PESTICIDES BOARD

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REPORT OF THE PESTICIDES BOARD EXPERT PANEL ON 2,4-D

11 SEPTEMBER 2000

Background

On 14 March 2000, Radio New Zealand ran a programme which discussed the findings of an Occupational Safety and Health (OSH) Chemical Panel which had been looking into allegations that a Northland man had suffered health effects after being exposed to spray drift of the herbicide 2,4-D in 1995. The Registrar of the Pesticides Board was included in the discussion, and consequently the Board was alerted to the findings of the OSH Panel. The Board discussed the programme at its meeting on 22 March 2000. Section 13(1)(a) of the Pesticides Act 1979 states that a principal function of the Board shall be "generally to promote the prudent, effective, and safe use of pesticides in New Zealand."

The discussion lead to the Board agreeing to set up an expert panel to look into the allegations, and any new information on 2,4-D arising from public submissions and data published by other regulatory authorities. The Panel was charged with making recommendations to the Board as to whether the registration of 2,4-D should be formally reviewed. This included the Panel considering whether there were any aspects of the uses of the currently registered products which were unacceptable, and they were asked to feel free to make any recommendations that they wished regarding any of the various formulations of 2,4-D and its salts and esters.

Formation of the panel

Nominations were sought from Occupational Safety and Health, the Environmental Risk Management Authority New Zealand, and the Ministry of Health to join the Registrar of the Pesticides Board (who is also the National Manager – Toxicology and Residues in the Ministry of Agriculture and Forestry) on the Panel.

The Panel members were:

Professor Bill Glass, Occupational Physician	Occupational Safety and Health
Dr Deborah Read, Senior Public Health Advisor	ERMA New Zealand
Jim Waters, Senior Advisor (Toxicology)	Public Health Programmes, Ministry of Health
John Reeve, National Manager (Toxicology and Residues)	MAF Food

Information considered by the Panel

At the time that the formation of the Panel was announced, the Registrar of the Board invited submissions from any persons who wished to put any new information in to the Panel. Many submissions were received, many of them forming part of a larger submission. For the purposes of this report, and its attachments, 32 submissions (some grouped) and two petitions from interested parties opposed to the use of 2,4-D were considered by the Panel. In addition, the following information was presented to the Panel:

- The OSH medical file on the Northland man that had been exposed to the spray drift.
- The Northland Medical Officer of Health's report on the 1995 Waiotira Overspray Incident.

Excerpts from:

- WHO Environmental Health Criteria 29, 1984.
- US EPA Draft Assessment for 2,3,7,8-TCDD and Related Compounds.
- US EPA Draft Inventory of Sources of Dioxin in the USA.
- US EPA Hazard Summary 2,4-Dichlorophenoxy acetic acid.
- Industry Task Force on 2,4-D Research Data.
- Ministry for the Environment Ambient Concentrations of selected organochlorines in soils.

- Hayes, WJ and Laws ER, Handbook of Pesticide Toxicology, Academic Press, 1991.
- Various product files on pesticide formulations registered and recently registered in New Zealand.

The considerations of the Panel

The Panel formally met on 22 June 2000, to discuss the information that had been sent to them prior to the meeting. At the outset, two major issues were identified:

- Was the information regarding the Northland man who had been exposed to 2,4-D indicative that change was necessary in the registration status of products containing 2,4-D and its derivatives?
- Was any of the other information before the Panel indicative that change was necessary?

The Panel members discussed many issues prior to their making decisions on the issues identified.

1. Was there any difference in toxicity of the different formulations of 2,4-D?

There was some data indicating that there were differences in foetal toxicity to some of the 2,4-D derivatives. There was no effect when the amine and sodium salts were tested, and post-implant mortality was seen when the ammonium salt and butyl ester were tested. Apart from this, there seemed no difference in the toxicities of the derivatives. 2,4-D and its salts and esters are classified as Standard Poisons, Harmful Substances, or not classified (depending on their formulation) in New Zealand. All but one formulated product are Standard Poisons. A survey of the product files for the identity of the excipients in the various formulations did not reveal any that would be likely to increase this classification. Most of the formulations had very similar excipients of known toxicity in them.

2. What is the dioxin content of 2,4-D and its formulations?

The Panel was aware that the impurity of 2,4-D that is of most concern is dioxin. The Panel agreed that 2,4-D as technical material does contain a detectable concentration of dioxins, but that it must also be made clear as to the relative toxicities of the different dioxins, and the level of their presence in 2,4-D. It was noted that the US EPA draft document on dioxin showed that that highest concentration of the most toxic dioxin (2,3,7,8-TCDD) was only slightly above the limit of quantification of the analytical method (0.13µg/kg compared with 0.1µg/kg), and that the average concentration was 0.06µg/kg (ie below the limit of quantification). Consequently, it has only been relatively recently that the presence of this dioxin was detected in 2,4-D. These levels are clearly lower than the level of 10µg/kg, which is the level accepted by the WHO in the herbicide 2,4,5-T that does not increasing the toxicity of the technical material. The levels of dioxin in 2,4-D would be unlikely to be detectable in formulated products.

The Panel agreed that the dioxins were not considered to be significant impurities because the concentration of the dioxins and their related dibenzofuran congeners present in 2,4-D were on average 0.7µg/kg as toxic equivalents of 2,3,7,8-TCDD, which is lower than the 10µg/kg level accepted by the WHO.

3. What is the source of the 2,4-D in NZ, and is it the same as that tested for dioxins in the USA?

2,4-D is manufactured in many countries of the world and that used in New Zealand could come from any of them. The important issue is that whichever source is used for New Zealand, the specifications made for that active ingredient must comply with those stated at the time of the registration of products containing it.

4. What contribution does pesticide use make to dioxin releases to land?

Members of the Panel commented that this contribution was likely to be very low, and suggested

that the Ministry for the Environment report "New Zealand inventory of dioxin emissions to air, land and water, and reservoir sources", published in March 2000, would provide details. This report indicates that the annual release (to land) estimate for all dioxins as a result of the use of halogenated pesticides is 0.13 – 0.15g International Toxic Equivalents/year. This compares to the total annual estimate to land of 26 - 54g International Toxic Equivalents/year. Thus, halogenated pesticide use represents between 0.28% and 0.5% of the total annual estimate of emission to land. The major sources of dioxins in land being identified as domestic waste burning (5.7g International Toxic Equivalents/year), residential solid waste (8.9g International Toxic Equivalents/year) and industrial solid waste (11.1g International Toxic Equivalents/year).

5. Did the different formulations influence the possibility of spray drift?
The Panel considered the effects of the volatility of the various salts and esters of 2,4-D. The following Table shows the volatility of the salts and esters that are, or recently have been available in New Zealand. The butyl ester formulation was implicated in the incident in which the Northland man was exposed. Formulations of this ester were deregistered by the Pesticides Board in 1996.

