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"Toxicology of Families of Chemicals Used as Herbicides in Forestry"

USDA/EPA SYMPOSIUM

THE USE OF HERBICIDES IN FORESTRY

February 21-22, 1978

Morris Cranmer, Ph.D.

Arlington VA

[redacted]

TOXICOLOGY OF FAMILIES OF CHEMICALS USED AS HERBICIDES IN FORESTRY

The production and use of herbicides has increased markedly during the last two decades. Because plants differ markedly from animals in physiology, biochemistry and hormonal activity, herbicides usually present little hazard of chemical toxicity to man and other vertebrates. Indeed, some compounds have very low toxicity in mammals, but even among herbicides as a family of chemicals, structural class are quite variable and there are representative highly toxic chemicals, some of which have caused fatal posionings and others which represent at least theoretical risks of cancer, birth defects and genetic and reproductive defects.

The compounds 2,4-dichlorophenoxyacetic acid (2,4-D) and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) as their salts and esters are the most prominent herbicides used in forest management. 2,3,7,8-tetrachlorodibenzo dioxin, a trace contaminent of 2,4,5-T, exhibits unusual toxicity and has created great controversy over theoretical birth defect risks. A comparison of teratogenic risks from 2,4,5-T and dioxin are presented as part of a risk estimation model.

The laboratory toxicity of a compound is relatively useless unless presented in the proper context of interaction with the species at potential risk. Estimates of route, rate and duration of exposure and other environmental effects impacting on the distribution of sensitivities in a population must all be considered before estimates of risks of toxicity become meaningful.

Toxicity of herbicides must be considered in the totality of the forest environment. In every forest there are a large number of other organisms including man, wildlife, insects, micro-organisms, shrubs, and annual and perennial plants living in intimate ecological relationships with trees. Each is an integral part of the natural forests, and any substantial natural or man induced change in the population of one organism is likely to have ecologically significant effects on one or more of the others. These changes can be reflected as alterations in the toxicological response.

The families of chemicals used in the various plant pest management tasks include, but are not limited to, chlorophenoxy compounds (2,4-D, 2,4,5-T), dinitrophenols (DNOC), bipyridyls (paraquat and diquat), carbamates (propham), substituted ureas (monuron and diuron), triazines (simazine), amides (propanil). The toxic effects produced by these compounds in experimental animals include cancer, birth defects, mutagenesis, interactions with organophosphate pesticides, uncoupling of oxidative phosphorylation, CNS, liver, kidney and lung pathology. The risk to man from the use of herbicides is mainly to the applicator and through accidental poisonings.

MORRIS F. CRANMER, Ph.D.

INTRODUCTION

What is the role of herbicides in fulfilling the need and improving the quality of our forest resources? The "products" provided by a forest depend upon the objectives of the managers and users of the land. In this sense, forests do not provide us with only one well-defined product, nor is there any single set of plants or any one organism that is undesirable in all forest situations. Also, the future of a forest with even a brief rotation from seedlings to mature or harvestable trees cannot be decided the year it is planted, if only because of shifting and unpredictable future values of its potential products.

Thus, the existence of many different objectives for different forest lands, or for a single forest over time, creates a situation in which it is important that managers avoid irreversible control decisions that might have unwanted toxicological effects in the future. This philosophy also suggests that control should not be aimed solely at killing pest plants and should be undertaken only when the activity of a pest plant can be clearly shown to interfere significantly with management objectives. This also suggests the need for careful cost/benefit analyses that ensure that those objectives will be served without undue cost or loss of other important benefits.

One out of every three acres in the United States is classified as forest land. The 750 million acres in forests would cover the United States east of the Missippi River with enough left over to carpet Texas and part of California. In addition, forest trees are important features of many urban and suburban areas

that are not classified as forest land. There are about 585 separate species of trees native to the United States, and, in addition, more than 90 foreign species have become naturalized here (Little, 1949). American forests are thus both of vast extent and great biological variety.

In every forest there are a large number of other organisms - animals (including insects), microorganisms, shrubs, and annual and perennial herbs - living in intimate ecological relationship with the trees. These relationships may be favorable, inimical, or essentially neutral to the survival and growth of the trees, depending on the specific forest situations. From the biological point of view, all of these organisms - trees, mammals, birds, insects, microbes, and secondary vegetation - fulfill characteristic ecological roles. Each is an integral part of the natural forests, and any substantial natural or man-induced change in the population of one organism is likely to have ecologically significant effects on one or more of the others.

About 165 of the native and introduced tree species are recognized as having major actual or potential importance to man, as sources of wood products, food, or medicine; as aesthetic features of the landscape; or as essential protective cover. As for the associated organisms, some may contribute directly to human welfare; game animals, flowering shrubs, birds, and bees are obvious examples.

Pests are organisms that diminish the value of resources in which man is interested. An organism can be classed as a forest plant pest only on the basis of a recognized set of forest management objectives and a clear understanding of the organism's

functions as an element in the particular ecosystem of which it happens to be a part. Trees may be "pests" if they obscure a cherished view, contribute unduly to fire or windstorm hazards to human habitation, or draw eccessive quantitites of moisture from a critical watershed or decrease potential yield.

This view of the forest pest problem differs in major degree, if not in kind, from the view of pests that is characteristic in crop agriculture and public health. In both those areas of concern, man's objectives are usually more single-minded than is the case in forestry. On public forest land, for example, the simultaneous existence of more than one valid objective for a single area is specifically recognized by the Multiple-Use Sustained Yield Act of 1960. On any forest site, the question of what management objectives are appropriate to the particular area becomes a central feature of any discussion of the forest pest situation.

Any discussion of the toxicological potential of a given use of a given herbicide must be constrained by the conditions of use. Forest land owned by private industry, which accounts for only 13.5 percent of the commercial forest land, is managed primarily for the profitable production of timber as a commodity for conversion into wood products. In national forests and other forests owned by the public, however, such commodity production is usually only one of a number of explicit forest management objectives, embraced within the broad concept of "multiple use". Here the relative priority of production of timber commodities and other forest uses such as providing sites for outdoor recreation or protecting watersheds is not clearly established on large portions

of the area involved. On the "other private" category of ownership (almost 60 percent of the forest land) we know that management objectives vary greatly among the 3 or 4 million individual owners, but there is little information that would permit us to identify ownership objectives on any one particular property.

This diversity of objectives make it virtually impossible to characterize any species categorically as a forest plant pest. Instead it forces us to consider forest plant pest problems within some explicit forest management framework, where the objectives of management are known, the significant ecological variables can be quantified, and management capabilities can be evaluated in relation to possible alternative pest control strategies.

FOREST AREA

From early in the century to early in the 1950's, forests appeared to increase modestly. That trend has now been reversed; total forest area in 1970 was about 1.7 percent less than it had been in 1962.

This relatively fixed total forest base, however, is under steadily increasing human pressure. Burgeoning public interest in recreation is resulting in steady enlargement of the forest area reserved for recreation and park purposes.

MAJOR FOREST LAND USES

The major uses of forest land include provision of habitat for wildlife, provision of an environment for diverse kinds of outdoor recreation, production of range forage for domestic livestock, protection of soil, protection and improvement of watersheds,

growing and harvesting of timber, and preservation of rare or unique natural ecological or scenic features. Preservation of unique features and provision of environment for outdoor recreation were the uses first recognized by federal policy, with passage of the Yellowstone Park Act (1872). Subsequently, recognition was given to timber production and watershed protection as the basis for reservation of national forests (1897). Since 1905, the importance of all the forest uses enumerated above has been recognized in a wide variety of federal and state legislation.

Forests have an unusual capability to accommodate use for several of the above purposes at the same time (e.g., soil and watershed protection, preservation of scenic features, and provision of wildlife habitat on a single forest area; or timber growing and certain types of recreation on the same area, at least during most of the timber growth cycle). This "multiple use" capability is recognized as the appropriate means for achieving management goals on much publicly owned land, and to some degree it is a feature of all forest management. Thus, it is essentially impossible to segregate forest areas by dominant type of use.

Wildlife Habitat

Virtually all forest land provides wildlife habitat, and many species, including the principal big game animals, are found primarily in forested areas. Use of forest land for hunting, fishing, and observation of wildlife has steadily increased. As in the case of soil and watershed protection, most organisms commonly regarded as forest pests appear to have only minor effects on wildlife habitat, because of the forest's ecological diversity.

timber growing approach biological senescence.

The forest products industry currently accounts for about 5 percent of the nation's gross national product (GNP) in the form of raw materials for housing, packaging materials, paper, and a multitude of other essential materials. To the extent that forest management techniques using herbicides increase timber volume, value, and growth, they contribute directly to the raw material supply on which this section of the national economy depends.

