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VIA EMAIL COSHITA@OEHHA.CA.GOV AND
FIRST CLASS MAIL

Ms. Cynthia Oshita
OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT
P.O. Box 4010, MS-19B
Sacramento, California 95812-4010

RE: *Opposition to Proposed Listing of "Chlorophenoxy Herbicides"*

Dear Ms. Oshita:

On behalf of the Industry Task Force II on 2,4-D Research Data (the "2,4-D Task Force" or "Task Force"), and in response to the June 12, 2009 "Request for Comments on Chemicals Proposed for Listing by the Labor Code Mechanism (Carcinogens)" (the "Request") published by the Office of Environmental Health Hazard Assessment ("OEHHA"), we hereby submit these comments opposing the proposed listing of "chlorophenoxy herbicides" on the basis that, insofar as this ill-defined grouping may be construed to include 2,4-dichlorophenoxyacetic acid and/or its salts and esters (collectively, "2,4-D"), the International Agency for Research on Cancer ("IARC") specifically has not identified 2,4-D, alone, as a carcinogen.

EXECUTIVE SUMMARY

2,4-D is an herbicide that has been used since the 1940s for selective control of broadleaf weeds. It is the third most widely used herbicide in the United States. 2,4-D is applied to control broadleaf weeds and is an important tool to the U.S. and California crop and non-crop economies.

The 2,4-D Task Force was formed in 1988 to develop and submit to the United States Environmental Protection Agency ("EPA") studies and data required to support the EPA reregistration of 2,4-D in accordance with the Federal Insecticide Fungicide and Rodenticide Act ("FIFRA") and the Food Quality Protection Act of 1996. The current members of the 2,4-D

Task Force are Dow AgroSciences, AGRO-GOR, and Nufarm USA. Since 1988 -- one year after the most recent IARC evaluation of "chlorophenoxy herbicides" -- the Task Force has submitted to EPA over 300 toxicology, ecotoxicity, plant and animal metabolism, environmental fate and residue studies, resulting in arguably the most thorough and modern scientific databases for any group of chemicals. EPA, after thoroughly reviewing these studies, produced an extensive Reregistration Eligibility Decision (the "2,4-D RED") in 2005.¹ In assessing the risks to humans and the environment from exposure to 2,4-D, EPA classified the carcinogenicity of 2,4-D as category 'D' (not classifiable as to human carcinogenicity) and reregistered the compound. After the 2,4-D RED was released, and after a further review of extensive epidemiological and animal studies, EPA released its Decision Not to Initiate Special Review for 2,4-D under FIFRA, stating: "Because the Agency has determined that the existing data do not support a conclusion that links human cancer to 2,4-D exposure, it has decided not to initiate a Special Review of 2,4-D..."²

OEHHA proposes to list "chlorophenoxy herbicides" under Proposition 65 pursuant to Health and Safety Code section 25249.8(a), the disputed "Labor Code listing mechanism." In its Request, and as to this proposed listing, OEHHA requests comments relating to whether IARC identified the specific chemical or substance as a known or potential human or animal carcinogen.

IARC has never identified 2,4-D as a carcinogen. In 1977, the most recent IARC review of 2,4-D, IARC concluded that human data were not sufficient to evaluate carcinogenicity and that no evaluation of the carcinogenicity of 2,4-D could be made on the basis of animal studies.³ In IARC's 1986 and 1987 evaluations of human, animal and genotoxicity data, IARC did not conclude that 2,4-D, as such, was a carcinogen and did not update its 1977 evaluation of animal and genetic toxicity data.⁴ Rather, IARC concluded that some human, animal and genotoxicity data relating to "chlorophenoxy herbicides," a generalized and ill-defined term corresponding to the equally generalized and ill-defined term used by the studies' authors, constituted a "limited" finding of possible carcinogenicity.⁵ Taken together, IARC's evaluations cannot form the basis

¹ The 2,4-D RED is available at http://www.epa.gov/oppsrrd1/REDS/24d_red.pdf.

² 72 Fed.Reg. 44510 (August 7, 2007).

³ *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans -- Some Fumigants, the Herbicides 2,4-D and 2,4,5-T, Chlorinated Dibenzodioxins and Miscellaneous Industrial Chemicals*, Volume 15 (1977) (hereinafter "1977 Monographs") (attached as Exhibit A hereto).

⁴ *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans -- Some Halogenated Hydrocarbons and Pesticide Exposures*, Volume 41 (1986) (hereinafter "1986 Monographs") (attached as Exhibit B hereto); *Overall Evaluations of Carcinogenicity: An Updating of IARC Monographs Volumes 1 to 42 (Supplement 7)* (1987) (hereinafter "Supplement 7"), (relevant pages of which are attached as Exhibit C hereto).

⁵ Significantly, in 1997 IARC investigators concluded that 2,4-D was not carcinogenic when they reviewed 21,863 male and female workers in 36 cohorts exposed to phenoxy herbicides, chlorophenols, and dioxins in 12

of including 2,4-D in the “chlorophenoxy herbicide” category that OEHHA now proposes to list as a carcinogen.⁶

Indeed, OEHHA itself has previously refrained from identifying 2,4-D as a high priority substance for consideration for listing under Proposition 65. Multiple regulatory bodies around the world have concluded that 2,4-D is not classifiable as a carcinogen. **Yet, as a chemical grouping, the term “chlorophenoxy herbicides” – itself an undefined term – could be interpreted as including this substance and its salts and esters.**

Such a result would be inconsistent with IARC’s classification of 2,4-D and IARC’s intent in coining the term “chlorophenoxy herbicides.” Further, given that OEHHA’s authority to list chemicals under Proposition 65 is limited to the identification of known carcinogens and reproductive toxins, the listing of a chemical that is neither -- like 2,4-D -- would directly contravene OEHHA’s authority. Finally, the grouping denoted as “chlorophenoxy herbicides” itself is scientifically and legally infirm, providing no notice to the regulated community or Proposition 65 prosecutors of what substances comprise it.

For the reasons explained herein, OEHHA should not proceed with this proposed listing. If it does proceed, OEHHA must clarify that the listing refers to the **exact** mixture that IARC reviewed, and not to the individual substances that comprise that mixture. Alternatively, if OEHHA proceeds with this proposed listing, it must clarify that the listing does **not** include 2,4-D, consistent with IARC’s evaluation of this compound.

As an organization representing technical registrants and producers of 2,4-D, the Task Force is concerned that the proposed listing, if it proceeds without any clarification, will lead to confusion and unnecessary, expensive and disruptive enforcement actions that would provide none of the public benefits sought to be gained by Proposition 65. With wide use of 2,4-D as a crucial tool to the citrus and other agricultural industries in California, such confusion and unnecessary litigation would have significant and undesirable impacts on California agriculture. The Task Force therefore submits these comments opposing the listing.

(footnote continued from previous page)

countries. Kogevinas M, Becher H, Benn T, Bertazzi PA, Boffetta P. 1997. Cancer mortality in workers exposed to phenoxy herbicides, chlorophenols, and dioxins. *Am J Epidemiol.* 145:1061-1075.

⁶ EPA itself has concluded that the chlorophenoxy herbicide epidemiology studies relied upon by IARC do not demonstrate that 2,4-D alone causes cancer. EPA 1994. *An SAB Report: Assessment of Potential 2,4-D Carcinogenicity. Review of the Epidemiological and Other Data on Potential Carcinogenicity of 2,4-D.* U.S. Environmental Protection Agency Science Advisory Board (SAB), Washington, D.C at page 14.

COMMENTS OPPOSING PROPOSED LISTING OF "CHLOROPHENOXY HERBICIDES"

I. BACKGROUND

A. 2,4-D

2,4-D is an herbicide in the phenoxy or phenoxyacetic acid family that has been used since the 1940s for selective control of broadleaf weeds. Over 600 agricultural and residential end-use products are registered for use in the United States. Weeds are the principal pest problem for crops, as they reduce crop yields and increase production costs.

2,4-D is one of the most widely used herbicides worldwide. According to EPA, total annual usage of 2,4-D in the United States is approximately 46 million pounds, with 30 million pounds (66%) used for agriculture and 16 million pounds (34%) used for non-agriculture. The major uses of 2,4-D in agriculture, nationwide, are on wheat and small grains, sorghum, corn, rice, sugar cane, low-till soybeans, rangeland, and pasture. It is also used on rights-of-way, roadsides, non-crop areas, forestry, lawn (including residential lawns) and turf care, and to control aquatic weeds. In California, 2,4-D has significant uses, including an economically vital role in the state's citrus economy along with major uses in economically significant industries such as almond and turf.

The importance of 2,4-D use as an herbicide cannot be overstated. According to a 1996 Department of Agriculture study,⁷ if 2,4-D were not available, costs to growers and other users would increase dramatically because of the consequent reliance on more expensive weed control measures. Consumers, too, would suffer increased costs for food and fiber. These increased costs are estimated to total \$1.68 billion annually in the U.S. alone. The same study also reviewed the 2,4-D epidemiology and toxicology data packages and concluded that after several decades of extensive use, "The phenoxy herbicides are low in toxicity to humans and animals...."

Multiple regulatory authorities worldwide, in fact, have evaluated the potential effects of 2,4-D on human health. The following bodies have concluded that existing data do not support the classification of 2,4-D as a carcinogen: OEHHA (2009)⁸; California Department of Pesticide

⁷ USDA 1996. *Biologic and Economic Assessment of Benefits from Use of Phenoxy Herbicides in the United States*. NAPIAP Report No. 1-PA-96.

⁸ OEHHA 2009. *Public Health Goals for Chemicals in Drinking Water -- 2,4-Dichlorophenoxyacetic Acid*, <http://www.oehha.ca.gov/water/phg/pdf/24dphg010209.pdf>.

Regulation (2000)⁹; United States Environmental Protection Agency (1997¹⁰, 2004a¹¹ 2004b¹², 2005¹³); Health Canada's Pest Management Regulatory Agency (2007)¹⁴; European Commission (2001)¹⁵; New Zealand (2003)¹⁶; and the World Health Organization (1996)¹⁷.

B. *Legal Basis For OEHHA's Proposed Listing Of "Chlorophenoxy Herbicides"*

OEHHA is proposing to list "chlorophenoxy herbicides" as a chemical "known to the state to cause cancer" under Proposition 65, pursuant to the so-called "Labor Code listing mechanism." This asserted mechanism for listing chemicals under Proposition 65 is the subject of substantial ongoing controversy. The background for that controversy is critical to determining whether the law requires or allows "chlorophenoxy herbicides" to be listed, and thus is summarized below.

⁹ California Environmental Protection Agency 2000. California Department of Pesticide Regulation, Medical Toxicology Branch. 2,4-D Chemical Code #000636 Tolerance #00142. SB 950 #176. September 26, 1986. Revised February 24, 2000.

¹⁰ USEPA 1997. Carcinogenicity Peer Review (4th) of 2,4-Dichlorophenoxyacetic Acid. Data Evaluation Record, January 29, 1997.

¹¹ USEPA 2004a. 2,4-D – Second Report of the Hazard Identification Assessment Review Committee. [HIARC] Health Effects Division of Office of Pesticide Programs. TXR No. 0051866. January 15, 2004.

¹² USEPA 2004b. 2,4-D: HED's Human Health Risk Assessment of the Reregistration Eligibility Decision (RED) Revised to Reflect Error-only Comments from Registrants. Health Effects Division of Office of Pesticide Programs. PC Code 030001; DP Barcode D287199. June 2, 2004.

¹³ USEPA 2005. Reregistration Eligibility Decision for 2,4-D. [RED] Office of Pesticide Programs. EPA 738-R-05-002. June 2005.

¹⁴ Health Canada 2007. Re-evaluation of the Agricultural, Forestry, Aquatic and Industrial Site Uses of (2,4-Dichlorophenoxy) acetic Acid [2,4-D]. Proposed Acceptability for Continuing Registration. PACR2007-06. 19 June 2007. www.pmra-arla.gc.ca/english/pdf/pacr/pacr2007-06-e.pdf.

¹⁵ European Commission Health & Consumer Protection Directorate-General 2001. Commission Working document. Review Report for the Active Substance 2,4-D Re-evaluation. 7599/VI/97-final, 1 October 2001.

¹⁶ Environmental Risk Management Authority [New Zealand ERMA] 2003. Substances to be transferred to the HSNO Act under Section 160(1)(a): Phenoxy Herbicides. <http://www.ermanz.govt.nz/hs/pesticides/phenoxy-herb-report.pdf>.

¹⁷ WHO Pesticide Residues in Food – 1996. Part II - Toxicological. FAO Plant Production and Protection Paper 140: 31-38; and WHO/PCS/97.1: 45-96. Rome September 1996.

OEHHA asserts that Health & Safety Code section 25249.8(a) imposes a “ministerial” duty on the agency to add substances to the Proposition 65 list of those chemicals “identified by reference in Labor Code Section 6382(b)(1) and those substances identified additionally by reference in Labor Code Section 6382(d).” Numerous parties, including the California Chamber of Commerce (“Chamber”) in litigation described below, contend that Section 25249.8(a) established the requirement to publish the list (and re-publish it annually), and that the inclusion of chemicals identified by reference to the Labor Code was merely a shortcut to be used for populating the “initial list” of chemicals quickly and efficiently by March 1, 1987, the deadline for its first publication. The substantive methods for adding chemicals appear at Section 25249.8(b), which defines a chemical as “known to the state to cause cancer” only where: (1) “in the opinion of the state’s experts it has been clearly shown through scientifically valid testing according to generally accepted scientifically principles to cause cancer,” or (2) “a body considered to be authoritative by such experts has formally identified it as causing cancer,” or (3) an “agency of the state or federal government has formally required it to be labeled or identified as causing cancer.”

The disputed interpretation of Section 25249.8(a) is the subject of litigation in *Sierra Club v. Schwarzenegger* (Alameda County Superior Court, Case No. RG07356881), consolidated with *California Chamber of Commerce v. Schwarzenegger* (San Diego County Superior Ct. Case No. 37-2008-00096549-CU-WM-CTL) (the “Labor Code Action”). On April 24, 2009, the Alameda County Superior Court entered an order finding that Health & Safety Code section 25249.8(a) imposed on OEHHA a ministerial duty to include, in the Proposition 65 chemical list, those substances identified by Labor Code sections 6382(b)(1) and (d). The court entered judgment in favor of the State on June 11, 2009, after acknowledging many times in open court that the issue would be resolved on appeal. The Chamber filed a Notice of Appeal on June 12, 2009, and is actively pursuing that appeal at this time.

Because the Superior Court’s order remains the subject of a pending appeal, the 2,4-D Task Force does not concede that the Labor Code listing mechanism is lawful, or that a chemical may be listed as “known to the State to cause cancer” if it does not meet one of the criteria by which that term is defined in Section 25249.8(b). The 2,4-D Task Force thus incorporates by reference herein all of the arguments made in the Chamber’s submissions in the Labor Code Action, and reserves its rights to pursue these and other arguments opposing the legal basis of the asserted Labor Code listing mechanism. Notwithstanding its adoption of the Chamber’s arguments and its reservation of rights, in this submission the 2,4-D Task Force proceeds on the assumption, for this submission only, that the viability of Labor Code listing mechanism may survive appeal.

C. *IARC Has Never Identified 2,4-D Alone As A Carcinogen And Other Regulatory Authorities, Including OEHHA, Have Not Classified 2,4-D As A Carcinogen*

In its Request, OEHHA identifies Labor Code section 6382(d) as the basis of its proposed listing of “chlorophenoxy herbicides.” That section references “substances within the scope of the federal hazard communication standard (29 C.F.R. Sec. 1910.1200).” Within that category of substances, OEHHA specifically requests the public to limit comments to whether the International Agency for Research on Cancer (“IARC”) or the National Toxicology Program (“NTP”) has identified the specific chemical or substance as a known or potential human or animal carcinogen.

Although IARC reviewed the carcinogenicity of an undefined assemblage of compounds it termed “chlorophenoxy herbicides” 22 years ago, it has never concluded that 2,4-D, alone, is a carcinogen even though IARC, in fact, has evaluated the impacts of 2,4-D alone from both animal and human studies available to the organization in 1977, 1986 and 1987. Indeed, multiple regulatory authorities, including OEHHA, have refrained from identifying 2,4-D as a carcinogen. Thus, as explained further herein, OEHHA must not proceed with a listing of “chlorophenoxy herbicides” that would include 2,4-D.

1. *IARC’s Monograph Program – Generally*

Because IARC examined compounds within a group of presumably related compounds at the same time, including studies on an overbroad and ill-defined group of substances ultimately referred to as “chlorophenoxy herbicides,” we briefly review IARC’s Monographs Program, and then review IARC’s evaluations of this assembled group of substances.

IARC, established in 1965, is part of the World Health Organization. IARC promotes international collaboration in cancer research. The IARC Section on Monographs publishes reviews that identify environmental factors that can increase the risk of cancer. In developing Monographs, IARC Working Groups review individual agents – substances, mixtures and groups of chemicals. IARC Monographs have reviewed more than 900 agents. A separate Working Group prepares each volume of Monographs.

Generally, IARC Monographs review data with respect to human exposure to an agent (e.g., epidemiological studies), experimental animal exposure to that agent and other (mechanistic) data relating to that agent. The Working Group preparing the particular Monographs volume analyze the adequacy of the available data and, for both human and animal data, classify the data into four categories: (1) sufficient evidence of carcinogenicity; (2) limited evidence of carcinogenicity; (3) inadequate evidence of carcinogenicity; and (4) evidence of lack of carcinogenicity.

The above classifications, in turn, are used in a matrix to establish the ultimate classification of the carcinogenicity of the agent. There are five categories of cancer hazard identification:

- | | |
|-------------|--|
| Category 1 | the agent is carcinogenic to humans; |
| Category 2A | the agent is probably carcinogenic to humans; |
| Category 2B | the agent is possibly carcinogenic to human; |
| Category 3 | the agent is not classifiable as to its carcinogenicity in humans; and |
| Category 4 | the agent probably is not carcinogenic to humans. |

Pertinent to the proposed listing here, Category 2B chemicals are those for which the Working Group has determined that “limited evidence of carcinogenicity” in humans exists, and that there is “absence of sufficient evidence of carcinogenicity” in experimental animals. “Limited” evidence of carcinogenicity in humans, to IARC, means that the evidence in humans is such that “chance, bias and confounding could not be ruled out with reasonable confidence.”¹⁸ In other words, it is as likely as not that the studies show any association between exposure and cancer -- a far cry from any acknowledgement by IARC that such association is clearly shown or even likely.

2. *IARC Did Not Classify 2,4-D As A Carcinogen In 1977*

IARC evaluated chemicals that included those that could be broadly stated to be “chlorophenoxy herbicides” twice, first in 1977 and then, again, in 1986, an evaluation that then was updated in a summary by IARC in 1987.¹⁹ **IARC has not revisited any of these compounds in over two decades.** In fact, and further undermining the relevance of IARC’s 1986 and 1987 evaluations to today’s market, one of the compounds IARC collected in its “chlorophenoxy herbicides” grouping, 2,4,5-T, no longer even exists because EPA canceled its FIFRA registration approximately 20 years ago.

IARC reviewed the carcinogenicity of 2,4-D alone, and not as a member of a chemical class, in 1977. IARC’s individual review of 2,4-D in 1977 is relevant because IARC considered data where humans and animals were exposed to 2,4-D alone and not as part of an exposure to multiple chemicals variously lumped together as “chlorophenoxy herbicides.” In 1977, IARC

¹⁸ Supplement 7 at page 30.

¹⁹ 1977 Monographs, 1986 Monographs, and Supplement 7, respectively.

evaluated the available animal studies on 2,4-D and concluded that these studies were “inadequate” for establishing evidence for carcinogenicity to animals.²⁰ Under human data, IARC concluded that there were “not sufficient data to evaluate the carcinogenicity to man.”²¹ In 1986, IARC reiterated its 1977 conclusion, exactly, and stated that, “No attempt has been made [by IARC] to update these data.”²² An identical process and conclusion of “inadequacies” were made following IARC’s evaluation of the genetic toxicity studies on 2,4-D. In short, when IARC has assessed the carcinogenicity of 2,4-D alone, which it did more than three decades ago, it did not classify it as a carcinogen.

3. *IARC’s Evaluations of “Chlorophenoxy Herbicides” Cannot Support A Listing of This Group That Would Include 2,4-D*

As discussed below, IARC’s classification of “chlorophenoxy herbicides” as a Category 2B carcinogen cannot support the inclusion of 2,4-D in OEHHA’s proposed listing of this ill-defined group of substances. Accordingly, OEHHA must not proceed with its proposed listing.

a. *IARC Did Not Classify 2,4-D As A Carcinogen In Its 1986 and 1987 Evaluations*

Over two decades ago, IARC reviewed the potential carcinogenicity of a collection of chemicals it labeled as “chlorophenoxy herbicides” IARC has not evaluated this group since then.²³ At that time, IARC evaluated a wide range of chemicals it considered related. Apparently, these chemicals were evaluated together because, at that time, there were a growing number of human studies that evaluated agricultural chemicals. These studies sometimes were only able to describe the exposures in broad terms such as “chlorophenoxy herbicides” but, more often than not, the studies were confounded by exposures to multiple chemicals beyond this broad and ill-defined group of broadleaf herbicides. Ultimately, and as discussed below in Section I.C.3.b, in 1986 this broad group of chemicals was given the term “chlorophenoxy herbicides” in an effort by IARC to coin a term that that agency believed could be associated with the few studies that illustrated “limited” association between exposures and cancer in humans.

²⁰ 1977 Monographs at page 130.

²¹ 1977 Monographs at page 130.

²² 1986 Monographs at page 380.

²³ 1986 Monographs and Supplement 7.

IARC, in its 1986 Monographs, identified several specific chemicals that were considered as part of its overall evaluations and detailed the contaminants present in the compounds used at that time. These chemicals included, but were not limited to:

(2,4-dichlorophenoxy)-acetic acid	2,4-D	CAS 94-75-7
(2,4,5-trichlorophenoxy)-acetic acid	2,4,5-T	CAS 93-76-5
2-(2,4,5-trichlorophenoxy) propanoic acid	Silvex	CAS 93-73-1
(4-chloro-2-methylphenoxyacetic acid)	MCPA	CAS 94-74-6
2-(4-chloro-2-methylphenoxy) propanoic acid	MCPP (Mecoprop)	CAS 93-65-2
2-(2,4-dichlorophenoxy)-propanoic acid	2,4-DP (Dichlorprop)	CAS 120-36-5

However, IARC's ultimate cancer classification of "chlorophenoxy herbicides" was based on studies that addressed only inexactly defined exposures, including exposures to chemicals well beyond the scope of specific compounds discussed in the chemistry sections of the 1986 Monographs. This broad group of chemicals and products was given the term "chlorophenoxy herbicides" by IARC to coincide with the loosely defined descriptions provided by the authors of the studies that IARC evaluated.

IARC's 1986 Monographs reviewed case reports, cohort studies and case control studies of persons occupationally exposed to multiple "similar" products that had accumulated in the public literature during the 10 years since IARC's 1977 evaluation of 2,4-D. IARC's 1986 Monographs did not reevaluate the animal studies that were assessed in the 1977 Monographs, but simply repeated its previous conclusion -- that the animal data on 2,4-D were "inadequate" and thus IARC could not assess the carcinogenicity of 2,4-D on the basis of experimental animal studies.²⁴ In evaluating the human data, IARC concluded that overall "there was limited evidence that **occupational exposure** to chlorophenoxy herbicides are carcinogenic to humans."²⁵ Based on studies that reported associations with cancer **only** when broadly defined

²⁴ 1986 Monographs at pages 380-81, including Table 16.

²⁵ 1986 Monographs at page 395.

exposures to “chlorophenoxy herbicides” were observed, IARC’s 1986 evaluation did not assess or offer an opinion about the carcinogenicity of 2,4-D.²⁶

IARC next reviewed “chlorophenoxy herbicides” in 1987 when it published its *Overall Evaluations of Carcinogenicity: An Updating of IARC Monographs Volumes 1 to 42 (Supplement 7)* (“Supplement 7”). Supplement 7 made “overall evaluations of carcinogenicity to humans for 628 agents (comprising more than 700 chemicals, **groups of chemicals**, industrial processes, occupational exposures and cultural habits) that had been evaluated in Volumes 1-42 of the Monographs.”²⁷ Among the groups of chemicals IARC updated in 1987 was “chlorophenoxy herbicides.” In this publication, IARC summarized the carcinogenicity of the broad group of substances that it termed “chlorophenoxy herbicides,” which apparently consisted of at least three (and perhaps more) substances, rather than the six (or perhaps more) evaluated in 1986, in a table as follows²⁸ :

	Human	Animal	Overall evaluation
Chlorophenoxy herbicides	L (limited)		2B
2,4-D		I (inadequate)	
2,4,5-T		I (inadequate)	
MCPA		ND (not determined)	

Only the broad and ill-defined mixtures of exposures to which IARC conferred the name “chlorophenoxy herbicides” was classified by IARC. 2,4-D remained unclassified, consistent with the 1977 evaluation and the data reviewed by IARC in 1977 and later.

As already discussed, IARC’s evaluation specific to 2,4-D up to 1987 concluded that the animal data on 2,4-D were “inadequate” for evaluation of carcinogenic potential and that the genetic activity data on 2,4-D were also inadequate for evaluating the carcinogenic potential of 2,4-D.²⁹ Those conclusions remained unchanged, and IARC refrained from classifying 2,4-D, alone, as a carcinogen, even though the 1986 and 1987 evaluations reviewed more recent scientific literature purporting to characterize 2,4-D-specific exposures (which remained confounded by exposures to other agricultural chemicals). Indeed, under “human” and “overall” carcinogenicity in Table 1 of Supplement 7 (see above), IARC left the corresponding boxes

²⁶ See 1986 Monographs at page 380 (“No attempt has been made to update these data [from prior evaluations].”)

²⁷ Supplement 7 at page 37. (Emphasis added.)

²⁸ Supplement 7, Table 1 at page 60.

²⁹ 1986 Monographs at page 381.

empty.³⁰ Instead, IARC limited its classification solely to the only term that could be used consistently with the findings in the literature, the single, ill-defined grouping for which it could find only “limited” data (human data where “chance, bias and confounding could not be ruled out with reasonable confidence”): “chlorophenoxy herbicides.”

**b. *IARC’s Undefined Term “Chlorophenoxy Herbicides”
Cannot Capture 2,4-D***

“Chlorophenoxy herbicides” is a non-specific term used for convenience’s sake by IARC, which cannot form the basis for any listing under Proposition 65, and which certainly cannot form the basis for a listing that would include 2,4-D.

A broad term never defined by IARC, “chlorophenoxy herbicides” is the term-of-art that IARC chose for a very simple reason. The *only* studies that IARC identified within the available literature that indicated any possible correlation between exposures to cancer were two studies of human populations whose potential exposures the studies’ authors only broadly described as being from a mixture of products that IARC called “chlorophenoxy herbicides.” *No* specific chemicals, and certainly not 2,4-D, were identified as specific agents in these studies. In contrast, in 1977, when IARC specifically evaluated 2,4-D and its salts and esters in animal and human studies, it found no correlations with cancer. Consequently, for its later evaluations, IARC used the only term-of-art that it apparently concluded could correlate with its “limited” findings in the scientific literature at the time: “chlorophenoxy herbicides.” This broad term has no definable scope since its only meaning, in fact, is directly derived from studies in which the authors themselves provide no chemical definition to the term.

IARC assessed 2,4-D in 1977, 1986, and 1987, with the later evaluations being part of its overall evaluation of this “chlorophenoxy herbicides” collection. IARC did not classify “2,4-D” as a carcinogen because, while its evaluation identified “limited” evidence in human studies on the ill-defined grouping of “chlorophenoxy herbicides,” as discussed above, IARC’s evaluations of 2,4-D found both the genetic toxicity, animal and human data inadequate for classification. So the broader, undefined term, “chlorophenoxy herbicides,” associated with IARC’s “limited” findings, was used in the IARC later cancer classification of this undefined grouping of

³⁰ Furthermore, in 1997 IARC investigators updated a 1995 study of 21,863 male and female workers in 36 cohorts exposed to phenoxy herbicides, chlorophenols, and dioxins in 12 countries, and concluded that 2,4-D is not carcinogenic. Kogevinas M, Becher H, Benn T, Bertazzi PA, Boffetta P. 1997. Cancer mortality in workers exposed to phenoxy herbicides, chlorophenols, and dioxins. *Am J Epidemiol.* 145:1061-1075. This 1997 finding, based on a review of IARC’s own multinational cancer registry of chlorophenoxy workers, that 2,4-D is **not** carcinogenic further undermines any suggestion that 2,4-D should be listed by OEHHA because of the 1987 Monographs that reviewed and classified “chlorophenoxy herbicides.”

substances. Even as to that, IARC's classification necessarily concedes that "chance, bias and confounding could not be ruled out with reasonable confidence."³¹ We elaborate further below.

In 1977, IARC evaluated the case studies and epidemiological data and found that the single cohort study available at that time was "not sufficient to evaluate the carcinogenicity of 2,4-D to man (because 2,4-D may be used with 2,4,5-T, which is contaminated with 2,7,8-tetrachlorodibenzo-para-dioxin)."³² IARC's evaluation of the human data in 1986 included many more epidemiological studies but, again, no studies identified an association of cancer with 2,4-D specific exposures, only to the ill-defined products termed "chlorophenoxy herbicides." When, in 1987, IARC summarized the assessment of "chlorophenoxy herbicides" in Supplement 7, a few additional epidemiological studies were summarized, including one involving non-Hodgkin's lymphoma in Kansas agricultural workers exposed to "2,4-D" (Hoar et al. 1986). Nevertheless, the lack of clarity in this study regarding chemical identification and the inability to separate out single-chemical exposures led IARC to keep its 1986 classification and its term-of-art unchanged (*i.e.*, "chlorophenoxy herbicides" remained as the subject of IARC's "limited" finding).

Therefore, following three evaluations of what would now be considered archaic data from an assemblage of compounds that are no longer relevant to the current marketplace, IARC was not able to identify even "limited" associations between 2,4-D, alone, and exposures to either humans or animals, or association with genetic toxicity. IARC was only able to find "limited" associations in a few studies performed at that time, which broadly defined exposures to a group of ill-defined substances that IARC decided to call "chlorophenoxy herbicides." If IARC were to evaluate the literature generated in the last 22 years, particularly with the high-quality studies generated after 1987, IARC would come to the same conclusion that **all other regulatory agencies** have come to in their respective evaluations of 2,4-D: **these substances (which this submission defines as including salts and esters) are not carcinogenic.**

D. *OEHHA Itself Has Refrained From Identifying 2,4-D As A Carcinogen*

In 1997, OEHHA proposed a "medium-high" priority for 2,4-D as a potential candidate for consideration by the Proposition 65 Carcinogen Identification Committee. Ironically, the primary basis for even this "*medium-high*" priority was Supplement 7 (OEHHA 1997). OEHHA acknowledged its reliance on IARC's classification in its response to objections raised by the 2,4-D Task Force to the proposed prioritization (OEHHA 1998). Although the prioritization was finalized as "medium-high" in 1997, 2,4-D has never undergone the process of consideration under the Proposition 65 "authoritative body" listing mechanism. The only conclusion to be

³¹ Supplement 7 at page 30.

