of the female.

R. L. ZIELHUIS

I completely agree, but I think of susccptibility in talking about responsiveness, it might just be a question of semantics. If you are more susceptible, it doesn't say it is significant for health. It is difficult to determine the significance for health because you have to first expose them and then wait and see what happens in 20 to 30 years.

M. R. ZAVON

No, I don't think that is necessary. I think that one possible approach, and I am sure there are many others, is to try to see in the female whether there are any other accompanying biochemical changes that are more apt to be; well, we are talking about protection of the nervous system-what happens with the female who shows this greater responsiveness that you demonstrated in other parameters that could be measured? Are there significant differences which would lead us to believe that this is a truly greater risk? At the present time, I would not put the woman in an area where she is apt to have significant exposure to lead, solely because of my concern about the fetus, not because of concern for the woman.

R. A. WILLOUGHBY

I believe I represent the only veterinary clinician in the room and, as we are not discussing diseases of animals possibly, I have no authority to enter this discussion. However, it concerns me to learn of the enhanced capacity of children and women to accumulate lead. Perhaps calcium metabolism is central and the key to explaining this phenomena, since in animals we know that the young animal has high calcium requirements and its blood lead values are higher than in adult male animals of the same species. The pregnant mare behaves similarly. I wonder if we should not consider that all animals, man or otherwise, will have an enhanced uptake of lead at any time when the calcium uptake is increased.

W. C. COOPER

I was going to ask Dr. Cole whether ILZRO had any idea of actual statistics-actual numbers-of women employed in production areas in lead that could be studied for this purpose.

J. F. COLE

I don't have the figures. Some years ago, we did look into the effects of lead on women working in the lead industry and it was difficult to come up with sizeable populations, at least among the member companies. Outside the member companies, there may be such populations. Certainly, it would seem to me, that if such populations do exist, it would be worthwhile to do some sort of epidemiologic study, retrospective, and if that isn't possible, perhaps even prospective, if they continue to work there. We do know that with the women's movement in the U. S. and throughout many parts of the world that there certainly are more women working in various kinds of industries including the lead industry than has been the case in the past.

T. BERITIĆ

I propose that more emphasis should be laid on the significance of alcoholism in the lead industry. First, alcohol itself impairs the heme synthesis. Second, alcohol effects the enzyme systems in the liver. Third, alcohol itself is likely to inhibit ALAD. Fourth, alcohol, at least in this country, is very often contaminated by lead. Is that enough? Would you like me to say something about how alcohol does effect the central and peripheral nervous system? I didn't hear a word against alcohol in industry, and I think it is very important. Even now and tonight in Dubrovnik.

M. STANKOVIC

Clearly, there is a regulation in Yugoslavia that work with lead is forbidden to women. So, in Yugoslavia, we have no female population working with lead in industry. But there are populations in the vicinity of lead plants, lead industry, and there are indications that there is influence of lead on women, mothers, etc. I think, as far as I know, there are investigations in progress in a smelter area. Also, I know there are investigations of pregnant women in the surroundings of another lead mine and smelter. Thank you.

R. L. ZIELHUIS

First, the topic. Then I want to go to the first remark of Dr. Tepper again. I think everybody feels, not that women are the weaker sex, but they still feel that women are not males. Not withstanding the emancipation movement and especially in regard to lead, we think the general opinion is, even though there might not be enough real facts, the general opinion is that women should not be allowed to work in the same

lead exposure in industry as now regarded acceptable for men. It may be that it has something to do with iron or with calcium, etc., but still we have the facts that you can't say to a women if she wants to work in the lead industry, »OK, you are allowed to work, but first you will have to change your calcium needs«. Therefore, I think that one of the conclusions, but also one of the recommendations, is to study this problem of different responsiveness, sensitivity, however you call it, of women.

Coming back to the start and also the end of this discussion this afternoon, I should like Dr. Tepper to come back to the points he wanted to start with and just raise the point again, now taking into account what has been said about no-effect levels, acceptable levels, etc., during this panel discussion. Most of the members of the panel, neither participants, didn't want to stick out their neck and say very definite things about permissible limits, etc. What do you want now to say about the first thing you started with, about the different tasks of physicians to propose facts and data and that determination of whether it is permissible is really a question of society? You started with this problem, and I think it's a good idea to end with it.

