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CONNECTIONS: THE EARLY HISTORY OF SCIENTIFIC AND MEDICAL RESEARCH ON “AGENT ORANGE”

David A. Butler, Ph.D.¹

INTRODUCTION

Scientists, accustomed to working with and advancing the state of the art, are apt to forget that those in earlier times did not possess the information they take for granted. Individuals in the legal profession tend to have a better appreciation for this reality since their work is grounded in the evolutionary process that defines precedent; indeed, questions of “who knew what and when” are central to some cases. However, lawyers and judges too can benefit from a better understanding of the facts and mindsets that have informed decisions made in the past.

Historical perspective is especially important for understanding environmental health questions because the field has advanced quickly in the past several decades, and the attitudes of exposed populations, industry, government, and medical, scientific, and legal professionals have changed accordingly. “Agent Orange”¹ litigation issues, for example, are the subject of many present-day challenges and fascinations. The events that preceded these challenges are no less interesting. Unfortunately, they remain

¹ The author is Senior Program Officer at the National Academy of Sciences, Institute of Medicine in Washington, D.C., and has directed a number of the National Academies’ studies of Vietnam veterans’ health.

¹ This paper uses the term “Agent Orange” as a catch-all to refer to all of the herbicides employed in Vietnam and the controversy that resulted from that action. The quotation marks are removed when referencing the particular chemical formulation that was given that name.

largely inaccessible to the legal community, in part because historical accounts of salient science and health issues tend to be focused on discrete subissues rather than the larger phenomena at hand² and because they tend to appear in journals or venues³ not frequented by legal scholars. This paper's goal is to address this gap by providing a lay summary of the primary events and advances that defined the "Agent Orange" issue up to the time that the U.S. government decided to suspend herbicide spray operations in Vietnam. In so doing, this paper provides a context for understanding some of the past actions of the parties to this long-running controversy.

I. THE 1870S-1900S: SETTING THE STAGE FOR THE MODERN INDUSTRIAL CHEMICAL AND HERBICIDE INDUSTRIES

The modern chemical industry evolved in the late 1800s as researchers invented and refined mass production processes. These advances led not only to the more-efficient manufacture of existing chemicals, but also to a significant expansion of the variety and properties of new compounds. Among the myriad papers relating experimental results, many of them produced by the formidable German chemical industry complex, is an 1872 account of experiments on wood preservatives.⁴ The researchers included a description of a byproduct of potassium pentachlorophenol production: octachlorodibenzo-*p*-dioxin (OCDD). This is the

² See generally Orvin C. Burnside, *The History of 2,4-D and Its Impact on Development of the Discipline of Weed Science in the United States*, in U.S. DEP'T AGRIC., No. 1-PA-96, NAT'L AGRIC. PESTICIDE IMPACT ASSESSMENT PROGRAM (NAPIAP) 5 (1996) (explaining the history of 2,4-D development); WILLIAM A. BUCKINGHAM JR., U.S. AIR FORCE, OPERATION RANCH HAND: THE AIR FORCE AND HERBICIDES IN SOUTHEAST ASIA, 1961-1971 (1982), available at https://www.airforcehistory.hq.af.mil/Publications/fulltext/operation_ranch_hand.pdf (detailing the Vietnam aerial spray program).

³ See generally NAT'L AGRIC. LIBR., *The Alvin L. Young Collection on Agent Orange*, available at www.nal.usda.gov/speccoll/findaids/agentorange/ (providing numerous references used in this paper).

⁴ V. Merz & W. Weith, *Zur Kenntnis des Perchlorphenols* [*On the Characteristics of Pentachlorophenol*], 5 BERICHTE DER DEUTSCHEN CHEMISCHEN GESELLSCHAFT 458 (1872).

earliest known reference to “dioxin” in the scientific literature. In brief, dioxins⁵ are a class of chemical compounds that are a modern-day public health concern because they accumulate in fat, exhibit high toxicity in some experimental animals, and have been associated with health problems in humans.⁶

An important innovation of this time was the implementation of electrolytic production methods to make chemicals. These methods, which use electric current to catalyze reactions, were far more efficient than earlier techniques and, as a result, led to a significant expansion of the commercial production of chlorine-based and other halogenated compounds.⁷ It appears in hindsight that this expansion had an unintended consequence: for the first time in the medical literature, descriptions and case reports of an acne-like occupational illness associated with exposure to halogens appear. Karl Herxheimer⁸ is responsible for the original account of this disease or was at least the first to refer to the condition by the name that it is now known—*chlorakne* or, in English, chloracne. The condition he described resulted from exposure to tars that were generated during an electrolytic process producing chlorine.⁹

A separate, and at this point distinct, line of scientific inquiry also produced knowledge that would later contribute to the “Agent Orange” story. James Troyer notes that three late nineteenth century botanists (Theophil Ciesielski, Charles Darwin, and Hermann Vöchting) independently established that a stimulus to one part of a plant might result in a response in a different part of the plant.¹⁰ Research conducted in the early twentieth century

⁵ See *infra* App. A (presenting a primer on dioxins).

⁶ NAT’L INST. ENVTL. HEALTH SCI., NAT’L INST. HEALTH, DIOXIN RESEARCH AT THE NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES (NIEHS), available at <http://www.niehs.nih.gov/oc/factsheets/dioxin.htm> (last modified Nov. 18, 2002).

⁷ The halogens are any of five related nonmetallic elements—fluorine, chlorine, bromine, iodine, or astatine—that readily form negative ions and are thus highly reactive.

⁸ Karl Herxheimer, *Über Chlorakne* [Regarding Chloracne], 46 MÜNCHENER MEDIZINISCHE WOCHENSCHRIFT 278 (1899).

⁹ See *infra* App. B (presenting a primer on chloracne).

¹⁰ James R. Troyer, *In the Beginning: The Multiple Discovery of the First Hormone Herbicides*, 49 WEED SCI. 290, 291 (2001) (citing Theophil Ciesielski,

established that this phenomenon was governed by chemical signaling and that plant growth was among the effects that were controlled in this manner. Frits Warmolt Went¹¹ was the first to isolate a growth-controlling substance—3-indoleacetic acid (IAA)—from plant tissues. This class of chemicals later came to be called plant “hormones” because they function in an analogous manner to animal hormones, that is, they produce an effect on the activity of cells remote from their point of origin. Meanwhile, a French viticulturist observed in 1896 that bouillie bordelaise (“Bordeaux mixture”)—a fungicide used in vineyards to control powdery mildew—also eradicated certain weeds.¹² He and other researchers in Germany and the United States pursued this finding and established that copper salts¹³ and other inorganic compounds would kill broadleaf weeds, but not cereals growing in the same area.¹⁴ This was the first indication that some chemicals had *selective* herbicidal properties, and the work stimulated investigations of herbicides that could be used in agricultural applications.

Untersuchungen über die Abwärtskrümmung der Wurzel [Investigations of the Downward Curvature of Roots], 1 BEITRAEGE ZUR BIOLOGIE DER PFLANZEN 1 (1872); CHARLES DARWIN, THE POWER OF MOVEMENT IN PLANTS 592 (1880); Hermann Vöchting, *Über die Lichtstellung der Laubblätter* [Regarding the Position of Leaves in Response to Light], 46 BOTANISCHE ZEITUNG 501 (1888)).