³² IARC Monograph Volume 15 (1977) at page 130.

drawn from this result is that neither the IARC classification nor the EPA documents used by OEHHA to generate its 1997 summary document were sufficient to trigger that process. And, even if OEHHA were to consider 2,4-D for listing under the substantive listing mechanism identified in Health & Safety Code section 25249.8(b), the weight of the extensive scientific evidence now available would require a finding that 2,4-D should **not** be listed.

In fact, in January 2009, OEHHA concluded its determination of a Public Health Goal (“PHG”) for 2,4-D.³³ With respect to its assessment of the carcinogenicity potential of 2,4-D, OEHHA concluded:

Due to lack of conclusive findings in the epidemiological data, and the lack of evidence in animal studies for carcinogenicity, **carcinogenicity is not used as the endpoint for the PHG.**³⁴

E. Other Jurisdiction’s Conclusions Regarding The Carcinogenicity Of 2,4-D

The following national and international regulatory bodies have concluded that existing scientific data do not support classifying 2,4-D as a carcinogen: United States Environmental Protection Agency (1997³⁵, 2004a³⁶ 2004b³⁷, 2005³⁸); Health Canada’s Pest Management

³³ *Public Health Goals for Chemicals in Drinking Water -- 2,4-Dichlorophenoxyacetic Acid*, <http://www.oehha.ca.gov/water/phg/pdf/24dphg010209.pdf> (OEHHA 2009) (the “PHG Document”).

³⁴ PHG Document at 24 (emphasis added).

³⁵ USEPA 1997. Carcinogenicity Peer Review (4th) of 2,4-Dichlorophenoxyacetic Acid. Data Evaluation Record, January 29, 1997.

³⁶ USEPA 2004a. 2,4-D – Second Report of the Hazard Identification Assessment Review Committee. [HIARC] Health Effects Division of Office of Pesticide Programs. TXR No. 0051866. January 15, 2004.

³⁷ USEPA 2004b. 2,4-D: HED’s Human Health Risk Assessment of the Reregistration Eligibility Decision (RED) Revised to Reflect Error-only Comments from Registrants. Health Effects Division of Office of Pesticide Programs. PC Code 030001; DP Barcode D287199. June 2, 2004.

³⁸ USEPA 2005. Reregistration Eligibility Decision for 2,4-D. [RED] Office of Pesticide Programs. EPA 738-R-05-002. June 2005. In 2007, EPA released its Decision Not to Initiate Special Review for 2,4-D under FIFRA, stating: “Because the Agency has determined that the existing data do not support a conclusion that links human cancer to 2,4-D exposure, it has decided not to initiate a Special Review of 2,4-D....” 72 Fed.Reg. 44510 (August 7, 2007).

Regulatory Agency (2007)³⁹; European Commission (2001)⁴⁰; New Zealand (2003)⁴¹; and the World Health Organization (1996)⁴².

In fact, when EPA reviewed the chlorophenoxy herbicides cohort and case control epidemiology studies relied upon by IARC, the agency found that the studies are not adequate to conclude that any form of cancer is causally associated with 2,4-D exposure. Thus, EPA's 1994 SAB/SAP Special Joint Committee -- charged by EPA to decide whether human epidemiologic studies provide evidence that 2,4-D is a human carcinogen -- reviewed the epidemiology studies relied on by IARC and concluded that "[t]he epidemiologic studies often do not provide information on exposures specific to the chemical 2,4-D. Most of the studies relate the risk to the general category of phenoxyherbicides ... If there is an apparent risk and the information on specific exposures is missing, then chemicals other than 2,4-D may account for the apparent risk."⁴³ The 2,4-D SAB/SAP Panel concluded that "[t]he data are not sufficient to conclude that there is a cause and effect relationship between the exposure to 2,4-D and NHL."⁴⁴

³⁹ Health Canada 2007. Re-evaluation of the Agricultural, Forestry, Aquatic and Industrial Site Uses of (2,4-Dichlorophenoxy) acetic Acid [2,4-D]. Proposed Acceptability for Continuing Registration. PACR2007-06. 19 June 2007. www.pmr-arla.gc.ca/english/pdf/pacr/pacr2007-06-e.pdf.

⁴⁰ European Commission Health & Consumer Protection Directorate-General. 2001. Commission Working document. Review Report for the Active Substance 2,4-D Re-evaluation. 7599/VI/97-final, 1 October 2001.

⁴¹ Environmental Risk Management Authority [New Zealand ERMA] 2003. Substances to be transferred to the HSNO Act under Section 160(1)(a): Phenoxy Herbicides. <http://www.ermanz.govt.nz/hs/pesticides/phenoxy-herb-report.pdf>

⁴² WHO Pesticide Residues in Food – 1996. Part II - Toxicological. FAO Plant Production and Protection Paper 140: 31-38; and WHO/PCS/97.1: 45-96. Rome September 1996

⁴³ EPA 1994. *An SAB Report: Assessment of Potential 2,4-D Carcinogenicity. Review of the Epidemiological and Other Data on Potential Carcinogenicity of 2,4-D*. U.S. Environmental Protection Agency Science Advisory Board (SAB), Washington, D.C., at page 14.

⁴⁴ *Id.*

II. OEHHA MUST NOT PROCEED WITH ITS PROPOSED LISTING OF “CHLOROPHENOXY HERBICIDES”

A. *If It Proceeds With This Proposed Listing, OEHHA Is Limited To Listing The Mixture Of “Chlorophenoxy Herbicides” That IARC Reviewed, Not The Individual Constituents Of That Mixture*

As explained at length above, IARC has never identified 2,4-D, alone, as a carcinogen. As OEHHA itself concedes, OEHHA’s authority to list chemicals under the asserted Labor Code mechanism is ministerial. Thus, OEHHA’s proposed listing, if it proceeds at all, must clarify that 2,4-D is *not* included in the category of “chlorophenoxy herbicides.”

1. *OEHHA Cannot Substitute Its Judgment For IARC’s*

Under the terms of the April 24, 2009 court order entered in *Sierra Club v. Schwarzenegger*, No. RG07-356881 (Cal. Super. Ct., Alameda County), OEHHA has a ministerial obligation to list chemicals referenced in California Labor Code section 6382(b)(1) and (d). OEHHA itself acknowledges the ministerial nature of its authority in its June 12, 2009 Request (“**Because these are ministerial listings....**”) (emphasis in original). The scope of this authority limits OEHHA’s discretion to weigh scientific evidence of carcinogenicity associated with the substances evaluated by IARC. As explained further below, OEHHA must limit the proposed listing, if it proceeds at all, to the mixture of substances IARC actually evaluated.

In *Western Oil and Gas Ass’n v. Air Resources Bd.* (1984) 37 Cal.3d 502, the California Supreme Court examined the scope of a California agency’s ministerial authority. In that case, several oil companies and their trade associations sued the California Air Resources Board (“CARB”), alleging (among other things) that certain air quality standards established by CARB were not based on recommendations by the California Department of Health Services (“DHS”) as required by law. *Id.* at 507. After examining the law, the relevant regulatory proceedings and CARB’s ministerial authority in establishing standards, the Court concluded that CARB had no discretion to disregard DHS’s recommendations. *Id.*

At issue in *Western Oil* was a provision of the Mulford-Carrell Air Resources Act, Health & Safety Code sections 39000, et seq., that imposed a mandatory duty on CARB to base its air quality standards on DHS’s health effects-based recommendations. *Id.* at 510. The Court concluded that “CARB must follow [DHS] recommendations for standards relating to health effects.” *Id.* at 511. Given that CARB also was required by statute to consider other factors as well in setting the standards, CARB was not required to adopt DHS’s recommendations wholesale. *Id.* Notwithstanding that, under its ministerial authority conferred by statute, “[w]hat [CARB] may not do is to substitute its judgment for that of [DHS] in determining health effects.” *Id.* (emphasis added).

A similar issue was resolved in *Fernandez v. California Dept. of Pesticide Regulation* (2008) 164 Cal.App.4th 1214. There, plaintiffs contended that the California Department of Pesticide Regulation (“DPR”) failed to properly consult with OEHHA in establishing regulations relating to the safety of persons working with or around methyl bromide. The Court of Appeal held that DPR has a ministerial duty, under Food and Agricultural Code sections 12980 and 12981, to develop regulations jointly with OEHHA and to defer to OEHHA’s assessments of worker risks. *Id.* at 1233. Concluding that DPR could not substitute its judgment for OEHHA’s on worker risk assessments, a subject reserved for OEHHA under the relevant statute, the court concluded that DPR’s failure to consult with OEHHA as part of its rulemaking process was a violation of law: “DPR may not itself determine the health effects of subchronic exposure to methyl bromide....” *Id.* at 1220; *see also id.* at 1235-36; *Mountain Lion Foundation v. Fish & Game Comm’n* (1997) 16 Cal.4th 105, 117 (“A ministerial decision involves only the use of fixed standards or objective measurements....”).

Pursuant to the precedent set by the above and other similar cases, OEHHA’s authority under the Labor Code listing mechanism is extremely limited. OEHHA already has acknowledged this limitation in other Labor Code listings. When OEHHA proposed to list areca nut as a carcinogen pursuant to this mechanism, it received a comment from AHPA stating that OEHHA should not list “areca nut” as such, but only the constituents of areca nut that are carcinogens. OEHHA responded: “OEHHA has proposed the listing of “areca nut” **based upon its identification in the IARC document.**”⁴⁵ Implicit in this response is OEHHA’s acknowledgement that it cannot substitute its judgment for IARC’s with respect to the substance(s) IARC evaluated in any particular Monograph.

2. *OEHHA Must Clarify The Proposed Listing To Avoid Inclusion Of 2,4-D*

IARC has never identified 2,4-D, alone, as a carcinogen. If any Labor Code listing is to proceed at all with respect to “chlorophenoxy herbicides,” it must proceed with respect to the **exact** mixture were evaluated by IARC. As already discussed above, in 1987 IARC evaluated the carcinogenic hazards presented by exposure to **all** “chlorophenoxy herbicides” reviewed. OEHHA must clarify the proposed listing to refer to that **exact** mixture, and not the individual constituents, such as 2,4-D, that may comprise that mixture. Put another way, OEHHA must clarify that only exposures to, or discharges of, **each and every substance solely as the mixture reviewed by IARC**, trigger Proposition 65’s legal obligations. Alternatively, OEHHA must clarify the listing to specifically **exclude 2,4-D**. Either of these clarifications would be entirely

⁴⁵ http://www.oehha.ca.gov/prop65/docs_admin/betel%20quid_areca%20nutresponses.pdf at 8-9 (emphasis added).

consistent with the fact that IARC has never identified 2,4-D as a carcinogen, as well as with the existing large body of data indicating that 2,4-D is not classifiable as a carcinogen.

IARC's classification of "chlorophenoxy herbicides" as possible carcinogens in 1986 and 1987 was based solely on epidemiology studies, not animal studies. Moreover, in the case control and cohort studies which serve as the basis for IARC's 1986 Monographs, the populations were occupationally exposed to **all** "chlorophenoxy herbicides," which IARC apparently defined in 1986 to include six (and perhaps more) herbicides (2,4-D; 2,4,5-T; Silvex; MCPA; Dichlorprop and MCPP) and which IARC apparently defined in 1987 to include three (and perhaps more) herbicides (2,4-D; 2,4,5-T; and MCPA).⁴⁶ Because the populations IARC reviewed were exposed to a combination of all "chlorophenoxy herbicides" and because IARC classified only the group and not the individual herbicides making up the group, IARC's classification logically and scientifically triggers the Proposition 65 listing of products containing each and every one of all six (or three) "chlorophenoxy herbicides."

Thus, a proposed listing of "chlorophenoxy herbicides" that explicitly or implicitly includes 2,4-D as a single constituent would be unlawful, in that OEHHA would be unlawfully substituting its judgment for IARC's. In addition, such a listing would contravene the considered judgment of many other agencies, including OEHHA itself. Moreover, excluding 2,4-D from any Proposition 65 listing based on IARC's 1987 review of chlorophenoxy herbicides is scientifically supported by the fact that regulators, such as EPA, have concluded that IARC's 1987 Category 2B classification of the group does not support a finding that 2,4-D alone is a carcinogen.

B. *The Listing of 2,4-D As A Substance Included In "Chlorophenoxy Herbicides" Would Contravene OEHHA's Authority*

Proposition 65 confers on OEHHA the authority to list those chemicals that are known to the State of California to cause cancer.⁴⁷ As discussed at length above, 2,4-D has not been classified as a carcinogen. OEHHA unlawfully would exceed its statutory authority if it were to include a chemical like 2,4-D, which not a carcinogen, in a Proposition 65 listing.

⁴⁶ Significantly, the mixtures that IARC evaluated no longer exists, since EPA canceled the registration of 2,4,5-T approximately 20 years ago. It is difficult to understand the practical benefit of listing a mixture to which no Californian – or indeed any person in the United States – will ever be exposed.

⁴⁷ Health & Safety Code § 25249.8.

C. *The Category “Chlorophenoxy Herbicides” Is Vague And Therefore Legally Infirm*

The classification “chlorophenoxy herbicides” is not a self-defining term. IARC has never defined precisely which herbicides are included in the class “chlorophenoxy herbicides.” Indeed, its 1986 Monographs apparently identified six herbicides, and its 1987 Supplement 7 apparently identified three – evidence that IARC itself finds the grouping of “chlorophenoxy herbicides” to be, at best, fluid. **Significantly, in 1987 at the time of IARC’s evaluations, the product spectrum and their compositions were significantly different than those existing in the current market.** For example, 2,4,5-T has not been used or available for more than two decades, when its FIFRA registrations were canceled -- further reinforcing the archaic nature of IARC’s “chlorophenoxy herbicide” grouping. Further, EPA, the California Department of Pesticide Regulation and other regulatory authorities do not use this term in a manner that defines all of the specific individual substances that are to be included. In the absence of a precise definition, OEHHA can only guess what herbicides IARC intended to include in its classification. This significant limitation is inherent in using an “overall” IARC listing for the purpose of listing a substance under Proposition 65.

Worse, given the purposeful lack of a definition for a group of substances that IARC decided to call “chlorophenoxy herbicides,” neither the regulated community nor Proposition 65 prosecutors would understand the actual scope of the substances identified by the proposed listing. Unsophisticated prosecutors may even consider plant growth regulators – critical to the California citrus industry – as “chlorophenoxy herbicides,” leaving defendants to pay the expense of arguing in court that plant growth regulators do not fall within this class. Such vagueness is fatal, as it provides no notice or due process to the regulated community.

III. CONCLUSION

For all the reasons discussed above, OEHHA must not proceed with the proposed listing of “chlorophenoxy herbicides.” IARC has never identified 2,4-D as a carcinogen. To the extent that this ill-defined “chlorophenoxy herbicide” group of substances could be construed to include 2,4-D, a listing that would include 2,4-D would be unlawful.

If OEHHA insists on proceeding with the proposed listing, it must:

1. Clarify that “chlorophenoxy herbicides” refers to each and every substance reviewed by IARC **solely as a mixture of those reviewed substances, and only as they existed prior to 1987**, and not the individual constituents like 2,4-D alone; or
2. Clarify that the proposed listing **excludes 2,4-D acid and esters or salts of 2,4-D.**

Ms. Cynthia Oshita
July 13, 2009
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Thank you for your consideration of these comments. We appreciate this opportunity to be heard on such an important issue.

Very truly yours,

A handwritten signature in cursive script that reads "Ann G. Grimaldi". The signature is written in black ink and is positioned to the right of the typed name.

Ann G. Grimaldi

SF:27372831.1

EXHIBIT A



WORLD HEALTH ORGANIZATION

INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

IARC MONOGRAPHS
ON THE
EVALUATION OF THE CARCINOGENIC RISK
OF CHEMICALS TO MAN

Some Fumigants, the Herbicides 2,4-D and 2,4,5-T,
Chlorinated Dibenzodioxins and Miscellaneous Industrial Chemicals

VOLUME 15

INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

LYON

AUGUST 1977

2,4-D AND ESTERS

1. Chemical and Physical Data

1.1 Synonyms and trade names

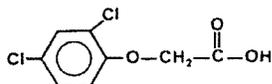
Chem. Abstr. Services Reg. No.: 94-75-7

Chem. Abstr. Name: (2,4-Dichlorophenoxy)acetic acid

Dichlorophenoxyacetic acid; 2,4-dichlorophenoxyacetic acid

For a representative list of other synonyms and trade names of products containing 2,4-D, its salts or esters, either as the sole active ingredient or as mixtures with other compounds, see Appendix A.

1.2 Chemical formula and molecular weight



$C_8H_6Cl_2O_3$

Mol. wt: 221.0

1.3 Chemical and physical properties of the pure substance

From Weed Science Society of America (1974), unless otherwise specified

- (a) Description: Odourless white crystals
- (b) Boiling-point: 160°C at 0.4 mm
- (c) Melting-point: 140-141°C
- (d) Spectroscopy data: Infra-red and ultra-violet spectra are given by Gore *et al.* (1971).
- (e) Solubility: Soluble in 95% ethanol and in acetone, dioxane and isopropyl alcohol
- (f) Stability: Stable up to and including its melting-point
- (g) Reactivity: Forms salts that are soluble in water

1.4 Technical products and impurities

Technical grade 2,4-D is available in the US as the free acid (98% purity), as salts (dimethylamine, mixed ethanolamine and isopropanolamine, lithium and sodium) and as esters of the following alcohols: isopropyl, *n*-butyl, sec-butyl, iso-octyl, 2-butoxyethyl and butoxypolypropylene glycol (US International Trade Commission, 1976a).

Of 28 samples of 2,4-D tested for content of chlorodibenzo-*para*-dioxins, one was found to contain <10 mg/kg hexachlorodibenzo-*para*-dioxin (Woolson *et al.*, 1972). Bis(2,4-dichlorophenoxy)methane has been identified as the major contaminant of 2,4-D, and bis(2,6-dichlorophenoxy)methane and 2,2',4,6'-tetrachlorodiphenoxy methane as minor contaminants (Huston, 1972).

N-Nitrosodimethylamine¹ has been detected at a level of 300 µg/l in dimethylamine salt of 2,4-D which was stored in metal containers the interiors of which had been presprayed with sodium nitrite as an antioxidant (Fine *et al.*, 1977).

Technical 2,4-D produced in Japan is more than 99% pure.

2. Production, Use, Occurrence and Analysis

For background information on this section, see preamble, p. 17.

2.1 Production and use

(a) Production

2,4-D was prepared in 1941 by the interaction of 2,4-dichlorophenol, monochloroacetic acid and sodium hydroxide (Pokorny, 1941), and a similar process is believed to be used in its commercial production.

Production was first reported in the US in 1944 (US Tariff Commission, 1946). The quantity of 2,4-D produced increased steadily between 1963 and 1968, when it reached a maximum of 36 million kg; production decreased to about 20 million kg in 1970 (US Department of Agriculture, 1973) and

¹See IARC, 1972

gradually increased again to an estimated 27 million kg in 1974. In 1975, three US companies reported production of 2,4-D acid; three others reported the production of esters or salts of 2,4-D, presumably from purchased acid. Separate production data for 1975 are available only for the dimethylamine salt of 2,4-D, 11.6 million kg of which were produced, and for the iso-octyl ester, 4.5 million kg of which were produced (US International Trade Commission, 1976a). In 1973, 115 thousand kg of 2,4-D acid and 57 thousand kg of mixed butyl esters were imported through the principal US customs districts (US Tariff Commission, 1974). In 1974, 365 kg of the mixed butyl esters were imported (US International Trade Commission, 1976b). Combined US exports of 2,4-D and 2,4,5-T amounted to 5.7 million kg in 1975 (US Department of Commerce, 1975).

The Federal Republic of Germany and the UK are the major producing countries in western Europe, where annual production is estimated to be 3-30 million kg; in eastern Europe it is estimated to be less than 10 million kg.

2,4-D was first produced commercially in Japan before 1945 by a process similar to that used in the US. Production in 1975 by two producers amounted to 511 thousand kg, and 176 thousand kg were exported.

About 90,000 kg were imported into Australia in 1975-76.

(b) Use

2,4-D is a systemic herbicide widely used for control of broadleaf weeds in cereal crops and sugar cane and on turf, pastures and non-cropland (Weed Science Society of America, 1974). It is also used to control the ripening of bananas and citrus fruits, to delay preharvest dropping of some fruits and in some countries as a fungicide for the control of *Alternaria* rots when lemons are to be held for storage (WHO, 1975).

An estimated 27 million kg of 2,4-D acid equivalent, largely in the form of esters and salts, were used in the US in 1975, as follows: wheat and other small grains, 31%; corn and grain sorghum, 26%; pasture and rangeland, 25%; industrial and commercial uses, 9%; lawns and turf, 5%; aquatic weed control, 3%; rice and fruit, 1%.

2,4-D was used to defoliate jungle areas in south Vietnam, where it was a component of 'Agent Orange' (a 50:50 mixture of the *n*-butyl esters of 2,4-D and 2,4,5-T, containing up to 30 mg/kg or more TCDD) (Davis, 1974). About 40 million litres of 'Agent Orange' were sprayed in south Vietnam between 1965-1971 for defoliation or crop destruction (Committee on the Effects of Herbicides in Vietnam, 1974).

National tolerances are in effect in several countries. Examples were reported to the Joint Meeting of the FAO Working Party of Experts on Pesticide Residues and the WHO Expert Committee on Pesticide Residues in 1975. The previously established acceptable daily intake for man of 0-0.3 mg/kg bw was considered and confirmed at this meeting (WHO, 1977).

The US Occupational Safety and Health Administration health standards for exposure to air contaminants require that an employee's exposure to 2,4-D does not exceed an eight-hour time-weighted average of 10 mg/m³ in the working atmosphere during any eight-hour work shift of a forty-hour work week. The corresponding standard in the Federal Republic of Germany is also 10 mg/m³, and the acceptable ceiling concentration in the USSR is 1 mg/m³ (Winell, 1975).

2.2 Occurrence

2,4-D is not known to occur as a natural product.

It is broken down by soil microorganisms, and there is reportedly no accumulation in the soil as a result of normal agricultural use (Weed Science Society of America, 1974).

In a continuing programme involving the monitoring of pesticide residues in food, the US Department of Health, Education and Welfare found a decreasing level of 2,4-D in food samples collected at retail outlets during the period 1965-1973. Between June 1964 and April 1965, 2,4-D was found in 10 of 216 composite food samples examined, including leafy vegetables, oils, fat and shortening, sugar and adjuvants (Duggan *et al.*, 1966). In 1973, an insignificant amount of 2,4-D was found during this programme: a trace was found in one of 360 composite potato samples (US Bureau of Foods, 1975).

Air samples were collected near wheat-growing areas around Pullman and Kennewick Highlands, Washington, USA between April and August 1964 after applications of 2,4-D. Although data were given for several products containing 2,4-D, those for the isopropyl ester were the highest: an average concentration of $0.116 \mu\text{g}/\text{m}^3$ and a maximum concentration of $1.96 \mu\text{g}/\text{m}^3$ of an aerosol form of the ester and an average concentration of $0.007 \mu\text{g}/\text{m}^3$ and a maximum concentration of $0.69 \mu\text{g}/\text{m}^3$ of the vaporized ester were found in 24-hour samples near Pullman (Finkelstein, 1969).

Residues of 2,4-D in pond waters declined from maximums of 0.345 and 0.692 mg/l in Florida and Georgia, respectively, to less than 0.005 mg/l 28 days after treatment and from 0.630 mg/l in Missouri pond waters to less than 0.005 mg/l 56 days after treatment. Residues in mud from the Florida and Georgia ponds never exceeded 0.05 mg/kg and had declined to trace or nondetectable levels 56 days after treatment. The highest residue found was 0.170 mg/kg in samples of mud taken on the first and third days in the most heavily treated Missouri pond. In mud from one Missouri pond, residues were detected as late as 28 days after treatment; no residues occurred in any ponds after that time (Schultz & Harman, 1974).

In September 1971, soil samples were obtained from an area in Thailand that had been used for calibrating aerial herbicide spray equipment and that had received about 940 kg/ha 2,4-D and large amounts of other herbicides in 1964-65. Two of 6 samples contained 0.18 and 0.21 kg/ha 2,4-D (Committee on the Effects of Herbicides in Vietnam, 1974).

2.3 Analysis

The Association of Official Analytical Chemists (AOAC) has published three Official Final Actions for the determination of 2,4-D in formulations: (1) titration, for formulations of the free acid; (2) determination of total chlorine after calorimetric destruction for formulations of 2,4-D compounds; and (3) infra-red spectroscopy for 3,6-dichloro-2-methoxybenzoic acid (Dicamba)/2,4-D formulations. Official First Actions have been published for determination of the free acid in formulations of 2,4-D esters by titration to pH 7, and for determination in formulations with 4-amino-3,5,6-trichloropicolinic acid (picloram) by high-pressure liquid

chromatography (Beroza, 1976; Horwitz, 1975). Results of collaborative studies of several of these methods have been published (Hammond, 1973; Malina, 1971; Skelly *et al.*, 1976).

Another method for determining 2,4-D in formulations involves gas chromatography of its trimethylsilyl derivative (Zweig, 1972). With a similar method, recoveries of $100.5 \pm 1\%$ compare favourably with those obtained using the AOAC infra-red spectroscopy method (Collier & Grimes, 1974).

Methods of analysis for 2,4-D residues in various commodities using gas chromatography have been summarized and tabulated in a recent review (WHO, 1975). In a more recent publication (WHO, 1977) attention was drawn to the low recoveries frequently encountered due to conjugation of 2,4-D with plant constituents. The Pesticide Analytical Manual (US Food & Drug Administration, 1975a,b) summarizes several methods for determining 2,4-D residues, using gas, thin-layer and paper chromatography; a general method for extraction and clean-up of chlorophenoxy acids in a variety of foods provides more than 80% recovery. Limits of detection for gas chromatography are in the order of 10 $\mu\text{g}/\text{kg}$ when microcoulometric detection is used and 0.2 $\mu\text{g}/\text{kg}$ with electron capture.

A gas chromatographic procedure has been used to separate mixtures of herbicidal acids as their pentafluorobenzyl derivatives, which generally provide better separation and better responses in the electron capture detector than do the methyl or silyl derivatives; the method has a sensitivity of 0.4 $\mu\text{g}/\text{kg}$ for 2,4-D (Chau & Terry, 1976). An automated, gel-permeation chromatographic procedure permits clean-up of pesticide residues in lipid-containing plant and animal extracts prior to their determination by gas chromatography with electron-capture detection, and provides recovery of more than 80% 2,4-D esters (Johnson *et al.*, 1976).

A low-temperature extraction and clean-up method is used to separate multiple residues of 2,4-D and other pesticides for eventual gas chromatographic analysis with electron capture and flame photometric detectors; 82-108% of added 4 mg/kg 2,4-D could be recovered (McLeod & Wales, 1972).

Gas chromatography combined with electron-capture detection has been used to determine 0.5 mg/kg 2,4-D residues in oysters (Duffy & Sheltoon, 1967) and 0.05 mg/kg in soil, wheat and barley (Khan, 1975).

3. Biological Data Relevant to the Evaluation of Carcinogenic Risk to Man

3.1 Carcinogenicity and related studies in animals

(a) Oral administration

Mouse: Groups of 18 male and 18 female (C57BL/6x3H/Anf)¹F₁ mice and 18 male and 18 female (C57BL/6xAKR)¹F₁ mice received commercial 2,4-D (90%, m.p. 136-140°C) according to the following dose schedule: 46.4 mg/kg bw in 0.5% gelatine by stomach tube at 7 days of age and the same amount (not adjusted for increasing body weight) daily up to 28 days of age; subsequently, the mice were given 149 mg/kg of diet. A further group of 18 male and 18 female (C57BL/6xAKR)¹F₁ mice were given oral doses of 100 mg/kg bw/day from 7-28 days of age and subsequently fed 323 mg/kg of diet. The experiment was terminated when the mice were about 78 weeks of age, at which time 15, 16, 16 and 16 given the lower dose level and 11 and 13 given the higher dose level were still alive in the respective groups. Tumour incidences were compared with those observed among groups of 79, 87, 90 and 82 control mice, which had either been untreated or had received gelatine only: the incidences were not significantly greater (P>0.05) when any group or combination of groups was considered. Similar results were obtained in groups of mice given 2,4-D isopropyl, butyl or isooctyl esters (99%, 99% and 97% pure) at doses of 46.4 mg/kg bw from 7-28 days of age and, subsequently, 111, 149 and 130 mg/kg of diet, respectively, up to 78 weeks of age (Innes *et al.*, 1969; NTIS, 1968a).

Rat: Groups of 25 male and 25 female 3-week old Osborne-Mendel rats were fed for two years on diets containing 0, 5, 25, 125, 625 or 1250 mg/kg of diet 2,4-D. The 2,4-D was 96.7% pure and contained no detectable levels of 2,7-dichloro- or 2,3,7,8-tetrachlorodibenzo-*para*-dioxin; the limit of sensitivity of the method of analysis was 1 mg/kg. The numbers of male and female rats with malignant tumours were 6 in controls and 8, 7, 7, 8

and 14 in the treated groups, respectively. Tumours were randomly distributed and were also found in ageing rats of this strain. According to the authors, a statistical increase ($P < 0.05$) in the number of treated rats with malignant tumours over controls was found only in males receiving the highest dose level (Hansen *et al.*, 1971).

Groups of 120 male and 45 female random-bred rats, weighing 80-100 g at the start of the test, were given 2,4-D as the amine salt (amount not specified) mixed in the food at a concentration which corresponded to a daily intake of one-tenth of the LD_{50} (not specified, but see Table 1, section 3.2). Two treated rats developed tumours (a mammary fibroadenoma and a haemangioma of the mesenterium) after 23 months, and one untreated rat had a mammary fibroadenoma after 27 months (Arkhipov & Koslova, 1974).