L. B. TEPPER

I agree with it. I think when we listen to what the various participants have said, we identify people who, for example, are concerned with a basic physiological phenomenon, nerve conduction time, and that is probably examined in the laboratory of the neurophysiologist. We then have a second echelon of evaluation. I think Dr. Chisolm, Dr. McNeil, Dr. Barltrop, who are clinicans, are in a position to reach some estimate of what these observed phenomena mean for real people, not squid axons or something of that sort. Then there comes the standard setting which reflects a public interpretation of the significance of the clinical phenomena. I think I am just repeating what I said at the onset, Dr. Zielhuis. The only additional point which might be made is that the neurophysiology laboratory, the neurophysiologist may have 8 votes, and maybe I have 1 vote, maybe the man on the street has no votes. In the treatment of clinical plumbism, Dr. Chisolm may have 10 votes, maybe I have 2 votes, and the man on the street has no votes. But when it comes to the judgemen as to the assumption of risk in terms of benefit received-whether it's the operation of the automobile or the utility of lead in our society in general, then Dr. Chisolm has one vote, and I have one vote, and the man on the street also has one vote, because we collectively as participants in society must make that risk/benefit judgement. The scientist is not excluded. He does not drop out of society because he is a scientist, but he doesn't have an opinion which should be weighted more than anyone else's. This is a reiteration of what I said earlier, I believe.

R. L. ZIELHUIS

I don't want to be too political, but I doubt whether Dr. Chisolm or you have the same number of votes as the man on the street if it is, let's say, the work of some worth, if it is talking about the assumption of risk of going to work. I understood what you said that scientists should propose facts. They should say what has been found and the real decision in regard to permissibility should be left to voting, to the public, not to government and all kind of organizations. One of the difficulties is if scientists start to make, not a proposal, but state their facts, the public just cannot say what this lead in blood exposure means, because it doesn't mean anything for nonspecialists. As soon as you start to say what the significance is in relation to health, you are already influencing politics, because you are already influencing the people. If you say that is a meaning, if you say it may have a meaning for pregnancy, this all being sure, you are taking, yourself, already, a certain part of the responsibility just by the way you are explaining the things, and you cannot get away with it. You have got to do that.

L. B. TEPPER

The difficulty is in expressing risk in terms of a common denominator. The public accepts the risk associated with the automobile, the public accepts probably some of Dr. Cooper's standard mortality ratios of industrial accidents. This seems to be accepted. Obviously, those disadvantageous events could be reduced in number at a higher cost of some sort. Perhaps it would be illustrative to consider one approach to the vinyl chloride carcinogenesis problem, where one really could not say there is a no risk level. But, a scientist could, perhaps, identify an exposure level which would bring the risk from that particular disease in line with other risks that our society experiences. Then, society could make a judgement that this is acceptable, knowing that no one is absolutely protected from angiosarcoma of the liver under these circumstances, but that the risk is made commensurate with the risk we incur daily in the pursuit of our normal lives. Now, how one expresses the lead risk in terms of a common denominator of this sort, which could be recognized by a political body, is, perhaps, something to which persons other than myself might contribute to.

E. KING

We had exactly this problem, and we answered it, with asbestos. We were the British Occupational Hygiene Society's Standard Committee, the »Asbestos« subcommittee of some five members plus co-opted members. We analysed the data available, and emerged with a dose response curve for asbestos and asbestosis. At the end, we had to decide

what was »reasonable«. We said and this is the standard accepted by the U. K. Government, in the U.S.A. (Albeit the Selikoff objections) and elsewhere, that we thought it was reasonable that an asbestos worker should run a 1% risk of minimal clinical asbestosis after 40 years in the industry. Our having stated it, it was accepted. I think we must do this with lead. We do our calculations. We decide what we (the experts) think is a reasonable level of response for lead workers. We state this. Then, if some parties wish to say that there should be no response, they are automatically putting themselves out of court. Otherwise they will have to state their alternatives. We simply said it. And having said it, it was accepted. I think this is the way we have to go with lead. You do your calculations. We decide ourselves what is a reasonable level of response for lead workers to anticipate. We say so. Then if people wish to say there should be no response, they are automatically putting themselves out of court, which means they have to say what their view of an acceptable response is.

