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EVALUATION OF THE TOXICOLOGY OF PCBs

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Prepared for

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I. EXECUTIVE SUMMARY

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Polychlorinated biphenyls (PCBs) are a class of chemical compounds that were widely used as lubricants and fluids in electrical equipment, among many other uses, until concerns about their potential hazards from environmental exposures arose in the 1970s. This report sets out an assessment of the available scientific literature concerning the hazards, particularly cancer, resulting from human exposure to PCBs. It was prepared under the guidance of a panel of internationally recognized experts in medicine, toxicology, and epidemiology and has been subjected to scientific peer review. (The curricula vitae of the panel are set out in Appendix A.) The panelists have unanimously endorsed the findings presented in the study.

The study focuses on whether low-level environmental exposure to PCB is likely to cause cancer in humans. The panel observes that other possible human impacts from low-level environmental exposures to PCBs are of far lower likelihood than any possible carcinogenic effects. Health effects, other than carcinogenicity, that have been observed following exposure of laboratory animals to PCB mixtures include liver and stomach lesions and reproductive effects. The panel notes that these effects, as well as skin lesions (i.e., chloracne) that have been reported in humans following exposure to very high levels of PCBs, occur at higher doses than those associated with risk levels of concern for potential carcinogenic effects. Thus, exposure levels that pose no significant risk of cancer should not be of concern with regard to other health effects.

A variety of epidemiologic studies have examined whether PCB-exposed workers have incurred a greater likelihood of cancer mortality than the general population. The report summarizes the literature in the field. The panel concludes that the body of epidemiological evidence does not demonstrate a causal relationship between PCB exposure and any form of cancer. This conclusion is confirmed by reviews of several other expert groups, including the EPA, FDA, and the World Health Organization. In light of the long-term and widespread usage of PCBs in numerous industrial settings and the extensive exposure of workers in some cases, it is likely that evidence of carcinogenicity would have already been revealed by the studies if PCBs were in fact a potent human carcinogen.

Experiments have also been conducted with laboratory animals to estimate the potential impacts of PCBs on humans. In such studies the subject animals are chronically exposed over a long time period to high doses of PCBs through, for example, the addition of PCBs to the animals' food. The studies show that, of the PCB mixtures that have been adequately tested, only certain mixtures -- commercial mixtures of PCBs containing approximately 60 percent chlorine by weight (Aroclor 1260 and Clophen A60) -- produce a statistically significant increase in the incidence of malignant liver tumors in rodents. In a study conducted by the National Cancer Institute, Aroclor 1254 (approximately 54% chlorine by weight) was not found to be carcinogenic. Other Aroclors have not been tested in acceptable animal bioassays for carcinogenicity. Clophen A30, which closely matches Aroclor 1242 in composition (approximately 42 percent chlorine by weight), has been tested; it causes an increase in benign (non-cancerous) liver tumors and is less potent than Clophen A60 when both mixtures were tested in bioassays of identical design.

Based on the fact that no statistically significant increase in malignant tumors is seen in animal studies with lower chlorinated PCB mixtures, the panel concludes that, if the lower chlorinated PCB mixtures are carcinogenic at all, their potencies are far less than those of mixtures with 60 percent chlorine content.

The panel points out that animal studies have limitations as a reliable indicator of effects in humans. Because of interspecies differences in factors such as absorption, metabolism, and elimination of a test substance, effects that are observed in animals may not occur in human populations, or may occur with different frequencies. Moreover, in order to apply the results from animal studies to humans, it is necessary to make adjustments to account for the fact that environmental exposures of humans are many orders of magnitude less than those to which the rodents were exposed in the animal studies. There are substantial experimental data from which it can be inferred that the carcinogenic effects, if any, from PCB exposure arise only after a certain threshold exposure has been exceeded. Thus, at the low doses that are typical from human environmental exposures to PCBs, the panel concludes that no cancer risk may exist.

Despite the limitations of the animal data, it is common for regulatory agencies to estimate potential risks to humans by extrapolating observations in highly exposed animals to humans. The typical extrapolation procedure also assumes the absence of a threshold and a direct proportion between risk and exposure at low doses. Such an application of the animal data reflects a policy decision to adopt a conservative estimate of potential human risk from exposure, and it is the approach taken in this report. Even if this approach were applied to the data on PCBs, however, the panel concludes that it is necessary, at the least, to recognize the differences in potency among the various types of PCB mixtures. The report defines the appropriate adjustments for the various mixtures.

In summary, while the data show that some carcinogenic effects are observed in rodents that are exposed over a long term to high doses of 60 percent chlorinated PCB mixtures, these animal data have uncertain implications for human exposure. Moreover, no statistically significant increase in malignancies are seen in animals exposed to high levels of lower chlorinated PCB mixtures. Thus, even if the animal data were deemed relevant to the environmental exposure of humans, at the least, adjustments must be made for lower potency of the lower chlorinated PCB mixtures. In any event, the panel concludes that the evidence does not demonstrate a causal relationship between exposure to PCBs of any type and any form of human cancer.

II. INTRODUCTION

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Polychlorinated biphenyls (PCBs) are a class of chemical compounds that were widely used as lubricants and as fluids in electrical equipment, among many other uses, until concerns about their potential hazards arose in the late 1970s.

This report examines the available scientific data regarding the potential carcinogenicity of commercial PCB mixtures. It has been prepared by a group of independent experts who have been engaged to assist Texas Eastern and subjected to scientific peer review. The curricula vitae of the members of the group are set out as Appendix A.

This analysis is confined to an examination of the data regarding the potential tumorigenicity of PCBs because this is the toxicity endpoint of primary concern with regard to low-level, environmental exposures to PCBs. Other health effects demonstrated in animal models occur at higher doses than the doses associated with risk levels of concern for potential tumorigenic effects. Thus, the exposure levels that pose no significant risk for tumorigenicity from chronic exposure should not be of concern for other health effects.

III. SCIENTIFIC EVIDENCE RELATED TO THE
TUMORIGENIC POTENTIAL OF PCBs

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A. Summary and Conclusions

This report provides a summary of epidemiological and toxicological data related to the potential tumorigenic effects of PCBs. The data reveal that there is insufficient evidence to classify PCBs as human carcinogens, i.e., the available epidemiological data do not show a causal relationship between PCB exposures and human cancer. This conclusion is supported by reviews conducted by several expert panels (e.g., EPA 1988, ATSDR 1987).

The data also show that certain mixtures of PCBs, those associated with Aroclor 1260,^{1/} produce excess tumors^{2/} of the liver in rodents in long-term feeding studies at very high doses. Because there is some equivocal evidence that other mixtures of PCBs may produce excess tumors in experimental animals, we cannot reject the hypothesis that other mixtures of PCBs (those associated with other Aroclors) are animal tumorigens. Nevertheless, it will be shown that, if these other mixtures of PCBs are tumorigens, they are certainly of lower tumorigenic potency (tumorigenic risk per amount of exposure) than those associated with Aroclor 1260.

^{1/} As will be discussed herein, there are a variety of different types of PCBs. Aroclor 1260 was a tradename for a particular PCB mixture containing 60 percent chlorine by weight. Lower chlorinated Aroclor mixtures (for example, Aroclors 1248 and 1242, 48 and 42 percent chlorine, respectively) were also widely used.

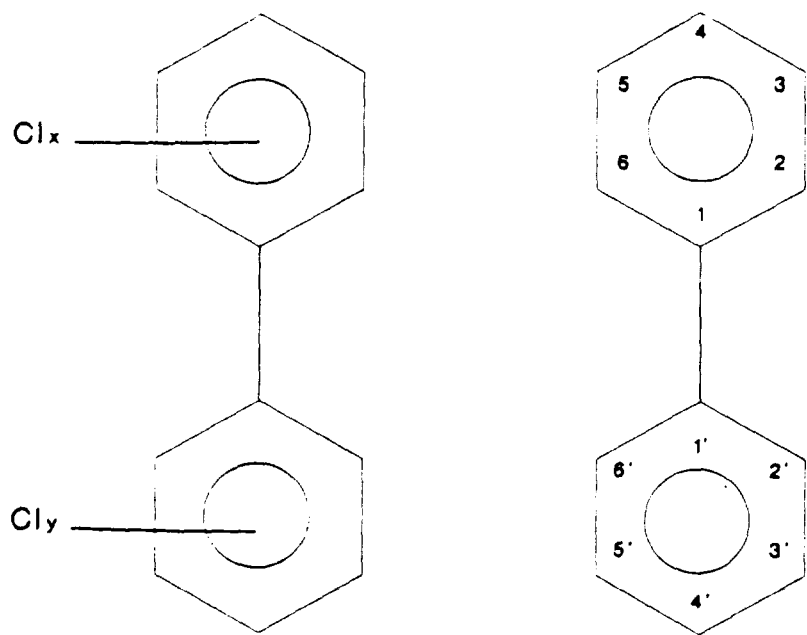
^{2/} The excess tumors may be either benign (non-cancerous) or malignant (cancerous). It is conservatively assumed by regulatory agencies that both types should initially be counted equally in estimating carcinogenic potency. PCBs are therefore referred to as tumorigens, i.e., capable of producing either type of tumor.

In the concluding part of this report, we shall present estimates of the tumorigenic potencies of the mixtures of PCBs associated with Aroclors 1260, 1254, 1248, 1242, and 1232. These potency values are included in this report because of their use in estimating the potential carcinogenic risk that might result from human exposure to these mixtures.

Before presenting a review of the data related to carcinogenicity, a discussion of the chemical compositions of various sets of PCBs is presented.

B. Chemical Composition of Aroclors

Polychlorinated biphenyls (PCBs) are mixtures of chemically related compounds. The various PCBs all share the same basic biphenyl (12-carbon) structure (figure 1) with a varying number of chlorine atoms. Up to ten of the carbon atoms of the biphenyl molecule can chemically bond (attach) to chlorine atoms. If only one chlorine atom is bonded to the biphenyl molecule, the product is referred to as monochlorobiphenyl. It is possible for the single chlorine atom to bond to carbon atoms in different positions in the biphenyl structure, and each such bonding creates a new chemical (figure 1). There are thus several different forms of monochlorobiphenyls that may have different properties. These different structures are referred to as monochlorobiphenyl isomers. Similarly, different isomers may be created when two chlorines are present (dichlorobiphenyls), when three chlorines are present (trichlorobiphenyls), etc., depending on the location of the chlorine atoms with reference to the carbon atoms in the biphenyl structure. PCBs that have different numbers of chlorines, e.g., 5 chlorines (pentachlorobiphenyls) and 6 chlorines (hexachlorobiphenyls), are called congeners. The various PCB mixtures are referred to as sets of congeners, even though some of these sets contain PCBs related to each other as isomers.



$$\left(\begin{array}{l} x + y = 1-10 \\ x, y \leq 5 \end{array} \right)$$

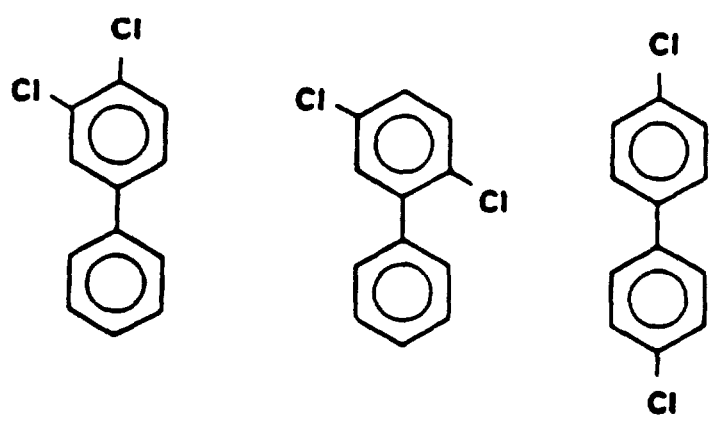


Figure 1. Structure and nomenclature of PCBs. Top left: Biphenyl structure with notation of variable number of chlorines. Top right: Biphenyl structure with numbering of carbon atoms for designating isomers. Bottom: Three isomers of dichlorobiphenyl: 3,4-dichlorobiphenyl, 2,5-dichlorobiphenyl, and 4,4'-dichlorobiphenyl.

Individual chlorinated biphenyls can be separated from a mixture by a technique called gas chromatography, and their structures can be confirmed using mass spectroscopy. Figure 2 is a schematic that was produced from the results of such a procedure for Aroclors 1260, 1254, and 1242. When the results of such a separation are represented in a graph (i.e., a chromatograph) as in figure 2, the horizontal location of the bar (labelled "Peak Number") is an indication of the specific PCB congener, or congeners if the separation is not complete. (The relation between these Peak Numbers and PCB congeners by chemical designation is described in Appendix B.) The height of the bar is a measure of the amount (i.e., mass fraction) of each of the various chlorinated biphenyls that are present. Such chromatographs are sometimes called fingerprints, because they can be used to determine the degree of similarity between two mixtures of chemicals even when all of the components of the mixture have not been identified.

Although the correlation is imperfect, as a general rule the number of chlorine atoms per biphenyl molecule increases with Peak Number. Most of the congeners in Aroclor 1260 have more than 4 chlorines, and the average is about 6 chlorines. The chlorine content of Aroclor 1254 is lower than for Aroclor 1260, averaging about five chlorines, and that of Aroclor 1242 lower still, averaging about three chlorines. Thus, although all three are mixtures of PCBs, the actual chemical composition of the mixtures (i.e., the fingerprint) is quite different. Even so, it is readily apparent from figure 2 that the spectra of congeners (i.e., the chemicals present) in the three mixtures overlap (i.e., have some chemicals in common for the mixtures), especially for Aroclor 1260 and Aroclor 1254. Aroclor 1260 has relatively little overlap with Aroclor 1242. Because the chemicals that comprise these mixtures are different, the chemical, physical, and toxicological properties of each mixture would also be expected to differ.

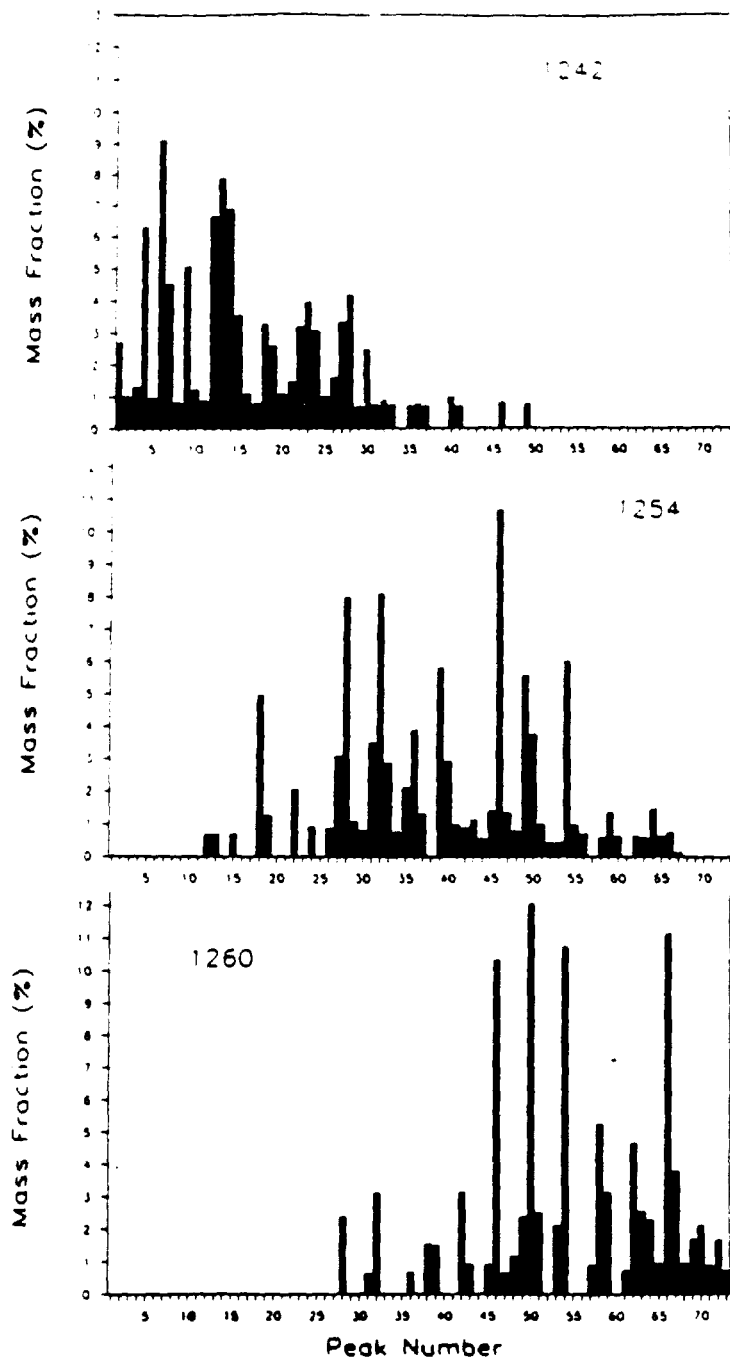


Figure 2. Distribution of mass fractions of PCB congeners in Aroclors 1242, 1254, and 1260.

influence the mortality experience of the study. For example, if drinking water contaminants increased the cancer mortality of the study (and local) populations, the use of cancer mortality rates based on the U.S. population would not account for this, whereas the use of local rates would.

Statistical analyses are generally conducted on the findings to determine whether any observed increase in the general or site-specific mortality rates in the exposed cohort is statistically significant.^{1/} It should be noted that the probability that one or more comparisons will be found to be statistically significant by chance alone increases with the number of comparisons that are made (e.g., number of site-specific cancer mortality rates in the study cohort vs. the number expected based on reference population rates) (Daniel 1983):

If a statistically significant increase in the overall or site-specific rate of cancer mortality is found in the study cohort, one must assess whether the observed difference might have resulted from bias in the manner of data collection. This involves evaluating the ability of the investigators to determine who was exposed (and to what extent) and the methods used for identifying cases of cancer mortality. One must also determine whether the finding might have resulted from the effects of uncontrolled or "confounding variables." This is done by assessing the degree to which investigators accounted for other risk factors (e.g., smoking) in the study design and analysis.

^{1/}The level of statistical significance, or p-value, is generally used to determine this. Traditionally, if a p-value is less than 0.05, chance (although always a possibility) is considered to be an improbable explanation of the results. Conversely, if the p-value is greater than 0.05, chance is considered to be a likely explanation for the observed effect, e.g., cancer.

Two other commercially produced PCBs -- Clophen A30 and Clophen A60 -- are relevant to this discussion. These substances were produced in West Germany and have compositions similar to the Aroclors. Specifically, Clophen A60 is approximately identical to Aroclor 1260, and Clophen A30 is similar to Aroclor 1242. The importance of these similarities will be discussed later.

C. Epidemiological Data

1. General Considerations

The study design that is most commonly used to examine the occurrence of cancers in PCB-exposed populations is a type of cohort study (mortality study) in which death from cancer (all cancers and site-specific^{1/} cancers) is the endpoint of interest. In the majority of these studies, the cancer mortality of the population exposed to PCBs is compared to cancer mortality rates of the general population. Standardized Mortality Ratios (SMRs) are then determined by dividing the number of cancer deaths (either total or site specific) in the exposed group by the number of deaths that would be expected by applying rates developed from a reference population. The choice of the reference population (e.g., U.S. average, regional, or state) is critical for the analysis because the normal occurrence of cancer or a particular type of cancer may vary with the population selected. It is often preferable to use a local population (i.e., from the same region or locality as the study population) as the reference population to account for possible unknown confounding variables that could

^{1/}Refers to the anatomical site (e.g., liver) at which the cancer was identified.

In the particular case of examination of epidemiological data related to cancer endpoints, there are a number of specific methodological issues that should be considered. These include:

Latency Period: For many cancer endpoints, a long interval may occur between exposure and detectable tumor development. Thus, any cohort study should have a sufficiently long period of follow-up to account for this factor.

Misclassification: It is necessary to classify accurately the exposure status of humans to the substance of interest over time. Important differences in interpretation of epidemiological findings may be obscured if persons are misclassified with regard to exposure.

Pathological Verification of Disease: It is important that investigators clearly state the methods used for identifying disease. There is considerable uncertainty associated with the diagnoses based on death certificates. These should be confirmed using pathology records whenever possible. This is especially important in identifying primary cancer sites because of the tendency of malignancies to metastasize, i.e., to spread to organs other than the site affected by the substance of interest.

Confounding Variables: Exposure to an agent, such as PCBs, may be associated with other possible determinants of cancer risk. For example, cancer rates differ on both a regional and community basis. These differences may in some cases be attributable to qualitative and quantitative variations in the

spectrum of environmental agents (e.g., chemicals in air and water) to which local populations are exposed. Exposure associated with personal habits (e.g., smoking) and past occupations may also account for an observed increase in cancer mortality in a study population. If information is available on the potential confounding variables, it may be possible to adjust for their effects in the analysis. In many cases, however, the relevant confounding variables may be unknown or difficult to measure, complicating the determination of conclusions regarding causation.

After assessing the possible effects of the above factors in an individual epidemiological study, it is generally necessary to apply certain additional criteria in making a judgment as to causality -- i.e., whether exposure to the agent was the cause of the observed health effect. These criteria are frequently presented and discussed in general textbooks of epidemiology (e.g., Rothman 1982, Mausner and Kramer 1985). Most authors base their discussions of the subject on the nine criteria that were noted by Hill (1965) as especially important for consideration when reaching a judgment on the causal nature of an association. The current practice among epidemiologists is to adopt a set of criteria that represent a modification of those originally presented by Hill. Mausner and Kramer (1985) identified the following criteria to evaluate the likelihood that an association is causal:

Strength of the Association: This criterion refers to the degree to which the incidence of the disease is elevated in the exposed population as compared to the control population. In mortality studies, the strength of the association is indicated by the magnitude of the Standardized Mortality Ratio (SMR).

Statistical analysis of the data is necessary to determine the likelihood that an observed association between exposure to an agent and the subsequent development of disease (e.g., as indicated by an elevated SMR) is a chance outcome or is indicative of a true association.

Dose-Response Relationship: This refers to the criterion that the risk of developing the disease usually increases as the exposure increases. The demonstration of such a dose-response relationship increases the likelihood of a causal association.

Consistency of the Association: This criterion refers to the repeated observation of an association in different populations under different circumstances (e.g., under different patterns of exposure).

Temporally Correct Association: Exposure to the suspected causative agent must precede the effect in time. Also, with respect to cancer, a sufficient latency period (i.e., period between exposure and the development of the disease) is necessary for the association between exposure to the agent and the development of disease to be biologically plausible.

Specificity of the Association: This criterion requires that exposure to a causative agent should lead to a unique effect. While the observation of specificity is strong evidence for causal association, its absence is of less significance. Some agents (e.g., smoking) have been strongly linked to multiple effects.

Coherence With Existing Information: This criterion usually refers to the extent to which a causal interpretation is biologically plausible given the current state of scientific knowledge. The likelihood of an association is stronger if it is supported by experimental evidence.

As noted by Rothman (1982), there is no rigid rule to specify when a causal relationship has been established. Any conclusion regarding the likelihood of a causative association is ultimately based on individual, expert judgment. The more criteria that are met for an exposure in question, the greater the likelihood of a causal association. The observation of a statistical association in one or more epidemiological studies usually is insufficient, by itself, to establish causation.

