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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

4 MAY 1977

SUBJECT: Dioxin: Position Document

TO: Dioxin Implementation Task Force

FROM: Edwin L. Johnson
Deputy Assistant Administrator
for Pesticide Programs

When we met last fall I agreed that the Agency would put together a summary of what it had learned since withdrawal of the hearings in 1974. You have been cooperating with EPA in the conduct of a monitoring program to determine the extent and frequency of dioxin (TCDD) residues in the environment as a result of the use of 2,4,5,-T and related pesticides. The attached document is a draft of our evaluation of phase I of the Dioxin Implementation Plan and a summary of our plan for proceeding with phase II of the program. As I indicated to you last fall, this document is being provided to you in advance of a formal release for comment and suggestions. It has also been made available to the Administrators Pesticide Policy Advisory Committee for the same purpose.

We intend to make the document final and release it generally in the latter part of May and we therefore would appreciate you submitting any comments or suggestions you have for modifying this document by May 19, 1977. All correspondence should be forwarded to Mr. W. Thomas Holloway WH-566, Office of Special Pesticide Reviews, Environmental Protection Agency 401 M Street S.W. Washington, D.C. 20460 (Telephone No. 202/755-9336). Your cooperation in this program in the past and your suggestions for this document as well as the future directions of the program will be greatly appreciated.

Attachment:

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Dioxin: Position Document

Dioxin Working Group
U.S. Environmental Protection Agency

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Dioxin: Position Document

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I. Background

A. Chemical and Physical Properties of TCDD

1. Synthesis

TCDD is not found naturally in the environment, its source comes as a by-product in the manufacturing process of several chemical products.

Although there are several synthetic routes for the formation of TCDD, the more common reaction occurs under conditions which are used to prepare 2,4,5-trichlorophenol, tetrachlorobenzene being the precursor compound. Under extreme saponification reactions, 2,4,5-trichlorophenol is formed. This reaction was first established by Schwetz, et al. (1). This means that TCDD or other chlorodibenzo-p-dioxins will always be present in trichlorophenol products and/or their derivatives, and that any use of these products will result in environmental contamination by dioxins.

2. Environmental Characteristics

Basically there are three ways in which TCDD may be introduced into the environment: (1) it may be present as a contaminant in chlorophenols or their derivatives, (2) it may be formed from chlorophenols or their monomeric chlorophenoxy derivatives under conditions of use or storage, or (3) it may be formed from phenoxyphenols or other polymeric derivatives under similar conditions. In those cases where TCDD residues have been found in environmental samples, it is not known at present which of these routes is responsible. Kearney's, et al. (2) study of the fate of TCDD in the environment, however, has resulted in the following observations:

1). TCDD does not leach vertically in soils;

2). Significant amounts of TCDD are not taken up by plants and none could be harvested in grain or soybeans;

3). TCDD disappears slowly from soils and about half is lost after one year. It is less persistent than most chlorinated hydrocarbon insecticides, but more persistent than 2,4,5-T;

4). TCDD is not translocated from the point of application on the leaf surface to other parts of the plant. Some of it is washed off with rain water;

5). TCDD destruction may be caused by sunlight in water, but not on soil surfaces;

6). TCDD is not made from breakdown products of 2,4,5-T in soils or in sunlight;

7). Although there are some residues in the liver, large amounts of TCDD fed in an animal's diet can be eliminated in the urine and feces;

8). TCDD was accumulated from water by fish in laboratory studies.

Further information on the persistence and mobility of TCDD in the environment will be available in late 1977 as a result of an interagency research agreement between EPA and USDA. The research being conducted at the USDA-ARS Degradation Laboratory is designed to provide data on the fate of TCDD when Silvex is applied in simulated home and recreational turf plots. Dr. Kearney is the Laboratory leader for the investigation.

Since TCDD is likely to be formed in the preparation of 2,4,5-trichlorophenol and since this compound is common to the manufacturing process of the pesticides 2,4,5-T, Silvex, Erbon, Ronnel and 2,4,5-trichlorophenol, all four compounds were included in the dioxin monitoring program as possible sources of TCDD contamination.

B. 2,4,5-T Litigation History

On October 29, 1969, the President's Science Advisor announced that a series of coordinated actions was being taken by several governmental agencies to restrict the use of the herbicide 2,4,5-trichlorophenoxyacetic acid (2,4,5-T). This was precipitated by the release of a screening study conducted by the Bionetics Research Laboratories in which it was found that mice and rats treated during early pregnancy with large doses of 2,4,5-T gave birth to defective offspring.