¹¹ Frits Warmolt Went, *On Growth-Accelerating Substances in the Coleoptile of Avena Sativa*, 30 PROCEEDINGS OF THE KONINKLIJKE NEDERLANDSE AKADEMIE VAN WETENSCHAPPEN 10 (1926); Frits Warmolt Went, *Wuchsstoff und Wachstum* [Growth-substance and Growth], 24 RECUEIL DES TRAVAUX BOTANIQUE NEÉRLANDAIS 1 (1928).

¹² COMM. ON THE EFFECTS OF HERBICIDES IN VIETNAM, NAT’L ACAD. SCI., *The Effects of Herbicides in South Vietnam: Part A - Summary and Conclusions*, II-1 (1974), available at <http://www.nal.usda.gov/speccoll/findaids/agentorange/text/00181.pdf>.

¹³ Copper sulfate is an active ingredient in Bordeaux mixture. *Id.* at II-1.

¹⁴ Burnside, *supra* note 2, at 5; see also A. Robert Mazur, *Weeds and Their Control*, USGA GREEN SECTION RECORD, Sept. 1969, at 1, available at <http://turf.lib.msu.edu/1960s/1969/690901.pdf>.

II. THE 1900-1940s: THE FIRST REPORTS OF U.S. HEALTH PROBLEMS FROM EXPOSURE TO DIOXIN-LIKE CHEMICALS

Many of the early reports of chloracne and other diseases now associated with acute dioxin intoxication in occupational settings were associated with the use of chlorinated naphthalenes.¹⁵ Although contemporaneous documentation is lacking, David E. Wells and Jacob de Boer noted that occupational exposure to chlorinated naphthalenes used in the production of gas masks during World War I was associated with numerous incidents of the disease.¹⁶

In 1927, Ludwig Teleky published (in German) an investigation of occupational chloracne, which reported that the fewer the chlorines present in the chlorinated naphthalene, the less the acne in the exposed subject.¹⁷ The first comprehensive study published in English¹⁸ was stimulated by health problems in

¹⁵ Polychlorinated naphthalenes (PCNs) consist of two benzene rings and comprise 75 congeners with between 1 and 8 chlorines; however, in naphthalenes, the rings are directly joined at two adjacent carbons. Their physical and chemical properties are largely similar to those of polychlorinated biphenyls (PCBs), and some exhibit dioxin-like toxicity.

¹⁶ David E. Wells & Jacob de Boer, *Polychlorinated Biphenyls, Dioxins and Other Polyhalogenated Hydrocarbons as Environmental Contaminants in Food*, in ENVIRONMENTAL CONTAMINANTS IN FOOD 305, 305-06 (Colin F. Moffat & Kevin J. Whittle eds., 1999).

¹⁷ Ludwig Teleky, *Die Pernakrankheit [Chloracne]*, 6 KLINISCHE WOCHENSCHRIFT 845 (1927); compare Cecil K. Drinker, *Report to the Monsanto Chemical Company* (Sept. 15, 1938) (evaluating, among other topics, the toxicity of "chlorinated diphenyl #1268"), available at http://www.chemicalindustryarchives.org/search/pdfs/anniston/19380915_545.pdf. This compound—now called Aroclor 1268 or PCB-1268—is highly (68%) chlorinated. Drinker found that it was less toxic than diphenyls that were not as highly chlorinated, exposing a flaw in Teleky's earlier presumption. *Id.* at 9-12.

¹⁸ Barry Commoner, *The Political History of Dioxin*, Keynote Address at the Second Citizens Conference on Dioxin (July 30, 1994), available at <http://www.greens.org/s-r/078/07-03.html> (noting, but not providing a citation for, a 1936 case history in the *Archives of Dermatology and Syphilology* that describes a Monsanto worker who "began work in the distillation of chlorinated diphenyl in April 1930"). The employee experienced severe chloracne and other symptoms that were present more than three years after the initial exposure. *Id.*

employees of the Halowax Corporation, which used chlorinated naphthalenes and PCBs (then called chlorinated diphenyls) to produce coatings for insulating, waterproofing, and fireproofing wires. Cecil Drinker, a physician researcher at Harvard University, was asked by Halowax in the spring of 1936 to investigate these problems, which included three fatal cases of jaundice.¹⁹ In their 1937 paper, Drinker and his colleagues discussed the findings of their laboratory investigations (using a rat model) into the effect of these chlorinated hydrocarbons on the liver. They concluded that systemic effects were possible, but that high-level exposure was required to trigger this result. Accordingly, they concluded that “[c]ompared to benzene . . . and many other compounds, these substances are very little toxic and operations employing them can easily be safeguarded.”²⁰ The Drinker et al. paper includes what is presented as a transcript of a colloquium convened to discuss the findings. Colloquium participants included the chief of the U.S. Public Health Service’s Division of Industrial Hygiene; state health officials from Connecticut, Massachusetts, and Ohio; representatives of the General Electric and Monsanto Chemical companies; and the president of Halowax Corporation.²¹

A number of English-language papers on chloracne and the health impacts of chlorinated naphthalenes followed Drinker’s seminal effort.²² Of particular interest is Leonard Greenburg and

¹⁹ Cecil K. Drinker et al., *The Problem of Possible Systemic Effects from Certain Chlorinated Hydrocarbons*, 19 J. INDUS. HYGIENE & TOXICOLOGY 283 (1937). These cases were previously described by Flinn and Jarvik, who were using laboratory animals to investigate the toxicity of chlorinated naphthalenes. F.B. Flinn & N.E. Jarvik, *Action of Certain Chlorinated Naphthalenes on the Liver*, 35 PROCEEDINGS OF THE SOC’Y FOR EXPERIMENTAL BIOLOGY & MED. 118, 119 (1936).

²⁰ Drinker, *supra* note 19, at 299.

²¹ *Id.* at 300-11.

²² See May R. Mayers & Mabel G. Silverberg, *Skin Conditions Resulting From Exposure to Certain Chlorinated Hydrocarbons*, 20 J. INDUS. HYGIENE & TOXICOLOGY 244 (1938); Cecil K. Drinker, *Further Observations on the Possible Systemic Toxicity of Certain of the Chlorinated Hydrocarbons with Suggestions for Permissible Concentrations in the Air of Workrooms*, 21 J. INDUS. HYGIENE & TOXICOLOGY 155 (1939); *Halowax Acne (Queries and Minor Notes)*, 12 JAMA 471 (1943); Lewis Schwartz & Samuel M. Peck,

colleagues' account of three young adults (two males and one female) "known to have been working with chlorinated naphthalenes and diphenyls" who died after presenting with jaundice and other symptoms.²³ These investigators recommended "conscientious reporting by physicians of *all* illnesses occurring among workers exposed to chlorinated naphthalenes and diphenyls, particularly cases that have been worked up, so that the clinical disease entities resulting from such exposures can be further clarified and thus more readily recognized in the future."²⁴

It is important to note that while these early research efforts associated various health problems with exposure to specific chemicals, they might reflect an incomplete evaluation of the full range of the subjects' exposures. Furthermore, it is unlikely that any tests for contaminants were conducted. While some compounds that workers were exposed to—notably Halowaxes—are strong chloracnegens themselves, impurities in others may have caused or contributed to the reported health problems.