Outdoor Recreation

Recreational use of forest land includes a great number of quite dissimilar activities. These range from the group viewing the cliffs of the Yosemite Valley from the veranda of a luxury hotel to the mountaineering party in the Brooks Range, and from the motorized family complete with camper, trailbikes, and portable televisions, all installed in the forest campground with hot showers and electricity, to the solitary cross-country hiker.

The amount of forest land used for these varied purposes is even less well known that is the amount used for timber growing, in part because much recreational service is provided by forests that are also used for other purposes. Certain forms of outdoor recreation are either dominant or codominant uses in units of the national and state park systems, national recreation areas, and the wilderness system. Some 60 million acres of land has been formally assigned to these units. In addition, recreation is a dominant use on portions of the national forests outside wilderness areas and is a permitted use on most multiple-use areas of the forests.

The trend in recreational use of forests has been almost explosively upward throughout most of the past 40 years. Except for the period of World War II, attendance rates at national and state parks and national forests have at least doubled during each successive decade.

The very diversity of forest recreation activities makes it difficult to generalize of herbicides that are used. The situation in campgrounds, picnic areas, and other sites designed for visitor occupancy may be quite different from the situation in the recreational forest, which simply forms the backdrop for hiking, riding, climbing, or viewing. In the latter sort of area, where recreational use is widely dispersed, the main goal of forest protection is to maintain aesthetic quality. Levels of production managment impact which would be considered seriously damaging to a campground or heavily used lakeshore may, in this case, be entirely acceptable.

In campgrounds and other occupancy sites on recreation areas, problems are likely to be much more localized but more numerous. At the same time, the relatively high value per acre of such sites may justify quite intensive methods of control. Local elimination of plants poisonous to human beings may be required. Dead and dying trees, in addition to possible unsightliness, increase the hazard to users from both fire and winds - hazards that must be kept at a minimum. Due to the high value, high accessibility, and close surveillance that characterize such areas, intensive and discriminating methods of control will usually be feasible.

Forage Production

Forage for domestic livestock is among the by-products of the outputs from forest land. There are, of course, large areas of true grassland within the administrative jurisdiction of such agencies as the USFS. But in addition, several important forest types (e.g., most hardwood types, pine types in the South and West) produce grass and herb ground covers of substantial forage value. Management of these forest types to increase nutritious forage may involve use of selective herbicides and unless properly controlled, could create pesticide residue problems.

Suburban and Urban Forest Use

Forests located within urban and suburban areas represent conditions where control must be considered in its intensive form. The values are high and are often assignable on a tree-by-tree basis. Side effects of any control measures are likely to be more critical than elsewhere, and the methods of control may be severely limited because of the close proximity of the human population. The problems are often multiplied by the presence of large numbers of exotic species and by cultivation practices such as irrigation and soil manipulation.

Although the circumstances of urban and suburban forestry have, until now, been radically different from those surrounding more conventional forms of forest management, it is becoming increasingly evident that the differences are mainly of degree. As time goes on, and as the intensiveness of forest management increases, the problems of control in the commercial and recreational forests will approach comparability with those of suburban

forestry, in magnitude of the values at stake, in the need to localize impacts.

PLANT PESTS

What are the plant pests and sites to be selectively controlled by herbicides? Various vegetation types are sometimes "pests" in relation to management objectives. Central to this subject is the concept that successful achievement of management objectives by itself has a major environmental impact. This must be kept distinct from the impacts of the specific control practices used to achieve them. Thus, the establishment of a Douglas fir forest or a stable shrub community has an effect that may last for centuries, encompassing all life systems, regardless of the method used to establish such a community.

Management objectives determine whether a plant is a pest on a particular site. Commodity-dominated management depends on replacement of stable brush or noncommercial trees with valuable species that may also be stable; the same stability of brushfields is regarded as a virtue in preventing the establishment of trees on rights-of-way. Although the objectives of management differ, the concepts of vegetation management are common to a wide variety of objectives.

Plant Pests in Production Forests

In special-use situations, such as seed orchards and tree nurseries, weeds are regarded as critically limiting on production. On the much larger acreage of commercial forest land where trees are grown for timber, however, weed species are only beginning

to receive attention commensurate with their impact on productivity.

In production forests, weeds may include trees of the same species as the crop tree or of different species, various shrubs, or herbaceous cover. The unwanted plants interfere either by preventing the regeneration of the desired species or by competing for site resources after a stand is already established.

Weeds That Prevent Regeneration

Prompt replanting of cutover lands is an effective and widely used means of ensuring regeneration in the presence of weed species. Where the land is cleared without reforestation, whether because of wildfires or lack of funds or interest on the part of the landowner, shrubs and grasses often increase in coverage or invade fairly rapidly. Sometimes acreage that has never been managed constructively will be overgrown with noncommercial species. Subsequent management for timber production will require removing or controlling the unwanted vegetation by mechanical or chemical means. The degree of control and the herbicide requried varies with the species to be planted.

Weeds That Compete for Site Resources

Low-grade tree or shrub species compete with more valuable species to some extent on nearly all of our forested lands. The reasons for weed dominance vary from place to place. Many stocking problems are a result of man's activities. These include logging without reforestation; disruption through mining, railroad, and grazing activities; and selected harvesting of high-grade trees. The last practice, which causes a gradual deterioration in quality, if not quantity, of production, has been of

particular importance. Over a span of up to 300 years, man has continually removed from forests the trees that he finds most valuable. This has left an increasing proprotion of trees of submarginal value, including those not well adapted to manufacturing, those that are too small to be usable, and those with insect- or disease-caused defects. A low-value forest remains in many areas.

Not all weed problems are man-made. Extensive fires have allowed the invasion of brush in some areas. In other areas, the natural vegetatinonal trend results in tree species that are less desirable from the land manager's point of view. In parts of the South, for example, pine species may be replaced by a variety of hardwood species if the successsional trends are left unchecked. Where the forest is managed for maximum timber production, the softwood species are often more desirable because of their faster growth rates and because there is a ready market for them. Management for softwoods in those areas requires periodic destruction of invading hardwoods, or management to minimize their instrusion. Herbicide use substitutes for wildfires, on which natural pine stands usually depend, but which are unacceptable by present-day standards.

The impact of undesirable vegetation on lands managed for timber production is undoubtedly substantial, although it is difficult to measure. Walker (1973) estimated the total acreage of commercial forest land supporting important amounts of undesirable vegetation at some 300 million acres. The trees on this very large acreage all suffer some loss of potential annual growth increment, a loss that may be as high as 55 percent. (This figure

is based on an estimated average productivity of 25 percent, with 80 percent of potential assumed to be a realistic production goal in native species.)

Plant Pests of Nontimber Forest Areas

Rangelands

About 630 million acreas of rangelands are grazed in the United States, much of it in the Rocky Mountain region. On some of this acreage, forest management for timber competes with management for grazing and (on public land) for wildlife forage. In general, however, the grazing resource has been considered of primary importance. The scattered trees, then, along with a diversity of shrubs, are the "weeds", and grasses and forbs are the "crop". The problem of persistence of the parent herbicide or contaminants or metabolites has been considered by some to represent a potential food chain problem for humans, for example with TCDD.

Recreation Areas

Where land is managed primarily for recreation, no specific plant is undesirable in its own right, except perhaps one that is poisonous to man. Vegetation in such areas is sometimes manipulated to provide a better wildlife habitat; such treatments may or may not act in direct opposition to the production of timber. Where a recreational facility is heavily used, it is sometimes necessary to clear out dead or dying trees that create hazards of fire or windfall. Sometimes relatively mature stands of timber are cut in order to provide ski slopes. In general,

however, it has been unnecessary and economically impractical to attempt to change the species composition of a forested recreation area.

In the West, many of the lands designated as recreation areas have never been deforested, and change would be unnucessary even if the land were managed for timber production. In the populous areas of the East, however, much of the forest land was once cleared for agriculture and is now dominated by what would be weed trees in a production forest. Today, a large part of that wooded land is valued primarily for recreation or residential use, so commercial forest productivity is not its major value.

Approaches to Control

Plant pests, in general, have a regional nature. Western areas, with dry summers, can stabilize in either grass or shrubs. Humid regions may stabilize in shrubs, but generally not in herbs. In the absence of such a shrub cover, a stand of trees, especially shade-tolerant species, can form a relatively stable vegetation type in both areas. These concepts are helpful in reaching management objectives for either rights-of-way or timber management.