Form of 2,4-D	**Volatility (mPa at 25 ^{o}C)**
2,4-D acid	0.02
2,4-D dimethylamine salt	1.0×10^{-7} (at 38 ^{o}C)
2,4-D ethylhexyl ester	0.48
2,4-D butyl ester	9.1

Volatility (the problem associated with the butyl ester formulations) is not the only contributor to spray drift. A number of variables may contribute. These are primarily related to either the spray application equipment used or to meteorological factors. When a solution is sprayed under pressure, it is atomised into droplets of varying sizes. The greater the spray pressure, the smaller the droplets become. Small droplets give good target coverage, but increase the potential for off target spray drift. Low volume spraying (that is spraying which uses low volumes of water as the carrier of the chemical), necessarily results in the individual spray droplets being more concentrated than those in high volume spraying. Low volume spraying results in the same amount of chemical being applied to a given target area as high volume spraying, but smaller droplets (at higher pressure) are required to ensure coverage. It is a common method for aerial application, as less water (weight) is required to be carried in order to apply the chemical. Droplet drift may also be affected by the operating speed, the height of release and the inclusion (or non-inclusion) of anti-drift additives. Wind velocity, air temperature and humidity are also likely to impact on the off target drift of spray droplets.

It is difficult, therefore, to be specific regarding the influence of formulation type on spray drift. Different formulations are likely to have some effect, but other influences may affect drift to a greater extent.

What can be stated is that the ethylhexyl ester of 2,4-D is approximately 20 times less volatile than the butyl ester, which it replaced.

6. Was there any difference in the efficacy of the ester and salt formulations?
All of the different forms of the 2,4-D are converted to the parent acid in plants, and the latter is the actual herbicide. Therefore there will be no differences in efficacy once absorbed. That absorption is likely to be affected by the chemical derivative of the 2,4-D present.

7. Was there any difference in application techniques for the different formulations (eg water rates, equipment used for the application)?
Application techniques will affect residues and influence spray drift. There are no particular

differences in the way in which the different forms of 2,4-D are applied. All can be applied by air, or by any of the ground application methods. However, at this point, the Panel discussed the question of the concentration of the spray being applied. It was alleged that the spray used in the incident in which the Northland man was affected was ten times more concentrated than label recommendations. It was understood that while higher spray concentrations were likely to be used when aerial application was being used, the actual rate of spraying was appropriately reduced to ensure that the amount of 2,4-D reaching the target (as x kg/ha) was as recommended on the label. The higher spray strength was used to reduce weight in the aircraft.

Information from the files clearly indicate that as spray became more concentrated, then droplet size tends to decrease and increased drift could be expected. The practice of using higher spray concentrations was thus of concern to the Panel because of what would appear to be an increased potential for spray drift.

8. What was the international status of the acceptability of the different 2,4-D derivatives?
The Panel was unaware that any regulatory authority has banned the use of 2,4-D other than in the form of its butyl ester.

9. Was there any evidence that the Northland man might be sensitised to 2,4-D?
The Panel had no information on which to comment specifically on this issue. The Panel noted that in general, there are marked individual differences in susceptibility to chemicals. It was known that the man had been exposed repeatedly to 2,4-D spray drift throughout the day (including some direct exposure to the spray being applied) while he was attempting to get evidence of spray drift on to his property. The Panel noted that some observers appeared to indicate that he was not actively avoiding exposure, that he had not worn protective clothing, and had not immediately washed the spray residues off his exposed skin. The OSH Chemical Panel report showed that he had suffered the effects of having an irritant chemical in prolonged contact with his skin. 2,4-D is known to be a skin and eye irritant and the Panel considered that 2,4-D was likely to be responsible as the OSH Chemical Panel had concluded.

General considerations

The Panel expressed a general concern about the lack of adequate precautions being taken by users to avoid exposure to the sprays. In spite of this, generally the use of 2,4-D does not seem to have lead to problems (particularly with respect to those most highly exposed such as mixers and loaders at spray operations). This case is the first such finding by the OSH Chemical Panel in New Zealand.

The claims that were supported by the OSH Chemical Panel were the signs and symptoms of an exposure to an irritant chemical, which in this case happened to be 2,4-D. The Panel concluded that acute ill health is an uncommon consequence of 2,4-D use in New Zealand. The symptoms claimed by the Northland man were what would have been expected and reflected the unusually higher exposure than that which would be expected for a casual bystander. The Panel therefore felt that the incident involving the Northland man did not seem to be any reason to take specific action on 2,4-D, in relation to Section 13(1)(a) of the Pesticides Act 1979 at this time, since the exposure of the person affected in this case was not not in the circumstances in which 2,4-D is normally used or likely to be used.

The overall feeling of the Panel was that most of the submissions were clearly identifying the issue of spray drift as the major concern, and the use of 2,4-D was almost a secondary issue. The Panel noted that proposals for the HSNO regulations were likely to deal with this issue through the setting of Environmental Exposure Limits and Tolerable Exposure Limits based on appropriate data.

However, in the meantime, the level of spray drift is heavily influenced by the volatility of the ingredients of the sprays, and any non-compliance with recognised Good Spraying Practices. The water volumes used in the application of pesticides was going to influence the question of volatility (the less the water, the greater the volatility), as was droplet size (droplets below 100 μ were more likely to drift). There was also a clear need to reinforce the message that users must wear the recommended protective clothing.

This lead to a discussion of the issue of using concentrated sprays when applying them by air. The Panel felt that this should be further looked into to ensure that the concentration of the sprays is the most appropriate - bearing in mind the conflict between increased concentration to allow a greater amount of chemical to be applied (to a greater area) per flight, and the likely increase in potential for drift to occur.

The Panel was particularly appreciative of the efforts that people had put into their submissions, and wished to thank all who had done so. The submissions gave the Panel a clear message as to the feelings of the different sectors of the population, and helped ensure that all the appropriate issues were put before them.

Recommendations

The Panel made the following recommendations:

- That after reviewing the information relating to the Northland spray drift incident in which a man was exposed to spray drift, and the other information that the Panel had before it, there did not seem to be any reason to formally review the current registration status of 2,4-D and its salts and esters in New Zealand at this time.

- That the practise of applying highly concentrated sprays (particularly in aerial applications) should be further looked into by the Ministry of Agriculture and Forestry to ensure that the concentrations being used were appropriate.

- That the benefits of wearing recommended protective clothing when using pesticides are actively promoted. This could be done via press releases from the Board and with leaflets put into outer containers of pesticides.

- That initiatives to deal with the general issue of spray drift should be supported. In this regard, the Panel noted the efforts of the Spray Drift Advisory Group which had been advising the Pesticides Board. It was hoped that this Group could be reactivated under an appropriate authority when the new legislation (Hazardous Substances and New Organisms Act) commences.

- That the submitters of information be sent letters of thanks for their efforts and be sent copies of this report and the accompanying Table of Submissions containing the responses of the Panel.

Appendix 1

The Board **received** and accepted the report, but discussed the recommendations and agreed the following:

1. The Board accepted the Expert Panel's conclusion that after reviewing the information relating to the Northland spray drift incident in which a man was exposed to spray drift, and the other information that the Panel had before it, there did not seem to be any reason for the Board to formally review the current registration status of 2,4-D and its salts and esters in New Zealand at this time. However the Board wished to highlight the actions suggested in recommendation 4.