III. THE 1930S-1940S: THE ADVANCEMENT OF PLANT HORMONE RESEARCH

The burgeoning research on plant hormones in the 1930s is now recognized as having laid the foundation for the modern herbicides industry. Fritz Kögl and colleagues²⁵ and Folke Skoog and Kenneth Thimann²⁶ are credited with first observing that IAA

Occupational Acne, 43 N.Y. STATE J. OF MED. 1711 (1943); Thomas P. Connelly & William C. Marsh, *Chloracne (Cable Rash)*, 42 U.S. NAVY MED. BULLETIN 403 (1944).

²³ Leonard Greenburg et al., *The Systemic Effects Resulting from Exposure to Certain Chlorinated Hydrocarbons*, 21 J. INDUS. HYGIENE & TOXICOLOGY 29, 36 (1939).

²⁴ *Id.* at 38 (emphasis in original).

²⁵ Fritz Kögl et al., *Über den Einfluss der auxine auf das Wurzelwachstum und die chemische Natur des Auxins der Graskoleoptilen* [Regarding the Influence of Auxins on Root Growth and the Chemical Nature of the Auxins Found in Maize Coleoptiles], 228 ZEITSCHRIFT FÜR PHYSIOLOGISCHE CHEMIE 104, 121 (1934).

²⁶ Folke Skoog & Kenneth V. Thimann, *Further Experiments on the Inhibition of the Development of Lateral Buds by Growth Hormone*, 20

could either promote or inhibit growth, depending on the concentration used. Several researchers soon identified natural compounds in urine and synthesized others that were chemically similar to IAA and had the same properties.²⁷ The term “auxin”²⁸ was coined to signify both natural and synthetic substances with these properties. The discovery by Percy Zimmerman and Frank Wilcoxon²⁹ that certain phenylacetic acids and naphthylacetic acids (NAA) acted as auxins was particularly important, as this generated interest in aryloxyacetic acids as potential plant growth regulators.³⁰

The aryloxyacetic acids that were to become the primary constituents of Agent Orange were first synthesized in the late 1930s. William Gladstone Templeman’s work in 1936 and 1937, which he documented in a 1939 paper, established that both IAA and NAA could have toxic effects in plants.³¹ However, these compounds were expensive to isolate and not stable in the environment, making them unsuitable for widespread use. Templeman, who was affiliated with Imperial Chemical Industries (ICI), tapped that company’s expertise to synthesize a number of chemically similar compounds. Among these was 2,4-dichlorophenoxyacetic acid (2,4-D), for which a patent application was filed in April 1941. Robert Pokorny, an American working for the specialty chemical company C.B. Dolge, is responsible for the first scientific publication that mentions 2,4-D and the other Agent Orange component: 2,4,5-trichlorophenoxyacetic acid (2,4,5-T). He disseminated one-paragraph descriptions of their synthesis, one after the other, in a March 27, 1941 submission to a section of the

PROCEEDINGS OF THE NAT’L ACAD. OF SCIENCES 480, 482-83 (1934).

²⁷ Burnside, *supra* note 2, at 5-6; Troyer, *supra* note 10, at 291.

²⁸ From the Greek *auxein* meaning “to grow.” See <http://dictionary.reference.com/search?q=auxin>.

²⁹ Percy W. Zimmerman & Frank Wilcoxon, *Several Chemical Growth Substances Which Cause Initiation of Roots and Other Responses in Plants*, 7 CONTRIBUTIONS FROM BOYCE THOMPSON INST. 209, 225-26 (1935).

³⁰ Burnside, *supra* note 2, at 5-6.

³¹ William G. Templeman, *The Effect of Some Plant Growth-Substances on Dry-Matter Production in Plants*, 7 EMPIRE J. OF EXPERIMENTAL AGRIC. 76 (1939).

Journal of the American Chemical Society called "New Compounds."³²

Other researchers were apparently monitoring these developments or working along similar lines because several advances regarding 2,4-D and 2,4,5-T took place over the next few years. Notable among the publications were Percy Zimmerman and Alfred Hitchcock's 1942 findings that 2,4-D was an auxin (establishing its mode of action) and that it was 300 times more powerful than indolebutyric acid, the most widely used growth promoter at the time.³³

IV. THE 1940S: HERBICIDES AND THE MILITARY

In addition to this publicly available work, other research was being conducted that would only become known after wartime secrecy concerns had passed. Gale Peterson³⁴ relates that the chair of the University of Chicago's botany department, Ezra Kraus, was central to this work. Kraus is credited with being the first to note that auxins might be useful as herbicides if applied at sufficiently high doses. An early 1941 letter sent by Kraus to two of his former graduate students—John Mitchell and Charles Hamner—documented the suggestion and led to their initiating research on

³² Robert Pokorny, *New Compounds: Some Chlorophenoxyacetic Acids*, 63 J. OF THE AM. CHEM. SOC'Y 1768 (1941), available at http://pubs.acs.org/cgi-bin/abstract.cgi/jacsat/1941/63/i06/f-pdf/f_ja01851a601.pdf.

³³ Percy W. Zimmerman & Alfred E. Hitchcock, *Substituted Phenoxy and Benzoic Acid Growth Substances and the Relation of Structure to Physiological Activity*, 12 CONTRIBUTIONS FROM BOYCE THOMPSON INST. 321 (1942).

³⁴ Gale E. Peterson, *The Discovery and Development of 2,4-D*, 41 AGRIC. HISTORY 243 (1967). Peterson's history is summarized and in some cases supplemented by the Midwest Research Institute's study of the ecological effects of repeated use of herbicides. See MIDWEST RESEARCH INST., ASSESSMENT OF ECOLOGICAL EFFECTS OF EXTENSIVE OR REPEATED USE OF HERBICIDES (1967) (project monitored by the Department of the Army under contract No. DAHC15-68-C-0119; ARPA Order No. 1086) [hereinafter MRI], available at <http://www.nal.usda.gov/speccoll/findaids/agentorange/text/03632.pdf>; see also Burnside, *supra* note 2; Troyer *supra* note 10. Troyer details the near simultaneous discovery of many of the important properties of phenoxy herbicides by a number of researchers.

the topic later that year.³⁵ Meanwhile, in October 1941, Secretary of War Henry Stimson asked the National Academy of Sciences (NAS) to form a committee to assess the state of knowledge in the field of biological warfare. In a late 1942 or early 1943 presentation to the “War Bureau of Consultants” committee,³⁶ Kraus suggested that “the toxic properties of growth-regulating substances for the destruction of crops or the limitation of crop production” might have military application and should be investigated.³⁷ In response to these comments and recommendations from the NAS committee, research was greatly accelerated. Camp Detrick, Maryland (later named Fort Detrick), which had recently been established as a center for weapons research, began work on herbicides and the U.S. Army poured funding into Kraus’s and other investigators’ studies.³⁸ Of the more than 1,000 potential agents screened, 2,4-D³⁹ and 2,4,5-T were found to be the most promising.⁴⁰ Field trials, including aerial spraying, were conducted in the Florida Everglades, and an ammonium thiocyanate formulation was developed for possible use in the Pacific Theater. However, that war ended without herbicides being used in a military application. It was not until the so-called “Malayan Emergency”—an insurgency that attempted to overthrow the British colonial administration of Malaysia—that herbicides were employed as a weapon. British troops used aerial dissemination of herbicides for defoliation and crop destruction

³⁵ Peterson, *supra* note 34, at 245 & n.12.

