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Environmental Health Criteria 29

2,4-DICHLOROPHENOXYACETIC ACID (2,4-D)

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NOTE TO READERS OF THE CRITERIA DOCUMENTS

While every effort has been made to present information in the criteria documents as accurately as possible without unduly delaying their publication, mistakes might have occurred and are likely to occur in the future. In the interest of all users of the environmental health criteria documents, readers are kindly requested to communicate any errors found to the Manager of the International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland, in order that they may be included in corrigenda, which will appear in subsequent volumes.

In addition, experts in any particular field dealt with in the criteria documents are kindly requested to make available to the WHO Secretariat any important published information that may have inadvertently been omitted and which may change the evaluation of health risks from exposure to the environmental agent under examination, so that the information may be considered in the event of updating and re-evaluation of the conclusions contained in the criteria documents.

IPCS TASK GROUP ON ENVIRONMENTAL HEALTH CRITERIA
FOR 2,4-DICHLORPHENOXYACETIC ACID

Members

- Dr E. Astolfi, Faculty of Medicine of Buenos Aires, Buenos Aires, Argentina (Chairman)
- Dr L.A. Dobrovolski, Kiev Institute of Labour, Hygiene and Occupational Diseases, Kiev, USSR
- Dr B. Gilbert, Centre for Research of Natural Products, University of Rio de Janeiro, Rio de Janeiro, Brazil
- Dr D. Grant, Foods Directorate, Health Protection Branch, Health & Welfare Canada, Ottawa, Ontario, Canada
- Dr O. Hutzinger, University of Amsterdam, Amsterdam, The Netherlands
- Dr R.N. Khanna, Industrial Toxicology Research Centre, Lucknow (UP) India
- Dr R.D. Kimbrough, Center for Environmental Health, Center for Disease Control, Department of Health and Human Services, Public Health Service, Atlanta, Georgia, USA.
- Dr D.G. Lindsay, Ministry of Agriculture, Fisheries & Food, London, England, (Rapporteur)
- Dr P.J. Madati, Ministry of Health, Dar-es-Salam, Tanzania

Representatives of Other Organizations

- Dr M.L. Leng, International Group of National Associations of Manufacturers of Agrochemical Products, c/o Dow Chemical Company, Midland, Michigan, USA.
- Dr T.F. McCarthy, Permanent Commission and International Association on Occupational Health

Secretariat

- Dr D. Riedel, Environmental Health Directorate, Health & Welfare Canada, Environmental Health Centre, Ottawa, Canada, (Temporary Advisor)
- Dr F. Valić, World Health Organization, Geneva, Switzerland, (Secretary)
- Mr J.D. Wilbourn, International Agency for Research on Cancer, Lyons, France

Observers

- Dr H. Spencer, US Environmental Protection Agency, Washington, DC, USA

ENVIRONMENTAL HEALTH CRITERIA FOR 2,4 DICHLOROPHENOXYACETIC ACID (2,4-D)

Further to the recommendations of the Stockholm United Nations Conference on the Human Environment in 1972, and in response to a number of World Health Assembly resolutions (WHA23.60, WHA24.47, WHA25.58, WHA26.68) and the recommendation of the Governing Council of the United Nations Environment Programme, (UNEP/GC/10, July 3 1973), a programme on the integrated assessment of the health effects of environmental pollution was initiated in 1973. The programme, known as the WHO Environmental Health Criteria Programme, has been implemented with the support of the Environment Fund of the United Nations Environment Programme. In 1980, the Environmental Health Criteria Programme was incorporated into the International Programme on Chemical Safety (IPCS). The result of the Environmental Health Criteria Programme is a series of criteria documents.

The Environmental Health Directorate, Health Protection Branch, Department of National Health and Welfare, Canada (Director-General Dr E. Somers) was responsible, as a Lead Institution of the IPCS, for the preparation of the first and second drafts of the Environmental Health Criteria Document on 2,4-D. Dr D. Riedel co-ordinated the work.

The Task Group for the Environmental Health Criteria for 2,4-D met in Ottawa from 4 to 11 July, 1983. The meeting was opened by Dr E. Somers. Dr A.B. Morrison, Assistant Deputy Minister, Department of National Health and Welfare, Canada welcomed the participants on behalf of the host government and Dr F. Valic, on behalf of the 3 co-sponsoring organizations of the IPCS (UNEP/ILO/WHO). The Task Group reviewed and revised the second draft criteria document and made an evaluation of the health risks of exposure to 2,4-D.

The efforts of all who helped in the preparation and the finalization of the document are gratefully acknowledged.

* * *

Partial financial support for the publication of this criteria document was kindly provided by the United States Department of Health and Human Services, through a contract from the National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina, USA - a WHO Collaborating Centre for Environmental Health Effects.

1. SUMMARY AND RECOMMENDATIONS FOR FURTHER STUDIES

1.1 Summary

1.1.1 Analytical methods

1.1.1.1 2,4-D, 2,4-D alkali metal salts or 2,4-D amine salts, and 2,4-D esters

The available analytical results concerning 2,4-dichlorophenoxyacetic acid (2,4-D) and its derivatives in herbicides and biological and environmental matrices were collected over a span of almost 40 years, by diverse and, until fairly recently, not sufficiently specific or sensitive methods. This makes comparison of most of the data reported in the literature difficult.

1.1.1.2 Contaminants in 2,4-D herbicides

Adequately specific and sensitive methods for the reliable identification of such potentially hazardous contaminants as the di-, tri-, and tetrachlorodibenzo-p-dioxin isomers and N-nitrosamines have only recently been developed. Available analytical data are limited to a few manufactured products.

1.1.2 Sources of environmental pollution

Most of the 2,4-D residues result from the production and use of 2,4-D herbicides. Other possible minor sources of 2,4-D include the use of 2,4-dichlorophenoxybutyric acid (2,4-DB).

Little information is available on the uses of 2,4-D products and the amounts used in various parts of the world.

The drifting of vapours of the more volatile short-chain 2,4-D esters may result in air pollution and crop damage, and these products are being replaced by less volatile long-chain esters or by amine salts.

The use of 2,4-D for aquatic weed control may lead to contamination of sources of irrigation and drinking-water. Environmental pollution also arises through inadequate disposal practice.

1.1.3 Environmental distribution and transformations

Various amounts of 2,4-D products applied to a target area may be distributed in the general environment, within a few hours or days, by the movements of air, water, or soil,

particularly during periods of rain, high winds, or high temperature.

2,4-D and its derivatives are fairly rapidly broken down by hydrolysis, photolysis, and by biological action.

Persistence or accumulation of 2,4-D residues from normal use is occasionally possible, mainly under dry or cold conditions where there is little biological activity.

Nothing is known about the environmental fate of the impurities present in 2,4-D herbicides.

1.1.4 Environmental exposure levels

Available data indicate that residues of 2,4-D rarely exceed 1 mg/kg in soil, several µg/litre in water, several µg/m³ in air, and a few tens of µg/kg in food sources. Exceptions may occur in the vicinity of 2,4-D herbicide spills, in water treated with aquatic 2,4-D herbicides, in berries and mushrooms grown in treated right-of-way areas, or when the herbicide is used in quantities far in excess of the rates applied in normal agricultural or forestry practice. No information is available on the corresponding exposure levels for the contaminants present in 2,4-D herbicides.

Exposure to 2,4-D, in the work environment, of persons producing, handling, or using herbicides may result in absorption of detectable amounts of 2,4-D.

1.1.5 Uptake and fate of 2,4-D in the body

2,4-D and its derivatives can be absorbed via the oral, dermal, and inhalation routes. General population exposure is mainly by the oral route, but under occupational and bystander exposure conditions, the dermal route is by far the most important.

Distribution of 2,4-D occurs throughout the body, but there is no evidence that it is accumulated. Transformation in mammals appears to occur only to a slight extent and mainly involves the production of 2,4-D conjugates with sugars or amino acids. A single dose is excreted within a few days, mainly with the urine, and to a much lesser extent in the bile and faeces.

Little is known about the uptake and subsequent fate of the contaminants of 2,4-D other than 2,4-dichlorophenol.

1.1.6 Effects on animals

1.1.6.1 Acute toxic effects

Death may result in mammals and birds administered oral doses of 2,4-D exceeding approximately 100-300 mg/kg body weight.

The most characteristic signs of severe 2,4-D poisoning are those of myotonia, but various other physiological, haematological, biochemical, and histological changes have been described.

The no-observed-adverse-effect level for a single dose of 2,4-D in animals has not been clearly established for all species.

No adequately documented reports of acute accidental 2,4-D poisoning of mammals or birds have been found.

1.1.6.2 Chronic toxic effects

The no-observed-adverse-effect level for some of the chronic adverse effects of 2,4-D in mammals has not been established firmly.

1.1.6.3 Teratogenic and reproductive effects

The no-observed-adverse-effect level for the teratogenic, embryotoxic, or fetotoxic effects of 2,4-D in mammals and birds appears to be about 10 mg/kg body weight per day.

1.1.6.4 Mutagenic effects

Studies available at present are not adequate for the quantitative evaluation of the mutagenic effects of 2,4-D and its derivatives in short-term tests. However, the evidence does not suggest that 2,4-D derivatives are potent mutagens.

1.1.6.5 Carcinogenic effects

The carcinogenic potential of 2,4-D and its derivatives such as the amine salts and esters has not been adequately tested. The reports on animal bioassays carried out so far are either too brief for proper evaluation, or have become the subject of scientific controversy.

1.1.7 Effects on human beings

1.1.7.1 Acute toxic effects

2,4-D drug trials and studies on volunteers have shown that doses of between 5 and about 30 mg/kg body weight do not cause any acute toxic effects.

Accidental and intentional 2,4-D poisonings indicate that the toxic effects of 2,4-D are the same in human beings as in other mammals. The lethal single oral dose is uncertain.

1.1.7.2 Chronic toxic effects

It is uncertain whether the chronic toxic effects of 2,4-D products reported in occupationally-exposed people are solely attributable to 2,4-D.

1.1.7.3 Teratogenic and reproductive effects

Scientifically valid studies have not shown any adverse reproductive effects in human beings accidentally or occupationally exposed to 2,4-D.

1.1.7.4 Mutagenic effects

The results of studies suggesting that occupational exposure to 2,4-D may result in chromosome abnormalities are equivocal.

1.1.7.5 Carcinogenic effects

The results of some epidemiological studies have suggested an association between exposure to phenoxy herbicides and increased incidences of malignant tumours and tumour mortality. It is not clear, at present, whether this represents a true association, and if so, whether it is specifically related to 2,4-D.

1.2 Recommendations for Further Studies

1.2.1 Analytical methods

Methods not requiring highly sophisticated and expensive equipment are available for the accurate, specific, and sensitive determination of 2,4-D residues in a wide variety of environmental and biological materials. However, it would be desirable to develop simpler but specific methods for the detection and quantification of dioxin contaminants.

1.2.2 Environmental exposure levels

Further studies should be undertaken to determine the total 2,4-D intake of various sub-populations in areas of 2,4-D use.

It would be desirable to monitor 2,4-D residues in aquatic organisms taken from lakes or rivers receiving discharges or treatment with 2,4-D.

Further work on the relationship between the factors influencing the dermal absorption of various 2,4-D formulated products in human beings and animals should be carried out.

1.2.3 Studies on animals

More animal studies are desirable to investigate the possible interactions between 2,4-D and other herbicides commonly used in conjunction with 2,4-D.

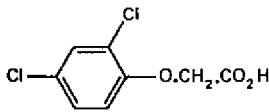
Further work is required to accurately define the no-observed-adverse-effect level for 2,4-D in long-term exposures.

Where unknown, the chronic toxicity of the alcohols and amines used in preparing 2,4-D derivatives, should be investigated.

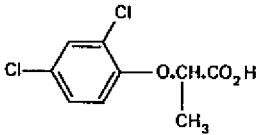
More studies are needed to assess the mutagenic potential of 2,4-D derivatives.

1.2.4 Studies on human beings

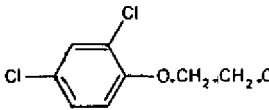
In the case of occupationally-exposed workers further consideration should be given to the chemobiokinetics of 2,4-D under repeated exposure conditions.



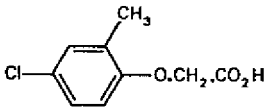
2, 4 - D
2, 4 - dichlorophenoxyacetic acid



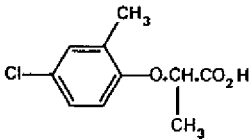
Dichlorprop (2, 4, - DP)
2 - (2, 4 - dichlorophenoxy) propionic acid



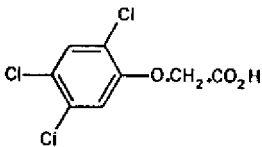
2, 4 - DB
(2, 4 - dichlorophenoxy) butyric acid



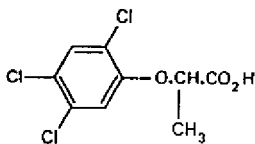
MCPA
4 - chloro - 2 - methylphenoxyacetic acid



Mecoprop (MCP)
 α - (4 - chloro - 2 - methylphenoxy) propionic acid



2, 4, 5 - T
2, 4, 5 - trichlorophenoxyacetic acid



Fenoprop (Silvex, 2, 4, 5 - TP)
2 - (2, 4, 5 - trichlorophenoxy) propionic acid

WHO 83983

Fig. 1. Structures of 2,4-dichlorophenoxyacetic acid (2,4-D) and chemically-related herbicides.

2. PROPERTIES AND ANALYTICAL METHODS

2.1 Physical and chemical properties of 2,4-D

2.1.1 Introduction

The structures of 2,4-dichlorophenoxyacetic acid (2,4-D) and of chemically-related phenoxy herbicides in common use are given in Fig. 1.

Some physical properties of 2,4-D and of the 2,4-D derivatives that are used in agriculture are summarized in Table 1.

2,4-D has growth-regulating and herbicidal properties in broad-leaved plants. Because of its solubility, 2,4-D is rarely used in the form of the acid; commercial 2,4-D herbicide formulations consist of the more soluble forms such as alkali salts, amine salts, or esters. These are combined with solvents, carriers, or surfactants and are marketed in the form of dusts, granules, emulsions, or oil and water solutions in a wide range of concentrations.

Table 1. Physical properties of 2,4-D

Molecular formula:	C ₈ H ₆ Cl ₂ O ₃
Relative molecular mass:	221.0
Melting point:	140-141°C
Solubility in water:	slightly soluble
Solubility in organic solvents	soluble
Vapour pressure	52.3 Pa at 160°C
pKa at 25 °C:	2.64-3.31

2.1.2 Synthesis of 2,4-D

2,4-D is commonly prepared by the condensation of 2,4-dichlorophenol with monochloroacetic acid in a strongly alkaline medium at moderate temperatures (Canada, NRC, 1978; Sittig 1980; Que Hee & Sutherland, 1981), or by the chlorination of phenoxyacetic acid, but this method leads to a product with a high content of 2,4-dichlorophenol and other impurities (Melnikov, 1971). Higher reaction temperatures and alkaline conditions during the manufacture of 2,4-D increase

the formation of polychlorinated dibenzo-p-dioxin (CDD) byproducts (Fig. 2). The alkali metal salts of 2,4-D are produced by the reaction of 2,4-D with the appropriate metal base. Amine salts are obtained by reacting stoichiometric quantities of amine and 2,4-D in a compatible solvent (Que Hee & Sutherland, 1974, 1981). Esters are formed by acid-catalysed esterification with azeotropic distillation of water (Que Hee & Sutherland, 1981) or by a direct synthesis in which the appropriate ester of monochloroacetic acid is reacted with dichlorophenol to form the 2,4-D ester (Canada, NRC, 1978).

2.1.3 Important chemical reactions of 2,4-D

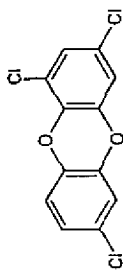
Pyrolysis converts various amine salts of 2,4-D to the corresponding amides (Que Hee & Sutherland, 1975). Pyrolysis of 2,4-D and its derivatives is likely to produce certain CDD isomers (section 2.1.4). 2,4-D is readily photodegraded (section 4.4.4).

2.1.4 Composition of technical 2,4-D materials

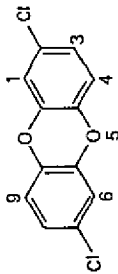
Technical 2,4-D may range in purity from less than 90% to 99%. Typical levels for impurities are listed in Table 2. Trace levels of CDDs have been found in amine and ester formulations (Table 3). It can be seen that the amine formulations tend to be less highly contaminated with di- and tetra-CDD than the ester products. The structures of these impurities are shown in Fig. 2.

The composition of technical 2,4-D depends on the manufacturing process and especially on the purity of 2,4-dichlorophenol when this is the starting material. During 2,4-D synthesis from monochloroacetic acid and 2,4-dichlorophenol, the latter compound as well as other ortho-chlorinated by-products can give rise to a wide variety of chlorinated by-products at a high temperature and high pH. Self condensation of 2,4-dichlorophenol may form 2,7-dichlorodibenzo-p-dioxin, while trichlorophenols may give rise to a mixture of 1,3,6,8- and 1,3,7,9-tetrachloro dibenzo-p-dioxins (but not 2,3,7,8-TCDD) by self-condensation, or to 1,3,7-trichlorodibenzo-p-dioxin by cross-condensation with 2,4-dichlorophenol.

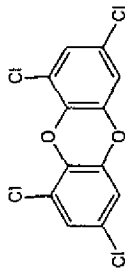
A different type of toxic trace impurity, namely N-nitrosamines, can occur in amine formulations of 2,4-D, especially when nitrite is added as a corrosion inhibitor for containers. Dimethyl-N-nitrosamine has been found in some 2,4-D dimethylamine products at levels of up to 0.3 mg/litre (Ross et al., 1977; Cohen, et al., 1978).



1, 3, 7 - trichlorodibenzo-p-dioxin

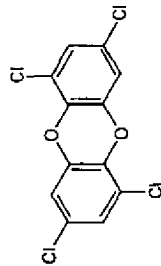


2, 7 - dichlorodibenzo-p-dioxin



1, 3, 7, 9 - tetrachlorodibenzo-p-dioxin

WHO 1982



1, 3, 6, 8 - tetrachlorodibenzo-p-dioxin

Fig. 2. Polychlorinated dibenzo-p-dioxin (CDD) byproducts.

Table 2. Typical levels of 2,4-D and major impurities in technical 2,4-D^a

Component	% range
2,4-dichlorophenoxyacetic acid	94 - 99
2,6-dichlorophenoxyacetic acid	1.5 - 0.5
2-monochlorophenoxyacetic acid	0.5 - 0.1
4-monochlorophenoxyacetic acid	0.8 - 0.2
bis(2,4-dichlorophenoxy) acetic acid	2.0 - 0.1
phenoxyacetic acid	trace - 0.2
2,4-dichlorophenol	0.6 - 0.1
2,6-dichlorophenol	0.048 - 0.001
2,4,6-trichlorophenol	0.14 - 0.001
2-chlorophenol	0.04 - 0.0004
4-chlorophenol	0.005 - 0.0004
water	0.8 - 0.1

^a From: Cochrane (1982).

Table 3. Ranges of levels of chlorinated dibenzo-p-dioxins (CDD) in 2,4-D amine and ester formulations ^a

Type of formulation	CDD isomers found ($\mu\text{g}/\text{kg}$) ^b			
	2,7-di-	1,3,7-tri-	1,3,6,8/ 1,3,7,9-tetra	2,3,7,8-tetra
2,4-D amines	nd ^c - 409	nd - 587	nd - 278	nd
2,4-D esters	nd - 23815	nd - 450	nd - 8730	nd

^a From: Cochrane et al. (1981).

^b Expressed in terms of 2,4-D.

^c nd (not detected < 1 $\mu\text{g}/\text{kg}$).

2.1.5 Volatility of 2,4-D derivatives

2,4-D esters with short-chain alcohols are highly volatile (Table 1). This influences the effectiveness of their application to target crops, their effects on neighbouring crops, and the degree of contamination of the atmosphere. 2,4-D alkali salts or amine salts are much less volatile than

esters (Carter, 1960; Canada, NRC, 1978; Que Hee & Sutherland, 1981, and section 4.1), and these products are to be preferred when the use of 2,4-D esters might lead to evaporative 2,4-D losses and to crop damage.

2.2 Determination of 2,4-D

2.2.1 General comments

General comments on criteria for acceptable analytical methods and on other pertinent aspects of 2,4-D determination can be found in the publications of Gunther (1962), Currie (1968), Kaiser (1973), Carl (1979), Kateman & Pijper (1981), Que Hee & Sutherland (1981) and Chau et al. (1982).

2.2.2 Analysis of technical and formulated 2,4-D products

In the past, the quality of 2,4-D products was assessed by an acid-base titration or by a total chlorine determination (Collaborative International Pesticides Analytical Council, 1970). These non-specific and thus inaccurate methods have been superseded by specific gas-liquid chromatography (GLC) or high pressure liquid chromatography (HPLC), making it possible to determine various by-products (Henshaw et al., 1975; Bontoyan, 1977; Skelly et al., 1977; Stevens et al., 1978; Cochrane et al., 1982). The isomer-specific HPLC method is now preferred by many 2,4-D producers and regulatory agencies. The chlorinated dibenzo-p-dioxins (CDDs) are usually produced only in trace amounts and are difficult to separate and identify; highly specialised equipment and skills are necessary (Crummett & Stehl, 1973; Huckins et al., 1978; Norström et al., 1979; Baker et al., 1981; Cochrane et al., 1981; Hass et al., 1981, and National Research Council of Canada Associate Committee on Scientific Criteria for Environmental Quality, 1981).

2.2.3 Determination of 2,4-D residues

All exposure determinations and risk assessments ultimately depend on accurate chemical analyses, and therefore some critical aspects of analysis for 2,4-D residues have been included in the present document.

Before 2,4-D residues can be measured, they have to be quantitatively extracted and purified to remove substances that could interfere with the final residue determination. They must then be converted to a stable product (derivative) suitable for determination with a given type of detector.