2. The Board agreed that the issue of applying highly concentrated sprays which uses greater spray pressure and should be dealt with by gathering the information as to the consequences of the practise such as smaller droplet size and subsequent increased spray drift. This information and recommendations for good spraying practises are in the NZ Agrichemical Education Trust Code of Practice (NZS 8409:1999). This information should then be disseminated to those groups involved in the decision making regarding the application of pesticides so that they would be able to make good decisions as to the best spray practises that should be used. The groups identified were sprayers and those contacting sprayers to apply pesticides to their land.

3. The Board agreed that there was value in reinforcing the messages as to the benefits of wearing the recommended protective clothing when using pesticides.

4. The Board recommended that the information gathered during the 2,4-D review, the report of the Expert Panel, summary of the submissions and Table of Submissions (with responses), should be sent on to ERMA NZ. ERMA NZ could then decide whether they wished to include 2,4-D in their review process once HSNO commenced. The information should also be sent to the Ministry for the Environment who are setting up a pesticide reduction strategy and an inquiry into spray drift so that the information could be considered in the process(es) associated with these initiatives. The Board agreed that its Spray Drift Advisory Group had made significant progress in dealing with the general issues of spray drift, and this Group should also be brought to the attention of MfE.

5. The Board agreed that the submitters of information to the Expert Panel should be thanked for their efforts, and be sent copies of the report and its accompanying Table of Submissions.

Appendix 2

For the reader's information, and to more fully explain the complex toxicology considered by the Panel, the following is extracted from the WHO/FAO Joint Meeting on Pesticide Residues (JMPR) Monographs of toxicological evaluations:

914. DICHLOROPHENOXYACETIC ACID, 2,4- (PESTICIDE RESIDUES IN FOOD: 1996 EVALUATIONS PART II TOXICOLOGICAL)

3. Observations in humans

Epidemiological studies have suggested an association between exposure to chlorophenoxyacetic acid herbicides, including 2,4-D, and two forms of cancer in humans: soft-tissue sarcomas and non-Hodgkin's lymphoma. The results of these studies are not consistent, however, the associations found are weak, and conflicting conclusions have been reached by the investigators. In addition, most of these studies did not provide information on exposure specifically to 2,4-D, and the risk was related to the general category of phenoxy herbicides, which might include 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) and substances contaminated with dioxins, specifically 2,3,7,8-TCDD. While some of the studies have shown a relationship between exposure to 2,4-D and non-Hodgkin's lymphoma, others (including those with positive results) have produced inconsistent findings, raising doubts about whether the relationship is causal.

(a) Case-control studies

(i) Soft-tissue sarcoma

Six case-control studies addressed the association between exposure to phenoxyacetic acid herbicides and chlorophenols and the development of soft-tissue sarcoma in humans. A positive association was reported in patients with exposure to either group of compounds in Sweden (Hardell & Sandstrom, 1979; Eriksson et al., 1981) and in female rice weeders in northern Italy (Vineis et al., 1986). None of these studies, however, reported an OR for exposure to 2,4-D. In contrast, a number of case-control studies in New Zealand and the USA failed to find an association between use of phenoxyacetic acid herbicides and the development of soft-tissue sarcoma (Smith et al., 1983, 1984; Hoar et al., 1986; Woods et al., 1987). The specific findings are described below.

Hardell and Sandstrom (1979) studied 21 living and 31 deceased male patients with soft-tissue sarcoma in northern Sweden who had been exposed to phenoxyacetic acids or chlorophenols; 220 controls were chosen from the general population. The cases of soft-tissue sarcoma were identified from the records of the Department of Oncology of the University Hospital of Umeå between 1970 and 1977. Information on patterns of use of herbicides and chlorophenols was obtained from questionnaires for 36.5% of the cases and 9.2% of the controls who recalled exposure to these compounds. There was a significant

($p < 0.001$), sixfold increase in risk for soft-tissue sarcoma (OR, 5.3; 95% CI, 2.4-11), with 13 cases who had been exposed to phenoxyacetic acids. Of these 13 cases, nine had been exposed to 2,4-D and 2,4,5-T combined, two to 2,4,5-T alone, one to MCPA alone, and one possibly to 2,4-D only. The authors noted that the effects of the individual chemical substances could not be evaluated, as nearly all of the exposed subjects were also exposed to chlorinated dioxins, including 2,3,7,8-TCDD.

Eriksson et al. (1981) confirmed the finding of Hardell and Sandstrom of an association between soft-tissue sarcoma and phenoxyacetic acids in southern Sweden, where MCPA and 2,4-D have been widely used. The study involved 110 cases of soft-tissue sarcoma reported in 1974-78 and 220 controls from the general population. The ORs were 6.8 (95% CI, 2.6-17) for exposure to any phenoxyacetic acid herbicide and 4.2 for exposure to chlorphenoxyacetic acid herbicides other than 2,4,5-T.

Vineis et al. (1986) studied cases of soft-tissue sarcoma among female rice weeders in northern Italy, where phenoxyacetic acid herbicides have been used since the beginning of the 1950s. Interviews were carried out with 68 persons (31 women) with histologically confirmed soft-tissue sarcoma and 158 controls (73 women) who had been exposed to 2,4-D, MCPA, and 2,4,5,-T. For live women who had been exposed to phenoxyacetic acid herbicides at any time, the OR was 2.7 (90% CI, 0.59-12). For women < 75 years old at the time of interview and who had been exposed in 1950-55, the age-adjusted OR was 15 (90% CI, 1.3-180).

Smith et al. (1983, 1984) investigated the association between soft-tissue sarcoma and exposure to phenoxyacetic acid herbicides in New Zealand. The authors selected 82 subjects with soft-tissue sarcoma and 92 controls with other types of cancer from the National Cancer Registry for the years 1976-80. The study failed to show any statistically significant association between use of the herbicides and soft-tissue sarcoma. The OR was 1.3 (90% CI, 0.7-2.5) for those potentially exposed and 1.6 (90% CI, 0.7-3.3) for those probably or definitely exposed for more than one day before the five years prior to cancer registration.

Hoar et al. (1986) conducted a population-based case-control study in Kansas, USA, where 2,4-D was the most commonly used herbicide; 2,4,5-T was also used, 'along with myriad other chemicals'. The study comprised 113 soft-tissue sarcoma cases identified through the University of Kansas Cancer Data Service for the years 1976-82 and 948 controls from the general population of the state. No consistent pattern of excess risk for soft-tissue sarcoma was seen for farmers when compared with non-farmers (OR, 1.0; 95% CI, 0.7-1.6), for herbicide use (OR, 0.9; 95% CI, 0.5-1.6) or for duration and frequency of herbicide use (OR, 1.1; 95% CI, 0.7-1.7).