³⁶ *Id.* at 246. The committee may have instead been the “ABC committee,” a successor working group given a nonsense name to hide the nature of its work.

³⁷ Ezra J. Kraus & John W. Mitchell, *Growth-Regulating Substances as Herbicides*, 108 BOTANICAL GAZETTE 301, 302 (1947).

³⁸ Peterson, *supra* note 34, at 248.

³⁹ *Id.*; Paul C. Marth & John W. Mitchell, *2,4-Dichlorophenoxyacetic Acid as a Differential Herbicide*, 106 BOTANICAL GAZETTE 224 (1944) (noting the one property that would make 2,4-D among the most popular of the commercial herbicides—it selectively killed dicotyledon plants (dicots, which include broadleaf plants like most weeds) while sparing monocotyledons (monocots, including grasses and many food plants like cereals and grains)). This meant it could be applied on fields and lawns without laying waste to desirable growth. 2,4,5-T also has this property.

⁴⁰ MRI, *supra* note 34.

between 1951 and 1953.⁴¹

V. THE LATE 1940S AND 1950S: THE BEGINNING OF LARGE-SCALE PHENOXY HERBICIDE PRODUCTION AND THE CONTINUATION OF CIVILIAN SECTOR RESEARCH

The commercialization and widespread use of 2,4-D and 2,4,5-T-based herbicides began in the years following the end of World War II, spurred in part by the results of wartime research efforts. As production processes were established and the industry geared up, large numbers of workers were exposed for the first time to the herbicides, their precursors, and unintentional contaminants. This led in 1949 to what is now regarded as the first mass health incident specifically attributable to the dioxin 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (2,3,7,8-TCDD or TCDD). The incident began on March 8, 1949 at a Nitro, West Virginia, plant operated by Monsanto Chemical Corporation. When the temperature and pressure in a reactor vessel (called an autoclave) that was used to make 2,4,5-trichlorophenol⁴² exceeded limits, a safety valve released and vented the vessel's contents into the air outside the building. Workers tasked with the cleanup (there was no decontamination) and repair of the unit and those who were in the vicinity in the days after the incident reported a number of symptoms, including eye and respiratory tract irritation, headache, dizziness, nausea, and severe skin irritation. Within weeks, chloracne, hyperpigmentation, liver function impairment, muscle pain, and a variety of central nervous system disturbances were observed. These health problems were documented in contemporaneous unpublished reports by physicians working for Monsanto,⁴³ but were not addressed in a peer-reviewed journal

⁴¹ VALERIE ADAMS, *CHEMICAL WARFARE, CHEMICAL DISARMAMENT* 74 (1990).

⁴² 2,4,5-trichlorophenol (abbreviated as trichlorophenol or TCP) is a chemical made in an intermediate step of the production process for 2,4,5-T and some other biocides.

⁴³ William F. Ashe & Raymond R. Suskind, *Reports on Chloracne Cases*, Monsanto Chemical Company, Nitro, WV (Oct. 1949 & Apr. 1950) (unpublished reports for Dep't of Env'tl. Health, College of Medicine, Univ. of

until 1980.⁴⁴ Interestingly, Marion Moses et al. indicated that while 117 workers developed chloracne as a result of the incident, an almost equal number (111) showed signs of chloracne prior to this exposure.⁴⁵

There were at least four other exposure incidents associated with TCP in facilities in Germany during the next five years: at a chemical plant in Nordrhein-Westfalen in 1949;⁴⁶ at two C.H. Boehringer Sohn facilities located in the middle Rhine in 1952 and 1953;⁴⁷ at a BASF (Badische Anilin- & Soda-Fabrik) factory in Ludwigshafen in 1953;⁴⁸ and at a Hamburg-Moorfleet plant working under contract to Boehringer in 1954.⁴⁹ The BASF incident also was the result of an autoclave explosion, and involved not only plant workers and persons performing the

Cincinnati); Raymond R. Suskind & William F. Ashe, A Clinical and Environmental Survey, Monsanto Chemical Company, Nitro, W.V. (July 1953) (unpublished report of the Kettering Laboratory, Univ. of Cincinnati) (the authors of this report are also cited as Atkins, Davis, and Suskind in some sources).

⁴⁴ Judith A. Zack & Raymond R. Suskind, *The Mortality Experience of Workers Exposed to Tetrachlorodibenzodioxin in a Trichlorophenol Process Accident*, 22 J. OCCUPATIONAL MED. 11 (1980).

⁴⁵ Marion Moses et al., *Health Status of Workers with Past Exposure to 2,3,7,8-Tetrachlorodibenzo-p-dioxin in the Manufacture of 2,4,5-Trichlorophenoxyacetic Acid: Comparison of Findings With and Without Chloracne*, 5 AM. J. INDUS. MED. 161, 164 tbl.1 (1984).

⁴⁶ E. W. Baader & H. J. Bauer, *Industrial Intoxication Due to Pentachlorophenol*, 20 INDUS. MED. & SURGERY 286 (1951); ALVIN L. YOUNG ET AL., *THE TOXICOLOGY, ENVIRONMENTAL FATE AND HUMAN RISK OF HERBICIDE ORANGE AND ITS ASSOCIATED DIOXIN V-7* (1978).

⁴⁷ H. Bauer et al., *Berufliche Vergiftungen bei der Herstellung von Chlorphenol-Verbindungen* [Occupational Poisonings in the Production of Chlorophenol Compounds], 18 ARCHIV FÜR GEWERBEPATHOLOGIE UND GEWERBEHYGIENE 538 (1961).

⁴⁸ P. J. Goldman, *Schwerste akute Chloracne, eine Massenintoxikation durch 2,3,6,7-Tetrachlorodibenzodioxin* [Severe Acute Chloracne, A Mass Intoxication Due to 2,3,6,7-Tetrachlorodibenzodioxin] 24 DER HAUTARZT 149 (1973); A. M. Thiess et al., *Mortality Study of Persons Exposed to Dioxin in a Trichlorophenol-Process Accident That Occurred in the BASF/AG on November 17, 1953*, 3 AM. J. INDUS. MED. 179, 179-80 (1953).

⁴⁹ A. Manz et al., *Cancer Mortality Among Workers in Chemical Plant Contaminated with Dioxin*, 338 LANCET 959 (1991).

cleanup, but also a child of one of the employees. The child apparently developed chloracne as a result of coming into contact with a contaminated towel and scarf.⁵⁰

Preliminary toxicologic research on the herbicides was also being conducted. LW Kephart reports that Kraus experimented on himself and found no ill effect from ingesting 0.5 grams of 2,4-D per day for three weeks.⁵¹ In 1946, John Mitchell and colleagues published the first animal studies of 2,4-D, stating that cows and sheep grazing on pastures treated with the compound did not manifest toxic effects.⁵² Other early studies include that of Nancy Bucher,⁵³ who found that repeated injections of 2,4-D did not influence the growth rate of sarcomas in mice, and that of Edwin Hill and Harold Carlisle,⁵⁴ who examined acute and subacute effects of ingestion in a variety of mammals and determined toxic doses.