When comparing analytical results, it should be kept in mind that the older methods of extraction and clean-up

contained considerable sources of errors, and that the early methods for measuring 2,4-D residues, such as colorimetry and spectrophotometry, were not as sensitive or specific as those developed in recent years.

2.2.3.1 Sampling, extraction, and clean-up

Methods for the sampling, extraction, and clean-up of 2,4-D residues in water, air, soil, and biological materials have recently been reviewed by National Research Council of Canada, Associate Committee on Scientific Criteria for Environmental Quality (1978) and by Que Hee & Sutherland (1981). Problems caused by the conjugate formation of 2,4-D with amino acids, proteins, sugars, or lipids, or the adsorption of 2,4-D onto container surfaces, including those of glass vessels, have been solved by Chow et al. (1971), Renberg (1974), Osadchuk et al. (1977), Løkke (1975), Jensen & Glas (1981), and Bristol et al. (1982). For sampling and extracting 2,4-D residues, the following references should also be consulted:

Air: Van Dyk & Visweswariah (1975), Farwell et al. (1976a,b), Grover et al. (1976), Johnson et al. (1977), Gluck & Melcher (1980), and Grover & Kerr (1981); water: Suffet (1973a,b), Renberg (1974), Mierzwa & Witek (1977), Chau & Thomson (1978); soil: Woodham et al. (1971); Smith (1972, 1976a), Foster & McKercher (1973); food: Que Hee & Sutherland (1981), Bjerke et al. (1972), Jensen & Glas (1981), Lokke (1975); biological media: Smith (1976b), (blood, urine); Senczuk & Pogorzelska (1981).

2.2.4 Derivatization and quantification

At present, gas-liquid chromatography with electron-capture detection (GLC-EC) is the most commonly used and generally most sensitive method (picogram level) for measuring 2,4-D residues.

To improve the sensitivity of detection, the 2,4-D has to be transformed (derivatized), usually to a methyl ester by reacting with BF_3 -methanol, diazomethane, or with concentrated sulfuric acid-methanol; the first method may give the best results (Munro, 1972; Horner et al., 1974; Olson et al., 1978).

For a recent review of derivatization methods and GLC columns for various substrates see Cochrane (1981).

Thin-layer chromatography (TLC) has been used for herbicide residue determination (Guardigli et al., 1971, Yip 1975). It has recently been recommended by Batora et al. (1981) as a simplified method for determining pesticide residues that requires a minimum of costly equipment. TLC is

suitable for food inspection and could be of use in the establishment of new residue laboratories in developing countries.

High-pressure liquid chromatography (HPLC) is less sensitive than GLC-EC i.e., nanogram (ng) versus picogram levels, but may be advantageous under some circumstances (Tuinstra et al., 1976; Arjmand et al., 1978; Connick & Simoneaux, 1982). Using mass fragmentography with deuterated internal standards it is possible to determine nanogram amounts of 2,4-D and related compounds in urine and plasma (De Beer et al., 1981); it is also suitable for chemobiokinetic studies on subtoxic doses of 2,4-D in blood.

2.2.5 Confirmation

The ultimate confirmatory technique is gas chromatography coupled with mass spectrometry and specific ion monitoring, with a sensitivity down to the femtogram level (Farwell et al., 1976a).

3. SOURCES OF ENVIRONMENTAL POLLUTION

3.1 Production of 2,4-D Herbicides

Comprehensive statistics on 2,4-D herbicide production or use were not available for review. According to the US Department of Agriculture, 3×10^8 kg of total herbicides were used in the USA alone, in 1981. In the past, 10% of the herbicide used was 2,4-D, which would account for a total use in the USA of about 3×10^7 kg. In 1975, an estimated 5×10^6 kg were produced in the United Kingdom. World-wide use of herbicides and annual production, which probably exceeds 5×10^7 kg per year, are increasing (National Research Council of Canada, Associate Committee on Scientific Criteria for Environmental Quality, 1978; Bovey & Young, 1980).

3.2 Uses

2,4-D alkali or amine salts or esters are used as agricultural herbicides against broad-leaf weeds in cereal crops as well as on pastures and lawns, in parks, and on golf courses at rates of about 0.2-2.0 kg active ingredient (acid equivalent) per hectare. Esters are also used at rates of up to 6 kg (acid equivalent) per ha to suppress weeds, brush, and deciduous trees along rights-of-way and in conifer plantations and conifer reforestation areas.

Granular formulations of 2,4-D are used as aquatic herbicides in or along irrigation and other canals, in ponds, and lakes at rates ranging from 1 to 122 kg/ha (Pal'mova & Galuzova, 1963; Smith & Isom, 1967; National Research Council of Canada, Associate Committee on Scientific Criteria for Environmental Quality, 1978; Bovey & Young, 1980).

2,4-D products can be used at very low application rates as growth regulators by application of aqueous foliar sprays containing 20 - 40 mg 2,4-D/litre on apple trees to reduce premature fruit drop, on potato plants to increase the proportion of medium-size tubers or to intensify the tuber skin colour of the red varieties (Bristol et al., 1982), and in citrus culture to reduce pre-harvest fruit drop and to increase fruit storage life.

The highly volatile ethyl, isopropyl, and butyl esters are being replaced by low-volatile esters or by amine salts to reduce crop damage resulting from 2,4-D vapour drift, and to decrease atmospheric pollution.

During recent years, the use of 2,4-D and 2,4,5-T in parks, forested recreation, and other areas frequently used by the public, has been reduced in some countries, because of

increasing concern about possible toxic effects, especially in relation to CDDs.

The ecological effects of using high rates of 2,4-D and repeated treatments have been reviewed by Bovey & Young (1980).

3.3 Disposal of wastes

3.3.1 Industrial Wastes

Environmental pollution with 2,4-D may occur as a result of the production and disposal of 2,4-D, or of its by-products, and of industrial effluents. Such pollution will be generally localised to the production site and to areas of waste dumping, and it is likely to be more dispersed if disposal or leaching has occurred into water courses. Combustion of 2,4-D and its by-products at low temperatures could lead to the formation of CDDs. A temperature approaching 1000 °C, however, gives almost complete destruction of 2,4-D (Sittig, ed., 1980). The spread of 2,4-D from waste dumps may be reduced by the use of properly enclosed impermeable clay-lined pits, away from water sources.

3.3.2 Agricultural wastes

Disposal of unused 2,4-D and washing of equipment may result in localised land pollution and also pollution of water supplies through direct contamination or leaching from soil.

4. ENVIRONMENTAL TRANSPORT, DISTRIBUTION, AND TRANSFORMATION OF 2,4-D

2,4-D does not persist or accumulate in the environment, as it is readily degraded by physical, chemical, and biological action. It is susceptible to photolysis in air and water, on soil, and on plant surfaces. Thus, the question of environmental distribution is limited to the immediate transfer of 2,4-D between compartments of the environment.

4.1 Drift and Volatilization in the Atmosphere

The atmosphere can be contaminated with 2,4-D during both its manufacture and use. The production of 2,4-D may result in the emission into the air of dichlorophenol, chloroacetic acid, and ammonia (Sittig, ed., 1980), in addition to 2,4-D vapours (Grover et al., 1976).

According to the formulation of 2,4-D used, environmental transfer into the atmosphere will occur by either drift (depending on the particle size of the droplet, the spray technique, and climatic conditions), or by volatilization, or by a combination of both. It is very difficult to calculate the extent to which drift or volatilization occurs, and this is illustrated by the range of 2,4-D concentrations observed in the air after 2,4-D use (Table 4).

The factors affecting the amount of herbicide spray that lands on a target crop and the proportion that is lost by drifting or volatilization have been described (Grover et al., 1972; Grover, 1976; Maybank et al., 1978; Que Hee & Sutherland (1981). Unwanted residues may be deposited on non-target crops (Akesson & Yates, 1961; Yates & Akesson, 1973). The National Research Council of Canada, Associate Committee on Scientific Criteria for Environmental Quality (1978) cited reports of drift damage caused in susceptible crops by phenoxy herbicide applications, particularly in cotton, tobacco, tomatoes, grapes, rapeseed, clover, and a number of horticultural species.

Widespread damage in vineyards and in other crops due to 2,4-D drift from sprayed wheat fields was reported by Robinson & Fox (1978) with two different damage patterns, one localized and the other widespread. The first was characterized by severe localized damage with a very clear gradient of decreasing severity away from the zone, following the drift of spray droplets in the immediate treatment area. The more widespread damage was of greater concern. It was characterized by more or less uniform symptoms and appeared to be attributable to the passage of a large cloud of vapour that may have extended

Table 4. Concentrations of total 2,4-D residues in ambient air

Site location No. of stations, height Regional characteristics	Days when 2,4-D was found		2,4-D residues µg/m ³ air		Predominant type of 2,4-D residue	Reference residue
	present	max.	Sample time	Mean ^a Max.		
	mean	max.	h	h		
Saskatchewan, Canada (1) 150 m (aircraft)	not stated		1 min	1.0 \bar{c}	2.5	butyl ester Elias (1975)
Saskatchewan, Canada (8) 2 m above ground level wheat area	48	36	24 h	0.5 \bar{c}	13.5	butyl ester Grover et al. (1976) ^{a, f}
			24 h	0-6 \bar{d}	-	isooctyl ester amine salt
			24 h	-	-	
California, USA (7-8) near ground level	41 (1973) 73 (1974)		24 h	0.4	0.9	high volatile Farwell et al. (1976)
			24 h	0.1	0.4	low volatile
			24 h	0.1	0.2	non volatile
Washington State, USA (2) near ground level, wheat area	105-106	81	24 h	0.2	2.2	isopropyl ester Adams et al. (1964) ^b
		65	24 h	0.09	2.2	butyl ester
		8	24 h	0.003	3.1	isooctyl ester

Table 4 (contd).

Washington State, USA	99-102	34	39	24 h	0.08	2.0	isopropyl ester droplets	Hamesberger &
(2) near ground level, wheat area		8	15	24 h	0.08	1.3	isopropyl ester vapour	Adams ^b
		18	22	24 h	0.07	1.0	butyl ester droplets	
		3	5	24 h	0.03	1.3	butyl ester vapour	
		1	1	24 h	0.005	0.5	isooctyl ester droplets	
		-	-	24 h	-	-	isooctyl ester vapour	
		4	5	24 h	0.01	0.5	acid, salts, droplets	
		5	5	24 h	0.04	5.1	acid, salts, vapour	

^a Values measured at different sites or at different times have been averaged and reduced to a single significant figure for simplicity.

^b At the time of these studies, GLC methods were less highly developed.

^c Centre of principal range observed.

^d Maximum values recorded in a previous study (Que Hee et al., 1975) were shown to be equivalent to concentrations existing directly over an open pan of formulated butyl ester; the implication was made that accidental laboratory contamination could have occurred.

^e The results of Maybank & Yoshida (1969), Maybank et al. (1978), and Stanley et al. (1971) could not be adapted to this table.

for several km. Both problems could have been avoided by the use of low-volatile preparations and proper application methods.

Volatilization of 2,4-D products in the air during the spraying operation and from the surface of plants and the soil is difficult to distinguish from the drift of spray droplets. Evaporation occurs to a greater extent with the highly volatile ethyl, isopropyl, or butyl esters; very little occurs with amine salt formulations, and it is greatly reduced when 2,4-D is dissolved in corn oil, cottonseed oil, or diesel oil (Marth & Mitchell, 1949). In one experiment, no significant amounts of 2,4-D amine, but 20-40% of the initially deposited 2,4-D butyl ester, and 10-15% of the octyl ester of 2,4-D vapourized within 2 h of spraying (Grover et al., 1972); less volatilization occurs with the higher esters of 2,4-D. For this reason, the use of the more volatile esters has been discontinued in some countries. Studies of 2,4-D aerial drift following ground spray operations have shown that only 3 - 8% of the applied herbicides drift as spray droplets when low volatile preparations are applied as large droplets. However, ultra-low-volume (ULV) applications by aircraft, or the use of highly volatile esters may cause as much as 25 - 30% of the 2,4-D sprayed to drift off the target (Grover et al., 1972; Maas & Kerksen, 1973; Maybank et al., 1978).

4.2 Movement Within and From the Soil

The movement of pesticides within and from the soil can be divided into three categories; diffusion, leaching, and surface movement. Diffusion is a localized process and depends on the concentration gradient of the pesticide in the soil medium, on the soil mineral type, and on the organic matter content, temperature, pH, and other factors. Leaching refers to the movement of pesticides through the soil profile with percolating water. Surface movement refers to wind erosion of dust particles and surface run-off in flowing water.

Examination of the behaviour of 2,4-D in soils (Liu & Cibes-Viade, 1973; Grover & Smith, 1974; Moreale & Van Bladel, 1980) has shown that organic matter, soil pH (surface horizons), and exchangeable aluminium (clay sub-horizons) are the key determinants for the percentage of 2,4-D adsorbed. As the adsorption/desorption process is the basic mechanism influencing herbicide availability, mobility, and degradation in soil, 2,4-D is likely to be more strongly bound in soils with a high content of organic matter than in those with a low content.

4.3 Contamination of Water

Residues of 2,4-D in aqueous systems can result from the deposition of spray drifts, the "washout" of 2,4-D in the vapour or droplet phase from the atmosphere during rainfall, the run-off from treated fields, or following the application of 2,4-D to water for the control of aquatic weeds. Industrial discharges, either from accidental spills or through sewage systems, may also contribute to the contamination of water. The National Research Council of Canada, Associate Committee on Scientific Criteria for Environmental Quality (1978) has tabulated data that demonstrate the influence of environmental factors on the clearance of 2,4-D and its derivatives from water. The principal processes involved are ester and amine hydrolysis, volatilization, microbial degradation, photolysis, and sorption. There is little movement of 2,4-D into drainage water in organic soils, because it is strongly bound to organic materials.

4.4 Environmental Transformation and Degradation Processes

4.4.1 Metabolism in plants

Plants hydrolyse 2,4-D esters to 2,4-D, which is the active herbicide (Morton et al., 1967; Matsunaka, 1972). Further metabolism in plants occurs through three mechanisms, namely, side-chain degradation, hydroxylation of the aromatic ring, and conjugation with plant constituents (Crafts, 1960; Morre & Rogers, 1960; Erickson et al., 1963).

4.4.1.1 Side-chain degradation

Degradation of the side-chain of 2,4-D has been observed in many plants (Loos, 1969), but in only a few species or varieties does it appear to play a major role in herbicide breakdown.

Luckwill & Lloyd Jones (1960a,b) suggested two degradation pathways leading to the formation of 2,4-dichlorophenol.

4.4.1.2 Ring hydroxylation

Thomas et al. (1964a,b), and, more recently, Feung et al. (1971, 1972, 1973b) identified 2,5-dichloro-4-hydroxyphenoxyacetic acid and 2,3-dichloro-4-hydroxyphenoxyacetic acid as major and minor phenolic acid metabolites, respectively. Evidence was found by Fleeker & Stein (1971) indicating hydroxylation resulting in the elimination of the 4-chloro substituent from the aromatic ring, in addition to

migration of the chlorine at the 4-position to an adjacent carbon on the ring. A small amount of 2-chloro-4-hydroxy-phenoxyacetic acid was produced from 2,4-D by wild buckwheat, wild oats, leafy spurge, and yellow foxtail.

4.4.1.3 Conjugation with plant constituents

Studies indicate that resistant crops, i.e., grasses and cereals, form water-soluble conjugates with sugars, whereas sensitive broad-leaved crops (such as beans) form mainly water-insoluble amino acid conjugates (Montgomery et al., 1971; Feung et al., 1971, 1972, 1973b, 1975).

4.4.2 Degradation of 2,4-D in the soil

Deposition of 2,4-D esters on the soil is followed fairly rapidly by hydrolysis. Burcar et al. (1966) observed that the 2,4-D iso-octyl ester disappeared after 2 weeks, though free acid could be detected up to 6 weeks after application. The breakdown of the iso-propyl, *n*-butyl, and iso-octyl esters of 2,4-D on three Canadian prairie soils was studied by Smith (1972) who found that after 24 h no iso-propyl or *n*-butyl esters remained, whereas 20-30% of the iso-octyl ester was still intact. The author concluded that an initial rapid phase of hydrolysis of the 2,4-D esters to the anion in soil was the result of chemical and not microbial action.

Microbial degradation of phenoxy herbicides does occur and has been comprehensively reviewed by Loos (1975), Cripps & Roberts (1978) and The National Research Council of Canada Associate Committee on Scientific Criteria for Environmental Quality (1978). Early studies of the persistence of 2,4-D in soil indicated that warm moist conditions and the presence of organic matter favoured the rapid disappearance of 2,4-D. Sterilization of the soil inhibited breakdown, indicating that the degradation was microbial. In addition, Pemberton (1979) reported the discovery of specific 2,4-D plasmids within some bacterial strains, transmitted from one cell to another, and carrying with them a genetic capability enabling the bacteria to degrade 2,4-D.

Two principal pathways have been proposed for the microbial degradation of 2,4-D in soil. Firstly the side chain may be removed to form 2,4-dichlorophenol, followed by orthohydroxylation of the phenol to produce a catechol (Bollag et al., 1968). The catechol may then be cleaved to yield a muconic acid and further conversion products. The second possible pathway is via a hydroxyphenoxyacetic acid intermediate (Evans et al., 1971).

4.4.3 Degradation in the aquatic ecosystem

A multitude of variables influence the partitioning and removal of phenoxy herbicides within an aquatic ecosystem. Detectable residues have been reported to persist for 4 weeks in some situations and up to 4 months in others (Frank & Comes, 1967; Wojtalik et al., 1971; Schultz & Harman, 1974). Photolysis is an important means of degradation of 2,4-D in natural water and is more rapid than that of 2,4,5-T (Crosby & Wong, 1973). The partition of residues between water and sediment will have an effect on the rate of breakdown, as will temperature and intensity of light. Anaerobic conditions will favour microbial breakdown. The effects of some of these factors have been tabulated by the National Research Council of Canada Associate Committee on Scientific Criteria for Environmental Quality (1978).

4.4.4 Photochemical degradation

Photodecomposition of 2,4-D was studied in detail by Crosby & Tutass (1966) and Boval & Smith (1973) and reviewed recently by Que Hee & Sutherland (1981). It leads to the formation of a variety of products but commonly involves reductive dechlorination of the acid, esters, and salts in aqueous or in organic solutions, with 2,4-dichlorophenol acting as a catalyst for the breakdown of 2,4-D, which may involve rupture of the aromatic ring. Que Hee & Sutherland (1981) studied the vapour and liquid phase photolysis of the n-butyl ester of 2,4-D and observed dechlorination at the second position with simultaneous reduction and re-arrangement to produce a variety of photoproducts. According to Boval & Smith (1973), carbon dioxide is the final oxidation product when aqueous solutions of 2,4-D undergo photodecomposition.

4.5 Bioconcentration

There is no evidence that bioconcentration of 2,4-D occurs through the food chain or in any compartment of the environment. This has been demonstrated by large-scale monitoring for 2,4-D residues in soils, foods, feedstuffs, wildlife, and human beings, and from examinations of the many routes of metabolism and degradation that exist in ecosystems (sections 5.1.3 and 5.1.4).

5. ENVIRONMENTAL LEVELS AND EXPOSURE

5.1 Levels of 2,4-D Residues in the Environment

Most of the available information on 2,4-D levels in the environment has been reviewed in detail (National Research Council of Canada, Associate Committee on Scientific Criteria for Environmental Quality, 1978; Ramel, 1978; Bovey & Young, 1980; Canada, Health & Welfare, 1980; Shearer & Halter, 1980; US EPA, 1980a). In comparing early and recent results, it should be kept in mind that the analytical procedures used before about 1965 were often unreliable and may have resulted in under- or overestimation of the actual levels of 2,4-D derivatives. No information is available on the levels of 2,4-D-related dioxin by-products in the environment.

5.1.1 In air

Some levels of 2,4-D in ambient air are shown in Table 4. These 2,4-D residues consist mainly of esters, particularly the highly volatile butyl esters (Bamesberger & Adams, 1966; Farwell et al., 1976b; Grover et al., 1976). Total 2,4-D residues in the air were found to decrease during periods of rain, suggesting a "washout effect" (Grover et al., 1976). In the majority of cases, the levels reported were those found shortly after spraying.

5.1.1.1 Field exposure

Concentrations of 2,4-D that occurred during and after herbicide use in the air of the work zone of people engaged in herbicide spray operations in various use situations, are given in Table 5. Workers involved in these operations were exposed to 2,4-D levels of up to 0.2 mg/m³ air during the period of actual application.

5.1.1.2 General environmental exposure

In large-scale studies in areas of intense 2,4-D use, about 40% of all air samples were found to contain between 0.01 and 0.1 µg 2,4-D/m³ (Grover et al., 1975). In a similar study undertaken by Que Hee et al. (1975), much higher levels were recorded in one urban location, reaching an average of 339 µg/m³ air during 3 days. However, Grover et al. (1976), in their subsequent work, showed that such concentrations could only be produced under artificial conditions that could not reflect environmental conditions. In a general programme of air monitoring undertaken in

Table 5. Concentrations of total 2,4-D in air related to occupational exposure

Herbicide product	Circumstances	Type of exposure monitoring	Days after spraying	Mean of 2,4-D concentrations in air (mg/m ³)	References
2,4-dimethyl-amine salt (0.9% aqueous solution)	agricultural spray operations with tractor-drawn equipment	Analyses of air in tractor cabs	0	0.02	Thiele et al. (1981a,b)
2,4-D butoxyethanol ester. 2% emulsion in water	Exposure during forest spray operation with tractor driven equipment	Analyses of air in breathing zone of workers	0	0.1-0.2	Kolmodin-Hedman & Erne (1980), Kolmodin-Hedman et al. (1979)
2,4-D isooctyl-ester in diesel oil	3-day aerial spray operation with single engine aircraft	Analyses of air in breathing zone of pilot and ground crew	0	0.002-0.1 ^a	Franklin et al. (1982)
2,4-D PGBE ester emulsion in water	Two 1-day aerial forest spray operation by helicopter	Analyses of air in breathing zone of ground crew	0	<0.00001 ^b	Lavy et al. (1982)

^a Application using large spray droplets.