2. Review of Studies

The potential biological effects of human exposure to PCBs have been examined in several populations, primarily workers exposed through occupational activities. As noted previously, EPA (1988) and the Agency for Toxic Substances and Disease Registry (ATSDR 1987) have concluded that the available data are not sufficient to demonstrate that PCBs cause cancer in humans. Nevertheless, the available data, and the strengths and weaknesses of the studies, are reviewed in this section.

The majority of these studies involve occupationally exposed cohorts, and most include only rough measures of exposure (e.g., duration of employment, employment category). The studies differ in the extent to which investigators were able to account for possible confounding variables. As noted above, in some cases such variables could account for any observed increases in cancer mortality in the study population.

a) Brown and Jones (1981); Brown (1987)

Brown and Jones (1981) reported the results of a retrospective mortality study of 2,567 electrical capacitor workers in two plants located in the United States. An update of this study was subsequently published by Brown in 1987. The type of PCB mixture used in the plants varied over the years and included Aroclors 1254, 1242, and 1016. (The latter is a purified version of Aroclor 1242.)

In the initial study (Brown and Jones 1981), the cohort was followed until January 1, 1976, and included all workers with at least 3 months of employment (after 1940) in areas where there was potential PCB exposure. The expected number of deaths in the cohort was determined using age-adjusted U.S. mortality rates (white males and white females) for the appropriate time periods. The total mortality in the study cohort was lower than expected (163 observed vs. 182 expected), as were the total number of cancer deaths (39 observed vs. 44 expected). The Standardized Mortality Ratio (SMR = [observed deaths/expected deaths] x 100) for cancer deaths in the study cohort was 89. Thus, there were fewer cancer deaths among those exposed to PCBs than would be expected in a general, non-exposed population.

With regard to site-specific cancer mortality, Brown and Jones (1981) reported a greater than expected number of deaths due to rectal cancer (4 observed vs. 1.19 expected) and cancer of the liver, gallbladder, and biliary passages (3 observed vs. 1.07 expected). These findings, however, were not statistically significant which strongly suggests that the observed increases are chance occurrences.

In the update of the original study, Brown (1987) followed the mortality experience of the

original cohort through 1982. Once again, the total mortality in the study cohort was lower than expected (295 observed vs. 317.6 expected), with an SMR of 78.

During the additional observation period no additional deaths from cancer of the rectum were observed, resulting in a lowering of the SMR from 336 to 211 (4 observed vs. 1.9 expected). Two more deaths from the disease categories that include cancers of the liver, gallbladder, or biliary passage were reported; these sites were not analyzed individually for statistical significance. This resulted in a statistically significant excess in mortality when the observed number of deaths from these different categories were combined (5 observed vs. 1.9 expected). But the grouping of the 5 cases of liver, gallbladder, and biliary tract cancer into one category (and thus treating them as a single disease) is questionable.^{1/} The etiology of the cancers also suggests that they should be considered separately. The evidence for an association between exposure to some environmental agents (e.g., mycotoxins, hepatitis B virus) and an increased risk of developing hepatocellular (liver cell) carcinoma is relatively strong, whereas that for cancer of the hepatobiliary tract (bile ducts found within the liver) is much less compelling (for example, see Zimmerman 1978). Moreover, none of the 5 cases that were grouped by Brown (1987) were identified as a primary carcinoma of the liver, suggesting that liver

^{1/}The International Classification of Diseases (ICD) code (Eighth Revision) for deaths from cancer at each of these sites is different, indicating that ICD considers them different diseases.

might merely be the common site of metastasis for cancers from sites of unrelated origin.

An analysis of the data did not show an increase in risk with an increase in latency (time since first employment) or any indication of a dose-response relationship (as measured by length of employment) among the deaths from cancers of the liver, gallbladder, or biliary tract. In discussing the study findings, Brown noted that, due to the small number of deaths and the variability of specific cause of death (i.e., within the category including mortality from malignancies of the liver, gallbladder, and biliary tract), it is difficult to interpret the significance of the findings with regard to PCB exposure.

b) Bertazzi et al. (1982, 1987)

Bertazzi and coworkers (1982) reported preliminary results of a retrospective mortality study of production workers in a capacitor manufacturing facility who were employed for at least 6 months between 1946 and 1970. During the early years of production, workers were primarily exposed to PCB mixtures containing 54% chlorine (Aroclor 1254 and Pyralene 1476) that were later replaced by mixtures containing 42% chlorine (Pyralene 3010 and 3011). Mortality was observed between 1954 and 1978 and compared to local rates. The authors reported a statistically significant increase in cancer mortality among males. The observed excesses in cancer deaths in males were primarily attributed to malignancies of the lymphatic and hematopoietic (blood forming) tissues and the digestive system.

In the update of this study (Bertazzi et al. 1987), the cohort was expanded to include non-production workers. The investigators also

decreased the minimum period of employment (after 1946) needed for inclusion in the cohort from 6 months to 1 week. The mortality experience of the cohort was followed from 1946 to 1982.

The short minimum exposure period is a major flaw in the study design. By defining the cohort in this manner, the authors could attribute cases of cancer mortality to PCB exposure that were likely due to other causes or factors. For example, of the 12 cases of mortality that were identified in females, only four were fully characterized with respect to parameters such as length of exposure, and one of these had an exposure period of only three months. It is possible that the remaining eight cases include women who were exposed for very limited periods, making it much less likely that the cancers were associated with work-related exposures.

The total number of deaths in the cohort by 1982 was 64 (30 men and 34 women). Bertazzi et al. used both national and local mortality rates (adjusted by age, sex, and year) to determine the expected number of deaths in the study cohort. Total mortality (i.e., from all causes) was not elevated for males, but there was a statistically significant increase in overall cancer deaths (as indicated by the Standardized Mortality Ratio [SMR]) and in cancers of the gastrointestinal tract, based on either national or local mortality rates.

In females, statistically significantly increased SMRs were observed only when local mortality rates were used to determine expected numbers of cause-specific deaths. Significant excesses were observed for the categories of deaths due to malignant tumors (cancers) (SMR = 226) and deaths due to hematologic neoplasms (cancers of the blood system) (SMR = 377). The local mortality rates

for females in the age group of concern (generally less than 45 years old), however, are associated with a high degree of uncertainty because of the relatively few deaths that occurred among women of this age group in the town (population 150,000).

Bertazzi et al. (1987) reported that when the data were analyzed by duration of exposure, latency, and the year of first exposure, no pattern or trend in mortality was observed for any category of cancer mortality in males or females. They also noted that, in some cases, an examination of the employment history of cancer victims tends to reduce the probability of an association with PCB exposure, in particular with regard to the males with the excess of digestive system cancer (6 observed vs. 1.7 [national] or 2.2 [local] expected). Upon closer analysis of these cases, the authors state that one individual with stomach cancer had been hired at an advanced age and received a very short exposure. Furthermore, two of the individuals (one with stomach cancer, one with pancreatic cancer) had been security guards with no history of direct PCB exposure. This suggests that only 3 of the observed cases may be in people who had any significant exposure to PCBs, and only one individual (with pancreatic cancer) was exposed for more than one year.

The findings of the epidemiological study conducted by Bertazzi et al. (1987) are not indicative of a causative link between exposure to PCBs and the subsequent development of cancer in humans. In the cancer mortality cases that were identified, no dose-response relationship was observed and no pattern was observed with regard to latency and disease. As noted by the authors, some of the male cancer mortality cases had little or no opportunity for direct PCB exposure. Finally,

interpretation of the study results is constrained by the small number of deaths that had occurred in the study cohort, the short minimum exposure period required for inclusion in the study cohort, and the use of relatively unstable local mortality rates as a standard of reference.

c) Gustavsson et al. (1986)

Gustavsson et al. (1986) reported the results of a study of the mortality and cancer incidence among a cohort of 142 male Swedish capacitor manufacturing workers during the period of 1965 to 1982 (with cancer incidence followed through 1980). The workers had been employed for a period of at least six months between 1965 and 1978 and had been exposed to Aroclor 1242 (or equivalent). Airborne PCB levels were measured at 0.1 mg/m^3 in 1973, with possibly higher levels in the 1960's.

A total of seven cancer deaths were identified in the cohort, which was not significantly different from the expected number (5.4), calculated using national statistics. There was also no tendency towards an increase in the mortality or cancer incidence in the most highly exposed subgroup of 19 workers. Although the results indicate no increase in cancer mortality in the study cohort during the study period, the results are not conclusive because of the small cohort size and brief follow-up period.

d) Bahn et al. 1976

Bahn et al. (1976) reported a statistically significant ($p < 0.001$) increase in deaths due to malignant melanoma (2 observed vs. 0.04 expected) in a small group (31) of research and development employees believed to have been heavily exposed to PCBs. The major pathways of exposure were not

identified by the authors. The workers were exposed to Aroclor 1254, among other chemicals, during various periods between 1949 and 1957. Although the authors suggest that PCB exposure may account for the observed excess of malignant melanoma, the small size of the study cohort and the fact that individuals were exposed to other toxic and potentially carcinogenic compounds during their employment makes it impossible to attribute the excess cancer cases to any specific agent.

Bahn et al. reported their findings in the form of a letter. They have never been presented in the form of an epidemiological study with data that can be independently evaluated and published in a journal for peer review. Therefore, these findings are difficult to evaluate as part of the "weight of evidence" regarding the carcinogenicity of PCBs in humans.

A letter by Lawrence (1977) questioned whether the study demonstrated any adverse effects from exposure to PCBs due to concomitant exposure of workers to other, possibly carcinogenic, chemicals. In response, Bahn et al. (1977) maintained the assertion of a "possible association" between PCBs and malignant melanoma, but agreed that the data were not conclusive.

e) Studies in Populations Following the Accidental Ingestion of PCBs, PCDFs, and Other Contaminants

Kuratsune et al. (1986) reported on the results of mortality studies of Japanese "Yusho" patients who had ingested contaminated rice oil in 1968. The oil was contaminated with Kanechlor 400 (similar in PCB composition to Aroclor 1248) as well as polychlorinated dibenzofurans (PCDFs) and polychlorinated quaterphenyls (PCQs). The

composition of the Kanechlor 400 involved in this incident had been altered (i.e., there was a much higher concentration of contaminants than the commercial grade mixture) as a result of its use in a heat exchanger. It is also probable that additional contaminants were generated during the use of rice oil in cooking.

In the 887 males who were included in the cohort, statistically significant increases in mortality from all malignancies (33 observed vs. 15.5 expected), liver cancer (9 observed vs. 1.6 expected), and lung cancer (8 observed vs. 2.5 expected) were reported, based on national rates. The use of local rates decreased the SMR for liver cancer from 560 to 390, which was still statistically significant. No SMR based on local mortality rates was calculated for lung cancer. No significant excesses in cancer mortality were observed for the 874 female patients included in the cohort.

There is evidence that confounding factors could have influenced the findings of Kuratsune et al. (1986). It has been reported that 70% of the identified Yusho patients are from two prefectures that have reported the highest incidence of liver cancers in Japan (Kuratsune 1986), suggesting the possible existence of local factors that have not been identified. For example, as reported in Ikeda et al. (1986), the rate of mortality from liver cancer was substantially different for the Yusho patients in Fukuoka prefecture than in Nagasaki prefecture. This led the authors to conclude that "Such a remarkably uneven geographic distribution of liver [sic] cancer deaths makes it hard to consider the observed increased risk of liver cancer as simply due to the poisoning." Kuratsune et al. (1986) were also unable to control for possible confounding

factors such as smoking habits (especially important with regard to the observed excess of lung cancers), drinking habits, and occupational exposures.

The liver cancer diagnoses on which Kuratsune et al. rely were obtained from death certificates, without any confirmation of pathology through tissue examination. The cases were thus not restricted to primary liver cancers, but also would have included cases in which the liver was a site of metastasis for cancers originating at other sites. The significance of the elevated incidence of liver cancer is thus subject to question.

Many investigators also believe that exposure to PCDF congeners is the primary cause of the symptom pattern observed in Yusho (Miyata et al. 1985, Kashimoto et al. 1985, Masuda 1985). They support this contention by reference to the high degree of toxicity (primarily to the liver) of certain of the PCDF congeners in laboratory animals. These toxic PCDF congeners (including 2,3,7,8-tetrachlorinated; 2,3,4,7,8-pentachlorinated; and 1,2,3,4,7,8-hexachlorinated dibenzofuran isomers) were identified in Yusho oil and in the tissues of Yusho victims (Miyata et al. 1985). As further evidence that PCDFs were the agents most likely responsible for the severity of Yusho symptoms, Kashimoto et al. (1985) and Hara (1985) refer to the relatively mild symptoms observed in PCB-exposed workers who had serum PCB levels similar to those observed in Yusho victims, but without detectable levels of PCDFs.

A second major outbreak of disease caused by ingestion of contaminated rice oil (called Yu-Cheng in Chinese) occurred in central western Taiwan in 1979. The oil that was responsible for this incident contained PCBs, PCDFs, and PCQs that were comprised of congeners similar to those identified in Yusho

specimens (Miyata et al. 1985). No data were located regarding the incidence of cancer mortality in Yu-Cheng victims. It is possible that there has been an insufficient number of deaths in this group for any meaningful analysis of mortality data.

3. Conclusions Regarding Epidemiology Data

Although several studies have investigated the possibility of an association between PCB exposure and human cancer, the results do not support a causal relationship. The primary reasons for this conclusion are:

- (i) Strength of the Association: When the excess cancer cases observed by Bertazzi et al. (1987) and Brown (1987) are examined closely, the relationship of the excess cancers to PCB exposure appears doubtful. For example, 2 of the 6 cases of digestive system cancer that were identified in the male subcohort by Bertazzi et al. were in individuals whose jobs involved little or no direct PCB exposure, and a third case was in a worker who began employment at an advanced age. Furthermore, any perceived linkage between any chronic effect and employment is dubious because the cohort includes individuals with only one week of employment. None of the 5 excess liver, gallbladder, or biliary tract cancers observed by Brown (1987) was identified as primary liver cancer, thus rendering suspect the identification of the liver as the target organ. The findings of statistically significant increases in liver cancer among male Yusho victims (Kuratsune et al. 1986) cannot be attributed to PCBs because of concurrent

exposure to high concentrations of other toxic contaminants (e.g., PCDFs).

- (ii) Dose-Response Relationship: In studies in which excess cancers were observed, there is no relationship between degree of PCB exposure and cancer risk. For example, in the follow-up study by Brown (1987), 4 of the 5 excess liver or biliary tract cancer cases were observed in the lowest exposure group, with none in the highest exposure category. Bertazzi et al. (1987) were also unable to identify a dose-response relationship between PCB exposure and increased cancer risk.

- (iii) Consistency and Specificity of the Association: There is no consistent pattern of associations among the various studies, either with respect to the type of human cancers observed or the nature and extent of PCB exposures.

- (iv) Temporally Correct Association: For some of the cases identified by Bertazzi et al. (1987), it appeared that there was little or no opportunity for exposure before development of disease. Also, no pattern of increased risk with an increase in latency was reported by Brown or Bertazzi et al.

- (v) Coherence With Existing Information: Experimental data do not suggest that PCBs are a causative agent for cancer in mammals at sites other than the liver. The evidence that PCBs are causative agents for liver cancer in humans is inadequate. A statistically significant increase in mortality from cancer

of the liver, gallbladder, or biliary tract (combined) was observed in one occupationally exposed cohort (Brown 1987); however, none of these cases were identified as primary liver cancer. There was no confirmation, by tissue analysis, of the Yusho liver cancer victims identified by Kuratsune et al. (1986). These cases were also not restricted to primary liver cancers.

There is insufficient evidence to show a causal relationship between PCB exposure and the subsequent development of any form of cancer. In light of the long-term and widespread usage of PCBs in the workplace and, in some cases, the extensive exposures of workers, it is likely that evidence of carcinogenicity in humans would have been observed in the various epidemiological studies discussed above if PCBs were in fact potent carcinogens.

D. Animal Studies

1. Introduction

The numerous human studies are insufficient to show that PCBs cause cancer in humans. When data from human exposure are inadequate to assess the potential hazards from a substance, experiments with laboratory animals are often performed to identify potential adverse effects that might occur in humans. While animal studies have been accepted as a general indicator of possible effects in humans, not all effects observed in all animals will occur in humans. A chemical-specific evaluation may indicate the data from animals is inappropriate, especially when the effects are observed in only one species of animal and cannot be duplicated in other species. For this reason, consistent results from studies in several species are required to justify convincingly that it is proper to

extrapolate results of studies of laboratory animals to humans.

Although laboratory animal testing is, in general, a useful tool for predicting the impact of an agent on humans, the limitations of these tests must be acknowledged. For some chemicals or chemical-specific effects (e.g., tumor forming potential), there can be considerable uncertainty with regard to the applicability of test results in predicting human response. The most obvious and important reason for this is the fact that such animals are physiologically different than the human species. No matter how convincing the results from animal studies, a question always remains about their relevance to human populations because of interspecies differences in factors such as absorption, metabolism, and elimination of a test substance.^{1/} In addition, some types of tumor responses (e.g., the rodent liver tumors that are the only clear animal response produced by any of the PCBs) are much less certain predictors of human cancer than are other types of tumor responses.^{2/} Finally, all studies must be critically evaluated with respect to the quality of test designs and conduct.

Although there are limitations associated with animal tests, such studies are frequently used for regulating

^{1/}For example, metabolic differences may undermine the validity of extrapolating from animals to man if the carcinogen is a metabolite of the original chemical and the animals used in the bioassay differ substantially from humans in their production of that metabolite.

^{2/}There is a high and variable incidence of liver tumors in various strains of commonly used laboratory mice, as well as a high spontaneous incidence in the livers of rats of preneoplastic cells (i.e., cells in an altered state that may have carcinogenic potential) that can be stimulated by promoting agents to produce tumors (Nutrition Foundation 1983, Schulte-Herman et al. 1983).

environmental carcinogens. The use of animal test data in this fashion, even when available human data do not suggest a problem (as in the case of PCBs), is based on the policy goal of regulators of providing maximum assurance of public health protection in the absence of complete scientific certainty.

For purposes of this report, the animal data on PCBs will be used to determine potential health risk because data from human exposures show no demonstrable health effects other than chloracne. Therefore, the animal data are presented on the most sensitive endpoint of concern with respect to PCBs: rodent tumorigenicity. In choosing this endpoint as the most sensitive, the conservative assumption is made (as it is by regulatory agencies) that all of the different commercial PCB mixtures are tumorigenic, even though this has not been demonstrated in laboratory or epidemiological studies.

There are effects other than tumorigenicity that have been observed in animals exposed to PCBs at relatively low exposure levels. These include reproductive effects such as reduced birth weight and hyperactivity in the offspring of exposed monkeys (Barsotti and Van Miller 1984, Bowman et al. 1981) and altered menstrual cycles in exposed monkeys (Allen et al. 1979), as well as induction of hepatic microsomal enzymes (enzymes produced by liver cells) in rats (Litterst et al. 1972). Tumorigenicity, however, is the most sensitive endpoint for low-level, environmental exposures to PCBs. Therefore, protection of public health based on tumorigenic risk is protective of adverse effects for other sensitive potential endpoints, such as reproductive effects. Other PCB-related effects would have to be considered if we were concerned with short term, high-level exposure to PCBs.

2. Animal Studies Regarding the Tumorigenicity of Commercial PCBs

The PCB mixtures that have thus far been tested in acceptable animal chronic bioassays for tumorigenicity

include Aroclor 1260, Clophen A60, Aroclor 1254, and Clophen A30. Each of these bioassays is discussed below.

There are no acceptable bioassays concerning the carcinogenicity of Aroclors 1248 or 1242. While there are some animal studies on Aroclor 1242; Aroclor 1248; and Kanechlors 300, 400, and 500 (Japanese commercial mixtures), which qualitatively add to the body of knowledge concerning the potential tumorigenicity of PCBs, these studies are not conclusive and cannot be relied upon for quantitative determinations. This is primarily because of inadequacies in the design (e.g., insufficiencies in study length, numbers of test animals, dose levels tested) of the studies that have been conducted to date. Cancer bioassays conducted by Industrial Bio-Test Laboratories (IBT) have generally been considered invalid by regulatory agencies (cf. Garmon 1981); therefore, this series of chronic animal studies on Aroclors 1242, 1254, and 1260 will not be used for this quantitative analysis.^{1/}

In light of the limited number of studies, the cancer potency factors for the various Aroclor mixtures must be derived from the sets of animal data for Aroclor 1260, Clophen A60, Aroclor 1254, and Clophen A30. The importance of the difference in tumorigenic potency among the congeners, as well as the procedure used for adjusting these data for use in risk assessments, is discussed later.

^{1/}Both the FDA and EPA consider these studies to be invalid because of severe procedural and record-keeping deficiencies. Also, the results of a re-evaluation of the original data by Calandra (1976) used terminology that does not conform to current practice for diagnosing hepatocellular proliferative lesions (tissue in which liver cells are dividing at an abnormally fast rate).

The analysis presented in this report follows the current regulatory practice of treating PCBs as complete carcinogens^{1/}. Several factors, however, demonstrate that some of the carcinogenic effects of PCBs are due to promotion rather than initiation:

1. A substantial number of experiments have shown that PCBs do not cause direct genetic effects in several assay systems (e.g., as reviewed by ATSDR 1988).
2. PCBs have been shown to cause the promotion of liver tumors in rodents initiated by other compounds (e.g., Kimura et al. 1976; Nishizumi 1976, 1979; Tatematsu et al. 1979; Preston et al. 1981).

Other compounds that act as promoters have threshold doses (e.g., a dose below which no effect is observed) that have been demonstrated experimentally (e.g., as reviewed in Butterworth and Slaga 1987 and Schulte-Hermann 1985). It is believed that a threshold exists for all chemicals that act solely as promoters.

These points have important implications for carcinogenic risks from exposure to PCBs at very low dosages, such as might arise from environmental

^{1/}The process of carcinogenesis is generally regarded as a multistage process. It is considered to consist of, at a minimum, an initial stage in which the genetic material of a cell is permanently altered (initiation) followed by later stages (that may occur many years later) in which the initiated cell undergoes changes which are not fully understood, but which include cell division (promotion). A complete carcinogen is a substance which acts as both an initiator and a promoter in that it can, by itself, cause an increase in tumor formation.

exposures. If the tumorigenic effects of PCBs in laboratory animals are solely or primarily due to promotion, the potential tumorigenic risk will be greatly overstated at very low dosages. Studies with other promoters indicate that the carcinogenic effects of promoters are, at least to some degree, reversible and that a threshold exposure level must be exceeded to produce any effect on carcinogenesis. Thus, the no-threshold, linearized multistage model, which assumes that any level of exposure has some risk, will overstate the risk, especially at low doses (exposures). If PCBs were solely promoters, no tumorigenic risk whatsoever would be expected from doses (exposures) that are below the threshold. It is thus very possible, even if the animal data are reliable indicators of effects in humans at high doses, that no risk would result from low-dose environmental exposures to humans.

a) Aroclor 1260

There are two cancer bioassays of Aroclor 1260: Norback and Weltman (1985) and Kimbrough et al. (1975).