The announcement, together with reports of an increased occurrence of birth defects by South Vietnamese newspapers (June and July 1969), elicited immediate reactions from governmental agencies, segments of the scientific community, various lay groups concerned with environmental problems, and from public communications media. Government-sponsored panels of experts, special commissions set up by scientific organizations, hearings before subcommittees of the U.S. Senate, and conferences attended by representatives from industry, government, and academia examined available data and heard expert opinions. None of these groups, however, were able to conclusively resolve the central question of whether 2,4,5-T, constituted a risk for human fetuses during pregnancy as currently produced and used. At least one reason for failure to reach a satisfactory resolution of the issue was the paucity of reliable, scientific evidence.

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Additional animal experiments performed early in 1970 confirmed that the purest available sample of 2,4,5-T given in large doses to pregnant mice, did indeed result in the birth of malformed offspring (3,4). It was later reported (5,6) that the 2,4,5-T formulation employed in these studies contained 30ug/g of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), one of the most toxic and potent teratogenic substances known (1,7). On April 14, 1970, precautionary actions were taken by the Secretary of Health Education and Welfare, who advised the Secretary of Agriculture that: "In spite of the uncertainties of the experimental data related to 2,4,5-T, the Surgeon General feels that a prudent course of action must be based on the decision that exposure to this herbicide may present an imminent hazard to women of child bearing age." Accordingly, on the following day the Secetaries of Agriculture, of Health, Education, and Welfare and of the Interior jointly announced the suspension of the registrations of 2,4,5-T for: "I. In all uses in lakes, ponds or on ditch banks. II. Liquid formulations for use around the home, recreation areas and similar sites" (USDA-PRD PR 70-1, 20 April, 1970). A notice for cancellation of registration was issued on May 1, 1970 for: "I. All granular 2,4,5-T formulations for use around the home, recreation areas and similar sites. II. All 2,4,5-T uses on crops intended for human consumption." (USDA-PRD PR 70-13, May 1, 1970) All registrants were advised of these actions, and two of the registrants, Dow Chemical and Hercules Incorporated, exercised their right under Section 4.e of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) [7 U.S.C. 135 et seq.] to petition for referral of the matter (for the cancellation of rice only) to an Advisory Committee.

As provided by that statute (8), the National Academy of Sciences supplied a list from which was selected a nine-member Advisory Committee of scientists with appropriate qualifications from universities and research institutes throughout the county. The charge given to the Committee was to: (a) consider all relevant facts, (b) submit a report and recommendations regarding registration for certain uses of 2,4,5-T, and (c) state the reasons or bases for these recommendations. The Report from the Committee was submitted to the Administrator of the Environmental Protection Agency on May 7, 1971 (9). The report recommended that 2,4,5-T may be permitted under certain conditions for uses in forestry, range and rights-of-way providing:

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1. That the limit of 0.1 ppm of contamination with TCDD be set for all future production of 2,4,5-T.

2. That 2,4,5-T be applied no more than once a year at any one site.

3. That 2,4,5-T be applied with proper caution so that it will not contaminate other areas where it may come into human contact. The Committee also recommended that this action be reviewed again when the existing deficiencies in information relative to possible magnification in the food chain of TCDD have been rectified by specific research directed toward that end.

In July 1972, Dow Chemical obtained an injunction against EPA enjoining further administrative action against 2,4,5-T. In 1973, the United States Court of Appeals for the Eighth Circuit overturned the injunction and administrative proceedings were allowed to go forward (10). Accordingly, a notice of intent to hold Public Hearings on all uses of 2,4,5-T brush-weed killer was filed with the EPA Hearing Clerk on July 20, 1973, under Section 6(b)(2) of FIFRA. All federally-approved uses of the controversial brush-and-weed killer, 2,4,5-T, alleged to have caused adverse effects on human and animal health, were to be explored in a public hearing scheduled for April 1974, following completion of an intensive monitoring program for detecting dioxin in the parts per trillion (ppt) range (38 FR 19869, July 24, 1973). The hearing was to afford ~~to~~ all concerned parties--manufacturers and formulators, the U.S. Department of Agriculture (USDA), the Environmental Defense Fund (EDF), and other interested groups as well as the EPA--the opportunity to present pertinent scientific, economic, and other relevant data needed by EPA to weigh the benefits of the herbicide against the risks involved.

The basic question to be resolved by EPA through the hearing process was whether the remaining Federal registrations of 2,4,5-T should be cancelled or the classification changed.