R. L. ZIELHUIS

Ladies and gentlemen, we have had now this panel discussion on future needs of research. We have talked about a lot of things; amongst other things, we talked about future needs of research, and I won't repeat them. I think I'm just giving over my task and I think everybody who has participated in this discussion could have gone on longer, maybe just until tomorrow, but still, I think, we fixed something. It will be difficult to put it in writing, but that's another question.

K. SCHWARZ

I want to come back very briefly to a comment which Dr. Tepper made. He indicated that we need new means to communicate in bioinorganic chemistry because it covers so many different fields. Until now there was no possibility to really get it all together. In the U.S.A. we are at the moment forming an International Association of Bioinorganic Scientists. Anyone who is interested in joining should drop me a note. The man who is leading the effort is Professor G. Schrauzer at the University of California in San Diego. He is also the founder of the journal »Bioinorganic Chemistry«, which serves already quite effectively as a means to bring the various workers in the field together.

J. F. COLE

Thank you very much. Thank you, Dr. Zielhuis for a very excellent job of getting us right on schedule and for leading the discussion. At this point, I would like to thank all the participants in the panel and our

speakers. I would like to also thank our interpreters who have done such a marvellous job during these two difficult days, the technical staff of the Institute for Medical Research and Occupational Health, our office staff here at the Inter-University Center who performed quite admirably during the preparation and during the conference itself. I think special thanks must go to Mrs. Fugaš and especially to Dr. Šarić for their wonderful hospitality and for all the arrangements that they have made here. Thank you one and all for coming. The conference is closed.

RESEARCH NEEDS FOR THE FUTURE

(Summary of panel discussion and recommendation)

R. L. ZIELHUIS, Chairman of the Panel

University of Amsterdam, The Netherlands

The main topic for discussion is: *Research needs.* However, the program does not specify the need *for whom.* One may distinguish three groups of persons or organisations, which may state their need for research; there is no guarantee that their needs will correspond:

— *research workers* never stop asking questions out of true scientific curiosity; they want to increase knowledge for the sake of knowledge itself. Moreover, research workers and institutes for research may »think up« needs for research, in order to maintain a steady flow of grants.

— *industry* may have need to receive scientifically more adequately based guidelines for protection of workers and general public.

— *governments,* at national and international level, may need more adequately based data for setting standards for protection of human health, and better means for screening and monitoring population groups at risk.

The members of panel and the audience, many of them involved in fundamental and applied research, should recognize that research needs, postulated by them, not necessarily correspond to needs felt by industry or governments.

There is no metal that has been studied so extensively and intensely as inorganic lead. There is always a risk for *positive feedback:* each study project automatically calls for another project. However, positive feedback easily leads to instability to disequilibrium. The panel and audience therefore should consider whether manpower and budget could not be used to more advantage, if dedicated to other aspects of human health; one never will solve the tremendous health risks caused by auto-

motive traffic (e. g. accidents, noise, exhaust of CO, NOx, hydrocarbons), if one only studies the health effects of lead in petrol.

For the sake of discussion the extensive area to be covered will be subdivided into four topics, to be dealt with subsequently:

I. Relation between external exposure and internal exposure
II. Relation between internal exposure and health effects
III. Screening and monitoring of general population groups
IV. Problems in regard to occupational health.

DISCUSSION

The four topics mentioned will be dealt with subsequently. Members of panel or audience who took part in the discussion are mentioned between brackets. Recommendations which have been brought forward, are presented under a separate heading.