The first toxicity studies of 2,4,5-T were conducted in the 1950s by Dow Chemical Company (Dow)⁵⁵ and the first publication of results was made in 1953.⁵⁶ The authors, who tested

⁵⁰ Goldman, *supra* note 48.

⁵¹ L. W. Kephart, *Panel Discussion on New Chemicals for Weed Control*, 2 PROCEEDINGS OF THE N. CENT. WEED CONTROL CONF. 68 (November 26-28, 1945).

⁵² J.W. Mitchell et al., *Tolerance of Farm Animals to Food Containing 2,4-Dichlorophenoxyacetic Acid* 5 J. ANIMAL SCI. 226, 232 (1946).

⁵³ Nancy L. R. Bucher, *Effects of 2,4-Dichlorophenoxyacetic Acid on Experimental Animals*, 63 PROCEEDINGS OF THE SOC'Y FOR EXPERIMENTAL BIOLOGY & MED. 204, 205 (1946).

⁵⁴ Edwin V. Hill & Harold Carlisle, *Toxicity of 2,4-Dichlorophenoxyacetic Acid for Experimental Animals*, 29 J. INDUS. HYGIENE & TOXICOLOGY 85, 94-95 (1947).

⁵⁵ COLIN M. MACLEOD, EXECUTIVE OFFICE OF THE PRESIDENT, REPORT ON 2,4,5-T: A REPORT OF THE PANEL ON HERBICIDES OF THE PRESIDENT'S SCIENCE ADVISORY COMMITTEE 39 (1971).

⁵⁶ Victor A. Drill & Tomiharu Hiratzka, *Toxicity of 2,4-Dichlorophenoxyacetic Acid and 2,4,5-Trichlorophenoxyacetic Acid: A Report on Their Acute and Chronic Toxicity in Dogs*, 7 A.M.A. ARCHIVES INDUS. HYGIENE & OCCUPATIONAL MED. 61 (1953). ENVTL. PROT. AGENCY, REP. OF THE ADVISORY COMM. ON 2,4,5-T TO THE ADMIN. OF THE ENVTL PROT. AGENCY, (1971) (incorrectly asserting that the first 2,4,5-T toxicology paper was not published until 1963) [hereinafter REPORT OF THE ADVISORY

the effects of ingestion on dogs, found that their highest dose level (20 mg/kg/day) resulted in death, but that animals that survived lower dose levels did not develop significant lesions in the liver or other organs. The extent to which the 2,4,5-T used in these experiments may have been contaminated with dioxins is not known.⁵⁷

VI. 1957: THE CONNECTION IS MADE

Thus, by the mid-1950s, there had been a series of incidents in which workers exposed to 2,4,5-trichlorophenol had experienced a set of health problems that had previously been seen in industries using polychlorinated naphthalenes (PCDDs) and polychlorinated biphenyls (PCBs). The physicians treating these workers had advanced various theories to explain the source of the health problems but had yet to identify a mechanism. The set of events that would clarify this connection began in 1956. Karl H. Schulz, a physician in the Department of Dermatology at the Eppendorfer Krankenhaus in Hamburg, was referred a patient from the Boehringer Hamburg-Moorfleet factory who was suffering from chloracne.⁵⁸ The case stimulated Schulz to begin studying chloracne problems at the facility. In cooperation with a chemist there named Georg Sorge, Schulz obtained samples of 2,4,5-T that had been manufactured at various levels of purity. Tests performed on rabbit ears showed that the highest purity samples (formulated for use in experimentation) did not elicit a skin reaction, while the

COMMITTEE], *available at* <http://www.nal.usda.gov/speccoll/findaids/agentorange/text/01152.pdf>.

⁵⁷ Later research would show that there are unusually large variations between and among species in susceptibility to TCDD's effects. For example, several thousand times more TCDD is needed to kill a hamster than a guinea pig, when doses are equalized by body weight. AGENCY FOR TOXIC SUBSTANCES & DISEASE REGISTRY, U.S. DEP'T HEALTH & HUMAN SERVICES, TOXICOLOGICAL PROFILE FOR CHLORINATED DIBENZO-*P*-DIOXINS 11 (1998) [hereinafter ATSDR], *available at* <http://www.atsdr.cdc.gov/toxprofiles/tp104.pdf>. This characteristic makes it difficult to translate animal tests of dioxin toxicity to humans.

⁵⁸ Bo Holmstedt, *Prolegomena to Seveso Ecclesiastes I* 18, 44 ARCHIVES OF TOXICOLOGY 211, 216 (1980).

so-called "technical grade" samples (formulated for use in chemical processes such as 2,4,5-T production) did.⁵⁹ This suggested that some impurity in lower-grade TCP was chloracnegenic. At about the same time, a team of researchers led by Wilhelm Sandermann of the University of Hamburg synthesized TCDD while investigating new chlorophenols for use as wood preservatives. An assistant on the team developed chloracne when some of the dried compound accidentally blew into his face.⁶⁰ He was referred to Schulz, who recognized the possible connection with his other chloracne cases and contacted Sorge.⁶¹ The chemist isolated TCDD from technical grade TCP and independently synthesized the dioxin; both yielded positive results in rabbit ear tests conducted by Schulz. The connection was confirmed when Schulz applied a 0.01% solution of TCDD to his forearm and developed a chloracneform lesion within the next several days.⁶²

In 1957, Schulz and a colleague published three papers (in German) implicating TCDD as the causative agent in the chloracne observed in persons exposed to chlorinated hydrocarbons.⁶³ Sandermann et al. also released their description of TCDD synthesis, again in German.⁶⁴ Michael Gough reports that although

⁵⁹ *Id.* at 217. There was no economic incentive to eliminate trace contaminants that did not affect the performance of the final product.

⁶⁰ MICHAEL GOUGH, DIOXIN, AGENT ORANGE: THE FACTS 31 (1986).

⁶¹ *Id.*

⁶² *Id.* at 33; Moses, *supra* note 45, at 161-62.

⁶³ J. Kimmig & K. H. Schulz, *Berufliche Akne (sog. Chlorakne) Durch Chlorierte Aromatische Zyklische Äther* [Occupational Acne (So-Called Chloracne) Due to Chlorinated Aromatic Cyclic Ether], 115 DERMATOLOGIA 540 (1957); J. Kimmig & K. H. Schulz, *Chlorierte Aromatische Cyclische Äther als Ursachen der Sogenannten Chlorakne* [Chlorinated Aromatic Cyclic Ethers as the Cause of Chloracne], 44 NATURWISSENSCHAFTEN 337 (1957); K. H. Schultz, *Klinische und Experimentelle Untersuchungen zur Ätiologie der Chlorakne* [Clinical and Experimental Investigations into the Etiology of Chloracne] 206 ARCHIV FÜR KLINISCHE UND EXPERIMENTELLE DERMATOLOGIE 589 (1957).

⁶⁴ W. Sandermann et al., *Über die Pyrolyse des Pentachlorphenols* [Regarding the Pyrolysis of Pentachlorophenols] 90 CHEMISCHE BERICHTE (BERICHTE DER DEUTSCHEN CHEMISCHEN GESELLSCHAFT) 690 (1957).

