UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

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MEMORANDUM

SUBJECT: Review of recent 2,4-D cancer epidemiology studies
Chemical#030001-81 (includes all salts, esters), DP Barcode 311464

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BACKGROUND

On January 14, 2004, a review of 2,4-D incidents and epidemiology studies was performed (Review of 2,4-D Incident Reports, DP Barcode D297233, Chemical#030001-81, includes all salts, esters). The carcinogenicity portion of that review is reproduced below:

Carcinogenicity

A Science Advisory Board/Scientific Advisory Panel Special Joint Committee reviewed available data on 2,4-D in 1994 and concluded that "the data are not sufficient to conclude that there is a cause and effect relationship between exposure to 2,4-D and non-Hodgkin's lymphoma" and 2,4-D has been classified in Group D, not classifiable as to human carcinogenicity (EPA, 1994). In 1996, HED reviewed the following five additional studies:

1. Waterhouse D, Carman WJ, Schottenfeld D, Gridley G, McLean S. Cancer incidence in the rural community of Tecumseh, Michigan: A pattern of increased lymphopoietic neoplasms. Cancer 77:763-770, 1996.

2. Zahm SH, Babbit PA, Weisenburger DD, Blair A, Saal RC, Vaught JB. The role of agricultural pesticide use in the development of non-Hodgkin's lymphoma in women. Archives of Environmental Health 48:353-358, 1993.

3. Morrison HI, Semenciw RM, Wilkins K, Mao Y, Wigle DT. Non-Hodgkin's lymphoma and agricultural practices in the prairie provinces of Canada. Scandinavian Journal of Work, Environment and Health 20:42-47, 1994.

4. Persson B, Fredriksson M, Olsen K, Beoryd B, Axelson O. Some occupational exposures as risk factors for malignant lymphomas. Cancer 72:1173-1778, 1993.

5. Kogevinas M, Kauppinen T, Winkelmann R, et al. Soft tissue sarcoma and non-Hodgkin's lymphoma in workers exposed to phenoxy herbicides, chlorophenols, and dioxins: two nested case-control studies. Epidemiology 6:396-402, 1995.

HED concluded after reviewing these five studies that:

> These studies are not sufficient to change the conclusions drawn by the Science Advisory Panel/Scientific Advisory Board. Only two studies, Zahm et al. 1993 and Kogevinas et al. 1995 looked specifically at exposure to 2,4-D and even in these studies, there were problems with correlation with exposure to other pesticides. Statistical significance was achieved for two types of cancer (Hodgkin's disease and soft tissue sarcoma). However, the earlier evidence for these two sites was generally much less supportive than it was for non-Hodgkin's lymphoma.

Since the 1996 review, very few new studies have examined the relationship between exposure to 2,4-D and cancer. The most recent review was in Critical Reviews in Toxicology by Garabrant and Philbert at the University of Michigan School of Public Health (2002). Their conclusion was "Overall, the available evidence from epidemiologic studies is not adequate to conclude that any form of cancer is causally associated with 2,4-D exposure." This review was conducted at the request of the Industry Task Force II on 2,4-D Research. Many of the studies reviewed by Garabrant and Philbert measured cancer risk among workers exposed to a variety of herbicides. For example, studies of licensed pesticide applicators included a number of exposures in addition to 2,4-D, in such a manner, that 2,4-D relative contribution to risk could not be determined. These studies are excluded from this review unless there was information on risks specific to 2,4-D or just 2,4-D and 2,4,5-T. Only five studies, four cohort and one case-control study, were identified that specifically assess the carcinogenicity of 2,4-D (Kogevinas et al. 1997, Zahm 1997, Lynge 1998, Burns et al. 2001, and Hardell et al. 1999).