In a population-based case-control study, Woods et al. (1987)

evaluated the relationship between occupational exposure of men in Washington State, USA, to phenoxyacetic acid herbicides and chlorinated phenols and the risk of developing soft-tissue sarcoma. The study comprised 128 cases of soft-tissue sarcoma and 694 randomly selected controls without cancer. No statistically significant association was seen with exposure to phenoxyacetic acid herbicides (OR, 0.89; 95% CI, 0.4-1.9).

(ii) Non-Hodgkin's lymphoma

The association between exposure to phenoxyacetic acid herbicides and the development of non-Hodgkin's lymphoma has been studied in Sweden, New Zealand, and Kansas, Washington, Nebraska, Iowa, and Minnesota, USA. The overall results of these studies suggest an association, although the evidence is not entirely consistent. Less clear, but still suggestive, is the evidence for a specific association between non-Hodgkin's lymphoma and exposure to 2,4-D. These studies must be interpreted with caution, however, because it is difficult to isolate the specific herbicide (or other factor) that is responsible for the association, which may be due to other chemicals that farmers mix with 2,4-D or with impurities in the 2,4-D that was sold commercially. The association with 2,4-D has not been replicated; and use of 2,4-D may serve as a surrogate for some other, unknown confounding factors. The specific findings are described below.

Hardell (1981) examined the association between exposure to phenoxyacetic acids or chlorophenols and malignant lymphoma in Sweden. The study comprised 60 hospitalized patients with Hodgkin's disease, 109 with non-Hodgkin's lymphoma, and 338 controls from the general population. The questionnaire method used was similar to that of Hardell and Sandstrom (1979). A significantly increased risk was found with exposure to phenoxyacetic acid herbicides (OR, 4.8; 95% CI, 2.9-8.1). Although risk estimates were not reported separately for Hodgkin's disease and non-Hodgkin's lymphoma, the authors reported no meaningful difference.

Hoar et al. (1986) conducted a population-based case-control study in Kansas, USA, that comprised 121 cases of Hodgkin's disease and 170 of non-Hodgkin's lymphoma identified through the University of Kansas Cancer Data Service for the years 1976-82, and 948 controls from the general population of the State. No association was seen between use of phenoxyacetic acid herbicides and Hodgkin's disease. When the rates of non-Hodgkin's lymphoma for non-farmers were used for comparison, associations of borderline significance were found for farming (OR, 1.4; 95% CI, 0.9-2.1) and for phenoxyacetic acid herbicide use (OR, 2.2; 95% CI, 1.2-4.1). The OR for use of herbicides on wheat, corn, sorghum, or pasture was 1.6 (95% CI, 0.9-2.6). The relative risk (RR) for non-Hodgkin's lymphoma was significantly increased when evaluated by number of days of exposure to herbicides per year and latency. Farmers exposed for more than 20 days per year

had a sixfold increase in risk for non-Hodgkin's lymphoma relative to non-farmers (OR, 6.0; 95% CI, 1.9-20). When exposure was restricted to users exposed only to 2,4-D (i.e. eliminating 2,4,5-T), the RR was increased (OR, 2.6; 95% CI, 1.4-5.0). In men exposed only to 2,4-D for > 20 days per year, the OR was 7.6 (95% CI, 1.8-32). The authors had reservations about the accuracy of this determination because of the way in which the questionnaire elicited dates and frequency of herbicide use. Frequent users who mixed or applied the herbicide themselves had an elevated risk (OR, 1.9; 95% CI, 1.1-3.3), and the risk was even higher (OR, 8.0; 95% CI, 2.3-28) for men who mixed or applied the herbicides and who were exposed for more than 20 days per year. An association was also found between the occurrence of non-Hodgkin's lymphoma and failure to use protective equipment, such as robber gloves and masks (OR, 2.1; 95% CI, 1.0-4.2), in comparison with those who protected themselves (OR, 1.5; 95% CI, 0.7-3.1). The results were difficult to interpret, because the information on exposure was gleaned exclusively from interviews with subjects or their next-of-kin. There is reasonable doubt about whether the next-of-kin would be knowledgeable about the subject's daily weed-control practices or be able to recall with precision such practices 15-20 years later. Furthermore, as no data were collected on the frequency or duration of 2,4-D use per se, it was not possible to estimate directly an association between the amount of exposure to 2,4-D and non-Hodgkin's lymphoma.

In another population-based case-control study, Woods et al. (1987) evaluated the relationship between occupational exposure of men in western Washington State, USA, to phenoxyacetic acid herbicides and chlorinated phenols and the risk of developing non-Hodgkin's lymphoma. The study comprised 576 cases of non-Hodgkin's lymphoma and 694 randomly selected controls with cancer. An association was found between non-Hodgkin's lymphoma and application of herbicides in farming (OR, 1.3; 95% CI, 1.0-1.7) or forestry (OR, 4.8; 95% CI, 1.2-19); however, the forestry sprayers reported combined use of 2,4-D and 2,4,5-T and use of commercial preparations containing other chemicals. The risk for developing non-Hodgkin's lymphoma was also increased for workers potentially exposed to phenoxyacetic acid herbicides in any occupation for a period of 15 years or longer during the 15 years before cancer diagnosis (OR, 1.7, 95% CI, 1.0-2.8). No statistically significant association was seen between non-Hodgkin's lymphoma and exposure to phenoxyacetic acid herbicides (OR, 1.2; 95% CI, 0.8-1.9), even at high levels. Men who reported using 2,4-D specifically had an OR of 0.73 (95% CI, 0.43-1.3), although it was difficult to determine if this OR was controlled for other exposures. In a later report, Woods and Polissar (1989) concluded that phenoxyacetic acid herbicide preparations (e.g 2,4-D and 2,4,5-T) per se do not independently increase the risk but may enhance the risks associated with use of various pesticides and other chemicals in agriculture.

Pearce et al. (1986, 1987) and Pearce (1989) studied non-Hodgkin's lymphoma and exposure to phenoxyacetic acid herbicides

in New Zealand. In contrast to the USA, where the herbicide evaluated was 2,4-D, the compound used predominantly in New Zealand in 1950-80 was 2,4,5-T. These studies comprised 183 men with non-Hodgkin's lymphoma and 338 male controls obtained from the New Zealand Cancer Registry for the years 1977-81. No excess risk was found (OR, 1.0; 90% CI, 0.7-1.5). When the risk for non-Hodgkin's lymphoma was examined by the number of days of use by year, the trend was not significant, but the risk did increase with use for 10-19 days per year (OR, 2.2; 95% CI, 0.4-13) and then decreased (OR, 1.1; 95% CI, 0.3-4.1) with use for > 20 days per year.