Nearly all vegetation control in forests has been carried out in intensively managed production forests or along rights-of-way. The control methods used on these two land areas are tactically similar, although the objectives, as described above, are quite different. Control of plant pests, unlike control of other pests, is only one part of an overall attempt to promote the development of a certain type of stand. Thus, in commercial forestry, the objective is the promotion of a stable forest of valuable trees;

along a right-of-way, the objective is to create a stable cover of shrubs or herbs. In both cases, unwanted vegetation must be controlled to release site resources for the establishment or enhancement of the desired cover. Following are some of the methods used in plant pest control.

Site Preparation

Broadcast application of herbicides from aircraft has gained in importance. This method generally involves the use of phenoxy herbicides, expecially 2,4,5-T, which provide fairly selective control of deciduous plants with minimal injury to conifers. Single aerial applications of 2,4,5-T are less effective in killing vegetation than even moderately intensive mechanical preparation, but the chemical method is also less costly and has no physical impact. Herbicides leave the soil intact and fail to reach or to damage seriously most ground cover under the brush canopy. Animal habitat generally sustains minimal disruption. Thus, even repeated application of short-lived herbicides or such herbicides combined with minimal mechanical treatment create less drastic surface disturbance than full-scale mechanical preparation.

Even after good site preparation, many planted areas need treatment in their second year, and some require further treatment after several years. Selective herbicides are used on conifers.

Removal of Competing Tree Species

The enormous volume of cull tree material that could be harvested in weed control operations in mature forests must be considered a resource. Most of it can be used as pulpwood with present-day technology, and other end uses are under development.

Its present low value is due to the availability of other sources of higher-quality wood fiber with lower labor requirements.

In the absence of increased demand for low-value wood, which would allow economic harvest of thinned material, forest weed control involves several chemical methods, including: tree injection, basal spraying, and aerial spraying. All are more or less effective means of diverting resources to high-quality trees, but each has a different environmental impact.

Injection of individual trees is effective and low in cost and may be accomplished with nonpersistent herbicides. Several hundred thousand acres, primarily in the South, are treated in this way each year. Basal spraying is also effective but may be more costly; its impact is similar to that of injection. It use is primarily confined to rights-of-way. Aerial spraying with rapidly degrading herbicides may be used effectively on shrubs, but it is not successful for large cull trees. Aerial sprays of currently registered herbicides have a general effect on ecosystem structure. As most of the herbicides are of short life and low toxicity, effects on wildlife are primarily related to habitat change. Prescribed fire may be used at frequent intervals to prevent or remove the understory of shrubs and hardwood trees that commonly develops in pine stands. This treatment is effective under some conditions, especially in the South, and it is also finding some use in the Pacific Northwest, where herbicides are used to prepare fuel by desiccation.

The forest weed problem is more likely to require man's intervention than other pest problems. Once dominant desirable trees are established, however, they tend to remain dominant, so that

continued trouble with weeds is unlikely. Therefore, a management plan that includes the harvesting or killing of low-value trees and provides for the establishement and culture of valuable species, eliminates the weed problem (Newton, 1973).

The use of chemicals involves crew training and discipline and although these have proven very difficult to overcome, there has been a recent increase in thinning operations using injection of low-toxicity organic arsenical herbicides. The chemical method involves less physical impact than manual thinning, and provides protection against insects and diseases.

Right-of Way Management for Vegetation Control

Herbicides have been widely used in right-of-way management for vegetation control in this country. In 1969, almost half of the 2,4,5-T used in the United States was applied to over 2 million acres of right-of-way (USDA, 1971) (this figure does not include rights-of-way treated by federal agencies). Other herbicides as well as 2,4-D have also been widely used, almost always as blanket sprays.

The use of blanket sprays, with heavy dependence on the phenoxy herbicides, is often ineffective in terms of the ultimate objective, which is essentially the control of tree growth. With the most widely used phenoxy herbicide, a 2,4-D/2,4,5-T mixture, a grassland is often the resulting cover after repeated applications. In most forested regions with moist summers, this vegetation type is readily invaded by tree seedlings from the contiguous forest, especially if the grassy cover is discontinuous. The result, then, is a cover type that tends to perpetuate the problem that one is

attempting to solve.

A technique that would result in the least disturbance to the existing vegetation and in the process create a shrub cover that would tend to arrest tree reproduction would be preferable. This is the opposite of brush control in forest plantings. In forest management it is well documented that dense shrub covers often necessitate the use of herbicides in order to open site conditions for forest regeneration. It is desirable to avoid tree regeneration along rights-of-way.

Although it has been argued that selective techniques are less economical than broadcast sprays, the relative economy depends upon whether one's point of view is short-term or long-term. Single blanket spray applications may be less costly than selective sprays, but repeated blanket spraying is required to obtain adequate control. If unwanted trees are root-killed by selective stump or basal techniques and a plant cover is created that tends to inhibit further tree establishment, the need for future spraying is minimized.

The fact that certain utilities, such as those in Connecticut, have essentially converted to the selective approach indicates that it is commercially feasible (Crain, 1969). Public pressure has played a role in changing vegetation manipulation practices (Goodwin and Niering, 1959, 1962; Niering and Goodwin, 1974) and will continue to be important in the future as citizens become more aware of the value of the right-of-way resource.

The maintenance principles discussed for right-of-way management are also applicable to vegetation management along forest roads within state, national, and commercial forests. The two major

management tools that have been used to maintain sight lines along forest roads are mechanical cutting and herbicides. The use of broadcast foliar sprays may destroy desirable herbaceous cover, and by drift may also affect adjacent nontarget vegetation.

Along firebreaks, cutting or selective spray techniques can also be used. Blanket sprays often result in a grassy cover that accentuates the fire hazard. An open mixture of broad-leaved herbaceous plants and low-growing shrubs may constitute a much more desirable plant cover in certain regions. The regional vegetational pattern will tend to dictate the most appropriate techniques.

LABORATORY TOXICOLOGY AND EPIDEMIOLOGY

The production and use of chemicals for destruction of forest plant pests have increased markedly during the last decade. Because plants differ markedly from animals in their morphology and physiology, it might be expected that herbicides would present little hazard of chemical toxicity to vertebrates. Indeed some compounds have very low toxicity in mammals, but even amoung the herbicides there are highly toxic chemicals, and a number of these have caused fatal poisonings in man.

TYPE OF OCCUPATIONAL DISEASE REPORTED CAUSED BY PESTICIDES AND OTHER AGRICULTURAL CHEMICALS IN CALIFORNIA IN 1969*

	TYPE OF DISEASE				
TYPE OF CHEMICAL	Systemic Poisoning	Respiratory Condition	Skin Condition	Other and Unspecified	Total All Types
Organic phosphate pesticides	140	4	12	75	231
Halogenated hydro-carbon pesticides	9	7	19	22	57
Herbicides	3	9	50	14	76
Fertilizers	---	8	28	7	43
Fungicides	2	3	21	1	27
Phenolic compounds	2	1	10	2	15
Sulfur	1	2	25	3	31
Organo-mercury compounds	1	---	---	1	2
Lead or arsenic	2	---	2	5	9
Miscell.-specified	5	1	15	7	28
Unspecified	9	12	162	21	204
Total	175	47	345	160	727

*From California Dept. of Public Health: Occupational Diseases in California Attributed to Pesticides & Other Agricultural Chemicals, 1969. Bureau of Occupational Health & Environment Epidemiology, Sacramento, 1969.

REPORTS OF OCCUPATIONAL DISEASE ATTRIBUTED TO PESTICIDES AND OTHER AGRICULTURAL CHEMICALS IN CALIFORNIA IN 1969*

TYPE OF CHEMICAL	TYPE OF INDUSTRY								
	Agri-culture	Manufac-turing	Con-struction	Trans-portation Communi-cation, Utilities	Trade	Struc-tural Pest Control	State and Local Govern-ment	Other	Total All
Organic phosphate pesticides	162	40	1	12	1	1	11	3	231
Halogenated hydro-carbon pesticides	19	15	2	6	2	3	8	2	57
Herbicides	44	4	1	5	--	--	18	4	76
Fertilizers	23	7	1	--	2	--	3	7	43
Fungicides	18	3	1	--	2	--	1	2	27
Phenolic compounds	5	5	3	1	--	--	1	--	15
Sulfur	28	1	1	--	--	--	1	--	31
Organo-mercury compounds	--	--	--	--	--	--	1	1	2
Lead or arsenic	4	1	1	1	--	--	1	1	9
Carbamates	1	2	--	--	--	--	--	1	4
Miscell.-specified	13	5	1	1	1	1	4	2	28
Unspecified	137	19	1	7	12	3	15	10	204
Total	454	102	13	33	20	8	64	33	727

*Abstracted from California Dept. of Public Health: Occupational Diseases in California Attributed to Pesticides and Other Agricultural Chemicals, 1969. Bureau of Occupational Health and Environmental Epidemiology, Sacramento, 1969.