Sorge did not turn out any papers, his research was applied by Boehringer to reduce TCDD contamination in the production process.⁶⁵

VII. THE LATE 1950S-1960S: MILITARY USES OF HERBICIDES AGAIN COME TO THE FORE

U.S. military interest in herbicides did not end with the WWII research effort, although the pace of work diminished after the end of the conflict. Wartime herbicide development and candidate screening programs were terminated in 1950, and a much lower level effort was carried on between 1950 and 1957 under the general rubric of anticrop warfare research.⁶⁶ Alvin Young and colleagues indicate that one of the findings made by Fort Detrick investigators (in 1951) was that mixtures of the butyl esters of 2,4-D and 2,4,5-T were the chemicals of choice for vegetation control.⁶⁷ Research also included some refinement of aerial dissemination hardware and the testing of formulations in Puerto Rico.⁶⁸

All herbicide research funding at Fort Detrick ended in fiscal year 1958 and the facility's remaining stock was turned over to the U.S. Department of Agriculture (USDA). However, only months later, the facility was asked to help clear vegetation from an

⁶⁵ Gough, *supra* note 60, at 33.

⁶⁶ WILLIAM F. WARREN, A REVIEW OF THE HERBICIDE PROGRAM IN SOUTH VIETNAM (1968), *available at* <http://www.nal.usda.gov/speccoll/findaids/agentorange/text/03121.pdf>.

⁶⁷ ALVIN L. YOUNG ET AL., THE TOXICOLOGY, ENVIRONMENTAL FATE AND HUMAN RISK OF HERBICIDE ORANGE AND ITS ASSOCIATED DIOXIN (1978), *available at* <http://www.nal.usda.gov/speccoll/findaids/agentorange/text/01165.pdf>.

⁶⁸ J. van Overbeek & Ismael Vélez, *Use of 2,4-Dichlorophenoxyacetic Acid as a Selective Herbicide in the Tropics*, 103 SCIENCE 472 (1946); F. P. HUDDLE, A TECHNOLOGY ASSESSMENT OF THE VIETNAM DEFOLIANT MATTER, REPORT TO THE SUBCOMMITTEE ON SCIENCE, RESEARCH, AND DEVELOPMENT OF THE COMMITTEE ON SCIENCE AND ASTRONAUTICS, 91ST CONG. (1st Sess. 1969), *available at* <http://www.nal.usda.gov/speccoll/findaids/agentorange/text/05167.pdf>.

artillery test range at Fort Drum in New York.⁶⁹ Some of the stock was retrieved and the operation was carried out in June 1959. An undiluted 1:1 mixture of butyl esters of 2,4-D and 2,4,5-T (this formulation was later called "Purple," and then "Agent Purple") was sprayed from booms attached to a helicopter⁷⁰ over a four square mile area at a concentration of approximately 6 lbs/acre.⁷¹ Operation director James W. Brown, a researcher in the Crops Division at Fort Detrick, reported that the leaves of the hardwood trees (primarily sugar maples) in the testing area turned color shortly after the application and appeared brown and dead after about a month.⁷²

The operation was deemed a success, and in May 1961, the Department of Defense's (DOD's) Advanced Research Projects Agency tasked Brown and other Fort Detrick researchers to travel to Vietnam and evaluate the effect of various herbicides, formulations, and application methods on indigenous trees and foodstuffs.⁷³ Of the eighteen formulations tested, the Agent Purple mix of 2,4-D and 2,4,5-T and one other formulation were deemed the best.⁷⁴ This determination was based not only on efficacy, but also on cost, availability of large quantities, and "known or proven safety in regard to their toxicity to humans and animals."⁷⁵

In the first aerial herbicide spray mission, which was conducted on January 10, 1962, Agent Purple was applied to an area adjacent

⁶⁹ KENT R. IRISH ET AL., DEP'T ARMY, INFORMATION MANUAL FOR VEGETATION CONTROL IN SOUTHEAST ASIA (Dec. 1969), *available at* <http://www.nal.usda.gov/speccoll/findaids/agentorange/text/00073.pdf>.

⁷⁰ JAMES W. BROWN, U.S. ARMY CHEM. CORPS RESEARCH & DEV. COMMAND, VEGETATIONAL SPRAY TESTS IN SOUTH VIETNAM, SUPPLEMENT (U) 26 (1962), *available at* <http://www.nal.usda.gov/speccoll/findaids/agentorange/text/00337.pdf>.

⁷¹ *Id.* at 9.

⁷² *Id.* at 10.

⁷³ *Id.* at 4, 9.

⁷⁴ *Id.* at 18-20. The other was Agent Blue, which was composed of the acid and sodium salt of cacodylic acid (also called dimethylarsinic acid). *Id.* at 19 tbl.1. Agent Blue was used against rice crops, where 2,4-D and 2,4,5-T were ineffective.

⁷⁵ *Id.* at 9.

to a target that had been sprayed with Agent Pink⁷⁶ during a test mission a few weeks earlier. Several available accounts of the program (known as “Operation Ranch Hand”) detail the conduct of the missions and the range of herbicide agents used.⁷⁷

VIII. THE MID- TO LATE-1960S: CONCERNS OVER HEALTH IMPACTS FROM WARTIME HERBICIDES EXPOSURE

Domestic manufacturers struggled to meet the great demand for herbicides that stemmed from the Vietnam conflict.⁷⁸ Among their efforts was an initiative by Dow in a Midland, Michigan, plant to expand its 2,4,5-T capacity through a new production process. Chloracne cases started appearing in the workforce soon after production began, and Dow responded by shutting down the facility and alerting other manufacturers to the problem. TCDD was implicated as the causative agent. When the plant reopened in 1966, it used a revamped production process that limited TCDD contamination to less than 1 part per million (ppm).⁷⁹

The mid-1960s was also a time of burgeoning interest in studies of the mutagenic, carcinogenic, and reproductive effects of chemicals. The National Cancer Institute launched an investigation

⁷⁶ *Id.* at 87. Agent Pink was a 60:40 mix of the n-butyl and isobutyl esters of 2,4,5-T. The formulation was used only sparingly during the war. *Id.* at 19 tbl.1.

⁷⁷ See, e.g., BUCKINGHAM, *supra* note 2; INSTITUTE OF MEDICINE, VETERANS AND AGENT ORANGE: HEALTH EFFECTS OF HERBICIDES USED IN VIETNAM (1994) [hereinafter IOM]. There are numerous subsequent publications in the VETERANS AND AGENT ORANGE report series, including 1996, 1998, 2000, 2002, and 2004 Updates. See also Jeanne Mager Stellman et al., *The Extent and Patterns of Usage of Agent Orange and Other Herbicides in Vietnam*, 422 NATURE 681 (2003).

⁷⁸ The need for Agent Orange and its chemical precursors exceeded the total domestic production capacity in late 1966 and the Defense Production Act of 1950 was invoked in March 1967 to accelerate delivery of supplies. See Jonathan Glasser, *The Government Contract Defense: Is Sovereign Immunity A Necessary Prerequisite?*, 52 BROOK. L. REV. 495, 512-14 (1986) (addressing some of the legal implications of invoking the Defense Production Act of 1950 for manufacturers of Agent Orange—a major issue in the *In re Agent Orange* litigation).