Zahm et al. (1990) examined the association between exposure to 2,4-D and the development of non-Hodgkin's lymphoma in eastern Nebraska, USA, in a population-based case-control study that comprised 201 white men with non-Hodgkin's lymphoma and 725 controls. The distinctive feature of this study was that specific information was obtained on the duration and frequency of 2,4-D use. No excess risk for non-Hodgkin's lymphoma was found in subjects with a history of ever having worked or lived on a farm (OR, 0.9; CI, 0.6-1.4), but men who mixed or applied 2,4-D had a 50% increased risk (OR, 1.5; 95% CI, 0.0-2.5). The risk was even higher for farmers who had handled (mixed or applied) 2,4-D for > 21 days per year (OR, 3.3; 95% CI, 0.5-22; $p = 0.051$). No association was seen, however, with the number of years 2,4-D was used on the farm ($p = 0.274$). The risk was also raised with the time that farmers wore their application work clothes before changing into clean clothes: the OR was 1.1 (95% CI, 0.4-3.1) when the clothes were changed immediately after handling and 1.5 (95% CI, 0.8-2.6) for those who changed clothes at the end of the work day or 4.7 (95% CI, 1.1-21) for those who waited until the following day or later to change their clothes. As in the study in Kansas, information on exposure was gleaned exclusively from interviews with subjects or their next-of-kin. The suggestion of an increased risk was based on only three patients with non-Hodgkin's lymphoma who reported use of 2,4-D for > 21 days per year, derived almost entirely from responses of next-of-kin. No trend of increasing risk with increasing days of use was seen when the patients themselves reported on their past exposure.

Cantor et al. (1992) studied pesticides and other agricultural risk factors for non-Hodgkin's lymphoma among men in Iowa and Minnesota, USA. The study comprised 622 white men with non-Hodgkin's lymphoma and 1245 white controls. In comparison with the rates for non-farmers, there was a small increase in risk for non-Hodgkin's lymphoma among men who had ever lived or worked on a farm as an adult (OR, 1.2; 95% CI, 1.0-1.5). No significant increase in risk was seen for subjects who had ever handled, mixed, or applied specific herbicides. Use of 2,4-D resulted in similar ORs in the following analyses: for those who had ever mixed or applied 2,4-D (OR, 1.2; 95% CI, 0.9-1.8); for those who had handled 2,4-D with protective equipment (OR, 1.2; 95% CI, 0.9-1.6) or without protective equipment (OR, 1.2; 95% CI, 0.9-1.7); and for those who first used 2,4-D before 1965 in Iowa (OR, 1.2; 95% CI, 0.9-1.9) and Minnesota (OR, 1.4;

95% CI, 0.9-2.3). The authors reported only limited information relevant to the hypothesis of an association between exposure to 2,4-D and cancer. Specific information on the frequency of use of 2,4-D was not reported.

(b) Cohort studies

Cohort studies conducted among workers with occupational exposure to phenoxyacetic acid herbicides have not confirmed the initial hypothesis of an association between exposure to 2,4-D and either soft-tissue sarcoma or non-Hodgkin's lymphoma. While the cohort studies conducted in Sweden, Finland, and the USA failed to show an association (Riihimaki et al., 1983; Wiklund & Holm, 1986; Wiklund et al., 1987; Bond et al., 1988; Wiklund et al., 1988; Wigle et al., 1990), positive results were seen in four further studies (Lynge, 1985; Coggon et al., 1991; Saracci et al., 1991), which, however, provide conflicting results, each showing an increase in the risk for only one of the two cancers of concern (a different cancer in each cohort). There was an increased risk for soft-tissue sarcoma among Danish workers employed in the manufacture of phenoxyacetic acid herbicides, principally MCPA (Lynge, 1985), but there was an insignificant increase in risk for soft-tissue sarcoma among workers exposed to multiple phenoxyacetic acid herbicides and chlorophenol (Saracci et al., 1991). A slight increase in the risk for non-Hodgkin's lymphoma was seen among British cohorts exposed to 2,4-D, MCPA, 2,4,5-T, and other phenoxyacetic acids in a manufacturing plant (Coggon et al., 1991). The specific findings are described below.

Lynge (1985) examined cancer incidence among Danish chemical workers involved in the manufacture of phenoxyacetic acid herbicides in two plants, with 3844 workers in one and 615 in the other. The phenoxyacetic acid herbicides manufactured in these two plants were 2,4-D, dichlorprop, and 2,4,5-T. Cancer cases were identified by linkage with the Danish National Cancer Registry, and the expected numbers of cancer cases were calculated from the incidence rates in the general Danish population. An excess of soft-tissue sarcoma was found, with five cases among male workers and 1.8 expected (relative risk [RR], 2.7; 95% CI, 0.88-6.3); no cases occurred in female workers (0.75 expected). When the latency exceeded 10 years, four cases of soft-tissue sarcoma were observed, with 1.1 expected (RR, 3.7; 95% CI, 1.0-9.4). It should be noted that the chemical plants in which the workers were employed manufactured diverse products, and three of the four patients with soft-tissue sarcoma had been employed for three months or less; only one had been assigned to chlorophenoxyacetic acid operations (0.26 expected). Malignant lymphomas occurred in seven men, with 5.3 cases expected (RR, 1.3; 95% CI, 0.52-2.7), and in one woman, with 1.2 expected (RR, 0.83). None of the seven cases of malignant lymphoma occurred in the department producing phenoxyacetic acid herbicides. The author did not estimate the RR specifically for exposure to 2,4-D.

Wiklund and Holm (1986) and Wiklund et al. (1988) studied 354 620 male Swedish agricultural or forestry workers, dividing the cohort into six subcohorts with different presumed exposure to phenoxyacetic acid herbicides. These workers were compared with a reference population of 1 725 845 workers who were not involved in agriculture or forestry. The study did not show a significant excess risk for soft-tissue sarcoma or non-Hodgkin's lymphoma in agricultural or forestry workers in comparison with other groups. Between 1961 and 1979, 331 cases of soft-tissue sarcoma were observed in the study cohort and 1508 in the reference group (RR, 0.9; 95% CI, 0.8-1.0). Non-Hodgkin's lymphoma occurred in 861 men in the study cohort. The RR was not significantly increased in any subcohort, did not differ significantly between the subcohorts, and showed no time-related increase in the total cohort or any subcohort.

Bond et al. (1988) investigated the mortality of 878 workers potentially exposed to 2,4-D and its derivatives during their manufacture, formulation, or packaging between 1945 and 1983. Exposure was estimated by establishing an 8-h time-weighted average for each task, and the workers were categorized into three exposure groups: < 0.5, 0.5-4.9, and > 5.0 mg/m3 per year. Special attention was given to deaths from brain neoplasms because of the brain astrocytomas seen in male rats fed 2,4-D in the diet; however, none of the 111 deaths in the cohort was due to a brain neoplasm. There were two deaths from non-Hodgkin's lymphoma (one with generalized lymphosarcoma and the other with reticulum-cell sarcoma) among a subset of workers with potential additional exposure to dioxins (two observed; 0.5 expected; RR, 3.9; 95% CI, 0.4-14). The authors concluded that the results did not support a cause-effect relationship between exposure to 2,4-D and mortality from all causes or from any specific cancer. Bloemen et al. (1993) reported the results of four years of additional follow-up, through 1986, for the cohort studied by Bond et al. No new deaths from non-Hodgkin's lymphoma were observed.