(b) Subcutaneous and/or intramuscular administration

Mouse: Groups of 18 male and 18 female (C57BL/6xC3H/Anf) F_1 mice and 18 male and 18 female (C57BL/6xAKR) F_1 mice were given single s.c. injections of 215 mg/kg bw 2,4-D (90% pure, m.p. 136-140°C) in dimethyl sulphoxide on the 28th day of life and observed up to 78 weeks of age, at which time 16, 17, 18 and 18 mice in the four groups, respectively, were still alive. Tumour incidences were compared with those in groups of 141, 154, 161 and 157 controls that were either untreated or were injected with dimethyl sulphoxide, 0.5% aqueous gelatin or corn oil. The tumour incidence in any group or combination of groups was not significantly different from that in controls ($P > 0.05$). No increase in the incidence of tumours was observed in similar groups of mice treated with single s.c. injections of 21.5 mg/kg bw butyl or 100 mg/kg bw isopropyl esters of 2,4-D (both 99% pure). Of mice treated with 21.5 mg/kg bw isooctyl ester of 2,4-D (97% pure), 5/17 females of the second strain developed reticulum-cell sarcomas ($P = 0.01$) (NTIS, 1968a).

3.2 Other relevant biological data

(a) Experimental systems

The toxicity of 2,4-D was reviewed by Dalgaard-Mikkelsen & Poulsen (1962).

Acute and short-term toxicity

There are species differences in the acute oral toxicity of 2,4-D and of its derivatives (Table 1). The symptoms of acute toxicity in mice, rabbits, guinea-pigs and rats are essentially similar (Bucher, 1946; Hill & Carlisle, 1947). Some animals died suddenly, apparently from ventricular fibrillation; those that did not die immediately developed stiffness of the extremities, incoordination, lethargy, stupor and coma prior to death (Hill & Carlisle, 1947). Symptoms of myotonia were evident in mice after the parenteral administration of 150-200 mg/kg bw; and in mice acutely intoxicated with 2,4-D, dilatation of the blood vessels of lungs, liver and kidneys was observed (Bucher, 1946). Rats and guinea-pigs administered lethal doses of 2,4-D exhibited congestion of the viscera and enlarged, swollen kidneys; microscopically, there was massive cloudy swelling of the proximal convoluted tubules with cast formation (Hill & Carlisle, 1947). S.c. injections of 100 mg/kg bw 2,4-D resulted in a decrease of both thyroid and body weights in male rats (Florsheim & Velcoff, 1962).

Oral administration of 625 mg/kg bw to rats resulted in changes in the levels of several serum enzymes and globulins (Szöcs *et al.*, 1970). 2,4-D was found to be a potent uncoupling agent for oxidative phosphorylation and to stimulate the respiration of rat liver mitochondria in a phosphate-deficient medium (Brody, 1952).

In dogs, toxic symptoms were often not present until 6 hours after oral administration of a lethal dose of 2,4-D; the animals became ataxic, with progressive increase in spasm. Death appeared to be due in most cases to hepatic congestion or to pneumonia. Pathological changes, limited to the gastrointestinal tract, lung and liver, followed the development of anorexia, weight loss and myotonia (Drill & Hiratzka, 1953). Dogs exhibited evidence of liver damage more frequently than other animals studied (Bucher, 1946; Drill & Hiratzka, 1953).

No toxic symptoms were noted in monkeys given 214 mg/kg bw orally, or 428 mg/kg bw intraperitoneally; however, oral plus i.p. injection of a total of 500 mg/kg bw 2,4-D caused nausea, vomiting, lethargy, muscular incoordination and head drop (Hill & Carlisle, 1947). Acute toxic doses

TABLE 1

Acute oral toxicity of 2,4-D and esters

Compound of 2,4-D	Species	Sex	LD ₅₀ (mg/kg bw)	Reference
Acid	Mice	M	375	Hill & Carlisle (1947)
	Mice	M	368	Rowe & Hymas (1954)
	Rats	M	375	" " "
	Rats		666	Hill & Carlisle (1947)
	Guinea-pigs	M&F	469	Rowe & Hymas (1954)
	Guinea-pigs		1000	Hill & Carlisle (1947)
	Rabbits		800	" " "
	Dogs		100	Drill & Hiratzka (1953)
	Chicks	M&F	541	Rowe & Hymas (1954)
	Butyl ester	Mice		380
Rats			1500	Schillinger (1960)
Rats			920	Konstantinova (1970)
Cats			820	" "
Esters of mono-, di- and tripropylene glycol butyl ethers	Rats	F	570	Rowe & Hymas (1954)
Isopropyl ester	Mice	M	541	Rowe & Hymas (1954)
	Rats	M&F	700	" " "
	Guinea-pigs	M	550	" " "
	Chicks	M&F	1420	" " "
Mixed butyl esters	Mice	F	713	Rowe & Hymas (1954)
	Rats	F	620	" " "
	Guinea-pigs	F	848	" " "
	Rabbits	M&F	1420	" " "
	Chicks	M&F	2000	" " "
Sodium salt	Mice		375	Rowe & Hymas (1954)
	Rats	F	805	" " "
	Rats		2000	Schillinger (1960)
	Guinea-pigs	M	551	Rowe & Hymas (1954)
	Rabbits		800	" " "
Alkanolamine salt	Chicks		380-765	Rowe & Hymas (1954)

of 2,4-D (765 mg/kg bw) produce fatty degeneration of the liver, spleen, kidneys and heart and haemorrhagic gastroenteritis in chickens (Bjorn & Northen, 1948), and acute toxic doses have similar effects in sheep and cattle (Palmer & Radeleff, 1964).

Subacute and chronic toxicity

2,4-D administered subcutaneously to mice at doses of 50-90 mg/kg bw once or twice daily for 3 weeks to 3 months produced no clear-cut chronic symptoms. Levels of 70 mg/kg bw and more retarded growth, probably by reducing food intake (Bucher, 1946).

Rats fed 1000 mg/kg of diet 2,4-D for one month showed no signs of toxic effects (Hill & Carlisle, 1947). No adverse effects were noted in young female rats fed 100 and 300 mg/kg of diet 2,4-D (purity unspecified) for periods of up to 113 days, while those given 1000 mg/kg of diet over the same period had increased mortality, depressed growth rate, slightly increased liver weight and slight cloudy swelling of the liver. Animals fed 3000 or 10,000 mg/kg of diet were sacrificed after 12 days because of food refusal and rapid weight loss. Increased liver and kidney weights and unstated slight pathological changes were noted in these organs (Rowe & Hymas, 1954).

No significant adverse effects were noted when 15 ml of each of 3 commercially available formulations of 2,4-D (the dimethylamine salt and the isooctyl and butyl esters) were administered 5 times weekly for 3 weeks to the intact and abraded skin of rabbits at two concentrations, 0.626% and 3.13% (the dimethylamine salt was diluted in water and the ester in either oil or water) (Kay *et al.*, 1965).

Groups of 3 male and 3 female beagle dogs were fed 10, 50, 100 or 500 mg/kg of diet 2,4-D (96.7% pure, with no detectable chlorodibenzo-*para*-dioxin content) for 2 years, starting at 6-8 months of age. Twenty-eight dogs that survived the 2-year period were clinically normal. No adverse effects related to 2,4-D administration were observed (Hansen *et al.*, 1971).

Dogs of both sexes were given 2, 5 or 10 mg/kg bw commercial 2,4-D (98.5% pure) orally by capsule for 5 days per week for 13 weeks; no signs

of toxicity were observed. Dogs given 20 mg/kg bw survived for periods ranging from 18-49 days, with loss of weight occurring after 7-12 days and with ataxia, increased muscle tonus and a terminal fall in lymphocyte count prior to death (Drill & Hiratzka, 1953).

Young pigs treated at varying intervals up to 103 days with 50, 100 or 300 mg/kg bw of the commercial triethanolamine salt or butyl ester of 2,4-D exhibited symptoms of intoxication and pathology analagous to those seen in laboratory animals. Clinical signs of anorexia and retarded growth were found in one animal given 51 doses of 50 mg/kg bw triethanolamine salt over 103 days. Pigs fed 500 mg/kg of diet triethanolamine salt of 2,4-D for up to 12 months developed locomotor disturbances of increasing severity after about one month. Animals sacrificed after 2-12 months had normal organ weights and no gross pathological changes. Clinico-chemical observations included lowered haemoglobin and haematocrit values, elevation of glutamic-oxaloacetic transaminase and reduced albumin and albumin: globulin ratios in the treated animals (Björklund & Erne, 1966).

Absorption, distribution and excretion

In rats, pigs, calves and chickens, 2,4-D administered in doses of 50-100 mg/kg bw orally as salts was readily absorbed and eliminated, mainly in the urine, with plasma half-lives varying from 3-12 hours (Erne, 1966a,b). The rate of 2,4-D elimination in rats was dosage dependent. Following administration of ¹⁴C-2,4-D, radioactivity was found in all organs and tissues examined (Khanna & Fang, 1966).

2,4-D esters are hydrolysed in animals. The phenoxy acids are excreted predominantly as such in the urine of rats after their oral administration, although a minor portion is conjugated with the amino acids glycine and taurine and with glucuronic acid (Grunow & Böhme, 1974). No 2,4-dichlorophenol was, however, detected in the urine of C57BL/6 mice treated subcutaneously with 2,4-D or its butyl or isooctyl esters. The rates of disappearance from the plasma of 2,4-D and its butyl and isooctyl esters following single s.c. injections of 100 mg/kg bw of the compounds to female C57BL/6 mice were: butyl ester>isooctyl ester>2,4-D (Zielinski & Fishbein, 1967).

After oral administration of 0.05 mg/kg bw 2,4-D to rats, traces were detected in the milk of lactating animals for 6 days. Within 24 hours after administration of 2,4-D to pregnant rats, 16.8% of the dose was detected in the uterus, placenta, foetus and amniotic fluid (Fedorova & Belova, 1974). 2,4-D was also found to pass the placental barrier in pigs (Björklund & Erne, 1966).

Embryotoxicity and teratogenicity

Results of teratological studies with 2,4-D were variable; teratogenic effects are observed with doses close to those which cause maternal toxicity.

Administration of 2,4-D or its isopropyl, butyl or isooctyl esters orally or subcutaneously during days 6-14 of pregnancy increased the incidence of foetal anomalies among BL6, AKR and/or C3H strains of mice but not among B6AK and A/Ha strains. The purity of the compounds was: 2,4-D, 90%, m.p. 136-140°C; isopropyl and butyl esters, 99%; isooctyl ester, 97% (NIIS, 1968a,b).

Sprague-Dawley rats were given 1000 mg/l 2,4-D in the drinking-water during pregnancy and for a further 10 months, and 2,4-D was administered to the second generation for up to 2 years. Pregnancy and parturition were normal; litter size was not significantly reduced, and no malformations were noted in the young. Except for retarded growth and increased mortality in the second generation, no unequivocal clinical or morphological changes were seen. When 2,4-D was administered at a concentration of 500 mg/kg of diet during the entire pregnancy of a sow, anorexia was noted; the newborn piglets were underdeveloped and apathetic, and 10/15 died within 24 hours. Continued feeding of 500 mg/kg of diet to the survivors until they were 8 months of age caused marked growth depression, persistent anaemia and moderate degenerative changes of liver and kidneys (Björklund & Erne, 1966).

Female rats (10 per group) were fed 2,4-D (purity unspecified) at levels of 0, 1000 and 2000 mg/kg of diet for 95 days and then mated with untreated males and continued on their respective diets through gestation and lactation. Pups born to females fed the highest level were small at

birth; 94% died before weaning; some deaths also occurred in pups of rats fed the lower level (T.B. Gaines & R.D. Kimbrough, cited by Hansen *et al.*, 1971).

The maximum tolerated oral dose of 2,4-D (98.7% purity, no chlorinated dibenzo-*para*-dioxins found with the limit of detection of 0.2 mg/kg) or an equimolar dose of 2,4-D propylene glycol butyl ether ester or of the isooctyl ester of 2,4-D had embryo-lethal and growth retarding effects but no teratogenicity when given to pregnant Sprague-Dawley (Spartan strain) rats on days 6-15 of gestation. Other signs of foetotoxicity were s.c. oedema, delayed ossification and wavy ribs. 2,4-D did not affect fertility, gestation, lactation or viability of the newborn; the propylene glycol butyl ether and isooctyl esters decreased viability of the newborn and lactation indices¹ (Schwetz *et al.*, 1971). Similar effects were observed in Wistar rats given single daily oral doses of 100-150 mg/kg bw 2,4-D or the butyl, isooctyl, butoxyethanol dimethylamine derivatives of 2,4-D on days 6-15 of pregnancy (Khera & McKinley, 1972).

No consistent embryotoxic effects were noted when 2,4-D was administered orally to hamsters at doses up to 100 mg/kg on days 6-10 of gestation (Collins & Williams, 1971).

Lutz-Ostertag & Lutz (1970) tried to simulate field conditions for spraying with 2,4-D and to evaluate the effect on pheasant eggs and development of chicks. A high mortality rate and morphological alterations were observed in the embryos and chicks, the toxicity apparently being higher than for mammalian species. Total or partial paralysis was observed in most of the surviving embryos, and 50% of the surviving chicks were sterile.

In a 3-generation reproduction study, Osborne-Mendel rats were fed 100 or 500 mg/kg of diet 2,4-D that was 96.7% pure, with no detectable (<1 mg/kg) 2,7-dichloro- or 2,3,7,8-tetrachlorodibenzo-*para*-dioxin. No adverse effects were observed. Diets containing 1500 mg/kg 2,4-D, while

¹lactation index: (pups weaned/pups alive on day 4) x 100

apparently affecting neither the fertility of either sex nor litter size, sharply reduced the percentage of pups surviving to weaning and the weights of the weanlings (Hansen *et al.*, 1971).

Mutagenicity

2,4-D was not mutagenic in *Escherichia coli* WP2 *hcr*⁺ or *hcr*⁻ or in *Salmonella typhimurium* strains TA1535, TA1536, TA1537 or TA1538 (Andersen *et al.*, 1972; Nagy *et al.*, 1975; Shirasu, 1975; Shirasu *et al.*, 1976; Zetterberg *et al.*, 1977).

In the *rec* assay, which is believed to give an indication of reparable DNA damage, 2,4-D was not more toxic to *Bacillus subtilis* M45 (*rec*⁻) than to H17 (*rec*⁺), suggesting that this compound does not damage DNA (Shirasu, 1975).

In *Saccharomyces cerevisiae* D4, gene conversion was increased by concentrations of 2,4-D above 400 µg/ml. Mitotic recombination in *S. cerevisiae* D5 was also increased by 2,4-D (300 µg/ml) (Siebert & Lemperle, 1974; Zetterberg *et al.*, 1977). *S. cerevisiae* RAD 18 (a histidine-dependent haploid strain) was reverted to histidine independence by 250 µg/ml 2,4-D. Toxic and mutagenic effects in *S. cerevisiae* were dependent on low pH (4.3) (Zetterberg, 1977) [Metabolic activation systems were not included in any of these tests].

In host-mediated assays with *S. typhimurium* strains TA1530 or TA1531, or with *S. cerevisiae* D4, no mutagenic effects were observed when adult male mice were given 6 mg 2,4-D (200 mg/kg) by gavage (Zetterberg *et al.*, 1977). Serum from orally dosed rats was not mutagenic to *S. typhimurium* (Styles, 1973).

The effect of 2,4-D on chromosome aberrations in cultured plant tissues is complex because 2,4-D is required as a plant growth regulator in tissue culture. Singh & Harvey (1975a,b) found an inverse correlation between 2,4-D concentration and chromosome aberrations in *Vicia hajastana* and *Haplopappus gracilis*. However, with a strain of *Nicotiana* that does not require 2,4-D it increased chromosome breakage (Ronchi *et al.*, 1976).

2,4-D induced chromosome aberrations in a number of cultivated plants and weeds. The cytological abnormalities included chromosome bridges, fragments, lagging chromosomes, C-mitoses and chromatin bodies (Mohandas & Grant, 1972).

No increase in the number of recessive lethals was observed when 2-day-old adult male *Drosophila melanogaster* flies were fed 4.5 or 9.0 mM 2,4-D in sucrose (Vogel & Chandler, 1974).

In vitro exposure of embryonic bovine kidney cells and of bovine peripheral blood cells to concentrations of 1-1000 µg/ml 2,4-D for 6-96 hours resulted in stimulation of mitosis. Chromosomal aberrations were not detected in the peripheral blood cells, but nucleolar irregularities and polyploid mitotic stages were observed in the kidney cells (Bongso & Basrur, 1973).

Treatment of cultured human lymphocytes with 2.5×10^{-7} M (0.02 µg/ml) 2,4-D increased the number of chromatid aberrations (single acentric fragments) and, to a lesser extent, of chromosomal aberrations (paired acentric fragments). In mice, toxic concentrations (100-300 mg/kg bw) of 2,4-D administered as a single oral dose significantly increased the frequency of aberrant metaphases (2-4-fold); single fragments were the primary aberration (Pilinskaya, 1974). 2,4-D had no effect on cultured cells nor on bone marrow after its oral administration to rats (Styles, 1973).

There was no detectable increase of micronuclei in the erythrocytes of mouse bone marrow after i.p. administration of 100 mg/kg bw 2,4-D (Jenssen & Renberg, 1976).

2,4-D did not increase dominant lethal mutations in mice when given as a single i.p. injection of 125 mg/kg bw, or when given orally on 5 successive days for a total dose of 75 mg/kg bw (Epstein *et al.*, 1972).

(b) Man

In a case of suicide of a 23-year old farming student, the total amount of 2,4-D in the body was estimated to be no less than 6 g, corresponding to a dose of about 80 mg/kg bw. All organs showed marked acute congestion. Severe, degenerative changes of the ganglion cells were found

in the central nervous system (Nielsen *et al.*, 1965).

A man who accidentally ingested about 30 ml of concentrated weedkiller containing 50% of a thiolcarbamate and 36% 2,4-D isooctyl ester in aqueous solution exhibited fibrillary twitching and paralysis of the intercostal muscles. There was evidence of generalized skeletal muscle damage, as indicated by marked elevation of the levels of several muscle enzymes, as well as haemoglobinuria and myoglobinuria. Recovery was complete after several months (Berwick, 1970).

No adverse effects were reported in a man who took 500 mg 2,4-D orally daily for 3 weeks (approximately 8 mg/kg bw/day) (E.J. Krauss, cited in Mitchell *et al.*, 1946).

When 2,4-D was used as a treatment for a patient in the terminal stages of disseminated coccidioidomycosis, no side-effects were observed following 18 i.v. doses over 33 days: in the 7th to the 17th injection the dose of 2,4-D was 800-960 mg (about 15 mg/kg bw), and the 18th dose was 2000 mg (about 37 mg/kg bw). A 19th and final dose of 3600 mg (67 mg/kg bw) produced symptoms of toxicity comprising a semi-stuporous status, fibrillar movements, hyporeflexia and urinary incontinence, which persisted for 24 hours. Seventeen days after the last administration, the patient died (Seabury, 1963).

Three cases of peripheral neuropathy have been reported following spraying of 2,4-D. Initial symptoms were nausea, vomiting, muscular weakness, diarrhoea and swelling or aching of the feet and legs, with malaise and headache, which persisted for 10-20 days. In one case, paresthesia in the extremities and pain in the legs appeared within 4-5 days, followed by twitching of the muscles in the calves and arms; fasciculations became generalized, without neurological or electromyographical changes. In the second case, one week after a second exposure to 2,4-D, numbness and aching of the fingers and toes occurred, followed 6 weeks later by a well-developed neuropathy. In the third case, after a second exposure, severe pains occurred in the legs, with swelling of the metacarpal joints of both hands; 5 months later flaccid paraparesis was seen (Goldstein *et al.*, 1959).

Similar case reports of poisoning in agricultural workers have been reported following spraying of 2,4-D (Monarca & Di Vito, 1961; Paggiaro *et al.*, 1974; Todd, 1962). The main initial symptoms were muscular weakness, vomiting, diarrhoea, fever, hyperthermia and tachycardia. In two cases, neurological symptoms occurred, which continued for 40 days to 2 years after exposure and included loss of deep-tendon reflexes and paralysis of thigh and leg muscles.

Assouly (1951) reported that workers employed in the fabrication of 2,4-D developed symptoms of somnolence, anorexia and gastralgia, increased salivation, a sweet taste in the mouth, a sensation of drunkenness, heaviness of the legs and hyperacusia.

Subjective clinical symptoms reported among workers using various esters and salts of 2,4-D included rapid fatigue, headache, loss of appetite and pains in the region of the liver and stomach. Sensitivity to taste and smell was lowered (Fetisov, 1966).

Bashirov (1969) examined 292 persons (248 men and 44 women) engaged in the manufacture of the amine salt and butyl ester of 2,4-D, with exposure ranging from under 5 years to 6-10 years (for 194 and 98 persons, respectively); 63% of these workers complained frequently of weakness, rapid fatigue, headache or vertigo. About 20% had disturbances of the cardiovascular system (mainly hypotension and bradycardia) and of the digestive organs (dyspeptic symptoms and gastritis). The various liver dysfunctions that were found were more pronounced in workers with longer exposures to the herbicides.

Changes in metabolic processes were observed in workers engaged in the production of 2,4-D, in particular, increases in blood cholesterol content, with no change in the lecithin:cholesterol ratio. Decreases in serum albumins, increases in globulins, decreases in blood sugar levels and altered responses to sugar loads were also noted (Lukoshkina *et al.*, 1970).

In a report on 220 workers exposed in a manufacturing plant to 30-40 mg/day 2,4-D for periods ranging from 0.5 to 22 years, Johnson (1971) stated [without providing any supporting evidence] that no 'meaningful'

differences were observed in [unspecified] clinical assessment, in comparison to a control group of 4600 men, and that no chromosomal effects were observed in 10 workers whose chromosomes were karyotyped.

Feldmann & Maibach (1974) studied the absorption through the skin of 4 µg/cm² ¹⁴C-labelled 2,4-D dissolved in a small amount of acetone. ¹⁴C activity was measured in urine over a 5-day period and compared with that in urine after i.v. administration of the compound: urinary excretion of 2,4-D after i.v. administration was 100% of the dose in 120 hours, while excretion after topical administration was 5.8% of the dose.

Kohli *et al.* (1974) administered 5 mg/kg bw pure 2,4-D in a gelatin capsule with water to 6 healthy male volunteers, aged 22-30 years. None of the subjects complained of any ill-effects; no changes in blood pressure, pulse rate, haemoglobin content or total or differential white cell counts were observed. 2,4-D was absorbed fairly rapidly; the highest concentration in blood was reached in 7-24 hours. In urine, 2,4-D was present as early as 2 hours after ingestion, and more than 75% was excreted in 96 hours without undergoing transformation in the body.

In 5 male volunteers given a single oral dose of 5 mg/kg bw 2,4-D, the half-life in the plasma was 11.7 hours, and elimination in the urine occurred with a half-life of 17.7 hours. About 82% was excreted as such and 12.8% as a conjugate (Sauerhoff *et al.*, 1976).

For details of adverse toxicological effects resulting from the spraying of 'Agent Orange' (a 50:50 mixture of the *n*-butyl esters of 2,4-D and 2,4,5-T, contaminated with up to 30 mg/kg or more TCDD) and other herbicides in Vietnam, see monograph on chlorinated dibenzodioxins, p. .

3.3 Case reports and epidemiological studies

Axelsson & Sundell (1974) reported that in a cohort study of Swedish railway workers exposed to a variety of herbicides a significant, two-fold excess of all cancers was observed in exposed workers, as compared with the national average. The situation was difficult to evaluate because of the combined exposure of many workers to more than one herbicide. Most of the excess, however, seemed to be due to exposure to 3-amino-1,2,4-triazole

(amitrole); within the subgroups that had been exposed to phenoxyacids (2,4-D and/or 2,4,5-T), only a small difference was detected: 5 cancers at all sites observed *versus* 2.8 expected. The authors stated, however, that use of 2,4-D and 2,4,5-T had probably been higher than that they could trace.

See also monograph on chlorinated dibenzodioxins, p. 41.

4. Comments on Data Reported and Evaluation

4.1 Animal data

2,4-D and several of its esters were tested in rats and mice by oral administration and in mice by subcutaneous administration. All of these studies had limitations, due either to inadequate reporting or to the small number of animals used. Therefore, although increased incidences of tumours were observed in one study in which rats received 2,4-D orally and in another in which mice received its isooctyl ester by subcutaneous injection, no evaluation of the carcinogenicity of this compound could be made.

4.2 Human data

The results of the single cohort study of a small number of workers exposed to various herbicides, including 2,4-D, 2,4,5-T and 3-amino-1,2,4-triazole (amitrole)¹, are not sufficient to evaluate the carcinogenicity of 2,4-D to man [Because 2,4-D may be used with 2,4,5-T, which is contaminated with 2,3,7,8-tetrachlorodibenzo-*para*-dioxin, see also monograph on chlorinated dibenzodioxins, p. 41].

¹See also IARC, 1974.

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EXHIBIT B



WORLD HEALTH ORGANIZATION

INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

IARC MONOGRAPHS
ON THE
EVALUATION OF THE
CARCINOGENIC RISK
OF CHEMICALS TO HUMANS

Some Halogenated Hydrocarbons and Pesticide Exposures

VOLUME 41

This publication represents the views and expert opinions
of an IARC Working Group on the
Evaluation of the Carcinogenic Risk of Chemicals to Humans
which met in Lyon,

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1986

OCCUPATIONAL EXPOSURES TO CHLOROPHENOXY HERBICIDES

These exposures were considered by a previous Working Group, in February 1982 (IARC, 1982a). Individual compounds — 2,4-dichlorophenoxyacetic acid (2,4-D), 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) and (4-chloro-2-methylphenoxy)acetic acid (MCPA) — were also considered earlier (IARC, 1977a, 1982b, 1983). Since that time, new data have become available, and these have been incorporated into the monograph and taken into consideration in the present evaluation.

1. Historical Perspectives

The first chlorophenoxy acetic herbicides, 2,4-D, 2,4,5-T and MCPA, were introduced for agricultural use in the mid-1940s; the chlorophenoxy propionic acid derivatives, 2-(2,4,5-trichlorophenoxy)propanoic acid (silvex), 2-(4-chloro-2-methylphenoxy)propanoic acid (mecoprop) and 2-(2,4-dichlorophenoxy)propanoic acid (dichlorprop), have been used since the mid 1950s and early 1960s. By the mid 1960s, chlorophenoxy herbicides, generally formulated as esters or amine salts, were the most widely used class of commercial herbicides. Agent Orange, a mixture of butyl esters of 2,4-D and 2,4,5-T, was used extensively during the US intervention in Viet Nam in 1961-1971, for defoliation.

The identification and characterization of the chlorinated dibenzo-*para*-dioxins (IARC, 1977b, 1982c), and especially the toxic 2,3,7,8-tetra isomer, in chlorophenoxy herbicides such as 2,4,5-T in the late 1960s resulted in greatly diminished use of this class of herbicides.

2. Production, Use, Occurrence and Analysis

2.1 Production

The synthesis of 2,4-D and 2,4,5-T was first reported in 1941 (Polunny, 1941). 2,4-D is currently produced by the reaction of 2,4-dichlorophenol with the sodium salt of monochloroacetic acid, typically followed by an acid treatment to convert the 2,4-D salt to an acid (Sittig, 1980). 2,4-D has also been prepared commercially by the chlorination of phenoxyacetic acid (International Programme on Chemical Safety, 1984). 2,4-D esters and

amine salts are produced by reaction with suitable alcohols or amines. 2,4,5-T and its derivatives are manufactured by the same process, using 2,4,5-trichlorophenol (Sittig, 1980). Chlorophenoxy ester herbicides can also be produced by direct reaction of chlorophenol with appropriate chloroacetic esters (International Programme on Chemical Safety, 1984). Commercial production and marketing of these compounds in the USA began in 1944 (Hamner & Tukey, 1944; US Tariff Commission, 1946).

MCPA was first produced commercially in 1945 (Hayes, 1982; Windholz, 1983). It is made by chlorination of 2-methylphenoxyacetic acid in 1,2-dichloropropane at 60-100°C, sometimes with iodine and ferric chloride catalysts. The product precipitates from the solvent after cooling. An alternate synthetic pathway involves reaction of 4-chloro-*ortho*-cresol with chloroacetic acid (Sittig, 1980).

Commercial production of mecoprop was started in 1957 in the UK (Worthing, 1977). It is produced by condensation of 2-chloropropanoic acid with 4-chloro-*ortho*-cresol (Sittig, 1980). Silvex was first marketed in 1953 in the USA (Worthing, 1977) and is manufactured by reaction of 2,4,5-trichlorophenol with sodium 2-chloropropanoate (Sittig, 1980). A related propanoic acid derivative, dichlorprop, was first described in 1944 and was first marketed by a UK company in 1961 (Worthing, 1983). It is produced commercially by condensation of 2-chloropropanoic acid with 2,4-dichlorophenol, or by chlorination of 2-phenoxypropanoic acid (Sittig, 1980).

Nine US companies manufacture technical or formulated 2,4-D products. In Europe, the Federal Republic of Germany, France, the UK and Spain each have two manufacturers of 2,4-D products, and the Netherlands, the German Democratic Republic and Austria each have one commercial producer. One manufacturer has been identified in Australia, Brazil, India, Japan, and the Philippines. Two manufacturers of 2,4-D products have been reported in Argentina (Anon., 1985).

Estimates of US production, exports and imports of all forms of 2,4-D for the past several years are presented in Table 1. Estimated use of 2,4-D in other countries is presented in Table 2.

Table 1. US production, exports and imports of 2,4-D (all forms) (millions of kg)^a

	1977	1978	1979	1980	1981	1982	1983	1984
Production	12.6	9.0	17.7	17.5	14.9	8.8	7.7	NR ^b
Exports	NR	3.0	5.4	3.4	2.9	5.8	4.7	7.1
Imports	1.2	1.6	0.9	0.2	0.1	3.2	4.9	NR

^aFrom US International Trade Commission (1979a,b, 1979a,b, 1980a,b, 1981a,b, 1982a,b, 1983a,b, 1984a,b, 1985). US Department of Commerce, 1979, 1980, 1981, 1982, 1983, 1984, 1985.

^bNR, not reported.