1. *Relation between external exposure and internal exposure*

The chairman recalled some points brought forward by various speakers during the symposium in regard to *over*-exposure (e. g. Willoughby, Barltrop, Boudène, Griffin, Tepper, Tsuchiya) and *under*-exposure (Schwarz):

— simultaneous exposure to various agents and interaction which may affect pharmacokinetics of lead, e. g. Cd, Zn, Ca
— nutritional factors which may affect absorption: protein-, Ca-, Fe--deficiency, empty stomach
— influence of chemical composition of Pb-compound
— influence of particle size and shape
— Pb as an essential nutrient
— specific sources of Pb exposure, e. g. soil, wine
— quantitative relationship between lead in air and lead in blood (PbB) and between oral intake and PbB.

Which research needs are to be brought forward?

The discussion may be summarized as follows:

1. In various widely separated geographic regions there appears to be to a certain extent a similarity in PbB levels, if specific over-exposure does not exist; this may be an indication of essentiality of Pb (Schwarz), even although nutritional status may largely differ (Barltrop). The lead line in bones in children with PbB 60 μg/100 ml could also be regarded as a consequence of a control mechanism to maintain a constant PbB level. One should not try to minimalize exposure to zero because of the potential essentiality of Pb. In a few studies plasma-Pb content appeared to be independent of Pb content in total blood; again this may indicate

the need for the human body to maintain a minimal exposure; however, serum Pb is very difficult to measure; the reported constant level may be the result of inadequate analytical techniques (King).

It was felt that even if Pb may be an essential element, a real risk of underexposure is hardly to be expected; the true health risk lies in overexposure.

Research workers were invited to join the Society for Bio-inorganic chemistry.

2. PbB should not be regarded as a very good indicator of interal exposure, particularly not in case of non-steady state exposure (Chisolm). Combination of PbB+protoporphyrin in erythrocytes (FEP) is to be preferred (Cole).

3. If PbB exceeds 30—40 μg Pb/100 ml, one should start looking for sources of overexposure; if PbB is evidently below 30 μg Pb/100 ml, no need exists to explore various external sources (Zielhuis).

4. Until now there does not exist clinical evidence that Pb deposited in bone can be significantly released again into blood and soft tissues, causing health effects (Barltrop). However, there is a need to study this more carefully, particularly in case of infectious diseases (Chisolm).

5. Relatively too much emphasis is put upon study of the quantitative relationship between Pb in air and PbB; much less study is performed on the relationship between Pb in food, water, beverages and PbB (Tsuchiya).

6. Too little is known about effects of Pb accumulation in the environment (soil, ocean).

7. Measurement of Pb in air levels in urban environments lack comparability of methods: place and type of sampling, measurement of particle size. The relationship between outdoor and indoor air concentrations should be more fully studied (Fugaš).

II. *Relation between internal exposure and health effects*

The chairman recalled some points raised by various speakers during the symposium (e. g. McNeil, Fugaš, Neuberger, Cooper): effects on non-haemoglobin-haemsynthesis; the lack of knowledge of no-effect levels; the question of hypersusceptibility of subgroups of the population; the question whether moderately raised levels of FEP in erythrocytes, or ALA in urine as such carry a significance to health; the contradictory evidence of the relationship between PbB levels and effects on the nervous system.

Which research needs have to be brought forward?

The discussion may be summarized as follows:

1. Until now population studies usually limit themselves to measure the presence of only one metal in blood, and the possible relationship with health effects. However, there is a need to measure simultaneously

various metals, e. g. Pb, Cd, Zn, Cu, in order to uncover possible interrelationships (Tepper).

2. PbB levels do not adequately measure Pb levels in target organs; one should study means to get a better insight, either directly or indirectly, into the critical Pb levels in various organs (Pallies). Animal experiments should also be undertaken for this purpose.

3. Too easily one tends to speak about »normal« PbB levels. However, what is »normal«? Is it the level found in population groups with no evident overexposure, or does »normal« indicate that level that is »good« for the individual? (Tepper). Study of this question is needed; it apparently is linked to the question of essentiality of Pb.

4. Evidently there is a need to study effects of Pb on nonhaemoglobinhaemsynthesis (Zielhuis).

5. Very little research is done on effects of Pb on immunosuppression; this might result in increased incidence of malignancies and infectious diseases (V. Stanković). However, there is no evidence of mortality due to malignancy and infectious diseases in cohort studies, as reported by Cooper.