Wigle et al. (1990) studied the mortality of almost 70 000 male farmers in Saskatchewan, Canada, identified in the 1971 Census of Agriculture. No excess mortality was seen for any cause of death, including non-Hodgkin's lymphoma, but a correlation was found between non-Hodgkin's lymphoma and area sprayed with herbicides. Among farmers with < 1000 acres (approx. 400 ha), the RR rose with the area sprayed with herbicides: < 100 acres (approx. 40 ha), RR, 1.3 (95% CI, 0.7-2.4); 100-249 acres (approx. 40-100 ha), RR, 1.9 (95% CI, 1.2-3.3), and > 250 acres (approx. 100 ha), RR, 2.2 (95% CI, 1.0-4.6). The authors reported that the cholorophenoxy compound in general use in the area was 2,4-D (90% by weight throughout the 1960s and 75% in the 1970s), but the exposure was not directly related to cases of the disease.

Coggon et al. (1991) examined cancer mortality and incidence at four factories in England that produced phenoxyacetic acid herbicides.

The four cohorts comprised 2239 men employed during 1964-85 who were exposed not only to 2,4-D, but also to MCPA, 2,4,5-T, and other phenoxyacetic acid herbicides. The subjects were traced through the National Health Service Central Registrar and the National Insurance Index, and their mortality was compared with that in the national population. No cases of soft-tissue sarcoma or Hodgkin's disease were identified, but there were two deaths from non-Hodgkin's lymphoma with 0.87 expected (RR, 2.3; 95% CI, 0.3-8.3), both of which occurred > 10 years after first exposure to phenoxyacetic acid compounds.

Green (1991) studied the mortality of forestry workers who had been employed for six months or more in forestry work at a Canadian public utility during the period of 1950-82. The cohort consisted of 1222 men exposed to 2,4-D and other phenoxyacetic acid herbicides. No overall excess mortality due to soft-tissue sarcoma or non-Hodgkin's lymphoma was seen. The only statistically significant finding was for suicide, with 11 cases observed and 5.2 expected.

Saracci et al. (1991) surveyed a population of 16 863 male and 1527 female production workers or sprayers in 10 countries, identified through the International Registry of Workers Exposed to Phenoxy Herbicides and their Contaminants, established by the International Agency for Research on Cancer and the US National Institute of Environmental Health Sciences. The cohorts of Lynge (1985), Coggon et al. (1991), and Green (1991), described above, were included. The workers were thus exposed to 2,4-D, dichlorprop, 2,4,5-T, MCPA, other phenoxyacetic acids, and a number of chlorinated phenols. There was no overall increase in mortality from any cause. Four deaths due to soft-tissue sarcoma were seen, with 2.0 expected (RR, 2.0; 95% CI, 0.53-5.0); three occurred in sprayers (RR, 8.8; 95% CI, 1.8-26), all occurred 10-19 years after first exposure, and two of the cases arose after exposure of less than one year. Since the workers were exposed to a number of chlorophenoxyacetic acid herbicides and chlorinated phenols, it could not be determined which, if any, of these chemicals was responsible for the reported increase in risk for soft-tissue sarcoma.

Riihimaki et al. (1983) studied 1926 Finnish farm workers who had been exposed to phenoxyacetic acid herbicides for at least two weeks between 1951 and 1971. There was no excess cancer risk, and no cases of soft-tissue sarcoma or non-Hodgkin's lymphoma were observed.

Wiklund et al. (1987) studied cases of non-Hodgkin's lymphoma and Hodgkin's disease among 20 245 Swedish pesticide applicators, 72% of whom were estimated to have been exposed to phenoxyacetic acid herbicides. The most commonly used pesticide was MCPA, but 2,4-D was also used. Lymphomas did not occur in excess: 11 cases of Hodgkin's disease (RR, 1.2; 95% CI, 0.6-2.2) and 21 cases of non-Hodgkin's lymphoma (RR, 1.0; 95% CI, 0.63-1.5) were observed, with 9.1 and 21 expected, respectively.

Asp et al. (1994) conducted an 18-year follow-up for cancer

mortality and morbidity in a cohort of 1909 men who had sprayed chlorophenoxyacetic acid herbicides (a mixture of 2,4-D and 2,4,5-T) in 1955-71. Overall mortality from cancer was slightly less than that in the general population (SMR, 0.83; 95% CI, 0.65-1.0), and none of the deaths was due to soft-tissue sarcoma or non-Hodgkin's lymphoma. One case of non-Hodgkin's lymphoma was found, with 2.8 expected; no cases of soft-tissue sarcoma were seen.

(c) Overall assessments of epidemiological studies

Over the past eight years, a number of scientific panels, convened under the auspices of various groups, have evaluated the epidemiological studies that addressed the possible association between use of phenoxyacetic acid herbicides, 2,4-D in particular, and the occurrence of soft-tissue sarcoma, non-Hodgkin's lymphoma, and Hodgkin's disease. Their conclusions are summarized below.

A working group convened by the International Agency for Research on Cancer (IARC, 1987) concluded that there was limited evidence that chlorophenoxy herbicides are carcinogenic to humans. 2,4-D could not be clearly distinguished from other chlorophenoxy herbicides, some of which contain dioxins.

The Ontario Pesticide Advisory Committee of the Ontario Ministry of the Environment (Anders et al., 1987), using IARC terminology, concluded that '...there is limited evidence of carcinogenicity in man from exposure to phenoxyacetic acid herbicides. In terms of exposure to 2,4-D specifically, the evidence must still be regarded as inadequate to classify it as a carcinogen.'

A panel at the Harvard School of Public Health (1990; Ibrahim et al., 1991) concluded: 'Although a cause-effect relationship is far from being established, the epidemiological evidence for an association between exposure to 2,4-D and non-Hodgkin's lymphoma is suggestive and requires further investigation. There is little evidence of an association between use of 2,4-D and soft-tissue sarcoma or Hodgkin's disease, and no evidence of an association between 2,4-D use and any other form of cancer.'

Munro et al. (1992) concluded: 'The case-control epidemiological studies that have been the source of the cancer risk hypothesis are inconclusive. Problems in assessing exposure based on patient's memories make these studies difficult to interpret. Cohort studies of exposed workers do not generally support the specific hypothesis that 2,4-D causes cancer. Taken together, the epidemiological studies provide, at best, only weak evidence of an association between 2,4-D and the risk of cancer.'

The Joint Committee of the Science Advisory Board/Scientific Advisory Panel (US Environmental Protection Agency, 1994) concluded '...that while there is some evidence that non-Hodgkin's lymphoma may occur in excess in populations which are likely to be exposed to

2,4-D, 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. The data are, however, sufficient to require continued examination of the issue through further studies.'