Chlorophenoxy Compounds

The compounds 2,4-dichlorophenoxyacetic acid (2,4-D) and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) as their salts and esters are probably the most familiar chemicals used as herbicides for control of broad-leaf weeds and forest woody plants along highways and utilities rights of way, as well as large scale respeciation. They exert their herbicidal action by acting as growth hormones in plants. They have no hormonal action in animals but their mechanism of toxic action is poorly understood. Animals killed by massive doses of 2,4-D are believed to die of ventricular fibrillation. At lower doses, when death is delayed, various signs of muscular involvement are seen including stiffness of the extremities, ataxia, paralysis, and eventually coma. Sublethal doses, singly or repeated, lead to a general unkempt appearance without specific signs except a tenseness and muscular weakness. Feeding studies in animals indicate that repeated exposures to doses just slightly smaller than the single toxic dose are tolerated, indicating little cumulative effect. In a case of suicide, an oral dose of not less than 6500 mg led to death. It has been estimated that the oral dose required to produce symptoms in man is probably about 3 to 4 g. Profound muscular weakness was noted in a patient recovering from an episode of acute poisoning by 2,4-D. Peripheral neuritis was reported for three men who had recent heavy occupational exposure to 2,4-D. Pathologic changes in experimental animals killed by the chlorophenoxy compounds are generally nonspecific with irritation of the stomach and some liver and kidney injury (Hayes, 1963).

The chlorophenoxy herbicides have produced contact dermatitis in man, and as mentioned earlier, a rather severe type of dermatitis, chloracne, has been observed in workmen involved in the manufacture of 2,4,5-T (Poland et al., 1971). This effect appears to be due primarily to the action of a contaminant, 2,3,7,8-tetrachlorodibenzo-ρ-dioxin.

Courtney at al (1970) reported that technical 2,4,5-T containing 30 ppm 2,3,7,8-tetrachlorodibenzo-ρ-dioxin (TCDD) caused an increase in the incidence of cleft palate and cystic kidney in C57BL/6 and ARK mice. Since then there has been considerable concern about whether 2,4,5-T is a human teratogen. Only minimal or no teratogenic or fetotoxic effect of 2,4,5-T in rats has been reported (Courtney and Moore, 1971; Emerson et al., 1971; Sparschu et al., 1971; and Khera and McKinley, 1972). The compound was not teratogenic in rabbits given 10 to 40 mg/kg/day on days 6 through 18 of pregnancy (Emerson et al., 1971) or in sheep given 100 mg/kg/day on days 14 to 36 of gestation (Binns et al., 1971). Collins and Williams (1971) reported an increase in fetal mortality, incidence of hemmorhage in live born and the number of malformations (primarily of the head region) in hamsters given 100 mg/kg/day of 2,4,5-T containing no detectable TCDD. No cleft palate was produced.

Following the report of Courtney et al., 1970, several papers have been published reporting a significant increase in cleft palate in several strains of mice given multiple doses of 2,4,5-T by the oral or subcutaneous routes (Courtney and Moore, 1971; Roll, 1971; Hart and Valerio, 1972; Neubert and Dillman, 1972; and Bage, et al., 1973). Courtney and Moore (1971) reported that analytical grade 2,4,5-T containing less than 0.05 ppm TCDD given by gavage on days 6 through 15 produced cleft palate and kidney anomalies in CD-1, C57BL/6J and DBA/2J mice. Roll (1971) observed a significant increase in fetal cleft palate and reduction in fetal weight in NMRI mice given 35 to 130 mg/kg/day of technical 2,4,5-T containing less than 0.1 or 0.05 ppm TCDD orally on days 6 to 15 of pregnancy. A dose level of 20 mg/kg/day was established as the teratogenic "no effect" level. Neubert and Dillman (1972) reported a frequency of cleft palate exceeding that in the controls with doses of 2,4,5-T higher than 20 mg/kg. They treated relatively large numbers of NMRI mice by gavage on days 6 to 15 of pregnancy with dosage levels of 8 to 120

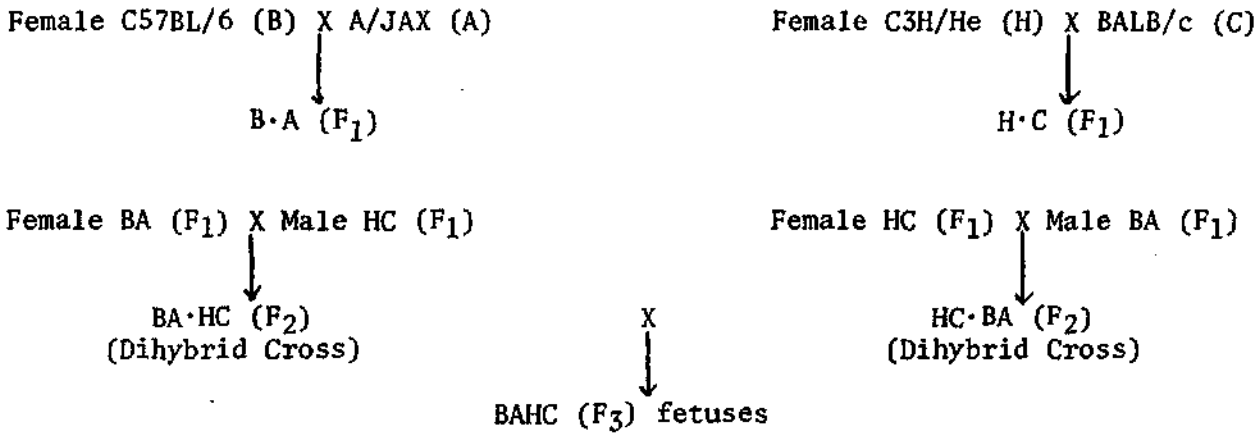
mg/kg of 2,4,5-T containing less than 0.02 ppm TCDD. Reduction in fetal weight was observed with doses as low as 10 to 15 mg/kg, but there was no clearcut dose-response relationship for fetal weight. They did not report any kidney malformations.

In 1973 a study designed to correct some of the deficiencies in existing information on the teratogenicity of 2,4,5-T was initiated at the National Center for Toxicological Research. The deficiencies were considered to be:

1. Inadequate numbers of test animals.
2. Inadequate or non-existent replications of tests.
3. Inadequate testing at doses below 100 mg/kg - needed for more valid dose-response studies.
4. Need for testing in different strains or stocks of mice.
5. Inadequate investigation of fetal kidney development to properly evaluate the reported "cystic-kidney"-effects.

This paper, one of a series reporting the results of the complete study, will deal with dose-response studies conducted with technical 2,4,5-T in four inbred strains of mice, one random-bred stock and a dihybrid stock developed from the four inbred strains. The endpoints considered are the incidence of cleft palate, embryolethality and fetal weight reduction.

Studies of the teratogenicity of 2,4,5-T were conducted in the four inbred strains of mice, C57BL/6, C3H/He, A/JAX, BALB/c, the random-bred CD-1 and a dihybrid cross of the inbred strains. All of the inbred strains were obtained from Jackson Laboratories, Bar Harbor, Maine, and the CD-1 from Charles River Breeding Laboratories, Wilmington, Massachusetts. The dihybrid cross was developed at the National Center for Toxicological Research, Animal Husbandry Division (NCTR), according to the following design:



The dihybrid cross was developed and tested because this outbred population was considered as offering the following advantages over the use of a "random-bred" population: (1) the dihybrid cross is reproducible and its gene pool is controllable, (2) belief that the dihybrid would be less susceptible to extraneous sources of environmental variability and that their fetuses, because of their hybrid vigor, would be less sensitive to the embryotoxic actions of 2,4,5-T, (3) a diversity of genotypes in which segregation patterns may more closely resemble the human population than inbred or "random-bred" animals. The inbred strains used were chosen because of their general availability, frequent use in other teratogenicity studies, and background information on their general characteristics including spontaneous and induced malformation rates. It is also known that these strains exhibit a wide range of cleft palate incidences as a consequence of treatment with cortisone.