^b One flagman was recorded as being exposed to 0.1 mg/m³.

citrus-growing regions in the USA, only one out of 880 samples analysed was found to contain 2,4-D, at a level of 0.004 mg/m³. The sites were not chosen in relation to 2,4-D use (Stanley et al., 1971).

5.1.2 In water

2,4-D, as well as chlorophenol residues resulting from the microbial transformation of 2,4-D, may occur in raw and finished supplies of drinking-water (Faust & Aly, 1963; US EPA, 1976, 1980a; National Research Council of Canada, Associate Committee on Scientific Criteria for Environmental Quality, 1978; Bovey & Young, 1980; Canada, Health & Welfare, 1980; Shearer & Halter, 1980).

Information on 2,4-D-related dioxins in water was not available.

Drinking-water in the USA is routinely analysed by the FDA as part of the beverage-food group in their "market basket" analysis programme; 2,4-D has not been detected in these studies, where the limit of detection is 0.005 mg/litre for beverages (Table 6). This indicates that drinking-water is not a significant source of human exposure outside directly sprayed areas.

The same conclusion can be drawn from the results of large-scale surveys of pesticide residues, including 2,4-D in surface waters in areas of 2,4-D use (Table 7).

Levels much higher than those found in these studies have been observed, but only in relation to local spills or direct contamination (Frank et al., 1979; Frank & Sirons, 1980). A very wide fluctuation has been found in water samples following treatment of bodies of water, shores, ditches, or stream banks with herbicides (Averitt, 1967; Frank & Comes, 1967; Bartley & Hatrup, 1970; Frank et al., 1970; Wojtalik et al., 1970; Frank, 1972; Whitney et al., 1973; Schultz & Harman, 1974; Schultz & Whitney, 1974; Paderova, 1975; Province of British Columbia, 1981). Occasional high contamination levels in samples of potable water have been reported following experimental treatments of reservoirs with 2,4-D (Wojtalik et al., 1971). However, the mean levels tended to remain below 2 µg/litre, even in samples of raw or processed water from 2,4-D-treated reservoirs (Smith & Isom, 1967; Wojtalik et al., 1971; Province of British Columbia, 1981). Generally, 2,4-D residues were < 0.1 µg/litre in two large-scale monitoring programmes of surface waters (Frank & Sirons, 1980; Gummer, 1980). This is not unexpected in view of the moderately rapid microbial degradation of 2,4-D in the environment (Robson, 1966; Averitt, 1967; Frank, 1972; Nesbitt & Watson, 1980a,b; Province of British Columbia, 1981).

Table 6. 2,4-D residues reported in market basket samples in the USA

Years	Types of samples analysed	Nature of samples containing residues	% of samples with residues	Residue levels (mg/kg)	References
1965-65	Total diets	sugars and adjuncts ^a	4.2	< 0.02-0.16	Duggan & Corneliussen (1972)
1966-66		leafy vegetables (1) low fats	3.0	< 0.02-0.03	
1967-67		leafy vegetables (2) oil fats (1)	1.7	0.03	
1968-68		dairy produce (1)	0.6	0.02-0.13	
1969-69		fruits (1), sugars (2)	0.3	< 0.2	
1970-70		leafy vegetables (1) dairy produce (1)	0.3	< 0.02	
1970-71	Total diets	leafy vegetables (3)	-	0.01-0.02	Manske & Corneliussen (1974)
1971-72	Total diets	dairy products (1)	-	0.01	Manske & Johnson (1975)
1973-80	Total diets		0	< 0.01	Manske & Johnson (1976) Johnson et al. (1981a,b) Johnson et al. (1979)
1972-73	Potatoes from fields treated with herbicide	raw, boiled or baked	-	< 0.02-0.12	Bristol et al. (1982)

^a No. of positives not specified.

Table 7. Concentrations of 2,4-D residues in surface water samples following application of 2,4-D to agricultural lands^a

Regional Characteristics	No. of samples in which 2,4-D was analysed	2,4-D applied in watershed (kg/ha)	2,4-D residues (µg/litre)		References
			mean ^b	max.	
Ontario, Canada 11 streams	949	0.8	<0.1	3.9 ^c	Frank & Sirons (1980)
Saskatchewan, Canada 3 rivers	15	-	2	21.6	Choi et al. (1976)
Western Canada 15 diverse sites	186	-	0.5 ^d	4.3 ^d	Gummer (1980)

- 1 Studies in which the analytical procedures were not described or were considered unreliable have not been included.
- 2 Values measured at different sites or at different times have been averaged and reduced to a single significant figure for simplicity.
- 3 Reported data are very close to analytical detection limits.
- 4 The maximum value, which raises the average value considerably, occurred in the effluent of an industrial plant.
- 5 Levels of 15.9 and 320 µg/litre were recorded at two sites but were related to spillage or actual spraying at the sampling locality.

2,4-D and especially its transformation product, dichlorophenol, at levels exceeding 20 µg/litre will impart an objectionable odour and taste to contaminated water (Pal'mova & Galuzova, 1963; Faust & Suffet, 1966). This organoleptic effect may reduce the likelihood of highly contaminated water being ingested. It is noteworthy that public water supplies containing "traces" of 2,4-D, and wells contaminated with 2,4-D or other herbicides have been shut down because of objectionable odours or tastes (Gribanov, 1968; Kramer & Schmaland, 1974; Frank et al., 1979).

5.1.3 In soil

Most of the information available at present concerning 2,4-D and other chlorophenoxy herbicide residues in soils has been reviewed by the National Research Council of Canada Associate Committee on Scientific Criteria for Environmental Quality (1978), Bovey (1980a), and by Que Hee & Sutherland (1981). In highly acidic soils, or in soils in cold or arid regions, 2,4-D degradation is apparently slow (Lavy et al., 1973; Buslovich & Milchina, 1976; Ou et al., 1978; Moreale & Van Bladel, 1980; Nesbitt & Watson, 1980b). However, even at about 20 - 2000 times the normal agricultural application rates, little or no detectable 2,4-D was left in soils under temperate climatic conditions with prolonged winters, after intervals of 385-440 days (Young et al., 1974; Stewart & Gaul, 1977; Bovey, 1980a). Furthermore, results of a laboratory study on 2,4-D degradation in the soil showed a half-life of 4 days (Altom & Stritzke, 1973). Several soil monitoring studies in North America, in areas with regular 2,4-D use, have shown residues in less than 10% of the samples, and at levels of less than 1 mg/kg (Stevens et al., 1970; Wiersma et al., 1972; Gowen et al., 1976).

The available data are inadequate for establishing regional and seasonal profiles of 2,4-D soil residues and of direct population exposure, but it is likely that direct exposure would be minor, except during or soon after herbicide application. Indirect exposure through the transfer of 2,4-D residues from soil to air, or food sources is assessed separately.

5.1.4 In food sources

Although 2,4-D and its transformation products do not tend to accumulate in plants and plant products, detectable residues of 2,4-D on food plants may be consumed by human

beings or animals and may thus contribute to the overall exposure of the human population to this chemical.

The results of pertinent studies on 2,4-D residues on or in foods, and in food sources for human beings and animals, are summarized in Tables 8-11. Theoretically, some contribution to the reported 2,4-D residues may have been partly derived from other phenoxy herbicides, as 2,4-DB undergoes beta-oxidation to 2,4-D in some plants and fish, and in cattle (Lisk et al., 1963; Gutenmann & Lisk, 1965; Sundström et al., 1979; Bovey, 1980a).

5.1.4.1 Residues in retail food supplies

The frequency of occurrence and the levels of 2,4-D residues in over 110 000 samples of a variety of different ready-to-eat foods, beverages, and infant and young children's diets, have been studied over the last 20 years in the USA (Lipscomb, 1968; Corneliussen, 1970, 1972; Duggan et al., 1971; Duggan & Corneliussen, 1972; Johnson et al., 1979, 1981a,b). The 2,4-D residues found in such samples are reported in Table 6. The theoretical daily intake resulting from these residues was variously estimated to be < 1-5 µg/person per day (Duggan & Corneliussen, 1972).

Studies undertaken since 1970 have failed to detect residues of 2,4-D in any of the US diet samples analysed, except for a single positive sample in the dairy product food group which was estimated at 0.01 mg/kg (Manske & Johnson, 1975).

5.1.4.2 Residues in fish and shellfish

Fish and shellfish may be exposed to 2,4-D as a consequence of aquatic herbicide use, or through the agricultural use of 2,4-D. The residues in the edible portions of such fish rarely exceed 1 mg/kg wet weight (Erne, 1974, 1975 and Table 8). Residues of 2,4-D have not been detected in retail samples of fish and shellfish analysed as part of the US "market basket" studies (section 5.1.4.1).

There is some evidence that the organoleptic properties of the 2,4-D residues may reduce the likelihood of the consumption of fish flesh contaminated with higher levels of 2,4-D (Gavrilova, 1965; Folmar, 1979).

5.1.4.3 Residues in wild fruits and mushrooms

Uncultivated fruits and mushrooms taken from areas where 2,4-D was used, or was likely to have been used, were examined

Table 8. 2,4-D residues reported in field studies on fish and shellfish

Country	Year(s)	2,4-D application rate	Types of samples	2,4-D residues in tissues (mg/kg)	References
USA	1961	0.1 mg/litre	oyster (1 species) fish (1 species)	1.6-2.0 0.3-1.0	Rutler (1965) Cope et al. (1970)
USA	1966	44.8-112 kg/ha	mussels clams fish (5 species)	< 0.14-1.12 < 0.14 < 0.14	Smith & Isom (1967)
USA	1968	112 kg/ha	fish (4 species)	< 0.10-0.24	Whitney et al. (1973)
USA	1969	22.4-44.8 kg/ha	mussels fish (8 species)	< 0.05-2.7 < 0.10-0.34	Wojtalik et al. (1971)
USA	1971	2.24-8.96 kg/ha	fish (3 species)	< 0.005-1.075	Schultz & Harman (1974)
USA	1971	4.48 kg/ha	fish (5 species)	0.000-0.162	Schultz & Whitney (1974)

for residues of 2,4-D by Erne & von Haartman (1973), Erne, (1980), Siltanen et al. (1981), and Frank et al. (1982). The results in Table 9 show that residues of 2,4-D in berries in field-trial studies have been as high as 30 mg/kg immediately after application, but residues in berries and mushrooms taken from the wild are generally < 1 mg/kg.

High residues of 2,4-D can produce disagreeable odours or flavours in wild fruits and vegetables (Ingelög et al., 1977; McArdle et al., 1961), and this may reduce the likelihood that highly contaminated foods are ingested.

5.1.4.4 Residues in food derived from animals

Domestic meat-, milk-, and egg-producing animals, and game animals may consume forage or feed containing 2,4-D residues, and thus, their tissues and products may contain residues. Published data on 2,4-D residues in feed and forage from the Northern Hemisphere are summarized in Table 10. Immediately after application of phenoxy herbicides, 2,4-D residues in or on grass generally average about 100 mg/kg for each kg of herbicide applied per hectare. Such residues decline with a half-life of about 1 - 2 weeks, to about 20 mg/kg, within 4 weeks of an application of 1 kg/ha (Leng, 1972). Residues in 2,4-D-treated feed grains are significantly lower than the levels reported above and no residues would be expected in meat, milk, or eggs from such sources (Table 10).

No residues of 2,4-D were detected (detection limit of 0.02 mg) in the milk of dairy cows fed 2,4-D at a level of 300 mg/kg total diet (Bjerke et al., 1972; Leng, 1972). A range of 0.06 - 0.08 mg 2,4-D/litre was found in the milk of cows fed for 3 weeks at a level of 1000 mg 2,4-D/kg total diet.

When young beef cattle were fed 2,4-D at levels of 300, 1000, and 2000 mg/kg total diet for 28 days, 2,4-D residue levels were highest in the kidney and liver, but did not exceed 0.1 mg/kg in muscle and fat, even at the highest dose level. (Clark et al., 1975; Leng, 1972, 1977). 2,4-D residues were not detected in more than 12 000 samples each of meat and dairy products analysed in the USA between 1963 and 1969 (Duggan et al., 1971).

Results of feeding studies with hares and reindeer in Scandinavia indicated that 2,4-D levels of 25 - 30 mg/kg forage (equivalent to an intake of about 1 mg 2,4-D/kg body weight per day) produce maximum 2,4-D residues of 1.1 mg/kg wet weight in liver, and 8.9 mg/kg in kidney tissues (Erne, 1974). Residues of 2,4-D were detected in the liver and

Table 9. 2,4-D residues in wild berries and mushrooms collected in fields or forests following application of phenoxyalkanoic herbicides

Country	Year(s)	Sample	2,4-D application rate (kg a.i./ha)	Days after treatment	No. samples analysed	2,4-D residues (mg/kg)	References
Canada ^a	1979-81	raspberries	1.1-3.9	2 14-35	124	2.6-31.0 0.1-3.3	Frank et al. (1982)
Finland ^a	1974-76	vaccinium berries jam mushrooms	2.5 not known	10-356 not known 14-300	44 1 28	2.2 < 0.05-1.2	Mukula et al. (1978)
Finland ^a	1975-76	vaccinium berries	0.25-2.25	365	not stated	< 0.05	Siltanen et al. (1981)
Sweden ^a	1970	raspberries vaccinium berries blueberries mushrooms	1.5-2.2 1.5-2.2 1.5-2.2 1.5-2.2	2-32 2-32 2-32 2-32	9 68 19 15	< 0.03-0.9 < 0.03-7.7 < 0.03-2.9 < 0.03	Erne & Von Haartman (1973) ^c
Sweden ^a	1973-79	vaccinium berries ^b raspberries blueberries cowberries mushrooms	0.25-2.25 not stated not stated not stated not stated	365 14 2 1-28 7	61 not stated not stated not stated 1	nd (< 0.05) nd-2.5 nd-10.0 nd-6.0 0.3	Erne (1980)
Sweden ^a		blueberries vaccinium berries raspberries	0.4-1.5 0.4-1.5 0.4-1.5	1-35 30-35 1-10	not stated not stated not stated	0.2-5.3 0.5-4.5 0.2-2.0	IngeLöf et al. (1977)

^a Samples taken from areas treated with 2,4-D.

^b Samples entering factory for processing.

^c Data from authors' Table 1.

Table 10. 2,4-D residues reported in samples of herbicide-treated forage or feed

Country	Year(s)	Type of samples	2,4-D application rate, (kg a.i./ha)	Post-treatment interval, (days)	No. samples examined & positive	2,4-D residues (mg/kg)	References	
Canada	1971	wheat plants	0.42	1-36	?	8.35-0.011	Cochrane & Russell (1975)	
Finland	1962-68	green forage (grass and clover)	1-4	7.21	?	600-3.7	Finnish State Institute of Agriculture (1963-1969)	
			3.5	7-28	?	13-0.4		
Finland	1974-76	aspen leaves and twigs	2.5	60-300	32	30-0.3	Mukula et al. (1978)	
		birch leaves and twigs		60-300	16	31-0.1		
		cowberry plants		365	8	< 26-0.05		
Germany, Federal Republic of		wheat, barley, rye, oat grains	0.375-0.735	64-101	?	< 0.015-0.01	Maier-Rode (1971)	
		wheat, barley, rye, oat straw				< 0.34-0.02		
Hungary	1971	silos corn	1.4-1.5	56-120	?	0.8-0.075	Bodai et al. (1974)	
Sweden	1972-76	barley, oats	?	?	3	0.7-0.4	Erne & Rutqvist (1979)	
		grass			7	0.4		
		lichens	?	?	2	0.4-0.2		
USA	1949	pasture plants	4.48	1	8	14.6-1.65	Grigsby & Farwell (1950)	
USA	1967	forage grasses	0.56-2.2	0-112	?	100-1	Morton et al. (1967)	
USA	1969	sorghum plants	1.4	2	?	1.06	Ketchersid et al. (1970)	
			1.4-2.8	30-60		< 5.25-0.2		
USA	1969	pasture plants	6.6-9.8	0-28	24	700-150	Leug (1972)	

Table 11. 2,4-D residues in game and domestic animals and animal products

Country	Year(s)	Species	2,4-D treatment rate (kg a.i./ha)	Post-treatment interval (days)	Type of samples examined	2,4-D residues (ng/kg)	References
Sweden	1968-1972	moose (<u>Alces alces</u>) deer (<u>Capreolus capreolus</u>) hares (<u>Lepus lepus</u>) pheasants grouse	game animals found dead, or shot by hunters in herbicide-treated areas	?	liver and kidney from 250 animals found dead	< 0.05-6	Erne (1974, 1975)
USA	1963	Jersey cow	50 ppm in diet for 4 days	0-2	liver and kidney from 130 animals shot by hunters	< 0.05-4.5 (2,4-D and 2,4,5-F)	Bache et al. (1966)

Table 11 (contd).

USA	1974(?)	adult beef cattle	0,9,30 or 60 mg 2,4-D acid/kg bw/day for 28 days (0, 300, 1000, 2000 mg/kg feed)	0	muscle fat liver kidney	< 0.05-0.07 < 0.13-0.34 < 0.05-0.23 2.53-10.9	Clark et al. (1975)
USA	1974(?)	adult sheep	2000 mg/kg feed for 28 days	0-7	muscle fat liver kidney	< 0.05-0.06 0.10-0.15 0.29-0.98 0.37-9.17	Clark et al. (1975)
USA	1965(?)	dairy cows	animals grazing on pasture sprayed with herbicide at 2,24 kg a.i./ha	2 4	milk	0.01-0.09	Klingman et al. (1966)
USA	1972	dairy cows	30, 300, 1000 mg/kg in feed for 2-3 weeks	0 1-3	milk	< 0.05-0.16 < 0.03	Ejerke et al. (1972) Lang (1972)
USSR	1975	"livestock"	?	?	muscle liver kidney	0.04 0.04 0.03 (mean)	Fyodorova et al. (1977)

kidney of a few game animals shot by hunters, or found dead in or near areas sprayed with phenoxy herbicides (Table 11, Erne, 1974,1975). The residues in muscle tissue were not measured but would be lower than in the liver and kidney, as indicated by the data summarized in Table 11.

On the whole, the available evidence indicates that 2,4-D is rarely detected in commercial foods and that residues in food taken from areas where 2,4-D has been sprayed will usually be < 1 mg/kg food. The liver and kidney from range animals are possible exceptions, but these contribute little to the total diet of the general population.

5.2 Occupational Exposure to 2,4-D During the Production, Handling, and Use of Chlorophenoxy Herbicides

During occupational exposure to 2,4-D, the chemical may be absorbed via the inhalation, oral, and dermal routes, but more than 90% of the total amount of 2,4-D or other chlorophenoxy compounds entering the body under these circumstances appears to be absorbed through the skin and excreted relatively quantitatively in the urine as the phenoxy acid and readily-hydrolysed conjugates (Kolmodin-Hedman et al., 1979,1980; Libich et al., 1981; Draper & Street, 1982; Franklin et al., 1982; Leng et al., 1982; Nash et al., 1982) (section 6).

Data from occupational exposure studies concerning the amounts of 2,4-D found on the clothing or on cloth patches worn by workers are not included in this review because the correlation between these amounts and amounts absorbed into the body and then excreted in urine is poor (Franklin et al., 1982; Lavy et al., 1982; Leng et al., 1982).

5.2.1 Industrial exposure

Several studies have been published on the levels of 2,4-D to which workers producing or packaging 2,4-D herbicides are exposed (Fetisov, 1966; Johnson, 1971; Juzwiak et al., 1973; Andreasik et al., 1979). In every case the amount of 2,4-D absorbed by the workers was uncertain and, therefore, the data are inadequate for estimating industrial exposure to 2,4-D. Workers manufacturing 2,4-D were also exposed to other chemicals (Assouly, 1951; Bashirov & Ter-Bagdasarova, 1970).

5.2.2 Exposure related to herbicide use

The available studies on the occupational exposure to 2,4-D of workers during the use of 2,4-D herbicides are summarized in Table 12. Studies on the exposure of back-pack

Table 17. Exposure related to herbicide use

Product	No. of people exposed	Type of application	Daily concentration of 2,4-D in urine (mg/litre) \bar{x}	Duration of collection of 24-h urine samples (days)	Total 2,4-D in urine excreted (mg/kg bw/day of exposure)	References
2,4-D and dicamba dimethylene salts in aqueous solution	2	boom spray single use repeated use	1 - 4 3 - 20	- -	- -	Draper & Street (1982)
2,4-D isooctyl ester in diesel oil	4	3 applications by single-engine aircraft	-	4	0.004 - 0.04	Franklin et al. (1982)
2,4-D/2,4,5-T butoxyethyl esters as 2% emulsion in water	4	tractor-drawn sprayers, forestry exposure daily, for one week	1 - 14	7	-	Kolmodin-Hodman (1979, 1980)

Table 12 (contd).

2,4-D PCBE ester	26	helicopter in forestry use	-	5	nd - 0.06 ^a nd - 0.02 ^b	Lavy et al. (1982)
2,4,5-T PCBE ester	7	Back-pack forestry use single exposures, one week apart	-	5	0.01 - 0.09 (2,4,5-T)	Leng et al. (1982)
2,4-D/2,4-DE and 2,4-D/picloram ^c	23	roadside and right-of-way Ground equipment incl. mist blowers	< 0.01 - 8 (one usually high result of 3l)	3	-	Libich et al. (1981)
2,4-DE	17	aircraft repaired exposure	-	7	0.006 - 0.02 ^d (mean values/day)	Nash et al. (1982)
2,4-D amine salt and ester	26	ground equipment (single exposure)	-	7	nd - 0.08	

^a No special precautions taken.
^b Protective clothing worn.
^c Preparation used not specified.
^d Mean values per day recorded for different individuals.
^e It is not possible to calculate the total 2,4-D excretion in urine from these data, because of individual variations in urine concentrations from day to day from sample to sample.

sprayers to 2,4-D have not been published. However, comparable exposure data are available for 2,4,5-T back-pack sprayers and they have been included in Table 12 for comparison. The levels of 2,4-D found in the air of the working zone in these and other studies have already been referred to in section 5.1.1.1 and Table 5.