During the preparation of the hearings, it was evident that the pesticide 2,4,5-T, per-se, posed no special cause for concern, when used as directed.*

* Note: 2,4,5-T, 2,4,5-TCP, Silvex, Erbon, and Ronnel are now under review in the Office of Special Pesticide Reviews (OSPR), EPA, as candidates for Rebuttable Presumption Against Reregistration (RPAR). The toxicity of these pesticides and/or the associated dioxin contaminant are considered in this review process.

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Residue monitoring analyses for 2,4,5-T in environmental samples, including food, have for the most part led to negative findings. In those cases where positive results were obtained, levels were low (normally less than 0.1 ppm). This conclusion was based primarily on the results of an EPA forced feeding study of the levels of 2,4,5-T in cows milk and calf tissue, following exposure. These observations, coupled to the low order of terategenicity for 2,4,5-T when tested at the highest purity available, lead to the conclusion that human exposure to 2,4,5-T from normal usage posed no discernible problem.

On May 10, 1974, the information hearing was expanded to include all insecticides and herbicides having in their manufacturing process 2,4,5-trichlorophenol (TCP). These include the pesticides Silvex, Erbon, Ronnel and 2,4,5-TCP all of which have the potential of containing TCDD.

On July 24, 1974, the Agency withdrew cancellation and information gathering proceedings initiated against the herbicide 2,4,5-T and related compounds. The proceeding was withdrawn because of the inability of the Agency to monitor food for residues of 2,4,5-T's highly toxic contaminant TCDD with the necessary analytical precision. The lack of evidence that 2,4,5-T use results in exposure of man to TCDD made a final determination on the "unreasonable adverse effects" caused by the use of 2,4,5-T extremely difficult, if not impossible. Accordingly, while the 2,4,5-T notice of hearing was withdrawn, the Agency stated that it:

> "will continue its TCDD residue monitoring program and will take such further action as it deems appropriate once the results of the monitoring project are available." 39 FR 24050 June 28, 1974.

On July 25-26, 1974 the Agency held a Dioxin Planning Conference in Washington, D.C. The public meeting was held primarily for those parties having an interest in the withdrawn 2,4,5-T/dioxin hearings. The nature of the meeting was to address data analysis and retrieval (in the areas of analytical methodology, toxicology and monitoring) with emphasis on analytical methodology for TCDD at the parts per trillion level (ppt). As a result, the Agency promulgated the Dioxin Implementation Plan which is designed to develop the required analytical methods for the determination of dioxin residues in environmental samples.

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II. Dioxin Implementation Plan

A. Introduction

In September 1974, the Agency sent out a Preliminary Dioxin Implementation Plan (DIP) to all attendees of the Planning Conference requesting that it be reviewed and that they provide input on what changes or additions would be advisable in the overall plan. After these responses were received, a final plan was prepared in February 1975. It consists of two parts, a short term monitoring program and a broad research plan which would take four to five years to complete. The EDF, USDA and Dow Chemical agreed to participate in a monitoring program established by EPA, which would utilize improved analytical methodology capable of TCDD detection at the ppt level.

The short term beef fat monitoring plan was a joint plan (representatives from EPA, USDA, EDF and Dow Chemical) in which beef fat and liver samples were to be collected at six month intervals to permit timely reevaluation of any available evidence for TCDD residues. Such reevaluation could lead to (1) modifications in plans for future research and monitoring and/or (2) reconsideration of the desirability of initiating some form of regulatory action on 2,4,5-T or other pesticides contaminated by TCDD. At each point all of the information then available should be considered even though the specific experiment producing it might not be completed. The guiding principles for the sampling plan were:

a. The samples should be representative of beef actually being consumed by some segment of the population.

b. The sample should represent cattle likely to be marketed for human consumption and grazed on lands treated with 2,4,5-T and thus likely to maximize the probability of containing 2,4,5-T (or TCDD).

Between February and March, 1975, the first 85 beef fat and 43 liver samples were collected. At the outset it was decided that emphasis would be placed on analytical methodology. Due to the complexity of the analytical technique to determine TCDD at the ppt level, analysis for these first 128 samples were delayed and not completed until May 1976. Approximately twenty-five percent of these samples was taken from non-treated areas, i.e., where 2,4,5-T or TCDD is not likely to be found. One laboratory prepared all sample extracts, and identical aliquots were sent to all participating analytical laboratories. The purpose of having one laboratory perform all cleanup of samples was to minimize possible errors in the procedure.