Technical grade 2,4,5-T of 97.9 $\pm$ 0.4% purity containing 0.06 ppm dioxin supplied by Dow Chemical Co., Midland, Michigan, was formulated so that appropriate dose levels (mg/kg) could be given in 0.2 cc of the vehicle per mouse. The vehicle consisted of 1 part acetone to 9 parts corn oil (volume/volume basis). The amount of 2,4,5-T in the vehicle was adjusted for 5 gm weight ranges, e.g. mice weighing 21 to 25 gm, and those weighing 26 to 30 gm were

dosed from different formulations to give the same dose levels in mg/kg. The appropriate amount of 2,4,5-T was dissolved in the acetone to give the concentration needed for treatment after further dilution of the solution in corn oil. A sample of each of the formulations was saved by the Chemistry Division for chemical analysis to verify 2,4,5-T concentration. No one formulation was used longer than for the nine day treatment period.

For breeding, the female mice were individually caged overnight with a male. Females with vaginal plugs the next morning (day 0) were designated as pregnant for purposes of treatment. Pregnant mice were housed in a 12 by 12 foot laminar air flow tent. The mice were distributed by random assignment into treatment groups with four mice per cage in shoe box-type plastic cages and supplied with food and water. Within a cage the mice were identified by ear clip.

Each test for a mouse strain or stock was designed to establish a dose-response curve for the teratogenic and embryo-toxic effect of 2,4,5-T. The tests were replicated from 4 to 8 times in each strain or stock with 28 to 204 litters in each replicate. The tests for establishing dose response curves in the CD-1 using five dose levels of 2,4,5-T were replicated eight times. However, the entire study was designed to test 2,4,5-T at two or three dose levels in CD-1, concurrently with each replication for all other strains and/or stocks of mice, using the CD-1 as a "positive" control, since this stock was known to be quite susceptible to cleft palate induction with cortisone. This accounts for the large number of litters that are included for some dose levels in presenting some of the results for the CD-1.

The order of treatment of the different groups of mice within a replicate was done in a random manner. The mice were dosed daily by gavage between 8:00 a.m. and 12:00 noon on days 6 to 14 of pregnancy. The control mice were given 0.2 cc per mouse of the acetone-corn oil vehicle. The animals were weighed just

before dosing on days 6, 9, and 12 of pregnancy. This allowed adjustment of the 2,4,5-T formulations for maternal mice which had gone from one 5 gm weight range category to another.

Any mice that were found dead or observed in a moribund state during or following treatment with 2,4,5-T before the date of scheduled sacrifice were sent to the Pathology Division for complete gross and microscopic histopathology examination. On day 17 of pregnancy the maternal mice were sacrificed, the uteri opened and examined for dead, resorbed, and viable fetuses. The viable fetuses were examined externally, weighed and placed in individual containers of Bouin's solution. At the time of sacrifice and removal of the uteri of each replicate of animals, five maternal carcasses each from the control group and the highest dose group from each strain were delivered immediately to Pathology for complete gross and microscopic histopathology examination. Using aseptic technique the entire intestinal tract was taken by the Diagnostics Division from each of four maternal control mice and four mice given the highest dose level of 2,4,5-T. Total bacterial counts, both aerobic and anaerobic, were determined for the intestinal contents to see if 2,4,5-T had any effect on the intestinal flora.

After about 48 hours storage in the Bouin's solution the fetuses were examined for cleft palate and other external malformations. They were then sent to Pathology for detailed examination of the kidneys. All fetuses were sexed internally when the kidneys were removed.

The teratogenic endpoints analyzed were incidence of cleft palate, resorptions and fetal weight reduction.

Probit analysis was done for percent of litters with cleft palate and percent of litters with at least one resorbed fetus pooled over all replicates for each dose level using Abbot's formula (Finney, 1971) to adjust for incidence of cleft palate or resorptions in the control mice.

For each strain or stock of mice linear regression analyses were done for average percent fetuses per litter with cleft palate, average percent fetuses resorbed per litter and for fetal weight reduction. These analysis were performed on values averaged over all replications for each dose level after extracting out the control values averaged over all replicates. Then an analysis of covariance was performed so as to adjust all means to a common dose level using the method described by Snedecor and Cochran (1967).

The gavaging of the mice was rotated among five technicians. To test whether or not there was any influence on the results because of variation in the technicians a two-way analysis of variance was performed on all strains or stocks of mice. There was no indication that embryolethality, fetal viability or incidence of cleft palate in the mice was influenced by difference in technique of treatment by the different technicians.

The wide spread use of the herbicide 2,4,5-T which contains even a small amount of the chemical impurity, 2,3,7,8-Tetrachloro-dibenzo-ρ-dioxin (TCDD) in Southeast Asia gave rise to a great deal of concern. Let me discuss briefly my opinion as to the relative risks both to man and the environment due to 2,4,5-T with less than 0.1 ppm 2,3,7,8-tetrachloro-dibenzo-ρ-dioxin (TCDD) and a comparison with TCDD from other routes of entry.

TCDD, of course, is very toxic to all species studied. TCDD and other dioxins contaminate many chlorinated phenols and related products (e.g. 2,4,5-T), in addition to other materials of much wider application (at least in the past) like hexachlorophene. Why then do we worry about TCDD in 2,4,5-T? Indeed, how did we come to realize that a compound as difficult to analyze as TCDD was present in such small quantities in a commercial product which contains many other contaminants in much greater quantities?

The commercial production of 2,4,5-T was hampered in the synthetic process. Toxic effects were many including hepatoporphyrin, vascular lesions, chloracne,

and photosensitivity. The process was improved from an industrial hygiene standpoint and production continued. Courtney (1970) at NIEHS studied 2,4,5-T with 27 ppm to TCDD and observed cleft palate and cystic kidney which substantially was described as hydronephrosis. Several other workers (e.g., Moore at NIEHS (1973)) observed the teratogenicity of TCDD in the μg/kg range. There were several groups, notably DOW Chemical, that considered presence of the dioxin as the causative agent in technical grade 2,4,5-T which contained varying amounts of TCDD, but it remained for Neubert (1972) to demonstrate that it required concentrations approaching 100 ppm of TCDD to produce a clear additive effect. Even so, the controversy raged on. At the NCTR we proved, I believe, as previously documented, that the currently available 2,4,5-T is teratogenic in several dose response studies and that the effect is not due to a generalized non-specific effect on the maternal animal, and the TCDD plays no discernible role at the current levels found in 2,4,5-T.

Gehring et al (1973) showed that the half-life of a sample of 15 mg/kg dose was approximately 1 day and would be expected to plateau on repeated treatments after 3 days. This is not terribly different than what is found for rats, and was shorter than found for dogs.

Kearney et al., in 1972 (1972) estimated for example that the half-life of TCDD in soil is about 1 year. There is a possibility that under certain conditions the ecological half-life could be longer (conjecture only). It seems to me that there are two concerns from TCDD: (a) environmental half-life; and (b) biomagnification in grazing animals. Lets take on the ecological half-life problem first and make some assumptions (recognizing that they represent over simplication of the problem): a probable ecological half-life of 1 year and an outside possibility of 10 years; 10 year's use of a product at a mean TCDD concentration of 25 ppm; and a subsequent 10-year period of use with a mean TCDD concentration of 0.1 ppm. Then, if we accept that:

$$\ln \frac{X}{X_o} = -k_1 t$$

$$\ln \frac{X}{X_o} = -(0.07) \text{ (first year)}$$

$$\frac{25 \text{ ppm}}{X_1} = \text{antiln of } 0.07 = 1.073$$

$$X_1 = \frac{25}{1.073} = 23.3 \text{ ppm}$$

What I will now do is calculate an estimate of the ecological burden over the 20-year time period.

EXAMPLE OF ECOLOGICAL BURDEN OF TCDD (OVER 20 YEARS)

Year	$t_{1/2}$ = 10 Years (ppm)	$t_{1/2}$ = 1 Year (ppm)
	a. Exposure at 25 ppm/Yr.	
1	23.3	12.5
3	23.3 + 042.0 = 065.3	12.5 + 09.4 = 21.9
6	23.3 + 094.8 = 118.1	12.5 + 12.1 = 24.6
10	23.3 + 150.1 = 173.4	12.5 + 12.5 = 25.0
	b. Exposure Continues at 0.1 ppm/Yr.	
11	0.09 + 161.7 = 161.8	0.05 + 12.50 = 12.55
13	0.09 + 140.8 = 140.9	0.05 + 03.15 = 03.20
16	0.09 + 114.4 = 114.5	0.05 + 00.44 = 00.49
20	0.09 + 086.9 = 087.0	0.05 + 00.07 = 00.12

Several observations need to be highlighted:

First, at t-½ = 1 year, 99% equilibrium occurs at 7 years at about the yearly exposure level. In other words, there will never be more TCDD remaining than is in the formulation being applied. Rephrased, if you wish to predict the level of TCDD, you would take the amount of 2,4,5-T applied and multiply by ppm TCDD contaminate. If this exposure continued, equilibrium would be reached at

approximately the end of the seventh year. However at t-½ = 10 years, the TCDD concentration is increased to about 7 times the applied concentration after 10 years and has yet to reach equilibrium.