Investigators at IARC updated an earlier study (Kogevinas et al. 1995) of a multinational cohort of primarily manufacturing workers exposed to chlorophenoxy herbicides (Kogevinas et al. 1997). There was no significant associations between 2,4-D exposure and soft-tissue sarcoma

(STS), NHL, and Hodgkin's disease among those not exposed to TCDD dioxin contaminants. The odds ratio for STS was 1.35 (95% CI 0.16 - 4.88) based on two observed cases. The odds ratio for NHL was 1.00 (95% CI 0.46 to 1.90) based on nine observed cases. The odds ratio for Hodgkin's disease was 0.27 (95% CI 0.01 to 1.51) based on one observed case.

Zahm (1997) reported on a cohort of pesticide applicators potentially exposed to 2,4-D up to 90-120 days per year. There were no cases of STS or Hodgkin's disease. The estimated odds ratio for NHL was 1.63 (95% CI 0.33 to 4.77) based on three cases. However, all three cases had potential exposure to DCPA, MCPP, dicamba, and organophosphate insecticides as well as 2,4-D. Therefore, the risk from exposure to 2,4-D alone cannot be specified.

Lynge (1998) examined cancer incidence in a cohort of 2,119 Danish phenoxy herbicide workers exposed between 1947 and 1993. However, most of these workers were exposed to MCPA rather than 2,4-D. No odds ratios were calculated for those workers primarily exposed to 2,4-D.

Burns et al. (2001) updated earlier studies of a cohort of 1,517 chemical workers who manufactured or formulated 2,4-D between 1945 and 1994. The odds ratio for NHL was 1.00 (95% CI 0.21 to 2.92) based on three cases. These three cases had relatively low exposures based on cumulative dose estimates compared to other workers in the cohort. There was one case of Hodgkin's disease compared to 0.6 expected which was not significant. Soft tissue sarcomas were not measured in this study. Burns et al. concluded there was "no evidence of an increased risk of death due to all causes or total malignant neoplasms. No significant risk of NHL was found".

The case-control study by Hardell et al. (1999) examined 404 cases of non-Hodgkin's lymphoma and 741 controls. None of the subjects had exposure to 2,4-D alone and exposure to 2,4-D and 2,4,5-T were not significantly associated with NHL (Odds Ratio = 1.3, 95% CI 0.7 to 2.3). A higher estimated odds ratio was found for those with less than 30 days exposure than for those with more than 30 days exposure, a finding that does not support dose-response.

Two additional studies that should be mentioned used an ecologic study design to determine whether chlorophenoxy herbicides were associated with cancer. One study examined cancer rates in four northern wheat producing states in the U.S. (Schreinemachers 2000). This study used wheat acreage as a surrogate for exposure to chlorophenoxy herbicides and determined cancer rates for grouped counties or individual counties based on tertiles of wheat acreage. As the author points out, this study "will generate hypotheses for more resource-intensive and definitive cohort and case-control studies where exposure information can be determined for individual subjects, thereby avoiding ecologic fallacies." Although a number of possible associations between high wheat acreage and cancer were identified, it is not possible to determine which cancer sites were due to chance, confounding, and other factors without further studies.

A second study in northern Italy examined incidence rates of lymphomas in rice-growing

areas where chlorophenoxy herbicides were used (Fontana et al. 1998). This study identified cases of Hodgkin's disease and non-Hodgkin's lymphoma in two provinces in both men and women for the time periods 1985-88 and 1991-93. Results of soil and water analyses performed in 1974-75 were used to classify 13 municipalities as having high exposure to 2,4-D and 2,4,5-TP. Levels of water contamination were similar for 2,4-D and 2,4,5-TP and there were no measurements of tetrachlorodibenzodioxin (TCDD). Although there was a significant association between non-Hodgkin's lymphoma in men and the high exposure area, it was not possible to say whether 2,4-D, 2,4,5-TP or TCDD was responsible for the association. Other confounding factors might also account for the observed association. A supplemental case-control study examined hematolymphopoietic cancers (NHL, Hodgkin's disease, and leukemias) and found some evidence for elevated risk among those with occupations in rice fields, but the odds ratios were not statistically significant and, as before, the association could not be tied, specifically to 2,4-D.

Based on the above reviews of the above studies, HED concludes there is no additional evidence that would implicate 2,4-D as a cause of cancer.