Norback and Weltman initially exposed 70 male and 70 female Sprague-Dawley rats to dietary concentrations of 100 ppm Aroclor 1260 for 16 months, 50 ppm for 8 subsequent months, and control diets for 5 months. The control group consisted of 63 male and 63 female control rats. At months 1, 3, 6, 9, 12, 15, and 18, four controls and six PCB-treated rats had partial hepatectomies (removal of the liver) in order to observe sequential morphological changes and progression to neoplasms^{1/}. One set of rats was

^{1/}The term neoplasm refers to a new and abnormal formation of tissue, which can be in the form of a tumor. A neoplasm may be benign (not spreading into surrounding tissues) or malignant (i.e., cancerous).

sacrificed at 24 months; at 29 months, terminal sacrifices on all remaining rats were completed. Sequential observations showed that an increase in the size of some liver cells (centrilobular cell hypertrophy) was present at 1 month; small organized regions of changes in liver cells (foci of hepatocyte alterations) were seen at 3 months; larger areas of liver cell (hepatocyte) alterations were observed after 6 months; benign, i.e., non-cancerous, tumors (neoplastic nodules) appeared at 12 months; and malignant tumors (trabecular carcinoma and adenocarcinoma)^{1/} were apparent later (after 15 and 24 months, respectively).

The total incidence in Norback and Weltman of trabecular carcinoma was 23% (21/93) with 2/46 and 19/47 in males and females, respectively. Adenocarcinoma appeared at an incidence of 26% (24/93) of which 24/47 occurred in females and 0/46 in males. Neoplastic nodules were observed in 8% (7/93) of the Aroclor 1260 animals (5 males and 2 females). Neoplastic nodules were observed in one female control animal, resulting in a total incidence of 1% (1/81) for neoplastic nodules in controls. No other hepatocellular neoplasms (liver tumors) occurred in the control group. Bile duct hyperplasia (excessive proliferation of normal cells), cysts, and adenofibrosis (benign tumor containing connective tissue) were seen in 38%, 8%, and 9% of the treated animals, and 5%, 1%, and 4% of the control animals, respectively. Although hepatocellular neoplasms were present in 96% of the treated females and 15% of the

^{1/}Adenocarcinoma refers to a malignant tumor arising from glandular tissue (in this case the liver); trabecular carcinoma refers to a specific type of liver cancer.

treated males, the neoplasms did not metastasize or cause increased mortality relative to controls.

An analysis of the data using Fisher's Exact Test shows the incidence of carcinoma in the females was statistically significantly greater than control females; however, this was not so for males. The incidence of total liver tumors (carcinomas and neoplastic nodules) in males and females was statistically significantly greater than their respective control groups.

Kimbrough et al. (1975) also performed a rodent bioassay for Aroclor 1260. Initially, 200 female Sherman strain rats were fed 100 ppm of Aroclor 1260 for 21 months. Dietary exposure was discontinued for six weeks before all exposed animals were sacrificed. The initial control group consisted of 200 female rats. Malignant tumors (hepatocellular carcinomas) were observed in 26 of the 184 surviving PCB-exposed rats, and benign (non-cancerous) tumors (neoplastic nodules) of the liver were observed in an additional 144 of the exposed rats. Only 1 of the 173 surviving control animals developed hepatocellular carcinoma while none of the control rats developed neoplastic nodules. Analysis of this data using Fisher's Exact Test shows the incidence of carcinoma in exposed rats was statistically significantly greater than in controls.

Kimbrough et al. (1975) also reported the incidence of tumors in organs other than the liver. A number of organ sites showed lower tumor incidence in PCB-treated animals than in the controls. If the total number of tumors at all sites is summed, however, the lower incidence of certain tumor types in the PCB-treated animals as compared to controls was more than counterbalanced by the increase in liver and other tumors compared to control animals.

b) Clophen A60

Clophen A60, the German commercial equivalent of Aroclor 1260, was tested in a cancer bioassay in Wistar rats by Schaeffer et al. (1984). Male Wistar rats received dietary concentrations of 100 ppm Clophen A60 over a period of 832 days. Malignant tumor (hepatocellular carcinoma) incidence in the treated group at 48% (61/126) was statistically significant compared to 0.76% (1/131) in controls. Benign tumors (neoplastic nodules) of the liver were also statistically significant at 49% (62/126) in the Clophen A60 group compared to 3.8% (5/131) in the control groups.

It is important to note, however, that there was a statistically significant lower survival in control animals compared to the Clophen A60 group, i.e., the animals that were exposed to PCBs tended to live longer than animals that were not exposed (controls). This lower survival of the control animals may have led to a lower tumor incidence in controls than might have been seen if survival among the controls had been equivalent to that of the exposed animals, because tumor incidence generally increases with age. When comparing animals with the same length of survival, however, there is still a statistically significant increase in liver tumors in the Clophen-exposed animals versus controls.

c) Aroclor 1254

The National Cancer Institute (NCI 1978) and Kimbrough and Linder (1974) conducted bioassays on the carcinogenicity of Aroclor 1254 in rats and mice, respectively.

The NCI study protocol consisted of 24 male and 24 female Fischer 344 rats that received diets containing either 0, 25, 50, or 100 ppm Aroclor 1254

for 104 to 105 weeks. There was a small, dose-related increase in the incidence of combined benign (adenoma) and malignant (carcinoma) tumors. There was a larger increase in the incidence of nodular hyperplasia.^{1/} Although the occurrence of the liver lesions in these rats was not statistically significant, none of the benign or malignant changes in the liver (including hyperplastic nodules, adenomas, or carcinomas) were observed in control animals. Additionally, four adenocarcinomas and one carcinoma of the gastrointestinal tract observed in treated rats may have been treatment related, according to NCI, because the historical incidence of these tumors in this laboratory is only 6/600 in males and 2/600 in females. In this bioassay, however, few sections of the stomach had been evaluated. NCI (1978) concluded that the high incidence of hepatocellular proliferative lesions in male and female rats were related to treatment, but that Aroclor 1254 was not carcinogenic in this bioassay.

A re-evaluation of the NCI data by Morgan et al. (1981), which focused only on the tumors of the gastrointestinal tract, revealed greater numbers of stomach tumors than originally reported. These tumors were not statistically significantly greater than controls and did not appear to be dose-related. When compared with the incidence of historical controls (includes all control animals of this strain from past studies), the total incidence of adenocarcinomas of the stomach in all dose groups

^{1/}Hyperplasia is the condition in which normal appearing cells are proliferating at an excessive rate. A nodule is a small aggregation of these cells.

combined (6/144) was significant. It is important to note, however, that the historical controls may not have been examined in a manner as sensitive to detecting tumors as that used by Morgan et al.

In a subsequent paper, Ward (1985) reported the results of the same re-evaluation by Morgan et al. including data concerning proliferative lesions of the liver, as well as the glandular stomach. This re-evaluation showed a statistically significant increase in benign (i.e., non-cancerous) tumors (hepatocellular adenomas) in male rats exposed to 100 ppm Aroclor 1254 compared to controls. The original NCI bioassay had only reported one hepatocellular adenoma in high-dose males; Ward reported seven adenomas. Ward also showed a dose-related trend in hepatocellular adenomas. This difference may be due to a disagreement in pathological evaluations of tissues.

In a study by Kimbrough and Linder (1974), 9/22 (41%) male BALB/cJ mice fed 300 ppm Aroclor 1254 for 11 months developed tumors of the liver (hepatomas). A similar group receiving the treated diet for only 6 months, followed by control diet for 5 months only had a 4% (1/24) incidence of hepatomas. No hepatomas were observed in 58 control mice. Additionally, all PCB-treated mice had enlarged livers and adenofibrosis of the liver. A major limitation of the study was the high early mortality with subsequent autolysis (tissue degeneration following the death of an animal), thereby eliminating over 50% of the original mice from the final results.

In sum, Aroclor 1254 has not been shown to be carcinogenic in animal studies. There is some evidence that there was a treatment-related increase in non-cancerous changes (hepatocellular proliferative lesions) in rats in the NCI (1978)

study; however, the response was weak (and not statistically significant). No conclusions can be drawn from the re-evaluation of these data by Ward (1985) and Morgan et al. (1981) because of uncertainties associated with their analyses. The findings of Kimbrough and Linder (1974) suggest a treatment-related increase in benign liver tumors in mice treated with Aroclor 1254. The interpretation of these results are limited by previously noted study inadequacies.

d) Aroclors 1248, 1242, and 1232

At present, there are no studies concerning the tumorigenicity of Aroclors 1248, 1242, or 1232 from which reliable carcinogenic potency factors could be derived. Mammalian carcinogenicity bioassays of acceptable quality (e.g., sufficient duration, number of test animals, and test doses) have not been conducted on these Aroclors. Moreover, these PCB mixtures may not be of sufficient tumorigenic potency to cause an observable increase in tumor incidence when tested in a standard rodent bioassay. There are, however, two primate studies (one on Aroclor 1248 and the other on Aroclor 1242) that describe modifications and lesions of the gastric mucosa. Although these studies do not show tumorigenicity as an endpoint, they may be qualitatively significant in light of the stomach adenocarcinomas observed in Aroclor 1254-exposed rats (NCI 1978, Morgan et al. 1981, Ward 1985).

Two studies, Allen et al. (1973) and Becker et al. (1979), reported PCB-induced changes in the stomach, but no increase in stomach tumors. The severity of the effect was correlated with the duration and level of exposure and was observed at relatively low concentrations (0.12 mg/kg/day in the

Becker et al. study). Neither of these studies was designed to examine carcinogenesis nor can they be used for cancer potency estimation of Aroclor 1248 or Aroclor 1242. When considered along with the results of the NCI bioassay, these results suggest that the stomach cannot be discounted as a potential target organ for PCB. It is important to note, however, that there has been no reported incidence of stomach tumors in bioassays of Aroclor 1260, Clophen A60, or Clophen A30. Further, the incidence of stomach tumors in Aroclor 1254-exposed animals was not significantly greater than in controls, was not dose related, and was so low that even if stomach tumors were considered, they would have no effect on the tumorigenic potency estimates derived in this document.

e) Clophen A30

Clophen A30, a German commercial PCB mixture similar to Aroclor 1242, was also tested in the previously-cited study by Schaeffer et al. (1984). Male Wistar rats received dietary concentrations of 100 ppm Clophen A30 over a period of 832 days. Liver cancer (hepatocellular carcinoma) incidence in the treated group was 3% (4/130), while in the control group the incidence of hepatocellular carcinoma was 0.76% (1/131). Non-cancerous tumors (neoplastic nodules) of the liver were 29% (38/130) and 3.8% (5/131) in the Clophen A30 and control groups, respectively. The incidence of neoplastic nodules but not the incidence of hepatocellular carcinoma (malignant tumors), in the Clophen A30 group was statistically significantly increased compared to controls.

f) Kanechlors 300, 400, and 500

Three rodent studies of Kanechlors 300, 400, and 500 add qualitative support to the variation of tumorigenic potency among the PCB mixtures. These include rat studies by Kimura and Baba (1973) and Ito et al. (1974) and mouse studies by Ito et al. (1973).

Kimura and Baba (1973) exposed male and female Donryu rats to Kanechlor 400; initial exposure was 38.5 ppm in diet but was increased to the very high dose of 616 ppm to keep pace with body weight gain. When severe body weight loss was observed, the dose was reduced to 462 ppm. The total Kanechlor consumption in females ranged from 700 to 1,500 mg and in males from 450 to 1,800 mg. Non-cancerous (adenomatous) nodules were observed in 6/10 of the females consuming more than 1,200 mg of Kanechlor 400; no such lesions were observed in the males. EPA (1988) concluded that this study was too short and the exposure level too high (treated animals received doses exceeding the maximum tolerated dose) to provide a good experimental basis for the determination of the carcinogenic potential of Kanechlor 400.

In a second rat study, Ito et al. (1974) exposed male Wistar rats (via feed) to 100; 500; or 1,000 ppm of either Kanechlor 300, 400, or 500 for 28 weeks to one year. Nodular hyperplasia was observed in all of the Kanechlor 500 dose groups and in the 100 and 1,000 ppm dose groups exposed to Kanechlor 400 and Kanechlor 300. The incidence of this nodular hyperplasia increased with dose as well as with percent chlorine content. EPA (1988) stated that this study does not demonstrate tumorigenicity, but it cannot be considered evidence of non-tumorigenicity because of the short duration and small number of subjects per group limit the ability of the study to

detect tumorigenicity. EPA also concluded that the nodular hyperplasia, which appeared as early as 40 weeks, further precludes considering this study a negative finding. In addition, this study did not include female rats, which in light of the Kimura and Baba (1973) study results, may be more sensitive than males.

In a series of mouse studies by Ito et al. (1973), male mice were exposed to either Kanechlor 500, 400, or 300 in feed at concentrations of either 500, 250, or 100 ppm for 32 weeks. Although liver weight increase in all treatment groups was greater than controls, liver cancer (hepatocellular carcinomas) and increase in the number of liver cells (nodular hyperplasia) were induced in only the high dose (500 ppm) group exposed to Kanechlor 500. Forty-two percent (5/12) of the high-dose Kanechlor 500 group showed hepatocellular carcinomas, while 58% (7/12) showed hyperplastic nodules. Amyloid degeneration^{1/} of the liver was observed in mice fed Kanechlor 500 or 400 at 250 ppm or 100 ppm, but not in the 500 ppm groups; however, according to the authors, the effects seen in the Kanechlor 500 group (nodular hyperplasia and hepatocellular carcinomas) could have masked any amyloid degeneration. Some mice fed Kanechlor 300 in the 500 ppm, 250 ppm, and 100 ppm dose groups also showed amyloid degeneration. None of the controls showed hepatocellular carcinomas, nodular hyperplasia, or amyloid degeneration. For evaluating carcinogenicity, interpretation of this study is

^{1/}This is a type of tissue or organ degeneration that is characterized by the deposition of a starchlike substance (amyloid) in the tissues.

limited by several factors including short study duration (52 weeks), lack of data on female mice, the small number of mice per dose group, and a lack of dose-response.

In conclusion, the Kanechlor data seem to indicate tumorigenic potential of these mixtures in rodents. The limitations of study design suggest that these data should not be used to derive a cancer potency factor; however, they do qualitatively support the liver as a site of action for PCBs in rodents.

g) Conclusions Regarding Animal Data on Tumorigenicity

There is clear evidence indicating that some of the highly chlorinated commercial PCB mixtures are tumorigenic in some animals. The responses are mostly limited to the livers in rats and mice, although there is a suggestion that some PCB mixtures may also affect the stomach of rats and monkeys.

There is uncertainty as to whether or not Aroclors 1248, 1242, and 1232 are tumorigenic in animals. Because there are no valid cancer bioassays for these mixtures, a comparison with other commercial PCB mixtures based on comparative composition is the only basis for evaluation. The best evidence for comparison comes from the study by Schaeffer et al. (1984) in which male rats were exposed to either Clophen A60 or Clophen A30. As previously explained, the Clophen A60 rats showed a 48% incidence of hepatocellular carcinoma, while the Clophen A30 rats showed only a 3% incidence of hepatocellular carcinoma that was not statistically significant. Although these results are not evidence for tumorigenicity for the lower-chlorinated Aroclors or Clophens, the data can be used to derive a

preliminary and conservative estimate of relative cancer potency. If we assume Clophen A60 parallels the cancer potency of Aroclor 1260 and Clophen A30 parallels that of Aroclor 1242, then we can conclude that the cancer potency of Aroclor 1242 is much lower (at least 16 times lower) than that of Aroclor 1260. The data for Aroclor 1254 qualitatively indicate an even lower potency than Aroclor 1260 than indicated by the Clophen data. These data, however, are not as well suited for use in quantitative estimation of cancer potency as the Clophen data because the data for Aroclor 1254 are from a different strain of rats than the data for Aroclor 1260.

It must be emphasized that reliance on the rodent liver-tumor data to estimate effects in humans may be conservative. As previously noted, the relevance of liver tumors in rodents to humans has been questioned because of the high and variable incidence of liver tumors in various strains of mice (e.g., Butler and Newberne 1975, Nutrition Foundation 1983, Clayson 1981) and the high spontaneous incidence in the livers of rats of preneoplastic cells that can be induced by promoting agents to produce tumors (e.g., Ogawa et al. 1981, Ward 1983, Schulte-Hermann et al. 1983).

Indeed, in a review of proliferative hepatocellular (liver) lesions of the rat, EPA (1986) has stated that, although neoplastic nodules are increased in animals receiving carcinogens and some neoplastic nodules may have "malignant potential," others may only be "hyperplastic" lesions and still others may regress following cessation of exposure. Thus, EPA (1986) stated that "the exact contribution of neoplastic nodules to the overall incidence of hepatocellular tumors in the rats is unclear at this

time." Nonetheless, despite the skepticism that must surround reliance on observations of hepatocellular tumors in rats as indicators of tumorigenic effects in humans, the standard regulatory practice is to assume these data are accurate predictors of carcinogenic potency in humans. This approach must be seen as possibly resulting in exaggeration of the hazards of PCBs.

E. Cancer Potency Differences Among PCB Congeners

1. Importance of Differences Among Mixtures of PCB Congeners

In light of the limitations in the available animal test data, a cautious approach would be to classify the various Aroclors as potential animal tumorigens. The considerations that lead to this position may be briefly summarized:

- (i) There are no valid test data on "Aroclors" other than Aroclor 1260 and Aroclor 1254.
- (ii) It is not clear which specific congeners are responsible for Aroclor 1260-induced tumorigenicity.^{1/} Figure 2 reveals that all commercial PCB products have some congeners in common. Thus, it is possible that all Aroclors contain some tumorigenic congeners.
- (iii) The tests of Aroclors 1260 and 1254 involved different strains of rats, and the different

^{1/}There are strong reasons to believe that substantial differences exist in the toxicity and tumorigenicity of various PCB congeners.

outcomes could possibly reflect differences in experimental design.

- (iv) Clophen A30 produces excess benign tumors in the rat liver, thereby suggesting a tumorigenic response for a mixture of congeners similar to that associated with Aroclor 1242.

For the above reasons the possibility of animal tumorigenicity cannot be ruled out for Aroclors other than Aroclor 1260. Nevertheless, the available data reveal clear differences in tumorigenic potencies among these sets of congeners. (By "potency" we refer to the incidence of tumors, i.e., risk, associated with a specific PCB dose.) These potency estimates are critical to an evaluation of PCB risks and are discussed in the next section.

There is some evidence that, for certain noncancer endpoints, the biological activity of PCBs increases with increasing chlorine content (see section III.E.3 for discussion). Studies by Ito et al. (1973) and Koller (1977) have shown that the degree of liver cell proliferation and pathologic alterations is much higher in mice chronically exposed to commercial PCB mixtures of higher chlorine content than to those with lower chlorine content. Hepatic microsomal enzyme induction potency also increases with increasing chlorine content (Litterst et al. 1972). PCBs containing 54% or greater chlorine content appear to be the most potent at inducing these effects. The differences in the ability of various PCB mixtures to elicit biological changes other than cancer may be important indicators of differences in tumorigenic potency as well. Some of these endpoints, such as liver cell proliferation, may be associated with cellular events that might affect the rate of tumor formation.

Thus, the observed differences in carcinogenic potency and in other biological effects among the PCB mixtures may be correlated, but a definitive causal relationship has not been established.

2. Relative Potencies of Aroclors

The most compelling evidence for potency differences among the commercial PCBs is derived from the studies of Clophen A60 and Clophen A30. These products were tested in experiments of identical design and yielded quite different outcomes. As previously shown, the incidence of hepatocellular carcinoma in the Clophen A60 rats was 16 times greater than the incidence in the Clophen A30 rats (Schaeffer et al. 1984). Combining the incidence of both hepatocellular carcinomas and neoplastic nodules yields a smaller difference in cancer potency between Clophen A60 and Clophen A30. Specifically, the tumorigenic potency of Clophen A30 proved to be at least 10 times less than that of Clophen A60. This comparison is based on the highly conservative assumption that the excess benign tumors observed in the Clophen A30 experiment should be given equal weight to the malignant tumors produced by Clophen A60. If the benign and malignant tumors are weighted differently, the potency difference is even greater.

Because of the strong chemical similarities between Clophen A60 and Aroclor 1260 and between Clophen A30 and Aroclor 1242, the data on the Clophens can be used to estimate the potency of (untested) Aroclor 1242 relative to that of Aroclor 1260. Specifically, we propose to assign a potency of 0.1 to Aroclor 1242 relative to 1.3 for Aroclor 1260 (see section III.F.2.b for discussion).

The potency difference observed for Clophens is supported by the results of the experiments involving Aroclors 1260 and 1254. Although the difference in potency between Aroclors 1260 and 1254 appears to be even greater than that between Clophens A60 and A30, it must be

recognized that the two Aroclors were assayed in different rat strains, whereas the two Clophens were tested in identical experiments. The difference in potencies between Aroclors 1260 and 1254 nonetheless suggests that our reliance on the potency differential between the Clophens is highly conservative, i.e., highly overestimates the tumorigenic potency of the less chlorinated Aroclors.

3. Information on Mechanism of PCB-Induced Toxicity Supports Potency Differences

The role of structure on the potencies of PCB isomers and congeners has been extensively investigated (Safe 1984). The most potent compounds, namely 3,3',4,4'-tetra-; 3,3',4,4',5-penta-; and 3,3',4,4',5,5'-hexachlorobiphenyl are all coplanar (i.e., flat) in structure and bind with high affinity to the aryl hydrocarbon (Ah) receptor.^{1/} These compounds, however, are either not detectable or are present in only trace levels in the lower chlorinated PCB mixtures.

Several studies have demonstrated that the responses caused by 11 monoortho analogs (i.e., specific congeners) of the coplanar PCBs resemble those described for the higher chlorinated commercial PCBs. This group of 11 congeners (see figure 3), although they are not coplanar, bind with low to moderate affinity to the Ah receptor but are much less potent than the coplanar PCBs. These 11

^{1/}The Ah receptor is a protein molecule that binds a variety of chlorinated hydrocarbons such as PCBs, polychlorinated dibenzofurans, and polychlorinated dibenzo-p-dioxins. Experiments have shown: (1) the strength of the binding varies among the isomers of each of these classes of compounds and (2) inbred strains of animals that have high levels of this receptor are more sensitive to some of the toxic effects of these chemicals than strains that have low levels of the receptor.