Comments

2,4-D was rapidly absorbed, distributed, and excreted after oral administration to mice, rats, and goats. At least 86-94% of an oral dose was absorbed from the gastrointestinal tract in rats. Once absorbed, 2,4-D was widely distributed throughout the body but did not accumulate because of its rapid clearance from the plasma and rapid urinary excretion. 2,4-D was excreted rapidly and almost exclusively (85-94%) in urine by 48 h after treatment, primarily as unchanged 2,4-D. No metabolites have been reported other than conjugates. Pharmacokinetic studies with salts and esters of 2,4-D have shown that the salts dissociate and esters are rapidly hydrolysed to 2,4-D, after which their fate was indistinguishable from that of the acid. The similarity in the fate of 2,4-D and its salts and esters explains their similar toxicity.

In humans who ingested 2,4-D, it was quickly absorbed and excreted rapidly in the urine; about 73% of the administered dose was found in the urine after 48 h. No metabolites were detected.

After dermal applications of 2,4-D to volunteers, < 5.8% of the dose was absorbed within 120 h. When the acid and its dimethylamine (DMA) salt were applied, about 4.5% of the acid and 1.8% of the salt were absorbed, and, of this, about 85% of the acid and 77% of the salt were recovered in the urine 96 h after application.

2,4-D, its amine salts, and its esters are slightly toxic when administered orally or dermally, the oral LD50 values being 400-2000 mg/kg bw and the dermal LD50 value generally exceeding 2000 mg/kg bw. In rats exposed to 2,4-D at the maximum attainable concentration (up to 5.39 mg/litre) by inhalation for 4 h, no deaths were seen. While 2,4-D and its amine salts and esters do not induce dermal irritation in rabbits or dermal sensitization in guinea-pigs, they cause severe eye irritation in rabbits. WHO has classified 2,4-D as 'moderately hazardous' (WHO, 1996).

In mice fed diets that provided 2,4-D at doses of 0, 5, 15, 45, or 90 mg/kg bw per day for three months, renal lesions were observed in animals of each sex at all doses. An NOAEL was not identified.

In mice fed diets providing 2,4-D at doses of 0, 1, 15, 100, or 300 mg/kg bw per day for 90 days, treatment-related changes were observed in animals of each sex at doses > 100 mg/kg bw per day. These effects included decreases in glucose level in females, decreases in thyroxine activity in males, and increases in absolute and/or relative kidney weights in males. The NOAEL was 15 mg/kg bw per day.

In rats fed diets providing 2,4-D at doses of 0, 1, 5, 15, or 45 mg/kg bw per day for 90 days, renal lesions were observed at doses > 5 mg/kg bw per day. The NOAEL was 1 mg/kg bw per day.

In rats fed diets providing 2,4-D at doses of 0, 1, 15, 100, or 300 mg/kg bw per day for 90 days, treatment-related changes were observed in animals of each sex at doses > 100 mg/kg bw per day. These effects included decreases in body-weight gain, haematological and clinical chemical alterations, changes in organ weights, and histopathological lesions in the adrenals, liver, and kidneys. The NOAEL was 15 mg/kg bw per day.

In six studies of toxicity, rats fed diets containing the diethanolamine (DEA), DMA, isopropylamine (IPA), or triisopropanolamine (TIPA) salts or the butoxyethylhexyl (BEH) or 2-ethylhexyl (EH) esters at acid-equivalent doses of 0, 1, 15, 100, or 300 mg/kg bw per day for 13 weeks, the results demonstrated the comparable toxicity of the acid, salts, and esters. The NOAEL was 15 mg acid-equivalent per kg bw per day for all six compounds.

Dogs were given gelatin capsules containing 2,4-D at 0, 0.03, 1, 3, or 10 mg/kg bw per day or diets containing 2,4-D, the DMA salt, or the EH ester at acid-equivalent doses of 0, 0.5, 1, 3.75, or 7.5 mg/kg bw per day for 13 weeks. Treatment-related findings were observed in the three studies at doses > 3.0 mg/kg bw per day. The NOAEL was 1.0 mg acid-equivalent per kg bw per day in all three studies.

In a two-year study of toxicity and carcinogenicity, mice were fed diets providing 2,4-D at doses of 1, 15, or 45 mg/kg bw per day. Increases in absolute and/or relative kidney weights and renal lesions were observed at 15 and 45 mg/kg bw per day. There was no evidence of carcinogenicity. The NOAEL was 1 mg/kg bw per day.

In another two-year study of toxicity and carcinogenicity, mice were fed diets providing 2,4-D at doses of 0, 5, 62.5, or 125 mg/kg bw per day (males) or 0, 5, 150, or 300 mg/kg bw per day (females). Dose-related increases in absolute and/or relative kidney weights and renal lesions were seen in animals of each sex at doses > 62 mg/kg bw per day. There was no evidence of carcinogenicity. The NOAEL was 5 mg/kg bw per day.

In another two-year study, rats received diets providing 2,4-D at doses of 0, 1, 5, 15, or 45 mg/kg bw per day. Renal lesions were seen in animals of each sex at doses > 5 mg/kg bw per day. There was no evidence of carcinogenicity. The NOAEL was 1 mg/kg bw per day.

In a further two-year study, rats were fed diets providing 2,4-D at doses of 0, 5, 75, or 150 mg/kg bw per day. Treatment-related effects were observed in animals of each sex at doses > 75 mg/kg bw per day. The effects included decreases in body-weight gains and food consumption, increases in serum alanine and aspartate aminotransferase

activities, decreased thyroxine concentrations, increases in absolute and relative thyroid weights, and histopathological lesions in the eyes, kidneys, liver, lungs, and mesenteric fat. There was no evidence of carcinogenicity. The NOAEL was 75 mg/kg bw per day in males and 5 mg/kg bw per day in females.

Dogs were fed diets providing 2,4-D at doses of 0, 1, 5, or 7.5 mg/kg bw per day for 52 weeks. At 5 and 7.5 mg/kg bw per day, body-weight gains were decreased, increases were seen in blood urea nitrogen, creatinine, alanine aminotransferase activity, and cholesterol, and histopathological lesions were seen in the kidneys and liver. The NOAEL was 1 mg/kg bw per day.

In a two-generation study of reproductive toxicity, rats received dietary doses of 2,4-D of 0, 5, 20, or 80 mg/kg bw per day. Reduced body weights of F1 dams and renal lesions in F0 and F1 adults were observed at 20 and 80 mg/kg bw per day. The NOAEL for parental and reproductive toxicity was 5 mg/kg bw per day.

In order to evaluate the dermal toxicity of 2,4-D and its salts and esters, rabbits received 15 dermal applications of the acid, the DEA, DMA, IPA, or TIPA salt, or the BEH or EH ester at acid-equivalent doses of 0, 10, 100, or 1000 mg/kg bw per day for 6 h per day on five days per week for 21 days. No systemic toxicity was seen at any dose, and no dermal toxicity was seen with the acid, the TIPA salt, or the BEH ester. Dermal lesions were observed in rabbits treated with the DEA, DMA, or IPA salt or the EH ester at doses > 100 mg/kg bw per day. The lesions were characterized as acanthosis, hyperkeratosis, oedema, inflammation, and epidermal hyperplasia. The NOAEL was 10 mg acid-equivalent per kg bw per day for dermal toxicity and 1000 mg acid-equivalent per kg bw per day (the highest dose tested) for systemic toxicity.