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B. Analytical

1. Phase I Beef Fat and Beef Liver Anaylyses

The primary analytical achievements of 1976 have been the; 1) completion of phase I beef fat and liver analyses using combined gas chromatographic (GC) and using high resolution, mass spectrometric (MS) techniques; 2) analysis of technical grade pesticides for TCDD residues; 3) further refinement of cleanup methodology for environmental samples; and 4) the development of a preliminary method for the extraction analysis of human tissues and milk for TCDD residues.

The progress made in the area of TCDD analytical methodology is noteworthy. By far the most significant data out of the above is the phase I beef and liver analyses. Based on the repeated ability of more than 1 laboratory to detect TCDD in identical sample aliquots, it is clear that dioxin can be detected at the ppt level. The data as reported by the collaborators at the June 15, 1976 meeting in Washington (see section V Appendix part A) are suggestive of TCDD residues in beef fat ranging from 20-60 ppt.

Phase I of the program was primarily intended to identify acceptable methods for extraction and analysis of TCDD in environmental samples. This phase of the program is essentially complete. A short term study (90 days) will be conducted, prior to initiation of phase II, to determine the optimal combination of extraction and analytical methods. Once this combination has been determined, the Agency will immediately proceed with the second phase of the program. Phase II will proceed under an experimental design intended to insure the accuracy and legal sufficiency of the analytical data being developed (see section III Future Analytical Studies).

2. Survey of Trichlorophenol Pesticides for TCDD Residues.

Samples of trichlorophenol materials were received from the basic manufacturers of pesticides for analysis of TCDD content by EPA. The limit of detection in the analysis was 0.1 ppm, corresponding to the 0.1 ppm limit for TCDD contamination of 2,4,5-T, as set by the 2,4,5-T Advisory Committee (NAS) in 1970. Seventy-three out of the 75 samples collected did not contain TCDD at the above limit of detection. The remaining 2 samples, ronnel and Na-2,4,5-T phenate are believed to contain 0.107 and 0.312 ppm of TCDD respectively. These samples will be reanalyzed for confirmation. If the residue level continues to exceed 0.1 ppm, the Agency will take regulatory action to insure that TCDD is reduced to an acceptable level.

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A second study of the TCDD residues in technical pesticides will begin in mid-1977. The limit of detection in this study will be 10ppb. Samples for this study will be taken by representatives from Pesticide Toxic Substances Enforcement Division, EPA. The data will provide EPA with a more comprenhensive analysis of the intrinsic level of TCDD residues in the pesticides under consideration, prior to use.

C. Toxicological Effect Level

The TCDD toxicology data is well documented in the EPA conference report of January, 1976 and in the May, 1976 addendum and therefore does not need to be reviewed extensively herein. Additional data however have been generated which expand our knowledge of the risks associated with human and nontarget exposure to TCDD. Dow Chemical Company has recently completed a two-year feeding study with 2,3,7,8-TCDD in male and female rats. Preliminary data indicate that at a level of 0.001 ug/kg/day of TCDD (which approximates 20 ppt TCDD in the rat's daily diet) the effect was similar to controls in all parameters measured. At the dose of 0.01 ug/kg/day however increased urinary excretion of porphyrin and increased liver weights were observed (personal communication, Dr. Koriba, Dow Chemical Co.). Toxicologists from the Criteria and Evaluation Division (CED), OPP, EPA have reviewed this data and established a range of 80 to 200 ppt as the effect level (EL) for human exposure to beef fat containing TCDD. To determine the EL it was assumed that the amount of TCDD in the beef was constant and that the amount of beef fat ingested is from 1 to 2.5% of a humans total diet.

The data generated thus far for the 85 beef fat and 43 liver samples analyzed in phase I of the monitoring program do not indicate that the EL for TCDD exposure through beef fat ingestion has been exceeded or reached. It is emphasized however that exposure to TCDD through ingestion of beef fat is only one possible source of exposure. The environmental samples scheduled for analysis in phase II of the Dioxin Implementation Plan range from soil to human types. The diversity of these samples is intended to provide EPA with a better understanding of the potential for TCDD to bioaccumulate once it is released into the environment and thus present multiple sources of exposure to humans or other non-target organisms.

III. Future Analytical Studies

Phase II of the Dioxin Implementation Plan is designed to provide the Agency with precise analytical data on the residues of TCDD in environmental samples.