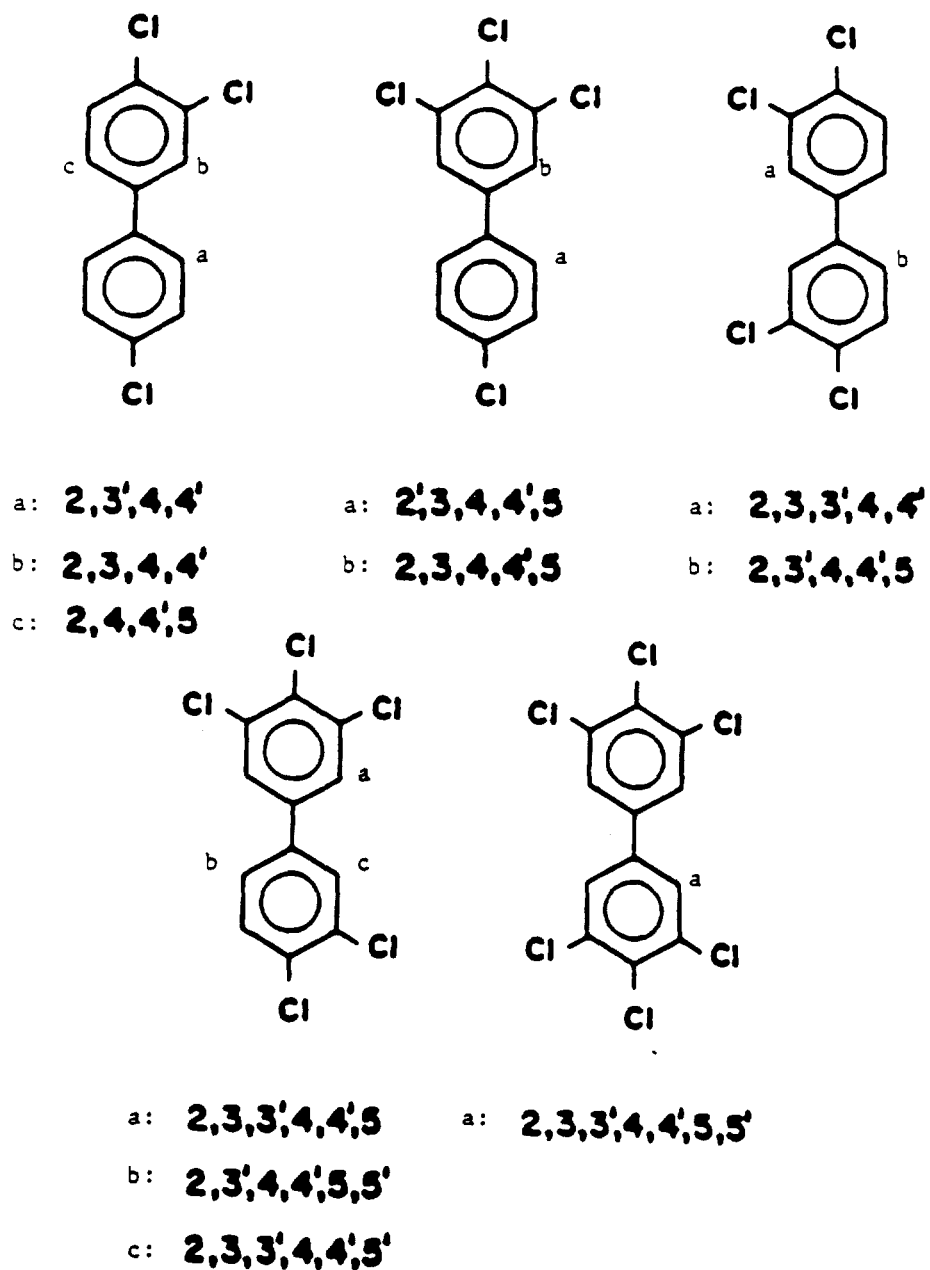


Figure 3. Monoortho substituted tetra-, penta-, hexa-, and heptachlorobiphenyls. Letters a, b, and c are alternate positions for chlorine substitution. For example in the first structure, the molecule is 2,3',4,4'-tetrachlorobiphenyl if a chlorine atom is in the "a" position.

PCBs, however, have been identified in the commercial Aroclors and are a major contributor to the activity of these mixtures.

The tumorigenic potencies of individual PCBs have not been determined; however, mechanistic studies indicate that PCBs and related halogenated aryl hydrocarbons act as tumor promoters. Moreover, at least in the skin model for carcinogenesis using hairless mice,^{2/} the observed structure-activity relationships confirm the role of the Ah receptor in this process. If one accepts the hypothesis that the mechanism of PCB tumorigenicity involves interaction with the Ah receptor, the structure-toxicity relationships that are also dependent on relative binding affinities for the Ah receptor protein can also be used to estimate tumorigenic potencies of individual PCBs and PCB mixtures.

F. Estimation of Potencies of PCB Mixtures

1. EPA Approach to Estimating Cancer Potency Factors

EPA (1986) has developed specific guidelines for risk assessment involving carcinogens. These guidelines require the derivation of a cancer potency factor (CPF) through the application of a mathematical model to extrapolate the observed dose-response data to very low doses at which humans are exposed (typically, hundreds of thousands of times lower than those used experimentally). It is not known whether the model is accurate; in fact,

^{2/}The skin of (genetically) hairless mice has been used as a model system for evaluating the potential of some chemicals to promote cancer. Usually, the cancer initiator is either injected or painted on the skin, followed by repeated applications of the suspected promoter. Appearance of skin lesions, including tumors, is recorded.

according to EPA, its use is designed to produce an upper limit on risks. The true risk, according to EPA (1986), is likely to be lower and could be zero.

EPA's CPFs are derived using the 95% upper bound of the slope of the linearized, multistage model for extrapolation to low doses. This model is based on certain assumptions about the action of carcinogens that may or may not be appropriate for PCBs. Furthermore, this model is one of the more conservative extrapolation models, i.e., it usually estimates a higher CPF than other models. Even though the analysis that follows is based on EPA's CPF, a further review of the scientific data may justify a different procedure for extrapolating to low doses.

EPA (1988) has calculated a CPF for PCBs of $7.7 \text{ (mg/kg/day)}^{-1}$ based on the Norback and Weltman (1985) study.^{1/} Prior to this, EPA (1984) had determined the CPF for PCBs to be $4.34 \text{ (mg/kg/day)}^{-1}$ based on the Kimbrough et al. study. Both of EPA's CPFs are based on studies in which rats were exposed to Aroclor 1260, and the agency has suggested that this CPF should be used for all PCBs. EPA (1988) has published, however, a "preliminary calculation" indicating a CPF of $2.6 \text{ (mg/kg/day)}^{-1}$ for Aroclor 1254 based on the 1978 NCI bioassay data. EPA states that, although the Aroclor 1260 data are the best for estimating the cancer potency of PCBs as a whole class of compounds, it is appropriate to ask whether existing data on other PCB mixtures are adequate for making separate cancer potency estimates. Citing limitations in the data for calculating separate

^{1/}The units on CPF are "risk per unit dose", where dose is expressed in mg/kg body weight/day. Multiplying "risk per unit dose" by the "estimated lifetime average daily dose" (in units of mg/kg body weight/day) yields an upper-bound estimate of lifetime risk.

cancer potency estimates for each PCB mixture, EPA has made a policy choice to use the CPF from Aroclor 1260 to characterize the upper limits on risks for all other PCB mixtures. As discussed below, EPA's approach is not supported by the available scientific information.

2. Modification of EPA Approach Based on Relative Potency Adjustment

EPA's cancer potency estimate for PCBs should be modified in two significant ways: a) the EPA potency estimate (based on Aroclor 1260) should be changed to reflect the lower potencies of Aroclor 1254, Aroclor 1248, Aroclor 1242, and Aroclor 1232; and b) the interspecies extrapolation factor used by EPA should be changed from a dosage per surface area scaling factor (i.e., $\text{mg}/\text{m}^2/\text{day}$) to a dose per unit body weight scaling factor (i.e., $\text{mg}/\text{kg}/\text{day}$).

a) Interspecies Scaling

The interspecies scaling (i.e., extrapolation) of dose is necessary to compensate for differences between humans and laboratory animals for such factors as size, lifespan, and basal metabolic rate. The most commonly used measures of dose are milligrams of chemical per kilogram of body weight of the animal per day ($\text{mg}/\text{kg}/\text{day}$) and milligrams of chemical per square meter body surface area per day ($\text{mg}/\text{m}^2/\text{day}$). Debate over the choice of dosage unit has centered on the appropriate measure for body size (kg body weight or m^2 body surface area) and on the temporal descriptor (per day or per lifetime) (cf. Hoel et al. 1975, Crump et al. 1980, Food Safety Council 1980, Allen et al. 1987). For carcinogenic compounds, both scaling factors have been used in risk assessment by different federal agencies, and both scaling factors were considered valid when

reviewed by the Office of Science Technology and Policy (OSTP 1985). For example, the EPA uses $\text{mg}/\text{m}^2/\text{day}$ while the Food and Drug Administration uses $\text{mg}/\text{kg}/\text{day}$. (EPA recently published a notice in which, among other matters, it requested comments on whether to modify its approach.)

The use of $\text{mg}/\text{m}^2/\text{day}$ as a scaling factor tends to give higher risk estimates per unit of dose than does $\text{mg}/\text{kg}/\text{day}$. (Risk is presumed in the linear no-threshold model to be directly proportional to dose.) For example, in extrapolating from mouse to man, the use of $\text{mg}/\text{m}^2/\text{day}$ will result in a risk estimate (per unit of dose) that is approximately 12 times greater than the estimate obtained using $\text{mg}/\text{kg}/\text{day}$. In extrapolating from rat to man the risk estimate is approximately 7 times greater when surface area scaling ($\text{mg}/\text{m}^2/\text{day}$) is used as opposed to $\text{mg}/\text{kg}/\text{day}$.

There are a number of reasons why extrapolation should be undertaken on a body weight basis. First, consider the basis of the surface area scaling factor. Hoel et al. (1975) proposed the use of dosage units in $\text{mg}/\text{m}^2/\text{day}$ on the basis of studies of the acute toxicity of anticancer drugs in humans and animals. In these studies, the acutely toxic level was similar in mouse, rat, hamster, dog, monkey, and man when dosage was expressed as $\text{mg}/\text{m}^2/\text{day}$. This finding is not unexpected. In many cases toxic substance are detoxified by the metabolic processes of the organism. The body surface area of an animal is an indirect measure of the animal's basal metabolic rate. It is this relationship between body surface area and metabolic rate that explains the interspecies similarity in dosages when expressed on a surface area basis. But this relationship for acute toxic effects does not

necessarily apply for other effects. The relationship between dose and body surface area, a priori means very little when considering chronic effects such as cancer.

In contrast, the Scientific Committee of the Food Safety Council (1980) favored the use of body weight as the basis for extrapolation. The council explained that "with long experience of the value of extrapolation on body weight basis, we recognize this as the most satisfactory procedure." Crump et al. (1980) and Allen et al. (1987) determined, based on an analysis comparing the carcinogenic potency of 13 chemicals in humans and rodents, that the unit of dosage measurement giving the closest correlation between species was mg/kg/day.

A similar conclusion was reached by Crouch (1983), after examining a large data set on chemicals that had been tested for carcinogenicity in more than one species. Some of the chemicals in this data set had also been studied epidemiologically in humans. Crouch (1983) found that he could derive a range of scaling factors to extrapolate among species, strains, or sexes, but argued that a body-weight scaling factor value of 1 (i.e., mg/kg/day) should be chosen for general extrapolation from rodents to humans.

In the absence of good evidence for the use of a more complex procedure, we believe that the use of mg/kg/day is the most appropriate basis for interspecies dosage comparison. In addition to its relative simplicity, this procedure appears to have the best empirical support (Crump et al. 1980, Allen et al. 1987).

b) Potency Differences

Based on the above discussion of interspecies scaling factors and the earlier discussion of observed potency differences, it becomes possible to derive potency factors for each commercial PCB mixture. EPA derived a potency factor of 7.7 per mg/kg/day for Aroclor 1260 based on the study by Norback and Weltman (1985). In deriving a potency value for this report, we preserve EPA's conservative linearized multistage low-dose extrapolation model, but modify the interspecies scaling procedure by about six-fold,^{1/} as discussed above. This leads to a potency factor of 1.3 per mg/kg/day for Aroclor 1260.

As noted earlier, Clophen A60 is at least ten times more potent than Clophen A30 in studies of identical design. Because Aroclor 1260 is similar in composition to Clophen A60 and Aroclor 1242 is similar to Clophen A30, it is reasonable to assume that Aroclor 1242 should exhibit a potency no more than one-tenth that of Aroclor 1260. We thus assign a potency to Aroclor 1242 of 0.13 per mg/kg/day. It should be noted, however, that there are no studies that show a statistically significant increase in tumors for any mixture of PCBs other than Aroclor 1260 and Clophen A60. The potency of the less chlorinated mixtures of PCBs may thus be appreciably less than our estimate.

A simple interpolation procedure can be used to assign potencies to the other Aroclors. The

^{1/}The potency value is based on a study in rats. EPA's estimate is 7.7 per mg/kg/day. We used actual body weight data from the Norback and Weltman study rather than the generic factor of 7.

procedure assumes that potency declines proportionally with chlorine content. This can be approached either through an analysis by percent chlorine content of a particular Aroclor type or through an analysis by average chlorine number by Aroclor type. For example, if potencies of 1.3 and 0.13 are assigned to Aroclor 1260 (60% chlorine) and Aroclor 1242 (42% chlorine), respectively, then potencies can be assigned to Aroclors 1254, 1248, and 1232 based on their respective percent chlorine: 54%, 48%, and 32%. Similarly, the potencies of Aroclor 1260 and Aroclor 1242 can be used as the basis for interpolation of potency factors for Aroclors 1254, 1248, and 1232 from the average number of chlorine atoms in each Aroclor.

Because commercial PCBs are complex hydrocarbon mixtures, which are not completely identical with respect to specific isomer content, chlorine number can vary within Aroclor type. In order to derive a potency value based on actual chlorine number, rather than percent chlorine, an average value for chlorine number per Aroclor type must be determined. Several approaches have been used to derive the average chlorine number: a probabilistic (pseudo-stochastic) approach in which chlorine number is calculated based on the relationship between percent chlorine and chlorine number in individual PCB congeners; an approach calculating the average chlorine number based on weight percentages of congeners in commercial PCBs; and an approach calculating the average chlorine number based on data present in an ENVIRON (1987) report listing amount (percent mass fraction) of specific congeners in Aroclors 1260, 1254, and 1242. Slight variations in the average chlorine number per Aroclor type are seen among these three different approaches. When these alternative

values of chlorine number are each used to derive a cancer potency estimate, however, virtually no difference in potency exists. Therefore, the values for cancer potency are virtually the same no matter which approach is used to derive average chlorine number.

The tumorigenic potency values derived for various Aroclors using a percent chlorine approach and an average chlorine number approach are presented in table 1. All potencies except the potency for Aroclor 1260 (that provides the basis for the other estimates) are rounded to one significant figure. It is evident that the cancer potency values derived using a percent chlorine approach are virtually identical to those using an average chlorine number approach. Because it is our hypothesis that the cancer potency of PCBs varies with chlorine number, it is probably more accurate to rely on the mean chlorine number.

It is important to note that the TPFs in table 1 have been developed by combining the incidence data for benign and malignant tumors. Some individuals have suggested that only malignant tumors should be used to estimate cancer potency. If the data on the incidence of animals with malignant liver tumors (carcinoma or adenocarcinoma) only, i.e., excluding neoplastic nodules, were used, the potency factor for Aroclor 1260 would be 0.98 per mg/kg/day. Based on an analysis of malignant tumors only, Clophen A60 is about 13 times more potent than Clophen A30. Hence, the potency of Aroclor 1242, which is similar in composition to Clophen A30, should exhibit a potency no more than one-thirteenth that of Aroclor 1260, if malignant tumors only are considered. This would reduce the potency value of Aroclor 1242 to 0.075 per mg/kg/day. These values are slightly lower than those estimated in table 1.

TABLE 1

Alternative Estimation of Tumorigenic Potency (TPF)
 Factors For Various PCB Mixtures -- Benign
 and Malignant Tumors Combined^{1/}

<u>PCB Mixture</u>	<u>% Chlorine</u>	<u>TPF (mg/kg/d)⁻¹ Based on % Chlorine</u>	<u>TPF (mg/kg/d)⁻¹ Based on Mean Chlorine Number</u>
Aroclor 1260	60	1.3	1.3
Aroclor 1254	54	0.9	0.8
Aroclor 1248	48	0.5	0.4
Aroclor 1242	42	0.1	0.1
Aroclor 1232	32	0.08	0.07

^{1/}Based on a comparison of data from Clophens A60 and A30, combining benign and malignant tumors as discussed in the text.

3. Uncertainties and Limitations

There are several important limitations that tend to contribute to the conservative nature of this analysis:

1. All environmental PCB mixtures are assumed to be potential animal tumorigens, even though data are available to support such a conclusion only for those closely resembling Aroclor 1260.
2. Those PCB mixtures that are known or potential animal tumorigens are assumed to have the potential to cause tumors in humans, notwithstanding the absence of evidence of a causal relationship from all available epidemiology data.
3. A linear, no-threshold, low-dose extrapolation model is used to estimate potencies for all PCBs, notwithstanding the fact that PCBs do not exhibit many of the characteristics of carcinogens for which such models were developed. Indeed, it is possible that there is a threshold dose that must be exceeded before PCBs could pose any cancer risk, whatsoever.

G. Conclusions

Although some workers have been exposed to high levels of PCBs for long periods of time, several studies of such populations have not provided information establishing that PCBs cause cancer in human beings. If PCBs were potent human carcinogens, it is likely that such an increase in cancers among these several worker populations would have been observed. Therefore, based solely on data from exposure of people, it is not possible to conclude that PCBs are carcinogenic to humans.

Of the PCB mixtures that have been tested in animals, those that are 60% chlorinated (i.e., Aroclor 1260 and Clophen A60) are carcinogenic in rats. Tests in other species have not been adequate to demonstrate or rule out carcinogenicity. PCB mixtures that are less chlorinated (i.e., Aroclor 1254, 54% chlorinated, and Clophen A30, 42% chlorinated) were not carcinogenic in rats, but the latter increased the incidence of non-malignant tumors. Two conclusions can be reached from these data:

1. Highly (60%) chlorinated PCBs are carcinogenic in one animal species.
2. Less chlorinated PCBs are either not carcinogenic or are substantially less potent than the more highly chlorinated mixtures.

Guided by these conclusions, it is possible to make several conservative hypotheses:

1. If 60% chlorinated PCBs are carcinogenic in one mammalian species, it is assumed they may be carcinogenic in others, including humans, i.e., Aroclor 1260 and Clophen A60 may be carcinogenic in humans. It must be noted that this is a conservative assumption, based on current regulatory practice.
2. Because there is some overlap in the congener composition of the commercially available PCB mixtures and because no data exist to determine unequivocally which of the congeners are responsible for the animal carcinogenicity, other mixtures of PCBs may be viewed as carcinogenic. Again, this is an assumption that is consistent with current regulatory practice.

3. If all PCBs are assumed to be tumorigenic in humans, the maximum potencies of less chlorinated PCBs can be estimated from the available bioassay data.

These hypotheses form the basis of the estimates of human carcinogenic potency that are derived in this report. As is discussed herein, however, these estimates constitute a conservative upper bound on cancer potency. In the case of PCBs, the carcinogenic risks to humans from environmental exposure are almost certainly less than our estimates and, in fact, could well be zero. EPA (1986) has also acknowledged the conservative nature of upper-bound cancer potency estimates.

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IV. REFERENCES

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- Schulte-Hermann, R. 1985. Tumor promotion in the liver. *Arch. Toxicol.* 57:147-158.
- Tatematsu, M., K. Nakanishi, G. Murasaki, Y. Miyata, M. Hirose, and N. Ito. 1979. Enhancing effect of inducers of liver microsomal enzymes on induction of hyperplastic liver nodules by N-2-fluorenylacetylamine in rats. *J. Natl. Cancer Inst.* 63:1411-1416.

- Ward, J.M. 1983. Increased susceptibility of livers of aged F344/NCR rats to the effects of phenobarbital on the incidence, morphology, and histochemistry of hepatocellular foci and neoplasms. J. Natl. Cancer Inst. 71:815-823.
- Ward, J.M. 1985. Proliferative lesions of the glandular stomach and liver in F344 rats fed diets containing Aroclor 1254. Environ. Health Perspect. 60:89-95.
- Zimmerman, H.J. 1978. Chemical hepatocarcinogenesis. In: Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. New York: Appleton-Century-Crofts, 145-164.

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APPENDIX A
CURRICULA VITAE OF MEMBERS OF THE EXPERT COMMITTEE

CURRICULUM VITAE

KENNETH H. CHASE, M.D., F.A.C.P.M.

WORK EXPERIENCE

- 1980 - - President, Washington Occupational Health Associates, Inc., Washington, DC
- 1980 - - Assistant Clinical Professor of Medicine, George Washington University School of Medicine, Washington, DC
- 1978 - 1980 - Director, Occupational and Environmental Medicine Programs, George Washington University School of Medicine, Washington, DC
- 1973 - 1980 - Assistant Professor of Medicine, Department of Medicine, George Washington University School of Medicine, Washington, DC
- 1970 - 1973 - Attending Physician, University of Maryland Health Center, College Park, MD
- 1970 - 1972 - Research Associate, National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD

EDUCATION

- 1972 - 1973 - Third Year Resident, Department of Medicine, Georgetown University Hospital, Washington, DC
- 1970 - 1972 - Research Associate, National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD
- 1969 - 1970 - Second Year Resident, Department of Internal Medicine, The University of Michigan Medical Center, Ann Arbor, MI
- 1968 - 1969 - First Year Resident, Department of Internal Medicine, The University of Michigan Medical Center, Ann Arbor, MI
- 1964 - 1968 - M.D., School of Medicine, University of California at Los Angeles
- 1964 - 1966 - Graduate School, Department of Physiology, University of California at Los Angeles
- 1962 - 1964 - B.A., (Mathematics), University of California at Los Angeles
- 1960 - 1962 - El Camino College, Los Angeles, CA

MEDICAL LICENSURE

- 1983 - New Jersey (#41838)
- 1982 - Tennessee (#13838)
- 1981 - New York (#147667)
- 1980 - Delaware (#C1001854)
- 1973 - District of Columbia (#3561)
- 1970 - Maryland (#0023674)
- 1969 - California (#A023674)

BOARD CERTIFICATION

- 1984 - American Board of Preventive Medicine (Occupational Medicine)
- 1973 - American Board of Internal Medicine
- 1968 - Board of Medical Examiners, State of California

MILITARY SERVICE

- 1970 - 1972 - United States Public Health Service, Surgeon (Lt. Commander), National Institutes of Health, Bethesda, MD

SCHOLARSHIPS, HONORS & AWARDS

- 1986 - Fellow, American Occupational Medical Association
- 1985 - Fellow, American College of Preventive Medicine
- 1981 - 1984 - American Medical Association Physician's Recognition Award
- 1977 - 1980 - American Medical Association Physician's Recognition Award
- 1974 - 1977 - American Medical Association Physician's Recognition Award
- 1971 - 1973 - American Medical Association Physician's Recognition Award
- 1972 - Distinguished Lecture Series, University of Utah
- 1966 - 1968 - Medical Scientist Fellowship, Life Insurance Medical Research Fund
- 1964 - Honors in Mathematics, University of California at Los Angeles

PROFESSIONAL ORGANIZATIONS

- Aerospace Medical Association
- American Academy of Occupational Medicine
- American College of Physicians
- American College of Preventive Medicine (Fellow)
- American Industrial Hygiene Association (Potomac Section)
- American Medical Association
 - Section Council on Preventive Medicine (AOMA Representative)
- American Occupational Medical Association (Fellow)
 - Committee on History, Mission, Goals, and Philosophy (Chairman)
 - Committee on Occupational Medicine Practice
 - Committee on Occupational and Clinical Toxicology
 - Section for Private Practitioners of Occupational Medicine (Co-Chairman)
- American Society of Internal Medicine
- District of Columbia Society of Internal Medicine
- Medical Society of the District of Columbia
 - Committee on Occupational and Environmental Health (Chairman)
- National Capital Occupational Medicine Association
 - Board of Directors; President-elect
- Society for Risk Analysis