Table 2. Consumption pattern of 2,4-D, MCPA and 2,4,5-T herbicides in some countries (tonnes), 1974-1982.^a

Country	2,4-D				MCPA				2,4,5-T			
	1974-1976	1980	1981	1982	1974-1976	1980	1981	1982	1974-1976	1980	1981	1982
Canada	3452											
Mexico	33	1500	1330	1136	131 ^c			40				
Argentina	226 ^c	1550	1520	1576	163	154	164	164			20	
Suriname		1 ^c	53									
Uruguay	140	190	135	80	4							
Cyprus	5	4	15		6	1 ^c	1		0.1	0.1		
India	44 ^c	338	400									
Japan	130	196	159			133	100	83				
Jordan		200	725	100								
Korea, Republic of	21	2	9	10								
Kuwait	0.1											
Pakistan	29	29	848	890								
Turkey	1478											
Austria	169	274	236	200	134	193	212	127	51	41	29	39
Czechoslovakia	294	102	81		1970	364 ^c	2183		11	9	11	
Denmark	210	308		324	595	615		760				
Finland	37				1003						54	
Greece	371				125							
Hungary	2579	2179	1906	1485	2238	298 ^c	3292	3342				
Iceland			0.1	0.2							20	29
Ireland					237							
Italy	543											
Malta						1						
Norway	109	17	16	19	280	215	203	240				

Table 2 (cont'd)

Country	2,4-D				MCPA				2,4,5-T			
	1974-1976		1982		1974-1976		1982		1974-1976		1982	
	1980	1981	1980	1981	1980	1981	1980	1981	1980	1981	1980	1981
Poland	1263	1014	1160	1916	1704	1438	2275	1399	10			
Portugal	5	15	0.4		52	39	22					
Sweden	111	33	38		1443	1343	1524					
Samoa		1							0.1	0.1		
Mauritius	98				11				19			
Sierra Leone	1											
Zimbabwe		3	4			27	30					

^aFrom Food and Agriculture Organization (1984).

^bMissing values do not necessarily indicate non-consumption.

Over the last 20 years, 13 US companies at one time produced 2,4,5-T (Esposito *et al.*, 1980). As a result of the gradual cancellation of its various pesticide registrations since 1970, 2,4,5-T is no longer produced in the USA. Three manufacturers have been identified in the Federal Republic of Germany — one in the UK, one in Australia (Anon., 1985), and one in New Zealand (Smith & Pearce, 1986). In 1981, 708 tonnes of 2,4,5-T were used in New Zealand (Smith *et al.*, 1983).

As late as 1975, US companies produced large quantities of 2,4,5-T (5.7 million kg) for export (US Department of Commerce, 1975). US imports of 2,4,5-T increased from 20 000 kg in 1979 to 278 000 kg in 1983 (US International Trade Commission, 1980b, 1984b). Consumption patterns in some other countries are summarized in Table 2.

MCPA is not produced in the USA. Five manufacturers have been identified in the UK, where the chemical was first produced. France and the Federal Republic of Germany each have two producers, and there is one manufacturer in each of the following countries: Austria, the Netherlands, Japan, Argentina, Australia (Anon., 1985) and Denmark (Lyng, 1985). Imports of MCPA into the USA have declined steadily from 0.95 million kg in 1976 to 0.24 million kg in 1983 (US International Trade Commission, 1977, 1984b). The US Environmental Protection Agency estimated MCPA consumption for domestic usage in 1980 at 2.1-2.9 million kg (Holtorf, 1982). MCPA consumption patterns in other countries are presented in Table 2.

Mecoprop is produced by three companies in the USA, three companies in the UK, two companies in the Federal Republic of Germany, and one firm each in the Netherlands, France (Anon., 1985) and Denmark (Lyng, 1985). Silvex, although once widely produced, is now manufactured by only two companies — one in Austria and one in the UK. In 1978, silvex and related salts were produced by three US companies (US International Trade Commission, 1979a). Dichlorprop is produced by four manufacturers in the UK, two in the Federal Republic of Germany, one in the Netherlands (Anon., 1985) and two in Denmark (Lyng, 1985).

2.2 Technical products and impurities

(a) Major chemical components

The structures of the acid forms of commercially important chlorophenoxy herbicides and pertinent identifying information are given in Table 3. These herbicides are typically formulated as esters or amine salt derivatives. Chlorophenoxy herbicide formulations used in agriculture and forestry may also contain organic solvents, emulsifiers, inert ingredients and other additives (Plimmer, 1980; Anon., 1985; Leng, 1986).

Common derivatives of 2,4-D include amine and alkali metal salts and esters. Of the amines, the dimethylamine salt is produced in highest quantities. The other amine salts that are produced include diethanolamine, triethanolamine, trimethylamine, oleylpropylene-diamine, dodecyl-/tetradodecylamine and heptylamine derivatives (Anon., 1985). Ester derivatives include ethyl, isoocetyl, butoxyethyl, ethyl hexyl and mixed butyl (Que Hee & Sutherland, 1981; Anon., 1985). High-purity sodium and lithium salts are also marketed

Table 3. Identification of chlorophenoxy herbicides

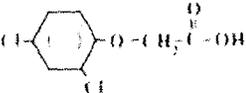
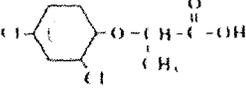
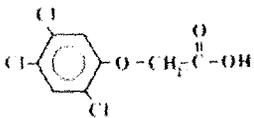
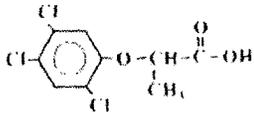
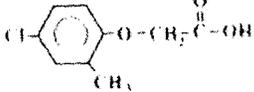
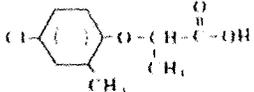
Common name [Chem. Abstr. Serv. Reg. No.]	Chem. Abstr. Name IUPAC Systematic Name [Synonym]	Structural and molecular formulae and molecular weight
2,4-D [94-75-7]	(2,4-Dichlorophenoxy)- acetic acid (2,4-Dichlorophenoxy)- acetic acid [2,4-D acid]	 $C_6H_4Cl_2O_2$ Mol. wt. 221.04
2,4-DP [120-36-5]	2-(2,4-Dichlorophenoxy)- propanoic acid 2-(2,4-Dichlorophenoxy)- propionic acid [Dichlorprop]	 $C_9H_8Cl_2O_3$ Mol. wt. 235.05
2,4,5-T [93-76-5]	(2,4,5-Trichlorophenoxy)- acetic acid (2,4,5-Trichlorophenoxy)- acetic acid	 $C_6H_3Cl_3O_2$ Mol. wt. 255.49
Silvex [93-77-1]	2-(2,4,5-Trichloro- phenoxy)propanoic acid 2-(2,4,5-Trichloro- phenoxy)propionic acid [2,4,5-TP; Fenoprop]	 $C_9H_5Cl_3O_3$ Mol. wt. 269.53

Table 3. (contd)

Common name [Chem. Abstr. Serv. Reg. No.]	Chem. Abstr. Name IUPAC Systematic Name [Synonym]	Structural and molecular formulae and molecular weight
MCPA [94-74-6]	(4-Chloro-2-methyl- phenoxy)acetic acid (4-Chloro- <i>ortho</i> - tolyl)oxyacetic acid [Agosone; Metaxon]	 $C_9H_8ClO_2$ Mol. wt. 200.63
MCPP [93-65-2]	2-(4-Chloro-2-methyl- phenoxy)propanoic acid 2-(4-Chloro- <i>ortho</i> - tolyl)oxypropionic acid [Mecoprop]	 $C_{10}H_{11}ClO_3$ Mol. wt. 214.6

(Anon., 1985). Formulated 2,4-D products normally contain one derivative, but may also contain other herbicides, especially other chlorophenoxyacetic or chlorophenoxypropanoic derivatives. Appendix A in Volume 15 of the *IARC Monographs* (IARC, 1977c) should be consulted for a more comprehensive listing of formulations.

The composition of technical-grade 2,4-D depends on the process by which it is produced and, when 2,4-dichlorophenol is used, on the purity of that compound. Ranges of impurities, other than dioxins and dibenzofurans, that are present in typical technical grades of 2,4-D are listed in Table 4.

N-Nitrosamines were reported to occur in earlier amine formulations of 2,4-D. *N*-Nitrosodimethylamine (see IARC, 1978) has been detected at levels of up to 0.3 mg/l in dimethylamine salts (Ross *et al.*, 1977).

2,4,5-T is formulated as products similar to those with 2,4-D. The most commonly marketed formulations contain mixed butyl esters; others include the isooctyl ester, the ethyl ester and the dimethylamine salt (Anon., 1985). A comprehensive list of 2,4,5-T formulations appears in Appendix A of Volume 15 of the *IARC Monographs* (IARC, 1977c); however, it should be noted that production of many formulations has been discontinued due to increasing regulatory constraints. Impurities that occur in technical products of 2,4,5-T are similar to those encountered in 2,4-D; Table 5 gives the major components of two formulations of technical-grade 2,4,5-T.

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

Component	Range (%)
2,4-D	94-99
2,6-Dichlorophenoxyacetic acid	0.5-1.5
2-Chlorophenoxyacetic acid	0.1-0.5
4-Chlorophenoxyacetic acid	0.2-0.8
Bis(2,4-dichlorophenoxy)acetic acid	0.1-2.0
Phenoxyacetic acid	trace-0.2
2,4-Dichlorophenol	0.1-0.6
2,6-Dichlorophenol	0.001-0.048
2,4,6-Trichlorophenol	0.001-0.14
2-Chlorophenol	0.0004-0.04
4-Chlorophenol	0.0004-0.005
Water	0.1-0.8

^aFrom International Programme on Chemical Safety (1984)**Table 5. Composition of two typical 2,4,5-T formulations^a**

Constituent ^b	Sample ^c	
	A	B
2,4,5-T acid (mg/l)	72	20
2,4,5-T isobutyl ester (g/l)	ND	150
2,4,5-T butyl ester (g/l)	ND	365
2,4,5-T 2-butoxyethyl ester (g/l)	500	ND
2,4,5-Trichlorophenol ($\mu\text{g/g}$)	250	460
2,5-D 2-butoxyethyl ester (g/l)	2.5	.. ^d
2,4-D 2-butoxyethyl ester (g/l)	1.2	.. ^d
3,4-D 2-butoxyethyl ester (g/l)	<0.4	.. ^d
Tetrachlorodibenzo- <i>para</i> -dioxin ($\mu\text{g/g}$)	0.06	0.12

^aFrom Sundstrom *et al.* (1979)^bAmounts calculated on the basis of weight or volume of formulation^cA, tractor-sprayed sample, B, aeroplane-sprayed sample, ND, not detected^dNot investigated

MCPA is marketed alone or in combination with other phenoxy herbicides. Potassium, sodium and dimethylamine salts, and ethyl, butyl, isooctyl and butoxyethyl esters are used in formulated products (Anon., 1985). An international listing of MCPA formulated products is given by Que Hee and Sutherland (1981).

The sodium salt of MCPA is available as a 75-80% soluble powder. MCPA is also marketed as 24-60% aqueous concentrates (salts) or emulsifiable liquids (Hayes, 1982). In the USA, the amine salt formulations have been most widely used (Soderquist & Crosby, 1975). Crude MCPA is 85-95% pure (Hayes, 1982); technical products of 94-96% purity (National Research Council, 1977) and 85-99% purity (Worthing, 1983) have been reported. The following ranges of impurities have been found (National Research Council, 1977): 2-methyl-6-chlorophenoxyacetic acid (1.5-3%); a mixture of 2-methyl-4,6-dichlorophenoxyacetic acid, 2-methylphenoxyacetic acid, 2-chlorophenoxyacetic acid, 2,6-dimethyl-4-chlorophenoxyacetic acid and 4-chlorophenoxyacetic acid (0.5-1.5%); chloro-*ortho*-cresol (0.5%); and water (1.0%). One commercial sample of MCPA was reported to contain approximately 4% 4-chloro-*ortho*-cresol (Hattula *et al.*, 1979).

Mecoprop is marketed alone or in combination with other herbicides. Formulations employ dimethylamine and diethanolamine salts, butyl and isooctyl esters and potassium salts (Anon., 1985). Commercial formulations containing mecoprop have been listed (Que Hee & Sutherland, 1981; Anon., 1985). Mecoprop technical products are mixtures of the (+) and (-) stereoisomers, of which only the (+) form is biologically active (Worthing, 1983).

Silvex, also known as fenoprop and 2,4,5-TP, is currently marketed to a very limited extent; only two US products in current use are known to contain silvex (Anon., 1985). Formerly marketed products contained mixtures of esters (Que Hee & Sutherland, 1981).

Dichlorprop, or 2,4-DP, is also used to a more limited extent than 2,4-D or MCPA. It is available as isooctyl and butyl esters, and as potassium or amine salts, alone or in combination with other similar herbicides. Esters are marketed as emulsions, and salts as aqueous solutions. Commercial formulations containing dichlorprop have been listed (Anon., 1985). As for mecoprop, technical-grade dichlorprop contains a mixture of (+) and (-) stereoisomers, of which only the (+) form is biologically active (Worthing, 1983).

(b) Chlorinated dibenzodioxin and dibenzofuran impurities

Commercial formulations of chlorophenoxy herbicides contain a series of nonpolar impurities including polychlorinated dibenzodioxins (PCDDs) (see IARC, 1977b) and polychlorinated dibenzofurans (PCDFs). (See also the monograph on occupational exposures to chlorophenols, section 2.2(b), p. 323.)

In 1973, Edmunds *et al.* reported the results of analyses of 80 samples of 2,4,5-T formulations in the range of 100% ester and 32 samples in the range of 50% ester formulations, obtained from stocks delivered to forest areas in the UK between January 1967 and April 1970 (mainly 1969 and 1970). The results are given in Table 6. The maximum value found was 28.3 $\mu\text{g/g}$ of 2,3,7,8-tetrachlorodibenzo-*para*-dioxin (TCDD).

Young *et al.* (1978) reported levels of TCDD found in more than 450 samples of the herbicide Agent Orange that were placed in storage in the USA and in the Pacific before 1978 (Table 7). Since Agent Orange was formulated as a 1:1 mixture of the butyl esters of 2,4,5-T and 2,4-D, the levels of TCDD in individual 2,4,5-T batches manufactured and used in the 1960s could have been as high as about 100 $\mu\text{g/g}$; the waste streams from a purification process could be even more highly contaminated. The weighted mean concentrations of TCDD in Agent Orange equal 1.98 $\mu\text{g/g}$. The level of TCDD in the single

Table 6. Concentrations ($\mu\text{g/g}$) of TCDD in 2,4,5-T alkyl ester herbicide formulations^a

TCDD concentration (range)	Number of samples in range	
	100% ester	50% ester
<0.005	25	8
0.05-0.09	14	0
0.10-0.19	19	5
0.20-0.29	9	3
0.30-0.39	6	1
0.40-0.49	2	1
>0.50	5 (1.74, 1.70, 1.51, 1.48, 1.30) ^b	14 (28.3, 27.2, 1.30, 1.26, 1.17, 0.95, 0.91, 0.80, 0.75, 0.65, 0.60, 0.58, 0.58, 0.55) ^b

^aFrom Edmunds *et al.* (1973)^bConcentrations in individual samples with >0.5 $\mu\text{g/g}$ TCDD**Table 7. Concentrations ($\mu\text{g/g}$) of TCDD in samples of Agents Orange and Purple^a**

Source of samples	Number of samples		Concentration of TCDD	
	Orange	Purple	Range	Mean
Johnston Atoll inventory, 1972 ^b	200	(4) ^c	0.05-47	1.91
Johnston Atoll inventory, 1974	10		0.07-5.3	1.68
NCBC, Gulfport inventory, 1972 ^d	42		0.05-13.3	1.77
NCBC, Gulfport inventory, 1975	238		0.02-15	2.11
Eglin AFB archived sample		1 ^e	-	45
Eglin AFB inventory, 1972	2		-	0.04

^aFrom Young *et al.* (1978)^bSurplus Agent Orange was shipped from South Viet Nam to Johnston Atoll (near Hawaii) for storage in April 1972^cFour of 200 samples may have been Agent Purple^dThe Naval Construction Battalion Center (NCBC), Gulfport, Mississippi, USA, served as a storage site for surplus Agent Orange from 1969 to 1977^eAgent Purple was used extensively in the evaluation of aerial spray equipment on Test Area C-52, Eglin Air Force Base (AFB) Reservation, Florida, USA, 1962-1964.

sample of Agent Purple (Table 7) was also quite high (45 $\mu\text{g/g}$). Agent Purple is a mixture of *n*-butyl-2,4-D (50%), *n*-butyl-2,4,5-T (30%) and isobutyl-2,4,5-T (20%).

In analysis using high-resolution gas chromatography/mass spectrometry and mass spectrometry, Rappe *et al.* (1978), Norström *et al.* (1979) and Rappe and Buser (1981)

reported that in other samples of Agent Orange, as well as in European and US 2,4,5-T formulations from the 1950s and 1960s, TCDD was the dominant compound of this group (Table 8). Only minor amounts of other PCDDs and PCDFs were found, and particularly lower chlorinated PCDDs in samples of Agent Orange. The analytical methods used in these studies of phenoxy herbicides are not isomer-specific; however, studies using isomer-specific methods have confirmed that the 2,3,7,8-isomer is the major tetra-CDD isomer in 2,4,5-T formulations (Buser & Rappe, 1978).

Table 8. Levels of TCDD ($\mu\text{g/g}$) in 2,4,5-T acid and 2,4,5-T ester formulations^a

Sample	Location	TCDD
2,4,5-T acid	1952, Sweden	1.10
2,4,5-T ester	unknown, Sweden	0.50
2,4,5-T ester	unknown, Sweden	<0.05
2,4,5-T ester	1960, Sweden	0.40
2,4,5-T ester	1962, Finland	0.95
2,4,5-T ester	1966, Finland	0.10
2,4,5-T ester	1967, Finland	<0.05
2,4,5-T ester	1967, Finland	0.22
2,4,5-T ester	1967, Finland	0.18
2,4,5-T acid	1964, USA	4.8
2,4,5-T acid	1969, USA	6.0
Agent Orange	unknown, USA	0.12
Agent Orange	unknown, USA	1.1
Agent Orange	unknown, USA	5.1

^aFrom Rappe *et al.* (1978), Norström *et al.* (1979), Rappe and Buser (1981)

Table 9 shows levels of TCDD in 2,4,5-T manufactured by the sole New Zealand producer. The average levels have decreased steadily since 1971, the first year for which such data were available (Smith & Pearce, 1986).

As a result of government regulations and general awareness of the toxicity of dioxins, efforts were made during the 1970s to control and minimize the formation of TCDD during 2,4,5-T production. In 16 samples of 2,4-D esters and amine salts from Canada analysed for the presence of PCDDs, eight out of nine esters and four out of seven amine salts were found to be contaminated, the esters having significantly higher levels than the amine salts. The tetra-CDD observed was the 1,3,6,8-isomer, as verified by gas chromatography with a synthetically prepared authentic standard (210-1752 ng/g in the esters, and 20-278 ng/g in the amine salts) (Cochrane *et al.*, 1982).

2.3 Use

The chlorophenoxy herbicides and their derivatives and analogues function by mimicking the action of a natural plant hormone, indoleacetic acid. Absorption and

Table 9. Average levels of TCDD (ng/g) in 2,4,5-T produced in New Zealand^a

Year	TCDD
1971	950
1972	470
1973	47
1974	33
1975	24
1976	27
1977	31
1978	22
1979	11
1980	14
1981	7.3
1982	8.5
1983	5.3
1984	5.9
1985	4.7

^aFrom Smith and Pearce (1986).

translocation of these compounds are necessary for herbicidal activity, and all herbicides in this class must be applied to the foliage of actively growing plants. Chlorophenoxy herbicides are used primarily for selective control of broadleaf weeds in cereal grains, pastures and turf and for removing unwanted brushy species in rangeland, forests and noncropland. Rates of application range from as low as 0.25 kg/ha in grain crops to as high as 16 kg/ha for spot treatment of individual trees in rights-of-way. Very dilute solutions of 2,4-D and silvex derivatives have also been used as growth regulators in fruit orchards. Chlorophenoxy herbicides are applied alone or as mixtures with other herbicides, in solutions, dispersions, or emulsions in water and/or oil, using equipment that produces large droplets to avoid spray drift (Hayes, 1982; Leng, 1986).

Registrations in the USA for 2,4-D and 2,4,5-T in the 1940s included many food crops, and use of these pesticides in the USA was up to nearly 17 million kg annually by 1960. By the mid-1960s, chlorophenoxy herbicides were the most important single class of herbicides. In 1966-1969, they were used for weed control on over 62 million acres (25 million ha) of US agricultural land, and annual US usage of all chlorophenoxy herbicides was nearly 20 million kg (Hazardous Materials Advisory Committee, 1974). It was also during the 1960s that 2,4-D and 2,4,5-T, principally as Agent Orange, were heavily used in South Viet Nam and Cambodia for defoliation of forests by the US Armed Forces. From 1961 to 1971, mixtures of 2,4-D and 2,4,5-T *n*-butyl esters and 2,4-D and picloram tri-isopropanolamine salts were applied at rates of up to 28.6 kg/ha to an estimated 2 million hectares of Vietnamese forests (almost 20% of the forested land area of South Viet Nam). It has been estimated that a total of 25 million kg of 2,4-D and 21 million kg of 2,4,5-T were applied during this time (Westing, 1971).

US production and use of 2,4,5-T and 2,4-D decreased markedly in 1969 and the early 1970s due to governmental restrictions on their use (Hazardous Materials Advisory Committee, 1974; Grant, 1979). In 1974, an estimated 452 000 kg of 2,4,5-T were used in the USA, the majority of which was applied to rangeland and pasture (US Environmental Protection Agency, 1979a).

Although MCPA has never attained the level of consumption of 2,4-D or 2,4,5-T, it has found specialized use for weed control in cereal grain production. US consumption of MCPA was 2.1-2.9 million kg in 1980 (Holtorf, 1982); most (70-71%) was used on wheat and rice.

Mecoprop is used similarly as a post-emergence herbicide for control of cleavers and chickweed in cereal grains (Worthing, 1983).

Silvex has been recommended for control of aquatic weeds, weeds in pasture, sugar cane and rice, and especially for brush. The triethanolamine salt has been used to reduce preharvest dropping of apples (Hayes, 1982; Meister, 1983). In California, for example, only approximately 360 kg were used in 1983 on pasture, rangeland and landscaped areas (California Department of Agriculture, 1984). All US registrations for silvex were cancelled in 1983 (US Environmental Protection Agency, 1983).

Dichlorprop has been used and is still recommended for removal of brush on rangeland and rights-of-way, and for control of aquatic weeds (Anon., 1985). Approximately 3150 kg of dichlorprop were used in California for these applications in 1983 (California Department of Agriculture, 1984).

2.4 Regulatory status and guidelines

By 1974, the US Environmental Protection Agency had cancelled all registrations for chlorophenoxy herbicides, except those pertaining to uses other than on foods and on rice paddies, pastures and rangelands (Anon., 1974). In 1983, all registrations for 2,4,5-T were cancelled, and this chemical can therefore no longer be used legally for any purpose in the USA (US Environmental Protection Agency, 1983). Registrations have also been cancelled in, e.g., Sweden, the Netherlands, the USSR and Australia (Anon., 1983). 2,4,5-T was banned in Italy in 1970 (Vineis *et al.*, 1986) and in the Federal Republic of Germany in 1985.

Occupational exposure limits for 2,4-D in 14 countries and for 2,4,5-T in nine countries have been reported and are presented in Table 10. Regulations pertaining to the pesticide use of chlorophenoxy herbicides are not reviewed or reported comprehensively in this monograph.

2.5 Occupational exposure

Exposure to chlorophenoxy herbicides may occur through inhalation, skin contact or ingestion. In most cases, the predominant route of occupational exposure has been by the absorption of spills or aerosol droplets through the skin (Leng *et al.*, 1982; International Programme on Chemical Safety, 1984). Measurements are usually reported in terms of

Table 10. Occupational exposure limits for 2,4-D and 2,4,5-T^a

Country	Year	Concentration (mg/m ³)	Interpretation ^b
Australia	1978	10	TWA
Belgium	1978	10	TWA
Finland ^c	1981	10	TWA
		20	STEL
Germany, Federal Republic of	1985	10	TWA
Hungary ^c	1974	10	TWA
Japan ^c	1978	10	TWA
The Netherlands	1978	10	TWA
Norway	1981	5	TWA
Romania ^c	1975	5	TWA
		10	Ceiling
Switzerland	1978	10	TWA
UK	1985	10	TWA
		20	STEL
USA	1985		
ACGIH		10	TWA
		20	STEL
OSHA		10	TWA
USSR ^c	1977	1	Ceiling
Yugoslavia	1971	10	Ceiling

^aFrom International Labour Office (1980), Direktoratet for Arbejdstilsynet (1981), Työsuojelaitos (1981), American Conference of Governmental Industrial Hygienists (ACGIH) (1985), Deutsche Forschungsgemeinschaft (1985), Health and Safety Executive (1985), US Occupational Safety and Health Administration (OSHA) (1985)

^bTWA, time-weighted average, STEL, short-term exposure limit

^c2,4-D only

herbicide concentrations in the breathing zone air or in the urine of exposed workers. Table 11 gives measurements of 2,4-D, 2,4,5-T and MCPA in the urine of workers in various industries and occupations. Monitoring of air, water and food outside areas of herbicide use has shown that the 2,4-D intake of the general population is below the present detection limits (International Programme on Chemical Safety, 1984). No quantitative data on background levels of chlorophenoxy compounds in urine and human tissues were available to the Working Group. However, the background levels of several 2,3,7,8-substituted PCDDs and PCDFs have been reported from Canada by Ryan *et al.* (1985) and from Sweden by Nygren *et al.* (1986) (Tables 12 and 13). The isomers and levels were very similar in the two studies.

Table 11. Concentrations (mg/l) of chlorophenoxy herbicides in the urine of exposed workers, by industry and activity

Industry and activity (country)	Substance measured	Concentration in urine ^c		Reference
		Mean (range)	No. of reported measurements (No. of workers)	
Production of herbicides				
Formulation of 2,4-D derivatives (Turkey)	2,4-D	1.37 (0.06-9.51)	(15)	Yural & Burgaz (1984)
Forerri				
Ground application (Australia)	2,4,5-T			Simpson <i>et al.</i> (1978)
injector gun		0.26 (0.23-0.31)	(3)	
knapsack master and power sprayer		0.99 (0.16-1.74)	(5)	
Tractor spraying (Sweden)	2,4-D	8 (3-14)	(4)	Kohlmöden-Hedman & Erne (1980)
	2,4,5-T	3.5 (1-11)	(4)	
Ground spraying (USA)	2,4,5-T			Leng <i>et al.</i> (1982)
backpack crew		6.29 (0.85-17.0)	(4)	
foremen		1.16 (0.03-3.80)	(4)	
Ground spraying (New Zealand)	2,4,5-T	0.61 (0.02-2.2)	(24) (5)	Ferry <i>et al.</i> (1982)
Aerial application (USA)				Lavy <i>et al.</i> (1982)
helicopter crew	2,4-D	<0.08* (NS)	524 (18)	Kangas <i>et al.</i> (1984)
Ground application in forest (Finland)	2,4-D + MCPA			
knapsack spraying		3.63 (0.06-10.5)	20 (1)	
brush saw spraying		2.12 (0.15-4.13)	7 (1)	
tractor spraying, driver		1.49 (0.09-3.33)	9 (1)	
tractor spraying, assistant		1.53 (0.11-4.66)	7 (1)	
ultra-low-volume spraying		2.99 (0.27-8.23)	8 (1)	

Table II (contd)

Industry and activity (country)	Substance measured	Concentration in urine ^a		Reference	
		Mean (range)	No. of reported measurements (No. of workers)		
<i>Forestry (contd)</i>					
Ground application along electric transmission line (Canada)	2,4-D	gun, roadside	1.42 (0.04-8.15)	53 (12)	Libich <i>et al.</i> (1984)
		gun, right-of-way	1.72 (0.15-5.45)	37 (8)	
		mist blowers, right-of-way	2.55 (0.44-5.07)	9 (3)	
		all-terrain vehicle with four spray guns			
	site A	6.17 (0.27-32.7)	25 (7)		
	site B	3.16 (0.63-12.4)	20 (5)		
Aerial application (Canada)	2,4-D	mixer loaders	0.33 (0.02-0.84)	18 (3)	Frank <i>et al.</i> (1985)
		supervisor	0.01	18 (1)	
		balloon men	(0.24-0.26)	18 (2)	
<i>Agriculture</i>					
Ground-boom spraying of grass pasture (USA)	2,4-D	tractor drivers	4.8 (0.12-20)	8 (2)	Draper & Street (1982)
		tractor sprayers	4.2 (<0.06-12)	8 (2)	
		Application (USA)			
	2,4,5-T	0.02 (NS)		Draper (1982)	
	2,4-D	0.006 (NS)			

Table III (contd)

Industry and activity (country)	Substance measured	Concentration in urine ^a		Reference	
		Mean (range)	No. of reported measurements (No. of workers)		
<i>Agriculture (contd)</i>					
Tractor spraying (Sweden)	2,4-D	sprayers	(ND-0.21)	(2)	Kolmodin-Hedman <i>et al.</i> (1983a)
		MCPA	1.7* (0.48-12.2)	(9)	
		MCPA	0.31* (ND-3.7)	(24)	
Airboat application (USA)	2,4-D	0.41 (0.12-0.67)	(4)	Nigg & Stamper (1983)	
<i>Aerial application (Turkey)</i>					
helicopter pilots	2,4-D	mixer	(ND-1.09)	(4)	Vural & Burgaz (1984)
		flagmen	0.58	(1)	
		supervisors	(1.01-1.92)	(2)	
		supervisors	(ND-1.16)	(6)	

^aAbbreviations: ND, not detected; NS, not specified; *, median

Table 12. Concentrations of major dioxins and furans (ng/kg) in A, ten human adipose tissue samples collected in 1980 from deceased hospital patients in eastern Ontario (Canada) and in B, 46 human adipose tissue samples collected in 1976 from accident victims across Canada^a

Analyte ^b	A		B				
	Average \pm SD	Range	No. positive		Average \pm SD	Range ^c	No. positive
			No. analysed				
TCDD	10.0 \pm 4.9	3.0-17.8	10	10	6.2 \pm 2.6	ND, 2.0-12.7	21/46
2,3,4,7,8-PeCDF	18.4 \pm 6.3	11.5-29.5	9	9	16.8 \pm 7.6	4.2-45.0	46/46
1,2,3,7,8-PeCDD	13.2 \pm 4.0	10.5-21.4	10	10	10.4 \pm 5.8	1.5-34.5	46/46
1,2,3,4,7,8-1,2,3,6,7,8-HxCDF	17.3 \pm 6.9	13.6-28.8	8	9	17.3 \pm 10.9	ND, 6.3-71.2	32/46
1,2,3,6,7,8-HxCDD	90.5 \pm 38.9	50-177	10	10	79.6 \pm 47.0	19.2-291	46/46
1,2,3,4,6,7,8-HpCDF	39.4 \pm 19.6	12.8-67	7	9	32.7 \pm 15.9	ND, 9.7-110	43/46
1,2,3,4,6,7,8-HpCDD	116 \pm 41.8	53-208	10	10	137 \pm 79	34.4-520	46/46
1,2,3,4,6,7,8,9-OCDD	611 \pm 226	317-985	10	10	796 \pm 458	202-2961	46/46

^aFrom Ryan *et al.* (1985).