⁷⁹ MACLEOD, *supra* note 55, at 17.

of the tumorigenic, mutagenic, and teratogenic potential of a number of insecticides and herbicides in 1965 and gave the contract to Bionetics Research Laboratories. Aerial spray operations in Vietnam significantly increased in 1966 and 1967, and there is evidence that the Viet Cong (VC)⁸⁰ became concerned about the health effects associated with exposure to herbicides. An Air Force tactical evaluation written in 1967 and declassified in 1974 stated:

Even some [Viet Cong] leaders have misconceptions of the effects of the herbicides. VC medical officers instruct members of units not to eat the contaminated food as it would "damage their health and cause stomach and liver disorders". . . . Another official VC document . . . directs the units to not allow livestock to graze in sprayed areas or to be given food that has been sprayed. VC officials also instructed the men to wear homemade or issued gas masks as "bodily contact would cause physical harm or in some cases even death."⁸¹

The report also stated that "[i]t must be remembered that the chemical spray is non-toxic and has had no effects on aircrews or [south Vietnamese] regular troops, nor have there been any ill-effects reported during use of these chemicals in the United States," and attributed claims to the contrary among the Vietnamese to mistaken beliefs or propaganda.⁸²

Opposition to the wartime use of herbicides within the academic community in the United States led to a series of position statements and petitions from individuals and organizations. These culminated in a September 13, 1967 letter from the president of the American Association for the Advancement of Science (AAAS) to

⁸⁰ "Viet Cong"—short for *Viet Nam Cong San* (Vietnamese communists)—is term used in the United States to refer to the rebels that fought for the National Front for the Liberation of Southern Vietnam, which was also known as the National Liberation Front. See <http://www.encyclopedia.com/html/v/vietclong.asp> (last visited Apr. 10, 2005).

⁸¹ CHARLES V. COLLINS, HERBICIDE OPERATIONS IN SOUTHEAST ASIA JULY 1961-JUNE 1967 54 (1967) available at <http://www.nal.usda.gov/speccoll/findaids/agentorange/text/03116.pdf>.

⁸² *Id.* at 47.

Secretary of Defense Robert McNamara suggesting that an independent study be initiated to evaluate the short- and long-term consequences of the military's use of herbicides in Vietnam.⁸³ The DOD had already commissioned the Midwest Research Institute to do such a study, which was released that December.⁸⁴ The report summarized the then-available literature on ecologic studies of the "extensive or repeated use of herbicides" and on toxicologic effects.⁸⁵ The authors recommended that additional research be undertaken into the possible teratogenic and carcinogenic activity of the active ingredient in Agent Blue, but did not offer any suggestions regarding 2,4,5-T or the other herbicides used in agent formulations.⁸⁶ Dioxin is not mentioned in the report's more than 370 pages of text.

Two events in the summer of 1969 changed the outlooks of many with regard to the safety of wartime herbicide spraying. Between June 26 and July 5, 1969, newspapers in Vietnam published accounts of increased rates of birth defects in areas in which spraying had taken place.⁸⁷ These reports raised public concern and prompted two surveys of hospital records.⁸⁸ Results of 2,4,5-T testing, conducted as part of the Bionetics study, also started circulating in public that summer. The study, which was the first to address an outcome related to low-level exposure, found that ingested and injected 2,4,5-T could cause birth defects in some

⁸³ See, e.g., BUCKINGHAM, *supra* note 2.

⁸⁴ See MRI, *supra* note 34, at 139.

⁸⁵ *Id.*

⁸⁶ *Id.* at 164.

⁸⁷ REPORT OF THE ADVISORY COMMITTEE, *supra* note 56, at 51.

⁸⁸ The results of one of the surveys were published in December 1970. ROBERT T. CUTTING ET AL., DEP'T DEF., CONGENITAL MALFORMATIONS, HYDATIDIFORM MOLES AND STILLBIRTHS IN THE REPUBLIC OF VIETNAM, 1960-1969 (1970), available at <http://www.nal.usda.gov/speccoll/findaids/agentorange/text/00579.pdf>. Findings from the second were presented a few months after the spray missions had been discontinued. MATTHEW S. MESELSON ET AL., HERBICIDE ASSESSMENT COMM'N AM. ASS'N FOR THE ADVANCEMENT OF SCI., BACKGROUND MATERIAL RELEVANT TO PRESENTATIONS AT THE 1970 ANNUAL MEETING OF THE AAAS 23-25 (1971), available at <http://www.nal.usda.gov/speccoll/findaids/agentorange/text/00900.pdf>.

laboratory animals.⁸⁹ These events compelled the White House to order a partial curtailment of the use of Agent Orange in Vietnam on October 29, 1969.⁹⁰ Concurrently, restrictions were placed on the use of 2,4,5-T on food crops.⁹¹ The Secretary of Health, Education, and Welfare,⁹² and the Secretaries of Agriculture and the Interior jointly announced the suspension of many uses of the herbicide on April 15, 1970; the DOD temporarily suspended the military use of 2,4,5-T the same day.⁹³ There were limited stocks of the other agent formulations and supplies quickly ran out. The last fixed-wing defoliation mission was flown on May 9, 1970, although limited crop destruction missions were carried out throughout the rest of the year. On January 7, 1971, aerial spray missions came to an end. Research on the longer term and lower exposure level effects of Agent Orange herbicides intensified soon thereafter, and investigations into dioxin’s biological effects and health impacts began in earnest. This work and its influence on policy and other issues are addressed in accompanying papers in this volume.

CONCLUSION

The early history of “Agent Orange” may therefore be viewed as a series of connections between what began in the late 1800s as distinct lines of scientific, technological, and medical inquiry.⁹⁴

⁸⁹ A paper reporting salient results appeared in the journal *Science* on May 15, 1970. K. Diane Courtney et al., *Teratogenic Evaluation of 2,4,5-T*, 168 *SCIENCE* 864 (1970). It included a note (apparently added on 9 April of that year) that stated that the 2,4,5-T used in testing was contaminated with ~30ppm TCDD. *Id.* at 866.

⁹⁰ REPORT OF THE ADVISORY COMMITTEE, *supra* note 56, at 3.

⁹¹ MACLEOD, *supra* note 55, at 8.

⁹² The U.S. Department of Health, Education, and Welfare was renamed the U.S. Department of Health and Human Services in 1980 upon the passage of the Department of Education Organization Act of 1979, 20 U.S.C. § 3441 (2005), which created a separate Department of Education. See <http://www.hhs.gov/about/hhshist.html>.

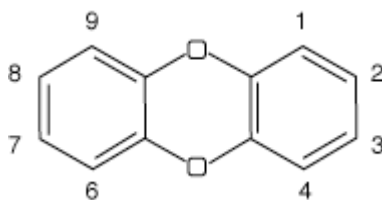
⁹³ BUCKINGHAM, *supra* note 2, at 166.

