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IMPACT OF DIOXIN ON IMMUNE SYSTEM

As a consequence of a news conference in Washington, DC, June 2, 1983, there has been increased publicity about the effects of 2,3,7,8-TCDD (dioxin) on the human immune system (See Appendix I). The information from the news conference needs to be placed in proper perspective.

Immunosuppression and decreased resistance to infections due to TCDD have been observed in several animal species, and hence, concern over the effects of TCDD on the human immune system are legitimate. However, studies on the human immune system in individuals exposed to TCDD have only recently (in the past five years) been conducted. The laboratory methods for these studies are highly sophisticated and extreme care must be exercised in quality control and assurance. Moreover, there is a lack of consensus on the interpretation of what such changes in the human immune system may mean to long-term survival.

The data by Dr. A. Milford Ward, revealed by Mr. Daschle on June 2, 1982, are examples of the difficulty in interpreting immunological data. Although Dr. Ward stated that "the TCDD exposed workers became more susceptible to minor infections, such as colds, the study could not document that they became more susceptible to serious illness." Indeed, Dr. George May the investigator responsible for collecting and submitting the samples to Dr. Ward, concluded in his 1982 publication in the British Journal of Industrial Medicine that the men exposed to TCDD and who had suppressed immune function (as determined by Ward) actually experienced far fewer sick days than their unexposed counterparts.

Immunocapability studies have also been conducted in the TCDD - exposed population at Seveso, Italy. Immune function was examined from September 1976 to March 1978 at four-month intervals in 45 children heavily exposed to TCDD and concurrently on a comparable group of 44 children who had not been exposed to TCDD. No significant differences in the immune response between the groups were detected. Furthermore, the occurrence of infectious diseases in the exposed population has been compared with the incidence of a nearby community of equal population. The conclusion of this study was that the infective pathology of the Seveso zone did not exceed the average of similar communities in Northern Italy.

The Air Force Health Study incorporated an indepth evaluation of the immune system between RANCH HAND personnel and their matched control. Data from this study will be available in fall 1983.

Conclusion: Although the Ward data are of scientific interest, the reproducibility of the results remain to be obtained in other TCDD exposed populations. In addition, the practical significance of the data has not been determined.

Recommendation: The VA should reserve comment on the importance of the Ward data until the Air Force Health Study is released. However, if it is determined that additional follow-up is required, it may be advantageous to talk by telephone to both Dr. Ward and Dr. May.

Questions that may be asked of both men are:

1. We have read of your analysis of the immune system in individuals exposed to TCDD, do you feel, based on these or any other work, that there is persuasive evidence that humans exposed have a risk of developing an immune deficiency state?

2. Do you have any recommendations as to immunologists in the U.S. with whom we can consult on the issue of the effects of dioxins on the human immune system?

APPENDIX

Dioxin and Immunological Disorders

RE: Ward Report and Daschle Press Conference, June 2, 1983

Note: The following information was obtained from Newspapers, magazine and journal sources and provide a review of the comments on the Ward Report and Daschle Press Conference.

On 2 June, U.S. Representative Tom Daschle (Democrat - South Dakota) held a press conference in Washington, D.C. to announce that a 1978 study in the United Kingdom (U.K.) on the effects on human health from exposure to dioxin "comes as close to a smoking gun as I think we're going to find" in proving that exposure to dioxin causes a broad range of health disorders, including those which Vietnam veterans claim have resulted from exposure to Agent Orange. The study was conducted by A. Milford Ward of the Royal Hallamshire Hospital in Sheffield, U.K., on workers who were exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) after an explosion in 1968 at a chemical factory in Derbyshire, U.K., run by Coalite and Chemical Products, Ltd. (CCP). Daschle, who is seeking legislation to compensate Vietnam veterans who claim to have been harmed by exposure to Agent Orange, said that Ward's study definitely links exposure to dioxin with various illness that result from dioxin's effect on the human immune system.