^bPeCDF, pentachlorodibenzofuran, PeCDD, pentachlorodibenzodioxin, HxCDF, hexachlorodibenzofuran, HxCDD, hexachlorodibenzodioxin, HpCDF, heptachlorodibenzofuran, HpCDD, heptachlorodibenzodioxin, OCDD, octachlorodibenzodioxin.

^cND, not detected.

Table 13. Levels of PCDDs and PCDFs (pg/g) found in human adipose tissue (wet-weight basis)^a

Analyte ^b	Sweden								German workers	Chemist workers		
	Mean value (n=31)	Range	Mean value exposed (n=13)	Range	Mean value non- exposed (n=18)	Range	Mean value cancer patients (n=17)	Range			Mean value non- cancer patients (n=14)	
TCDD	3	0-9	2	0-9	3	2-6	3	2-9	3	2-6	100	NA
1,2,3,7,8-PeCDD	10	3-24	6	3-24	9	4-18	9	4-24	9	3-18	18	5
1,2,3,4,7,8-HxCDD	ND										ND	ND
1,2,3,6,7,8-HxCDD	15	3-55	19	8-55	12	3-18	18	3-55	12	8-18	48	12
1,2,3,7,8,9-HxCDD	4	3-5	5	3-13	4	3-5	4	3-13	4	3-5	12	5
1,2,3,4,6,7,9-HpCDD	ND										ND	ND
1,2,3,4,6,7,8-HpCDD	97	12-380	104	20-380	85	12-176	100	12-380	85	20-168	20	100
OCDD	414	90-763	398	90-763	421	98-679	408	90-620	421	182-763	80	374
2,3,7,8-TCDF	3.9	0.3-11	3.7	0-7.2	4.2	0.3-11	3.4	0.3-7.2	4.6	0-11	<1	*
1,2,3,7,8-PeCDF	ND										ND	ND
2,3,4,7,8-PeCDF	54	9-87	50	15-87	32	9-54	45	9-87	33	11-65	32	26
1,2,3,4,7,8-1,2,3,4,7,9-HxCDF	6	1-15	7	2-15	5	1-6	6	1-15	5	2-7	11	12
1,2,3,6,7,8-HxCDF	5	1-13	5	2-13	4	1-5	5	1-13	4	2-7	5	*
2,3,4,6,7,8-HxCDF	2	1-7	2	1-7	2	1-4	2	1-7	2	1-4	2	38
1,2,3,4,6,7,8-HpCDF	11	1-49	14	5-49	10	1-18	13	1-49	10	5-16	17	17
1,2,3,4,6,7,9-HpCDF	ND										ND	ND
1,2,3,4,6,8,9-HpCDF	ND										ND	ND
1,2,3,4,7,8,9-HpCDF	ND										ND	ND
OCDF	4										NA	240

^aFrom Nygren *et al.* (1986). ND, not detected (<1); NA, not analysed.

^bFor abbreviations used, see footnote to Table 12; TCDF, tetrachlorodibenzofuran, OCDF, octachlorodibenzofuran.

(a) *Production plants*

A mean urinary concentration of 1.37 mg/l 2,4-D was measured in workers involved in the production and formulation of 2,4-D herbicides (Vural & Burgaz, 1984). No data on levels of chlorophenoxy herbicides to which workers were exposed in industrial accidents were available to the Working Group.

Nygren *et al.* (1986) also analysed adipose tissue from two occupationally exposed persons (a German chemical factory worker and a laboratory chemist) and found a dramatically different pattern of PCDDs and PCDFs from that seen in the general population (see Table 13). The fat sample from the German worker was obtained more than 30 years after he was highly exposed to TCDD in a German factory, in November 1953. The level of TCDD in this sample was 25-30 times higher than in the normal Swedish population. Moreover the ratio of TCDD:1,2,3,7,8-penta-CDD was >5, whereas it is usually approximately 0.5 or lower, and the ratio of TCDD:2,3,7,8-tetra-CDF was >30, whereas it is usually close to 1.0. The chemist had synthesized more than 80 different PCDF isomers in the few years before the biopsy was taken.

(b) *Forestry and agriculture*

The highest urinary levels of 2,4-D, 2,4,5-T and MCPA are reported from ground spraying operations in forestry work. According to measurements made in Australia, Canada, Finland, New Zealand, Sweden and the USA, mean concentrations ranging from 0.3 to 8 mg/l are common during this type of herbicide application (see Table 11). During aerial spraying, the exposure levels were lower - 0.01-0.33 mg/l on average.

Some studies have reported exposure data as estimated dose per body weight. Teng *et al.* (1982) summarized the exposure of forestry workers in the USA to 2,4,5-T as follows: mixers, 12-138 µg/kg bw; backpack sprayers, 19-104 µg/kg bw; spray tractor drivers, 33-49 µg/kg bw; helicopter pilots, <1-44 µg/kg bw; supervisors, 2-30 µg/kg bw; and flagmen <1-3 µg/kg bw. Lavy *et al.* (1982) reported mean doses from <1-56 µg/kg bw among aerial applications of 2,4-D in the USA. These results are similar to those reported for 2,4-D in Canadian studies: 4-39 µg/kg bw (Franklin *et al.*, 1982) and <1-22 µg/kg bw (Frank *et al.*, 1985). Nash *et al.* (1982) estimated 2,4-D exposures during agricultural use of the herbicide as 20 µg/kg bw for mixers and loaders and <10 µg/kg bw for pilots and ground applicators.

In agriculture, herbicides are often used as mixtures or in combination, and workers may therefore be exposed both to chlorophenoxy herbicides and other pesticides as well as to emulsifiers, solvents and other additives. In a study of 24 farmers, median urinary concentrations of 0.31 mg/l MCPA, 0.23 mg/l dichlorprop and 0.28 mg/l mecoprop were measured. In professional sprayers, the median levels of the three compounds were 1.7, 0.74 and 2.0 mg/l, respectively (Kolmodin-Hedman *et al.*, 1983a).

During ground spraying using hand-held sprayers, mist blowers or tractor-driven equipment, the airborne concentrations of 2,4-D, MCPA and dichlorprop ranged from 10 to 300 µg/m³ (Kolmodin-Hedman & Erne, 1980; Kangas *et al.*, 1984; Libich *et al.*, 1984). During mixing and spraying operations along power line rights-of-way, airborne concentration of 2,4,5-T esters were <10-60 µg/m³ (Herwin & Smith, 1978). During aerial

application of herbicides, exposure levels to 2,4-D were <20 µg/m³ (Franklin *et al.*, 1982; Lavy *et al.*, 1982). In one case, a breathing zone concentration of 143 µg/m³ was measured (Franklin *et al.*, 1982).

The study by Nygren *et al.* (1986) included a total of 31 persons (see Table 13). Of these, 13 had been exposed to chlorophenoxy herbicides and 18 were nonexposed controls. No difference was seen between these two groups in the levels and patterns of PCDDs and PCDFs in adipose tissue, although a long time may have elapsed between exposure and sampling. In addition, no difference in PCDD and PCDF levels was found between 17 persons with cancer (soft-tissue sarcomas, lymphomas) and 14 noncancer patients.

(c) *Miscellaneous*

In one extensive occupational monitoring programme undertaken in New South Wales, Australia, in 1979-1980, urine samples were analysed for herbicide residues. The subjects included pesticide factory staff, pest control operators, farmers, park workers and others potentially exposed to 2,4-D or 2,4,5-T. No 2,4-D or 2,4,5-T was detected (<0.001 mg/l) in 735 and 377 of 973 samples, respectively. Most of the other samples contained <0.1 mg/l, and only 27 contained >1 mg/l 2,4-D and 40, >1 mg/l 2,4,5-T (Simpson, 1982).

Exposure of soldiers and the general population to dioxin in connection with the military use of chlorophenoxy herbicides in Viet Nam has been the subject of much concern among veterans in the USA and Australia and the population in Viet Nam. Shepard and Young (1983) reported a study in which very low levels of tetra-CDD, believed to be the 2,3,7,8-isomer, were detected in adipose tissue from some Viet Nam veterans; however, the levels were not believed to correlate well with known exposure data or with health status. Experimental conditions were not described in this report. A more detailed description of these data is provided by Gross *et al.* (1984), who give the analytical methods and the quality control programmes used. The results of the total study are given in Table 14. The authors concluded that Viet Nam veterans designated by the Veterans' Administration as 'heavily exposed' to Agent Orange had detectable amounts of TCDD in adipose tissue, the levels found for two of the three 'heavily exposed' veterans were higher than those for other Viet Nam veterans or for the controls.

2.6 Analysis

Selected methods for the analysis of chlorophenoxy herbicides in the air and in the urine of exposed workers are summarized in Table 15.

Analysis of dermal exposure pads has been used in several studies to evaluate skin contact with herbicides (see, e.g., Franklin *et al.*, 1982; Lavy *et al.*, 1982; Sell & Maulen, 1983). Chlorophenoxy herbicides have also been measured in plasma (see, e.g., Kolmodin-Hedman *et al.*, 1979; Åkerblom *et al.*, 1983).

Methods for the analysis of chlorinated dibenzodioxins and dibenzofurans have been reviewed (Rappe & Buser, 1981); see also the monograph on occupational exposures to chlorophenols, section 2.6, p. 337).

Table 14. TCDD levels (ng/kg) in adipose tissue of US veterans^a

Group (code number)	Concentration	Limit of detection
Heavily exposed veterans		
10	23	4
10	35	9
19	ND	3
26	99	10
26	63	6
Lightly exposed veterans		
1	ND	5
13	ND	2
15	7	4
28	7	5
28	8	6
34	5	3
Possibly exposed veterans		
6	5	3
8	5	3
9	ND	3
11	3	2
12	9	3
14	4	3
16	ND	4
24	5	3
24	5	4
25	12	4
25	10	3
27	ND	6
29	13	5
30	ND	3
Controls		
5	4	4
7	3	2
17	4 ^b	3
18	ND	4
20	5	4
21	6	3
23	8	2
23	6	3
31	7	4
32	4	4
33	14	7
US Air Force scientists		
2	5	2
3	4	1
4	6	2

^aFrom Gross *et al.* (1984), sample sizes ranged from 2.2 to 11.6 g for each extraction, amounts of internal standard used varied from 2.0-2.6 ng/extraction, ND, not detected.

^bDuplicate analyses of same extract.

Table 15. Methods for the analysis of chlorophenoxy herbicides

Sample matrix	Substance measured	Sample preparation	Assay procedure ^a	Limit of detection ^b	Reference
Air	2,4-D	Collect in Amberlite XAD-2 tube, desorb (hexane or sodium hydroxide); acidify, methylate (boron trifluoride in methanol), extract (benzene)	GC	0.01 µg m ⁻³ (small samples) 0.05 µg m ⁻³ (larger tubes)	Johnson <i>et al.</i> (1977)
	2,4-D 2,4,5-T	Collect in bubbler (ethanol); hydrolyse	TLC/spectro-photometry	50 µg m ⁻³	Koivumäki Bedman <i>et al.</i> (1979)
	2,4-D 2,4,5-T	Collect on filter, extract (methanol)	HPLC, UV	150 µg m ⁻³	Eller (1984)
	2,4-D	Collect on filter, XAD-4 resin, Soxhlet extract (acetone), methylate (diazomethane)	GC/EC (confirmed by TLC/GC-MS)	0.01 µg m ⁻³	Draper & Street (1982)
	2,4-D MCPA, di- chloroprop, mecaprop	Collect on bubbler (distilled water); acidify	HPLC, UV	1 µg m ⁻³	Åkerblom <i>et al.</i> (1983)
	2,4-D, dichloroprop	Collect in Fluorid tubes, desorb (methanol), hydrolyse, methylate (boron trifluoride in methanol), extract (benzene)	GC/EC	0.2 µg m ⁻³	Utch <i>et al.</i> (1984)
	2,4-D MCPA	Collect on filter/bubbler (ethanol), hydrolyse, extract (chloroform), dissolve (methanol)	HPLC, UV	-	Kangas <i>et al.</i> (1984)
Home	2,4,5-T	Hydrolyse (alkali), extract (benzene), methylate (diazomethane), clean-up (silica gel)	GC/EC	-	Bous <i>et al.</i> (1976)
	2,4-D	Basify, acidify; clean-up (XAD-2), extract (sodium bicarbonate in acetonitrile), methylate (diazomethane), dissolve (hexane)	GC/EC	-	Smith & Hasden (1979)
	2,4-D 2,4,5-T, silvex	Hydrolyse (acid), extract (diethylether); acid-base partition, methylate (diazomethane)	GC/EC	50 µg l	Draper (1982)
	2,4,5-T	Hydrolyse, extract	HPLC, UV	-	Ferry <i>et al.</i> (1982)

Table 15 (contd)

Sample matrix	Substance measured	Sample preparation	Assay procedure ^a	Limit of detection ^b	Reference
Urine (contd)	2,4-D/ MCPA, mecoprop, dichlorprop	Hydrolyse (acid), clean-up (Sep-Pak), extract (phosphate buffer), derivatize (pentafluorobenzyl bromide); dissolve (hexane)	GC/FC	50 µg/l	Åkerblom <i>et al.</i> (1983)
	2,4-D	Hydrolyse (alkali), acidify, clean-up (Sep-Pak), methylate (boron trifluoride in methanol), extract (hexane)	GC/EC	70 µg/l	Seil & Matten (1983)
	2,4-D	Hydrolyse (acid), extract (benzene), methylate (dimethyl sulphate); clean-up (silica gel)	GC/EC	30 µg/l	Vural & Burgaz (1984)
	2,4-D	Hydrolyse (alkali), wash (dichloromethane); acidify; extract (diethylether); methylate (boron trifluoride in methanol), extract (benzene)	GC/EC	0.5 µg/l	Frank <i>et al.</i> (1985)

^aGC, gas chromatography; HPLC, thin-layer chromatography; HPLC, high performance liquid chromatography; UV, ultraviolet detection; EC, electron capture detection; MS, mass spectrometry

^bThe limits of detection are not always comparable, because they are listed as given by the authors

Because dermal absorption is an important route of exposure to chlorophenoxy herbicides, biological monitoring is useful in estimating the absorbed dose. Urine concentrations provide the most accurate estimate of body burden, because of slow absorption, it is best to collect samples after a few days of exposure. [See also pp. 383-384, on which kinetic studies are discussed.]

3. Biological Data Relevant to the Evaluation of Carcinogenic Risk to Humans

3.1 Experimental data

Evaluations of the degrees of evidence for the carcinogenicity in animals and for activity in short-term tests of the chlorophenoxy herbicides considered in previous *IARC Monographs* are listed in Table 16. No attempt has been made to update these data.

Table 16. Chlorophenoxy herbicides and their major impurity considered in this monograph that have previously been evaluated in the *IARC Monographs*^a

Chemical	Evidence for carcinogenicity in animals	Evidence for genetic activity in short-term tests
2,4-D	adequate	adequate
MCPA ^b	no data	adequate
2,4,5-T	adequate	adequate
TCDD	sufficient	adequate

^aFrom IARC (1982a,b) except where noted

^bFrom IARC (1983)

3.2 Biological effects in humans other than cancer

(a) Toxic effects

The literature on acute poisonings and on the health effects of occupational exposures to chlorophenoxy herbicides have been reviewed recently (IARC, 1977a, 1983; International Programme on Chemical Safety, 1984; Suskind & Hertzberg, 1984). Most of the toxicological information is derived from cases of acute poisoning.

Suicide patients who ingested chlorophenoxy acids died from circulatory collapse without distinct post-mortem findings. Non-fatal intoxications with 2,4-D have resulted in acute parasympathetic nervous system symptoms and, particularly, persistent neurological dysfunction, according to case reports. A surviving case of MCPA intoxication recovered without reported sequelae. The subacute effects reported frequently from health surveys of 2,4,5-T manufacturing workers, including those exposed during accidents, are acneform eruptions (chloracne), fatigue, nervousness and irritability; chloracne is a persistent and consistent clinical marker. Exposure to TCDD has also been associated with impairment of liver function, peripheral neuropathy, personality changes, porphyria cutanea tarda, and hypertrichosis and hyperpigmentation (IARC, 1977b).

(b) Effects on reproduction and prenatal toxicity

Field and Kerr (1979) found a positive correlation between the annual usage of 2,4,5-T in Australia in 1965-1976 and the prevalence rate of neural tube defects at birth in subsequent years in New South Wales. During 1969-1975, the use of commercial 2,4,5-T in Hungary increased from 46 to 1200 tonnes; however, over the period 1970-1976, the incidences of stillbirths, spina bilida and anencephalus declined, and the incidences of cleft palate, cleft lip and cystic kidney disease remained relatively stable (Thomas, 1980).

A study in Arkansas, USA, involved dividing the state into high, medium and low use of 2,4,5-T between 1948 and 1974 on the basis of rice acreage. No significant difference in rates of facial cleft was found among the different areas between 1943 and 1974 (Nelson *et al.*, 1979).

The US Environmental Protection Agency (1979b) investigated spontaneous abortion rates in three areas of Oregon, USA, in relation to 2,4,5-T spray practices in 1972-1977. Significantly higher rates were found in the area in which 2,4,5-T was used. [The Working Group noted that the methods used for case ascertainment were inadequate.]

The possible effects of aerial spraying were studied in the Northland region of New Zealand by dividing it into seven areas according to the extent of 2,4,5-T spraying, as assessed by a detailed review of the records of the companies involved. Maternal exposure was determined by area of residence. An association was found for all birth malformations combined and for club foot, hypospadias and epispadias and heart defects separately. No association was found with central nervous system defects, nor with cleft lip or palate (Hanify *et al.*, 1981).

[The Working Group noted that the above studies were ecological surveys, and suffered from the usual limitations.]

A survey of the occupations of the fathers of children recorded in the Office of Population Censuses and Surveys register of congenital malformations in England and Wales (1974-1979) showed an increased risk of facial clefts in children of gardeners, groundsman and agricultural workers, who were regarded as potentially exposed to herbicides (Balarajan & McDowall, 1983). No increased risk of these malformations was seen in children of fathers in agriculture or forestry in Oxfordshire and West Berkshire in the years 1965-1974 (Golding & Sladden, 1983).

Two case-control studies were carried out on possible reproductive effects in soldiers who had served in Viet Nam and had had potential exposure to Agent Orange, a mixture of butylesters of 2,4,5-T and 2,4-D contaminated with TCDD. An Australian study, involving 8517 case-control pairs, found a relative risk of 1.02 (95% confidence limits, 0.78-1.32) for veterans fathering children with birth anomalies compared to non-veterans (Donovan *et al.*, 1984). A US study, involving 7133 babies born to Viet Nam veterans, found an overall relative risk of 0.97 (Erickson *et al.*, 1984).

A study of pregnancy outcome of wives of professional pesticide sprayers was conducted in New Zealand (Smith *et al.*, 1981). The herbicide sprayed predominantly was 2,4,5-T. There were 1172 births among applicator families in the study period (1969-1979 for spraying of 2,4,5-T; 1960-1979 for spraying of any pesticide) and 1122 births among a comparison group of agricultural contractors. Information was gained by postal questionnaire, with an overall response rate of 89% among applicators and 83% of agricultural contractors. Major congenital defects were reported in 2% (24) of births to applicators and 1.6% (18) of births to agricultural contractors; the difference was not significant, and the rates were similar to those for the general population. Similar rates were seen for the two groups for stillbirth (0.9% versus 1.0%) and miscarriage (8.6% versus 9.3%).

In a further analysis of a subset of these data, those pregnancy outcomes associated with spraying of 2,4,5-T by the father in the same year as the birth or the year before (427) were selected and compared with pregnancy outcomes not associated with spraying of any herbicide in that period of time (352) (Smith *et al.*, 1982a). The relative risk for congenital defects among children of exposed fathers was 1.19 (90% confidence limits, 0.58-2.45) and that for miscarriage 0.89 (90% confidence limits, 0.61-1.30).

(c) *Absorption, distribution, excretion and metabolism*

(i) *2,4,5-T*

In five male volunteers who received an oral dose of 5 mg/kg bw 2,4,5-T, there was almost complete gastrointestinal absorption. Disappearance from blood and appearance in urine followed first-order kinetics and showed a half-time of 23 h. An average of 88.5% of the dose was excreted in the urine within 96 h of administration, and the renal clearance was 180-260 ml/min. No acid-labile conjugate or free trichlorophenol was detected in the urine. 2,4,5-T bound reversibly to plasma proteins (98.7%), and the relative volume of distribution was 0.079 l/kg. Faecal excretion was <1% of the dose (Gehring *et al.*, 1973).

In a similar study, in which 2, 3 or 5 mg/kg bw 2,4,5-T were administered orally, maximum plasma concentrations were detected 7-24 h after administration. Following a 5-mg/kg dose, the disappearance half-time averaged 18.8 h, and the average relative volume of distribution was 0.157 l/kg. For all doses, an average of 63-79% of the dose was recovered in the urine within 96 h of administration (Kohli *et al.*, 1974a).

Potential inhalation exposure could account for only approximately 1% of the total amount of 2,4,5-T recovered within four days in the urine of spray applicators, whereas the estimated dermal exposure was potentially 1000 times greater, indicating the relative importance of exposure *via* the dermal route (Lavy *et al.*, 1980).

(ii) *2,4-D*

In a study on the kinetics of 2,4-D, five male volunteers received an oral dose of 5 mg/kg bw. Absorption was almost complete, as indicated by the recovery of 88-106% of the dose in the urine within 144 h. When elimination of 2,4-D from plasma was followed in three subjects, the average disappearance half-time was 11.6 h. For two subjects, the relative volumes of distribution were 238 and 294 ml/kg, respectively; an apparent biphasic clearance was exhibited by a third subject. Approximately 80% of the 2,4-D was excreted unchanged in the urine and the remainder as an acid-labile conjugate (Sauerhoff *et al.*, 1977a).

Rapid (half-time, 2.5 h) and extensive gastrointestinal absorption of 2,4-D was also found by Kohli *et al.* (1974b), who observed an elimination half-time of 33 h and a volume of distribution of 0.1 l/kg.

From a comparison of urinary excretion of 2,4-D after intravenous administration and application of 4 µg/cm² on forearm skin, the dermal absorption of 2,4-D was calculated to be 5.8%. Dermal absorption was protracted, with peak concentrations detected in the urine three days after exposure (Feldman & Maibach, 1974). After exposure of ground sprayers to 2,4-D, peak concentrations in the blood and urine were detected after 0 to at least three (blood) or four (urine) days, and the apparent half-time for urinary excretion of 2,4-D was 14-79 h (calculated from data presented by Nash *et al.*, 1982; Nash *et al.*, 1982; Taskar *et al.*, 1982). Frank *et al.* (1985) calculated that a maximum of 4.5% of the amount of 2,4-D deposited on the bare skin of a bystander directly sprayed with 2,4-D was absorbed. In

occupational exposures, skin appears to be the most important route of absorption (Draper & Street, 1982; Lavy *et al.*, 1982; Kolmodin-Hedman *et al.*, 1983a; Kangas *et al.*, 1984; Libich *et al.*, 1984; Frank *et al.*, 1985).

(iii) MCPA

In five volunteers (three men, two women) given 15 µg/kg bw MCPA orally, the highest plasma concentrations were seen after 1 h. Urinary excretion was almost complete by 24 h, at which time approximately 40% of the dose had been recovered (Kolmodin-Hedman *et al.*, 1983b). In a similar study (four men), an average of 55% of a 5-mg oral dose was recovered in the urine within 96 h (Fjeldstad & Wannag, 1977).

In a study on dermal absorption in five volunteers (three men, two women), soft-paper pads saturated with 10 ml of a 10% aqueous solution of MCPA were applied on the skin of the thigh for 2 h and the pad covered with surgical tape. Peak plasma levels occurred at about 24 h (two subjects). By 144 h, approximately 2 mg MCPA (0.2% of the applied dose) had been recovered in the urine; the peak of urinary excretion was seen 24-48 h after application (Kolmodin-Hedman *et al.*, 1983b).

Dermal absorption is an important factor in occupational exposure to MCPA, since time-weighted average concentrations of the compound in breathing-zone air samples were only <0.1 mg/m³, whereas concentrations in the urine of exposed workers reached 12 µg/ml (Kolmodin-Hedman *et al.*, 1983a).

(iv) Silvex

Silvex, in powder form, was given orally to eight volunteers (seven men, one woman) at a dose of 1 mg/kg, and its concentration in plasma and urine was studied. Silvex was almost completely absorbed; peak concentrations in plasma were reached in 2-4 h. The disappearance of silvex from the plasma was best described by a two-compartment model, with relative volumes of distribution for each compartment of 81-158 ml/kg and 45-163 ml/kg, respectively. Each compartment followed first-order kinetics, and the two successive half-times for plasma disappearance were 0.9-6.9 h, and 9.0-33.0 h, respectively. Within 144 h, urinary excretion of silvex, which decreased bi-exponentially, amounted to 66-95% of the dose (as silvex and silvex conjugates). In the urine, 29-80% of silvex was excreted unchanged and the rest as acid- and base-labile conjugates; glycine conjugates were not detected. Up to 3% of the dose was detected in the faeces (Sauerhoff *et al.*, 1977b).

(v) Other

Dichlorprop and mecoprop have been detected in the urine of exposed farmers and spraymen (Kolmodin-Hedman *et al.*, 1983a).

(d) Mutagenicity and chromosomal effects

The genetic effects of chlorophenoxy herbicides and their contaminants have been reviewed (Wassom *et al.*, 1977/1978; Seiler, 1978; Grant, 1979).

Mukahy (1980) examined the incidences of chromosomal aberrations and sister chromatid exchanges (SCEs) in 15 soldiers ten years after serving in the Australian armed forces in Viet Nam for periods ranging from six to 15 months. Eight control subjects were matched for age and sex who had no history of industrial or agricultural exposure to herbicides. The mean frequency of chromosomal aberrations in peripheral lymphocytes was 5.06 per 100 cells in the exposed group versus 4.38 in the controls. SCE frequencies were 5.25 and 5.45 per cell, respectively. The differences were not significant.

A study which reported that exposure to chlorophenoxy herbicides during spraying in South Viet Nam induced chromosomal aberrations in humans was judged to be based on inadequate data (reviewed by National Academy of Sciences, 1974).

An analysis of lymphocyte chromosomes of agricultural workers in Idaho, USA, with extensive occupational exposure to pesticides was reported by Yoder *et al.* (1973). A group of 26 herbicide-exposed workers was compared with 16 controls. The list of the most commonly used herbicides comprised 14 formulations, but the predominant exposures were to amitrole, 2,4-D and atrazine. Blood samples were drawn both off-season and mid-season and cultured for 48 h. Only 25 metaphases were examined from each. From off-season to mid-season the mean number of chromatid gaps in the herbicide-exposed group increased four fold (from 0.38 ± 0.10 to 1.38 ± 0.22 per person per 25 cells). In the same group, chromatid breaks increased 25 fold (from 0.07 ± 0.05 to 1.81 ± 0.35). The off-season aberration frequencies were, however, very low as compared with the control group (off-season, 0.63 ± 0.22 for gaps and 0.31 ± 0.12 for breaks), although it is possible to use subjects as their own controls. The authors concluded that the increased incidence of chromosomal aberrations was probably due to exposure to herbicides, although it was not possible to distinguish which herbicide formulations were responsible. [The Working Group noted the small number of cells examined and that possible confounding factors were not taken into consideration.]

SCE frequency was studied in 57 herbicide and pesticide sprayers in New Zealand (Crossen *et al.*, 1978). 2,4,5-T and 2,4-D were mentioned as two of the 30 formulations most commonly encountered in the study. Overall, there was no difference in SCE frequency between the control group and the sprayers (mean rates, 7.65 versus 8.48). The sprayers were divided into three groups: those with no protection, those with some protection (either clothing, gloves or respirator) and those with full protection. Those with no protection had a significantly higher mean SCE rate than the control group (mean rate, 9.03 versus 7.65) but the authors noted that the length and level of exposure could also have influenced the findings. There was no difference in SCE rate between those who used herbicides exclusively and those using both herbicides and pesticides. [The Working Group noted that confounding factors such as smoking were not taken into consideration.]

Hogstedt *et al.* (1980) studied peripheral lymphocyte chromosomes from ten Swedish workers who had worked with several pesticides for two to 29 years (mean, 13 years). Among the pesticides used were MCPA, mecoprop and 2,4-D, none had used 2,4,5-T, dinoseb (2-sec-butyl-4,6-dinitrophenol) or amitrole during the last two years. The control group consisted of seven farm workers who had never worked with pesticides. Cells were cultured for 72 h, and 200 cells from each subject were analysed. No significant difference in

the frequency of chromosomal aberrations was found between the two groups (gaps, 1.7 per 100 cells *versus* 1.6 in the controls; breaks and exchanges, 2.4 *versus* 2.8).

Linnaïmaa (1983) studied SCEs in lymphocytes of workers in Finland spraying forest foliage with chlorophenoxy herbicides containing amine salts and esters of 2,4-D and MCPA, or mixtures of the two. Three successive blood samples were taken from 50 male sprayers (who had used protective clothing); the first before the spraying season, the second in the middle of the spraying season and the third within two days after the subject had finished spraying, in order to follow possible exposure-related changes. Urine samples were taken at the same time as the second blood sample. Levels of 2,4-D and MCPA in the urine, which were used as an indicator of exposure, varied from 0.00 to 10.99 mg/l (mean, 1.80 mg/l). Suitable chromosome preparations were obtained from 35 herbicide workers and 15 controls not working with herbicides. No significant difference in SCF frequency was observed in samples taken before, during or after the exposure; the nonexposed control group fell in the same range. Smokers in both groups had significantly higher mean values than nonsmokers. The average frequencies of SCEs/cell in nonsmoking sprayers were 8.6, 8.0, and 8.8 before, during, and after spraying, respectively, *versus* 8.1 in nonsmoking controls. The corresponding values for the smokers were 9.7, 9.5, 9.9 *versus* 10.0.

Some individuals with similar exposure were also studied for frequency of chromosomal aberrations (Mustonen *et al.*, 1986). Where possible, 100 first-division metaphases were examined from each of 19 workers and 15 controls. No difference was found between the two groups. The percentage of aberrant cells (gaps included) in controls was 1.5 ± 0.3 in nonsmokers and 1.9 ± 0.4 in smokers. In exposed subjects, the respective percentages were 1.2 ± 0.5 and 1.8 ± 0.4 .

3.3 Case reports and epidemiological studies of carcinogenicity to humans

(a) Case reports

A number of reports describe the occurrence of cancer in workers exposed to ECDD (see IARC, 1977b). A case report describes three cases of soft-tissue sarcoma in US veterans 10-13 years after exposure to Agent Orange (Sarma & Jacobs, 1982). Palva *et al.* (1975) described a case of aplastic anaemia in a farmer three months after exposure to MCPA in Finland (he had also used herbicides during the previous five years); a year later he developed acute myelomonocytic leukaemia (Timonen & Palva, 1980).