In studies undertaken before 1980, only the amounts of 2,4-D in the air, on the clothing, or on the skin were determined, except for 2 urinary 2,4-D values reported by Shafik et al. (1971). Thus the amounts of 2,4-D actually absorbed cannot be reliably estimated from these early reports and are not included in Table 12.

After 1980, several detailed occupational exposure studies were carried out to determine the amounts of 2,4-D or other chlorophenoxy acids absorbed by various members of ground and aerial spray teams, using a variety of equipment for dispersing aqueous or oil solutions or emulsions (Kolmodin-Hedman et al., 1979; Kolmodin-Hedman & Erne, 1980; Libich et al., 1981; Draper & Street, 1982; Franklin et al., 1982; Lavy et al., 1982; Leng et al., 1982; Nash et al., 1982).

The total 2,4-D urinary excretion levels reported in Table 12 reflect a wide variety of uses and show that the excretion does not usually exceed 0.1 mg 2,4-D/kg body weight per day of exposure. However, so far, a comprehensive comparison of the relative exposures resulting from different methods of application and different 2,4-D derivatives (amine salts and esters) or formulations (aqueous, oil) cannot be carried out, because the available data are still incomplete. The amount of 2,4-D absorbed depends on the type of work performed, and on the degree of care taken to avoid direct dermal contact with the herbicide concentrate, spray solution, or spray. The most heavily-exposed workers tend to be the mixer-loaders, who handle the herbicide concentrate, and the spray personnel. However, if careful, they may be exposed to less 2,4-D than, for example, a pilot of a spray plane who is not careful (Franklin et al., 1982; Leng et al., 1982; Lavy et al., 1982; Nash et al., 1982). The reports by Libich et al. (1981) and Leng et al. (1982) on ground spray crews indicate that, even under unfavourable working conditions, the amount of 2,4-D absorbed may be greatly reduced simply by wearing clean gloves and overalls, and by making the workers more aware of the importance of safe work habits.

As the chemobiokinetic profiles of urinary 2,4-D output are reported in only a few of the studies, summarized in Table 12, it is not possible to estimate the total 2,4-D intake in all cases.

The results of the studies by Libich et al. (1981) and by Draper & Street (1982) suggest that using single-exposure studies to estimate the peak exposure levels reached by workers exposed several days in succession may give an underestimation.

No information is available on the amounts of chlorinated dibenzodioxins, or other by-products or contaminants, absorbed as a consequence of occupational exposure to 2,4-D herbicides.

In one extensive occupational monitoring programme undertaken in 1979-82, about 3000 urine samples were analysed for herbicide residues (Simpson, 1982). The subjects included pesticide factory staff, pest control operators, farmers, park workers, and others potentially exposed to 2,4-D. During the first year of the study, no 2,4-D was detected (< 0.001 mg/litre) in 735 of 973 samples. Most of the other samples contained less than 0.1 mg/litre and only 27 contained more than 1 mg/litre. The highest value was 31 mg/litre. The study is continuing.

5.3 Exposure of Bystanders to 2,4-D

Aerial drift and other forms of pesticide transport, as well as the contamination of surfaces during or after herbicide production, distribution, or use, may bring 2,4-D into contact with bystanders, i.e., persons other than those who are occupationally exposed. Few studies of bystander exposure to 2,4-D or other chlorophenoxy herbicides have been published. Studies available for review included that of Lavy et al. (1982) concerning 9 supervisors and observers present at two helicopter forest spray operations using 2,4-D propyleneglycol butylether (PGBE) ester, respectively, for unspecified durations. These people excreted a maximum of 1.3 µg 2,4-D/kg body weight. In a forest ground spray operation with tractor-drawn equipment, 2,4-D was not detected (< 0.05 mg/litre) in the urine of bystanders (Kolmodin-Hedman et al., 1980). Additional bystander exposure studies for various 2,4-D use patterns are desirable. However, the 2,4-D intake of bystanders is unlikely to exceed the 2,4-D intake during occupational exposure.

5.4 Estimated Exposure of the General Population in 2,4-D-Use Areas

Data useful for estimating the intake by the general population of 2,4-D residues in the environment including those in food sources have been generated. The present calculations of the intake of the general population in an area of 2,4-D use are based on these data and on a series of

stated assumptions aimed at obtaining a moderate over-estimation rather than underestimation of the actual exposure.

5.4.1 Intake of 2,4-D residues from air

On the basis of available information, it can be assumed that the general population in areas of 2,4-D herbicide use would rarely be exposed to 2,4-D concentrations exceeding 0.1 $\mu\text{g}/\text{m}^3$ air.

Assuming an air level of 0.1 μg 2,4-D/ m^3 , a body weight of 60 kg, an air intake of 20 m^3 per day, and a 100% retention of 2,4-D, it can be calculated that the respiratory intake would be 0.03 μg 2,4-D/kg body weight per day.

5.4.2 Intake of 2,4-D residues from potable water

The larger surveys of potable water (Table 7) show mean 2,4-D residues in surface water to be generally < 0.1 $\mu\text{g}/\text{litre}$, but for the present estimate, it is assumed that potable water from surface sources or from treatment plants, during a period of about 10 days after reservoir treatment, can contain an average 2,4-D residue level of 2 $\mu\text{g}/\text{litre}$ (Wojtalik et al., 1971 and Table 7). Assuming a 2,4-D concentration in water of 2 $\mu\text{g}/\text{litre}$, a body weight of 60 kg, a water intake of 2 litres per day (Canada, Health & Welfare, 1980), and a 100% absorption of the ingested 2,4-D, it can be calculated that the 2,4-D intake of the general population in a 2,4-D use area resulting from water could approach 0.07 $\mu\text{g}/\text{kg}$ body weight per day, which could occur for about 10 days.

Insufficient data are available to give a reliable estimate of 2,4-D intake from ground water sources, but it is likely to be lower than the above value.

5.4.3 Intake of 2,4-D residues from soil

2,4-D on soil particles ingested with food or water, or carried into the air and inhaled, is considered to be part of the exposure due to residues in air, water, or food and is therefore assumed to be completely covered in these exposure estimates.

5.4.4 Intake of 2,4-D residues from food

The data in Tables 8 - 11 indicate that there is unlikely to be any exposure of the general population to 2,4-D residues in retail food supplies. The possibility that individuals are exposed to contaminated local sources of food has been assessed in section 5.1.4. In the case of milk or muscle

meat, it can be assumed that no individual will be exposed to levels in excess of 0.02 mg/kg of these foods, the limit of detection of the method of analysis used. Assuming a concentration of 0.02 mg 2,4-D/litre in milk, and a consumption of 1.5 litre per day, the maximum intake from this source would be 0.0005 mg/kg body weight per day for a 60 kg adult. Individuals who consume wild berries taken from 2,4-D-treated areas could be exposed through this food source. Assuming consumption of 100g of berries per serving and a maximum 2,4-D concentration of 1 mg/kg, the intake from this source would be 0.002 mg/kg body weight per serving.

5.4.5 Total exposure of the general population in a 2,4-D-use area

The above considerations suggest that the total daily 2,4-D intake of the population in use areas will not normally exceed about 2 µg/kg body weight per day during the application period (Table 13).

Table 13. Components of estimated exposure to 2,4-D

Exposed Group	Estimated amount of intake (µg 2,4-D/kg bw/day)	Source of 2,4-D
<u>Occupational</u>		
i. Factory workers	insufficient data	mainly dermal contact
ii. Applicator crews	100 ^a	
iii. Bystanders	- ^b	
<u>General population in areas with 2,4-D use</u>		
	0.03	air
	0.07	water
	0.5	milk
	ND	retail food
	2.0	wild berries, mushrooms etc.

^a Based on total urinary output after several days of exposure.

^b Unlikely to exceed occupational exposure.

5.4.6 Total exposure of persons occupationally exposed in agriculture

An accurate maximum occupational intake of 2,4-D cannot be determined on the basis of the limited studies undertaken. However, the available data suggest that work performed in the

preparation of, and during, agricultural application of 2,4-D herbicide will probably result in an exposure of not more than about 0.1 mg 2,4-D/kg body weight per day, providing that minimum precautions are taken against excessive exposure.

5.4.7 Total exposure of the general population outside areas of 2,4-D use

Monitoring of air, water, and food outside areas of known 2,4-D use show that intake is below present detection limits.

6. CREMOBIOKINETICS AND METABOLISM

With the exception of recent occupational exposure studies and studies on animals published in 1979 or later, the available information on the uptake, distribution, transformation, and excretion of 2,4-D by human beings and other mammals has already been reviewed by Leng (1977), National Research Council of Canada, Associate Committee on Scientific Criteria for Environmental Quality (1978), Young et al. (1978), Bovey (1980a,b), Shearer (1980), and United States Veterans' Administration (1981).

6.1 Uptake via Different Routes of Exposure

6.1.1 Uptake by inhalation

6.1.1.1 Animals

Burton et al. (1974) found that small amounts of 2,4-D instilled into the rat lung were rapidly absorbed, apparently by a non-saturable process following first-order kinetics, with an absorption half time of 1.4 - 1.7 min. The kinetics of the absorption of 2,4-D vapours or aerosols in the respiratory tract of animals have not yet been studied.

6.1.1.2 Human beings

The uptake of 2,4-D and of 2,4-D derivatives via the human respiratory tract does not appear to have been studied under controlled conditions. However, the observations of Kolmodin-Hedman & Erne (1980), Libich et al. (1981), Franklin et al. (1982), and Lavy et al. (1982) on people occupationally exposed to 2,4-D indicated that only a small percentage of the total amount of 2,4-D absorbed via all routes of exposure was taken in through the respiratory tract.

6.1.2 Dermal uptake

6.1.2.1 Animals

Mice whose tails had been immersed in 2,4-D butyl or crotyl ester solutions, 4 h daily for 3-5 days, absorbed lethal amounts of the chemicals (Fetisov, 1966). However, the actual doses absorbed and other details were not given. In contrast, no major ill effects were reported in studies in which rabbits were treated percutaneously for 2 or 3 weeks with 130-180 mg/kg body weight/day of a 50% aqueous solution of 2,4-D octyl ester, or with unspecified amounts of solutions

of 2,4-D dimethylamine salt in water, or oil solutions of 2,4-D isooctyl or butyl ester (Vinokurova, 1960; Kay et al., 1965).

6.1.2.2 Human beings

Only 5.8% of a dilute solution of ^{14}C -labelled 2,4-D in acetone applied at a dose of $4 \mu\text{g a.i./cm}^2$ to the ventral forearm of adults was excreted in the urine compared with 100% of a small intravenous dose (Feldmann & Maibach, 1974) (Table 14). The 2,4-D excretion in urine is delayed and more prolonged after dermal application than after intravenous or oral administration (Feldmann & Maibach, 1974; Sauerhoff et al., 1977), and complete elimination may take about one week (Levy et al., 1982; Leng et al., 1982). Cases of acute occupational 2,4-D poisoning following combined dermal and inhalation exposures (Monarca & Divito, 1961; Tsapko, 1966; Paggiaro et al., 1974), as well as occupational exposure studies (Table 12), suggest a fairly efficient dermal absorption of 2,4-D. However, the importance of solvents, surfactants, and other ingredients of the herbicides in the uptake of 2,4-D via the dermal route still needs to be defined.

6.1.3 Oral uptake

6.1.3.1 Animals

The uptake of 2,4-D from the gut of rats, mice, guinea-pigs, cattle, pigs, and sheep appears to be similar in both rapidity and extent to that observed in human beings (Mitchell et al., 1946; Lisk et al., 1963; Bache et al., 1964a; Erne, 1966a,b; Milhaud et al., 1970; Shafik et al., 1971; Buslovich et al., 1973; Fedorova & Belova, 1974; Clark et al., 1975; Senczuk & Pogorzelska, 1975, 1981; Van Peteghem & Heyndrickx, 1975). In some of the ungulates, 2,4-DB acid, and 2,4-D amine salts or esters are at least partially converted to 2,4-D in the rumen, before being absorbed (Gutenmann et al., 1963; Lisk et al., 1963). Some of the esters may be less well absorbed from the gut than the acid or its alkali or amine salts (Erne, 1966a; Buslovich et al., 1973), but the uptake mechanisms for 2,4-D and its salts or esters is not known, and thus deserves further study.

6.1.3.2 Human beings

Information on the uptake of 2,4-D by human beings via the oral route has been gathered in studies on two groups of 5-6 volunteers each, who ingested single doses of 5 mg 2,4-D/kg body weight (Table 14), and by chemobiokinetic studies on

Table 14. Chemobiokinetics of 2,4-D in human beings following administration under controlled conditions

Product	Dose and dosing schedule	Subjects	Observations	Toxic effects EL NOEL _a (mg/kg bw) single dose	References
14C-2,4-D (New England Co., and Amersham Searle Co.)	1) Intravenous injection: Dose (7 µCi) not stated as 2,4-D/weight unit 2) Dermal application: 1 x 4 µg 2,4-D (in acetone)/cm ² of skin of forearm. Application site was not washed for 24 h	6 (sex & age not stated) 6 (sex & age not stated)	Scintillation counting 1) 100% of dose excreted in urine urine in 120 h. Mean t _{0.5} = 13 h 2) 5.8% of applied dose excreted in 120 h	? ?	Feldmann & Maibach (1974)
2,4-D, 99% pure (Dow Chemical Co.)	Oral administration: 1 x 2, 3, or 5 mg/kg bw, in gelatin capsule, with water, following breakfast	6 (adult M)	gas chromatography of blood & urine samples; no ill effects; no changes in clinical parameters: blood pressure, pulse rate, Hb, WBC counts (total & differential); mean plasma clearance t _{0.5} = 33 ± 3.1 h; peak plasma conc. at 7-24 h = 40 mg/litre; ~75% of dose excreted in urine in 96 h "no metabolic transformation at up to 5 mg/kg"	? 5	Khanna & Kohli (1977); Kohli et al. (1974)
2,4-D, analytical grade	Oral administration: 1 x 5 mg/kg bw as a slurry in milk, or in powder form, with some water, following breakfast	6 (adult M, 70-90 kg)	gas chromatography - mass spectro- metry of blood & urine samples; no ill effects; essentially all of the dose absorbed; peak plasma conc. = 10-30 mg/litre within 24 h; mean plasma clearance t _{0.5} = 11.6 h; mean urinary excretion t _{0.5} = 17.7 h; total excreted amount ~82% of dose administered; 4.8-27.1% of excreted compound was conjugated	? 5	Sauethoff et al. (1976, 1977)

^a NOEL = No-observed-adverse-effect level.

individuals who, with suicidal intent, swallowed lethal or non-lethal amounts of various 2,4-D herbicides (Geldmacher-Von Mallinckrodt & Lautenbach, 1966; Rivers et al., 1970; Kohli et al., 1974; Sauerhoff et al., 1976, 1977; Khanna & Kohli, 1977; Young & Haley, 1977; Prescott et al., 1979) (Table 15). These results show that single doses of 2,4-D are fairly rapidly and completely absorbed from the human digestive tract, unless the dose is so large that toxic effects interfere with absorption. However, in the two studies on volunteers, considerable individual variation in the rate and extent of absorption from the digestive tract was observed. The absorption mechanism appears to involve first-order kinetics (Kohli et al., 1974; Khanna & Kohli, 1977) and may fit a single- or multi-compartment chemobiokinetic model, depending on individual characteristics (Sauerhoff et al., 1977).

6.2 Distribution and Transformation in the Body

6.2.1 Animals

The absorption and distribution kinetics and metabolism of pure 2,4-D and of a variety of pure or commercial 2,4-D or 2,4-DB amine salts and esters have been repeatedly studied both in vivo and in vitro in a wide variety of animals including rats, mice, rabbits, guinea-pigs, cattle, sheep, goats, pigs, chickens, fish, and spiny lobsters (Gutenmann & Lisk, 1965; Erne & Sperber, 1974; Guarino & Arnold, 1979; James, 1979; Koschier & Pritchard, 1979; Pritchard & James, 1979; Pritchard & Miller 1980). The considerable differences observed in the relative amounts of residues found in the cells and plasma of mouse, rat, and horse blood, after dosing animals or after in vitro addition of 2,4-D (Erne, 1966a; Jenssen & Renberg, 1976), in different tissues of rats, mice, and sheep (Erne, 1966a,b; Lindquist & Ullberg, 1971; Milhaud et al., 1970; Buslovich et al., 1973; Clark et al., 1975; Elo & Ylitalo, 1979), and in the soluble and particulate fractions of rat tissues (Khanna & Fang, 1974) support the idea that there is more than one physiological compartment for 2,4-D storage. The distribution volumes appear to be equivalent to the volume occupied by about 25-50% of the body mass (Erne, 1966a).

2,4-D is reversibly bound to blood plasma proteins, particularly albumins, possibly at sites for which it competes with related compounds. The same sites are apparently also binding sites for palmitic acid and thyroxine. The extent of 2,4-D binding depends, in part, on pH and 2,4-D concentration (Florsheim et al., 1963; Erne, 1966b; Kolberg et al., 1973; Hacque et al., 1975; Mason, 1975; Örberg, 1980a), and may

Table 15. Chemobiokinetics of 2,4-D in human beings following accidental or intentional ingestion of herbicides

Products	Circumstances	Subject	Observations	References																				
2,4-D	suicide; ingestion of unknown amount of herbicide	F, 33 years	death in about 30 h; post mortem concentration: <table border="1" style="margin-left: 20px;"> <tr> <td>blood urine</td> <td>mg/litre</td> <td>brain</td> <td>mg/kg</td> <td>liver</td> <td>mg/kg</td> <td>lung</td> <td>mg/kg</td> <td>heart</td> <td>mg/kg</td> </tr> <tr> <td>23</td> <td>164</td> <td>100</td> <td>116</td> <td>88</td> <td>63</td> <td></td> <td></td> <td></td> <td></td> </tr> </table> no metabolites were identified	blood urine	mg/litre	brain	mg/kg	liver	mg/kg	lung	mg/kg	heart	mg/kg	23	164	100	116	88	63					Celdmacher-Von Mallinckrodt & Lautenbach (1966)
blood urine	mg/litre	brain	mg/kg	liver	mg/kg	lung	mg/kg	heart	mg/kg															
23	164	100	116	88	63																			
Herbicide containing 2,4-D plus MCPA ("U-6 COMBI") (BASF Ludwigshafen)	suicide; ingestion of unknown amount of herbicide	F, 51 years, 66 kg	death in about 96 h; concentration of 2,4-D plus MCPA: <table border="1" style="margin-left: 20px;"> <tr> <td>blood urine</td> <td>mg/litre</td> <td>liver</td> <td>mg/kg</td> <td>kidney</td> <td>mg/kg</td> <td>muscle</td> <td>mg/kg</td> </tr> <tr> <td>42</td> <td>470</td> <td>100</td> <td>trace</td> <td>40</td> <td></td> <td></td> <td></td> </tr> </table> 2,4-dichlorophenol not detected; several other metabolites or herbicide byproducts found, but not identified	blood urine	mg/litre	liver	mg/kg	kidney	mg/kg	muscle	mg/kg	42	470	100	trace	40								
blood urine	mg/litre	liver	mg/kg	kidney	mg/kg	muscle	mg/kg																	
42	470	100	trace	40																				
Herbicide containing 2,4-D plus mecoprop (10%) + (20%)	suicide attempt; ingestion of 6.7g 2,4-D and 7.6g mecoprop	M, 39 years	severe toxic effects; unconsciousness; recovery within 11 days following treatment by alkaline diuresis; initial plasma concentration; 2,4-D = 400 mg/litre, mecoprop = 750 mg/litre; no pretreatment change in 2,4-D level following alkaline diuresis; plasma clearance $t_{1/2}$ = 3.7 h for 2,4-D, 11-28 h for mecoprop 0.5	Prescott et al. (1979)																				

affect the rate and extent of renal 2,4-D excretion (Pritchard & James, 1979; Pritchard & Miller, 1980) and thus the toxicity of 2,4-D.

In pregnant mammals, up to about 17% of a single dose of 2,4-D may rapidly cross the placenta to reach the embryos or fetuses (Lindquist & Ullberg, 1971; Fedorova & Belova, 1974; Antonenko, 1977).

Pigs and rats hydrolyse 2,4-D esters both in the gut and after absorption in the body (Erne, 1966a,b). Observations from several studies indicate that 2,4-D is not significantly metabolized in animals, except in ruminants. No ^{14}C was produced by rats given C^1 - or C^2 -labelled ^{14}C -2,4-D (Khanna & Fang, 1966). No 2,4-dichlorophenol (2,4-DCP) was detected in the tissues of mice or rats dosed by various routes with 2,4-D (Zielinski & Fishbein, 1967; Shafik et al., 1971; Federova & Belova, 1974; Grunow & Böhme, 1974). However, residues of 2,4-DCP were detected in the milk of dairy cows fed 100 mg 2,4-D/kg diet for 3 weeks (Bjerke et al., 1972; Leng, 1972), and in the livers and kidneys of cattle and sheep fed up to 2000 mg/kg diet for 4 weeks (Clark, 1975; Leng, 1972, 1977). These 2,4-DCP residues probably resulted from the bacterial degradation of 2,4-D in the rumen of the animals. Bacterial degradation may also account for the 2,4-DCP reported by Antonenko (1977) in pregnant or lactating rats and rat fetuses.

Other investigators did not detect 2,4-DCP in the tissues of mice or rats dosed with 2,4-D by various routes (Zielinski & Fishbein, 1967; Shafik et al., 1971; Fedorova & Belova, 1974; Grunow & Böhme, 1974).

Results of studies on experimental animals have suggested that 2,4-D conjugates are formed in the kidney tubules (Erne, 1966a,b; Erne & Sperber, 1974; Grunow & Böhme, 1974).

Taurine and glycine conjugates, as well as various other unidentified conjugates of 2,4-D have been found in the urine of rats, pigs, chickens, and the dogfish shark (Squalus acanthias) (Erne, 1966b; Erne & Sperber, 1974; Grunow & Böhme, 1974; Koschier & Pritchard, 1979). However, in rats and pigs, only about 10-20%, and in the chicken, less than 5% of the total amount of 2,4-D appeared to be excreted in this form. In the dogfish shark, the taurine conjugate may be primarily formed in the tubular cells of the kidney (Koschier & Pritchard, 1979). The site and mechanism of 2,4-D conjugation seem to be unknown in the other species.