Daschle and Dr. Joseph K. Prince, and Environmental Protection Agency toxicologist from Chicago who accompanied him at the press briefing, claimed the study found a statistically significant number of the 94 men in the exposed groups suffered damage to their immunological systems that made them susceptible to cancer and a number of other dreaded diseases. The two said that if the findings of Dr. Ward withstand further scrutiny, they would go a long way toward explaining the baffling array of ailments claimed by persons exposed to dioxin, ranging from severe acne to mental instability and cancer.

Prince also claimed Ward's research corroborated his own findings in a still unpublished study of 47 railroad workers who had been exposed to dioxin in a 1979 tanker car accident in Missouri.

Representative Daschle said that the 1978 study connects dioxin to the wide variety of dissimilar ailments that Vietnam veterans attribute to their exposure to Agent Orange. Linking dioxin to the immune system "draws all the strings together and puts it all in perspective," said Dr. Prince.

Daschle also used the press conference to criticize Dow Chemical Co. of Midland, Michigan, for "misleading" the public by withholding the results of the study. Daschle claimed that Dow has known about Ward's study since 1980, but has remained silent about it to suppress its conclusions about dioxin's dangers. Daschle said that Dow released a copy of the study to EPA in 1980 when EPA was gathering evidence to support its decision for banning the manufacture of 2,4,5,-T and Silvex, and that, in fact, Ward had conducted the study for Dow.

When contacted by Mr. Jay Smith, Associate Editor of the weekly publication Hazardous Materials Intelligence Report, Dr. Ward noted, however, that Daschle "overstated" the conclusions of his study and was incorrect about Dow's role in the study. Ward said that for his study, he compared three groups of about 28 workers each: the first group worked for CCP in Derbyshire and was on-site at the time of the 1968 explosion, the second group worked for CCP but was off-site at the time of the explosion, and the third group did not work for CCP. He told Smith that the first group was exposed to about 400 parts per million (ppm) of TCDD, and that workers in that group developed chloracne and suffered a "minor but definite" suppression of their immune responsiveness, causing them to miss two to three times as many work days as their counterparts in the other two study groups. Ward said that although the exposed workers became more susceptible to "minor infections," such as colds, the study could not document that they became more susceptible to serious illnesses, such as cancer, as a result of exposure to TCDD. He noted that he has kept in touch with many of the workers involved in his study, and that the basic pattern of their susceptibility to illnesses appears not to have changed.

Ward told Smith that he initially analyzed blood samples from CCP workers for George May, who was conducting health studies on exposed CCP workers for the company. Ward said that CCP was interested only in limited studies that would indicate whether any serious health effects resulted from exposure to the TCDD. Ward said that shortly thereafter, Hoffman-LaRoche & Co. of Basel, Switzerland, asked him to perform a more detailed study of the CCP workers, which he did in confidence for Hoffman-LaRoche. Ward said that Hoffman-LaRoche, which was a major stockholder of CCP, may have been interested in further studies after the 1976 explosion at the plant of the Hoffman-LaRoche subsidiary, L. Givaudon & Co., S.A., of Vernier, Switzerland, in Seveso, Italy, which contaminated 1,800 hectares of land with TCDD. Ward said that Dow eventually obtained a copy of the study from Hoffman-LaRoche.

George Archibald of The Washington Times also interviewed Dr. Ward and reported that his findings were rather different than those reported by Daschle to Archibald; Ward found that exposure of the men to rather high levels of dioxin "had only temporarily interfered with their natural immunity to common illnesses." Ward acknowledged that the study was done on a confidential basis but said the findings were later shared with government and industry people in Britain.

His research involved two group of men who had been exposed to dioxin at least 10 years earlier and a third group that had not been exposed. However, Ward said his research actually found that exposure of his subjects to relatively high levels of dioxin had only temporarily interfered with their natural immunity from common illnesses.

"This had the result that the exposed individuals suffered an increased incidence of minor infections - coughs and colds, common flu-like illnesses not resulting in more than three or four days of loss of work," he stated.