A clinical study of 123 male patients with non-Hodgkin's lymphoma in Sweden found that four of five patients with cutaneous lesions reported spraying large areas with chlorophenoxy herbicides (Olsson & Brandt, 1981).

(b) Cohort studies

A cohort of 348 railroad workers in Sweden exposed for 45 days or more during 1957-1978 to 2,4-D, 2,4,5-T or amitrole were investigated in a follow-up study (Axelson *et al.*, 1980) [see also monograph on amitrole in this volume, p. 309]. There was a deficit of deaths from all causes (45 observed, 49 expected) but an excess from malignant neoplasms

(17 observed, 11.9 expected). In a subcohort exposed to 2,4-D or 2,4,5-T but not amitrole, there were six deaths from cancer with 5.6 expected, all of which occurred in those first exposed ten years or more before death (3.1 expected). In a subcohort exposed to both amitrole and chlorophenoxy herbicides (2,4-D or 2,4,5-T), there were six deaths from cancer with 2.9 expected, of which all six (with 1.8 expected; $p < 0.005$) occurred in those first exposed ten years or more before death; there were altogether three deaths from stomach cancer with 0.5 expected in men first exposed to chlorophenoxy herbicides ten years before death. The men were also exposed to other organic (e.g., monuron and diuron) and inorganic chemicals (e.g., potassium chlorate).

Hogstedt and Westerlund (1980) studied the mortality of 142 male forestry workers in Sweden exposed to 2,4-D and 2,4,5-T in 1954-1967, and 244 male forestry workers without such exposures (follow-up, 1954-1978). Five deaths from cancer were observed among those exposed *versus* 6.4 expected from national rates. Among unexposed workers there were 10 observed deaths from cancer *versus* 14.7 expected. Among 16 exposed foremen, five incident cases of cancer were found in the Swedish Cancer Registry against 1.4 expected ($p < 0.02$), while three cases of cancer were seen in 126 exposed workers with 8.4 expected ($p < 0.05$). These eight cases were localized in the stomach (1), pancreas (2), lung (1), skin (1), prostate (2) and bladder (1). The expected value for soft-tissue sarcoma among the exposed was about 0.1. Foremen were exposed to chlorophenoxy herbicides for an average of 176 days and workers for 30 days.

Bathel (1981) performed a study encompassing the 14 districts of the German Democratic Republic (excluding Berlin); 1658 male subjects who had been active for at least five years as agricultural workers or agronomists between 1948 and 1972 were potentially exposed to 2,4-D and MCPA. Cancer incidence in the group was assessed through county tumour reference centres and death certificates; 124/169 neoplasms were histologically verified. Fifty cases of bronchial carcinoma occurred between 1970 and 1978 *versus* 27.5 expected from national morbidity rates. One case of soft-tissue sarcoma and five of lymphatic neoplasms were observed. [The Working Group noted that smoking was not taken into account in this study, but that differences in smoking habits are unlikely to explain a relative risk of the magnitude observed.]

Riihimäki *et al.* (1982, 1983) examined a cohort of 1926 male Finnish workers involved in brush control for at least two weeks between 1951-1971. These workers were exposed to 2,4-D and 2,4,5-T, among other agents. The follow-up period was from 1972-1980, and 16 694 person-years were represented. The observed rates were compared with expected numbers from national death rates. Only 26 cancer deaths were noted with 36.5 expected. In the subgroup with over 10 years' latency, 20 cancers were observed whereas 24.3 were expected [standardized mortality rate (SMR), 82; 95% confidence interval (CI), 50-127], including 12 lung cancers (expected, 11.1) [SMR, 108; 95% CI, 56-189] and four cancers of the stomach and oesophagus (expected, 3.7) [SMR, 108; 95% CI, 30-277]. No lymphoma or soft-tissue sarcoma was observed. Cancer incidence was also studied, with similar results. The authors point out, however, that the small size of the cohort, the brief follow-up period and the low exposure limited the utility of this study.

Lynge (1984, 1985) studied 4563 persons employed by two chemical plants in Denmark which produced 2,4-D, dichlorprop, MCPA, mecoprop and 2,4,5-T in the period 1947-1981. 2,4,5-T was produced mainly from 1951-1959 from 2,4,5-trichlorophenol made externally, and 2,4,5-T esters were made from 2,4,5-T produced externally up to 1981. 2,4-D and MCPA were manufactured by chlorination of the phenol or cresol; during 1960-1970, up to 50% of the MCPA was produced as spray-dried MCPA sodium salt. Incident cases of cancer were identified by record linkage with data in the Danish Cancer Registry. From the year production of chlorophenoxy herbicides started in the two plants (1947 and 1951, respectively) until 1982, there were, for the total cohort, 159 cancers of all sites *versus* 160.6 expected in men and 49 observed *versus* 55.9 expected in women. The observed numbers of cases for individual sites of cancer did not differ statistically significantly from the expected numbers. Among persons first exposed ten years or more before cancer diagnosis, there were 11 cases of stomach cancer *versus* 6.3 expected (nonsignificant). No case occurred among women. Two cases occurred in men employed in the manufacture and packaging of chlorophenoxy herbicides *versus* 1.5 expected. Seven cases of malignant lymphoma were observed among men with 5.4 cases expected; among women, there was one case with 1.2 expected. No case was observed among men or women manufacturing and packaging chlorophenoxy herbicides. Among men, there were five cases of soft-tissue sarcoma *versus* 1.8 expected (relative risk, 2.72; 95% CI, 0.88-6.34); no case was diagnosed among women (0.75 expected). For the four men with more than ten years' latency since first exposure, the relative risk estimate was increased to 3.67 (95% CI, 1.00-9.39). Only one had been assigned to the manufacture and packaging of chlorophenoxy herbicides, two were working in shipping and one in pigment milling. The durations of employment of these men were 90, 30, three and 0.5 months. At these plants, 59% of men and 50% of women had been employed for less than one year. Among the subgroup of persons employed in the manufacture and packaging of chlorophenoxy herbicides, there were 11 cases of lung cancer among men *versus* 5.3 expected ($p < 0.05$); there was no excess in women, but five cases of cervical cancer were seen *versus* 1.8 expected (nonsignificant).

Mortality odds ratios for service in Viet Nam were estimated for 1496 veterans discharged in 1970-1973 and who died in New York State, USA, between 1970 and 1980. Of these, 555 had served in Viet Nam. A ratio of 1.09 (95% CI, 0.18-6.70) was found for soft-tissue sarcoma in Viet Nam veterans *versus* non-Viet Nam veterans (Lawrence *et al.*, 1985).

As pointed out in the monograph on occupational exposures to chlorophenols (p. 319), workers involved in manufacturing 2,4,5-T itself (rather than the precursor 2,4,5-trichlorophenol) may be exposed to both 2,4,5-trichlorophenol and 2,4,5-T. Some of the manufacturing cohort studies referred to in that monograph are also, therefore, relevant to 2,4,5-T itself.

Potential exposure to 2,4,5-T was reported by Ott *et al.* (1980) in their mortality study of a small cohort of 204 workers which identified one cancer death, with 1.3 expected, in workers exposed for more than one year (see monograph on occupational exposures to chlorophenols, p. 342).

Engelhart *et al.* (1984) carried out a review of cases reported in cohort studies and of several additional case reports of soft-tissue sarcoma (see monograph on occupational exposures to chlorophenols, p. 343). [The Working Group considered that some over- or underascertainment of soft-tissue sarcoma is possible.]

The mortality study reported by Cook *et al.* (1986) involved potential exposure to both trichlorophenol and 2,4,5-T, although the report focused on TCDD exposure in trichlorophenol manufacture. There were five cases of non-Hodgkin's lymphoma (SMR, 238; 95% CI, 77-556) but no dose-response relationship to TCDD exposure. No dose-response analysis was presented of potential 2,4,5-T exposure (see monograph on occupational exposures to chlorophenols, p. 343). [The Working Group noted that it was difficult to determine the exposure of the workers to 2,4,5-T.]

(c) Case-control studies

(i) Soft-tissue sarcoma

The first case-control study of soft-tissue sarcoma followed the observation of a number of patients at a cancer clinic in Sweden who had reported previous exposure to chlorophenoxy herbicides (Hardell & Sandström, 1979). A total of 52 male patients, 21 living and 31 deceased, were identified from records of the Department of Oncology of the University Hospital of Umeå as having been admitted with a diagnosis of soft-tissue sarcoma between 1970 and 1977. Four matched controls were selected for each case, from the National Population Registry for living patients, and from the National Registry for Causes of Death for deceased patients. Exposure was ascertained through a postal questionnaire with a variety of questions about exposure; the answers were supplemented by telephone without knowledge of case or referent status. For deceased patients and controls, the procedure was the same, but contact was made with the next of kin. In an attempt to verify occupational exposures, questionnaires were also sent to the employers of persons stating work in forestry, saw mills and pulp industries. According to the authors, employers' statements from the latter two industries agreed closely with the statements given by the interviewed persons and the same was therefore assumed to be true for exposure to chlorophenoxy herbicides—but there were many non-respondents from the forestry companies. A requirement for being classified as exposed was at least one full day of exposure more than five years before the tumour was diagnosed. When patients and controls with exposure to chlorophenols were excluded, the relative risk estimate was 5.3 (95% CI, 2.4-11.5), with 13 cases exposed. Of the 13 cases, 12 had been exposed to 2,4,5-T or 2,4-D, and one to MCPA alone; combined exposure to 2,4,5-T and 2,4-D was reported by nine cases. The exposure of two cases consisted solely of working on ground that was wet from earlier spraying. Latency from first exposure was predominantly in the range of 10-20 years. The median duration of exposure was three to four months (range, two days to 49 months). As three of these patients were those that had been identified earlier and initiated the study, a calculation was made after exclusion of three cases and their controls; this did not affect the results (relative risk, 4.7; 95% CI, 2.0-10.7). [The Working Group noted that, according to the authors, a further four exposed patients had been reported as cases before the case-control study was published, but no calculation was presented based on their exclusion.]

A second study (Eriksson *et al.*, 1981) of soft-tissue sarcoma was undertaken in southern Sweden, where MCPA and 2,4-D have been used widely in agriculture. The study involved 110 living and deceased cases reported in 1974-1978 and 220 referents selected by methods similar to those used in the first study (Hardell & Sandström, 1979), and with the same assessments and requirements for exposure. A relative risk estimate of 8.5 was obtained for exposure to chlorophenoxy herbicides alone for more than 30 days (seven cases), and one of 5.7 for exposures of less than or equal to 30 days (seven cases). The odds ratio for exposure to chlorophenoxy herbicides other than 2,4,5-T was 4.2 [95% CI, 1.3-15.8].

An initial analysis of occupations recorded on the National New Zealand Cancer Registry between 1976 and 1980 (102 cases compared to 306 controls) did not find an excess of soft-tissue sarcoma cases in agriculture and forestry workers compared with patients with cancers of other sites on the cancer registry (Smith *et al.*, 1982b). Subsequently, 82 cases (or their next-of-kin) of soft-tissue sarcoma were interviewed by telephone regarding past occupations and specific use of chlorophenoxy herbicides by an interviewer who was unaware of the case/referent status of the person, and the results were compared with those of 92 randomly selected referents with cancers at other sites (Smith *et al.*, 1984). In 43% of the cases and 34% of the referents, the patient gave the data himself or herself. Since the results were not affected by such stratification, only results of unstratified analyses were reported. An odds ratio of 1.6 (90% CI, 0.7-3.3) was calculated for those who had probably or definitely been exposed for more than one day more than five years prior to diagnosis of the tumour (17 cases). None of the cases was in a professional applicator.

Another study was undertaken with interviews of 51 further cases appearing on the Cancer Registry up to 1982 (Smith & Pearce, 1986). Cases were identified as in the first study, and histology reports were reviewed for each case. Eligible patients or their next-of-kin were interviewed by telephone by the same experienced interviewer, who was unaware of the case/referent status of the person. Referents were selected from a large series used for another study on lymphoma and multiple myeloma (Pearce *et al.*, 1986), who had been interviewed in the same manner and comprised 315 cancer patients (excluding lymphoma, multiple myeloma and soft-tissue sarcoma). The odds ratio for exposure for more than one day more than five years prior to registration was 0.7 (90% CI, 0.3-1.5). The combined estimate, using data from both the previous study (Smith *et al.*, 1983) and the present one, for 133 cases compared with 407 referents, was 1.1 (90% CI, 0.7-1.8). The proportions of exposed referents were 0.14 for the first study and 0.15 for the second study. None of the cases occurred in a professional applicator.

A population-based case-referent study was conducted in northern Italy (Vineis *et al.*, 1986). Thirty-seven male and 31 female patients with soft-tissue sarcoma formed the case series and 85 males and 73 females made up the referent series. Of the cases, 24 were deceased, and they were matched by municipality of residence with 36 deceased referents. The living referents were drawn randomly from the population of each province. Cases and referents, or their next-of-kin, were interviewed by a trained interviewer, who was unaware of their case/referent status, by means of a personal visit; 16 cases and 37 referents gave information by post. Information on various uses of herbicides, mainly 2,4-D, MCPA and 2,4,5-T (until 1970), was collected in detail and assessed by two experts in agricultural

chemistry, who were unaware of the case/referent status of the person. Exposure to herbicides in these provinces was mainly associated with rice weeding, an activity traditionally performed by women. The highest exposure to herbicides occurred in the early 1950s, when rice weeding was still performed manually but chlorophenoxy herbicides were being tested and introduced. An age-adjusted odds ratio of 0.91 was found for living men with suspected exposure, and one of 2.7 (90% one-tailed CI, 0.59-12.37) for living women. An age-adjusted odds ratio of 15.5 (1.3-180.3) was found for living women under the age of 75 years, exposed between 1950-1955. For deceased females, the odds ratio, based on four exposed cases of likely and certain exposure, was 1.05 (0.21-5.1). Only one dead male case had been exposed. The authors suggested that geographical overmatching had occurred for deceased cases and referents. [The Working Group noted that two of the exposed cases were Kaposi's sarcoma.]

A case-control study ascertained Viet Nam service for 281 men with soft-tissue sarcoma and for a matched control group (Greenwald *et al.*, 1984). Cases were diagnosed between 1962 and 1980 and identified on the New York State Cancer Registry. The odds ratio for service in Viet Nam was 0.53 (95% CI, 0.21-1.31), with ten cases reporting service in Viet Nam. An odds ratio of 0.70 was obtained for those reporting contact with Agent Orange, ICD10 of 2,4,5-T. [The Working Group noted that bias may have arisen as a result of the choice of control group. Furthermore, exposure may have occurred to many other chemicals, and the time between exposure and disease was short.]

(ii) Malignant lymphoma

Concerns about chlorophenoxy herbicides and lymphoma arose in Sweden when a number of male patients with histiocytic lymphoma reported past exposure to chlorophenoxy herbicides. A case-control study of 169 cases of malignant lymphoma (60 Hodgkin's disease, 105 non-Hodgkin's lymphoma, four unclassifiable) was then undertaken, including 338 controls (Hardell *et al.*, 1981). The study design, including ascertainment of exposure, was similar to that of the Swedish soft-tissue sarcoma studies (see Hardell & Sandström, 1979). A relative risk estimate of 4.8 (95% CI, 2.9-8.1) was obtained for exposure to chlorophenoxy herbicides, excluding cases and controls exposed to chlorophenols. Stratifying by duration of exposure, the relative risk estimate was 4.3 for less than 90 days, and 7.0 for 90 days or more exposure to chlorophenoxy herbicides. Most chlorophenoxy herbicide-exposed cases reported exposure to both 2,4,5-T and 2,4-D (25 cases); two reported exposure to 2,4,5-T, 2,4-D and MCPA, seven to 2,4-D alone, and five to MCPA alone (Hardell, 1981a). No 'noticeable difference' in excess risk could be demonstrated between Hodgkin's disease and non-Hodgkin's lymphoma.

In New Zealand, an analysis of reported occupation appearing on the New Zealand Cancer Registry indicated an excess of malignant lymphoma and multiple myeloma among men in agricultural occupations during 1977-1981. Although 734 cases and four controls per case were selected from the Registry, the main findings concerned a subgroup of 88 cases of malignant lymphoma, classified as ICD 202 which covers non-Hodgkin's lymphoma other than lymphosarcoma and reticulosarcoma. An odds ratio of 1.76 (95% CI, 1.03-3.02) was obtained for those under the age of 65 working in agriculture (Pearce *et al.*, 1985). However,

a subsequent interview study of 83 cases classified as ICD 202 (see monograph on occupational exposures to chlorophenols, p. 344) did not suggest that exposure to chlorophenoxy herbicides was the explanation, since an odds ratio of 1.3 (90% CI, 0.7-2.5) was obtained when the controls were people with other cancers, and an odds ratio of 1.0 (0.5-2.1) when general population controls were used for people probably or definitely exposed for more than one day not in the five years before cancer registration (Pearce *et al.*, 1986).

(iii) Nasal and nasopharyngeal cancer

In the study of Hardell *et al.* (1982), described in the monograph on occupational exposures to chlorophenols (p. 344), an odds ratio of 2.1 (95% CI, 0.9-4.7) was found for exposure to chlorophenoxy herbicides.

(iv) Colon and liver cancer

The same Swedish authors tested the assumption that a greater recall of past herbicide exposure by patients with soft-tissue sarcoma and lymphoma than by the controls may have produced the earlier findings. A study was conducted involving 157 male colon cancer patients (Hardell, 1981b), who were interviewed in the same manner as in the earlier studies, and whose exposure was compared with that of the combined controls from the two earlier studies from the same region (Hardell & Sandström, 1979; Eriksson *et al.*, 1981). A relative risk estimate of 1.3 (95% CI, 0.6-2.8) was obtained based on 11 exposed cases (out of 154) and 43 exposed referents (out of 541).

Hardell *et al.* (1984) performed a case-control study in the northern region of Sweden on 103 primary liver cancer cases diagnosed in 1974-1981 and 206 controls, with a study design similar to that of the earlier studies (Hardell & Sandström, 1979; Eriksson *et al.*, 1981). Of the cases, 8.2% reported exposure to chlorophenoxy herbicides versus 6.5% among the referents (odds ratio, 1.7; 95% CI, 0.7-4.4). The study indicated an association between exposure to organic solvents and primary liver cancer.

Vân (1984) investigated previous exposure to herbicides during wartime for 21 male cases of primary hepatic carcinoma admitted to the Viet Duc Huu Ngai Hospital of Hanoi, Viet Nam, in January to September 1982, and for 42 control subjects admitted in the same months for gastrointestinal diseases. Cases and controls were aged 18-50 years. Six of 21 cases and 3/42 controls had been living, working or fighting in sprayed regions of South Viet Nam, at the time of spraying or subsequently, for a length of time ranging from eight to 77 months. No information was available on possible confounding factors. [The Working Group noted that the possibility of bias, exposures to many unknown chemicals and the short reported latency make the study uninformative.]

[The possibility of recall bias in the Swedish case-referent studies has been discussed by the authors (Axelson, 1980; Hardell, 1981a,b; Hardell *et al.*, 1981; Hardell & Axelson, 1982; Hardell *et al.*, 1984). Had a significant recall bias existed, the studies on colon cancer (Hardell, 1981b) and liver cancer (Hardell *et al.*, 1984) would have been expected to give significantly elevated odds ratios for herbicide exposure; such findings were not reported.]

[The New Zealand studies used other cancer patients as controls. However, a comparison of such controls with general population controls also interviewed by telephone did

not reveal differences in past exposure frequency (Pearce *et al.*, 1986). The use of other cancers as controls does not therefore explain the difference in findings between the Swedish and New Zealand studies.

[The Working Group noted that none of the cases of soft-tissue sarcoma seen in New Zealand occurred in a professional herbicide applicator. The Working Group noted differences in the use patterns of chlorophenoxy herbicides in Sweden and New Zealand, e.g., hand-notching and application of amine salts to trees was used in Sweden. Also, no information was available on the solvents, emulsifiers and other additives in the chlorophenoxy herbicide formulations used in Sweden and New Zealand. Limited information is available on the levels of TCDD in formulations used in Sweden and New Zealand, but the data indicate contamination at about the same level.]

4. Summary of Data Reported and Evaluation

4.1 Exposure data

Chlorophenoxy herbicides have been produced extensively since the 1950s for use in agriculture and as defoliants, although production and use are now decreasing in many countries. Widespread occupational exposure to chlorophenoxy herbicides and their chlorinated dibenzodioxin impurities is known to have occurred during their production, formulation, application and disposal. Increased urinary levels of chlorophenoxy compounds and increased concentrations of some chlorinated dibenzodioxins in adipose tissue have been measured in highly exposed persons. The presence of dibenzodioxins and dibenzofurans has been demonstrated in the adipose tissue of nonoccupationally exposed people in many countries.

During occupational exposure, such as ground spraying and other manual application of these herbicides, dermal absorption is a major route of entry into the body.

In manufacturing plants, exposures occur during the handling of raw materials, intermediates, finished products and process wastes. High-level short-term occupational exposures have also been caused by industrial accidents.

4.2 Experimental data

Previous IARC evaluations of the carcinogenicity to experimental animals of several individual chlorophenoxy herbicides and of 2,3,7,8-tetrachlorodibenzo-*para*-dioxin (TCDD), an impurity found in some of these herbicides, are summarized in section 3.1.

4.3 Human data

Studies comparing the occurrence of congenital malformations in areas and periods characterized by different usage of chlorophenoxy herbicides were uninformative with regard to the teratogenicity of these agents. Two case-control studies on birth anomalies

among the children of Australian and US veterans and of New Zealand pesticide sprayers showed no excess risk associated with paternal exposure to herbicides.

No study was available of pregnancy outcomes of women exposed occupationally to chlorophenoxy herbicides.

In one study of persons exposed to chlorophenoxy herbicides during military operations in Viet Nam, conducted ten years after exposure, no increase in the incidence of chromosomal aberrations or sister chromatid exchanges was observed.

Cytogenetic studies have been carried out on workers occupationally exposed to chlorophenoxy herbicides during spraying. In three of the studies, there was also exposure to other herbicides, and the effect of chlorophenoxy herbicides could not be assessed. Studies in which occupational exposure was only to chlorophenoxy herbicides showed no increased incidence of chromosomal aberrations or sister chromatid exchanges.

In a large Danish cohort study of chemical workers exposed to chlorophenoxy herbicides [particularly (4-chloro-2-methylphenoxy)acetic acid (MCPA), 2-(4-chloro-2-methylphenoxy)propanoic acid (mecoprop), 2,4-dichlorophenoxyacetic acid (2,4-D) and 2-(2,4-dichlorophenoxy)propanoic acid (dichlorprop)], as well as other chemicals, no overall increase in cancer incidence rate was observed, but there were significantly increased risks of soft-tissue sarcoma and lung cancer in different subcohorts, which were not necessarily those with the highest exposures to chlorophenoxy herbicide preparations. A Finnish cohort study of brush control workers with short follow-up time showed no increased risk. A small Swedish cohort study of railroad workers who sprayed herbicides showed an increased risk of cancers at all sites combined for those exposed to both chlorophenoxy herbicide preparations and other herbicides. An excess incidence of all cancers was also reported from a very small cohort of Swedish forestry foremen exposed to chlorophenoxy herbicide preparations and other herbicides. A study of long-term pesticide applicators in the German Democratic Republic, heavily exposed to a number of chemicals, including 2,4-D and MCPA, demonstrated an increased risk of bronchial carcinoma.

A population-based case-control study conducted in northern Sweden showed a statistically significant association between exposure to chlorophenoxy herbicides, especially in forestry, and the occurrence of soft-tissue sarcomas. A second study on this type of tumour was conducted in southern Sweden, where a significant increase in the risk of developing soft-tissue sarcomas was associated with previous exposures to chlorophenoxy herbicides, mainly in agriculture. An increased risk of soft-tissue sarcoma was described among highly exposed Italian rice weeders in a population-based case-control study. A case-control study from New Zealand did not demonstrate an increased risk of soft-tissue sarcoma in people exposed to chlorophenoxy herbicides.

A statistically significant association between malignant lymphoma and exposure to chlorophenoxy herbicides was found in a Swedish case-control study; however, no such association was seen in a case-control study of these tumours from New Zealand. In a Danish cohort of chemical workers exposed to chlorophenoxy herbicides, there was also no increased risk of malignant lymphoma.

Three Swedish case-control studies of colon, liver and nasal cancer, respectively, which used the same study design and methods as in the studies on soft-tissue sarcoma and malignant lymphoma, did not demonstrate significantly increased risks. Exposure recall bias of cancer patients thus does not seem to explain the differences between the results of the Swedish and the New Zealand case-control studies of soft-tissue tumours and lymphomas.

In summary, well-conducted case-control studies have provided the most information on the association between cancer and occupational exposure to chlorophenoxy herbicides. Statistically significant elevated odds ratios have been observed for cancers at some sites, but not consistently, in independent studies. The results of one cohort study on the incidence of soft-tissue sarcoma support the finding in case-control studies of an increased relative risk for these tumours. Other cohort studies have added little information. No consistent exposure-response relationship emerged from the different studies, and, in the studies that found an association, exposures were shorter than those usually associated with occupation-related cancers.

4.4. Evaluation^a

There is limited evidence that occupational exposures to chlorophenoxy herbicides are carcinogenic to humans.

5. References

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^aFor definition of the italicized term, see Preamble, p. 22.

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APPENDIX: SUMMARY OF FINAL EVALUATIONS

Compound	Degree of evidence ^a		
	Humans	Animals	Short-term tests
Dichloromethane	I	S	S
1,1,1,2-tetrachloroethane	ND	I	I
Pentachloroethane	ND	I	I
1,3-Dichloropropene	I	S	I
1,2-Dichloropropane	ND	I	I
Bis(2-chloro-1-methylethyl)ether	ND	I	I
Methyl chloride	I	I	S
Methyl bromide	I	I	S
Methyl iodide	ND	I	S
Chlorofluoromethane	ND	I	I
Chlorodifluoromethane	I	I	I
2-Chloro-1,1,1-trifluoroethane	ND	I	I
Polybrominated biphenyls	I	S	NI
Amitrole	I	S	I
Chlorophenols (occupational exposures to)	I	-	-
Chlorophenoxy herbicides (occupational exposures to)	I	-	-

^aI, inadequate; S, sufficient; ND, no data; I, limited; NI, no evidence. For definitions of the degrees of evidence, see pp. 16, 20, 21 and 22 of the Preamble to this volume.

EXHIBIT C



WORLD HEALTH ORGANIZATION

INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

IARC MONOGRAPHS
ON THE
EVALUATION OF THE CARCINOGENIC
RISKS TO HUMANS

Overall Evaluations of Carcinogenicity: An Updating
of *IARC Monographs Volumes 1 to 42*

SUPPLEMENT 7

LYON, FRANCE

1987

(b) *Experimental carcinogenicity data*

Data relevant to the evaluation of the carcinogenicity of the agent in animals are summarized. For each animal species and route of administration, it is stated whether an increased incidence of neoplasms was observed, and the tumour sites are indicated. If the agent produced tumours after prenatal exposure or in single-dose experiments, this is also indicated. Dose-response and other quantitative data may be given when available. Negative findings are also summarized.

(c) *Human carcinogenicity data*

Results of epidemiological studies that are considered to be pertinent to an assessment of human carcinogenicity are summarized. When relevant, case reports and correlation studies are also considered.

(d) *Other relevant data*

Structure-activity correlations are mentioned when relevant.

Toxicological information and data on kinetics and metabolism in experimental animals are given when considered relevant. The results of tests for genetic and related effects are summarized for whole mammals, cultured mammalian cells and nonmammalian systems.

Data on other biological effects in humans of particular relevance are summarized. These may include kinetic and metabolic considerations and evidence of DNA binding, persistence of DNA lesions or genetic damage in humans exposed to the agent.

When available, comparisons of such data for humans and for animals, and particularly animals that have developed cancer, are described.

13. EVALUATION

Evaluations of the strength of the evidence for carcinogenicity arising from human and experimental animal data are made, using standard terms.

It is recognized that the criteria for these evaluations, described below, cannot encompass all of the factors that may be relevant to an evaluation of the carcinogenicity of an agent. In considering all of the relevant data, the Working Group may assign the agent to a higher or lower category than a strict interpretation of these criteria would indicate.

(a) *Degrees of evidence for carcinogenicity to humans and to experimental animals and supporting evidence*

It should be noted that these categories refer only to the strength of the evidence that these agents are carcinogenic and not to the extent of their carcinogenic activity (potency) nor to the mechanism involved. The classification of some agents may change as new information becomes available.

(i) *Human carcinogenicity data*

The evidence relevant to carcinogenicity from studies in humans is classified into one of the following categories:

Sufficient evidence of carcinogenicity: The Working Group considers that a causal relationship has been established between exposure to the agent and human cancer. That is, a positive relationship has been observed between exposure to the agent and cancer in studies in which chance, bias and confounding could be ruled out with reasonable confidence.

Limited evidence of carcinogenicity: A positive association has been observed between exposure to the agent and cancer for which a causal interpretation is considered by the Working Group to be credible, but chance, bias or confounding could not be ruled out with reasonable confidence.

Inadequate evidence of carcinogenicity: The available studies are of insufficient quality, consistency or statistical power to permit a conclusion regarding the presence or absence of a causal association.

Evidence suggesting lack of carcinogenicity: There are several adequate studies covering the full range of doses to which human beings are known to be exposed, which are mutually consistent in not showing a positive association between exposure to the agent and any studied cancer at any observed level of exposure. A conclusion of 'evidence suggesting lack of carcinogenicity' is inevitably limited to the cancer sites, circumstances and doses of exposure and length of observation covered by the available studies. In addition, the possibility of a very small risk at the levels of exposure studied can never be excluded.

In some instances, the above categories may be used to classify the degree of evidence for the carcinogenicity of the agent for specific organs or tissues.

(ii) *Experimental carcinogenicity data*

The evidence relevant to carcinogenicity in experimental animals is classified into one of the following categories:

Sufficient evidence of carcinogenicity: The Working Group considers that a causal relationship has been established between the agent and an increased incidence of malignant neoplasms or of an appropriate combination of benign and malignant neoplasms (as described on p.23) in (a) two or more species of animals or (b) in two or more independent studies in one species carried out at different times or in different laboratories or under different protocols.

Exceptionally, a single study in one species might be considered to provide sufficient evidence of carcinogenicity when malignant neoplasms occur to an unusual degree with regard to incidence, site, type of tumour or age at onset.

In the absence of adequate data on humans, it is biologically plausible and prudent to regard agents for which there is *sufficient evidence* of carcinogenicity in experimental animals as if they presented a carcinogenic risk to humans.