6.2.2 Human beings

Studies on human volunteers who ingested pure 2,4-D, and on cases of accidental or voluntary acute poisoning with various 2,4-D herbicides have shown that 2,4-D is very rapidly

absorbed from the gut and carried in the blood to cells and tissues throughout the body, but that is not extensively transformed (Tables 14, 15) (Curry, 1962; Herbich & Machata, 1963; Nielsen et al., 1965; Dudley & Thapar, 1972; Coutselinis et al., 1977). The kinetics following ingestion suggest a 1- or 2-compartment distribution, depending on individual characteristics (Sauerhoff et al., 1977; Young & Haley, 1977). Following absorption of purified 2,4-D, or of herbicides containing only 2,4-D, no transformation products, including 2,4-dichlorophenol, were found in blood or tissues. After ingestion of herbicides containing 2,4-D and other compounds, some 2,4-D metabolites or manufacturing by-products were detected in tissues, but were not identified (Geldmacher-Von Mallinckrodt & Lautenbach, 1966; Prescott et al., 1979). Unidentified 2,4-D conjugates were also found in urine following ingestion of pure 2,4-D. These conjugates represented up to 27% of the 2,4-D ingested (Sauerhoff et al., 1976, 1977). Of the 5 North American volunteers studied by these authors, only one did not produce a conjugate; in contrast, apparently none of the 6 Indian subjects studied by Kohli et al. (1974) and by Khanna & Kohli (1977) produced 2,4-D metabolites.

6.3 2,4-D Levels in Body Tissues and Fluids

6.3.1 Animals

2,4-D levels in the blood and organs of mammals have been determined, e.g., by Erne (1966a,b), Milhaud (1970), Buslovich et al. (1973), Khanna & Fang (1974), Clark et al. (1975), Jenssen & Renberg (1976), and Elo & Ylitalo (1979). The highest residue levels were usually found in liver, kidney, lungs, spleen, and heart. In a study by Fedorova & Belova (1974), 6 - 8% of the amount of 2,4-D administered was found in all of the tissues examined in rats dosed orally 26 - 35 days previously with this chemical. However, the 2,4-D residue levels quoted were close to the limit of detection for the analytical method used.

6.3.2 Human beings

In volunteers, each of whom ingested a single dose of 5 mg 2,4-D/kg body weight, the 2,4-D levels in blood plasma reached peaks of about 10-45 mg/litre within about 7-24 h, and then declined (Kohli et al., 1974; Khanna & Kohli, 1977; Sauerhoff et al., 1977). In one group of workers occupationally exposed to 2,4-D for one week while using ground equipment for spraying (Kolmodin-Hedman et al., 1979), plasma levels ranged from the detection limit (0.02 mg/l) to 0.2 mg/litre, while

urinary levels ranged from 1 to 14 mg/litre. Urinary 2,4-D levels reported in other occupational exposure studies are summarized in Table 12. However, it should be noted that analysis of single urine specimens is not adequate for estimating the dose absorbed by individuals, because excretion follows a diurnal pattern and continues for several days after dermal exposure (Leng et al., 1977; Sauerhoff et al., 1979; Lavy et al., 1982). Thus, levels found after several days of spraying will probably be higher than first day levels, as reported by Libich et al. (1981) and Draper & Street (1982). However, excretion of 2,4-D should be completed within one week following the last exposure (Feldmann & Maibach, 1974; Lavy et al., 1982; Leng et al., 1982).

The toxic and lethal levels of 2,4-D in human blood and tissues are still not well defined. A woman with reportedly 335 mg 2,4-D/litre plasma did not show any signs of poisoning; in general, the acute lethal levels of 2,4-D appear to lie between 447 and 826 mg/litre plasma (Herbich & Machata, 1963; Nielsen et al., 1965; Geldmacher-Von Mallinckrodt & Lautenbach, 1966; Coutselinis et al., 1977; Prescott et al., 1979). The lowest lethal 2,4-D levels in blood or tissues were recorded several days after the chemical was ingested, i.e., after most of the 2,4-D had probably been eliminated. Among the different organs examined post mortem in cases of fatal 2,4-D poisoning, liver and kidney tended to contain the highest concentrations of 2,4-D, while brain and other fatty organs, and muscle including the heart, usually had lower 2,4-D levels (Table 15) (Curry, 1962; Herbich & Machata, 1963; Nielsen et al., 1965; Geldmacher-Von Mallinckrodt & Lautenbach, 1966; Dudley & Thapar, 1972; Coutselinis et al., 1977). As in the case of blood, the values for the different tissues may vary according to the proportion of 2,4-D eliminated by the time death occurs.

6.4 Elimination and Biological Half-Life

The term "biological half-life" will be used to indicate the time required to eliminate one half of a single dose of 2,4-D, or to reduce 2,4-D residues in the body fluids or tissues to one-half of the peak concentration. Biological half-life, as defined here, is a useful concept with which it is possible to make rough comparisons of the elimination rate of 2,4-D with that of other toxic chemicals.

6.4.1 Animals

The half-life values recorded in mammals fall into the range observed in the rat (Erne, 1966a,b; Federova & Belova, 1974; Khanna & Fang, 1974), with the exception of the very low

value for 2,4-D butyl ester in whole mouse carcasses (0.85-1.11 h) observed by Zielinski & Fishbein (1967). Results of the investigations conducted by these authors also suggest that prior dosing with 2,4-D ("priming") may increase the rate of elimination of 2,4-D butyl ester in mice, presumably through stimulation of the renal excretory mechanism.

An important correlation between diet and 2,4-D elimination rate was observed by Öberg (1980b) in the goat. A protein-poor diet reduced the 2,4-D plasma clearance rate by about 20-50%, possibly because of decreased renal size and renal blood flow.

The many species-related factors known to affect the rate of 2,4-D elimination make interspecies comparisons difficult, and often the published reports do not include such details as diet, age, sex, and body weight of the test animals, type and purity of the test compounds, and important environmental factors such as the ambient temperature, which are necessary for valid comparisons.

6.4.2 Human beings

The studies on volunteers and on cases of accidental or voluntary 2,4-D poisoning summarized in Tables 14 and 15 show that human beings excrete 2,4-D mainly in the urine, and that the blood plasma clearance times depend on the dose, individual characteristics, and the presence or absence of compounds that may competitively inhibit 2,4-D excretion. For single oral doses of 2,4-D, the biological half-life in blood plasma is about one day, depending on the circumstances. However, forced alkaline diuresis may reduce this to as little as 3.7 h (Sauerhoff et al., 1977; Prescott et al., 1979).

In occupationally-exposed people, absorption of successive daily doses of 2,4-D makes its biological half-life difficult to determine, but for single occupational exposures it has been estimated to be 35-48 h (Nash et al., 1982).

6.5 Chlorinated dibenzo-p-dioxins (CDDs)

The metabolism in the rat of several dibenzo-p-dioxins, including the 2,7-CDD found in 2,4-D, was described by Tulp & Hutzinger (1978). The primary pathway of transformation appears to involve hydroxylation at the 2-, 3-, 7-, or 8-position in the molecule; some sulfur-containing conversion products have also been identified.

7. EFFECTS OF 2,4-D ON ANIMALS

7.1 General Introduction

Many studies of the toxicity of 2,4-D were carried out before the possible toxicological importance of manufacturing by-products, such as 2,6-dichlorophenoxyacetic acid, 2,4,6-trichlorophenoxyacetic acid (2,6-D and 2,4,6-T) monochlorophenoxyacetic acid, or N-nitroso compounds, was known or appreciated.

Furthermore, 2,4-D may be contaminated with several chlorinated dibenzo-p-dioxins (section 2.1.4). The toxicity of a number of these contaminants has not been examined in detail, but whether or not their presence would affect the toxicity of 2,4-D and its derivatives would depend on the amount of CDD present in the product, and on the inherent toxicity of the particular CDD isomers. The most toxic CDD isomer, namely 2,3,7,8-TCDD (Schwetz et al., 1973; McConnell et al., 1978; Leng, 1979; Kociba & Schwetz, 1982), is not normally found in 2,4-D products (see also section 2.1.4). However, there have been instances in which the same manufacturing equipment was used to produce both 2,4,5-T and 2,4-D, resulting in cross-contamination of 2,4-D with 2,4,5-T and 2,3,7,8-TCDD (US EPA, 1982).

Studies of structure-activity relationships using in vitro systems have shown that the CDDs that may be present in 2,4-D and its derivatives have a much lower biological activity than 2,3,7,8-TCDD (Poland & Glover, 1973; Poland & Kende, 1974; Poland et al., 1976; Bradlaw et al., 1980; Knutson & Poland, 1980). However, except for a study of the carcinogenic potential of 2,7-dichlorodibenzodioxin (2,7-DCDD) (US National Cancer Institute, 1979), the chronic toxicity of the CDD detected in 2,4-D and its derivatives has not been studied.

2,4-D has been in use as a herbicide for nearly 40 years, and during this time a great deal of literature on the toxicology of this chemical has accumulated. The extent to which its toxicity to various organisms has been tested, and the types of 2,4-D products used for such testing have varied over the years. Earlier 2,4-D products probably contained higher concentrations of trace contaminants than the 2,4-D in use today, and therefore it may have been found to be more toxic in earlier than in more recent studies. In addition, the generally accepted standards and protocols for pesticide toxicity tests have changed, making some of the older tests inadequate by present day standards. For these reasons, attention has been focused on the more recent studies. The older studies are, in many instances, only cited for completeness and should be used with caution, especially when

ascribing specific toxic effects to unspecified 2,4-D products and when establishing an effect level or no-observed-adverse-effect level for adverse effects of 2,4-D. The Task Group noted that a number of additional studies on 2,4-D are at present in progress. As the additional information becomes available, the present document will need to be updated.

7.2 Acute Effects

The reports of experimental studies to define the toxic and other effects of 2,4-D or its derivatives cover a wide range of organisms commonly referred to as "animals", including worms, molluscs, arthropods, lower vertebrates, birds, and mammals. Much of this information, especially on acute toxic effects, was recently tabulated by the National Research Council of Canada, Associate Committee on Scientific Criteria for Environmental Quality (1978), Schneider (1979), Bovey & Young (1980), Shearer & Halter (1980), and the Commission of the European Communities (CEC, 1981).

The usual mandatory acute and subacute safety tests for pesticides include assays for eye and skin irritancy and for skin sensitization, and determinations of the acute oral, percutaneous, and parenteral lethal doses, or of the corresponding lethal concentrations in the air, diet, or water.

7.2.1 Skin and eye irritancy

2,4-D does not appear to be an eye or skin irritant (Schneider, 1979). Adequate tests of the potential irritative properties of 2,4-D derivatives have not been reported in the literature.

7.2.2 Skin sensitization

No adequate published information is available on the dermal sensitization potential of 2,4-D and its derivatives in mammals.

7.2.3 Lethal doses and concentrations (LD₅₀ and LC₅₀)

The lethal potential of a chemical is usually measured as the dose (mg/kg body weight), or as the concentration in the air, diet, or water (mg/kg, mg/m³, mg/litre, respectively) that will kill 50% of the test animals in a specified time interval. These amounts are referred to as the LD₅₀ or LC₅₀. For 2,4-D and its derivatives, and for 2,4-D herbicide formulations, these statistically estimated values vary depending on the test product, the test species, and the route and frequency of administration (Tables 16 and 17).

Table 16. Acute oral toxicity of 2,4-D, esters, and salts

Compound	Species	Sex	LD ₅₀ (mg/kg bw)	Reference
2,4-D	mouse	M	375	Hill & Carlisle (1947)
	mouse	M	368	Rowe & Hymas (1954)
	rat	M	375	Rowe & Hymas (1954)
	rat		666	Hill & Carlisle (1947)
	guinea-pig	M & F	469	Rowe & Hymas (1954)
	guinea-pig		1000	Hill & Carlisle (1947)
	rabbit		800	Hill & Carlisle (1947)
	Jog		100	Drill & Hiratzka (1953)
butyl ester	mouse		380	Konstantinova (1970)
	rat		1500	Schillinger (1960)
	rat		920	Konstantinova (1970)
	cat		820	Konstantinova (1970)
esters of mono-, di-, and tripropylene glycol butyl ethers	rat	F	570	Rowe & Hymas (1954)
isopropyl ester	mouse	M	541	Rowe & Hymas (1954)
	rat	M & F	700	Rowe & Hymas (1954)
	guinea-pig	M	550	Rowe & Hymas (1954)
mixed butyl esters	mouse	F	713	Rowe & Hymas (1954)
	rat	F	670	Rowe & Hymas (1954)
	guinea-pig	F	848	Rowe & Hymas (1954)
	rabbit	M & F	1420	Rowe & Hymas (1954)
sodium salt	mouse		375	Rowe & Hymas (1954)
	rat	F	805	Rowe & Hymas (1954)
	rat		2000	Schillinger (1960)
	guinea-pig	M	551	Rowe & Hymas (1954)
	rabbit		800	Rowe & Hymas (1954)

7.2.3.1 Acute oral LD₅₀

7.2.3.1.1 Mammals

Published acute oral LD₅₀ values vary for different 2,4-D products and test species (Table 16). It appears that 2,4-D has a moderate acute toxicity for mammals (WHO, 1976).

7.2.3.1.2 Birds

Table 17 shows published oral LD₅₀ values for chickens.

Table 17. Acute LD50 for various 2,4-D products in domestic chickens (*Callus domesticus*)

Product	Animals	Procedure	LD50 (mg/kg bw)	Acid equivalent	References
2,4-D	chick, M & F	P.O., in olive oil	541 (358-817)	541	Rowe & Hymas (1954)
2,4-D Na salt	adult hen	P.O., in water	655	645	Loktionov et al. (1973)
2,4-D alkanolamine salts	chick	P.O., in water	> 380 < 765	368	Pjorn & Northorn (1958) Rowe & Hymas (1954)
2,4-D amine salt	6-month chicken	P.O., in water	1950	1038	Loktionov et al. (1973)
2,4-D butyl esters	chick, M & F	P.O., undiluted	2000 (1350-2960)	1503	Rowe & Hymas (1954)
2,4-D butoxyethyl esters	chick, 330 g	P.O., in food	900	588	Whithead & Partigrew (1972)
2,4-D isopropyl esters	chick, M & F	P.O., in olive oil	1420 (1127-1789)	1145	Rowe & Hymas (1954)
2,4-D/2,4,5-T (1:1), butyl ester	chick, M & F 3 weeks old	P.O., undiluted	4000 (2700-5900)	-	Rowe & Hymas (1954)

7.2.3.2 Acute dermal LD₅₀

7.2.3.2.1 Mammals

— Reports by Buslovich (1963) and Fetisov (1966) indicate that, under extreme test conditions, mice and rats may absorb lethal amounts of 2,4-D amine salts and esters through their skin, but no acute dermal LD₅₀ values were available for review.

7.2.3.3 Acute inhalation LC₅₀

No accurate measurements of acute inhalation LC₅₀ values for 2,4-D products were available.

7.2.3.4 Parenteral LD₅₀

The acute parenteral LD₅₀ values reported for various laboratory animals and 2,4-D products ranged from 220 to 666 mg a.i./kg body weight (National Research Council of Canada, Associate Committee on Scientific Criteria for Environmental Quality, 1978; Young et al., 1978; Schneider, 1979).

7.2.4 Acute toxicity in aquatic organisms

— The available reports indicate great differences in acute LC₅₀ values obtained with different test species, and with different 2,4-D derivatives and test formulations. The esters appear to be considerably more toxic than the water-soluble salts. For fish, the LC₅₀ for various 2,4-D isooctyl ester products may range from 5 to 68 mg/litre for bluegill sunfish (Lepomis spp.) and from 62 to 153 mg/litre for rainbow trout (Salmo gairdneri) (Schneider, 1979). This variability may, in part, be due to differences in test animal species and strains, in test conditions (temperature, pH, O₂ tension, mineral content of water), and, in part, to the effects of chemicals other than 2,4-D in the herbicide formulations, or of 2,4-dichlorophenol, which may occur in water as a decomposition product of 2,4-D (Holcombe et al., 1980). Discussions on this variability can be found in numerous reviews: Way (1969), Katz et al. (1972), National Research Council of Canada, Associate Committee on Scientific Criteria for Environmental Quality (1978), and of Halter (1980), as well as in the reports of studies by Harrisson & Rees (1946), King & Penfound (1946), Lopez (1961), Hughes & Davis (1963), Butler (1965), Hiltibran (1967), Mount & Stephan (1967), Alabaster (1969), Sanders (1970a), Andrushaitis (1972), Cooke (1972), Shim & Self (1973), Fabacher & Chambers (1974), Meehan et al. (1974), Nishiuchi & Yoshida (1974), Rehwooldt et al.

(1977), Vardía & Durve (1981), and particularly in the extensive and methodical investigation of Pravda (1973).

Similar information on aquatic invertebrates is available in the review of Mackenthun & Keup (1972) and in the studies of Hooper (1958), Sudak & Claff (1960), Beaven et al. (1962), Rawls (1965), Sanders (1970b), Klekowski & Zvirgzds (1971), Wierzbicka (1974a,b), and Caldwell et al. (1979).

The observations of Hansen et al. (1972, 1973) and Folmar (1976) indicate that fish and aquatic invertebrates will try to avoid water containing toxic amounts of 2,4-D products.

7.3 Subchronic and Chronic Toxicity

7.3.1 Mammals

Most of the published long-term studies with mammals have already been reviewed by Bodyagin et al. (1969), Way (1969), IARC (1977, 1982), National Research Council of Canada, Associate Committee on Scientific Criteria for Environmental Quality (1978), Young et al. (1978), Bovey & Young (1980), Shearer (1980), and US Veterans' Administration (1981).

In the long-term as in the short-term studies on mammals, the test products were mainly administered orally. The composition of the test products was not adequately known by present standards, but many of the tests were carried out with more or less purified 2,4-D or its alkali salts. It is difficult to decide to what extent the available results reflect the toxicological properties of the present 2,4-D products, in which the maximum contents of CDD and other toxic by-products are kept at very low levels.

A long-term feeding study in the rat (Hansen, 1971) was evaluated by FAO/WHO JMPR in 1971 (FAO/WHO, 1972). It was concluded that a no-observed-adverse-effect level in the rat was equivalent to 31 mg/kg body weight per day. However, new studies on mice and rats are in progress.

7.3.1.1 Clinical signs of poisoning

Signs of toxic effects on the digestive tract, such as diarrhoea, vomiting, dysphagia, decreased gut motility, irritation, or necrotic changes (in dogs including necrosis of oral tissues) are likely to appear in animals following the absorption of high doses of 2,4-D or its derivatives by the oral, dermal, or inhalation routes, and after parenteral injections (Bucher, 1946; Hill & Carlisle, 1947; Drill & Hiratzka, 1953; Rowe & Hymas, 1954; Thomssen, 1958; Björklund & Erne, 1966; Erne, 1966a; Palmer & Radeleff, 1969). Blood-tinged discharges from the nose, and in dogs also nasal and eye irritation and skin lesions may also occur (Bucher,

1946; Hill & Carlisle, 1947; Kosyan et al., 1974). Cattle may suffer from tympanitis, and may show signs of thirst (Björklund & Erne, 1966). However, some of the signs of "2,4-D poisoning" reported in herbivores pastured on 2,4-D-treated vegetation may have been caused by the ingestion of inherently poisonous plants (Maclean & Davidson, 1970). Pigs may refuse to eat feed containing high amounts of 2,4-D (Strach & Bohosiewicz, 1964), but sheep have been reported to feed avidly on 2,4-D-treated vegetation (Sadykov et al., 1972).

Characteristic signs of severe 2,4-D poisoning in mammals appear to be muscular weakness, stiffness, stilted gait, and muscle spasms (myotonia), alleviated by exercise and exacerbated by rest. There may also be muscular incoordination progressing to paralysis especially in the hind limbs; in rodents, caudal rigidity has also been observed. These clinical signs are the result of the myotoxic action of 2,4-D discussed below, which, through its effects on the heart, may also lead to hypo- or hypertension, cardiac fibrillation, and death. Prolonged inactivity may also occur and may lead to pulmonary congestion, emphysema, and pneumonia (Bucher, 1946; Hill & Carlisle, 1947; Drill & Hiratzka, 1953; Vinokurova, 1960; Björklund & Erne, 1966; Gorshkov, 1972; Sadykov et al., 1972; Kosyan et al., 1974).

At high doses, 2,4-D and its derivatives may act as a central nervous system depressant and cause lethargy, slowed respiration, stupor, coma, and death (Bucher, 1946; Hill & Carlisle, 1947; Drill & Hiratzka, 1953; Vinokurova, 1960; Desi et al., 1962a,b; Desi et al., 1962a,b; Kosyan et al., 1974; Elo & Ylitalo, 1977, 1979).

7.3.1.2 Effects on food and water consumption, and on body weight

Relatively high concentrations of 2,4-D or its derivatives in the diet or drinking water, or given by capsule, gavage, or parenterally, may cause a reduction in food and water consumption, and weight loss or reduced body weight gain in rats (Rowe & Hymas, 1954; Thomssen, 1958; Björklund & Erne, 1966; Chang et al., 1974; Chen et al., 1981; Gorshkov, 1972), as well as in dogs (Bucher, 1946; Drill & Hiratzka, 1953), in pigs (Strach & Bohosiewicz, 1964; Björklund & Erne, 1966), in rabbits (Loktionov et al., 1973), in cattle (Rowe & Hymas, 1954; Björklund & Erne, 1966; Palmer & Radeleff, 1969; McLennan, 1974), and sheep (Palmer & Radeleff, 1969). However, the same authors, as well as Guseva (1956) and Hansen et al. (1971) did not observe these effects at low doses or low dietary concentrations of 2,4-D. In fact, in the studies by Raoul & Marnay (1948) and Strach & Bohosiewicz (1964) on rats and piglets fed low dietary concentrations of 2,4-D, an

unimpaired appetite and an improved body weight gain was seen in some groups of animals. In these studies, the dosages ranged between 15 and 119 mg 2,4-D/kg body weight.