Now considering a continued exposure at the lower TCDD contamination level (i.e., 0.1 ppm), the rate of decrease in the improvement of the environment would only be detectable after 8 years of use if a t-½ = 1 year, and would only be detectable after 70 years if an ecological half-life of 10 years is correct.

Also, the percentage contribution of 0.1 ppm TCDD would never be more than 1% of the residue which results in a single year of 25 ppm application. Application of a single year of 25 ppm TCDD would require 8 years to decrease to the level obtainable after continued use of 0.1 ppm TCDD. The situation of a 10-year half-life is worse in terms of what we have already done to the environment, but demonstrates a smaller relative contribution of 0.1 ppm TCDD than the t-½ = 1 year at 25 ppm.

How about the toxicological significance of the effect of the two 10-year periods? Although the significance would vary greatly for each species, its place in the food chain, etc., again, lets consider a simplified version of possible numbers for the sake of discussion. Total the ppm x numbers of years at a ppm for a 1- and a 10-year half-life and you get 225 ppm-years for 1-10 years and 26 ppm-years for 11-20 years with t-½ = 1 year, and 1053 ppm-years for 1-10-year period and 1209 for 11-20-year period for t-½ = 10.

If one compares using linear extrapolation of the damage which has occured in a 10-year application of 25 ppm TCDD with t½ = 1 year, it would take 2250 years of use of 0.1 ppm TCDD to produce the same "damage" as would have already been done or with a t-½ = 10 over 10,000 years of use.

If one used an extrapolation procedure, which I believe is more reasonable, of probit analysis and exprimentally produced slopes, one approaches a million

years before an equivalent toxic accumulation could be accomplished. I personally believe as far as damage to the environment is concerned, this becomes even more ridiculous when we know the use of 2,4,5-T will never approach past levels and most 2,4,5-T used had more than 25 ppm TCDD as compared to the 0.1 ppm used today.

Does this mean that I am not concerned about biomagnification? It does not. Again, however, I must point out that TCDD, as an example, does have a half-life in animals, as well as in the environment and that the variance of each "system" considered is great and, in fact, frequently less than the numbers I have selected for illustrative purposes. Also, we would expect the biomagnification to be on the decline for at least 10 years utilizing the examples previously described.

I believe that dioxins in the environment are important, but I feel that pesticides will contribute little, if untoward control over the quality of production is maintained. The problem lies not with the pesticide, but with industrial chemicals escaping into the environment. As an example, let me draw on data from a May 1975 article by Carter et al. (1975). Between February and October of 1971, waste oil residues of hexachlorophene production plant in Missouri amounting to about 50,000 kg contaminated with 350 ppm TCDD was sprayed to control dust. To equal this, one would have to use at least 400,000,000 lbs of currently available 2,4,5-T. This abuse of industrial waste disposal is not isolated and must be stopped.

Along the same line, and emphasizing the need for careful adherence to safety in chemical manufacturing is the recent explosion in Seveso, Italy. An explosion at a Swiss subsidiary of Hoffman La Roche caused a 500-gallon vat of trichlorophenol to explode ( ) releasing approximately 4.4 lbs of TCDD. The chlorophenol is used in the production of hexachlorophene. Here it must also be remembered that in chemical reactions involving high temperatures or

pressures where chlorinated phenols are precursors, the potential for forming a chlorinated dioxin exists, but not even all the tetrachlorinated dioxins possess similar levels of toxicity, i.e., the 2,3,7,8-TCDD isomer is by far more toxic than the other isomers.

Let me finish this note with one more thought. The ED_{06} for cleft palate for TCDD is approximately 1 µg/kg/day. The ED_{06} for cleft palate is approximately 10 µg/kg/day for 2,4,5-T. Simply stated, the concentration of TCDD would have to bioaccumulate to at least 1,000 times the concentration of bioaccumulated 2,4,5-T before the effect due to TCDD was equal to 2,4,5-T. This, of course, has to be superimposed on the probability of 2,4,5-T being able to bioaccumulate to an effective dose level. Some good work needs to be done on the pharmacokinetics of TCDD in food stuff likely to be consumed by man and modeling of man's biological half-life.

After we have combined animal toxicology and human exposure data, we must determine if levels of contaminants actually exist in food. Great strides have been made in the last 20 years. Gas chromatography has become a common laboratory workhorse with sensitivities proceeding from 1950's thermal conductivity (10^{-6}g), to 1955's flame ionization (10^{-9}g), to 1960's electron capture (10^{-12}g), to gas chromatography mass spectrometry (10^{-15}g).

$$\frac{ED_{06}\ 2,4,5\text{-T}}{ED_{06}\ TCDD} = \frac{10\ mg}{1\ ug} = K_{[e]} = 10,000$$

TCDD is 10,000 times more teratogenic than 2,4,5-T.

$$\frac{[2,4,5\text{-T}] + [TCDD]}{TCDD} = \frac{1}{1x10^{-7}} = K_{[c]} = 10,000,000$$

There is 10,000,000 times less TCDD than 2,4,5-T.

$$\frac{K_{[c]}}{K_{[e]}} = 1,000$$

After we have determined the potential for toxicity and the presence of a residue, we are usually still faced with the necessity of extrapolating the toxic results from high doses to observed human exposure levels. This, in my opinion, is, and will remain, the greatest challenge of all.

Dinitrophenols

Several substituted dinitrophenols alone or as salts of aliphatic amines or alkalies are used in weed control. Several human poisonings by dinitro orthocresol (DNOC) have been reported (Bidstrup and Payne, 1951). Signs and symptoms of acute poisoning in man include nausea, gastric upset, restlessness, sensation of heat, flushed skin, sweating, rapid respiration, tachycardia, fever, cyanosis, and finally collapse and coma. The illness runs a rapid course with death or recovery generally within 24 to 48 hours. These signs and symptoms reflect an increased metabolic rate, which may exceed several times normal values and is dose-dependent. If heat production exceeds the capacity for heat loss, fatal hyperthermia may result. Chronic exposure to dinitro-orthocresol may also produce fatigue, restlessness, anxiety, excessive sweating, unusual thirst, and loss of weight. A yellow staining of the conjunctiva has been noted, and cataract formation is another possible sequela of chronic dinitro-orthocresol exposure. Blood levels of DNOC below 10 ppm are considered of trivial importance; levels of 11 to 20 ppm indicate appreciable absorption; and above these blood levels toxic manifestations are likely. Levels greater than 50 ppm are critically dangerous. After removal of the poison from the skin or gastrointestinal tract, treatment consists of ice baths to reduce fever and administration of oxygen to assure maximal oxygenation of the blood. Fluid and electrolyte therapy may be necessary to replace loss by sweating. Atropine sulfate is absolutely contraindicated in cases of poisoning by dinitrophenolic compounds, and therefore care should be taken to avoid a misdiagnosis of organophosphate poisoning. Symptoms of poisoning and their

severity are enhanced when the environmental temperature is high. In very cool weather blood levels as high as 50 ppm have been tolerated without symptoms. The oral LD_{50} of DNOC in rats is approximately 30 mg/kg (Hayes, 1963, 1971).

It will be noted that the nitrocresol compounds produce symptoms of toxicity similar to those produced by dinitrophenol and therefore probably act by uncoupling of oxidative phosphorylation as has been proposed for dinitrophenol. Compounds that produce uncoupling of oxidative phosphorylation also have the peculiar property of rapidly producing rigor mortis after death. Studies on the toxicology of substituted nitrophenols used in agriculture may be found in a report by Spencer and coworkers (1948).