REVIEW OF MORE RECENT CANCER EPIDEMIOLOGY STUDIES RELATED TO 2,4-D

EPA received comments on the 2,4-D Risk Assessment; Docket ID No. OPP-2004-0167 US EPA. 2,4-D on August 23, 2004 from environmental groups concerning the HED's Human Health Risk Assessment for the Reregistration Eligibility Decision (RED) Revised to Reflect Error-only Comments from Registrants. PC Code 030001; DPBarcode D293129.

Additional Human Studies

Additional epidemiologic studies not cited above mentioned in this letter included the following three epidemiologic studies:

Hardell L, Eriksson M. 2003. Is the decline of the increasing incidence of non-Hodgkin's lymphoma in Sweden and other countries a result of cancer preventive measures? Environmental Health Perspective 111:1704-6.

McDuffie HH, Pahwa P, McLaughlin JR, Spinelli JJ, Fincham S. et al. 2001. Non-Hodgkin's lymphoma and specific pesticide exposures in men: cross-Canada study of Pesticides and Health. Cancer Epidemiology, Biomarkers & Prevention 10:1155-1163.

Swaen GMH, van Amelsvoort LGPM, Slangen JJM, Mohren DCL. 2004. Cancer mortality in a cohort of licensed herbicide applicators. International Archives of Occupational and Environmental Health 77:293-295.

Key sections of each of these three studies related to the weight-of-evidence for an

association between cancer and 2,4-D are reviewed below in order.

A key finding of the Hardell and Eriksson (2003) study is found in the concluding paragraph which is quoted in full here:

> Finally, we must emphasize that any single subject may be exposed to several of the agents discussed here, with the potential for interaction in lymphomagenesis. This of course complicates the calculation of the attributable fraction for a single agent. In this article we do not cover all aspects of lymphomagenesis, but we show that the ban of carcinogenic chemicals may be one explanation for the decline in incidence within a rather short time, although the quantitative effect of an individual agent cannot be defined.

This conclusion, stated by the authors, summarizes the principle difficulty with the earlier Hardell and Eriksson (1999) and the Fontana et al. (1998) studies: "it was not possible to say whether 2,4-D, 2,4,5-TP or TCDD was responsible for the association. Other confounding factors might also account for the observed association."

Similar to the Hardell and Eriksson (2003) study above, McDuffie et al. (2001) noted a similar problem in teasing out the specific exposures responsible for the association with non-Hodgkin's lymphoma:

> Among individual compounds, our results that related to exposure to 2,4-D, mecoprop, dicamba, malathion, DDT, carbaryl, lindane, aldrin, captan, and sulfur compounds were not attenuated after simultaneous adjustment for same medical covariates. Clearly, we had few exposed men whose exposure was limited to one pesticide or to one class of pesticides. Our results show elevated risk for exposure to multiple herbicides, insecticides, and fungicides.

This study found an adjusted odds ratio for the association between 2,4-D and non-Hodgkin's lymphoma that was marginally significant (odds ratio = 1.32, 95% confidence interval 1.01 to 1.73). An analysis for dose-response using "days per year" as the surrogate measure for dose did not find any significant results for 2,4-D or the evidence of a trend. The authors noted that "Cases experienced a significantly higher frequency of exposure to phenoxyherbicides, to dicamba or a mixture including dicamba, to 2,4-D, and to mecoprop". As with other case-control studies the authors noted the limitations of potential for recall bias and for misclassification of pesticide exposure. This study did find some evidence for an association between 2,4-D and NHL. However, their final models found stronger relationships for NHL and a personal history of cancer; a history of cancer in first-degree relatives; and exposure to dicamba-containing herbicides, to mecoprop, and to aldrin. This means that, in this study, there was stronger evidence for an association with dicamba mixtures, mecoprop, and aldrin, than there was for 2,4-D. Strength of the relationship and dose-response are important considerations in a weight-of-evidence determination. In this study, the relatively weak though significant association with 2,4-D exposure and the absence of dose-response do not support a causal explanation.