SELECTED RESEARCH & CONSULTING ACTIVITIES

- 1985 - - Project Director for the City of Los Angeles Department of Water & Power to develop/support a comprehensive Environmental Health Management System - characterize hazards of nearly 500 chemical products; extensive IH sampling and analysis; develop handling and monitoring procedures
- 1985 - - Project Director for the Edison Electric Institute to conduct a comprehensive critical review of health effects literature relevant to PCBs, dibenzofurans and dioxins including risk assessments for complex mixtures
- 1984 - 1985 - Project Director for major U.S. utility to assess adequacy and health risks associated with PCB clean-up procedures
- 1984 - - Project Director for Commonwealth Edison project to determine adequacy of capacitor clean-up standards, including spill modeling and health risk assessment
- 1983 - 1986 - Consultant to Clement Associates, Inc; literature review and risk assessment for workers at risk of exposure to PCB-containing fluids including dioxins and dibenzofurans for the Electric Power Research Institute; literature review update on Agent Orange for the Veterans Administration
- 1983 - - Consultant to Chemical Waste Management, Inc.; evaluate the environment of hazardous waste workers at risk of exposure to numerous waste chemicals and metals; develop a corresponding occupational medical surveillance program on nationwide basis
- 1982 - - Consultant to the Federal National Mortgage Association (Fannie Mae); provide occupational health support services to the Supervisor, Health Administration for corporate staff employees
- 1982 - - Project Director for USDA to provide occupational medical support services on a nation-wide basis for employees of the Agricultural Research Services Agency
- 1982 - 1983 - Consultant to Washington Metropolitan Area Transit Authority (METRO); review of existing medical services program to the end of recommending changes and enhancements required to provide more effective control of Worker's Compensation costs
- 1981 - - Consultant to University of Maryland; evaluate the occupational environments of 6,000 employees and recommend medical surveillance procedures for those at risk of exposure to a combination of pesticides, herbicides, noise, radiation, toxic chemicals and dusts and biohazards
- 1981 - - Consultant to Printing Industries of Metropolitan Washington, DC, Inc.; design and implementation of Hearing Conservation Programs for 70 member companies, including sound level surveys, audiometric testing and processing, training programs and computerized recordkeeping
- 1981 - - Consultant to George Washington University; design and implementation of medical monitoring program for employees engaged in pesticide and herbicide formulation and application
- 1981 - - Consultant to Kiplinger Washington Editors, Inc.; design, implementation and staffing of a comprehensive employee health program for 600 workers at risk of exposure to noise, pigments and organic solvents

- 1981 - - Consultant to VERSAR, Inc.; design and implementation of medical surveillance programs for workers at risk to PCBs, dioxins, dibenzofurans and other toxic chlorinated hydrocarbons in California and New York
- 1980 - - Senior Physician for Occupational and Environmental Medicine, Biometric Research Institute; program development in various occupational and environmental health projects with emphasis on clinical correlations
- 1980 - 1982 - Consultant to The Washington Post; evaluate and recommend procedures for monitoring exposures to organic solvents, ink pigments, lead fumes, noise and other hazardous agents
- 1980 - 1981 - Consultant to the U.S. International Communication Agency; design and coordinate clinical, toxicologic and industrial hygiene surveys of workers exposed to toxic chemicals (ketones, plasticizers and polymers)
- 1979 - - Consultant to various law firms and insurance companies; evaluate and prepare expert witness testimony in cases involving occupational or environmental exposures to asbestos, benzene, diisocyanates, lead, lindane, PCBs, and other substances
- 1979 - - Consultant to AMTRAK; design and execution of controlled studies to evaluate the toxicity of chlorinated hydrocarbons including PCBs, trichlorobenzene and trichloroethylene in exposed workers
- 1979 - 1981 - Consultant to PEPCO; advise management on medical monitoring procedures for exposures to lead, PCBs and noise
- 1979 - 1980 - Consultant to U.S. Department of Energy; case review and recommendations under the Energy Building Temperature Restrictions for the Office of Hearings & Appeals
- 1978 - 1979 - Advisor to Project Director, GWU Science Communications Division; Occupational Cancer Training Project, funding by NCI and OSHA
- 1978 - 1979 - Co-investigator, GWU Department of Medicine; effects of low-level ionizing radiation on rates of death by cancer, funded by the Nuclear Regulatory Commission
- 1977 - 1978 - Special Consultant to Assistant Secretary for Health (HEW); investigation and report on quality of medical care at St. Elizabeth's Hospital (NIMH)
- 1976 - 1979 - Member, Institutional Review Board; Medical Research Applications, Inc. Phase III Clinical Toxicologic Studies of LAAM (LL- alpha -acetyl - methadol) in addict population, funded by NIDA (NIH)
- 1976 - 1977 - Medical Consultant, METRO; part of occupational health team concerned with diving medicine
- 1975 - 1979 - Medical Director, AMTRAK; responsible for design and implementation of medical policies and procedures including toxicologic medical surveillance programs
- 1974 - 1980 - Attending Physician; George Washington University Medical Center Employee Health Service
- 1974 - 1975 - Medical Consultant, AMTRAK; development of medical standards for all field employees

- 1974 - - Executive physical program design and implementation for Washington offices of Union Pacific, RCA, AMTRAK, American Petroleum Institute, Exxon, Peat, Marwick & Mitchell, National School Boards Association, and others
- 1970 - 1973 - Attending Physician; University of Maryland Health Center, College Park, MD
- 1970 - 1972 - Electroencephalographic correlates of "autistic" Rhesus monkeys; National Institute of Child Health and Human Development
- 1970 - 1972 - Neuropathologic studies of the auditory cortex in squirrel monkeys; National Institute of Child Health and Human Development
- 1969 - 1970 - Computerized methodology for aldosterone assays in double dilution radioisotope techniques; University of Michigan Department of Endocrinology
- 1966 - 1968 - Epidemiologic and physiologic studies in multiple sclerosis; Departments of Neurology, UCLA School of Medicine and the Royal Victoria Infirmary, Newcastle-Upon-Tyne, England
- 1966 - 1967 - Efficacy of measles vaccine in field studies; UCLA School of Public Health
- 1965 - 1966 - Autonomic integrity in immunosympathectomized mice; UCLA Department of Physiology
- 1964 - 1965 - Embryological morphogenesis: Computer verification of mathematicochemical theories of pigment pattern formation; UCLA Department of Zoology
- 1963 - 1964 - Molecular orbital calculations of chemical binding energies by computer methods; UCLA Department of Chemistry
- 1962 - 1964 - Power spectral analysis of EEGs in humans and chimps; NASA Space Biology Lab, UCLA Brain Research Institute
- 1962 - 1963 - Uterine contraction-fetal heart rate studies by computer analysis; Loma Linda School of Medicine

SCIENTIFIC PUBLICATIONS

- Chase, K.H.: Health Effects of Halogenated Hydrocarbons in Zenz, C. (ed.), Occupational Medicine (Chicago: Year Book Medical Publishers, 2nd edition), in preparation
- Chase, K.H.: Pericardial Fibrosis As A Complication of Pleuropulmonary Asbestosis, in preparation
- Chase, K.H., Whysner, J.A.: Risk Assessment in Occupational Health in McCunney, R. (ed.), Handbook of Occupational Medicine (Boston: Little, Brown, 1st edition), accepted for publication.
- Anstadt, G.W., Chase, K.H., Clever L.H., et al., Occupational Medicine Forum, Journal of Occupational Medicine, 28:266-269, 1987.
- Chase, K.H.: Polychlorinated Biphenyls (PCBs) - Update 1982, Journal of Occupational Medicine, 24:332, 1982
- Chase, K.H., Wong, O., Thomas, D., et. al., Clinical and Metabolic Abnormalities Associated with Occupational Exposure to Polychlorinated Biphenyls (PCBs), Journal of Occupational Medicine, 24:109-114, 1982

- Investigational report on the quality of medical care at St. Elizabeth's Hospital (NIHM), Office of the Assistant Secretary for Health (DHEW), 1977
- AMTRAK Manual of Medical Procedures, National Railroad Passenger Corporation, April 1976
- Autistic Pathology: Evidence for Underlying Neural Substrate, with Drs. David Symmes, Marvin Eisengart and Mark Healey, Proceedings of the American Neurological Association, Washington, DC, 1972
- Signal Processing in the Auditory Cortex, with Drs. John Newman and Zvi Wollberg, Proceedings of the American Neurological Association, Washington, DC, 1972
- Endocrine Function in Multiple Sclerosis, with Drs. Henry Miller and Paul Millac, Journal of Neurology, Neurosurgery and Psychiatry, 32: 414-418, 1968
- Circadian Temperature Rhythm and Vision in Multiple Sclerosis, with Dr. Norman Namerow, Neurology, 18:417-422, 1968
- Measles in Los Angeles County: I. Epidemiological Characteristics of Cases and Vaccine Utilization, 1963 & 1966, with Dr. Suzanne Dandoy, in Public Health Reports
- Cardiac Responses of Immunosympathectomized Mice, with Bernice Wenzel, Ph.D., in Perceptual and Motor Skills, 23: 1009-1010, Southern Universities Press, 1966

SCIENTIFIC PRESENTATIONS

- Environmental and Occupational Health Hazards: Johns Hopkins University -- Baltimore, 1986
- Medical Surveillance in the Hazardous Waste Industries: American Academy of Occupational Medicine -- Washington, DC, 1986
- Resource Speaker on Occupational Medicine: Boston University Center for Industry and Health Care -- Boston, 1985
- Medical Surveillance in the Hazardous Waste Industries: American Academy of Industrial Hygiene -- Orlando, 1985
- PCBs, Dibenzofurans and Dioxins: American Occupational Health Conference -- Los Angeles, 1984
- Indoor Air Pollution: National Capital Area Lung Association -- Washington, DC, 1984
- Selected Topics in Occupational Medicine: Uniformed Services University of the Health Sciences -- Bethesda, 1984
- Moderator, Occupational Medicine Seminars: American Occupational Health Conference -- Washington, DC, 1983
- Health Hazards of Polychlorinated Biphenyls (PCBs): Association of American Railroads -- Baltimore, 1983
- Toxicity of Selected Chlorinated Hydrocarbons: Aerospace Industries Association -- Philadelphia, 1982
- Polychlorinated Biphenyls (PCBs) and Pyrolysis Products: American Occupational Health Conference -- Toronto, 1982
- Clinical Syndromes in Occupational Medicine: The George Washington University Hospital -- Washington, DC, 1982
- Toxic Hazards in Occupational Medicine: Georgetown University Hospital -- Washington, DC, 1981

Toxicity of Selected Chlorinated Hydrocarbons: Wilson Hospital --
Binghamton, NY, 1981

Clinical and Metabolic Abnormalities in Occupational Exposure to
Polychlorinated Biphenyls (PCBs): American Occupational
Health Conference -- Atlanta, 1981

Occupational Exposure to Toxic Substances: Greater Southeast Community
Hospital -- Washington, DC, 1981

The Occupational History in Clinical Medicine: American Medical Student
Association -- Washington, DC 1980

Clinical Toxicity of Polychlorinated Biphenyls: Medical Society of the
District of Columbia -- 1980

Medical Aspects of Toxic Substance Litigation: U.S. Department of Justice
Conference on Toxic Substance Litigation -- Pentagon, 1980

Cancer Hazards in Construction Conference: Building and Construction
Trades Department, AFL-CIO -- Phoenix, 1979

Symposium Chairman, Selected Topics in Occupational Medicine: Medical
Society of the District of Columbia -- 1979

Industrial Hygiene Problems and Solutions in the U.S. Railroad Industry:
Association of American Railroads Medical Section --
Denver, 1979

Management of Chronic Renal Failure: Georgetown University Hospital
Department of Medicine -- 1973

Societal and Medical Consequences of Drug Abuse: Distinguished Speakers
Program, University of Utah -- Salt Lake City, 1972

Computer Programming Strategies for the PDP-12 Computer: Behavioral
Biology Branch, National Institute of Child Health and Human
Development -- Bethesda, 1971

Neurocybernetics and the Question of Practical Application: Department
of Neurology, Royal Victoria Infirmary -- Newcastle-upon-Tyne,
England, 1967

CURRICULUM VITAE

John Doull, Ph.D., M.D.

OFFICE: University of Kansas Medical Center
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and Therapeutics
39th & Rainbow Blvd.
Kansas City, KS 66103
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Overland Park, KS 66209
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SOCIAL SECURITY NUMBER: 513-22-5613

DATE/PLACE OF BIRTH: September 13, 1922, Baker, Montana USA

MARITAL STATUS: Married to Vera M. Orsborn, March 1, 1958

CHILDREN: Ellen Jane, 1959; John Kelling, 1961; James Douglas, 1961

EDUCATION:

B.S., Chemistry, Montana State College, Bozeman, Mont., 1944
US Navy, Electronics, 1944-1946
Ph.D., Pharmacology, Univ. of Chicago, Chicago, Ill., 1950
M.D., Medicine, Univ. of Chicago, Chicago, Ill., 1953

PROFESSIONAL EXPERIENCE:

University of Chicago Medical School

Research Assistant, Univ. of Chicago Toxicity Laboratory, 1946-1950
Research Associate, US Air Force Radiation Laboratory and Univ. of Chicago
Toxicity Laboratory, 1951-1953
Assistant Director, US Air Force Radiation Laboratory & Toxicity
Laboratory, 1954-1967
Assistant Professor, Department of Pharmacology, 1956-1957
Associate Professor, Department of Pharmacology, 1957-1967

University of Kansas Medical Center

Professor of Pharmacology and Toxicology, Department of Pharmacology,
Toxicology and Therapeutics, 1967-
Co-Director, Clinical Pharmacology-Toxicology Center, 1967-1968
Director, Univ. of Kansas Medical Center Safety Office, 1978-1985
Director, Center for Environmental and Occupational Health, 1986-

PROFESSIONAL SOCIETY MEMBERSHIPS:

American Chemical Society, 1949-
 Kansas City Regional Chapter, 1967-
American Industrial Hygiene Association, 1950-
Radiation Research Society, 1953-1980
American Society for Pharmacology and Experimental Therapeutics, 1953-
 Environmental Pharmacology Committee, 1975-1978
Society for Experimental Biology and Medicine, 1954-
New York Academy of Sciences, 1954-1975
American Association for the Advancement of Science, 1954- (Fellow, 1958-)
Society of Toxicology (Charter Member), 1961
 Technical Committee, 1967-1968
 Education Committee, 1974-1976
 Membership Requirement Revision Committee, 1975-1976
 Biomed Research Oversight Committee, 1977-1978
 Central States Regional Chapter, 1986-
 Program Committee (Chairman), 1985-1986
 Finance Committee, 1986-1987
 Awards Committee (Chairman), 1987-1988
 Nominating Committee (Chairman), 1988-1989
 Council Member, 1981-1988
 Vice President Elect, 1984-1985
 Vice President, 1985-1986
 President, 1986-1987
 Past-President, 1987-1988
American Academy of Clinical Toxicology, 1970-
 Board of Trustees, 1972-1977
Canadian Academy of Clinical Toxicology, 1976-
 Program Committee, 1976-1977
The Toxicology Forum, 1979-
 Board of Directors, 1981-1982
American Board of Toxicology, 1979-1983
 Chairman Examination Committee, 1979-1982
 Vice President, 1981-1982
 President, 1982-1983
American Water Works Association, 1983-
 Kansas Regional Section, 1983-

EDITORIAL BOARDS:

Toxicology and Applied Pharmacology, 1970-1982
Forum for the Advancement of Toxicology, 1973-1983
AACTION (American Academy of Clinical Toxicology), 1974-1977
Environmental Health Sciences, 1976-
Archives Internationales de Pharmacodynamie et de Therapie, 1976-
Journal of Environmental Pathology and Toxicology, 1977-
Health & Environment Digest, 1987-

CONSULTANTSHIPS

ChemAgro Corp., Kansas City, MO, 1950-1980
Walter Reed Army Institute for Research, 1960-1963
 Radiation Protection Panel, 1962-1963
 Atomic Defense Support Agency, Group N-3, 1961-1962
White House Evaluation Study (Woolridge Report), 1962-1963
NIH Special Grants Program Advisory Panel, 1962
NIH Toxicology Study Section, 1965-1970
HEW Secretary's Commission on Pesticides (Mrak Report), 1968-1969
 Subcommittee on Interactions, 1968-1969
Midwest Research Institute, 1969-
Institute for Clinical Toxicology, Houston, Texas, 1969-1973
National Academy of Sciences, National Research Council, 1970-
 Toxicology Information Program (Chairman), 1970-1975
 Food Protection Committee, 1974-1979
 Committee on Non-nutritive Sweeteners, 1974-1975
 Safe Drinking Water Committee, 1975-1978 (Chairman, 1976-1978)
 Pesticides Subcommittee (Chairman), 1975-1977
 Committee to Revise Publication 1138, 1976-1977
 Chronic Toxicity Subcommittee (Chairman), 1976-1977
 Board on Toxicology and Environmental Health Hazards, 1978-1986
 Board on Environmental Sciences and Toxicology, 1986-
 IOM Food Safety Policy Subcommittee, 1978-1979
 Committee to study Saccharin and Food Safety Policy, 1978-1979
 IOM Advisory Committee on CDC Study of Vietnam Veteran Health, 1985-
 1988
 Committee on Toxicity Testing Strategies (Chairman), 1982-1984
 Committee on Mixtures (Chairman), 1986-1988
 Committee on Toxicology (Chairman), 1987-
Environmental Protection Agency, Washington, D.C., 1976-
 FIFRA Science Advisory Panel, 1976-1980
 Worker Re-entry Protocol Group, 1977-1978
 Committee on Tolerances, 1978-1979
 Science Advisory Board, Environmental Health Committee, 1980-
 Organics Subcommittee (Chairman), 1986-
 Estimating Risks from Dioxins/Dibenzofurans, 1986-1987
 Severity of Effects Ranking Schemes, 1985-1986
 Acute Toxics Committee, 1986-1987
 Hazard Ranking System Committee, 1987-1988
National Institute of Environmental Health Sciences, 1975-1978
 NIEHS Advisory Council, 1975-1978
 University-Based Centers Subcommittee (Chairman), 1975-1978
 Second Task Force on Human Health and the Environment, 1976-1977
 Biologic Mechanisms and Toxicity Subcommittee, 1976-1977
F.E.M.A., Washington, D.C., Expert Panel Member, 1977-
National Advisory Committee, California Primate Center, Davis, 1977-1980
CPC International, Englewood Cliffs, Toxicology Assessment Group, 1978
Best foods, Union, NJ, Food Safety and Nutrition Board, 1978-
OTA, Washington, Panel on Assessment of Environmental Contaminants, 1978
Rohm and Haas, Philadelphia (Medical Dept.), 1980-
Stauffer Chemical Corp., Pesticide Advisory Group, 1980-1984
National Toxicology Program, Board of Scientific Counselors
 Ad Hoc Panel on Chemical Carcinogenesis Testing & Evaluation, 1982-
 1984

DHHS Advisory Committee on Long-term Health Effects of Phenoxy Herbicides
 and Contaminants, 1982-1985
 National Sanitation Foundation, Ann Arbor, 1983-
 Council of Public Health Consultants, 1983-
 Health Advisory Board, 1983-
 Drinking Water Additives Peer Review Group, 1987-
 Nutrition Foundation, Washington
 Predictive Role of Mouse Liver Tumors Committee, 1982-1983
 UAREP, Panel on Health Aspects of Waste Chemical Disposal, 1983-1984
 Kansas Dept. Health and Environment, Topeka, 1983-
 Toxicology Advisory Committee, 1983-
 Governors Advisory Committee on Radon (Chairman), 1987-
 National Institute of Occupational Safety and Health, 1984-1987
 Board of Scientific Counselors, 1984-1987
 Pillsbury Corp., Minneapolis, 1984-
 White House Advisory Panel on Ranchhand Veterans, 1984-1986
 Clean Sites Inc., Alexandria, Technical Advisory Panel, 1984-
 Naylor Dana Institute, Advisory Panel on Acetaminophen, 1986-1987
 Black and Veatch Engineering Corp., Kansas City, 1986-1987
 Denver Water Department Reuse Demo. Project Advisory Committee, 1986-
 Scientific Advisory Panel on Ground Water Recharge (California), 1987
 Water Resource Recovery Pilot Plant Project (Tampa, FL), 1987-
 Health Effects Group (Chairman), 1987-
 Monsanto Chemical Corp., St. Louis Alachlor Review Panel, 1987-1988
 International Life Sciences Institute, Risk Science Institute, 1988-

LOCAL COMMITTEES:

Poison Control Center Committee (Chairman), 1968-1980
 Pharmacy and Therapy Committee (Chairman), 1969-1984
 Basic Science Lectureship Committee, 1970-1972
 Health Care Delivery systems Committee, 1971-1972
 Research Committee, 1971-1973
 Animal Care Committee, 1972-1974
 Computer Committee (Chairman), 1972-1974
 Search Committee for Chair of Biochemistry, 1975
 Search Committee for Dean of School of Nursing (Chairman), 1975
 Education Committee, 1976-1977
 Faculty Promotion and Tenure Committee, 1976-1977
 Curriculum Implementation Committee, 1976
 Ad Hoc Ethics Committee, 1976
 Long Range Planning Committee, 1976
 Information Systems Advisory Committee, 1977
 Medical Center Safety Committee (Chairman), 1978-1983
 Radiation Safety Committee, 1978-1983
 Biohazards Committee, 1978-1983
 Engineering Safety Committee, 1978-1983
 Committee for Intercampus Liaison (Chairman), 1978-1980
 Search Committee for Director of Biomedical Engineering (Chairman), 1980
 Search Committee for Graduate School Dean (Chairman), 1980
 Task Force on Need for School of Public Health, 1980
 Education and Curriculum Committee, 1984-1987
 Center for Environmental and Occupational Health, 1986-
 Executive Advisory Committee, 1986-
 External Advisory Committee, 1986-

HONORS/AWARDS:

Sigma Xi, 1960
Alpha Omega Alpha, 1973
The Kenneth P. DuBois Award, 1985

BOOKS/BOOK CHAPTERS:

Essays in Toxicology (F. Blood, ed.), Academic Press, New York, Effect of Physical Environmental Factors on Drug Response, 1972.

Casarett and Doull's Toxicology: The Basic Science of Poisons, Macmillan Publishing Co., Inc., New York.

First Edition (L. J. Casarett and J. Doull, eds.), 1975
Second Edition (C. D. Klaassen, M. O. Amdur and J. Doull, eds.), 1980
Third Edition (C. D. Klaassen, M. O. Amdur and J. Doull, eds.), 1986

Insecticide Biochemistry and Physiology (C. Wilkinson, ed.), Plenum Press, NY, The Treatment of Insecticide Poisoning, 1976.

Information Technology in Health Science Education (E. Deland, ed.), Plenum Pub. Co., Use of CATS in Pharmacology, 1978.

Food Safety (H. Roberts, ed.), Wiley & Sons, New York, Chapter 7, Food Safety and Toxicology, 1981.

Complex Mixtures, National Academy Press, Washington, D.C., 1988.