⁹⁴ This inquiry takes its inspiration from *Connections* (BBC and Time Life 1978), a series of documentaries on the history of major scientific and technical

While much remains to be learned, we now have more than thirty-five years of relatively intense research to consult when making decisions about the effects of herbicide and dioxin exposure on humans. The antecedents addressed here yield perspective on the decisions made by industry executives, government officials, and military planners by shedding light on when they may have been aware of particular elements of the “Agent Orange” story.

Appendix: A Dioxin Primer

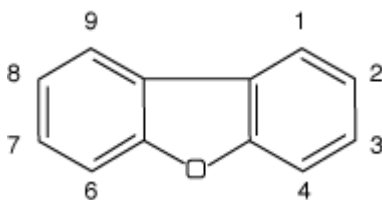
“Dioxin” is the general name given to organic compounds containing carbon, oxygen, and hydrogen with one to eight chlorine atoms. Chlorinated dibenzo-*p*-dioxins (CDDs) are a family of seventy-five different compounds (called congeners) that share the parent chemical structure illustrated by the stylized diagram below:



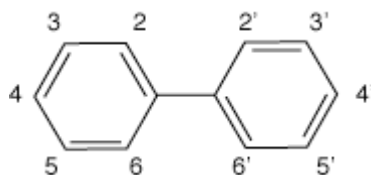
A chemist would describe this structure as comprising two benzene rings (hence, *dibenzo*) joined via two oxygen bridges (*dioxin*) at adjacent carbons on the benzene rings; the “-*p*-” in the chemical name is an abbreviation for *para*, the nomenclature for the position of the oxygens with respect to one another. The seven polychlorinated dioxins (PCDDs) that have chlorine atoms at the 2, 3, 7, and 8 positions are more toxic than other congeners. Among these, the congener with four chlorine atoms at these positions only—2,3,7,8-tetrachlorodibenzo-*p*-dioxin (2,3,7,8-TCDD)—is the most potent and by far the most studied.⁹⁵ 2,3,7,8-TCDD is often (and confusingly) shorted to “dioxin” in the popular literature.

⁹⁵ ATSDR, *supra* note 57, at 11 (stating that 2,3,7,8-TCDD is the “most extensively studied CDD and it has been shown to cause a large number of adverse health effects in animals”).

Researchers often include two structurally-related compounds in their consideration of health effects: chlorinated dibenzofurans (CDFs) and so-called “dioxin-like” polychlorinated biphenyls (PCBs):



dibenzofuran parent structure



biphenyl parent structure

CDFs differ from CDDs by having one direct carbon-carbon bond substitute for one of the oxygen bridges. There are ten polychlorinated dibenzofurans (PCDFs) with chlorine atoms at the 2, 3, 7, and 8 positions out of the 135 congeners.⁹⁶ A single carbon-carbon bond unites the two benzene rings that make up the basic structure of PCBs. This bond allows the rings to rotate relative to one another, which means that many do not have the planar structure that contributes to the toxic potential of PCDDs and PCDFs. However, the World Health Organization identifies two coplanar (also called “non-ortho substituted”) PCB congeners—3,3',4,4',5-pentachlorobiphenyl (PCB-126) and 3,3',4,4',5,5' hexachlorobiphenyl (PCB-169)—as having considerable dioxin-like toxicity and ten similar congeners as having some dioxin-like toxic potential.⁹⁷

When evaluating the dioxin-related toxicity of a chemical

⁹⁶ This is different than the number of PCDDs with this configuration because the structure of PCDFs allows combinations of chlorine atoms that are not physically possible with PCDDs.

⁹⁷ Martin Van den Berg et al., *Toxic Equivalency Factors (TEFs) for PCBs, PCDDs, PCDFs for Humans and Wildlife*, 106 ENVTL. HEALTH PERSPECTIVES 775 (1998).

exposure, health researchers often use toxic equivalents (TEQs). TEQ is a means of calculating the toxicity-weighted masses of exposures consisting of mixtures of dioxins. It employs toxic equivalency factors (TEFs) that indicate the potency of a congener with relation to 2,3,7,8-TCDD, which has the reference value of 1. TEFs are consensus values derived from the results of *in vivo* (animal) and *in vitro* (cellular) studies and are different for humans and other animals because species vary greatly in their sensitivity to dioxin. The TEQ of a mixture is the sum of the concentrations of the congeners in it multiplied by their TEFs.

APPENDIX B: A CHLORACNE PRIMER

Chloracne is an acne-like rash characterized by the formation of large numbers of comedones (plugs of sebaceous and dead skin material stuck in the opening of a hair follicle) on the face. In more severe cases, cysts also form on the shoulders, chest, back, abdomen, and extremities. Dioxin-associated chloracne can result from skin contact, ingestion, or inhalation exposure.⁹⁸ However, chloracne is not considered to be a good biomarker for dioxin exposure because individuals vary widely in the dose required to induce a skin reaction.⁹⁹ Over the years, several names have been used to refer to what is here termed "chloracne," including Pernakrankheit or Perna disease (because it was caused by exposure to *perchloronaphthalene*), chloric or chlorine acne, halogen acne, Halowax acne, and cable rash.¹⁰⁰ The mechanism by which dioxin causes skin lesions is not understood. Early researchers thought that skin exposure to dioxin-containing chemicals plugged the pores, but because the effect also occurs in inhalation and ingestion exposures, this explanation is clearly inadequate. Acute dioxin intoxication has other health

⁹⁸ CANADIAN CENTRE FOR OCCUPATIONAL HEALTH AND SAFETY (CCOHS), *What is Occupational Acne?*, available at <http://www.ccohs.ca/oshanswers/diseases/acne.html> (last updated Dec. 1, 1997).

⁹⁹ IOM, *supra* note 77, at 262.

¹⁰⁰ P. D. HOWE ET AL., WORLD HEALTH ORGANIZATION, CHLORINATED NAPHTHALENES, CONCISE INT'L CHEM. ASSESSMENT DOC. 34, 27 (2001), available at <http://www.who.int/ipcs/publications/cicad/en/cicad34.pdf>.

consequences, including gastrointestinal symptoms (nausea, vomiting, epigastric pain, and loss of appetite) and liver damage.¹⁰¹ As early as 1919 it was known that these symptoms appeared in animals fed chlorinated naphthalenes.¹⁰² Epidemiologic studies also indicate long-term effects from low-level exposure. A full discussion of this sometimes-controversial topic is beyond the scope of this paper. However, several sources address it, including the Institute of Medicine's *Veterans and Agent Orange* series of reports and the U.S. Environmental Protection Agency's ongoing dioxin reassessment.¹⁰³

¹⁰¹ Alexandra Geusau et al., *Severe 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) Intoxication: Clinical and Laboratory Effects*, 109 ENVTL. HEALTH PERSPECTIVES 865, 865-66 (2001).

¹⁰² K.B. LEHMANN, *KURZES LEHRBUCH DER ARBEITS - UND GEWERBEHYGIENE* [SHORT TEXTBOOK OF WORK AND TRADE HYGIENE] (1919).

¹⁰³ IOM, *supra* note 77; *see also* U.S. ENVTL. PROT. AGENCY, EXPOSURE AND HUMAN HEALTH REASSESSMENT OF 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN (TCDD) AND RELATED COMPOUNDS, REVIEW DRAFT, PART I (Dec. 2003), *available at* <http://www.epa.gov/ncea/pdfs/dioxin/nas-review/>.