The study by Swaen et al. (2004) updated a cohort study of 1,341 licensed herbicide applicators in the Netherlands. The analysis was based on 196 deaths in the cohort as of January 2001. A survey of use in 1980 found that 112,308 kg of pesticides were applied in the Dutch municipalities where these workers were employed. Of this total 86% of the use was herbicides and the leading herbicide, by far, was simazine which accounted for 27% of the herbicide use. Another 36% was characterized as granulates or not specified. The herbicide 2,4-D was the fourth most used herbicide (after diuron 6.4% and paraquat 6.0%) accounting for 3.7% of the reported usage. There were no cases of lymphatic gland or lymphoreticular sarcomas and just one case of other lymphoma versus 2.4 cases expected. The only cancer with a significant excess was skin cancer which had a 3.6 times excess (95% confidence interval, 1.1 to 8.3), which the authors acknowledge may be due to excess exposure to sunlight. A non-significant increase of multiple myeloma was reported in this cohort based on 3 observed cases versus 1.4 expected (95% confidence interval, 0.4 to 6.1 times expectation). However, the authors of the study drew no conclusions suggesting that 2,4-D was likely associated with any form of cancer.

In summary, the Hardell and Eriksson (2003) study suggests that the decline in NHL starting in 1990 in Sweden may be related to the ban of a 2,4-D/2,4,5-T in 1977. However, they acknowledge the difficulty of distinguishing affects due to just 2,4-D and other phenoxy herbicides, and especially the dioxin contaminant. The study by McDuffie et al. (2001) found weak evidence of an association between NHL and 2,4-D and stronger evidence for other pesticides. The study by Swaen et al. (2004) was not specific to 2,4-D and, in any case had relatively limited power to detect effects based on just 196 deaths. Together these three studies add very little to our understanding of the cancer epidemiology specifically related to 2,4-D.

Additional Dog Studies

Four other relevant studies cited by the environmental groups in their August 23, 2004 letter involved dogs and NHL:

Gavazza A, Presciuttini S, Barale R, Lubas G, Gugliucci B. 2001. Journal of Veterinary Internal Medicine 15:190-195.

Glickman LT, Raghavan M, Knapp DW, Bonney PL, Dawson MHl. 2004. Herbicide exposure and the risk of transitional cell carcinoma of the urinary bladder in Scottish Terriers. Journal of the American Veterinary Medical Association 224:1290-1297.

Hayes HH, Tarone RE, Cantor KP. 1995. On the association between canine malignant lymphoma and opportunity for exposure to 2,4-dichlorophenoxyacetic acid. Environmental Research 70:119-125.

O'Brien DJ, Kaneene JB, Getis A, Lloyd JW, Swanson GM, Leader RW. 2000. Spatial and temporal comparison of selected cancers in dogs and humans, Michigan, USA, 1964-1994. Preventive Veterinary Medicine 47:187-204.

Key sections of each of these three studies related to the weight-of-evidence for an association between cancer and 2,4-D are reviewed below in order.

Gavazza et al. (2001) performed a case-control study on 101 confirmed lymphomas with 191 dogs referred to the same veterinary hospital without any form of cancer. Controls were matched with respect to province of residence, age, sex, and breed. A telephone interview was administered to the dog owners one month to one year after the lymphoma diagnosis. The results, as reported by the authors, were that "Two variables were positively and independently associated with the disease, namely residency in industrial areas (odds ratio [OR]: = 8.5; 95% confidence interval [CI], 2.3-30.9) and use of chemicals by owners, specifically paints or solvents (OR = 4.6; 95% CI, 1.7-12.6) . . . Variables describing animal care and pesticide use were either not associated with the disease or were uninformative." The August 23, 2004 letter from environmental groups commented on these negative findings "Gavazza, lead investigator of most of the negative CML findings below, was hired by the 2,4-D Industry Task Force to investigate the positive CML findings that had undergone high quality peer review. Other than these questionably-published CML negative results, it is highly notable that there are hardly any negative results published – not even in one of the few less rigorous quality journals".