BIBLIOGRAPHY

1. DuBois, K. P., Doull, J., Salerno, P. R., and Coon, J. M. Studies on the toxicity and mechanism of action of p-nitrophenyl diethyl thionophosphate (Parathion). *J. Pharmacol. Exp. Ther.* 95: 79 (1949).
2. DuBois, K. P., Doull, J., and Cochran, K. W. Effects of acute beryllium poisoning on carbohydrate metabolism. *Proc. 116th Meeting Amer. Chem. Soc.*, p. 57 (1949).
3. DuBois, K. P., Doull, J., and Coon, J. M. The cholinergic action of alkyl pyrophosphoramidate. *J. Pharmacol. Exp. Ther.* 98: 6 (1950).
4. Cochran, K. W., Doull, J., Mazur, M., and DuBois, K. P. Acute toxicity of zirconium, columbium, strontium, lanthanum, cesium, tantalum and yttrium. *J. Ind. Hyg. Occup. Med.* 1: 637 (1950).
5. DuBois, K. P., Doull, J., and Coon, J. M. Studies on the toxicity and pharmacological actions of octamethyl pyrophosphoramidate (OMPA, Pestox III). *J. Pharmacol. Exp. Ther.* 99: 376 (1950).
6. DuBois, K. P., Cochran, K. W., and Doull, J. Inhibition of citric acid synthesis *in vitro* by x-irradiation. *Proc. Soc. Exp. Biol. Med.* 76: 422 (1951).
7. Doull, J., DuBois, K. P., and Geiling, E. M. K. The biosynthesis of radioactive bufagin. *Arch. Int. Pharmacodyn.* 86: 454 (1951).
8. Doull, J., Hermann, R. G., Geiling, E. M. K., and DuBois, K. P. Effects of bufagin on the respiration of cardiac muscle and other tissues. *Arch. Int. Pharmacodyn.* 86: 487 (1951).
9. Doull, J., and DuBois, K. P. Toxicity and anticholinesterase action of tetra-n-propyl dithionopyrophosphate. *J. Pharmacol. Exp. Ther.* 106: 382 (1952).
10. DuBois, K. P., Doull, J., Deroin, J., and Cummings, O. K. Studies on the toxicity and mechanism of action of some new insecticidal thionophosphates. *Arch. Ind. Hyg. Occup. Med.* 8: 350 (1953).
11. DuBois, K. P., Doull, J., Okinaka, A. J., and Coon, J. M. Studies on the toxicity and pharmacological actions of symmetrical and unsymmetrical diethyl bis(dimethylamido) pyrophosphate. *J. Pharmacol. Exp. Ther.* 107: 464 (1953).
12. Doull, J., and DuBois, K. P. Influence of hibernation on survival time and weight loss of x-irradiated ground squirrels. *Proc. Soc. Exp. Biol. Med.* 84: 367 (1953).
13. Doull, J. Studies on the cholinesterase activity of tissues of irradiated animals. *J. Pharmacol. Exp. Ther.* 110: 14 (1954).
14. Okinaka, A. J., Doull, J., Coon, J. M., and DuBois, K. P. Studies on the toxicity and pharmacological actions of bis(dimethylamido) fluorophosphate (BFP). *J. Pharmacol. Exp. Ther.* 112: 231 (1954).

15. Fitch, F. W., Doull, J., and Wissler, R. W. Histopathology of the irradiated hibernating ground squirrel (*Citellus tridecemlineatus*). *A.M.A. Arch. Path.* 60: 644 (1955).
16. Hallesy, D. W., and Doull, J. Acute and chronic toxicity of orange B and orange 1 in rats. *J. Pharmacol. Exp. Ther.* 116: 26 (1956).
17. Doull, J. Irradiation and survival in hibernating animals. *Med. Sci.* 1: 27 (1956).
18. Landahl, H. D., Hasegawa, A. T., and Doull, J. Effect of whole body x-irradiation on the heat production and temperature regulation of rats and mice. *Radiat. Res.* 5: 488 (1956).
19. Doull, J., Plzak, V., and Noble, J. F. Synthesis and radioprotective properties of chlorinated O-dialkylaminopropionamideo- and O-dialkylaminopropylaminodiphenyl sulfide derivatives. *J. Med. Pharm. Chem.* 1: 171 (1959).
20. Doull, J., Plzak, V., and Brois, S. J. Protective effects of various phenone derivatives against radiation lethality in x-irradiated mice. *Radiat. Res.* 11: 439 (1959).
21. Noble, J. F., Hasegawa, A. T., Landahl, H. D., and Doull, J. Effect of fractionation on survival of mice following chronic exposure to x-irradiation. *Radiat. Res.* 11: 457 (1959).
22. Doull, J. Chemical antidotes for radiation injury. *Arch. Environ. Health* 2: 284 (1961).
23. Vesselinovitch, D., DuBois, K. P., Fitch, F. W., and Doull, J. Mammalian toxicity and histopathologic effects of 2,6-dibutyl-4-nitrophenol. *Toxicol. Appl. Pharmacol.* 3: 713 (1961).
24. Doull, J., Plzak, V., and Root, M. Protection against chronic radiation lethality in mice. *Radiat. Res.* 16: 578 (1962).
25. Doull, J., Plzak, V., and Brois, S. J. A survey of compounds for radiation protection. *USAF School of Aerospace Med. Report*, No. 62-29: 1 (1962).
26. Doull, J., Plzak, V., and Root, M. Toxicity and radioprotective activity of p-aminopropiophenone in mice. *Radiat. Res.* 16: 588 (1962).
27. Plzak, V., and Doull, J. Toxicity and radioprotective effects of acetyl p-aminopropiophenone in mice. *Radiat. Res.* 19: 228 (1963).
28. Oldfield, D. G., Doull, J., Plzak, V., Hasegawa, A., and Sandberg, A. Protection of proton-irradiated mice with p-aminopropiophenone (PAPP) and 2-mercaptoethylamine (MEA). *Radiat. Res.* 19: 229 (1963).
29. Plzak, V., Hasegawa, A. T., and Doull, J. Radioprotective effects of cyclobutane derivatives in mice. *Radiat. Res.* 22: 224 (1964).
30. Vesselinovitch, D., and Doull, J. Effect of adding Co-ral to the diet of rats and mice. *Lab. Anim. Care* 14: 325 (1964).

31. Doull, J., Oldfield, D. G., and Plzak, V. Chemical protection against high energy proton radiation in mice. *Blood, The Journal of Hematology* 24: 638 (1964).
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39. Goldstein, G. M., and Doull, J. Treatment of nitrite-induced methemoglobinemia with hyperbaric oxygen. *Proc. Soc. Exp. Biol. Med.*, 138: 137 (1971).
40. DeFeo, F. G., Fitzgerald, T. J., and Doull, J. Synthesis and biologic activity of p-hydroxylaminopropiophenone. *J. Med. Chem.*, 15: 1185 (1972).
41. Doull, J. The effect of physical environmental factors on drug response. In *Essays in Toxicology* (W. J. Hayes, ed.), Chapter 2, Academic Press, New York, N.Y. (1972).
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43. Hurwitz, A., and Doull, J. Effect of irradiation on gastrointestinal drug absorption. *Radiat. Res.* 59: 606 (1974).
44. Doull, J. Factors influencing toxicity. In *Casarett and Doull's Toxicology: The Basic Science of Poisons* (J. Doull and L. J. Casarett, eds.), Chapter 5, Macmillan Publishing Co., Inc., N.Y. (1975).
45. Doull, J., and Casarett, L. J. (eds.). *Casarett and Doull's Toxicology: The Basic Science of Poisons*, Macmillan Publishing Co., Inc., N.Y. (1975).

46. Doull, J. Evaluation of the toxicity of food additives. *Proc. Sixth Internat. Congress of Pharmacol.* 6: 115 (1975).
47. Doull, J. Pesticide-induced delayed neurotoxicity. In *Pesticide Induced Delayed Neurotoxicity* (R. L. Baron, ed.), EPA 600/1-76-025, Chapter 8, Washington, D.C. (1976).
48. Doull, J. The treatment of insecticide poisoning. In *Insecticide Biochemistry and Physiology* (C. A. Wilkerson, ed.), Chapter 16, Plenum Press, New York, N.Y. (1976).
49. Doull, J., and Walaszek, E. J. The use of Computer Assisted Teaching Systems in Pharmacology. In *Computers in Medical Education* (E. DeLand, ed.), Chapter 12, Plenum Pub. Co., New York, N.Y. (1977).
50. Doull, J., Klaassen, C. D., and Amdur, M. O. (eds.). *Casarett and Doull's Toxicology: The Basic Science of Poisons*, 2nd Ed., Macmillan Publishing Co., Inc., N.Y. (1980).
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52. Misawa, M., Doull, J., Kitos, P. A., and Uyeki, E. M. Teratogenic effects of cholinergic insecticides in chick embryos. I. Diazinon treatment on acetylcholinesterase and choline acetyltransferase activities. *Toxicol. Appl. Pharmacol.* 57: 20-29 (1981).
53. Misawa, M., Doull, J., and Uyeki, E. M. Mechanisms of teratology induced by organophosphates. *8th Int. Congress of Pharmacology*, July 19-24, Tokyo, Japan (1981). (Abst.)
54. Eigenberg, D., Pazdernik, T., and Doull, J. Hemoperfusion: a possible alternative method for treating organophosphate insecticide poisoning. *The Toxicologist* 1: 136 (1981).
55. Doull, J. Assessing pesticide toxicity in man and correlations with laboratory animal studies. In J. Miyamoto et al. (ed.). *IUPAC Pesticide Chemistry*, Kyoto, Japan, Pergamon Press (1983).
56. Klaassen, C. D., Amdur, M. O., and Doull, J. (eds.). *Casarett and Doull's Toxicology: The Basic Science of Poisons*, 3rd Ed., Macmillan Publishing Co., Inc., N.Y. (1986).
57. Doull, J., and Bruce, M. C. Origin and scope of toxicology. In *Casarett and Doull's Toxicology: The Basic Science of Poisons* (C. D. Klaassen, M. O. Amdur and J. Doull, eds.), pp. 3-10, Macmillan Publishing Co., Inc., N.Y. (1986).

CURRICULUM VITAE
OF
DR. SEYMOUR L. FRIESS

EDUCATION

Bachelor of Arts (A.B.) degree, University of California at Los Angeles, 1943.

Master of Arts (M.A.) degree, University of California at Los Angeles, 1944.

Doctor of Philosophy (Ph.D.) degree, University of California at Los Angeles, 1947.

EMPLOYMENT

Research Chemist, Manhattan Engineering District, 1944-46.

Instructor, Department of Chemistry, University of Rochester, 1948-51.

Biosciences Research and Administration, Naval Medical Research Institute, 1951-79.

Research Scientist; 1951-58.

Head, Physical Biochemistry Division, 1958-65.

Chairman, Physiological Sciences Department, 1965-70.

Chairman, Environmental Biosciences Department, 1970-79.

Managing Director; Drill, Friess, Hays, Loomis and Shaffer, Inc., 1980-.

PROFESSIONAL SOCIETY MEMBERSHIPS

American Chemical Society.

International Society of Toxinology

Society of Toxicology

The Society of the Sigma Xi

Undersea Medical Society

Washington Academy of Sciences

HONORS

Adjunct Professor, Department of Pharmacology, Uniformed Services
University of the Health Sciences, the Medical School, 1977-1982.

Honorary Chair, Institute of Biophysics, University of Brazil at Rio de
Janeiro, as Chief of the Laboratory of Molecular Pharmacology, 1961-80.

Phi Beta Kappa.

Du Pont Fellow in Chemistry, 1946-47.

Past-President, Society of Toxicology, 1975-76.

Member, Editorial Board, Toxicology and Applied Pharmacology,
1964-69; Associate Editor, 1970-79.

Member, Editorial Board, Toxicon, 1965-.

Member, Editorial Board, Toxic Substances Journal, 1978-.

Member, Editorial Board, Perspectives in Toxicology, 1979-.

Member, Scientific Advisory Board, Chemical Industry Institute
of Toxicology, 1979-1982.

Past-President, American Board of Toxicology, Inc., 1979-1982.

Past-President, International Union of Toxicology, 1980-1983.

Distinguished Fellow Award, Society of Toxicology, 1981.

PROFESSIONAL ACTIVITIES

Member, Committee on Toxicology, Assembly of Life Sciences, National
Academy of Sciences-National Research Council, 1967-76.
(Vice-Chairman, 1968-71).

Member and Chairman, Advisory Panels on Research Programs in Space
Biology, National Aeronautics and Space Agency, 1970-75.

Member, Toxicology Information Program Committee, Assembly of Life
Sciences, National Research Council-National Academy of Sciences, 1972-77.
(Chairman, 1976-77).

Member, Ad Hoc Advisory Committee on Carbon Monoxide, Department of
Health, Education and Welfare, U.S. Public Health Service, Bureau of
Community Environmental Management, 1972.

Chairman, Scientific Panel for the NASA Apollo-Soyuz Test Program,
1974-75.

Member, Environmental Protection Agency-National Academy of Sciences
Advisory Committee on Tolerance for the Pesticide Leptophos, 1976.

PROFESSIONAL ACTIVITIES (continued)

Member, Environmental Protection Agency-National Academy of Sciences Advisory Committee on Tolerance for the Pesticide Leptophos, 1976.

Advisor, Sub-Committee on Program Development and Administration, Review Committee on the National Center for Toxicological Research, National Academy of Sciences-National Research Council, 1976-1978.

Member, Bureau of Biomedical Sciences (Consumer Product Safety Commission) Review Committee, National Academy of Sciences-National Research Council, 1977-1978.

Liaison Representative, Department of Defense, to the Inter-agency Testing Committee, Advisory to the Administrator of the Environmental Protection Agency for the Toxic Substance Control Act, 1976-1979.

Member, National Toxicology Program, Board of Scientific Counselor's Technical Reports Review Subcommittee, Carcinogenesis Bioassay Review, 1982-1985.

Member, U. S. Department of Agriculture, Expert Panel on Food Toxicology, 1982-1983.

Member, Committee on Safe Drinking Water, National Research Council-National Academy of Sciences, Board on Toxicology and Environmental Health Hazards, 1983-1985.

Member, Subcommittee on Pharmacokinetics, Committee on Safe Drinking Water, National Research Council-National Academy of Sciences, Board on Environmental Studies and Toxicology, 1986-

PUBLICATIONS

Author or co-author of approximately 130 papers in the scientific literature. (Bibliography available upon request.)

AREAS OF SPECIAL INTEREST AND COMPETENCE

Toxicology of industrial and military chemicals; neuromuscular pharmacology and toxicology; enzyme kinetics and mechanisms of action; physiology and pathology of chemoreceptors; chemical kinetics; hazard assessment and safety evaluation; regulation of toxic substances; hyperbaric toxicology and physiology.

PERSONAL

Birth date:

July 1, 1922

Married:

July 11, 1953 (Mary Eugenia Tarver)

Children:

Philip L.
Martin C.

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6522 Lone Oak Court
Bethesda, Maryland 20817

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JOSEPH V. RODRICKS, Ph.D.

EDUCATION

1969-70 Postdoctoral Scholar, University of California, Berkeley, California
1968 Ph.D., Biochemistry, University of Maryland
1963 M.S., Organic Chemistry, University of Maryland
1960 B.S., Chemistry, Massachusetts Institute of Technology

CERTIFICATION: Diplomate, American Board of Toxicology, 1982-1987
Renewed, 1987-1992

EXPERIENCE

Dr. Rodricks is one of the founding Principals of ENVIRON Corporation. He is an internationally recognized expert in assessing the risks to human health of exposure to toxic substances. He is also Associate Professor of Chemistry (part-time) at the University of Maryland. His experience at ENVIRON has included the following:

- Reviewed data and prepared exposure and risk assessments for trade associations and private firms on arsenic, benzene, phthalate esters, dioxins, nitrosamines, methylene dianiline, PCBs, ethylene dibromide, diesel emissions, ethylene oxide, and numerous other industrial chemicals and environmental pollutants.
- Developed new methodology and evaluated health risks associated with toxic and mining waste disposal sites, including several Superfund sites.
- Completed comprehensive risk assessments on several color and food additives for a major trade association and several private firms.
- Provided expert testimony in several court cases and administrative hearings involving toxic waste and other chemical hazards.
- Provided expert testimony before six different Congressional committees: poultry risks, groundwater contamination, food safety, risk assessment, policy and practices.
- Assisted manufacturers in planning and carrying out toxicology studies in support of food additive petitions, medical device approvals, and pesticide registrations.
- Provided expert consultancy on risk assessment methods for the Risk Science Institute, Department of Energy, several offices of the Environmental Protection Agency, the Occupational Safety and Health Administration, the Office of Technology Assessment, and the General Accounting Office.
- Prepared reviews and critical analyses of several NTP bioassays for a variety of trade associations and private firms.

EXPERIENCE (Continued)

- Prepared Case Study materials and conducted risk assessment training programs for EPA and several private and State organizations.
- Prepared risk assessments on several pesticides for private firms and assisted in responding to EPA's Special Review programs.
- Developed the human and environmental risk portions of the basic Risk/Cost Policy Model for EPA's hazardous waste program.
- Developed the methodology to be used by EPA under the National Contingency Plan for evaluating the public health risks of remedial actions at Superfund sites.
- Assisted the Occupational Safety and Health Administration in the preparation of occupational carcinogen regulations, including general policy and specific policy on arsenic.

Before founding ENVIRON Corporation, Dr. Rodricks held the following positions:

- Director, Life Sciences Division, Clement Associates. In that position, he had the following experience:
 - Directed the performance of toxic substances risk assessments for the Occupational Safety and Health Administration, the Environmental Protection Agency, state governments, and commercial clients with emphasis on pesticides, environmental pollutants, occupational carcinogens, and food and color additives.
 - Personally performed quantitative risk assessments on selected carcinogens, including exposure assessment, hazard evaluation, and quantitation of risk for numerous public and private clients.
 - Assisted private concerns in the development and monitoring of protocols for purposes of fulfilling regulatory requirements for toxicology testing.
 - Assisted in and directed the production of science policy documents for the Council on Environmental Quality, U.S. Congress, Office of Technology Assessment, and federal and state administrative agencies.
- Deputy Associate Commissioner for Health Affairs (Science), U.S. Food and Drug Administration. Principal advisor to the Commissioner of FDA on all matters of science affecting regulation of foods, drugs, cosmetics, veterinary products, biological products, radiation-emitting devices, medical devices, and diagnostic products.

EXPERIENCE (Continued)

Chaired the Interagency Regulatory Liaison Group, Risk Assessment Workgroup. Produced official carcinogen risk assessment guidelines adopted by CPSC, FDA, EPA, OSHA, and USDA. This guideline also served as the basis for government-wide carcinogen policy.

Developed, proposed, and implemented policies relating to the use of scientific information in regulatory decision-making. During this period, special emphasis was placed on the use of quantitative risk assessment in regulation.

Directed scientific staff providing final scientific review and advice to Commissioner and to FDA's Office of General Counsel on all regulations proposed by the various Bureaus of FDA.

Directed several intra-agency task forces concerned with the development and use of scientific information in FDA, including the Agencywide Task Force on Research Planning, the Intra-agency Toxicology Coordinating Group, and the FDA Mass Spectrometry Committee.

Commissioner's representative to National Cancer Advisory Board, National Toxicology Program, OECD Chemicals Testing Program, Regulatory Council (for carcinogen policy), National Task Force on Cancer, Heart, and Lung Disease and numerous other national and international organizations and committees.

- Assistant to the Director, Bureau of Foods, Food and Drug Administration. Performed many of the same types of functions described above, but with concern only for scientific and regulatory problems associated with foods and cosmetics. Organized and directed production of FDA's Bureau of Foods Research Plan. Held major responsibility for risk assessment and regulation of carcinogenic animal drug residues, naturally-occurring toxicants such as aflatoxins and other mycotoxins, and PCBs.
- Associate Director for Regulatory Affairs, Division of Toxicology, Bureau of Foods, FDA. Supervised four branch chiefs in the Division of Toxicology. These four branches provided the toxicology review of all substances in foods and cosmetics that are regulated by FDA.

Advised Director of Division of Toxicology on adequacy of toxicology data to support FDA approval of regulated substances.

Worked with Associate Division Director for Research to develop toxicity research programs in support of regulation.

JOSEPH V. RODRICKS, Ph.D.

EXPERIENCE (Continued)

- FDA Program Manager, Mycotoxins and Other Natural Toxicants. Developed, coordinated, and implemented all FDA programs on this group of regulated food contaminants.
- Deputy Director, Division of Chemistry, Bureau of Foods, FDA. Planned and implemented research programs on the development of analytical methods for toxic metals, industrial pollutants, aflatoxins and pesticides. Developed and implemented regulatory policy regarding the acceptability of methods of analysis for food additives and animal drug residues.
 - Laboratory Scientist and then Branch Chief, Division of Food Chemistry, Bureau of Science, FDA. Developed analytical methods for aflatoxins and other mycotoxins. Conducted structure-activity studies on aflatoxin standards used for aflatoxin. Worked with Associate Division Director for Research to develop toxicology research programs in support of regulation.
 - Associate Professor of Chemistry, University of Maryland (Evening Division). Teach courses in general chemistry, organic chemistry, and introductory biochemistry.

AWARDS

Horace T. Smith Scholarship, Massachusetts Institute of Technology, 1956-1958

Gillette-Harris Research Fellowship, University of Maryland, 1964-1965

Department of Health, Education and Welfare Training Award, University of California at Berkeley, 1969-1970

FDA Award of Merit, 1973, 1978

Guest Lecturer, University of California at Davis, awarded under National Institute of Health Training Program, 1976

Commissioner's Special Citation, FDA, 1980

NATIONAL ACADEMY OF SCIENCES/NATIONAL RESEARCH COUNCIL APPOINTMENTS

- Member, Committee on Neurotoxicology and Risk Assessment, 1987-1989
- Member, Committee on Human Health Risk Assessment of Using Subtherapeutic Levels of Antibiotics in Animal Feeds, 1987-1988.
- Chairman, Committee on Public Health Risks of Poultry Inspection Programs. Food and Nutrition Board. 1985-1987.

JOSEPH V. RODRICKS, Ph.D.

NATIONAL ACADEMY OF SCIENCES/NATIONAL RESEARCH COUNCIL APPOINTMENTS (Continued)

- Member, Planning Group. Research Needs in Risk Assessment, 1986.
- Member, Board on Toxicology and Environmental Health Hazards. 1982-1985.
- Member, Committee on Toxicology, 1978-1982.
- Member, Committee on Institutional Mechanisms for Risk Assessment, 1981-1983.
- Member, Food and Nutrition Board (Consultancy). Study on U.S.D.A. Programs on Meat and Poultry Residues. 1984.
- Workshop on Neurotoxicity Risk Assessment. (Co-Chairman). Safe Drinking Water Committee. 1985.

PROFESSIONAL MEMBERSHIPS AND ADVISORY BOARDS

Diplomate of the American Board of Toxicology, 1982-1987. Renewed, 1987-1992.

Member, Steering Committee. National Science Foundation study on Biorisk (Risks of Biotechnology). 1984 - 1985.

Member, Advisory Board, Federation of American Societies of Experimental Biology, FDA Study of Interspecies Extrapolation, 1986.

Advisor, U.S. General Accounting Office, Project on Evaluation of EPA's Drinking Water Standards, 1986.

Member, Advisory Group. U.S. General Accounting Office. Review of Risk Evaluation Methods, 1985 - 1986.

Board of Directors, American Academy of Toxicological Sciences.

Society for Risk Analysis.

American College of Toxicology.

American Chemical Society.

American Association for the Advancement of Science.

Association of Official Analytical Chemists.

Advisory Board, American Chemical Society Publications, 1975-1978.

JOSEPH V. RODRICKS, Ph.D.