Bipyridyl Compounds

Paraquat and diquat are the best-known compounds of this class of herbicides, which are increasing in use. Cases of accidental or suicidal fatalities resulting from paraquat poisoning have been reported (Campbell, 1968). Pathologic changes observed at autopsy in all of these fatal human poisonings showed evidence of lung, liver, and kidney damage. Some cases had myocarditis, and one case showed transient neurologic signs. The most striking pathologic change was a widespread cellular proliferation in the lungs. This pathology was also evident in a suicide case in which the paraquat was injected subcutaneously. In this case the victim died in respiratory distress, and the main pathologic findings at autopsy were in the lungs. Hence, paraquat produces lung damage even when administered by routes in which exposure of the lung is secondary. Although ingestion of paraquat results in gastrointestinal upset within a few hours after exposure, the onset of respiratory symptoms and eventual death by respiratory distress may be delayed for several days. In a case involving a six-year-old child the concentration of paraquat present in the liver and kidney at necropsy was 208 mg per 100 g of kidney. One accidental

case involved an individual who mistakenly took a mouthful of the herbicide from a "stout" bottle, and although he spat it out almost immediately, 14 days later cyanosis and severe dyspnea developed. The patient who administered paraquat by subcutaneous injection had chest radiograph changes three days after administration, but did not develop respiratory symptoms for an additional 11 days.

The toxicology of bipyridyl herbicides was reviewed by Conning and associates (1969). In animal studies all species examined showed the same response after a single large dose of paraquat given by mouth or by subcutaneous or intraperitoneal injection. There was an early onset of hyperexcitability, which in some cases led to convulsions or incoordination. The animals died over a period of ten days after administration. Early deaths were not associated with any specific systemic pathology. Later deaths that occurred at two to five days after administration usually were accompanied by severe pulmonary congestion and edema with hyaline membrane formation and inflammatory infiltrates. Animals that survive the pulmonary edema associated with a single dose occuasionally show pregression of lung lesions to fibrosis and eventual death from respiratory failure. As in man, a single dose may produce pulmonary fibrosis in the dog. The feeding of 0.03 percent or more of paraquat in the diet of experimental animals led to the production of pulmonary fibrosis in most all of the animals. Studies of organ cultures of lungs treated with paraquat revealed extensive necrosis of alveolar cells. Inhalation of paraquat aerosols for several hours produces severe congestion, alveolar edema, and bronchial irritation two to three days after the exposure. However, if the animal survives during this period there is, surprisingly, no further chronic fibrosis produced.

The LD_{50} for paraquat in guinea pigs, cats, and cows is in the range of 30 to 50 mg/kg. Rats appear to be somewhat more resistant with an LD_{50} of about

125 mg/kg. The LD_{50} for man is estimated at about 40 mg/kg (Conning et al., 1969). Studies of several species indicate that absorption of paraquat from the gastrointestinal tract is relatively low, in no cases exceeding 20 percent of the administered dose. There is a rapid disappearance from the blood with 90 to 100 percent of the dose excreted in the urine within 48 hours. Since there is a long delay until onset of respiratory signs, this compound has been classified among the "hit-and-run" type of toxic agents. Exposure of the skin to solutions of dipyridyls results in erythemia and a mild reactive hyperkeratosis, which may be associated with pustule formation.

Diquat produces acute and chronic effects that differ from those produced by paraquat in that marked effects on the lung are not observed. Oral doses near the LD_{50} produce hyperexcitability leading to convulsions and distention of the gastrointestinal tract with discoloration of intestinal fluids. The only pathology associated with long-term feeding of diquat at levels of 0.05 percent was the production of cataracts in about ten months. A related compound, chlormequat, has as its target organ the kidney. In both rats and dogs, kidney lesions were the only striking pathology noted in both acute and chronic studies.

It has been suggested that the mechanism of the herbicidal action of the dipyridyls is mediated by free radical reactions, and a similar mechanism has been proposed for the action in mammals. Gage (1968) has shown that free radicals can be produced from paraquat and diquat incubated in the presence of reduced NADP and liver microsomes.

Carbamate Herbicides

This class of herbicides contains a large number of aromatic and aliphatic esters, which for the most part have relatively low acute toxicities (Dalgaard-Mikkelsen and Poulsen, 1962; Woodford and Evans, 1965). The compound propham

is a typical example of this class of herbicides. Its LD_{50} by oral administration in rats and rabbits was of the order of 5000 mg/kg. Feeding rats dietary concentrations of 1000 ppm for three months produced no signs of effects on general condition and growth, fertility, or pathologic changes. Barbane is somewhat more toxic than propham with an oral LD50 of 600 mg/kg for rats and rabbits and 24 mg/kg for guinea pigs. Daily oral administration of 75 mg/kg for 22 days produced some loss of weight, while half of this quantity produced no toxic action. Feeding experiments with rats showed no toxic action of 150 ppm in the diet for 18 months. Barbane, however, is a potent skin-sensitizing agent in man, and allergic reactions and rash may develop on subsequent contact.

Substituted Ureas

Like the carbamate herbicides the substituted ureas are, as a class, rather nontoxic by acute oral administration. Monuron and diuron are typical examples with LD_{50} values in rats of over 3000 mg/kg. They are also without toxic action when fed at relatively high concentrations in the diets of rats and dogs for several months to two years.

Triazines

Most members of this class of herbicides also have low oral acute toxicities ranging above 1000 mg/kg. Simazine was nontoxic to a variety of animal species including mice, rats, rabbits, chickens, and pigeons. Rats survived daily doses of 2500 mg/kg for four weeks (Dalgaard-Mikkelsen and Poulsen, 1962). Simazine is, however, more toxic to sheep and cattle. Sheep were killed by three daily doses of 250 mg/kg, 14 daily doses of 100 mg/kg, or 31 daily doses of 50 mg/kg. Cattle were killed by three daily doses of 250 mg/kg (Palmer and Radeleff, 1964). The acute toxicity of atrazine to rats is greater than for simazine; however, cattle and sheep appear to be more resistant to atrazine than to simazine.

The herbicide amitrole (3-amino-1H-1,2,4-triazole), although not classified as a triazine, is structurally somewhat similar. This compound also has a very low acute oral toxicity to rats and mice (ranging from 15,000 to 25,000 mg/kg). However, amitrole is a rather potent antithyroid agent, and feeding levels of 2 ppm in the diet resulted in significant effects on thyroid function (Strum and Karnovsky, 1971). These functional changes occurred after only one week of feeding of amitrole, and goiters can be induced by amitrole with long continuous administration. Amitrole given to rats in the diet at 100 ppm for two years resulted in the development of thyroid adenomas and adenocarcinomas. This has resulted in prohibition of this compound for use as a herbicide where residues might occur on food crops. Amitrole inhibits peroxidase activity in livers and thyroids, and the mode of action in producing thyroid tumors appears to be related to the goitrogenic effect of amitrole with resultant increased TSH (thyroid-stimulating hormone) since other antithyroid agents that result in TSH stimulation also can produce thyroid tumors experimentally (Sinha et al., 1965). The amitrole case illustrates an important principle in toxicology, that is, the fallacy of assuming safety purely on the basis of low acute toxicity. As is illustrated by this compound, which is practically nontoxic acutely, rather profound functional changes can occur that directly or indirectly may lead to irreversible pathology, e.g., cancer.

Amide Herbicides

Several aniline derivatives esterified with organic acids are currently used as herbicides. These compounds also have relatively high oral LD_{50}s for rats. A typical example is the herbicide propanil, which is used extensively to control noxious weeds in rice crops. The rice plant is selectively resistant to the herbicidal action of propanil because it contains an acylamidase that hydrolyzes propanil to 3,4-dichloroaniline and propionic acid. An interesting

case of herbicide potentiation was observed in field studies in which propanil was applied to rice following the application of organophosphate insecticides. This procedure resulted in damage to rice plants and was subsequently explained on the basis that the organophosphates inhibited the hydrolysis of propanil, and thus the parent compound was preserved and exerted its herbicidal action in the rice (Matsunaka, 1968). Williams and Jacobson (1966) demonstrated that mammalian livers also contained an amidase that hydrolyzed propanil, and they speculated that organophosphates and carbamates might potentiate the actue mammalian toxicity of this herbicide. Studies of interactions did not reveal a significant potentiation, however. Further investigation demonstrated that inhibition of liver acylamidase by triorthocresyl phosphate (TOCP) prevented the cyanosis that was observed when mice were given toxic doses of propanil (Singleton and Murphy, 1973). The cyanosis was due to methemoglobin formation following hydrolysis to 3,4-dichloroaniline. Other signs of poisoning, i.e., CNS depression and death, were not prevented by inhibiting the hydrolysis of the herbicide. It appears, therefore, that aromatic amides that are hydrolyzed to aniline derivatives may produce methemoglobin, but that the acute lethal action is due to a different mechanism.

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TOXICOLOGY OF FAMILIES OF CHEMICALS USED AS HERBICIDES IN FORESTRY

The production and use of herbicides has increased markedly during the last two decades. Because plants differ markedly from animals in physiology, biochemistry and hormonal activity, herbicides usually present little hazard of chemical toxicity to man and other vertebrates. Indeed, some compounds have very low toxicity in mammals, but even among herbicides as a family of chemicals, structural class are quite variable and there are representative highly toxic chemicals, some of which have caused fatal posionings and others which represent at least theoretical risks of cancer, birth defects and genetic and reproductive defects.