The study by Glickman et al. 2004 examined herbicide exposure and the risk of transitional cell carcinoma (TCC) in the urinary bladder in Scottish Terriers. Exposure to phenoxyherbicides was significantly associated with TCC (odds ratio 4.34, 95% confidence interval 1.98 - 9.54). In addition to 2,4-D, the dogs in this study were also exposed to MCPP and MCPA which are pheoxyherbicides. The authors noted that the risk of TCC increased with the body weight of the dogs and that "This raises the possibility that inert ingredients, including solvents, emulsifiers, and spreaders, in lawn and garden pesticides might be responsible" for the associations reported.

O'Brien et al. (2000) examined spatial and temporal patterns of cancer in both dogs and humans. This study did not specifically address the risk of carcinogenicity of 2,4-D, but rather provides evidence that the pattern of cancers in humans and dogs are not independent. In the authors own words, "While the design of this exploratory study does not allow conclusions about the causes of the clustering of the study cancers to be drawn, our findings do suggest substantial interspecies variation in geographic occurrence. The results are not uniformly consistent with a scenario where aggregation of canine cancers inevitably followed areas of high human population, nor with one where processes determining aggregation were unaffected by environmental factors that vary from place to place." They concluded that "Local environmental influences acting as risk factors for these cancers are one hypothetical explanation for the substantial spatial variations noted." The authors caution "It is imperative that the limitations of this study be kept in mind. Here, the spatial distributions of diseased dogs were compared to diseased humans, and a relationship found. What was not studied, and thus cannot be assessed, is whether a similar spatial relationship–if found–would suggest that etiological factors were unlikely to be responsible for the spatial dependencies noted between human and canine cases." In short, this study demonstrated the feasibility of using studies of domestic animals as indicators of cancer risks in humans, but it did not specifically address the risk of 2,4-D.

The study by Hayes et al. (1995) is a follow-up to their earlier report that demonstrated an association between canine malignant lymphoma and opportunity for exposure to 2,4-D. It includes several ancillary analyses not covered in the original study. These analyses show that risk estimates were not affected by type of control group (i.e., tumor control or nontumor control), by method of response (i.e., telephone or self-administered), or by geographic area. The authors concluded by stating:

> All critiques noted that the magnitude of the association we reported is small and in the range which could well be explained by bias or confounding. We acknowledged both possibilities in our report (Hayes et al., 1991). Given the relatively low exposure levels and the problems related to exposure assessment, odds ratios of magnitude 1.3 or 1.4 must be interpreted with caution. We concur with one reviewer, however, that a greatly increased risk would be inconsistent with the limited nature of the exposure (Washington State University Field Disease Investigation Unit, 1992). All critiques correctly conclude that our study does not prove that 2,4-D exposure in the home environment is a cause of malignant lymphoma in companion dogs. Rarely can a single epidemiological study prove causation, and we concluded only that exposure to 2,4-D in the home environment warrants further investigation (Hayes et al., 1991).

In summary, there was one study supporting an association between 2,4-D exposure in Scottish Terriers and bladder cancer and one study supporting the conclusion that lymphomas in dogs were not associated with exposure to 2,4-D. A second Hayes et al. study is cited to show that the earlier criticisms of that study are not supported by additional, more detailed analysis. None of the authors of the above studies would support a finding that 2,4-D is a likely cause of cancer in dogs, but some would likely support the finding that 2,4-D is a possible cause of lymphomas in dogs or bladder cancer in Scottish Terriers. These authors would likely agree that other causes particularly exposure to other ingredients in herbicides such as solvents, emulsifiers, and spreaders might be responsible for the observed associations.

References

Burns CJ, Beard KK, Cartmill JB. 2001. Mortality in chemical workers potentially exposed to 2,4-dichlorophenoxyacetic acid (2,4-D) 1945-94: an update. Occup Environ Med. 58(1):24-30.

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Fontana A, Picoco C, Masala G, Prastaro C, Vineis P. 1998. Incidence rates of lymphomas and environmental measurements of phenoxy herbicides: ecological analysis and case-control study. Archives of Environmental Health 53:384-387.

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cc: 2,4-D file (030001)
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