PROFESSIONAL MEMBERSHIPS AND ADVISORY BOARDS (Continued)

American Oil Chemists' Society - American Association Cereal Chemists, Association of Official Analytical Chemists Joint Mycotoxin Committee, 1976-1979.

Association of Official Analytical Chemists, Publications Advisory Board, 1975-1979.

Association of Official Analytical Chemists, Policy Advisory Board, 1981-1984.

United States-Japan, Cooperation on the Development and Utilization of Natural Resources (UJNR) Panel on Toxic Micro-organisms, 1974-1980.

National Institutes of Environmental Health Sciences, Second National Task Force for Development of Research Priorities in Environmental Health, 1976.

Guest Faculty Member, New York University Course on Environmental Health, 1977-1979.

Food and Agriculture Organization of the United Nations, Consultant on Mycotoxins, 1976-1978.

Associate Editor, Risk Analysis, Journal of the Society for Risk Analysis, 1980-1982.

Vice President, Society for Risk Analysis, 1980-1981.

Consultant on Academic Planning, Biology Curriculum, Whitman College, Walla Walla, Washington, 1980.

Board of Councilors, Society for Risk Analysis, 1981-1983.

American Chemical Society, Advisory Committee on Resource Conservation and Recovery Act.

CONGRESSIONAL AND RELATED TESTIMONY

- "Poultry Inspection: The Basis for a Risk-based Approach". Presented to Subcommittee on Livestock, Dairy and Poultry; House Committee on Agriculture. June 2, 1987.
- "Alternative Approaches to Risk Assessment" Before Proposition 65 Science Advisory Panel. Sacramento, CA. December 16, 1987.
- "Potential Health Impacts of Groundwater Contaminants." Presented to Senate Environmental and Public Works Committee, June 17, 1985.

JOSEPH V. RODRICKS, Ph.D.

CONGRESSIONAL AND RELATED TESTIMONY (Continued)

- "Comments on HR4192. The Risk Assessment Research and Demonstration Act of 1983." Presented to: Subcommittee on Natural Resources, Agricultural Research and Environment. Committee on Science and Technology. House of Representatives, May 17, 1984.
- "Risk Assessment in the Federal Government." Presented to: Subcommittee on Department Operations, Research, and Foreign Agriculture. Committee on Agriculture. House of Representatives, Hearing on Pesticides Regulation, April 6, 1983.
- "Risk Assessment and Food Safety." Presented to Senate Public Health Committee. Hearings on New Food Safety Legislation, May, 1982.
- "Use of Risk Assessment by FDA." Presented to Committee on Science and Technology. House of Representatives, May 10, 1980.
- "Benzene Risks." Presented to: California Air Resources Board. Sacramento, January 25, 1985.

OTHER PROFESSIONAL ACTIVITIES

Chairman, FDA Intra-agency Task Force for Development of "Criteria and Procedures for Evaluating Assays for Carcinogenic Residues"

Project Officer, Research projects developed under Special Foreign Currency Program

- "Coordinated Research Project on Mycotoxins," All-India Institute of Medical Sciences, New Delhi, and National Institute of Nutrition, Hyderabad, 1976-1980
- "Food Plants Containing Toxins," National Research Council, Cairo, 1976-1979
- "Balkan Nephropathy," National Institutes of Health-Ministry of Health, Yugoslavia (Advisor), 1973

Advisor, Research Projects conducted under FDA Visiting Foreign Scientists program. Supervised visiting scientists from Egypt, India, Israel, 1975-1978

FDA Program Manager, Mycotoxins and Other Natural Toxicants, 1972-1978. Planning, research coordination, budgetary planning, regulatory policy

Project Officer or Advisor, twelve different FDA research contracts on food safety, 1969-1978

Bureau of Foods Representative, FDA Public Hearing on Animal Drug Uses of Diethylstilbestrol, 1976-1977

JOSEPH V. RODRICKS, Ph.D.

OTHER PROFESSIONAL ACTIVITIES (Continued)

Expert witness on toxicology and chemistry of residues in food-producing animals - FDA Public Health on Animal Drug Uses of Diethylstilbestrol, 1977

Drafter and co-author of FDA Regulations on Aflatoxin Contamination of Foods and on PCBs in Fish, 1977-1979

Drafter and co-author of FDA Criteria for Safety Evaluation of Animal Drug Residues and Food Additives, 1977-1979

Chairman, FDA Intra-agency Task Force on Research Planning, 1977-1980

PUBLICATIONS

Rodricks, J.V., Brett, S. and Chinchilli. 1988. "Review and Evaluation of Risk Associated with Occupational Exposures to Benzene". Submitted to Risk Analysis.

Rodricks, J.V. 1988. Origins of Risk Assessment in Food Safety Decision-Making. J. Amer. College Toxicol. (accepted).

Rodricks, J.V. and Turnbull, D. "Use of Biological Data in Risk Assessment: An Example Involving DEHP" in Environmental Risk Assessment (Paustenbach, D., Ed.) J. Wiley & Sons. To be published, 1988.

Tardiff, R.G. and Rodricks, J.V. (eds). 1987. Toxic Substances and Human Risks. Plenum Press. New York. 445 pp.

Tardiff, R.G. and Rodricks, J.V. 1987. "Comprehensive Risk Assessment" in Tardiff, R.G. and Rodricks, J.V. (eds.) 1987. op cit.

Brown, S.L., Brett, S., Gough, M., Rodricks, J.V., Tardiff, R.G. and Turnbull, D. 1988. "Review of Interspecies Risk Comparisons". Regulatory Toxicol. Pharmacol. (accepted).

Rodricks, J.V., Frankos, V., Turnbull, D. and Tardiff, R.G. 1987. "Risk Assessment for Effects Other Than Cancer". in Felix, C.W. (Ed.). Food Protection Technology. Lewis Publishers, Inc., Chelsea, MI. pp 61-74.

Rodricks, J.V. 1988. "Issues in Decision-Making" Introduction to Panel Discussion. Proceedings of the International Discussion Group on Carcinogenicity Studies. Accepted for publication.

Harris, R.H., Rodricks, J.V., Clark, C.S., and Popadopoulos, S.S., "Adverse Health Effects at a Tennessee Hazardous Waste Disposal Site" in Andelman, J.B. and Underhill, D.W. (Eds.). Health Effects from Hazardous Waste Sites. Lewis Publishers, Inc., Chelsea, MI. pp 221-240.

PUBLICATIONS (Continued)

Rodricks, J.V. 1986. "FDA's Ban on the Use of DES in Meat Production". Agriculture and Human Values. Vol. III (nos. 1 and 2). pp 10-25.

Rodricks, J.V. et al. 1986. Elements of Toxicology and Chemical Risk Assessment. A Handbook for Nonscientists, Attorneys and Decision-Makers. ENVIRON Corp. Second Edition, 1988.

Rodricks, J.V., Brett, S., and Wrenn, G. 1987. "Significant Risk Decisions on Federal Regulatory Agencies". Regulatory Toxicology and Pharmacology, 1,307-320.

Rodricks, J.V. and Turnbull, D. 1987. "Interspecies Differences in Peroxisomes and Peroxisome Proliferators". Proceedings, International Symposium on Peroxisome Proliferation. Toxicology and Industrial Health. Vol. 3 (No. 1). 197-225.

Rodricks, J.V. 1987 "Concluding Remarks:" International Symposium on Peroxisome Proliferators. Toxicology and Industrial Health. Vol. 3. (No. 1). 227-229.

Rodricks, J.V. 1986. Improving the Use of Risk Assessment in Regulation. Comments in Toxicology Vol. I. No. 1 (1986).

Rodricks, J.V. "Risk Estimation" In: Proceedings of the Second National Conference for Food Protection. U.S. Department of Health and Human Services. Food and Drug Administration. 1984. pp. 39-49.

Rodricks, J.V. "Government Data Requirements for Risk Assessment." In: Risk Management of Existing Chemicals. Chemical Manufacturers Association. Washington, DC 1984. pp. 80-90.

Rodricks, J.V. and Tardiff, R.G. "Conceptual Basis for Risk Assessment." In: Assessment and Management of Chemical Risks. Rodricks, J.V. and Tardiff, R.G. (Eds.) American Chemical Society. Washington, DC 1984. Reprinted in ChemTech. July, 1984.

Rodricks, J.V., Risk Assessment and Product Misuse. Chemical Times and Trends. April, 1984.

Rodricks, J.V. and Turnbull, D. 1985. Assessment of Possible Carcinogenic Risk to Humans from Exposure to Di-(2-Ethylhexyl)phthalate (DEHP). J. Am. College of Toxicology 4 (2). 111-145 1985.

PUBLICATIONS (Continued)

Rodricks, J.V. and Turnbull, D. "Risk Assessment: Biological Considerations" In: Handbook of Carcinogen Testing. Milman, H. and Weisburger, E. (Eds). Noyes Publishing Co. New York, 1985.

Rodricks, J.V. et al. Ground water Contamination and its Impacts. Prepared for Office of Technology Assessment, Congress of the United States. See: Protecting the Nation's Ground water from Contamination OTA. Washington, DC 1984. Two Volumes.

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JOSEPH V. RODRICKS, Ph.D.

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Risk Assessment Research Needs. Risk Science Institute. Washington, DC. April 1986.

Moderator. Panel on Issues in Decision-Making. International Discussion Group on Carcinogenesis Studies. Chapel Hill, NC. June 1986.

Risk Assessment for Ethylene Oxide Residues on Medical Devices. Health Industries Manufacturers Association. Washington, DC. October 1986.

Benzene Risks. Testimony before OSHA during Administrative Hearings on Benzene standard-setting. March 1986.

Risk Assessment for Effects Other Than Cancer. National Food Protection Conferences. Ann Arbor. August 1986.

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Consistency of SOM with Current Methods in Risk Assessment, Animal Health Institute Symposium. Washington, DC. January 1986.

JOSEPH V. RODRICKS, Ph.D.

PRESENTATIONS (Continued)

Developments in Pesticide Risk Assessment, Executive Enterprises Pesticide Regulation Conference. Washington, DC. September-1985.

Risk Assessment Research in EPA, EPA Today, (EEM Conference). Washington, DC. November 1985.

Panelist on Food Contaminants. Food and Drug Law Institute, Washington, DC. Dec. 1984.

Selective Skin Penetration of Colors Applied to the Skin. Society of Cosmetic Chemists. New York, NY. Dec. 1984.

Panelist and Chairman Risk Assessment Guidelines. Center for Energy and Environmental Management Conference. Arlington, VA. Nov. 1984.

Skin Penetration Studies and Risk. The Cosmetics, Toiletries and Fragrance Association. Boston, MA. October 1984.

Historical Perspective on Risk Assessment and Regulation. National Agricultural Chemicals Association. Washington, DC. October 1984.

Principles of Toxicology: National Association of Attorneys-General. Washington, DC. October 1984.

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Risk Assessment: Sensitivity Analyses. Risk Assessment Task Force. Chemical Manufacturers Association. Washington, DC. June 1984.

Principles of Risk Assessment. Mobil Oil Co. Toxicology Laboratories. Princeton, NJ. May 1984.

Improving Risk Assessment. Food Protection Conference. Washington, DC. May 1984.

Toxicology and Food Safety Evaluation. Institute for Food Technology. Richmond, VA. May 1984.

EDB. Grocery Manufacturers Association. Washington, DC. May 1984.

Risk Assessment in Federal Decision-making. National Governor's Association. Task Force on Drinking Water. Washington, DC. 1983.

Use of Percutaneous Absorption Data in Risk Assessment. CTFA Symposium on Percutaneous Absorption. Washington, DC. 1983.

JOSEPH V. RODRICKS, Ph.D.

PRESENTATIONS (Continued)

Risk Assessment in the Federal Government. National Governor's Association Conference on Toxic Substances Control. St. Charles, MO. 1983.

DEHP Risk Assessment. Chemical Manufacturers Association. Meeting on Phthlate Esters. Washington, DC. 1983.

Role of Risk Assessment on Protecting Against Product Liability. Chemical Specialities Manufacturers Association Annual Meeting. Washington, DC. 1983.

Can Risk Assessment be Improved? Conference on Toxic Substances Control Act. Center for Energy and Environmental Management. Arlington, VA. 1983.

Government Data Needs for Risk Assessment. Chemical Manufacturers Association Meeting. Washington, DC. 1983.

Institutional Mechanisms for Risk Assessment. The Brookings Institute. Washington, DC. 1983.

Guidelines for Risk Assessment: Recommendations of an NAS Committee. National Academy of Sciences. Washington, DC. 1983.

Use of Risk Assessment in Decision-Making. American Chemical Society. Annual Meeting. Washington, DC. 1983.

Protecting the Public Against Chemical Risks. Maryland Department of Public Health. Conference on Toxics. Towson, MD. 1983.

Risk and its Assessment. Grocery Manufacturers of America Workshop on Food Safety. Arlington, VA. 1983.

Risk Assessment. Cosmetics, Toiletries and Fragrances Association Annual Meeting. Philadelphia, PA. 1983.

Limitations in Traditional Approaches to Safety Evaluation. USDA. Washington, DC. 1983.

General Principles of Risk Assessment. USDA, Washington, DC. 1983.

Conceptual Basis for Risk Assessment. Chemical Health and Safety Division, American Chemical Society. Kansas City, MO. September, 1982.

Safety Assessment for TCDDs. International Conference on Tetrachlorodibenzodioxin. Arlington, VA. November 1981.

JOSEPH V. RODRICKS, Ph.D.

PRESENTATIONS (Continued)

Assessing the Risks of Food Constituents. American Association for the Advancement of Science. Washington, DC. January 1982.

Biological Basis for Risk Assessment. International Conference on Chemical Safety, Boston, MA. February 1982.

Strategy and Planning for Risk Assessment. International Conference on Chemical Safety, Boston, MA. February 1982.

Strategy and Planning for Risk Assessment. CTFA Scientific Conference, Washington, DC. January 1982.

Presentation of Results of Risk Assessment, CTFA Scientific Conference, Washington, DC. January 1982.

Risk Assessment, Georgetown University, Department of Pharmacology, Washington, DC. March 1982.

FDA's Scientific Dilemma, American Chemical Society, Annual Meeting, Las Vegas, NV. March 1982.

Models for Risk Assessment. Food and Drug Law Institute, Washington, DC. June 1982.

General principles of food safety. International Workshop and Symposium on Mycotoxins, National Research Centre, Cairo, Egypt. September 1981.

Chronic disease and mycotoxins. Mycotoxin Working Group, Food Safety Panel Committee, Agricultural Research Council, United Kingdom, London. April 1981.

Chronic disease and mycotoxins. Mycotoxin Working Group, Food Safety Panel Committee, Agricultural Research Council, United Kingdom, London. April 1981.

Quantitative risk assessment. Cosmetic, Toiletory, and Fragrance Association, Annual Meeting, New Orleans, LA. October 1980.

Risk assessment and regulation. Testimony before Committee on Science and Technology, U.S. House of Representatives, Washington, DC. June 1980.

The role of toxicology in regulation. Science Advisory Board, National Center for Toxicological Research, Jefferson, AR. May 1980.

Carcinogen regulation at FDA. Symposium on Government Carcinogen Policy, sponsored by Legal Times of Washington, June 1980.

JOSEPH V. RODRICKS, Ph.D.

PRESENTATIONS (Continued)

Assessing mycotoxin health risk. Meeting of the Association of Official Analytical Chemists, San Francisco, CA. 1979.

Carcinogens in edible animal products. Meeting of the Animal Health Institute, San Francisco, CA. 1979.

Overview of aflatoxin. For symposium on aflatoxin, Arizona Department of Health Sciences, Phoenix, AZ. 1979.

The role of the analytical chemist in regulation. American Chemical Society National Meeting, Washington, DC. 1979.

The concept of risk. Meeting of the Cosmetic, Toiletry and Fragrance Association, Colorado Springs, CO. 1978.

Food safety. For Department of Pharmacology, University of Mississippi, Oxford, MS. 1978.

Mycotoxins and other natural toxicants. FASEB Meeting, Atlantic City, NJ. 1978.

Cost-benefit analysis in regulation of food hazards. Annual Meeting of the Association of Food and Drug Officials of the United States, Indianapolis, IN. 1978.

Risk assessment. Guest lecture, Cornell University. 1978.

Mycotoxins and public health. Presented before the Second International Congress of Mycology, Tampa, FL. 1977.

Food safety. For Department of Environmental Health, New York University, New York, NY. 1977.

Discussion of FAO guidelines on mycotoxin surveillance. FAO/UNEP Conference, Nairobi. 1977.

Role of the analyst in regulation. Assoc. Official Analytical Chemists Annual Meeting, Denver, CO. 1976.

Mycotoxins. University of California, Davis, CA. 1976.

Aflatoxins. Stanford Research Institute, Menlo Park, CA. 1976.

What are aflatoxins? National Peanut Council Seminars for Producers, Albany, GA, Dallas, TX, and Norfolk, VA. 1976.

Aflatoxins in edible animal products. Conference on Mycotoxins in Human and Animal Health, College Park, MD. 1976.

PRESENTATIONS (Continued)

Public health implications of toxigenic fungi. Presented before the Microbiology Research Conference, Monticello, IL. 1974.

Naturally occurring food toxins. For Virginia Polytechnic and State University, Blacksburg, VA. 1974.

Mode of action of stachbotrys toxins. Meeting of the International Association of Microbiological Societies, Tokyo. 1974.

Aflatoxins. Lectures delivered at University of Delhi, University of Calcutta, University of Karachi, and Pakistan Council for Scientific and Industrial Research, Lahore. 1974.

Cottonseed and aflatoxin. University of Arizona, Phoenix Workshop. 1974.

Mycotoxin residues in animal tissues. University of Missouri, Columbia. 1973.

Mycotoxins and mycotoxicoses. Meeting of the Consumer Protection Institute (CASA), 1973.

Toxins occurring naturally in foods. Workshop of the National Canners Association, Washington, DC. 1972.

Analytical methods for toxicants occurring naturally in foods. Symposium on Analysis for Trace Contaminants in Foods. Meeting of the American Chemical Society, Middle Atlantic Region, Philadelphia, PA. 1972.

Stachybotryotoxicoses. For U.S. Department of Agriculture lecture program, New Orleans, LA. 1973.

Naturally occurring toxins--the chemistry and toxicology of the paralytic shellfish. For U.S. Department of Agriculture lecture program, Peoria, IL. 1973.

FDA attitudes on mycotoxins. North Central Regional Meeting on Mycotoxins, USDA, Manhattan, KS. 1972.

Current mycotoxin research at the FDA. Symposium on Mycotoxins, International Union of Pure and Applied Chemistry, Goteberg, Sweden. 1972.

Toxic chemicals of natural origins which can appear in foods. Seminar of the University of Maryland Chemistry Department, College Park, MD. 1971.

JOSEPH V. RODRICKS, Ph.D.

PRESENTATIONS (Continued)

Fungal metabolites which contain substituted 7,8-dihydrofuro (2,3-b) furans. Symposium on Natural Food Toxicants. Meeting of the American Chemical Society, Atlantic City, NJ. 1968.

SYMPOSIUM CHAIRMAN AND/OR ORGANIZER

American Chemical Society. Symposium on Risk Assessment, Kansas City, MO. September 1982.

American Chemical Society 3-day Symposium on Mycotoxins and Toxic Phytoalexins, Atlantic City, NJ. September 1974.

United States-Japan Natural Resources Cooperation, 5-day International Conference on Mycotoxins in Human and Animal Health, College Park, MD, October 1976.

National Center for Toxicological Research, Hormone Symposium, Little Rock, AR. October 1976 and October 1977.

Gordon Research Conference, Biochemistry of Fungi. August 1976.

Risk Assessment Principles. Workshop for the Environmental Protection Agency. March 1985.

Society for Risk Analysis. Workshop on Perceived vs. Actual Risk, Washington, DC. June 1981.

U.S. Department of Agriculture. Workshop on Risk Assessment. Washington, DC. October, 1983 and January, 1984.

Interdisciplinary Discussion Group on Carcinogenicity Studies, Chapel Hill, NC. June 1986.

CURRICULUM VITAE

SAFE, STEPHEN H.

November, 1987

PROFESSOR
VETERINARY PHYSIOLOGY AND PHARMACOLOGY

BIRTHDATE AND BIRTHPLACE: May 14, 1940
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S.S. NUMBER: 032-42-0830

MARITAL STATUS: Married

Wife: Lorna M. Safe

Children: Sara, June 23, 1966
Carol, July 17, 1969

EDUCATION:

B.Sc., Queen's University, 1962
M.Sc., Queen's University, 1963
D. Phil., Oxford University, 1965

FIELDS OF SPECIALIZATION:

Biochemistry
Toxicology

ACADEMIC APPOINTMENTS AND PROFESSIONAL EXPERIENCE:

Academic:

Research Assistant, Oxford University, 1966
Research Associate, Harvard University, 1967
Associate Research Office, National Research Council of Canada, 1968-73
Associate Professor, University of Guelph, Canada, 1973-77
Professor, University of Guelph, Canada, 1977-81
Professor, Veterinary Physiology and Pharmacology, Texas A&M University,
1981-present
Chester J. Reed Chair in Toxicology, 1983
Senior Scientist, Institute of Occupational and Environmental Medicine,
Texas A&M University, 1983-present
Distinguished Professor, Texas A&M University, 1984-Present
Adjunct Professor, University of Guelph, 1985-Present

ACADEMIC APPOINTMENTS AND PROFESSIONAL EXPERIENCE: (continued)

Other:

Chemical/Toxicological Consultant
Wellington Science Associates - Environmental Consulting Firm

PROFESSIONAL AND HONORARY SOCIETIES:

Chemical Institute of Canada
Canadian Federation of Biological Societies
American Association for Cancer Research
American Society for Mass Spectrometry
American College of Toxicology
American Chemical Society
The Chemical Society
Canadian Society for Toxicology
Sigma Xi
International Society for the Study of Xenobiotics
Society of Toxicology

AWARDS, HONORS, LISTINGS, AND PATENTS:

NSERC Research Scholarship, 1962
Commonwealth Scholarship, 1963-1966
Sigma Xi Award for Excellence in Research, 1977
Queen's Silver Jubilee Medal, 1978
Queen's Quest Lecturer, 1980
Royal Society of Chemistry Award For Health, Safety or Environmental
Chemistry, 1984
Distinguished Lecturer in Toxicology Seminar Series, University of Nebraska
Medical School, Omaha, 1986

COMMITTEE EXPERIENCE:

Chemical Institute of Canada (Chairman - Wellington Section), 1974
Departmental Promotion and tenure, library, publicity, 1977-79
Guelph-Waterloo Centre Coordinating Committee, 1978-79
College - Promotion and Tenure Committee, 1978
University - Senate, Guelph-Toronto Toxicology Centre Committee, 1979-1981
Chairman, Toxicology Grants Committee- Health and Welfare, Canada, 1980-84
Environment Canada - Task Force on Hazardous Waste Definition, 1979
Panel Member, NRC Associate Committee on Scientific Criteria for
Environmental Quality, Chlorinated Phenols, 1981
Panel Member, NRC Associate Committee on Scientific Criteria for
Environmental Quality, Polychlorinated Dibenzo-p-dioxins; 1981
Ontario Ministry of the Environment - Dioxin Advisory Group, 1983-present
Canadian Centre for Toxicology-Steering Committee, 1979-present

COMMITTEE EXPERIENCE: (continued)

Consultant, E.P.A. Environmental Criteria and Assessment Office, 1983-present
Consultant, Science Advisory Board of E.P.A., 1984-present
Member, National Advisory Environmental Health Sciences Council, 1984-1988
Senior Scholars Committee, Texas A&M University, 1984-present
Chairman, Senior Scholar's Committee, Texas A&M University
International Advisory Board, Dioxin Symposia, 1980-present
President-Elect, Gulf Coast Society of Toxicology Chapter, 1986
Biochemistry Head Search Committee, Texas A&M University, 1987
Vice Chancellor Agriculture Search Committee, Texas A&M University, 1987

CONSULTATIVE EXPERIENCE:

CTV — scientific consultant
Sciex Ltd. — analytical consultant
JRB Associates — toxicology consultant
Wellington Environmental — toxicology consultant
Environment Canada — toxicology consultant
NSERC — toxicology consultant
Numerous legal firms — toxicology consultant
Environmental Protection Agency
New York State Department of Law
U.S. Department of Justice
ICAIR Life Sciences
Malcom Pirnie Inc.