He said medical knowledge and research techniques "were not quite as well developed as they are now" and that further study of dioxin's toxic effects is still needed. But he added, "There was no evidence from this study of increased cancer risk."

Daschle was also taken to task by a Dow official for implying that the Midland, Mich., firm had tried to cover up Ward's study.

Bob Charlton, a Dow spokesman, criticized "Daschle's media event," claiming that it gave an inaccurate picture of Dow's role in the study. He noted that Dow did provide a copy of the study to EPA in 1980 and that Dow feels that the study should be made public. Charlton added that the U.K. Advisory Committee on Pesticides issued a statement in 1980 which said that the findings in Wards' study conflicted with findings in other studies, and that they were "not supported by any clinical evidence." In May 1980, the U.K. Health and Safety Executive also publicly issued a review of the study which noted that the limits of the survey restricted the study's conclusions.

Dr. R. Kilpatrick, Chairman of the U.K. Advisory Committee on Pesticides released in May 1980 the following review of the Coalite accident:

In 1968 a similar explosion took place at the Coalite in the U.K. Among the 14 persons in the immediate vicinity of the plant, one man was killed by a falling wall. Of the remainder, 11 showed abnormalities in liver function tests soon after exposure, but these were within normal limits 10 days later when production was restarted. 79 workers developed chloracne over the face and neck over the next 7 months. Effects on the back of the arms, legs, back and sternal areas were also sometimes noted. No additional abnormalities in the liver function or urine analysis were found.

Further work associated with this incident has indicated a possible effect on serum lipid profiles of exposed men, and claims have been made of an increased risk of cardiovascular disease and impaired liver function. A survey of workers exposed to TCDD in 1968 was undertaken by the company's Medical Officer in conjunction with a number of hospitals in the region. The results of this survey have subsequently been assessed by the Employment Medical Advisory Service (EMAS). EMAS have pointed out that for methodological reasons it was unjustifiable to extrapolate the findings in any general way but that the study served the limited purposes of providing a cross sectional view of the health status of this group of employees at the time and of providing individual profiles which may be of future clinical value. The biochemical findings suggested that the group known to have been exposed to TCDD and which had developed chloracne had undergone some induction of liver enzymes and that there was also an increased incidence of serum lipid abnormalities in the TCDD-exposed group. The significance of both these effects is unclear at present. A study of immune capability suggested that deficiencies of IgM and IgD might be present in the TCDD-exposed group. EMAS point out that this finding conflicts with those from other published reports e.g. in

children at Seveso, and has not been substantiated by any clinical evidence of impaired immunological competence. EMAS concluded that the study confirmed that the participants could be regarded as being within normal range of clinical findings for healthy working individuals, with the exception of two diabetics whose results were excluded. No clinically recognizable overt or covert disease had been demonstrated, though the longer term significance of the biochemical and immunological findings awaits elucidation. As far as those workers who had been studied are concerned there is no evidence of liver or cardiovascular disease and as such these findings are in agreement with the Monsanto findings.

The medical offices described in the review by the Advisory Committee was Dr. George May. June 1982, Dr. May published the results of his study "Tetrachlorodibenzodioxin. A survey of Subjects Ten Years After Exposure". The study was published in the British Journal of Industrial Medicine 1982, 39:128-135. The abstract of the article is as follows:

Ten years after an incident following which 79 workers developed chloracne due to exposure to tetrachlorodibenzodioxin a study was undertaken to establish the current state of health of the affected employees remaining in the company's (Coalite Oils and Chemicals Ltd., a subsidiary company of Coalite Group Ltd.) employment. The opportunity was used to examine effects on mortality, morbidity, carcinogenesis, reproduction, teratogenicity, fetotoxicity, biochemistry, immunology and genetic change. Concurrently, control groups were established with which to make comparison. The control groups selected from within the works matched the study group in respect of sex and age but it was not possible to match them for occupation and social status. Half the affected subjects still have minor chloracne. Other than this there is no evidence that they have been adversely affected in any way.