Observations of Thomssen (1958), Strach & Bohosiewicz (1964), Martynov (1970), Gorshkov (1972), Sadykov et al. (1972), and Erne (1974), on hares (Lepus timidus), European elk, pigs, and rats suggest that, given a choice, animals will refuse to eat food or to drink water containing more than a certain amount of 2,4-D, and that this may, in part, be because of the strong characteristic odour and taste of this compound, or of organic solvents such as diesel fuel that are used in herbicide formulations or as diluents.

7.3.1.3 Effects on the central nervous system (CNS)

It has been suggested that the signs of central nervous system depression in animals severely poisoned with 2,4-D are related to a partial breakdown of the blood-brain barrier, possibly as a result of damage to capillary vessels, and a subsequent accumulation of 2,4-D in the CNS (Desi & Sos, 1962a,b; Elo & Ylitalo, 1977, 1979).

However, further studies are needed to clarify the mechanism(s) by which 2,4-D acts on the central nervous system.

7.3.1.4 Effects on the peripheral nervous system

No peripheral neuropathy was attributed to 2,4-D in the available reports on short-term and long-term studies with 2,4-D in a variety of animals (Shillinger & Naumova, 1957; Stupnikov, 1959). The partial or complete paralysis, especially of the hind legs, of 2,4-D poisoned animals reported already by Bucher (1946) and Hill & Carlisle (1947) may be a myotoxic rather than a neurotoxic effect of 2,4-D. Moreover, in severe 2,4-D poisoning, a general weakness may lead to inactivity that might be interpreted as paralysis.

No signs of neuropathy were reported by Kay et al. (1965) in rabbits given large percutaneous doses of 2,4-D dimethylamine salt, 2,4-D butyl ester, or 2,4-D isooctyl ester. In similar studies in which rats or rabbits were exposed by the dermal route, Buslovich (1963) reported myotonia and death in rats given unspecified doses of 2,4-D amine salt or 2,4-D butyl ester, but no peripheral neuropathy, while Vinokurova (1960) found 130-180 mg of a 50% aqueous emulsion of 2,4-D octyl ester/kg body weight to have "no systemic effect" on rabbits.

The neurotoxic effects in animals of 2,4-D and of other related compounds have not been adequately studied. Further research is required to elucidate the mechanism of the neurotoxic and myotoxic action of 2,4-D in animals.

7.3.1.5 Myotoxic effects

Most of the studies of the effects of 2,4-D on vertebrate muscles were carried out because the 2,4-D-induced abnormalities resemble a heritable muscle disorder in human beings, namely myotonia congenita (Hofmann et al., 1966; Laskowski & Dettbarn, 1977). As a rule, high doses of 2,4-D (1/4 to 1/2 LD₅₀) are required to obtain severe and prolonged myotonia. The effects of 2,4-D on muscle cells are complex, and include disturbances in: the activity of various enzymes (leading, for example, to increased lactate production); potassium levels; membrane resistance; and in chloride conductance. There are also shifts in calcium-binding sites, changes in muscle and nerve cell electrical potentials, and mitochondrial structural and ultrastructural degenerative changes in muscle (Eyzaguirre et al., 1948; Kuhn & Stein, 1964, 1965, 1966; Heene 1966, 1968, 1975; Hofmann et al., 1966; Kenigsberg, 1968; Stein & Kuhn, 1968; Bodem et al., 1971; Preiss & Rossner, 1971; Seiler, 1971; Buslovich & Koldobskaya, 1972; Rüdiger et al., 1972; Senges & Rüdiger, 1972; Brody, 1973; Danon et al., 1976; Iyer et al., 1976; Bretag & Caputo, 1978; Dux et al. 1978; De Reuck et al., 1979; Eberstein & Goodgold, 1979; Mazarean et al., 1979a,b). Similar effects are produced by the chlorophenoxy drug clofibrate (atromid) (Pierides et al., 1975; Smals et al., 1977). None of the available studies on 2,4-D-induced myotonia were designed to establish no-observed-adverse-effect levels for the various myotoxic effects in intact animals, and therefore additional studies should be carried out for this purpose.

7.3.1.6 Cardiovascular effects

As part of its myotoxic action, 2,4-D and its derivatives may in high doses cause biochemical, physiological, and structural damage to the myocardium in vitro and in vivo (Bodem et al., 1971; Preiss & Rossner, 1971; Rüdiger et al., 1972; Mazarean et al., 1979a,b).

7.3.1.7 Haematological effects

Shifts have been reported in the number or types of erythrocytes, leukocytes, or bone marrow cells, or changes in haemoglobin levels, in a variety of laboratory and domestic mammals given 2,4-D or 2,4-D derivatives (Bucher, 1946; Hill & Carlisle, 1947; Drill & Hiratzka, 1953; Shillinger & Naumova, 1957; Schillinger, 1960; Björklund & Erne, 1966; Hansen et al., 1971; Sadykov et al., 1972; Loktionov et al., 1973; Kosyan et al., 1974; and Halliop et al., 1980).

7.3.1.8 Effects on blood chemistry

Rowe & Hymas (1954) were apparently the first investigators to monitor blood chemistry in 2,4-D-treated animals. They did not observe any adverse effects at 2,4-D dietary levels as high as 300 mg 2,4-D/kg in rats treated for 113 days.

Other investigators noted changes in various serum, plasma, or erythrocyte enzyme activity levels, and shifts in the levels of electrolytes, glucose, blood proteins, or other chemicals in response to treatment with 2,4-D or 2,4-D derivatives in rats, rabbits, cattle, pigs, or sheep, or in blood from such animals to which 2,4-D was added in vitro (Shillinger & Naumova, 1957; Schillinger, 1960; Björklund & Erne, 1966; Shevchenko, 1966; Dzhaparov & Tsilikov, 1969; Hunt et al., 1970; Szöcs et al., 1970; Gorshkov, 1972; Kosyan et al., 1974; Kuzminskaya & Bersan, 1975; Chen et al., 1981). Some of the changes in transaminase (SGOT, SGPT), blood urea nitrogen (BUN), or glucose levels appeared to be secondary to myotoxic, nephrotoxic, or hepatotoxic effects of high doses of 2,4-D.

7.3.1.9 Other biochemical effects observed in vivo or in vitro

Sufficiently high doses of 2,4-D may induce changes in mitochondrial oxygen consumption and oxidative phosphorylation, in electrolyte, ascorbic acid, glycogen, lipid, and nucleic acid contents of organs, tissues, cells, organelles, or cell fractions from a variety of mammals (Brody, 1952, 1973; Guseva, 1956; Baker et al., 1960; Kuhn & Stein, 1964; Heene, 1966, 1967, 1968; Shevchenko, 1966; Philleo & Fang, 1967; Kenigsberg, 1968; Dzhaparov & Tsilikov, 1969; Stanosz, 1969; Buslovich & Koldobskaya, 1972; Graff et al., 1972; Buslovich et al., 1973; Abo-khatwa & Hollingworth, 1974; Chang et al., 1974; Nikandrov, 1974; Venkaiah & Patwardhan, 1978; Podolak, 1979).

7.3.1.10 Pulmonary effects

No pulmonary abnormalities were reported in studies with mice, rabbits, rats, or dogs conducted by Bucher (1946), Drill & Hiratzka (1953), Rowe & Hymas (1954), Shillinger & Naumova (1957), Schillinger (1960), or Björklund & Erne (1966). In contrast, Hill & Carlisle (1947) and Palmer (1972) noted congestion of pulmonary vessels, pulmonary petechial haemorrhages, and pulmonary edema or emphysema in mice, rats, dogs, cattle, or sheep that died of 2,4-D poisoning.

7.3.1.11 Hepatotoxic effects

Rabbits, rats, mice, dogs, cattle, or sheep treated for a prolonged period with toxic doses of 2,4-D were found to develop a subacute toxic hepatitis with congestion of hepatic blood vessels, and cloudy swelling, fatty infiltration, local necrosis, degeneration, or atrophy of hepatocytes, especially of the parenchyma in the centrilobular areas (Bucher, 1946; Hill & Carlisle, 1947; Drill & Hiratzka, 1953; Rowe & Hymas, 1954; Björklund & Erne, 1966; Szöcs et al., 1970; Palmer, 1972). High doses of 2,4-D may induce a proliferation of peroxisomes and increased levels of mixed function oxidases in liver cells of rats and hamsters (Buslovich et al., 1982; Vainio et al., 1982, 1983).

Changes in the levels of certain liver enzymes such as maleate or succinic dehydrogenase, and in ascorbic acid or glycogen content or hippuric acid production have also been reported (Schillinger & Naumova, 1957; Baker et al., 1960; Dzhaparov & Tsilikov, 1969; Szöcs et al., 1970; Buslovich et al., 1973; Chang et al. 1974; Nikandrov, 1974). Some of the results concerning liver glycogen levels in rats suggest a reverse trend at high doses, as Dzhaparov & Tsilikov (1969) found that a dose equivalent to 1/16 LD₅₀ per day lowered the liver glycogen content, while Chang et al. (1974) observed the opposite effect at doses of about 100 mg/rat per day.

7.3.1.12 Effects on the kidney

In early studies with high doses of 2,4-D, signs of impaired kidney function, increased relative kidney weight, and of gross and histological abnormalities (parenchymatous degeneration, hypertrophy, and hyperplasia, cloudy swelling especially in the cells of the proximal convoluted tubules, and glomerular lesions) were noted in mice, rats, and dogs (Bucher, 1946; Hill & Carlisle, 1947; Drill & Hiratzka, 1953; Rowe & Hymas, 1954). That the kidney is a target organ for the structural, physiological, and chemical effects of 2,4-D was confirmed repeatedly by later and more detailed studies on a wider range of test species including pigs, goats, and sheep (Schillinger, 1960; Björklund & Erne, 1966; Erne, 1966a; Stanosz, 1969; Hunt et al., 1970; Milhaud et al., 1970; Gorshkov, 1972; Palmer, 1972; Senczuk & Pogorzelska, 1975; Koschier et al., 1978; Örberg, 1980a). In a recent 13-week study on rats, the no-observed-adverse-effect level for histological changes induced with pure 2,4-D in mammalian kidney appeared to be 15 mg/kg body weight per day (Chen et al., 1981).

7.3.1.13 Effects on endocrine organs

Swelling and congestion of the thyroid were noted by Palmer (1972) in cattle and sheep fatally poisoned with various 2,4-D products. Effects of 2,4-D on iodide uptake by the thyroid gland were first described by Sos & Kertai (1958) and studied further by Florsheim & Velcoff (1962), Florsheim et al. (1963), Tsilikov (1969), and Gorshkov (1972). Their results indicate that doses of 5-250 mg 2,4-D sodium salt or equivalent /kg body weight per day have a stimulatory effect on thyroid function.

Effects of 2,4-D on adrenal function and its relationship to muscle carbohydrate metabolism and 2,4-D-induced myotonia have been studied by Kenigsberg (1968), and by Buslovich & Koldobskaya (1972). 2,4-D-induced changes in adrenal or thyroid function may also be implicated in the abnormal temperature regulation in 2,4-D-treated rats described by Sudak et al. (1966). However, it is noteworthy that Buslovich (1963) was unable to induce a change in the body temperature of rats by giving 15-20 oral doses of 2,4-D sodium salt, amine salt, or butyl ester at a level of 1/10 or 1/5 LD₅₀/day.

7.3.1.14 Effects on the digestive tract

Vomiting, diarrhoea, hyperaemia, bloody exudates in the gut, necrotic changes in the mucosa, and other non-acute toxic effects on the digestive tract have been reported after administration of high doses of 2,4-D by either the oral or parenteral route in mice, rats, and dogs (Bucher, 1946; Hill & Carlisle, 1947; Drill & Hiratzka, 1953; Kosyan et al., 1974). However, Hansen et al. (1971) did not observe any such effects in a 2-year feeding study at dietary levels of 2,4-D corresponding to about 37.5 and 67.5 mg 2,4-D/kg body weight per day, respectively, for rats and dogs. Their observations on dogs contrast with those of Drill & Hiratzka (1953) who found repeated doses of 20 mg 2,4-D/kg body weight per day to be fatal in 3 out of 4 dogs studied by them.

7.3.2 Birds

The published reports on the toxic effects of 2,4-D and 2,4-D products in birds deal mainly with chickens (Gallus domesticus) and game birds. The available data on cumulative oral lethal doses for game birds have been summarized in Table 18; studies on the reproductive, embryotoxic, and teratogenic effects of 2,4-D are dealt with in section 7.3.6.

The clinical signs of 2,4-D poisoning in birds appear to be similar to those in mammals, and the kidney seems to be the

Table 18. Cumulative oral lethal doses of 2,4-D herbicides for game birds

Product	Species	Dietary LD ₅₀ (mg a.i./kg diet) ^a	Cumulative LD ₅₀ (mg a.i./kg bw) ^a	References
2,4-D diethylamine salt	quail (young)	5000	28 000	Dewitt et al. (1962)
	mallard duck (young)	5000	8250	
	mallard duck (adult)	5000 > 2500	8250 > 34 000	
2,4-D butoxyethanol ester	quail (young)	5000	38 000	
	quail (adult)	5000	40 700	
	pheasant (young)	5000	29 500	
	mallard duck (adult)	5000	> 33 000	

a a.i. = active ingredient.

most sensitive organ. No adverse effects were reported in chickens fed dietary levels of 1000 mg/kg for 21 days (142 mg/kg body weight) whereas kidney enlargement occurred in chickens fed 5000 mg/kg of diet for 21 days (Whitehead & Pettigrew, 1972).

7.3.3 Cold-blooded animals

The literature on the chronic effects of 2,4-D and its derivatives on cold-blooded animals (poikilotherms) was not reviewed in detail. The available reports indicate that for aquatic vertebrates in general, 2,4-D esters are more toxic than 2,4-D amines, and that the overall no-observed-adverse-effect level for toxic effects on fish for the esters is at or near 1 mg/litre (King & Penfound, 1946; Zhiteneva & Chesnokova, 1973; Fabacher & Chambers, 1974; Meehan et al., 1974). 2,4-dichlorophenol, which may occur in water as a by-product or transformation product of 2,4-D, is similarly toxic to fish (Holcombe et al., 1980).

7.4 Fetotoxicity, Teratogenicity, and Reproductive Effects

The scientific literature contains a fairly large number of reports on the fetotoxic, teratogenic, and reproductive effects of 2,4-D in livestock and in laboratory animals. However, most of the observations on livestock are either too sketchy to be useful or neglect to take into account various confounding factors. Examples of this are studies by Björklund & Erne (1966) on a single pregnant pig, by Sadykov et al. (1972) on sheep grazing on pastures apparently containing a high percentage of poisonous plants, and the report by Bodai et al., (1974), on reproductive disturbances in cattle feeding on either 2,4-D-treated vegetation possibly including poisonous plants, or on contaminated silage.

Some of the studies carried out with rodents under laboratory conditions also provide little useful information, either because it is difficult or impossible to determine the dose levels used in the studies (Weinmann, 1957; Schuphan, 1963, 1965, 1969; Schiller, 1964; Buslovich et al., 1976); or because the information provided is insufficient and the studies cannot be properly evaluated (Bucher, 1946; Hansen et al., 1971; King et al., 1971). The study by Weinmann (1957) can be considered invalid, as a high mortality occurred in both control and experimental animals, when they were exposed to cold stress because of construction work affecting the animal quarters during the winter months. Moreover, Weinmann (1957) and several other authors, including Schuphan (1963, 1965, 1969) Schiller (1964), Schillinger (1960), and Shillinger & Naumova (1957) did not in fact examine the effects of 2,4-D, but rather the effects of foods or food

extracts prepared from crops that had been sprayed with 2,4-D, and, in some cases, also with other plant growth substances. As none of these authors appears to have carried out an analysis to demonstrate the presence of 2,4-D residues in the test material, it is questionable whether the test animals ingested any 2,4-D or 2,4-D residues, and these studies are therefore not reviewed in detail. Buslovich et al. (1976) tested only a single dose level (1/2 LD₅₀) and this reduces the usefulness of their study. Pertinent reports are discussed below.

7.4.1 Rats

7.4.1.1 Effects on adult rats

No deleterious effects on the health or fertility of rats receiving the maximum tolerated dose of 87.5 mg/kg body weight in terms of 2,4-D or its molar equivalent of the isooctyl ester or the propylene glycol butyl ether ester per day, on days 6 - 15 of pregnancy, were reported by Schwetz et al. (1971) and Unger et al. (1980). Even higher amounts of 2,4-D or its equivalent in 2,4-D derivatives were used by Björklund & Erne (1966), Hansen et al., (1971) and Khara & McKinley (1972) with similar results.

Reduced testis and prostate size, abnormal spermatogenesis (and also liver and kidney damage) were reported by Schillinger (1960) in some of the male rats given 375 mg/kg body weight per day (about 1/4 LD₅₀) of a Soviet-made 2,4-D butyl ether formulation containing polyethylene glycol alkyl phenyl ether surfactant. These effects were not noted at 1/10 of this dose level, i.e., at 37.5 mg/kg body weight per day. Some of the toxic effects reported by Schillinger (1960) may have been caused by the surfactant, but as a surfactant control group was not included in this study, this cannot be confirmed. Thus, the available studies suggest that the no-observed-adverse-effect level for reproducing adult rats lies between 37.5 and 87.5 mg 2,4-D/kg body weight per day.

7.4.1.2 Effects on offspring

Björklund & Erne (1966) gave pregnant rats a 2,4-D concentration in drinking-water of 1000 mg/litre during pregnancy, and for the following 10 months. No effects on reproduction were noted.

Hansen et al. (1971) fed male and female rats dietary levels of technical 2,4-D of 100, 500, and 1500 mg/kg (ppm), and the rats were bred through 3 successive generations. At dietary levels of 100 and 500 mg/kg, no effects were noted. However, at a dietary level of 1500 mg/kg, survival of pups to

weaning was reduced. The number of pups surviving ranged from 70 - 97% in the control group and from 60 - 93% at the 100 and 500 mg/kg (ppm) dietary levels; survival at the highest dose ranged from 20 - 62%.

Resorptions, reduced fetal weight and size, enlarged ventricles of the brain and haemoperitoneum were found by Buslovich et al. (1976) in the offspring of rats treated with two different 2,4-D derivatives at a dose of one-half LD₅₀ (value unspecified). Schwetz et al. (1971) dosed female rats from day 6 - 15 of pregnancy by gavage at dose levels of 0, 12.5, 25, 50, and 87.5 mg/kg body weight per day with 2,4-D or equimolar dose levels of the propylene glycol butyl ether (PGBE) and the isooctyl esters (IO). At doses of 50 and 87.5 mg/kg, a decrease in fetal body weight was noted for all three compounds.

Subcutaneous oedema, delayed ossification of sternbrae, sternbrae with split centres of ossification, wavy ribs, and lumbar ribs increased with increasing doses, for at least one of the agents studied. However, these anomalies were not significantly increased at the 12.5 or 25 mg/kg dose level for the 3 compounds. A small but significant increase in the incidence of subcutaneous oedema was observed in fetuses from dams receiving 12.5 mg/kg molar equivalent of IO. The incidence of missing sternbrae was significantly increased at dose levels of 87.5 mg/kg for 2,4-D and 12.5 and 87.5 mg/kg for PGBE.

Unger et al. (1980), in a later study, using the same dosing regimens for 2,4-D IO and 2,4-D PGBE did not observe the effects reported by Schwetz et al., except for a statistically significant increase in rib buds at the highest dose (87.5 mg/kg) tested for both compounds ($P < 0.05$).

Khera & McKinley (1972) dosed female rats from day 6 - 15 of pregnancy by gavage with 2,4-D, 2,4-D IO, 2,4-D butyl ester, 2,4-D butoxyethanol ester and 2,4-D dimethylamine salt. The butyl and isooctyl ester depressed fetal weight and decreased fetal viability at the highest dose of 150 mg/kg body weight. Wavy ribs, additional ribs, retarded ossification and sternal defects, fused ribs, small-sized distorted scapula and micromelia were observed as anomalies among the treated groups. A statistically significant increase in malformed fetuses was noted at 2,4-D levels of 25 mg/kg body weight ($P < 0.05$) and at levels of 150 mg/kg or more for the other compounds.

Konstantinova et al. (1975) reported hemorrhage into internal organs in the fetuses of rats treated with a 2,4-D level of 50 mg/kg body weight.

The results of all these studies suggest that dosage levels of less than 12.5 mg/kg body weight for the various 2,4-D derivatives do not cause fetotoxic or teratological

effects in rats, and the results of the more recent study by Unger et al. (1980) indicate that higher doses may be without deleterious effects on the fetuses.

Thus, at present, a daily dose level of 10 mg 2,4-D or 2,4-D acid equivalent/kg body weight can be considered to be without significant fetotoxic or teratogenic effects in rats.

7.4.2 Mice

The report by Courtney (1977) indicated that in CD-1 mice, doses of 1 mM/kg body weight of 2,4-D and its n-butyl and PGBE esters reduced fetal body weight, and increased fetal mortality. The compounds were also teratogenic, inducing cleft palates, at levels of 124 mg/kg body weight per day (2,4-D or acid equivalent) or more. However, the 2,4-D isopropyl and isooctyl esters appeared to be less teratogenic than 2,4-D, as they did not induce birth defects at a 2,4-D equivalent level of 124 mg/kg body weight per day. Furthermore, the 2 esters did not induce fetal death in CD-1 mice at doses of 2,4-D equivalent up to 221 mg/kg body weight per day.

7.4.3 Birds

In the 1960s and 1970s, a number of tests of the embryotoxic, teratogenic, and other reproductive effects of 2,4-D were carried out on birds' eggs and embryos. These results may not apply to mammals, because bird embryos develop in a closed environment different from that of mammalian embryos, and because birds differ anatomically from mammals.