6. Clearly there is a need for more study on morbidity and mortality of Pb exposed population groups, either workers or general populations. In the study in workers reported by Cooper there was also exposure to other agents, particularly in smelter workers, and there was a lack of quantitative exposure indices; in the study reported by Fugaš standardised techniques for measuring morbidity and mortality of a heavily exposed general population group (smelter area) had not yet taken place.

7. In population studies one may find highly increased levels of FEP, particularly in children; pediatricians often do not start any treatment. So, the epidemiologist does not know what to do with the facts he has available, at least not in regard to individual patients (Wagner). How can he distinguish between raised FEP due to Pb overexposure and due to Fe-deficiency?

8. Although one usually assumes that children are more susceptible to Pb overexposure than adults, the factual evidence for this is not so strong (Barltrop). Animal studies suggest that young animals have different pharmacokinetics of lead, but one is not sure that this is also true for humans, Moreover, the groups of children studied often are of school-age; we need to know more about effects of Pb on children of lower age groups (1—2 yr) (Chisolm). The general opinion however was, that although increased susceptibility of children not always may be unequivocally proven, it appears to be a prudent policy to base oneself on the assumption stated.

9. There is a need to study health effects in subjects with moderate overexposure (PbB 70 μg Pb/100 ml), particularly paying attention to subgroups with e. g. inborn errors of metabolism (Cooper).

10. There certainly is a need for further study of no-effect levels (PbB, FEP), and dose-response relationships for various health effects. The panel was very hesitant to postulate even provisional no-effect levels for health effects in children and adults.

III. *Screening and monitoring of the general population*

The chairman distinguished between screening and monitoring:

— screening aims at detecting individual subjects at risk of overexposure, an approach to be compared with screening programs for cervix-carcinoma, lung tuberculosis; such a program was brought forward during the symposium by Chisolm.

— biological monitoring for indirect measurement of total external exposure, an brought forward by Tepper, Tsuchiya, Boudène; individual data are primarily relevant as contributing to the total group distribution.

There are many questions to answer, e. g. which groups should be examined, and by which methods (e. g. PbB, FEP, Pb in hair, nails, teeth); which method best serves the objective of the program, and what is the most efficient method; how are the data affected by intervening factors, such as age, nutrition, disease; how to provide representativity of groups examined; which are the permissible levels?

Which research needs have to be stated?

The discussion may be summarized as follows:

1. Screening programs are based upon the assumption that there exist certain no-effect levels in regard to e. g. effects on nervous system. What are these levels, does FEP provide a better prediction than PbB? (Chisolm).

2. Up till now screening and monitoring programs in children have mainly been carried out in USA. There is probably a large difference in exposure risk to children in other countries. In these countries relatively few data exist on levels in these age groups; there certainly is a need to expand on this.

3. In population studies one often only presents data on arithmetic average levels and standard deviation. In many cases the distribution of levels is not Gaussian. Not the average level is a good indicator of group exposure, but the distribution of levels in the group studied. Therefore, data should preferably be presented as percentile distributions (Zielhuis).

4. There certainly is a need for standardisation of methods for measurement of health effects. This applies to measurement of biochemical values, e. g. FEP, Zn-EP, as well as to measurement of nerve conduction velocity, EEG, EMG pattern, hyperactivity, performance tests. Moreover the relevance in regard to health should be made clear and values as expected in non-overexposed population groups should be given (Zavon).

IV. *Problems in regard to occupational health*

The chairman recalled the fact that effects of Pb on the health of workers was not the main topic of the symposium; only one of the papers presented (Cooper) exclusively discussed occupational mortality; nevertheless, several times during the discussions problems regarding workers health were bronght forward (Hernberg, Zielhuis). The women, particularly in regard to EEP levels, came up: what are the relevant parameters for early detection of health impairment in workers? What is the significance of possibly increased susceptibility of adult women, particulary in regard to EEP levels, when emancipation movements demand equal opportunities for females and males? Do such equal opportunities result in inequal health risks?

What research needs exist according to panel and audience?