AREAS OF RESEARCH INTEREST:

Biochemical Toxicology of Pollutants
Mechanisms of Toxicity

COMMUNITY/CIVIC ACTIVITIES:

Numerous hearing and court appearances for civic groups regarding
environmental problems
Various church and young people's activities

TITLES OF THESIS AND/OR DISSERTATION:

The Ullmann Reaction (Thesis)
Polyacetylenes from Dahlia (Dissertation)

SCIENTIFIC PUBLICATIONS:

1. Safe, S., Allen, M., and Moir, R.Y.: Metameconine as a Model Compound in the study of Aromatic Reactions. Can. J. Chem. 40:2402-2408, 1962.

2. Safe, S. and Moir, R.Y.: Stereochemical Configuration of Some Phthalideisoquinoline Alkaloids. *Can. J. Chem.* 42:160-162, 1964.
3. Safe, S. and Moir, R.Y.: A Series of Model Compounds for the Study of Aromatic Reactions. *Can. J. Chem.* 43, 337-342, 1966.
4. Jones, E.R.H., Safe, S. and Thaller, V.: Natural Acetylenes Part XXIII. AC_{18} Polyacetylenic Ketoaldehyde Related to Falcarinone from an Umbellifer (*Pastinaca Sativa* L.). *J. Chem. Soc. (C)*:1220-1221, 1966.
5. Aplin, R.T. and Safe, S.: Electron Impact-Induced Rearrangements of Natural Polyacetylenes. *Chem. Comm.*, 140-142, 1967.
6. Jones, E.R.H., Safe, S. and Thaller, V.: Natural Acetylenes Part XXVI. Transformations of Phenyl Polyacetylenes in the Tubers of *Dahlia* Hybrids. *J. Chem. Soc. (C)*:1038-1041, 1967.
7. Aplin, R.T., Durham, L.J., Kanazawa, Y. and Safe, S.: 2-O- $-D$ -Galactosylpyranosylglycerol from *Laurencia Pinnatifida*. *J. Chem. Soc. (C)*:1346-1347, 1967.
8. Brewer, D., Rahman, R., Safe, S. and Taylor, A.: A New Toxic Metabolite of *Pithomyces Chartarum* Related to the Sporidesmins. *Chem. Comm.*, 1471, 1968.
9. Safe, S. and Taylor, A.: Stereochemistry of the Reaction of Epipolythiadioxopiperazines with Triphenylphosphine. *Chem. Comm.*, 1466-1467, 1969.
10. Rahman, R., Safe, S. and Taylor, A.: Sporidesmins. Part IX. Isolation and Structure of Sporidesmin. *J. Chem. Soc. (C)*:1665-1668, 1969.
11. Safe, S.: Hydrogen Randomization Between Phenyl Groups in the Electron Impact-Induced Fragmentation of Substituted Diphenylacetylenes. *Chem. Comm.*, 534-535, 1969.
12. Safe, S., Jamieson, W.D., Pilgrim, W.R. and Wolfe, S.: Electron Impact-Induced Rearrangements of Substituted 1-Phenylpropynes. *Can. J. Chem.* 48:1171-1174, 1970.
13. Safe, S.: Preparation of Iodobenzene- d_5 and Diphenylacetylene- d_5 . *J. Label. Cpd.* 6:197-198, 1970.
14. Safe, S. and Taylor, A.: Sporidesmins. Part X. Synthesis of Polysulphides by Reaction of Dihydrogen Disulphide with Disulphides and Thiols. *J. Chem. Soc. (C)*:432-435, 1970.
15. Chin, C., Cutler, M.C., Jones, E.R.H., Lee, J., Safe, S. and Thaller, V.: Natural Acetylenes. Part XXXI. C_{14} -Tetrahydropyranyl and other Polyacetylenes from the Compositae *Dahlia Coccinea* Cav. Var. *Coccinea*. *J. Chem. Soc. (C)*:314-322, 1970.

PUBLICATIONS: (continued)

16. Safe, S.: Timing of Hydrogen Randomization in Substituted Diphenylacetylenes. *Org. Mass. Spectrom.* 3:239-240, 1970.
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APPENDIX B
COMPOSITION OF DIFFERENT PCB AROCLORS

Table B-1 shows data on the distribution of congeners in three different commercial PCB mixtures. The columns on the right show the mass fractions not for individual congeners but for small groups of congeners that pass through a gas chromatograph in essentially the same time. All of the columns on the left are different ways of identifying the peaks in the chromatograms; for example, Peak No. 1 exits a certain GC after about 20.4 minutes. It contains two 2-chlorine congeners, one with chlorines in the 2 and 2' positions (different rings) and one with chlorines in the 2 and 6 positions (same ring). These are identified as PCB No. 4 and PCB No. 10, respectively, in the Ballschmitter scheme.

The data can be better visualized graphically. Figures B-1 to B-3 show "mass spectra" for the three Aroclors 1242, 1254, and 1260. These spectra differ from the GCs for these samples in the following three ways:

1. The heights of the peaks are the mass fractions. In the real GCs, the peak heights are not in the same proportions, because of differences in peak widths and variations in sensitivity of the device.
2. The peaks are spaced uniformly, not with the time of transit through the GC, because we simply number them.
3. We have not compiled data on the least prominent peaks of the GC, even though they are visible on the GC plot.

Clearly the mass is concentrated at long transit times for Aroclor 1260 and at short ones for Aroclor 1242. Transit time is correlated strongly, although imperfectly, with chlorine number. Aroclor 1254 has an intermediate distribution and

TABLE B-1

Peak No.	Peak Location (minutes)	Peak Identifier (Ballschmitter)	Congener Identity	Mass Fraction (%)		
				1260	1254	1242
	20.4	4,10	2,2',2,6			
	21.4	7,9	2,4',2,5			2.690
	21.8	6	2,3'			0.990
	21.9	8,5	2,4',2,3			1.310
5	22.5	19	2,6,2'			6.270
	23.3	15,18	2,5,2',4,4'			0.940
	23.4	17	2,4,2'			9.110
	23.6	27,24	2,6,3',2,3,6			4.480
	23.9	16,32	2,3,2',2,6,4'			0.810
10	24.6	26	2,5,3'			5.040
	24.7	25	2,4,3'			1.210
	24.8	31	2,5,4'			0.880
	24.9	28	2,4,4'		0.662	6.630
	25.1	33,53	2',3,4';2,6,2',5'		0.673	7.860
15	25.4	22,51	2,3,4',2,4,2',4'			6.870
	25.6	45	2,3,6,2'		0.672	3.530
	25.8	46	2,6,2',3'			1.080
	25.9	52,73	2,5,2',5'			0.790
	26.1	49	2,4,2',5'		4.956	3.250
20	26.2	47	2,4,2',4'		1.244	2.580
	26.3	48,75	2,4,5,2';2,4,6,4'			1.080
	26.6	104,44	2,3,2',5'			1.460
	26.7	37,42,59	3,4,4';2,3,2',4';2,3,6,3'		2.056	3.190
	26.9	64,71	2,3,6,4';2,6,3',4'			3.960
25	27.2	40	2,3,2',3'		0.905	3.050
	27.7	74	2,4,5,4'			0.990
	27.8	70	2,5,3',4'		0.847	1.570
	27.9	66,95	2,4,3',4';2,3,6,2',5'		3.079	3.340
	28.1	91	2,3,6,2',4'	2.365	8.005	4.200
30	28.4	56,60	2,3,3',4';2,3,4,4'		1.051	0.690
	28.6	84,92	2,3,6,2',3';2,3,5,2',5'		0.790	2.460
	28.8	101,90	2,4,5,2',5';2,3,5,2',4'	0.629	3.477	0.740
	28.9	99	2,4,5,2',4'	3.103	8.130	0.860
	29.2	83	2,3,5,2',3'		2.869	0.730
35	29.3	97	2,4,5,2',3'		0.743	
	29.5	87	2,3,4,2',5'		2.121	0.700
	29.6	85	2,3,4,2',4'	0.666	3.879	0.760
	29.7	136	2,3,6,2',3',6'		1.290	0.700
	29.8	77	2,3,6,3',4'	1.541		
40	29.8	110	3,4,3',4'	1.480	5.824	
	30.1	82	3,4,2',3'		2.911	0.980
	30.2	151	2,3,5,6,2',5'		0.976	0.680
	30.3	135	2,3,5,2',3',6'	3.120	0.867	
				0.909	1.118	

PCB CONGENER DATA

TABLE B-1 (continued)

Peak No.	Peak Location (minutes)	Peak Identifier (Ballschmitter)	Congener Identity	Mass Fraction (%)		
				1260	1254	1242
45	30.3	124	3,4,5,2',4'		0.559	
	30.4	107	2,3,5,3',4'	0.909	1.395	
	30.6	149,118	2,4,5,3',4';2,3,6,2',4',5'	10.346	10.719	0.780
	30.9	114,143	2,3,4,5,4';2,3,5,6,2',3'	0.646	1.333	
	31.2	146	2,3,5,2',4',5'	1.160	0.781	
50	31.4	132,105	2,3,4,3',4';2,3,4,2',3',6'	2.374	5.610	0.730
	31.5	153	2,4,5,2',4',5'	12.083	3.744	
	31.8	141	2,3,4,5,2',5'	2.501	0.976	
	32.0	130	2,3,4,2',3',5'		0.435	
	32.1	137	2,3,4,5,2',4'	2.095	0.435	
	32.4	138,163	2,3,4,2',4',5';2,3,5,6,3',4'	10.754	6.022	
	32.5	158	2,3,4,6,3',4'		0.965	
55	32.6	129	2,3,4,5,2',3'		0.691	
	32.8	178	2,3,5,6,2',3',5'	0.904		
	33.1	187	2,3,5,6,2',4',5'	5.246	0.584	
	33.4	128	2,3,4,2',3',4'	3.117	1.345	
	33.8	167	2,4,5,3',4',5'		0.598	
	33.9	185	2,3,4,5,6,2',5'	0.721		
	34.1	174	2,3,4,5,2',3',6'	4.655	0.608	
60	34.3	177	2,3,5,6,2',3',4'	2.524	0.573	
	34.5	156,171	2,3,4,5,3',4';2,3,4,6,2',3',4'	2.274	1.444	
	35.1	172	2,3,4,5,2',3',5'	0.932	0.601	
	35.5	180	2,3,4,5,2',4',5'	11.155	0.722	
	36.9	170	2,3,4,5,2',3',4'	3.776	0.122	
	37.1	190	2,3,4,5,6,3',4'	0.941		
	37.8	201	2,3,4,6,2',3',4',5'	1.670		
65	38.1	196,203	2,3,4,5,6,2',4',5';2,3,4,6,2',3',4',5'	2.102		
	40.0	195	2,3,4,5,6,2',3',4'	0.888		
	41.7	194	2,3,4,5,2',3',4',5'	1.656		
	44.0	206	2,3,4,5,6,2',3',4',5'	0.714		
	70					

1254 SPECTRUM

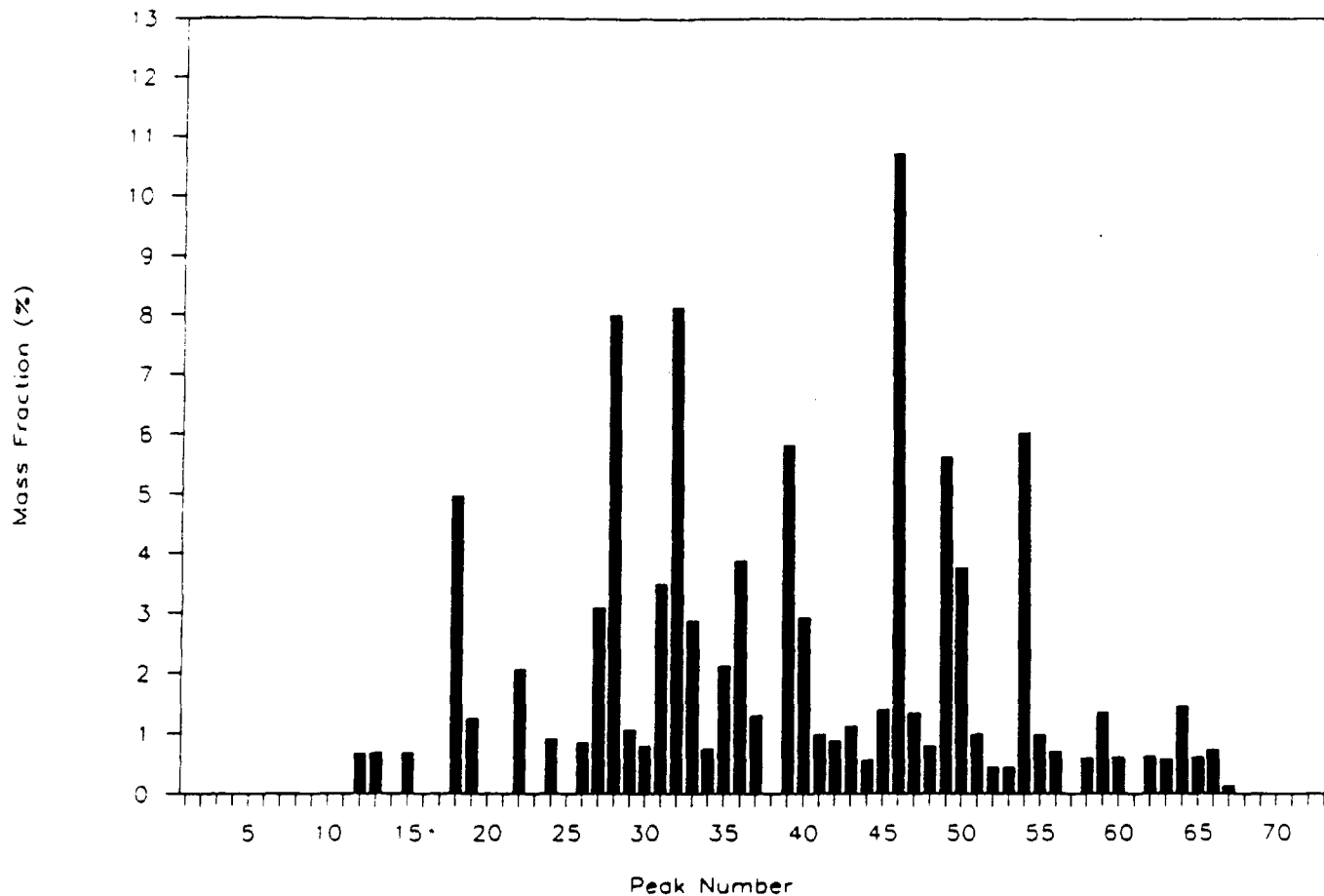


FIGURE B-2 Distribution of mass fractions by congener in Aroclor 1254.

1260 SPECTRUM

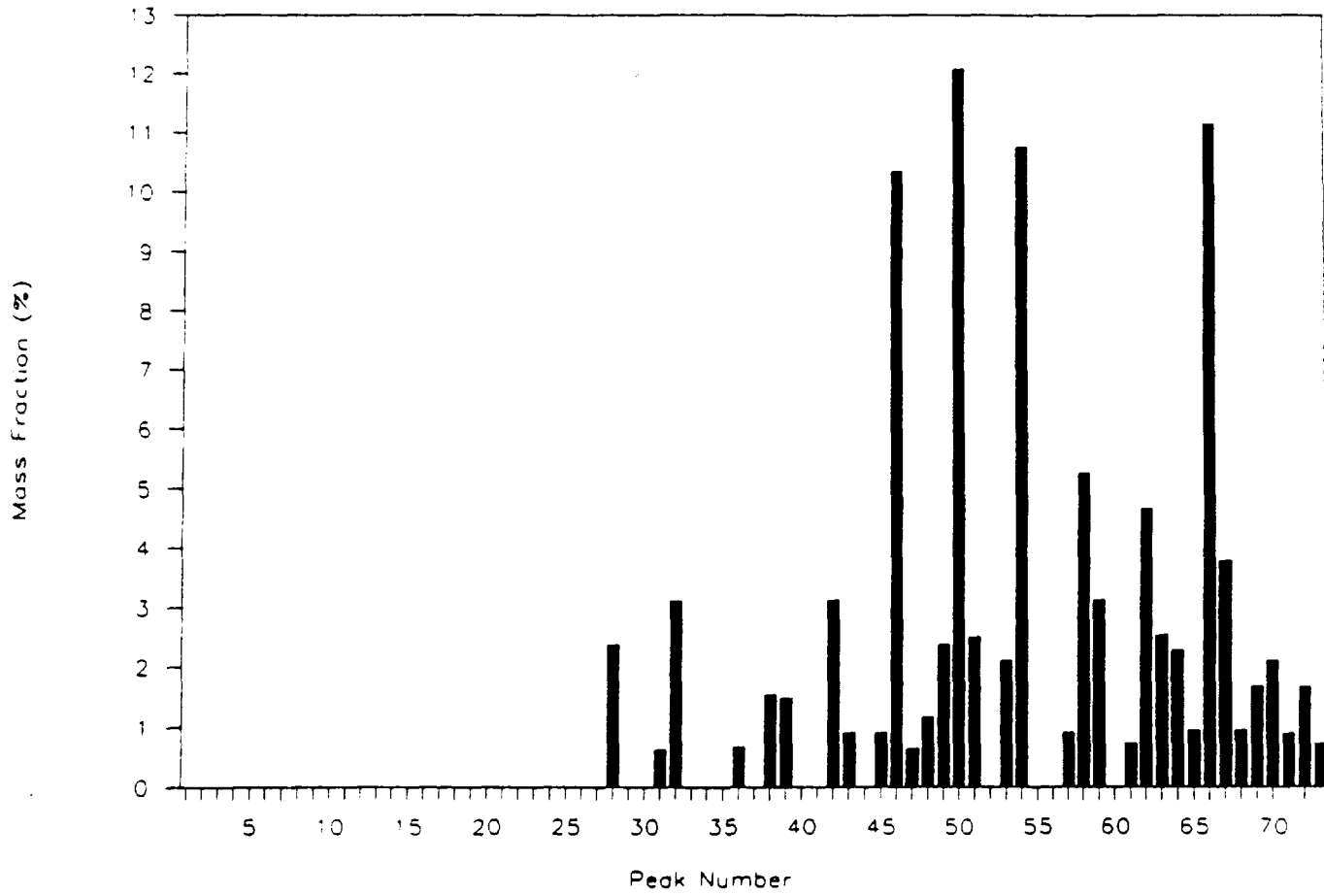


FIGURE B-3 Distribution of mass fractions by congener in Aroclor 1260.

1260 SPECTRUM

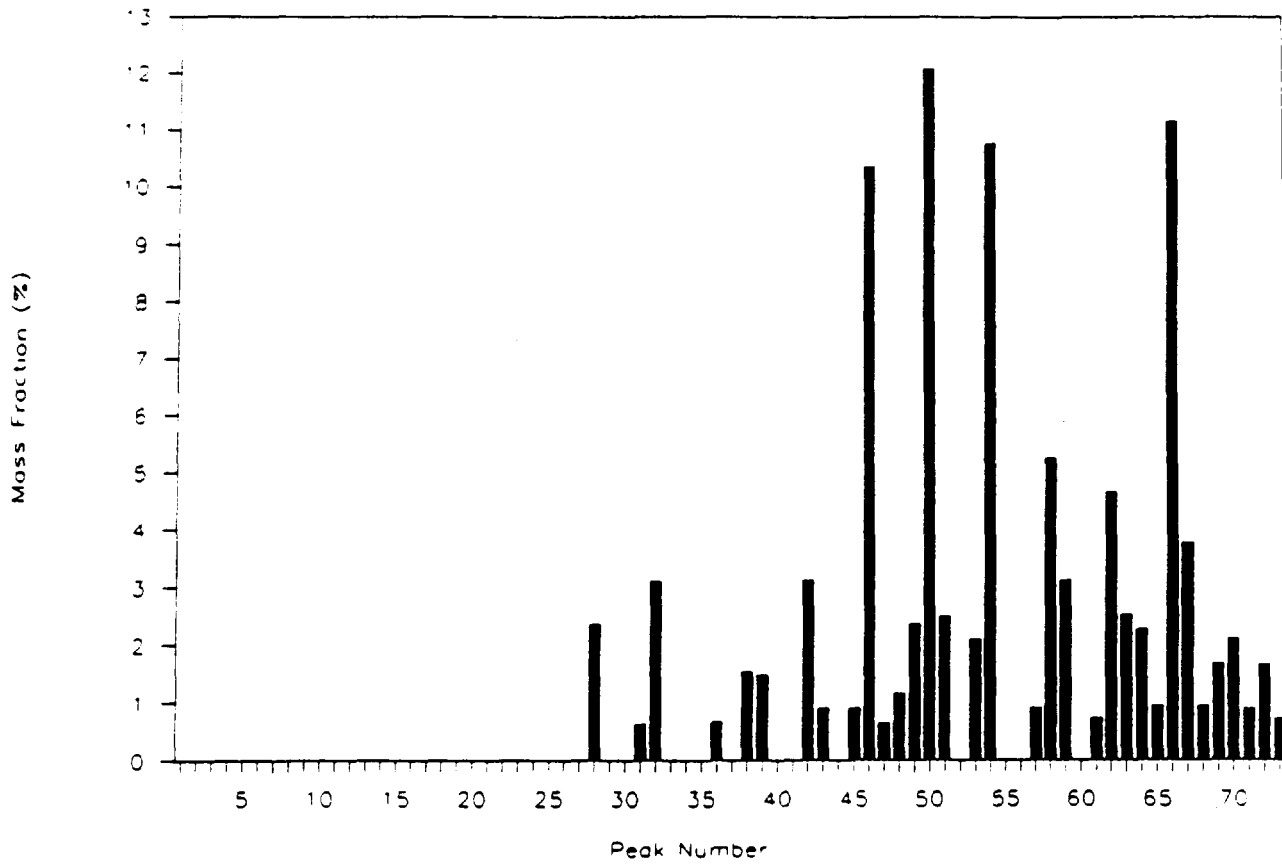


FIGURE B-3 Distribution of mass fractions by congener in Aroclor 1260.

overlaps substantially with both of the other commercial mixtures. About 2/3 of the mass of Aroclor 1242 is in the "Aroclor 1254 region" and about 90% of the mass of Aroclor 1260 is in that region. Only about 10% of the mass of Aroclor 1242 is in the "Aroclor 1260 region."