Lutz-Ostertag & Lutz (1970, 1974) reported mortality and severe deformities in wild bird embryos exposed to 2,4-D amine salt, but they did not provide crucial experimental details, and other investigators (Dunachie & Fletcher, 1967, 1970; Kopschke, 1972; Grolleau et al., 1974; Gyrd-Hansen & Dalgaard-Mikkelsen, 1974; Somers et al., 1974a,b,c; Hilbig et al., 1976a,b; Spittler, 1976) were unable to duplicate their results either with 2,4-D amine salts or esters. Some of the teratogenic effects attributed to 2,4-D by Lutz-Ostertag & Lutz (1970, 1974) resemble those induced by excessively high incubation temperatures (Nielsen, 1968), and may thus have been experimental artifacts.

On the whole, the available studies on bird embryos indicate that the no-observed-adverse-effect level for 2,4-D-induced embryotoxic and teratogenic effects lies near 0.5 mg active ingredient/egg (equivalent to about 10 mg/kg) and is thus similar to that in mammals.

7.4.4 Cold-blooded animals

The available literature contained little information concerning the possible reproductive, embryotoxic, or teratogenic effects of 2,4-D or 2,4-D derivatives on cold-blooded animals.

7.4.4.1 Amphibians

Lopez (1961) noted that the motility of frog spermatozoa was not affected by low concentrations of 2,4-D or its sodium salt, and that the inhibition of movement, or the lysis observed under some conditions were caused by changes in the pH of the test solution. Aqueous solutions of less than 0.05% 2,4-D sodium salt did not induce any macroscopic abnormalities in developing frog eggs or embryos (Lhoste & Roth, 1946), while Cooke (1972) did not find either toxic effects or 2,4-D residues in frog tadpoles exposed for 1 or 2 days to up to 50 mg 2,4-D/litre. According to Sanders (1970a) a commercial 2,4-D dimethylamine salt had an LC₅₀ of 100 mg/litre for frog tadpoles.

7.4.4.2 Fish

Only three brief reports were available on the effects of 2,4-D on developing fish eggs and embryos. Andrusaitis (1972) found that 2,4-D reduced the oxygen consumption of 32-cell blastomeres, and increased the oxygen consumption in 64-128 cell blastomeres of Misgurnus fossilis. In a study by Mount & Stephan (1967), 2,4-D butoxyethanol ester (BEE) at a concentration of up to 0.31 mg/litre, or 2,4-D at 0.80 mg/litre did not reduce the reproduction rate in fathead minnows (Pimephales promelas), whereas 2,4-D BEE at 1.5 mg/litre killed minnow eggs in 48 h. Rehwooldt et al. (1977) similarly found that 0.1 mg 2,4-D/litre did not have any adverse effect on reproduction in guppies.

These reports suggest that the no-observed-adverse-effect level of 2,4-D BEE for the reproductive or teratogenic effects of 2,4-D in fish may be about 1 mg a.i./litre water.

7.5 Mutagenicity and Related Effects

7.5.1 2,4-D and its derivatives

Studies on the mutagenicity of 2,4-D and its derivatives have been reviewed by Andersen et al. (1972), National Research Council of Canada, Associate Committee on Scientific Criteria for Environmental Quality (1978), Ramel (1978), Seiler (1978), Vachkova-Petrova (1978), Kas'yanenko & Koroleva

(1979), Murthy (1979), Shearer (1980), US Veterans' Administration (1981), Waters et al. (1981), and Linainmaa (1983).

A recent IARC Working Group (IARC, 1982) evaluated the activity of 2,4-D and derivatives in short-term tests. It was reported that 2,4-D induced unscheduled DNA synthesis in cultured human fibroblasts (Ahmed et al., 1977a), but not in rat hepatocytes (Probst et al., 1981). 2,4-D was not mutagenic in bacterial systems (Andersen et al., 1972; Sherasen et al., 1976; Zetterberg, 1977; Moriya et al., 1983). 2,4-D was mutagenic in yeast, when tested at low pH (Zetterberg et al., 1977), but was not active under other conditions (Zetterberg, 1977) or in a host-mediated assay (Zetterberg et al., 1977). Results of four studies on Drosophila melanogaster were reported to be positive (Rasmuson & Persson-Svahalín, 1978): results of three other studies were negative (Berin & Buslovich, 1971; Vogel & Chandler, 1974; Magnusson et al., 1977; Rasmuson & Svahlin, 1978).

2,4-D was reportedly mutagenic in cultured Chinese hamster ovary (CHO) cells (Ahmed et al., 1977b), but did not induce a statistically significant increase in sister chromatid exchanges (SCEs) in CHO cells in vitro (Linainmaa, 1983). Chromosomal effects have been reported in plants (Khalatkar & Bhargava, 1982).

Chromosomal aberrations or SCEs were found in cultured human lymphocytes (Pilinskaya, 1974; Korte & Jatal, 1982), but chromosomal aberrations were not found in cultured embryonic bovine kidney cells (Bongso & Basrur, 1973).

In mice, single oral doses of 100 - 300 mg 2,4-D/kg body weight reportedly induced chromosomal aberrations (Pilinskaja, 1974), but micronuclei were not found in mice after ip injection of single doses of 100 mg 2,4-D/kg body weight (Jenssen & Renberg, 1976). 2,4-D was not active in a dominant lethal test in mice (Epstein et al., 1972), and did not induce SCEs in rats after oral administration of 2,4-D amine salt at daily doses of 100 mg/kg body weight for two weeks (Linainmaa et al., 1983). Recent evidence (Buslovich et al., 1982; Vainio et al., 1982) suggests that 2,4-D may have an indirect effect on genetic material via the production of active oxygen radicals derived from peroxisome proliferation, which has been demonstrated in in vivo and in vitro studies in liver cells of rats and hamsters (Reddy et al., 1980, 1982; Vainio et al., 1982; Gray et al., 1983).

At present, available studies are inadequate to evaluate the genetic effects of 2,4-D and its derivatives in short-term tests (IARC, 1982). No data on cell transformation are available.

7.6 Carcinogenic Effects on Experimental Animals

7.6.1 2,4-D and its derivatives

A number of studies have been carried out on mice and rats to assess the potential carcinogenic effects of 2,4-D and its derivatives. Two IARC Working Groups have reviewed these studies (IARC, 1977, 1982) and concluded that it was not possible to make an evaluation on the basis of the available data. 2,4-D and several of its esters were tested by oral administration and by a single sc injection in the newborn of 2 strains of mice (Innes et al., 1969); 2,4-D or its amine salts were also tested in rats by oral administration (Arkhipov & Kozlova, 1974; Hansen et al., 1971).

Nearly 20 years have passed since these studies were carried out and because of basic flaws in their design and execution, it is unlikely that further reviews of these studies will lead to generally accepted conclusions. The Task Group was aware that further long-term studies in mice and rats were in progress, and these should prove useful in the future evaluation of the potential carcinogenicity of 2,4-D.

7.6.2 Contaminants in 2,4-D

2,7-DCDD was tested for carcinogenicity in mice and rats fed dietary levels of 5000 and 10 000 mg/kg for 90 weeks, followed by a short observation period of about 1 - 10 weeks, at which time all animals were killed. Sufficient numbers of animals survived to evaluate the development of late-appearing tumours. Although an increased incidence of hepatocellular adenomas and carcinomas was observed in treated male mice (20/50 in the low dose and 17/42 in the high dose compared with 8/49 in matched controls), it was noted that the incidence of liver tumours in historical controls ranged from 16 - 32%. No tumorigenic effects were found in rats (US National Cancer Institute, 1979).

8. EFFECTS ON MAN, CLINICAL AND EPIDEMIOLOGICAL STUDIES

The available clinical and epidemiological studies fall into 4 groups: (a) studies on patients treated with 2,4-D as an anticancer drug (Apffel, 1959a) or antibiotic (Seabury, 1963), (b) reports on acute 2,4-D poisoning due to voluntary or accidental ingestion of herbicides (Tables 19 and 20), (c) reports on workers (mainly men) overexposed to 2,4-D during the manufacture, processing, or use of 2,4-D herbicides, and (d) epidemiological studies on groups of people who were actually or potentially exposed as a result of herbicide spray programmes, or who lived in areas in which herbicides were used. With the exception of the case studies of Apffel (1959a) and Seabury (1963), almost all of the reports deal with mixed exposures to 2,4-D and other chemicals, and therefore it is often unclear to what extent 2,4-D, its alkali or amine salts, or its esters contributed to the effects reported by the authors of the studies.

Much of the literature on acute poisonings and on the health effects of occupational overexposure to 2,4-D or other chlorophenoxy compounds or their toxic by-products has been recently reviewed by Pocchiari et al. (1979), Bovey & Young (1980), Huff et al. (1980), National Research Council of Canada, Associate Committee on Scientific Criteria for Environmental Quality (1981), CEC (1981), Rappe & Buser (1981), US Veterans' Administration (1981), Coggon & Acheson (1982), Hay (1982), IARC (1982,1983), and Dobrovolski (unpublished data, 1983). However, most of these reviews concentrated on 2,4,5-T, Agent Orange, and other herbicides used in the Vietnam war, or on industrial accidents resulting in massive exposures to largely undefined mixtures of chlorophenols, chlorinated dibenzodioxins, and other reaction products. In contrast, the present review focuses mainly on 2,4-D herbicides.

In evaluating human exposure to mixtures of chemicals that include 2,4-D and various concentrations of contaminants of 2,4-D, it is in many instances difficult or impossible to determine whether any of the described effects can actually be attributed to the exposure to 2,4-D or its derivatives.

8.1 Acute Poisoning and Occupational Overexposure

Pertinent reports on acute poisoning with 2,4-D, or of the effects of occupational overexposure to 2,4-D herbicides are summarized or cited in Tables 19 and 20.

Signs and symptoms of acute over-exposure to 2,4-D or its derivatives occurred after ingestion or absorption of large amounts, or where poor occupational hygiene was practised leading to pronounced dermal absorption of the material. It

Table 19. Acute toxicity of 2,4-D, fatal poisonings with herbicides containing 2,4-D

Product(s)	Circumstances	Sex of victim	Body weight or age	Dose ingested	2,4-D concentration in tissues (mg/kg)	Effects and outcomes	References
<u>a) Fatal poisonings</u>							
2,4-D diethyl ester (DICOTEX EXTRA)	not stated	F	50.8 kg	60-90 g (1180-1770 mg DICOTEX/kg bw)	40-400	coma; death in about 2 days; degeneration of convoluted kidney tubules	Curry (1962)
"2,4-D" 400g a.i./litre	suicide	M	?	~ 125 ml	? (< 400 bw)	loss of consciousness, coma, generalized muscular hypotonia, loss of all reflexes, hypotension, hyperglycaemia, proteinuria; death in 12 h	Delarrard & Barbaute (1969)
"pure" 2,4-D acid in kerosene	suicide	M	55 kg	?	57.6-407.9	coma, myotonia, fever, pulmonary emphysema and edema, liver necrosis, degeneration of kidney tubules; death in 6 days	Dudley & Thapar, (1972)
"2,4-D"	suicide	F	?	?	20-116	loss of consciousness, vomiting, uterine bleeding, tachycardia, and circulatory failure; death in about 30 h; edema and congestion of brain; fatty liver cell changes; fatty changes in kidney tubules; pulmonary hyperaemia & edema with isolated haemorrhages	Geldmacher-Van Mallinckrodt & Lautenbach, (1966)
"2,4-D"	suicide	M	?	"at least" 13.5 g		stiffness in legs, vomiting, loss of consciousness; death in 14 h; hyperaemia and edema of brain; pulmonary edema	Herbich & Machata (1963)

Table 19 (contd).

2,4-D dimethylamine formulation	suicide	M	75 kg	120 ml (80 mg/kg)	12.5-7700	vomiting; congestion, pulmonary embysama; CNS congestion & perivascular haemorrhages, severe degeneration of ganglion cells; death within hours of ingestion	Nielsen et al., (1965)
Herbicide containing 2,4-D, mecoprop (MCP) and chlorpyrifos	suicide	M	26 years	360 ml 2,4-D and mecoprop amine salt (10.6%, 11.6% a.i.) and 360 ml chlorpyrifos in karosene (6.7% a.i.) plus few granules Warivarin (0.025% a.i.)	plasma 321 (1.6 h) 540.9 (21 h) 480.8 (30 h)	clinical and pharmacokinetic study coma with pin-point pupils, tachycardia, hypertension, myoclonus, diarrhoea, then hypotension, cardiac arrhythmias, asystole, and death after 30 h	Osterloh et al., (1983)
					urine (on admission): 230.3		
					gastric content (on admission): 108.2		
					Tissues (post mortem)		
					2,4-D = 600 mg/kg brain: 186.4		
					bw; meco- blood: 389.5		
					prop = 600 liver: 293.5		
					mg/kg bw heart: 301.2		
					kidney: 315.0		

Table 20. Acute or non-acute effects attributed to occupational or bystander overexposure to 2,4-D herbicide

Target organ or organ system	Types of effects	References
Central nervous system	i) unconsciousness	Radionov et al. (1967); Paggiaro et al. (1974)
	ii) electroencephalograph changes	Kontek et al. (1972); Andreasik et al. (1979)
	iii) subjective symptoms	Assouly (1951); Goldstein et al. (1959); Monarca & Divito (1961); Foissac-Gegoux et al. (1962); Berkley & Magee (1963); Belomyttseva (1965); Fattisov (1966); Radionov et al. (1967); Bashirov (1969); SARE (1972); Andreasik et al. (1979); Kuzyk (1979)
		Foissac-Gegoux et al. (1962); Todd (1962); Belomyttseva & Karimova (1963); Bashirov (1969)
Peripheral nervous	i) polyneuritis	Monarca & Divito (1961); Foissac-Gegoux et al. (1962); Todd (1962)
	ii) partial paralysis	Monarca & Divito (1961); Foissac-Gegoux et al. (1962); Todd (1962)
	iii) functional changes	Monarca & Divito (1961); Foissac-Gegoux et al. (1962); Berkley & Magee (1963); Belomyttseva (1967); Wallis et al. (1970); Andreasik et al. (1979); Singer et al. (1982)
	iv) subjective symptoms	Foissac-Gegoux et al. (1962); Berkley & Magee (1963); Wallis et al. (1970); Paggiaro et al. (1974)
Skeletal muscles	i) myotonia, myoglobinuria, fibrillation stiffness	Wallis et al. (1970)
	ii) muscle damage or atrophy	Assouly (1951); Foissac-Gegoux et al. (1962); Todd (1962); Fattisov (1966); Radionov et al. (1967); Bashirov (1969); Wallis et al. (1970)
	iii) subjective symptoms	Assouly (1951); Monarca & Divito (1961); Bashirov (1969); Kuzyk (1979)
Digestive system	i) vomiting, diarrhoea	Goldstein et al. (1959); Monarca & Divito (1961); Todd (1962); Belomyttseva (1967); Radionov et al. (1967); Paggiaro et al. (1974); Dennis (1976)
	ii) various functional disorders or subjective symptoms	Assouly (1951); Monarca & Divito (1961); Bashirov (1969); Wallis et al. (1970); Kuzyk (1979)

Table 20 (contd).

Respiratory system	i) irritation, coughing	Assouly (1951); Belomyttseva & Karimova (1963); Belomyttseva (1965); Wallis et al. (1970); Andreasik et al. (1979)
	ii) functional disorders	Belomyttseva & Karimova (1963); Bashirov (1969); Wallis et al. (1970)
Circulatory system	i) functional changes: - cardiac involvement - vascular involvement	Belomyttseva & Karimova (1963); Belomyttseva (1967); Winkelmann (1960); Bashirov (1969); Paggiaro et al. (1974); Andreasik et al. (1979)
	ii) haematological or chemical changes	Monarca & Divito (1961); Todd (1962); Belomyttseva (1967); Radionov et al. (1967); Long et al. (1969); Paggiaro et al. (1974); Andreasik et al. (1979)
	iii) subjective symptoms	Radionov et al. (1967); Bashirov (1969); Andreasik et al. (1979)
Liver	functional abnormalities	Belomyttseva & Karimova (1963); Belomyttseva (1967); Bashirov (1969); Andreasik et al. (1979)
Kidney	functional abnormalities	Monarca & Divito (1961); Foissac-Gegoux et al. (1962); Belomyttseva (1967); Bashirov (1969); Paggiaro et al. (1974); Andreasik et al. (1979)
Skin	i) irritation or allergic reactions	Belomyttseva (1967); Radionov et al. (1967); Dennis (1976); Kuzyk (1979)
	ii) desquamation	Foissac-Gegoux et al. (1962)
	iii) chloracne	Londono (1966)
Reproductive system	functional abnormalities (women) decreased libido (men) impotence	Flika et al. (1975) Andreasik et al. (1979) Espir et al. (1970)

is unlikely that, with good agricultural practice, good personal protection, and occupational hygiene, resulting in exposures to low concentrations of 2,4-D, any of the acute symptoms and signs reported below would be expected to occur.

The observations of Apffel (1959a) and Seabury (1963) on patients treated with 2,4-D suggest that the acute no-observed-adverse-effect level for biological effects in human beings may be as high as 36 mg of purified 2,4-D/kg body weight, or its equivalent in alkali or amine salts or esters. The lack of subjective or clinical effects in studies in which volunteers ingested low doses (5 mg/kg body weight) of purified 2,4-D also supports the idea that a dose of a few mg/kg body weight is unlikely to be toxic (Khanna & Kohli, 1977; Sauerhoff et al., 1977). However, it is less certain whether this is true also of the less pure commercial 2,4-D products. From the point of view of occupational and bystander safety, it is reassuring that no reports were found of fatal poisonings following dermal exposure or inhalation, though temporary unconsciousness and other severe acute effects have been attributed to massive combined dermal and inhalation exposures to 2,4-D herbicides.

Most poisonings with 2,4-D herbicides involved formulations containing more than one toxic ingredient, including solvents, surfactants, and other additives. The symptoms and clinical signs therefore tended to vary with different products.

8.1.1 Neurotoxic effects of 2,4-D and related compounds

Some of the case reports cited below on poisonings with, and occupational overexposures to, herbicides indicate that 2,4-D and other chlorophenoxy compounds may affect both the central and peripheral nervous systems.

8.1.1.1 Effects on the central nervous system

In addition to subjective symptoms of the central nervous system, impaired coordination, impaired responses to external stimuli, unconsciousness, coma, and death have been observed in human beings mainly after absorption of lethal or nearly lethal doses of 2,4-D. The acute effects on the central nervous system seem to resemble those produced by alcohol, sedative drugs, or aromatic chlorinated hydrocarbons rather than those produced by organophosphate or carbamate neurological poisons (Geldmacher Von Mallinckrodt & Lautenbach, 1966; Prescott et al., 1979). Acute cerebral demyelination occurred in a suicide who ingested a solution of 2,4-D in kerosene (Dudley & Thapar, 1972). Severe degeneration of brain ganglion cells was observed in another

suicide who drank a herbicide product containing 2,4-D in the form of water-soluble dimethylamine salt (Nielsen et al., 1965). It is therefore possible that lethal doses of chlorophenoxy compounds may cause structural as well as functional damage to the brain.

Cranio-cerebral and peripheral functional nerve damage was noted by Bezuglyi et al. (1979) in a group of women occupationally overexposed to 2,4-D herbicides and other pesticides. Electro-encephalographic (EEG) abnormalities were observed in tractor drivers spraying herbicides containing 2,4-D, MCPA, or mecoprop (Kontek et al., 1973), in "individuals exposed to" chlorophenoxy herbicides, including 2,4-D and MCPA (Bielski & Madra, 1976) and in workers packaging 2,4-D sodium salt (Andreasik et al., 1979). On the other hand, a case of neuropathy with EEG abnormalities and flaccid quadriplegia, originally attributed to occupational overexposure to MCPA, was diagnosed as being of viral origin (Nayrac et al., 1958), and therefore some of the neurological damage attributed to 2,4-D, may have been caused by viruses. There is some evidence that 2,4-D herbicides may affect the sensory system, as Andreasik et al. (1979) and Assouly (1951) reported intolerance to certain odours, hypersensitivity to noise, and other sensory abnormalities in workers producing or packaging 2,4-D herbicides, while Fetisov (1966) reported hyposmia and other sensory deficiencies in similarly-exposed workers.

8.1.1.2 Effects on the peripheral nervous system

"Peripheral neuropathy" and reduced peripheral nerve conduction velocities have been reported in workers producing 2,4-D and 2,4,5-T (Poland et al., 1971; Singer et al., 1982). More than one dozen other studies of persons overexposed to chlorophenoxy herbicides also indicated detrimental effects of 2,4-D products on the peripheral nervous system (Goldstein et al., 1959; Goldstein & Brown, 1960; Foissac-Gegoux et al., 1962; Todd, 1962; Berkley & Magee, 1963; Wallis et al., 1970; Bezuglyi et al., 1979). Long-lasting flaccid paraparesis or quadriparesis following skin contact with 2,4-D herbicides was reported by Goldstein et al. (1959) and Goldstein & Brown (1960). Abnormal tendon reflexes in these or similar cases were reported by the same authors and by Andreasik et al. (1979), Berkley & Magee (1963), and Foissac-Gegoux et al. (1962). Cases of sensory neuropathy attributed to the ingestion of, or dermal exposure to, 2,4-D herbicides have also been reported by Monarco & Divito (1961), Foissac-Gegoux et al. (1962), Todd (1962), Wallis et al. (1970), Sare (1972), and Bezuglyi et al. (1979). However, no signs of peripheral neuropathy were reported by Apffel (1959a), Seabury (1963),

Paggiaro et al. (1974), and Prescott et al. (1979), in similar cases of massive exposure to 2,4-D herbicide, and in patients given relatively large amounts of purified 2,4-D or 2,4,5-T salts or esters as drugs. One explanation for this may be great individual differences in susceptibility to poisoning with chlorophenoxy herbicides (Rosenberg, 1980), as attested by the case of a 58-year-old woman who "was fully conscious with no clinical evidence of toxicity" after ingesting enough herbicide to allegedly attain 2,4-D and mecoprop blood plasma concentrations of 335 and 400 mg/litre respectively (Prescott et al., 1979). By comparison, Herbich & Machata (1963) reported that a plasma concentration of 447 mg 2,4-D/litre caused death in a 46-year-old man.