Limited evidence of carcinogenicity: The data suggest a carcinogenic effect but are limited for making a definitive evaluation because, e.g., (a) the evidence of carcinogenicity is restricted to a single experiment; or (b) there are unresolved questions regarding the adequacy of the design, conduct or interpretation of the study; or (c) the agent increases the incidence only of benign neoplasms or lesions of uncertain neoplastic potential, or of certain neoplasms which may occur spontaneously in high incidences in certain strains.

Inadequate evidence of carcinogenicity: The studies cannot be interpreted as showing either the presence or absence of a carcinogenic effect because of major qualitative or quantitative limitations.

Evidence suggesting lack of carcinogenicity: Adequate studies involving at least two species are available which show that, within the limits of the tests used, the agent is not carcinogenic. A conclusion of evidence suggesting lack of carcinogenicity is inevitably limited to the species, tumour sites and doses of exposure studied.

(iii) *Supporting evidence of carcinogenicity*

The other relevant data judged to be of sufficient importance as to affect the making of the overall evaluation are indicated.

(b) *Overall evaluation*

Finally, the total body of evidence is taken into account; the agent is described according to the wording of one of the following categories, and the designated group is given. The categorization of an agent is a matter of scientific judgement, reflecting the strength of the evidence derived from studies in humans and in experimental animals and from other relevant data.

Group 1 — The agent is carcinogenic to humans.

This category is used only when there is *sufficient evidence* of carcinogenicity in humans.

Group 2

This category includes agents for which, at one extreme, the degree of evidence of carcinogenicity in humans is almost sufficient, as well as agents for which, at the other extreme, there are no human data but for which there is experimental evidence of carcinogenicity. Agents are assigned to either 2A (probably carcinogenic) or 2B (possibly carcinogenic) on the basis of epidemiological, experimental and other relevant data.

Group 2A — The agent is probably carcinogenic to humans.

This category is used when there is *limited evidence* of carcinogenicity in humans and *sufficient evidence* of carcinogenicity in experimental animals. Exceptionally, an agent may be classified into this category solely on the basis of *limited evidence* of carcinogenicity in humans or of *sufficient evidence* of carcinogenicity in experimental animals strengthened by supporting evidence from other relevant data.

Group 2B — The agent is possibly carcinogenic to humans.

This category is generally used for agents for which there is *limited evidence* in humans in the absence of *sufficient evidence* in experimental animals. It may also be used when there is *inadequate evidence* of carcinogenicity in humans or when human data are nonexistent but there is *sufficient evidence* of carcinogenicity in experimental animals. In some instances, an agent for which there is inadequate evidence or no data in humans but *limited evidence* of carcinogenicity in experimental animals together with supporting evidence from other relevant data may be placed in this group.

Group 3 — The agent is not classifiable as to its carcinogenicity to humans.

Agents are placed in this category when they do not fall into any other group.

Group 4 — The agent is probably not carcinogenic to humans.

This category is used for agents for which there is *evidence suggesting lack of carcinogenicity* in humans together with *evidence suggesting lack of carcinogenicity* in experimental animals. In some circumstances, agents for which there is *inadequate evidence* of or no data on carcinogenicity in humans but *evidence suggesting lack of carcinogenicity* in experimental animals, consistently and strongly supported by a broad range of other relevant data, may be classified in this group.

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Table 1. Degrees of evidence for carcinogenicity in humans and in experimental animals, and overall evaluations of carcinogenicity to humans for agents evaluated in *IARC Monographs* volumes 1-42

Agent	Degree of evidence for carcinogenicity ^a		Overall evaluation ^a
	Human	Animal	
A- α -C (2-Amino-9H-pyrido[2,3-b]indole) ^b [40, 1986]	ND	S	2B
Acetaldehyde	I	S	2B
Acetamide ^c	ND	S	2B
Acridine orange ^d [16, 1978]	ND	I	3
Acriflavinium chloride ^d [13, 1977]	ND	I	3
Acrolein	I	I	3
Acrylamide ^b [39, 1986]	ND	S	2B
Acrylic acid ^d [19, 1979]	ND	ND	3
Acrylic fibres ^d [19, 1979]	ND	ND	3
Acrylonitrile	L	S	2A
Acrylonitrile-butadiene-styrene copolymers ^d [19, 1979]	ND	ND	3
Actinomycin D	I	L	3
Adriamycin ^e	I	S	2A
AF-2 [2-(2-Furyl)-3-(5-nitro-2-furyl)acrylamide] ^b [31, 1983]	ND	S	2B
Aflatoxins	S	S	1
Agaricine ^b [31, 1983]	ND	I	3
Aldrin	I	L	3
Allyl chloride ^b [36, 1985]	ND	I	3
Allyl isothiocyanate ^b [36, 1985]	ND	L	3
Allyl isovalerate ^b [36, 1985]	ND	L	3
Aluminium production	S		1
Amaranth ^d [8, 1975]	ND	I	3
5-Aminoacenaphthene ^d [16, 1978]	ND	I	3
2-Aminoanthraquinone ^b [27, 1982]	ND	L	3
<i>para</i> -Aminoazobenzene ^c	ND	S	2B
<i>ortho</i> -Aminoazotoluene ^b [8, 1975]	ND	S	2B
<i>para</i> -Aminobenzoic acid ^d [16, 1978]	ND	I	3

^aND, no adequate data; ESL, evidence suggesting lack of carcinogenicity; I, inadequate evidence; L, limited evidence; S, sufficient evidence. For definitions of terms and overall evaluations, see Preamble, pp. 30-32.

^bOverall evaluation based only on evidence of carcinogenicity in monograph [volume, year] (see Methods, p. 39) or in Supplement 4

^cDegree of evidence in animals revised on the basis of data that appeared after the most recent monograph and/or on the basis of present criteria (see Methods, pp. 39-40)

^dDegree of evidence not previously categorized; evaluation made according to present criteria on the basis of data in monograph [volume, year] (see Methods, p. 39)

^eOther relevant data, as given in the summaries here or in monograph [volume, year], influenced the making of the overall evaluation (see Methods, pp. 38-39)

Table 1. (contd)

Agent	Degree of evidence for carcinogenicity ^a		Overall evaluation ^a
	Human	Animal	
4-Aminobiphenyl	S	S	1
1-Amino-2-methylantraquinone ^b [27, 1982]	ND	L	3
2-Amino-5-(5-nitro-2-furyl)-1,3,4-thiadiazole ^b [7, 1974]	ND	S	2B
4-Amino-2-nitrophenol ^d [16, 1978]	ND	I	3
2-Amino-5-nitrothiazole ^b [31, 1983]	ND	L	3
11-Aminoundecanoic acid ^b [39, 1986]	ND	L	3
Amitrole	I	S	2B
Anaesthetics, volatile	I		3
Cyclopropane		ND	
Diethyl ether		ND	
Divinyl ether		ND	
Enflurane		I	
Fluroxene		ND	
Halothane		I	
Isoflurane		I	
Methoxyflurane		I	
Nitrous oxide		I	
Androgenic (anabolic) steroids	L		2A
Oxymetholone		ND	
Testosterone		S	
Angelics ^b [40, 1986]			
Angelicin plus ultraviolet A radiation	ND	L	3
5-Methylangelicin plus ultraviolet A radiation	ND	L	3
4,4'-Dimethylangelicin plus ultraviolet A radiation	ND	ND	3
4,5'-Dimethylangelicin plus ultraviolet A radiation	ND	L	3
4,4',6-Trimethylangelicin plus ultraviolet A radiation	ND	ND	3
Aniline	I	L	3
<i>ortho</i> -Anisidine ^b [27, 1982]	ND	S	2B
<i>para</i> -Anisidine ^b [27, 1982]	ND	I	3
Anthanthrene ^b [32, 1982]	ND	L	3
Anthracene ^c	ND	I	3
Anthranilic acid ^d [16, 1978]	ND	I	3
Apholate ^d [9, 1975]	ND	I	3
Aramite ^{®b} [5, 1974]	ND	S	2B
Arsenic and arsenic compounds	S	L	1*
Asbestos	S	S	1
Attapulgit	I	L	3
Auramine (technical-grade)	I	S	2B
Manufacture of auramine	S		1
Aurothioglucose ^d [13, 1977]	ND	L	3
5-Azacytidine ^b [26, 1981]	ND	L	3
Azaserine ^b [10, 1976]	ND	S	2B

*This evaluation applies to the group of chemicals as a whole and not necessarily to all individual chemicals within the group (see also Methods, p. 38).

Table 1. (contd)

Agent	Degree of evidence for carcinogenicity ^a		Overall evaluation ^a
	Human	Animal	
Azathioprine	S	L	1
Aziridine ^d [9, 1975]	ND	L	3
2-(1-Aziridinyl)ethanol ^d [9, 1975]	ND	L	3
Aziridyl benzoquinone ^d [9, 1975]	ND	L	3
Azobenzene ^d [8, 1975]	ND	L	3
Benz[<i>a</i>]acridine ^b [32, 1983]	ND	I	3
Benz[<i>c</i>]acridine ^b [32, 1983]	ND	L	3
Benz[<i>a</i>]anthracene ^{b,e} [32, 1983]	ND	S	2A
Benzene	S	S	1
Benzidine	S	S	1
Benzidine-based dyes ^e	I		2A
Direct Black 38 (technical-grade)		S	
Direct Blue 6 (technical-grade)		S	
Direct Brown 95 (technical-grade)		S	
Benzo[<i>b</i>]fluoranthene ^b [32, 1983]	ND	S	2B
Benzo[<i>j</i>]fluoranthene ^b [32, 1983]	ND	S	2B
Benzo[<i>k</i>]fluoranthene ^b [32, 1983]	ND	S	2B
Benzo[<i>ghi</i>]fluoranthene ^b [32, 1983]	ND	I	3
Benzo[<i>a</i>]fluorene ^b [32, 1983]	ND	I	3
Benzo[<i>b</i>]fluorene ^b [32, 1983]	ND	I	3
Benzo[<i>c</i>]fluorene ^b [32, 1983]	ND	I	3
Benzo[<i>ghi</i>]perylene ^b [32, 1983]	ND	I	3
Benzo[<i>c</i>]phenanthrene ^b [32, 1983]	ND	I	3
Benzo[<i>a</i>]pyrene ^{b,e} [32, 1983]	ND	S	2A
Benzo[<i>e</i>]pyrene ^b [32, 1983]	ND	I	3
<i>para</i> -Benzoquinone dioxime ^b [29, 1982]	ND	L	3
Benzoyl chloride	I	I	3
Benzoyl peroxide ^b [36, 1985]	I	I	3
Benzyl acetate ^b [40, 1986]	ND	L	3
Benzyl violet 4B ^b [16, 1978]	ND	S	2B
Beryllium and beryllium compounds	L	S	2A
Betel quid			
With tobacco	S	L	1
Without tobacco	I	L	3
Bis(1-aziridinyl)morpholinophosphine sulphide ^d [9, 1975]	ND	L	3
Bis(2-chloroethyl)ether ^d [9, 1975]	ND	L	3
<i>N,N</i> -Bis(2-chloroethyl)-2-naphthylamine (Chlornaphazine)	S	L	1
1,2-Bis(chloromethoxy)ethane ^d [15, 1977]	ND	L	3
1,4-Bis(chloromethoxymethyl)benzene ^d [15, 1977]	ND	L	3
Bis(chloromethyl)ether and chloromethyl methyl ether (technical-grade)	S	S	1

Table 1. (contd)

Agent	Degree of evidence for carcinogenicity ^a		Overall evaluation ^a
	Human	Animal	
Bis(2-chloro-1-methylethyl)ether ^b [41, 1986]	ND	L	3
Bitumens	I		3
Steam-refined and cracking-residue bitumens		L	
Air-refined bitumens		I	
Extracts of steam-refined and air-refined bitumens		S	2B
Bleomycins ^e	I	L	2B
Blue VRS ^d [16, 1978]	ND	L	3
Bracken fern	I	S	2B
Brilliant Blue FCF ^d [16, 1978]	ND	L	3
1,3-Butadiene	I	S	2B
1,4-Butanediol dimethanesulphonate (Myleran)	S	L	1
<i>n</i> -Butyl acrylate ^b [39, 1986]	ND	I	3
Butylated hydroxyanisole (BHA) ^b [40, 1986]	ND	S	2B
Butylated hydroxytoluene (BHT) ^b [40, 1986]	ND	L	3
Butyl benzyl phthalate ^b [29, 1982]	ND	I	3
β -Butyrolactone ^b [11, 1976]	ND	S	2B
γ -Butyrolactone ^{b,c} [11, 1976]	ND	I	3
Cadmium and cadmium compounds	L	S	2A
Cantharidin ^d [10, 1976]	ND	L	3
Caprolactam ^c	ND	ESL	4
Captan ^b [30, 1983]	ND	L	3
Carbaryl ^d [12, 1976]	ND	I	3
Carbazole ^b [32, 1983]	ND	L	3
3-Carbethoxypsoralen ^{b,c} [40, 1986]	ND	I	3
Carbon blacks	I	I	3
Carbon-black extracts		S	2B
Carbon tetrachloride	I	S	2B
Carmoisine ^d [8, 1975]	ND	I	3
Carrageenan			
Native ^{b,c} [31, 1983]	ND	I	3
Degraded ^b [31, 1983]	ND	S	2B
Catechol ^d [15, 1977]	ND	I	3
Chlorambucil	S	S	1
Chloramphenicol	L	I	2B
Chlordane/Heptachlor	I	L	3
Chlordecone (Kepone) ^b [20, 1979]	ND	S	2B
Chlordimeform ^b [30, 1983]	ND	I	3
Chlorinated dibenzodioxins (other than TCDD) ^d [15, 1977]	ND	I	3

Table 1. (contd)

Agent	Degree of evidence for carcinogenicity ^a		Overall evaluation ^a
	Human	Animal	
α -Chlorinated toluenes	I		2B
Benzyl chloride		L	
Benzal chloride		L	
Benzotrichloride		S	
Chlorobenzilate ^b [30, 1983]	ND	L	3
Chlorodifluoromethane	I	L	3
Chloroethyl nitrosoureas			
Bischloroethyl nitrosourea (BCNU)	L	S	2A
1-(2-Chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU) ^e	I	S	2A
1-(2-Chloroethyl)-3-(4-methylcyclohexyl)-1-nitrosourea (Methyl-CCNU)	S	L	1
Chlorofluoromethane ^b [41, 1986]	ND	L	3
Chloroform	I	S	2B
Chlorophenols	L		2B
Pentachlorophenol		I	
2,4,5-Trichlorophenol		I	
2,4,6-Trichlorophenol		S	
Chlorophenoxy herbicides	L		2B
2,4-D		I	
2,4,5-T		I	
MCPA		ND	
4-Chloro- <i>ortho</i> -phenylenediamine ^b [27, 1982]	ND	S	2B
4-Chloro- <i>meta</i> -phenylenediamine ^b [27, 1982]	ND	I	3
Chloroprene	I	I	3
Chloropropham ^d [12, 1976]	ND	I	3
Chloroquine ^d [13, 1977]	ND	I	3
Chlorothalonil ^b [30, 1983]	ND	L	3
<i>para</i> -Chloro- <i>ortho</i> -toluidine ^b [30, 1983]	ND	S	2B
2-Chloro-1,1,1-trifluoroethane ^b [41, 1986]	ND	L	3
Cholesterol	I	I	3
Chromium and chromium compounds			
Chromium metal	I	I	3
Trivalent chromium compounds	I	I	3
Hexavalent chromium compounds	S	S	1*
Chrysene ^b [32, 1983]	ND	L	3
Chrysoidine	I	L	3
CI Disperse Yellow 3 ^d [8, 1975]	ND	I	3
Cinnamyl anthranilate ^b [31, 1983]	ND	L	3
Cisplatin ^e	I	S	2A
Citrinin ^b [40, 1986]	ND	L	3
Citrus Red No. 2 ^b [8, 1975]	ND	S	2B

*This evaluation applies to the group of chemicals as a whole and not necessarily to all individual chemicals within the group (see also Methods, p. 38).

Table 1. (contd)

Agent	Degree of evidence for carcinogenicity ^a		Overall evaluation ^a
	Human	Animal	
Clofibrate	I	L	3
Clomiphene citrate	I	I	3
Coal gasification	S		1
Coal-tar pitches	S	S	1
Coal-tars	S	S	1
Coke production	S		1
Copper 8-hydroxyquinoline ^d [15, 1977]	ND	I	3
Coronene ^b [32, 1983]	ND	I	3
Coumarin ^d [10, 1976]	ND	L	3
Creosotes	L	S	2A
<i>meta</i> -Cresidine ^b [27, 1982]	ND	I	3
<i>para</i> -Cresidine ^b [27, 1982]	ND	S	2B
Cycasin ^b [10, 1976] (see also Methylazoxymethanol and its acetate)	ND	S	2B
Cyclamates	I	L	3
Cyclochlorotine ^d [10, 1976]	ND	I	3
Cyclopenta[<i>cd</i>]pyrene ^b [32, 1983]	ND	L	3
Cyclophosphamide	S	S	1
Dacarbazine	I	S	2B
D & C Red No. 9 ^d [8, 1975]	ND	I	3
Dapsone	I	L	3
Daunomycin ^b [10, 1976]	ND	S	2B
DDT	I	S	2B
Diacetylaminoazotoluene ^d [8, 1975]	ND	I	3
<i>N,N'</i> -Diacetylbenzidine ^b [16, 1978]	ND	S	2B
Diallate ^b [30, 1983]	ND	L	3
2,4-Diaminoanisole ^b [27, 1982]	ND	S	2B
4,4'-Diaminodiphenyl ether ^b [29, 1982]	ND	S	2B
1,2-Diamino-4-nitrobenzene ^d [16, 1978]	ND	I	3
1,4-Diamino-2-nitrobenzene ^d [16, 1978]	ND	I	3
2,4-Diaminotoluene ^b [16, 1978]	ND	S	2B
2,5-Diaminotoluene ^d [16, 1978]	ND	I	3
Diazepam	I	I	3
Diazomethane ^d [7, 1974]	ND	L	3
Dibenz[<i>a,h</i>]acridine ^b [32, 1983]	ND	S	2B
Dibenz[<i>a,f</i>]acridine ^b [32, 1983]	ND	S	2B
Dibenz[<i>a,c</i>]anthracene ^b [32, 1983]	ND	L	3
Dibenz[<i>a,h</i>]anthracene ^{b,e} [32, 1983]	ND	S	2A
Dibenz[<i>a,f</i>]anthracene ^b [32, 1983]	ND	L	3
7 <i>H</i> -Dibenzo[<i>c,g</i>]carbazole ^b [32, 1983]	ND	S	2B
Dibenzo[<i>a,e</i>]fluoranthene ^b [32, 1983]	ND	L	3

Table 1. (contd)

Agent	Degree of evidence for carcinogenicity ^a		Overall evaluation ^a
	Human	Animal	
Dibenzo[<i>h,rst</i>]pentaphene ^d [3, 1973]	ND	L	3
Dibenzo[<i>a,e</i>]pyrene ^b [32, 1983]	ND	S	2B
Dibenzo[<i>a,h</i>]pyrene ^b [32, 1983]	ND	S	2B
Dibenzo[<i>a,i</i>]pyrene ^b [32, 1983]	ND	S	2B
Dibenzo[<i>a,l</i>]pyrene ^b [32, 1983]	ND	S	2B
1,2-Dibromo-3-chloropropane	I	S	2B
Dichloroacetylene ^b [39, 1986]	ND	L	3
<i>ortho</i> -Dichlorobenzene	I	I	3
<i>para</i> -Dichlorobenzene	I	S	2B
3,3'-Dichlorobenzidine	I	S	2B
<i>trans</i> -1,4-Dichlorobutene ^d [15, 1977]	ND	I	3
3,3'-Dichloro-4,4'-diaminodiphenyl ether ^b [16, 1978]	ND	S	2B
1,2-Dichloroethane ^b [20, 1979]	ND	S	2B
Dichloromethane	I	S	2B
2,6-Dichloro- <i>para</i> -phenylenediamine ^b [39, 1986]	ND	L	3
1,2-Dichloropropane ^b [41, 1986]	ND	L	3
1,3-Dichloropropene (technical-grade)	I	S	2B
Dichlorvos ^b [20, 1979]	ND	I	3
Dicofol ^b [30, 1983]	ND	L	3
Dieldrin	I	L	3
Diepoxybutane ^b [11, 1976]	ND	S	2B
Di(2-ethylhexyl)adipate ^b [29, 1982]	ND	L	3
Di(2-ethylhexyl)phthalate ^b [29, 1982]	ND	S	2B
1,2-Diethylhydrazine ^b [4, 1974]	ND	S	2B
Diethyl sulphate	L	S	2A
Diglycidyl resorcinol ether ^b [36, 1985]	ND	S	2B
Dihydrosafrole ^b [10, 1976]	ND	S	2B
Dihydroxymethylfuratrizine ^b [24, 1980] (<i>see also</i> Panfuran S)	ND	I	3
Dimethoxane ^d [15, 1977]	ND	L	3
3,3'-Dimethoxybenzidine (<i>ortho</i> -Dianisidine)	I	S	2B
3,3'-Dimethoxybenzidine-4,4'-diisocyanate ^b [39, 1986]	ND	L	3
<i>para</i> -Dimethylaminoazobenzene ^b [8, 1975]	ND	S	2B
<i>para</i> -Dimethylaminoazobenzenediazo sodium sulphonate ^d [8, 1975]	ND	I	3
<i>trans</i> -2-[(Dimethylamino)methylimino]-5-[2-(5-nitro-2-furyl)vinyl]-1,3,4-oxadiazole ^b [7, 1974]	ND	S	2B
3,3'-Dimethylbenzidine (<i>ortho</i> -Tolidine) ^b [1, 1972]	ND	S	2B
Dimethylcarbonyl chloride ^e	I	S	2A
1,1-Dimethylhydrazine ^b [4, 1974]	ND	S	2B
1,2-Dimethylhydrazine ^b [4, 1974]	ND	S	2B
1,4-Dimethylphenanthrene ^b [32, 1983]	ND	I	3

Table 1. (contd)

Agent	Degree of evidence for carcinogenicity ^a		Overall evaluation ^a
	Human	Animal	
Dimethyl sulphate ^e	I	S	2A
1,8-Dinitropyrene ^b [33, 1984]	ND	I	3
Dinitrosopentamethylenetetramine ^d [11, 1976]	ND	I	3
1,4-Dioxane	I	S	2B
2,4'-Diphenyldiamine ^d [16, 1978]	ND	I	3
Disulfiram ^d [12, 1976]	ND	I	3
Dithranol ^d [13, 1977]	ND	I	3
Dulcin ^d [12, 1976]	ND	I	3
Endrin ^d [5, 1974]	ND	I	3
Eosin ^d [15, 1977]	ND	I	3
Epichlorohydrin ^e	I	S	2A
1-Epoxyethyl-3,4-epoxycyclohexane ^d [11, 1976]	ND	L	3
3,4-Epoxy-6-methylcyclohexylmethyl-3,4-epoxy-6-methylcyclohexane carboxylate ^d [11, 1976]	ND	L	3
cis-9,10-Epoxysearic acid ^d [11, 1976]	ND	I	3
Erionite	S	S	1
Ethionamide ^d [13, 1977]	ND	L	3
Ethyl acrylate ^b [39, 1986]	ND	S	2B
Ethylene ^d [19, 1979]	ND	ND	3
Ethylene dibromide ^e	I	S	2A
Ethylene oxide	L	S	2A
Ethylene sulphide ^d [11, 1976]	ND	L	3
Ethylene thiourea	I	S	2B
Ethyl methanesulphonate ^b [7, 1974]	ND	S	2B
N-Ethyl-N-nitrosourea ^{b,e} [17, 1978]	ND	S	2A
Ethyl selenac ^d [12, 1976]	ND	I	3
Ethyl tellurac ^d [12, 1976]	ND	I	3
Eugenol ^b [36, 1985]	ND	L	3
Evans blue ^d [8, 1975]	ND	L	3
Fast Green FCF ^d [16, 1978]	ND	L	3
Ferbam ^d [12, 1976]	ND	I	3
Fluometuron ^b [30, 1983]	ND	I	3
Fluoranthene ^{b,c} [32, 1983]	ND	I	3
Fluorene ^b [32, 1983]	ND	I	3
Fluorides (inorganic, used in drinking-water)	I	I	3
5-Fluorouracil	I	I	3
Formaldehyde	L	S	2A
2-(2-Formylhydrazino)-4-(5-nitro-2-furyl)thiazole ^b [7, 1974]	ND	S	2B
Furazolidone ^b [31, 1983]	ND	I	3

Table 1. (contd)

Agent	Degree of evidence for carcinogenicity ^a		Overall evaluation ^a
	Human	Animal	
Fusarenon-X ^b [31, 1983]	ND	I	3
Glu-P-1 (2-Amino-6-methyldipyrido[1,2- <i>a</i> :3',2'- <i>d</i>]imidazole) ^b [40, 1986]	ND	S	2B
Glu-P-2 (2-Aminodipyrido[1,2- <i>a</i> :3',2'- <i>d</i>]imidazole) ^b [40, 1986]	ND	S	2B
Glycidaldehyde ^b [11, 1976]	ND	S	2B
Glycidyl oleate ^d [11, 1976]	ND	I	3
Glycidyl stearate ^d [11, 1976]	ND	I	3
Griseofulvin ^c	ND	S	2B
Guinea Green B ^d [16, 1978]	ND	L	3
Gyromitrin ^c	ND	L	3
Haematite and ferric oxide			
Ferric oxide	I	ESL	3
Haematite	I	I	3
Underground haematite mining with exposure to radon	S		1
Hexachlorobenzene	I	S	2B
Hexachlorobutadiene ^b [20, 1979]	ND	L	3
Hexachlorocyclohexanes (HCH)	I		2B
Technical-grade HCH		S	
α -HCH		S	
β -HCH		L	
γ -HCH (Lindane)		L	
Hexachloroethane ^b [20, 1979]	ND	L	3
Hexachlorophene ^b [20, 1979]	ND	I	3
Hexamethylphosphoramide ^b [15, 1977]	ND	S	2B
Hycanthone mesylate ^d [13, 1977]	ND	I	3
Hydralazine	I	L	3
Hydrazine	I	S	2B
Hydrogen peroxide ^b [36, 1985]	ND	L	3
Hydroquinone ^d [15, 1977]	ND	I	3
4-Hydroxyazobenzene ^d [8, 1975]	ND	I	3
8-Hydroxyquinoline ^d [13, 1977]	ND	I	3
Hydroxysenkirkine ^d [10, 1976]	ND	I	3
Indeno[1,2,3- <i>cd</i>]pyrene ^b [32, 1983]	ND	S	2B
IQ (2-Amino-3-methylimidazo[4,5- <i>f</i>]quinoline) ^b [40, 1986]	ND	S	2B
Iron and steel founding	S		1
Iron-dextran complex	I	S	2B
Iron-dextrin complex ^d [2, 1973]	ND	L	3
Iron sorbitol-citric acid complex ^d [2, 1973]	ND	I	3

Table 1. (contd)

Agent	Degree of evidence for carcinogenicity ^a		Overall evaluation ^a
	Human	Animal	
Isatidine ^d [10, 1976]	ND	L	3
Isonicotinic acid hydrazide (Isoniazid)	I	L	3
Isophosphamide ^b [26, 1981]	ND	L	3
Isopropyl alcohol manufacture (strong-acid process)	S		1
Isopropyl alcohol	I	I	3
Isopropyl oils	I	I	3
Isosafrole ^d [10, 1976]	ND	L	3
Jacobine ^d [10, 1976]	ND	I	3
Kaempferol ^b [31, 1983]	ND	I	3
Lasiocarpine ^b [10, 1976]	ND	S	2B
Lauroyl peroxide ^b [36, 1985]	ND	I	3
Lead and lead compounds			
Inorganic	I	S	2B
Organolead	I	I	3
Leather industries			
Boot and shoe manufacture and repair	S		1
Leather goods manufacture	I		3
Leather tanning and processing	I		3
Light Green SF ^d [16, 1978]	ND	L	3
Luteoskyrin ^d [10, 1976]	ND	L	3
Magenta	I	I	3
Manufacture of magenta	S		1
Malathion ^{b,c} [30, 1983]	ND	I	3
Maleic hydrazide ^d [4, 1974]	ND	I	3
Malonaldehyde ^b [36, 1985]	ND	I	3
Maneb ^d [12, 1976]	ND	I	3
Mannomustine ^d [9, 1975]	ND	L	3
MeA- α -C (2-Amino-3-methyl-9H-pyrido[2,3-b]indole) ^b [40, 1986]	ND	S	2B
Medphalan ^d [9, 1975]	ND	I	3
MeIQ (2-Amino-3,4-dimethylimidazo[4,5-f]quinoline) ^b [40, 1986]	ND	I	3
MeIQx (2-Amino-3,8-dimethylimidazo[4,5-f]quinoxaline) ^b [40, 1986]	ND	I	3
Melamine ^b [39, 1986]	ND	I	3
Melphalan	S	S	1
6-Mercaptopurine	I	I	3
Merphalan ^b [9, 1975]	ND	S	2B
Methotrexate	I	I	3

Table 1. (contd)

Agent	Degree of evidence for carcinogenicity ^a		Overall evaluation ^a
	Human	Animal	
Methoxychlor ^{b,c} [20, 1979]	ND	I	3
5-Methoxypsoralen ^e	I	S	2A
8-Methoxypsoralen (Methoxsalen) plus ultraviolet radiation	S	S	1
Methyl acrylate ^b [39, 1986]	ND	I	3
2-Methylaziridine ^b [9, 1975]	ND	S	2B
Methylazoxymethanol and its acetate ^b [10, 1976]	ND	S	2B
Methyl bromide	I	L	3
Methyl carbamate ^d [12, 1976]	ND	I	3
Methyl chloride	I	I	3
1-Methylchrysene ^b [32, 1983]	ND	I	3
2-Methylchrysene ^b [32, 1983]	ND	L	3
3-Methylchrysene ^b [32, 1983]	ND	L	3
4-Methylchrysene ^b [32, 1983]	ND	L	3
5-Methylchrysene ^b [32, 1983]	ND	S	2B
6-Methylchrysene ^b [32, 1983]	ND	L	3
<i>N</i> -Methyl- <i>N</i> ,4-dinitrosoaniline ^d [1, 1972]	ND	L	3
4,4'-Methylene bis(2-chloroaniline) (MOCA) ^e	I	S	2A
4,4'-Methylenebis(<i>N,N</i> -dimethyl)benzenamine ^b [27, 1982]	ND	L	3
4,4'-Methylene bis(2-methylaniline)	I	S	2B
4,4'-Methylenedianiline ^b [39, 1986]	ND	S	2B
4,4'-Methylenediphenyl diisocyanate ^d [19, 1979]	ND	ND	3
2-Methylfluoranthene ^b [32, 1983]	ND	L	3
3-Methylfluoranthene ^b [32, 1983]	ND	I	3
Methyl iodide ^b [41, 1986]	ND	L	3
Methyl methacrylate ^d [19, 1979]	ND	I	3
Methyl methanesulphonate ^b [7, 1974]	ND	S	2B
2-Methyl-1-nitroanthraquinone (uncertain purity) ^b [27, 1982]	ND	S	2B
<i>N</i> -Methyl- <i>N'</i> -nitro- <i>N</i> -nitrosoguanidine (MNNG) ^e	I	S	2A
<i>N</i> -Methyl- <i>N</i> -nitrosourea ^{b,e} [17, 1978]	ND	S	2A
<i>N</i> -Methyl- <i>N</i> -nitrosourethane ^b [4, 1974]	ND	S	2B
Methyl parathion ^c	ND	ESL	3
1-Methylphenanthrene ^b [32, 1983]	ND	I	3
Methyl red ^d [8, 1975]	ND	I	3
Methyl selenac ^d [12, 1976]	ND	I	3
Methylthiouracil ^b [7, 1974]	ND	S	2B
Metronidazole	I	S	2B
Mineral oils			
Untreated and mildly-treated oils	S	S	1
Highly-refined oils	I	I	3
Mirex ^b [20, 1979]	ND	S	2B

Table 1. (contd)

Agent	Degree of evidence for carcinogenicity ^a		Overall evaluation ^a
	Human	Animal	
Mitomycin C ^b [10, 1976]	ND	S	2B
Modacrylic fibres ^d [19, 1979]	ND	ND	3
Monocrotaline ^b [10, 1976]	ND	S	2B
Monuron ^d [12, 1976]	ND	L	3
MOPP ¹ and other combined chemotherapy including alkylating agents	S	I	1
5-(Morpholinomethyl)-3-[(5-nitrofurfurylidene)amino]-2-oxazolidinone ^b [7, 1974]	ND	S	2B
Mustard gas (Sulphur mustard)	S	L	1
Nafenopin ^b [24, 1980]	ND	S	2B
1,5-Naphthalenediamine ^b [27, 1982]	ND	L	3
1,5-Naphthalene diisocyanate ^d [19, 1979]	ND	ND	3
1-Naphthylamine	I	I	3
2-Naphthylamine	S	S	1
1-Naphthylthiourea (ANTU)	I	I	3
Nickel and nickel compounds	S	S	1*
Niridazole ^b [13, 1977]	ND	S	2B
Nithiazide ^b [31, 1983]	ND	L	3
5-Nitroacenaphthene ^b [16, 1978]	ND	S	2B
5-Nitro-ortho-anisidine ^b [27, 1982]	ND	L	3
9-Nitroanthracene ^b [33, 1984]	ND	ND	3
6-Nitrobenzo[<i>a</i>]pyrene ^b [33, 1984]	ND	I	3
4-Nitrobiphenyl ^d [4, 1974]	ND	I	3
6-Nitrochrysene ^b [33, 1984]	ND	I	3
Nitrofen (technical-grade) ^b [30, 1983]	ND	S	2B
3-Nitrofluoranthene ^b [33, 1984]	ND	I	3
5-Nitro-2-furaldehyde semicarbazone ^d [7, 1974]	ND	I	3
1-[(5-Nitrofurfurylidene)amino]-2-imidazolidinone ^b [7, 1974]	ND	S	2B
<i>N</i> -[4-(5-Nitro-2-furyl)-2-thiazolyl]acetamide ^b [7, 1974]	ND	S	2B
Nitrogen mustard	L	S	2A
Nitrogen mustard <i>N</i> -oxide ^b [9, 1975]	ND	S	2B
2-Nitropropane ^b [29, 1982]	ND	S	2B
1-Nitropyrene ^b [33, 1984]	ND	L	3
<i>N</i> '-Nitrosoanabasine ^b [37, 1985]	ND	L	3
<i>N</i> '-Nitrosoanatabine ^b [37, 1985]	ND	I	3
<i>N</i> -Nitrosodi- <i>n</i> -butylamine ^b [17, 1978]	ND	S	2B
<i>N</i> -Nitrosodiethanolamine ^b [17, 1978]	ND	S	2B
<i>N</i> -Nitrosodiethylamine ^{b,e} [17, 1978]	ND	S	2A
<i>N</i> -Nitrosodimethylamine ^{b,e} [17, 1978]	ND	S	2A
<i>N</i> -Nitrosodiphenylamine ^b [27, 1982]	ND	L	3

¹Combined therapy with nitrogen mustard, vincristine, procarbazine and prednisone

*This evaluation applies to the group of chemicals as a whole and not necessarily to all individual chemicals within the group (see also Methods, p. 38).