The compounds 2,4-dichlorophenoxyacetic acid (2,4-D) and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) as their salts and esters are the most prominent herbicides used in forest management. 2,3,7,8-tetrachlorodibenzo dioxin, a trace contaminent of 2,4,5-T, exhibits unusual toxicity and has created great controversy over theoretical birth defect risks. A comparison of teratogenic risks from 2,4,5-T and dioxin are presented as part of a risk estimation model.

The laboratory toxicity of a compound is relatively useless unless presented in the proper context of interaction with the species at potential risk. Estimates of route, rate and duration of exposure and other environmental effects impacting on the distribution of sensitivities in a population must all be considered before estimates of risks of toxicity become meaningful.

Toxicity of herbicides must be considered in the totality of the forest environment. In every forest there are a large number of other organisms including man, wildlife, insects, micro-organisms, shrubs, and annual and perennial plants living in intimate ecological relationships with trees. Each is an integral part of the natural forests, and any substantial natural or man induced change in the population of one organism is likely to have ecologically significant effects on one or more of the others. These changes can be reflected as alterations in the toxicological response.

The families of chemicals used in the various plant pest management tasks include, but are not limited to, chlorophenoxy compounds (2,4-D, 2,4,5-T), dinitrophenols (DNOC), bipyridyls (paraquat and diquat), carbamates (propham), substituted ureas (monuron and diuron), triazines (simazine), amides (propanil). The toxic effects produced by these compounds in experimental animals include cancer, birth defects, mutagenesis, interactions with organophosphate pesticides, uncoupling of oxidative phosphorylation, CNS, liver, kidney and lung pathology. The risk to man from the use of herbicides is mainly to the applicator and through accidental posionings.

MORRIS F. CRANMER, Ph.D.

ECOLOGICAL BURDEN OF TCDD (OVER 20 YEARS)

Cranmer

Year	$t_{1/2}$ = 10 Years (ppm)	$t_{1/2}$ = 1 Year (ppm)
	a. EXPOSURE AT 25 ppm/Yr.	
1	23.3	12.5
3	23.3+42.0 = 65.3	12.5+9.4 = 21.9
6	23.3+94.8 = 118.1	12.5+12.1 = 24.6
10	23.3+150.1 = 173.4	12.5+12.5 = 25.0
	b. EXPOSURE CONTINUES AT 0.1 ppm/Yr.	
11	0.09+161.7 = 161.8	0.05+12.5 = 12.5
13	0.09+140.8 = 140.9	0.05+3.15 = 3.2
16	0.09+114.4 = 114.5	0.05+0.44 = 0.49
20	0.09+86.9 = 87.0	0.05+0.07 = 0.12

ECOLOGICAL HALF-LIFE (EQUATION)

$$\ln \frac{x}{xo} = -k_1 t$$

WHERE: $k_1 = \frac{.7}{t\frac{1}{2}} = \frac{0.7}{10} = 0.07$

THEN: $\ln \frac{x}{xo} = -(0.07)$ (1 rst yr)

AND: $\ln -0.07 \frac{25 \text{ ppm}}{x_1}$ = tiln antiln of 0.08

= 1.073

$\therefore X_1 = \frac{25}{1.073} = 23.3$ ppm

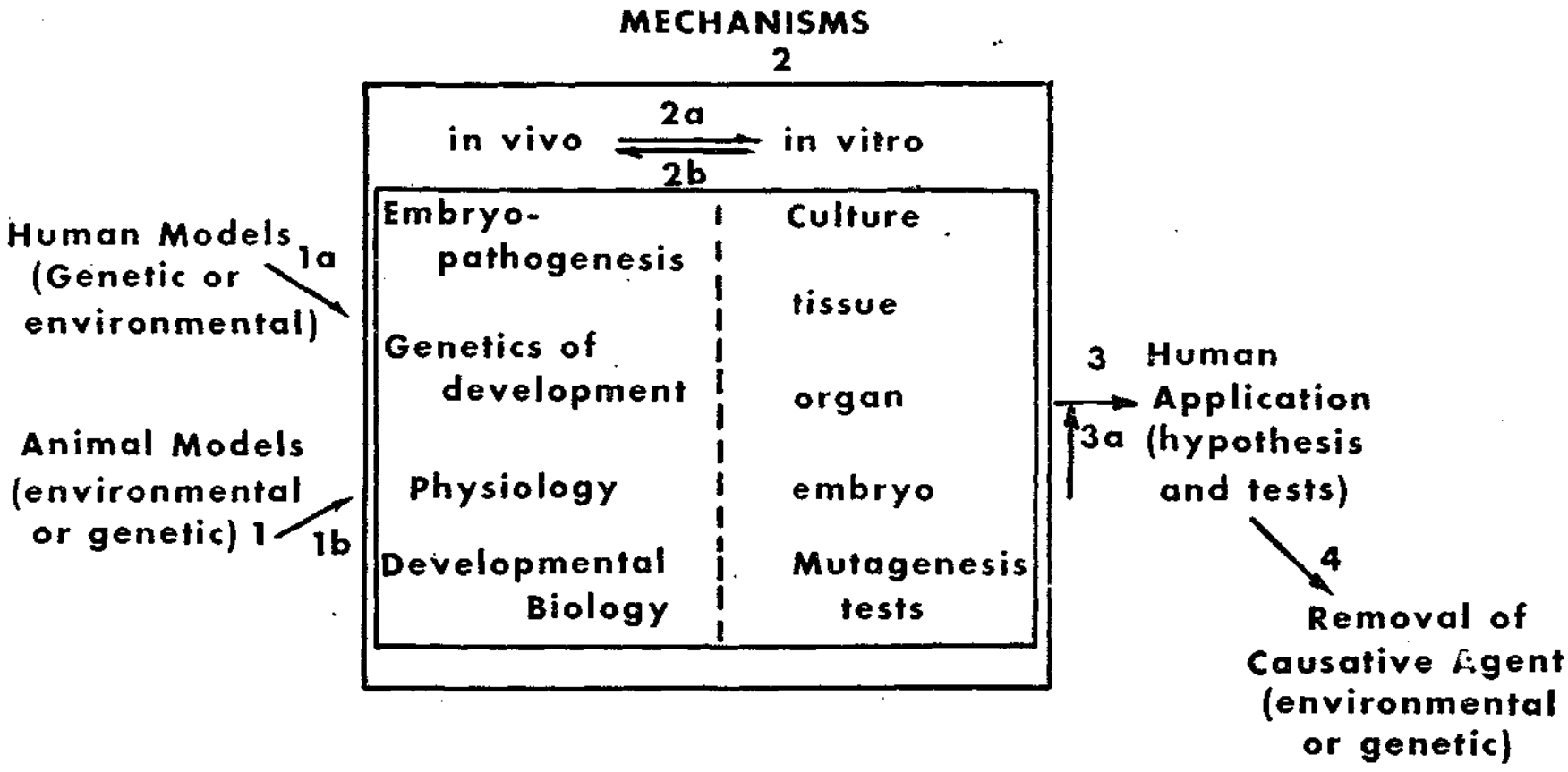
BIOACCUMULATION
(2,4,5-T vs TCDD)

$$\frac{[2,4,5\text{-T}] + [\text{TCDD}]}{[\text{TCDD}]} = \frac{1}{1\times10^{-7}} = K[c] = 10{,}000{,}000$$

$$\text{TCDD} = \frac{[2,4,5\text{-T}]}{10{,}000}$$

$$\frac{K\ [c]}{K\ [e]} = 1{,}000$$

CONGENITAL DEFECTS--MECHANISMS--APPLICATION AND REMOVAL



OBSERVED FRACTION	FRACTION OF TEST DOSAGE FOR RISK = 10^{-8}	
	1 PROBIT/LOG	2 PROBITS/LOG
0/50	1/18,000	1/130
0/100	1/8,300	1/91
0/500	1/1,800	1/42
0/1000	1/1,000	1/32

EXTRAPOLATED DOSES FROM SIMILAR RESULTS

Proportion with tumors	Probit	Logistic	One-hit
10^{-3}	1.5×10^{-2}	3.1×10^{-3}	1.4×10^{-3}
10^{-6}	1.4×10^{-3}	9.8×10^{-6}	1.4×10^{-6}
10^{-8}	4.1×10^{-4}	1.6×10^{-7}	1.4×10^{-8}