Herbicide ingredients other than 2,4-D and related compounds might be at least partly responsible for the observed neurotoxic effects. In particular, organic solvents, emulsifiers, and ethylene glycol present in herbicide formulations have been mentioned in this connection (Goldstein & Brown, 1960; Goldwater, 1960). Solvents such as alcohols and trichloroethylene, used in the manufacture of the active herbicide ingredients, might account for some of the abnormalities observed in workers involved in the production of chlorophenoxy compounds (Assouly, 1951; Bashirov, 1969; Bashirov & Ter-Bagdasarova, 1970).

Some of the reported cases of central nervous system dysfunction or peripheral neuritis may have been merely coincidental to the herbicide exposure, as there are many known causes of neuropathy, such as nutritional and hereditary factors, infectious diseases, and many toxic chemicals, including alcohol (Freeman, 1975). Thus, alcoholism may have been a contributory factor in one case of "2,4-D polyneuropathy" reported by Brandt (1971).

Further studies of the possible effects of 2,4-D and other chlorophenoxy compounds or their by-products on the human nervous system are desirable, including studies of behavioural effects measurable by recently-developed test batteries (Baker et al., 1983).

8.1.2 Myotoxic effects of 2,4-D

Muscle fibrillations, myotonia, myoglobinuria, muscular weakness and other indications of a myotoxic effect of 2,4-D have been reported in patients treated with large doses of purified 2,4-D products by Apffel (1959a) and Seabury (1963), as well as in cases of suicidal or accidental ingestion of 2,4-D herbicides or following occupational over-exposure (Herbich & Machata, 1963; Berwick, 1970; Dudley & Thapar, 1972; Prescott et al., 1979). In laboratory animals, myotonia and structural or biochemical muscle lesions can be reliably

induced by doses in excess of about 100 mg 2,4-D/kg body weight. In human beings, the threshold dose for gross myotoxic effects certainly exceeds 5 mg/kg body weight per day, and may be above 36 mg/kg body weight per day (Seabury, 1963; Khanna & Kohli, 1977; Sauerhoff et al., 1977).

8.1.3 Cardiopathies and cardiovascular effects

Myocardial dystrophy, myocarditis, cardiac arrhythmias or fibrillations, a slowed heart rate, or electrocardiographic (ECG) changes were observed in human beings who ingested herbicides containing 2,4-D (Duric et al., 1979) or 2,4-D and mecoprop (Prescott et al., 1979), and also after occupational overexposure to chlorophenoxy herbicides (Belomyttseva, 1965; Khibin et al., 1968; Zakharov et al., 1968; Paggiaro et al., 1974; Kaskevich & Sobolova, 1978; Andreasik et al., 1979; Prescott et al., 1979). However, in other cases of acute poisoning with 2,4-D herbicides, the ECG was essentially normal (Berwick, 1970; Monarca & Divito, 1961).

Thus, further studies are desirable to determine the threshold 2,4-D doses at which electrophysiological cardiac abnormalities can be observed, and to determine whether they result from a direct effect on the nerve conducting system of the heart, or secondarily from a toxic action on the myocardium.

It has been suggested that allergic reactions and an increased sensitivity may be involved in 2,4-D-related cardiac arrhythmias (Winkelmann, 1960; Rea, 1978).

Both hypertension and hypotension have been reported following exposure to high doses of 2,4-D (Apffel, 1959a; Kaskevich & Sobolieva, 1978; Bezugly et al., 1979), but no conclusions could be drawn from these studies.

8.1.4 Haematological effects

Monarca & Divito (1961), Todd (1962), Radionov et al. (1967), Bashirov (1969), Bashirov & Ter-Bagdasarova (1970), Brandt (1971), Andreasik et al. (1979), and Bezuglyi et al. (1979) observed haematological changes such as mild anaemia, bone marrow depression, mono- or lymphocytosis or eosinophilia, changes in erythrocyte volume or size, or methaemoglobinaemia following ingestion of, or overexposure to 2,4-D. However, these changes may have been due to other causes, as Apffel (1959a) did not observe either haematological changes or effects on haematopoiesis in patients given 0.1-0.3 g of purified 2,4-D per day as an anticancer drug.

8.1.5 Blood chemistry effects

Hyperglycaemia, hypercholesterolaemia, elevated levels of blood urea, transaminase (SGOT, SGPT), and creatine phosphokinase (CPK), or altered blood albumin, globulin, or phospholipid levels following acute poisoning with, or occupational overexposure to 2,4-D were reported by Bashirov (1969), Bashirov & Ter-Bagdasarova (1970), Berwick (1970), Lukoshkina et al. (1970), Brandt (1971), Bezuglyi et al. (1979), Duric et al. (1979) and Prescott et al. (1979). However, Bashirov (1969) reported hypoglycaemia (< 700 mg/litre) and abnormally slow return to normal values in glucose tolerance tests in about one-third of a group of workers producing 2,4-D. Increased activity of erythrocytic glycolytic enzymes was found in Polish workers packaging 2,4-D sodium salt (Andreasik et al., 1979). In one case of intentional 2,4-D poisoning, there was hyperglycaemia (De Larrard & Barbaste, 1969), while in some cases of 2,4-D overexposure, blood glucose abnormalities were not observed (Goldstein et al., 1959). Apffel (1959a) never observed hyperglycaemia in his patients, on the contrary, daily doses of 1-1.25 g 2,4-D led to hypoglycaemia. Thus, under some circumstances, high doses of 2,4-D apparently can affect glucose metabolism, and produce hypo- or hyperglycaemia. Gamble (1975) proposed that 2,4-D might inhibit certain APT-dependent enzymes and thus affect lipid metabolism.

8.1.6 Pulmonary effects

Pulmonary emphysema, oedema, hyperaemia and haemorrhages were found in cases of fatal poisonings due to 2,4-D herbicide ingestion (Herbich & Machata, 1963; Geldmacher-Von Mallinckrodt & Lautenbach, 1966; Dudley & Thapar, 1972). It is not clear whether the acute pulmonary effects were caused by the 2,4-D preparations or by the solvents such as kerosene or fuel oil. However, it is unlikely that the pulmonary emphysema was caused by acute exposure to 2,4-D.

Dyspnoea or respiratory tract irritation were occasionally reported following occupational overexposure of 2,4-D production workers or herbicide sprayers (Assouly, 1951; Belomyttseva, 1964; Bashirov, 1969; Bezuglyi et al., 1979).

8.1.7 Hepatotoxic effects

Liver necrosis or fatty liver cell changes were observed in 2 fatal cases following 2,4-D herbicide ingestion (Geldmacher-Von Mallinckrodt & Lautenbach, 1966; Dudley & Thapar, 1972). In several non-fatal 2,4-D poisonings, no biochemical evidence of liver damage was noted, and neither

Apffel (1959a) nor Seabury (1963) reported indications of liver damage in patients treated with up to 2.5 g/day of purified 2,4-D, salts, or esters. Hyperbilirubinaemia, elevated urobilinogen levels, or liver enlargement were reported in workers occupationally exposed both to 2,4-D herbicides and to other chemicals (Belomyttesva, 1964, 1965; Bashirov, 1969; Bashirov & Ter-Bagdasarova, 1970; Kaskevich & Sobolova, 1978; Andreasik et al., 1979).

8.1.8 Nephrotoxic effects

Degeneration of, or fatty changes in kidney tubules, or proteinuria, increased blood urea levels, and other indications of a nephrotoxic effects were observed in cases of fatal or nearly fatal herbicide ingestion (Goldstein et al., 1959; Curry, 1962; Geldmacher-Von Mallinckrodt & Lautenbach, 1966; Brandt, 1971; Dudley & Thapar, 1972; Duric et al., 1979). Impaired renal function was reported in occupationally-exposed persons by Bashirov (1969), Bashirov & Ter-Bagdasarova (1970), Paggiaro et al. (1974), and by Andreasik et al. ((1979). On the other hand, neither Apffel (1959a) nor Seabury (1963) reported any evidence of kidney damage in their patients, some of whom received in excess of 2 g of pure 2,4-D per day.

8.1.9 Effects on the digestive tract

Vomiting, diarrhoea, nausea, and other indications of toxic effects on the digestive tract were observed by Apffel (1959a) in patients injected intramuscularly with large doses (up to 2.5 g) of purified 2,4-D products.

The same effects have also been noted after ingestion of large doses of 2,4-D herbicides, or after combined inhalation and dermal overexposure (Goldstein et al., 1959; Monarco & Divito, 1961; Nielsen et al., 1965; Tsapko, 1966; Radionov et al., 1967; Paggiaro et al., 1974; Dennis, 1976; Kuzyk, 1979; Prescott et al., 1979). However, no gastrointestinal symptoms were reported by volunteers who ingested a single dose of 5 mg pure 2,4-D/kg body weight (Khanna & Kohli, 1977; Sauerhoff et al. 1977). Thus, an intake of more than 300 mg 2,4-D per adult appears to be required to induce acute toxic effects on the gastrointestinal tract.

8.1.10 Effects on endocrine organs

Andreasik et al. (1979) found an impaired iodine uptake by the thyroid, and decreased thyroxine, thyroxine clearance, and thyroxine iodine values in workers packaging 2,4-D sodium salt. Since these workers were exposed to a variety of chemicals, these results need confirmation.

8.1.11 Irritative and allergenic effects

Chronic tonsillitis and paranasal sinusitis were reported in workers packaging 2,4-D sodium salt (Andreassik et al., 1979).

Acute eye or skin irritation, as well as skin reactions of an allergic type, including anaphylactoid purpura (allergic angitis) and contact eczema have been reported in agricultural and forestry workers following occupational exposure to 2,4-D herbicides (Winkelmann, 1960; Radionov et al., 1967; Balo-Banga et al., 1973; Jung & Wolf, 1977; Kuzyk, 1979). Jung & Wolf (1977) found that exposure to the vapour of a 2,4-D/2,4,5-T formulation in diesel oil (SELEST 100) caused an acute allergic reaction in the skin of sensitized herbicide applicators, and that the allergic reactions were caused by the mixture of 2,4-D/2,4,5-T esters and not by the diesel oil.

8.2 Epidemiological Studies of the Chronic Effects of 2,4-D

Much concern has been raised about the phenoxy herbicides, including 2,4-D, especially in relation to birth defects and cancer in human beings.

Several episodes have also been reported in which defined populations were exposed to mixtures of 2,4-D and 2,4,5-T, in which the 2,4,5-T was contaminated with various amounts of 2,3,7,8-tetrachlorodibenzodioxin (2,3,7,8-TCDD) (Bleiberg et al., 1964; Huff et al., 1980). It is now generally accepted that chloracne and porphyria cutanea tarda observed in these studies were caused by exposure to 2,3,7,8-TCDD and not by exposure to 2,4,5-T or 2,4-D (Kimbrough, 1980).

The following sections concentrate on epidemiological studies or other related studies on human beings in which actual or potential exposures to 2,4-D products alone or to mixtures of 2,4-D with other chlorphenoxy herbicides were demonstrated.

8.2.1 Reproductive, fetotoxic, and teratogenic effects

Although effects on reproduction have been demonstrated in animals with 2,4,5-T, 2,4-D and 2,3,7,8-TCDD, all of the attempts made to determine whether human beings suffer similar effects have been frustrated by the poor design of the studies, inadequate determination of exposure, or inadequate information about the background incidence of spontaneous abortions and other abnormal reproductive outcomes, by inadequate evaluation of confounding variables, by inadequate assessment of exposure, and by mixed exposures (Aldred et al., 1978; Lee, 1978; Field & Kerr, 1979; Brogan et al., 1980;

Hanify, 1980; Carmelli et al., 1981). For these reasons they are not discussed in detail in this report.

Conclusive evidence of reproductive effects caused by 2,4-D in populations that might be exposed to chlorophenoxy herbicides is unlikely to be obtained from new epidemiological studies on indirectly-exposed populations living in, or adjacent to, areas in which phenoxy herbicides are used. Doses of 2,4-D absorbed by bystanders are far below those expected to be toxic, as shown by occupational exposure studies with 2,4-D and 2,4,5-T herbicides (section 5). Any effects induced by such small amounts would probably be obscured by more potent confounding factors (Janerich, 1973; Karkinen-Jääskeläinen & Saxén, 1974; Saxén et al., 1974; Elwood & Rogers, 1975; Granroth et al., 1977, 1978; James, 1977; Holmberg, 1979; Lappe, 1979; Schacter et al., 1979).

Additional studies on female workers occupationally exposed to significantly higher levels of 2,4-D than bystanders would be useful to clarify some of the uncertainties raised by past studies, if sufficiently large cohorts could be identified.

8.3 Studies on Mutagenic Effects in Workers Exposed to 2,4-D

Lymphocytes from ten workers exposed to 2,4-D esters during the manufacture of 2,4-D herbicides, or from 15 workers packaging 2,4-D sodium salt, did not show any chromosome abnormalities (Johnson, 1971; Andreasik et al., 1979). Chromosome or chromatid abnormalities in lymphocytes from some pesticide sprayers applying a variety of agricultural chemicals, including in some cases 2,4-D, were observed by Yoder et al. (1973) and Crossen et al. (1978). Högstedt et al. (1980) did not observe any significant increases in chromosome abnormalities in workers exposed to 2,4-D and other pesticides.

The induction of SCEs among workers occupationally exposed to the phenoxy herbicides 2,4-D and MCPA has been recently studied. The subjects used only 2,4-D and MCPA or mixtures of the two for spraying, and the exposure levels were estimated by determining the urinary 2,4-D and MCPA excretion by the workers. No dose-related differences in the frequencies of SCEs could be found either in relation to the exposure level or to the length of the exposure (Linnainmaa, 1983b).

Although some studies suggest that occupational exposure to 2,4-D may result in chromosome abnormalities, the results are conflicting. Moreover, the possibility of mixed exposure and other confounding variables cannot be excluded in the studies with positive results.

8.4 Carcinogenic effects

8.4.1 Epidemiological studies

In two case-control studies of soft-tissue sarcoma (Hardell & Sundström, 1979; Eriksson et al., 1981) and one of lymphoma (Hardell et al., 1981), exposure to phenoxyacetic acids (mainly 2,4,5-T, 2,4-D, and MCPA) was associated with approximately 5-fold increases in the risk of soft-tissue sarcomas. Exposure to 2,4-D, either with or without MCPA exposure, also increased relative risks. In the study of malignant lymphomas, 7 cases and 1 control were apparently exposed to 2,4-D only (relative risk, 19.6; 95% confidence interval, 4.3-89.8).

In a different case-control study with a small number of cases and controls, no increased risk was observed (Smith et al., 1982).

A follow-up was also carried out on 348 railroad workers exposed for more than 45 days during the period 1957-72 to the herbicides 2,4-D, 2,4,5-T, atrazine, mecoprop, dichloropropionic acid, and amitrole (Axelson & Sundell, 1974). The authors found a significant increase in cancer mortality and morbidity among workers exposed to amitrole.

Axelson et al. (1980) reported a further follow-up of these workers, up to October, 1978, accumulating 5541 person-years. The herbicide exposure of the workers was analysed in terms of exposure to either amitrole, or phenoxy acids, or to a combination of the two. A 10-year lapse period from the first day of exposure was used as the induction latency. They found 15 cases of cancer versus 6.87 expected (relative risk, 2.2). In the cohort with combined exposure to amitrole and phenoxy acids, 6 cases were observed versus 1.78 expected (relative risk, 3.4); in the group exposed to amitrole alone, 3 tumours were observed versus 1.95 expected (relative risk, 1.5); and 6 cancers were observed versus 3.14 expected (relative risk, 1.9) in the phenoxy acid-exposed group. All cancers, as well as cancers of the stomach, occurred in statistically-significant excesses in the cohort as a whole. In the groups exposed to amitrol plus phenoxy acids, there was a significant excess of all cancers. In the group exposed only to phenoxy acids, stomach cancer occurred in significant excess (2 observed, 0.33 expected; relative risk, 6.1). No soft-tissue sarcomas were identified, but the statistical power of this study to detect an excess of a rare cancer was limited.

Högstedt & Westerlund (1980) conducted a retrospective mortality study on 142 forestry workers exposed to phenoxy pesticides and 244 unexposed forestry workers, comparing their mortality experience with national statistics. Work

supervisors, who were more highly exposed to phenoxy herbicides than the others, had a significantly elevated tumour mortality (5 observed, 1.4 expected). No particular tumour type predominated, and no soft-tissue sarcomas were observed, though the authors noted that the study had limited statistical power and was inconclusive, because of the relatively short follow-up period.

Riihimäki et al. (1982) reported on a prospective cohort study of 2,4-D and 2,4,5-T spray personnel which was in progress. Because of the small number of deaths and the brief follow-up period, no conclusions can so far be drawn from this study.

Follow-up studies on cohorts of pesticide sprayers, farmers, and agricultural workers occupationally exposed to a variety of chemicals, in some cases including phenoxy herbicides, have been reviewed by IARC (1983).

Follow-up studies on groups of industrial workers exposed to chlorophenols, 2,4,5-T, or other chlorophenoxy compounds, and to 2,3,7,8-TCDD or other dioxins, during the manufacture of chlorophenoxy herbicides, have recently been reviewed by Huff et al. (1980) and IARC (1983).

8.4.2 Evidence on the carcinogenicity of 2,4-D

The available studies suggest that an association exists between mixed exposure to phenoxy herbicides, chlorinated phenols, and chlorinated dibenzodioxins, and an increased incidence of soft tissue sarcomas and malignant lymphomas. It is not clear, at present, whether these findings represent true associations, and further studies are in progress (Muir & Wagner, 1981) to clarify this point. Since many of the tumour cases had been exposed to combinations of phenoxy herbicides and their contaminants as well as other chemicals, it is not known whether exposure to 2,4-D is specifically associated with the development of soft tissue sarcomas.

8.5 Treatment of Poisoning in Human Beings

Successfully treated cases of 2,4-D poisoning indicate that forced alkaline diuresis is helpful in reducing the level of 2,4-D in the blood and tissues (Young & Haley, 1977; Prescott et al., 1979). Heart and kidney damage should be anticipated and counteracted in cases of severe poisoning (Duric et al., 1979).

In cases of acute poisoning due to 2,4-D, the nearest Poison Control Centre should be contacted for additional information on symptoms and recommended treatment.

9. EVALUATION OF HEALTH RISKS TO MAN FROM EXPOSURE TO 2,4-D

9.1 General Considerations

In areas of 2,4-D herbicide production, handling, or use, the highest exposure will be incurred by those who are directly involved in these processes, followed by bystanders indirectly exposed to 2,4-D vapour, dust, or droplets, or to contaminated vegetation, soil, or water. In these two groups, exposure will usually be via the skin. The general population in 2,4-D-use areas would be exposed to a lesser extent, mainly through food containing 2,4-D residues and to a lesser extent through 2,4-D residues in water. The contribution from air is negligible. As far as the general population is concerned, 2,4-D intake from any source, is negligible.

9.2 Estimated Intake of 2,4-D by the Population in a 2,4-D-use Area

The total contribution from air, food, and water is estimated to be 0.3 - 2 µg/kg body weight per day (Table 13).

9.2.1 Intake by bystanders

Given the limited data available and the many uncertainties involved, an adequate estimate of 2,4-D intake by bystanders is not possible at this time, but it should generally be less than that for occupationally-exposed persons.

9.2.2 Occupational intake

Workers using 2,4-D may, on average, absorb about 0.1 mg 2,4-D/kg body weight per day. However, this level may be exceeded if good occupational hygiene is not practiced (section 5.2). Simple precautions against excessive exposure can reduce the amount of 2,4-D uptake.

9.3 Safety Factors

9.3.1 Definitions

For the present assessment, the safety factor is defined as the integer obtained by dividing the overall no-observed-adverse-effect level for a known adverse effect of 2,4-D (determined from all available information on human

beings or animals) by the daily exposure value (absorbed dose of 2,4-D) for the various exposed groups.

9.3.2 Determination of safety factors

9.3.2.1 Acute poisoning

Based on clinical studies in which 2,4-D was injected into patients as a drug, the no-observed-adverse-effect level for signs and symptoms of acute 2,4-D poisoning in children and adults appears to be at or near 36 mg/kg body weight (section 8.1). Based on the available studies of the amounts of 2,4-D absorbed by occupationally-exposed person, bystanders, and populations in 2,4-D-use areas, the safety factors for acute 2,4-D poisoning are likely to be:

- (a) much greater than 1000 for the general population in 2,4-D-use areas;
- (b) at least 360 for occupationally-exposed spraying crews.

The margin of safety for persons with excessive occupational exposures would be smaller.

9.3.2.2 Chronic toxicity

Dose-effect relationships for the chronic toxic effects of 2,4-D or 2,4-D derivatives are available only from animal studies. The no-observed-adverse effect levels for certain chronic toxic effects of 2,4-D in animals have not been firmly established, and for this reason safety factors cannot be established (section 7.2.1) for all of the chronic effects of 2,4-D.

9.3.2.3 Embryotoxic, fetotoxic, and teratogenic effects

The no-observed-adverse-effect level for embryotoxic, fetotoxic, or teratogenic effects of 2,4-D in mammals appears to lie at 10 mg/kg body weight per day (section 7.3.1.2). Assuming that the same is true for human beings, then the corresponding safety factors for the various exposed groups are:

- (a) much greater than 1000 for the general population in 2,4-D-use areas;
- (b) 100 for occupationally-exposed spraying crews using precautions against excessive exposure.

9.3.2.4 Mutagenic effects

The available information was inadequate for an assessment of the mutagenic potential of 2,4-D in mammals.

9.3.2.5 Carcinogenic effects

Available animal bioassays and epidemiological studies are inadequate for an assessment of the carcinogenic potential of 2,4-D or of its derivatives.

9.4 Evaluation of Health Risks from 2,4-D Exposure

From the data available at present, the Task Group assumes that a possible health risk will exist, when the safety factor is less than 100.

9.5 Recommendations on Exposure

Results of recent exposure and occupational health studies suggest that excessive exposure to 2,4-D can be avoided by fairly simple measures of occupational hygiene, such as those recommended in two pertinent publications of the International Labour Office (ILO, 1977, 1979). Laundering procedures for 2,4-D-contaminated clothing have been published by Easley et al. (1983), and these should be considered.

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