Table 1. (contd)

Agent	Degree of evidence for carcinogenicity ^a		Overall evaluation ^a
	Human	Animal	
<i>para</i> -Nitrosodiphenylamine ^b [27, 1982]	ND	I	3
<i>N</i> -Nitrosodi- <i>n</i> -propylamine ^b [17, 1978]	ND	S	2B
<i>N</i> -Nitrosofolic acid ^d [17, 1978]	ND	I	3
<i>N</i> -Nitrosoguvacine ^b [37, 1985]	ND	ND	3
<i>N</i> -Nitrosoguvacoline ^b [37, 1985]	ND	I	3
<i>N</i> -Nitrosohydroxyproline ^d [17, 1978]	ND	I	3
3-(<i>N</i> -Nitrosomethylamino)propionaldehyde ^b [37, 1985]	ND	ND	3
3-(<i>N</i> -Nitrosomethylamino)propionitrile ^b [37, 1985]	ND	S	2B
4-(<i>N</i> -Nitrosomethylamino)-4-(3-pyridyl)-1-butanal (NNA) ^b [37, 1985]	ND	I	3
4-(<i>N</i> -Nitrosomethylamino)-1-(3-pyridyl)-1-butanone (NNK) ^b [37, 1985]	ND	S	2B
<i>N</i> -Nitrosomethylethylamine ^b [17, 1978]	ND	S	2B
<i>N</i> -Nitrosomethylvinylamine ^b [17, 1978]	ND	S	2B
<i>N</i> -Nitrosomorpholine ^b [17, 1978]	ND	S	2B
<i>N</i> -Nitrososarcosine ^b [37, 1985]	ND	S	2B
<i>N</i> -Nitrosopiperidine ^b [17, 1978]	ND	S	2B
<i>N</i> -Nitrosoproline ^d [17, 1978]	ND	I	3
<i>N</i> -Nitrosopyrrolidine ^b [17, 1978]	ND	S	2B
<i>N</i> -Nitrososarcosine ^b [17, 1978]	ND	S	2B
Nitrovin ^b [31, 1983]	ND	I	3
Nylon 6 ^d [19, 1979]	ND	I	3
Ochratoxin A	I	L	3
Oestradiol mustard ^d [9, 1975]	ND	L	3
Oestrogens, progestins and combinations			
Oestrogens			
Nonsteroidal oestrogens	S		1*
Diethylstilboestrol	S	S	1
Dienoestrol		L	
Hexoestrol		S	
Chlorotrianisene		I	
Steroidal oestrogens	S		1*
Oestrogen replacement therapy	S		1
Conjugated oestrogens		L	
Oestradiol-17 β and esters		S	
Oestriol		L	
Oestrone		S	
Ethinylestradiol		S	
Mestranol		S	

*This evaluation applies to the group of chemicals as a whole and not necessarily to all individual chemicals within the group (see also Methods, p. 38).

Table 1. (contd)

Agent	Degree of evidence for carcinogenicity ^a		Overall evaluation ^a
	Human	Animal	
Progestins	I		2B
Medroxyprogesterone acetate	I	S	2B
Chlormadinone acetate		L	
Dimethisterone		I	
Ethinodiol diacetate		L	
17 α -Hydroxyprogesterone caproate		I	
Lynoeestrenol		I	
Megestrol acetate		L	
Norethisterone		S	
Norethynodrel		L	
Norgestrel		I	
Progesterone		S	
Oestrogen-progestin combinations			
Sequential oral contraceptives	S		1
Dimethisterone and oestrogens		I	
Combined oral contraceptives	S		1 ¹
Chlormadinone acetate and oestrogens		L	
Ethinodiol diacetate and oestrogens		L	
Lynoeestrenol and oestrogens		I	
Megestrol acetate and oestrogens		L	
Norethisterone and oestrogens		L	
Norethynodrel and oestrogens		S	
Norgestrel and oestrogens		I	
Progesterone and oestrogens		L	
Investigational oral contraceptives		L	
Oestrogen-progestin replacement therapy	I		3
Oil Orange SS ^b [8, 1975]	ND	S	2B
Orange I ^d [8, 1975]	ND	I	3
Orange G ^d [8, 1975]	ND	I	3
Oxazepam ^d [13, 1977]	ND	L	3
Oxyphenbutazone ^d [13, 1977]	ND	ND	3
Panfuran S (containing dihydroxymethylfuratrizine) ^b [24, 1980]	ND	S	2B
Parasorbic acid ^d [10, 1976]	ND	L	3
Parathion ^b [30, 1983]	ND	I	3
Patulin ^b [40, 1986]	ND	I	3
Penicillic acid ^d [10, 1976]	ND	L	3
Pentachloroethane ^b [41, 1986]	ND	L	3
Perylene ^b [32, 1983]	ND	I	3
Petasitenine ^b [31, 1983]	ND	L	3
Phenacetin	L	S	2A
Analgesic mixtures containing phenacetin	S	L	1
Phenanthrene ^b [32, 1983]	ND	I	3

¹There is also conclusive evidence that these agents have a protective effect against cancers of the ovary and endometrium (see summary, p. 297).

Table 1. (contd)

Agent	Degree of evidence for carcinogenicity ^a		Overall evaluation ^a
	Human	Animal	
Phenazopyridine hydrochloride	I	S	2B
Phenelzine sulphate	I	L	3
Phenicarbazide ^d [12, 1976]	ND	L	3
Phenobarbital	I	S	2B
Phenoxybenzamine hydrochloride ^b [24, 1980]	ND	S	2B
Phenylbutazone	I	ND	3
<i>meta</i> -Phenylenediamine ^d [16, 1978]	ND	I	3
<i>para</i> -Phenylenediamine ^d [16, 1978]	ND	I	3
<i>N</i> -Phenyl-2-naphthylamine	I	L	3
<i>ortho</i> -Phenylphenol ^b [30, 1983]	ND	I	3
Phenytoin	L	L	2B
Piperonyl butoxide ^{b,c} [30, 1983]	ND	I	3
Polyacrylic acid ^d [19, 1979]	ND	ND	3
Polybrominated biphenyls	I	S	2B
Polychlorinated biphenyls	L	S	2A
Polychloroprene ^d [19, 1979]	ND	ND	3
Polyethylene ^d [19, 1979]	ND	I	3
Polymethylene polyphenyl isocyanate ^d [19, 1979]	ND	ND	3
Polymethyl methacrylate ^d [19, 1979]	ND	I	3
Polypropylene ^d [19, 1979]	ND	I	3
Polystyrene ^d [19, 1979]	ND	I	3
Polytetrafluoroethylene ^d [19, 1979]	ND	I	3
Polyurethane foams ^d [19, 1979]	ND	I	3
Polyvinyl acetate ^d [19, 1979]	ND	I	3
Polyvinyl alcohol ^d [19, 1979]	ND	I	3
Polyvinyl chloride ^d [19, 1979]	I	I	3
Polyvinyl pyrrolidone ^d [19, 1979]	ND	L	3
Ponceau MX ^b [8, 1975]	ND	S	2B
Ponceau 3R ^b [8, 1975]	ND	S	2B
Ponceau SX ^d [8, 1975]	ND	I	3
Potassium bis(2-hydroxyethyl)dithiocarbamate ^d [12, 1976]	ND	L	3
Potassium bromate ^b [40, 1986]	ND	S	2B
Prednisone	I	I	3
Procarbazine hydrochloride ^e	I	S	2A
Proflavine salts ^b [24, 1980]	ND	I	3
Pronetalol hydrochloride ^d [13, 1977]	ND	L	3
1,3-Propane sultone ^b [4, 1974]	ND	S	2B
Propham ^d [12, 1976]	ND	I	3
β -Propiolactone ^b [4, 1974]	ND	S	2B
<i>n</i> -Propyl carbamate ^d [12, 1976]	ND	L	3

Table 1. (contd)

Agent	Degree of evidence for carcinogenicity ^a		Overall evaluation ^a
	Human	Animal	
Propylene ^d [19, 1979]	ND	ND	3
Propylene oxide ^e	I	S	2A
Propylthiouracil	I	S	2B
Ptaquiloside ^b [40, 1986]	ND	L	3
Pyrene ^{b,c} [32, 1983]	ND	I	3
Pyrido[3,4- <i>c</i>]psoralen ^b [40, 1986]	ND	I	3
7-Methylpyrido[3,4- <i>c</i>]psoralen ^b [40, 1986]	ND	I	3
Pyrimethamine ^d [13, 1977]	ND	L	3
Quercetin ^b [31, 1983]	ND	L	3
<i>para</i> -Quinone ^d [15, 1977]	ND	I	3
Quintozene (Pentachloronitrobenzene) ^d [5, 1974]	ND	L	3
Reserpine	I	L	3
Resorcinol ^d [15, 1977]	ND	I	3
Retrorsine ^d [10, 1976]	ND	L	3
Rhodamine B ^d [16, 1978]	ND	L	3
Rhodamine 6G ^d [16, 1978]	ND	L	3
Riddelliine ^d [10, 1976]	ND	I	3
Rifampicin ^b [24, 1980]	ND	L	3
Rubber industry	S	I	1
Rugulosin ^b [40, 1986]	ND	I	3
Saccharated iron oxide ^d [2, 1973]	ND	L	3
Saccharin	I	S	2B
Safrole ^b [10, 1976]	ND	S	2B
Scarlet Red ^d [8, 1975]	ND	I	3
Selenium and selenium compounds ^d [9, 1975]	I	I	3
Semicarbazide hydrochloride ^d [12, 1976]	ND	L	3
Seneciophylline ^d [10, 1976]	ND	ND	3
Senkirkine ^b [31, 1983]	ND	L	3
Sepiolite ^b [42, 1987]	ND	I	3
Shale-oils	S	S	1
Shikimic acid ^b [40, 1986]	ND	I	3
Silica			
Crystalline silica	L	S	2A
Amorphous silica	I	I	3
Sodium diethyldithiocarbamate ^d [12, 1976]	ND	I	3
Sodium <i>ortho</i> -phenylphenate ^c	ND	S	2B
Soots	S	I	1
Spironolactone	I	L	3

Table 1. (contd)

Agent	Degree of evidence for carcinogenicity ^a		Overall evaluation ^a
	Human	Animal	
Sterigmatocystin ^b [10, 1976]	ND	S	2B
Streptozotocin ^b [17, 1978]	ND	S	2B
Styrene ^e	I	L	2B
Styrene-acrylonitrile copolymers ^d [19, 1979]	ND	ND	3
Styrene-butadiene copolymers ^d [19, 1979]	ND	ND	3
Styrene oxide ^{b,e} [36, 1985]	ND	S	2A
Succinic anhydride ^d [15, 1977]	ND	L	3
Sudan I ^d [8, 1975]	ND	L	3
Sudan II ^d [8, 1975]	ND	L	3
Sudan III ^d [8, 1975]	ND	I	3
Sudan Brown RR ^d [8, 1975]	ND	I	3
Sudan Red 7B ^d [8, 1975]	ND	I	3
Sulfafurazole (Sulphisoxazole)	I	I	3
Sulfallate ^b [30, 1983]	ND	S	2B
Sulfamethoxazole	I	L	3
Sunset Yellow FCF ^d [8, 1975]	ND	I	3
Symphytine ^b [31, 1983]	ND	I	3
Talc			
Not containing asbestiform fibres	I	I	3
Containing asbestiform fibres	S	I	1
Tannic acid and tannins ^d [10, 1976]	ND	L	3
Terpene polychlorinates (Strobane [®]) ^d [5, 1974]	ND	L	3
2,2',5,5'-Tetrachlorobenzidine ^b [27, 1982]	ND	I	3
2,3,7,8-Tetrachlorodibenzo- <i>para</i> -dioxin (TCDD)	I	S	2B
1,1,1,2-Tetrachloroethane ^b [41, 1986]	ND	L	3
1,1,2,2-Tetrachloroethane	I	L	3
Tetrachloroethylene	I	S	2B
Tetrachlorvinphos ^b [30, 1983]	ND	L	3
Tetrafluoroethylene ^d [19, 1979]	ND	ND	3
Thioacetamide ^b [7, 1974]	ND	S	2B
4,4'-Thiodianiline ^b [27, 1982]	ND	S	2B
Thiouracil ^d [7, 1974]	ND	L	3
Thiourea ^b [7, 1974]	ND	S	2B
Thiram ^d [12, 1976]	ND	I	3
Tobacco products, smokeless	S	I	1
Tobacco smoke	S	S	1
Toluene diisocyanates ^b [39, 1986]	ND	S	2B
<i>ortho</i> -Toluidine	I	S	2B
Toxaphene (Polychlorinated camphenes) ^b [20, 1979]	ND	S	2B

Table 1. (contd)

Agent	Degree of evidence for carcinogenicity ^a		Overall evaluation ^a
	Human	Animal	
Treosulphan	S	ND	1
Trichlorfon ^b [30, 1983]	ND	I	3
1,1,1-Trichloroethane ^b [20, 1979]	ND	I	3
1,1,2-Trichloroethane ^b [20, 1979]	ND	L	3
Trichloroethylene	I	L	3
Trichlorotriethylamine hydrochloride ^d [9, 1975]	ND	I	3
T ₂ -Trichothecene ^b [31, 1983]	ND	I	3
Triethylene glycol diglycidyl ether ^d [11, 1976]	ND	L	3
2,4,5-Trimethylaniline ^b [27, 1982]	ND	L	3
2,4,6-Trimethylaniline ^b [27, 1982]	ND	I	3
4,5',8-Trimethylpsoralen	I	I	3
Triphenylene ^b [32, 1983]	ND	I	3
Tris(aziridinyl)- <i>para</i> -benzoquinone (Triaziquone)	I	L	3
Tris(1-aziridinyl)phosphine oxide ^d [9, 1975]	ND	I	3
Tris(1-aziridinyl)phosphine sulphide (Thiotepa) ^e	I	S	2A
2,4,6-Tris(1-aziridinyl)- <i>s</i> -triazine ^d [9, 1975]	ND	L	3
1,2,3-Tris(chloromethoxy)propane ^d [15, 1977]	ND	L	3
Tris(2,3-dibromopropyl) phosphate ^e	I	S	2A
Tris(2-methyl-1-aziridinyl)phosphine oxide ^d [9, 1975]	ND	I	3
Trp-P-1 (3-Amino-1,4-dimethyl-5 <i>H</i> -pyrido[4,3- <i>b</i>]indole) ^b [31, 1983]	ND	S	2B
Trp-P-2 (3-Amino-1-methyl-5 <i>H</i> -pyrido[4,3- <i>b</i>]indole) ^b [31, 1983]	ND	S	2B
Trypan blue ^b [8, 1975]	ND	S	2B
Uracil mustard	I	S	2B
Urethane ^b [7, 1974]	ND	S	2B
Vinblastine sulphate	I	I	3
Vincristine sulphate	I	I	3
Vinyl acetate ^b [39, 1986]	ND	I	3
Vinyl bromide ^{b,e} [39, 1986]	ND	S	2A
Vinyl chloride	S	S	1
Vinyl chloride-vinyl acetate copolymers ^d [19, 1979]	ND	I	3
4-Vinylcyclohexene ^b [39, 1986]	ND	L	3
Vinyl fluoride ^b [39, 1986]	ND	ND	3
Vinylidene chloride	I	L	3
Vinylidene chloride-vinyl chloride copolymers ^d [19, 1979]	ND	ND	3
Vinylidene fluoride ^b [39, 1986]	ND	I	3
<i>N</i> -Vinyl-2-pyrrolidone ^d [19, 1979]	ND	ND	3

Table 1. (contd)

Agent	Degree of evidence for carcinogenicity ^a		Overall evaluation ^a
	Human	Animal	
Wollastonite	I	L	3
Wood industries			
Carpentry and joinery	L		2B
Furniture and cabinet making	S	I	1
Lumber and sawmill industries (including logging)	I		3
Pulp and paper manufacture	I		3
2,4-Xylidine ^d [16, 1978]	ND	I	3
2,5-Xylidine ^d [16, 1978]	ND	I	3
Yellow AB ^d [8, 1975]	ND	I	3
Yellow OB ^d [8, 1975]	ND	L	3
Zearalenone ^b [31, 1983]	ND	L	3
Zectran ^d [12, 1976]	ND	I	3
Zineb ^d [12, 1976]	ND	I	3
Ziram ^d [12, 1976]	ND	I	3

mutagenicity in bacteria. Pentachlorophenol did not induce strand breaks in DNA from bacteriophage. It gave negative results in a host-mediated assay with mice using bacteria as indicators⁷.

2,4,6-Trichlorophenol induced somatic mutations in the spot test in mice *in vivo*. It induced mutation but not gene conversion or crossing-over in yeast and was not mutagenic to bacteria⁷.

Neither 2,3,4,6-tetrachlorophenol nor 2,4,5-trichlorophenol was mutagenic to bacteria⁷.

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CHLOROPHENOXY HERBICIDES (Group 2B)

A. Evidence for carcinogenicity to humans (*limited*)

In a Danish cohort study of chemical workers exposed to chlorophenoxy herbicides [particularly (4-chloro-2-methylphenoxy)acetic acid (MCPA), 2-(4-chloro-2-methylphenoxy)propanoic acid (mecoprop), 2,4-dichlorophenoxyacetic acid (2,4-D) and 2-(2,4-dichlorophenoxy)propanoic acid (dichlorprop)], as well as other chemicals, no overall increase in cancer incidence rate was observed, but there were significantly increased risks for soft-tissue sarcoma and lung cancer in some subcohorts, which were not necessarily those with the highest exposures to chlorophenoxy herbicide preparations¹.

A recently reported cohort of 5784 male employees in a UK company that manufactured, formulated and sprayed MCPA and other pesticides, but only small amounts of 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), had no general excess mortality from cancer. Three potentially exposed workers died from nasal carcinoma, however. One death due to soft-tissue sarcoma approximately equalled the expected rate. No excess of lymphoma was seen².

A Finnish cohort study of brush control workers with short follow-up time showed no increased cancer risk. A small Swedish cohort study of railroad workers who sprayed herbicides showed an increased risk of cancers at all sites combined for those exposed to chlorophenoxy herbicide preparations and other herbicides. An excess incidence of all

cancers was also reported from a very small cohort of Swedish forestry foremen exposed to chlorophenoxy herbicide preparations and other herbicides. A study of long-term pesticide applicators in the German Democratic Republic, heavily exposed to a number of chemicals, including 2,4-D and MCPA, demonstrated an increased risk of bronchial carcinoma¹.

Two population-based case-control studies conducted in northern and southern Sweden, respectively, showed a statistically significant association between exposure to chlorophenoxy herbicides, especially in forestry and agriculture, and the occurrence of soft-tissue sarcomas. An increased risk of soft-tissue sarcoma was described among highly exposed Italian rice weeders in a population-based case-control study. However, a case-control study from New Zealand did not demonstrate any increased risk of soft-tissue sarcoma in people exposed to chlorophenoxy herbicides¹. Nor did a recently reported population-based case-control study of soft-tissue sarcoma and lymphoma in Kansas, USA, find any association between soft-tissue sarcoma and exposure to 2,4-D³.

A statistically significant association between malignant lymphoma (Hodgkin's and non-Hodgkin's) and exposure to chlorophenoxy herbicides was found in a Swedish case-control study¹. The population-based case-control study of soft-tissue sarcoma and Hodgkin's and non-Hodgkin's lymphoma in Kansas showed that use of 2,4-D was associated with non-Hodgkin's lymphoma, especially among farmers who had been exposed for more than 20 days per year, among whom there was an approximately six-fold excess, and among those who had mixed or applied the herbicides themselves. Hodgkin's lymphoma was not, however, found to be associated with herbicide exposure³. No significant or consistent association was seen in a case-control study of these tumours from New Zealand, and in a Danish cohort of chemical workers exposed to chlorophenoxy herbicides there was also no significantly increased risk of malignant lymphoma^{1,4}. Farmers and forestry workers in Washington State, USA, with exposure to phenoxy herbicides had a significantly increased risk of non-Hodgkin's lymphoma. People of Scandinavian descent in the area had an increased risk of soft-tissue sarcoma in connection with phenoxy herbicide exposure, but no increased risk of non-Hodgkin's lymphoma⁵.

Three Swedish case-control studies of colon, liver, and nasal and nasopharyngeal cancer, which used the same study design and methods as in the studies on soft-tissue sarcoma and malignant lymphoma, did not demonstrate significantly increased risks, although a risk ratio of 2.1 was reached for nasal and nasopharyngeal cancer¹.

A record-linkage study using census data on occupation and cancer registry information in Sweden did not reveal any excess of soft-tissue sarcoma among agricultural and forestry workers^{6,7}. However, on the basis of occupational titles, the elevated risks seen in Swedish case-control studies of soft-tissue sarcoma and lymphoma were reduced to 1.4 or less⁸. A UK study based on data from cancer registration showed a slightly but significantly increased risk of soft-tissue sarcoma among farmers, farm managers and market gardeners, but not in other subgroups in forestry and farming⁹. No association with soft-tissue sarcoma has been found with military service in Viet Nam, despite potential exposure to phenoxy herbicides^{1,10}, although there is a case report in this respect¹.

B. Evidence for carcinogenicity to animals (*inadequate* for 2,4-D and 2,4,5-T)

2,4-D and several of its esters were tested in rats and mice by oral administration and in mice by subcutaneous administration. All of these studies had limitations, due either to inadequate reporting or to the small number of animals used. Therefore, although increased incidences of tumours were observed in one study in which rats received 2,4-D orally and in another in which mice received its isooctyl ester by subcutaneous injection, no evaluation of the carcinogenicity of this compound could be made¹¹.

2,4,5-T was tested in mice by oral and subcutaneous administration. All of the studies had limitations due to the small numbers of animals used. Therefore, although an increased incidence of tumours at various sites was observed in one study in which 2,4,5-T (containing less than 0.05 mg/kg chlorinated dibenzodioxins) was given orally, no evaluation of the carcinogenicity of this compound could be made on the basis of the available data¹². In rats fed diets containing three different concentrations of 2,4,5-T, the incidences of all tumour types were comparable to those in the control groups, with the exception that the incidence of interfollicular C-cell adenomas of the thyroid was increased significantly in female rats receiving the lowest dose. This increase was not considered to be related to treatment since it was not dose-related and the female control group had an unusually low incidence of thyroid adenomas¹³.

A study of the incidence of small-intestinal adenocarcinoma in groups of sheep from different farms showed an association with use of phenoxy herbicides, as elicited by farmers' responses to a questionnaire. However, other herbicides were in use, and there was no documentation of exposures¹⁴.

No adequate data were available on the carcinogenicity of MCPA¹⁵.

C. Other relevant data

In single studies, lymphocytes of persons occupationally exposed to chlorophenoxy herbicides, including 2,4-D, did not show increased frequencies of sister chromatid exchanges or chromosomal aberrations. Other studies could not be assessed since workers were also exposed to other formulations. A single study of herbicide and pesticide sprayers exposed to 2,4,5-T, in which a small increase in the incidence of sister chromatid exchanges was reported, could not be assessed since workers were also exposed to other formulations. Persons occupationally exposed to MCPA did not have increased frequencies of sister chromatid exchanges (one study) or chromosomal aberrations in their lymphocytes¹⁶.

2,4-D did not induce dominant lethal mutations, micronuclei or sister chromatid exchanges in rodents treated *in vivo*. Pure 2,4-D did not induce chromosomal aberrations in human lymphocytes *in vitro*, whereas a commercial formulation did. 2,4-D induced sister chromatid exchanges and unscheduled DNA synthesis in human cells *in vitro*. It did not induce sister chromatid exchanges but did induce mutation and inhibited intercellular communication in Chinese hamster cells *in vitro*. 2,4-D induced somatic mutation in *Drosophila*, but conflicting results were obtained for induction of sex-linked recessive lethal mutations; it did not induce aneuploidy. 2,4-D caused chromosomal aberrations and was

mutagenic in plants. It induced mutation, gene conversion and mitotic recombination in yeast. It was not mutagenic to bacteria or bacteriophage. The *n*-butyl and *iso*-octyl esters of 2,4-D were also not mutagenic to bacteria¹⁶.

2,4,5-T induced chromosomal aberrations in bone-marrow cells of Mongolian gerbils, but not in spermatogonia of Chinese hamsters, and aneuploidy in oocytes of rats treated *in vivo*. It did not induce micronuclei in mice or dominant lethal mutations in mice or rats *in vivo*. 2,4,5-T inhibited intercellular communication in Chinese hamster V79 cells *in vitro*. There was weak evidence for the induction of sex-linked recessive lethal mutations in *Drosophila*; it did not induce aneuploidy or somatic mutation. It induced chromosomal aberrations in plants. It was mutagenic to yeast, but neither 2,4,5-T nor the *n*-butyl-, *iso*-butyl or *iso*-octyl ester of 2,4,5-T was mutagenic to bacteria¹⁶.

MCPA did not induce structural chromosomal aberrations or micronuclei in mice treated *in vivo*; weakly positive results were obtained for sister chromatid exchanges in cells of Chinese hamsters treated *in vivo* and *in vitro*. It was weakly active in inducing sex-linked recessive lethal mutations but did not induce aneuploidy in *Drosophila*. MCPA and its methyl ester were mutagenic to yeast but not to bacteria¹⁶.

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CHLOROPRENE (Group 3)

A. Evidence for carcinogenicity to humans (*inadequate*)

In one study, an excess of lung and skin cancers was related to occupational exposure to chloroprene. In another investigation, no excess of lung or other type of cancer was reported among chloroprene workers. There is one case report of an angiosarcoma of the liver in a worker exposed to chloroprene¹.

B. Evidence for carcinogenicity to animals (*inadequate*)

A number of experimental studies were considered to be inadequate for an evaluation of the carcinogenicity of chloroprene¹. In a further study² in which chloroprene was given orally to pregnant rats and their offspring were treated for life by stomach tube, the total incidence of tumours was similar in treated and untreated animals.

C. Other relevant data

An increased incidence of chromosomal aberrations was found in the lymphocytes of workers exposed to chloroprene³.

Chloroprene induced dominant lethal mutations in rats and chromosomal aberrations in bone-marrow cells of mice treated *in vivo*. It induced transformation in one hamster cell line but did not induce mutation in Chinese hamster cells. It induced sex-linked recessive lethal mutations in *Drosophila* and was mutagenic to bacteria³.

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