In a study of developmental toxicity, pregnant Sprague Dawley rats were given 2,4-D in corn oil by gavage at doses of 12.5, 25, 50, 75, or 88 mg/kg bw per day during days 6-15 of gestation. There was no maternal toxicity. Fetotoxicity was manifested as decreased fetal body weights at doses > 50 mg/kg bw per day. The NOAELs were 88 mg/kg bw per day for maternal toxicity and 25 mg/kg bw per day for developmental toxicity.

In a further study, pregnant Fischer 344 rats received 2,4-D in corn oil by gavage at doses of 8, 25, or 75 mg/kg bw per day during days 6-15 of gestation. Decreased body-weight gain of dams at the high dose during the treatment period and increased incidences of skeletal variations (7th cervical and 14th rudimentary ribs and missing sternebrae) were observed at 75 mg/kg bw per day. The NOAEL was 25 mg/kg bw per day for both maternal and developmental toxicity.

The developmental toxicity of the DEA, DMA, IPA, and TIPA salts and the BEH and EH esters was evaluated in pregnant rats after oral administration during days 6-15 of gestation. The acid-equivalent doses tested were 11, 55, or 110 mg/kg bw per day for DEA; 12.5, 50, or 100 mg/kg bw per day for the DMA salt; 9, 25, or 74 mg/kg bw per day for the IPA salt; 12, 37, or 120 mg/kg bw per day for the TIPA salt; 17, 50, or 120 mg/kg bw per day for the BEH ester; and 10, 30, or 90 mg/kg bw per day for the EH ester. The maternal and developmental toxicity of the salts and esters of 2,4-D was comparable to that of the acid. Maternal toxicity, as evidenced by reduced body-weight gain during treatment, was seen in all dams at the high dose of each compound; in addition, mortality, clinical signs, and reduced food consumption were seen in dams given 120 mg/kg bw per day TIPA salt. Although embryo- and fetotoxicity and teratogenicity were observed with the high dose of the TIPA salt, this may be attributed to maternal toxicity; none of the other compounds had such effects. No external gross or visceral anomalies (malformations or variations) were observed in any of the fetuses, but skeletal variations were seen at the high dose of each compound except the IPA salt which were similar to those seen in the fetuses of dams given the acid. The overall NOAELs were approximately 10 mg acid-equivalent per kg bw per day for maternal toxicity and 50 mg acid-equivalent per kg bw per day for developmental toxicity.

In a study of developmental toxicity, pregnant rabbits were given 2,4-D orally at 0, 10, 30, or 90 mg/kg bw per day during days 6-18 of gestation. Maternal toxicity, which included clinical signs, abortions, and reduced body-weight gain during and after the treatment period, was seen only at the high dose. No gross, visceral, or skeletal malformations or variations were seen in fetuses at any dose. The NOAELs were 30 mg/kg bw per day for maternal toxicity and 90 mg/kg bw per day (the highest dose tested) for developmental toxicity.

The developmental toxicity of the DEA, DMA, IPA, and TIPA salts and the BEH and EH esters was evaluated in rabbits after oral administration during days 6-18 of gestation. The acid-equivalent doses tested were 10, 30, or 60 mg/kg bw per day for the DEA salt; 10, 30, or 90 mg/kg bw per day for the DMA salt; 10, 30, or 75 mg/kg bw per day for the IPA salt; and 10, 30, or 75 mg/kg bw per day for the TIPA salt and for the BEH and EH esters. Unlike 2,4-D, which produced maternal toxicity only at the high dose, most of the amine salts and esters were maternally toxic at the middle and high doses, as evidenced by mortality, clinical signs of neurotoxicity, abortions, and decreases in body-weight gain. No gross, visceral, or skeletal malformations or variations were seen in fetuses at any dose. The overall NOAELs were approximately 10 mg acid-equivalent per kg bw per day for maternal toxicity and 90 mg acid-equivalent per kg bw per day (the highest dose tested) for developmental toxicity.

In summary, of the four salts tested for developmental toxicity,

only the TIPA salt had developmental toxicity in rats and only at a maternally toxic dose; no developmental toxicity was seen in rabbits with this or the other salts. Consequently, the Meeting concluded that the developmental toxicity of the TIPA salt is of little concern.

The genotoxic potential of 2,4-D has been adequately evaluated in a range of assays in vivo and in vitro. Overall, the responses observed indicate that 2,4-D is not genotoxic, although conflicting results were obtained for mutation in Drosophila. In a more limited range of assays, the DEA, DMA, IPA, and TIPA salts and the BEH and EH esters were also not genotoxic in vivo or in vitro. The Meeting concluded that 2,4-D and its salts and esters are not genotoxic.

In rats given single doses of 2,4-D at 0, 15, 75, or 250 mg/kg bw by gavage, there were no treatment-related gross or neuropathological changes at any dose. Animals of each sex at the highest dose exhibited incoordination and gait abnormalities on day 1, but the signs had disappeared by day 5. The NOAEL was 75 mg/kg bw. When rats were fed diets containing 2,4-D at doses of 0, 5, 75, or 150 mg/kg bw per day for 12 months, neurotoxicity, manifested as increased relative forelimb grip strength, was seen in animals of each sex at 150 mg/kg bw per day. The NOAEL was 75 mg/kg bw per day.

Epidemiological studies have suggested an association between the development of soft-tissue sarcoma and non-Hodgkin's lymphoma and exposure to chlorophenoxy herbicides, including 2,4-D. The results of these studies are not, however, consistent; the associations found are weak, and conflicting conclusions have been reached by the investigators. Most of the studies did not provide information on exposure specifically to 2,4-D, and the risk was related to the general category of phenoxyacetic acid herbicides, a group that includes 2,4,5-T, which can be contaminated with dioxins. Case-control studies provide little evidence of an association between the use of 2,4-D and soft-tissue sarcomas. Although some case-control studies have shown a relationship with non-Hodgkin's lymphoma, others (even the positive studies) have produced inconsistent results, raising doubt about the causality of the relationship. Cohort studies of exposed workers have not confirmed the hypothesis that 2,4-D causes either neoplasm.

The Meeting was informed of the on-going 'Agricultural Health Study' initiated in North Carolina and Iowa, USA, and of a study of pesticide applicators in Finland. The Agricultural Health Study addresses both cancer and non-cancer risks in men and women directly exposed to pesticides and other agricultural agents, including neurotoxicity, reproductive effects, immunological effects, kidney disease, non-malignant respiratory disease, and the growth and development of their children.

The Meeting concluded that the toxicity of the salts and esters of 2,4-D was comparable to that of the acid. An ADI was therefore established for the sum of 2,4-D and its salts and esters, expressed

as 2,4-D. An ADI of 0-0.01 mg/kg bw was established on the basis of the NOAEL of 1 mg/kg bw per day in the one-year study of toxicity in dogs and the two-year study in rats and using a safety factor of 100.

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