The discussion may be summarized as follows:

1. There appears to be a consensus that at PbB=40—80 μg Pb/100 ml no evident clinical effects exist in male workers. However, one should feel uneasy in extrapolating this finding to female workers (Cooper). Study is clearly needed. Recently in females increased disturbance particularly of haemsynthesis (FEP) has been brought forward; there is a need to study also other health effects in women, in order to assess the relevance of increased FEP for health more adequately (Zavon). One should particularly pay attention to intervening factors: Fe-, Ca deficiency (Willoughby).

2. One should study more extensively the problem of alcoholism in lead exposed workers; alcoholic beverages themselves may contain Pb, and in addition alcohol may affect ALAD-levels (Beritić).

V. *The role of the research worker*

In addition to discussion on the four topics as mentioned above, the role of research workers in defining health risks for workers and general populations, was brought forward during the panel discussion. This discussion merits to be included in this summary.

During the symposium various speakers discussed basic and clinical aspects of Pb exposure. Many data have been brought forward. However, the question can be raised who has to define the acceptability of health risks for general population and workers, who has to decide upon permissible limits, either in regard to external or internal exposure (Tepper)? The research worker has to provide facts, to establish no-effect levels, dose response relationships, mechanisms of toxic actions, etc.; he should present the probability of health effects in relation to external exposure; this is his task as research worker, in fundamental and in applied research. In addition, he is a member of the public; in this sense, he is equal to other members of the public, he has the same vote as the man in the street. The research worker should not determine

the social acceptability of risks; assumption of risks is a public affair, to be determined by the public itself, which should base its decision on data provided by research workers.

However, the research worker not only has to provide facts, he also has the task to explain the significance of these facts in regard to health. Health is poorly defined; health is also a matter of public decisions, of social choice, and is not purely based upon hard facts. So, the interpretation of data in regard to health is a matter of scientific judgement and of personal choice (Zielhuis).

The research worker has a dual role:

1. as research worker: to provide basic facts, and relate these to health
2. as member of the public: to define acceptability of risk, to weigh benefits against risk

There is always the danger that research workers play too important a role in defining risks, risks for other members of the public, risks to which the research workers themselves are not exposed, e. g. in case of general population exposure around point sources.

RECOMMENDATIONS

1. There is a need for research on *factors affecting pharmacokinetics* (absorption, distribution in body) of lead: interaction with other elements, nutritional factors, particle size, chemical composition.
2. There is a need for research on the *relationship between Pb in air* and *Pb in blood*, and even more so for research on the relationship between *ingested Pb and Pb in blood*, taking into account the various intervening factors mentioned above.
3. There is a need for research on effects of *accumulation of Pb in the environment*.
4. There is a need for research on the possibility of *release of Pb from bone deposits*, particularly in overexposed children with infectious disease.
5. There is a need for research on levels of *internal exposure to several metals simultaneously*, in order to elucidate interrelationships.
6. There is a need for research on *internal exposure levels in various target organs*.
7. There is a need for research on *morbidity and mortality paterns* with standardised methods, particularly in moderately exposed groups at risk, taking into account various intervening factors affecting pharmacokinetics and pharmacodynamics also paying attention to inborn errors of metabolism, age and sex.
8. There is a need for research on *no effect levels* (e. g. PbB, FEP) and *dose-response relationships* for various health effects, in various age groups, and in males and females separately.

9. There is a need for research on *PbB- and FEB-levels in children,* particularly outside the USA.

10. There is a need for research on *biological monitoring* of internal exposure levels and health effects in *children of young age* groups (1—2 yr).

11. There is a need for research on *standardisation of methods* used in screening and monitoring of population groups; this applies to levels of internal exposure, to biochemical effects, and to effects on various functions, particularly of the nervous system; the distribution of parameters in non-overexposed population groups should be studied. The relevance for health should be assessed. The data should be presented in percentile distributions.

12. There is a need for research on *influence of sex on response to Pb,* particularly in view of the increased demand of females to receive the same opportunities for jobs as males.

13. There is a need for research on *effects of alcohol* consumption on health and total Pb exposure in Pb exposed workers.