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THE EPIDEMIOLOGIC INVESTIGATION OF THE HEALTH STATUS OF MONSANTO EMPLOYEES WITH PAST EXPOSURE TO CHLOROPHENOLS, CHLORPHENOXY ACID ESTERS, AND THEIR DIOXIN CONTAMINANTS AT THE W.G. KRUMMRICH PLANT IN SAUGET, ILLINOIS

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REVIEW OF THE LIPID SECTION

by Robert E. Olson, M.D., Ph.D.

This project has been reviewed by the Biohazards Committee in three separate meetings during the past two years, the first on August 30, 1988, the second on July 12, 1989, the third on August 24, 1989. In back up of these reports at the Biohazards Committee meetings, I received copies of portions of the earlier manuscript devoted to lipid disorders. I have compared the copy of these earlier versions (1989) with the one submitted to me last month, and find very little difference in the text of the manuscript under the headings: 7.6.8 Lipid Metabolism, 8.7.1 History of Lipid Disorders, 8.7.2 Serum Lipids, and 9.6.1 Disorders of Lipid Metabolism: Conclusions.

The Committee made several criticisms of the data, analysis and conclusions present in the manuscript which was available in 1989. It appears to me that Dr. Hyrhorczuk and his colleagues paid little attention to these comments in writing this final draft. This final draft is still muddled and characterized by inattention to the limitations of statistics on small groups and with no regard to internal inconsistencies in the data regarding a possible effect of dioxin on serum lipids.

The error of the methods of cholesterol, triglycerides, and the apopeptides in this study are of the order of ± 5 to 10 percent. Statistical differences of the order of [P=.05] in groups as small as 15 to 20 persons cannot be considered statistically significant and certainly are not biologically significant. Furthermore, differences among small groups do not mirror differences between exposed and unexposed large groups. This is the problem that runs through this document and the conclusions. Also, I think it is useless to apply multivaried correlation studies to items like cholesterol, triglycerides, lipoprotein fractions, and apopeptides without a rationale that suggests that there is some meaning to these correlations. Some obvious meaningful correlations did emerge from this study, namely that LDL goes up with age, that men have higher LDL's than women, that HDL is inversely related to triglycerides, and a number of other correlations that have been documented quite well in the outside literature.

Dr. Hyrhorczuk persists in attributing changes in lipid metabolism to dioxin exposure when it is clear that there is no difference in the whole population between exposed and unexposed, nor is there a difference in plasma lipids between those individuals who have had chloracne and those who did not. Using chloracne as a proper internal indicator for significant dioxin exposure leads me to the conclusion that these small differences are sampling errors and should be ignored. Furthermore, we don't have a complete list of lipid values for each group. In those groups showing elevated cholesterol and triglycerides, a few patients with marked lipid elevations who have hyperlipidemias from a genetic cause would greatly skew the interpretation of the results.

Furthermore, we have the report by Dr. Collins in our minutes of August 24, 1989 that showed that in a retrospective study of 11 workers in Department 268 based on MEHI analysis of lipid measurements made over a period of years, the mean cholesterol average of 235. In addition, Dr. Collins studied a group of 40 individuals who had ever been associated with the Department 268, and found the average cholesterol was 221 mg/dl, not different from the 235 found in the MEHI cohort or the average value found for 303 controls in the Krummrich plant. It is concluded by Dr. Collins that the apparent change in cholesterol levels of the small number of people only in Department 268 reported by Dr. Hyrhorczuk is likely to be artifact based on incomplete sampling or faulty modeling of age. Also, it is significant that these workers were last exposed to dioxin 15 years before they were studied.

With this preamble I proceed now to discuss the conclusions of Dr. Hryhorczuk regarding the lipid metabolism presented in page 435 and numbered 9.6.1. The first conclusion is that "while workers with current or past chloracne were significantly more likely to report a history of 'high fat (or cholesterol) in the blood' (compared to controls). The percentage of individuals reporting "high fat or cholesterol" in the blood" is not reported, nor the frequency with which blood was drawn over the past 15 years. With the error of history taking at least 20 percent, I doubt that [P=.04] constitutes a significant difference. MOre important was the fact that there were no differences in serum lipids or apoproteins between the workers with chloracne and controls.

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I think contrasting department 237, as I said earlier, with Department 268 is of no significance since there were only 55 people studied out of 80 in department 237 and only 31 people studied out of 42 in Department 268. With small probabilities of a difference [P=.034], I would be inclined to ignore them, particularly in the light of comparative studies with the MEHI statistics. Furthermore, we don't have a distribution of the actual lipid values to see if there were some significant hyperlipidemias from another cause present in the group from Department 268. About 5 percent of healthy Americans, on average, will demonstrate hyperlipidemia.

The statement in the conclusion "definite conclusions regarding the effects of exposure of 2,3,7,8-TCDD on serum lipids must await future studies of larger numbers of exposed workers, preferably with a measurement of 2,3,7,8-TCDD concentrations in blood or adipose tissue." is misleading. This statement implies that the data on workers in Department 268 is a preliminary finding that will lead to finite results. I don't think there is any evidence for that.

The attention given to serum apoproteins B and E is also distorted beyond its significance. Serum apoprotein B is associated with LDL and the correlation between the two in this study is fairly good. Serum apoprotein E is associated with two major classes of lipoproteins, VLDL and HDL. The statement "the associations of apoprotein B and E with work in Department 268 in our study were robust" is a confusing statement because the relationship between apoprotein E and its two major lipoproteins is not clear. Furthermore, none of the apo E isoproteins

significantly higher levels of VLDL and a trend towards lower HDL in persons with chloracne compared to those without chloracne. No significant differences were seen in triglycerides, cholesterol, and LDL-cholesterol. In fasting sera, 90 percent of the triglycerides are carried in VLDL which provides another inconsistency. The discussion is anecdotal about a few men here and a few men there that have been observed to have elevated triglycerides, after exposure to dioxin. Pasderova et al. described 80 workers exposed to TCDD in the 1960's, 55 of whom were followed for 10 years. Although they initially had abnormal lipids, after 10 years of follow up there was no significant difference in mean levels of lipids. That should also give Hryhorczuk cause to consider whether or not anybody after 15 years would still bear the stigma of dioxin on serum lipids.

With Suskinds study at the Nitro plant in 1979, 86 percent of the exposed and zero percent of the unexposed had chloracne. There were no significant differences in mean levels of cholesterol, triglycerides, LDL cholesterol and HDL cholesterol between exposed and nonexposed persons with or without chloracne.

Finally toward the end of the discussion (p 436), Hyrhorczuk repeats the claim about apopeptides B and E in Department 268. The serum apoproteins B and E were significantly higher than controls in Department 268 and these associations were independent of age, race, gender, alcohol, BMI and diabetes. He fails to mention that this group represents 5 percent of the exposed sample. He says "the results of our study provide the first observations on serum levels of apoproteins in

workers exposed to 2,3,7,8-TCDD." The question is how much exposure since workers in Department 268 were exposed to 2,4D as well as 2,4,5T, the latter being the only precursor of 2,3,7,8-TCDD. No measurements of exposure to 2,3,7,8-TCDD were made.

In summary, the presentation of data and conclusions in this section is scientifically unsound. Basically this is a negative study and Hyrhorczuk is trying to manipulate it into a positive study. He should be prevented from doing that.