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The purpose of the design is to establish a practicable expermental procedure that (a) will permit development of a "best fit" recovery curve (or curves) for quantification of 35 CI-TCDD spiked in beef fat and liver at levels ranging from 0 to 100 ppt, and (b) will allow statistically reliable measurements of the following parameters:

1. The accuracy and precision with which ppt levels of 35 CI-TCDD added to beef fat and liver can be extracted at OPP's Pesticide Monitoring Laboratory and quantified at the collaborative analytical laboratories;

2. The accuracy and precision with which these analytical laboratories can quantify ppt levels of 35 CI-TCDD provided as standards;

3. The relationships between measurements of TCDD in standards and measurements of TCDD extracted from beef fat and liver spiked at the same levels as the standards;

4. The consistency of laboratory performance throughout the experiments, as measured by the relative magnitude of statistical interactions;

5. The precision of PML's extraction procedure relative to the precision of the GC-MS quantitation.

Based on the ability of the collaborator to detect TCDD in spiked samples, an evaluation can be made of the validity of the TCDD levels reported in blind environmental samples. It is anticipated that the above procedure can be applied to all environmental samples scheduled for analysis on phase II. Highest priority however will be given to the analysis of phase II beef (fat and liver) and human (fat, liver, and milk) samples.

The Agency presently has a total of 167 human samples (milk, liver, adipose) in storage at our Pesticide Monitoring Facility, Bay St. Louis, Miss. These samples were collected in Mississippi and Arkansas from persons who might have been exposed to TCDD through the use of 2,4,5-T on rice.

Additionally, EPA is establishing a voluntary biopsy and mother's milk monitoring program in Oregon, to further investigate the significance of direct and indirect human exposure to TCDD through the use of 2,4,5-T. This program is intended to provide EPA with information on the significance of indirect and direct human exposure to TCDD through the comparison of samples taken from persons living in urban versus forested sites, respectively.

For specific details on the phase II analytical procedures refer to Section V, Appendix, part B.

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IV. Summary

EPA is investigating the frequency and level of TCDD residues in the environment as basis for determining the toxicological risk associated with human and other non-target exposure to TCDD.

A. Phase I of the Dioxin Implementation Plan was primarily designed to identify acceptable research approaches for extraction and analysis of TCDD residues in environmental samples. Existing data indicate that the methods are satisfactory for analysis of beef samples (fat and liver) and that TCDD is present in a small percentage (3.5%) of the beef fat samples taken from cattle with a known exposure to 2,4,5-T. All of the beef liver samples analyzed were negative. As a part of phase I, the Agency is conducting further research to determine the acceptability of these methods for analysis of other sample types (humans, small mammals, birds, soil, etc.) and the optimal combination of extraction and analytical methods. The latter study will be short term (90 days) in order that the Agency might rapidly proceed with phase II analysis.

B. The Agency has analyzed 75 samples of pesticides which, due to their manufacturing process, could contain TCDD. Seventy three of the 75 samples analyzed, did not contain TCDD at or above the 0.1 ppm tolerance level set by the Science Advisory Committee in 1970. The 2 remaining samples ronnel, and Na-2,4,5-T phenate are believed to contain .107 ppm and .312 ppm of TCDD respectively. These samples will be reanalyzed for confirmation. If confirmed EPA will take regulatory action to insure that the level of TCDD in the affected pesticides is reduced to the 0.1 ppm level.

An additional analytical study for TCDD residues in technical grade pesticides will be conducted in 1977. This study will analyze a greater number of samples at a lower limit of detection (10 ppb) than the preceeding analyses. EPA is presently selecting an analytical laboratory for this research.

C. Phase II of the Dioxin Implementation Plan is intended to provide the Agency with increased information on the range and possible tendency of TCDD to bioaccumulate in the environment.

All analyses in phase II will be based on a statistical approach designed to improve the precision of the quantification of TCDD residues reported.

Analyses of the human (fat, liver and milk) and beef (fat and liver) samples now in storage will receive the highest priority when the Agency proceeds with phase II of the plan.

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D. Existing beef fat and liver analytical data from phase I of the Dioxin Implementation Plan do not indicate that the toxicological effect level for exposure to TCDD through ingestion of contaminated beef, has been exceeded. This is only one source of exposure however. Additional analytical data are necessary to assess the overall toxicological risk associated with accumulative exposure from different sources of TCDD.

In addition to the human samples now in storage, EPA is establishing an elective biopsy and mothers milk program in Oregon to further assess the potential for human exposure to TCDD through the use of 2,4,5-T.

V. Appendix

A. Interpretation of Phase I Data by Analytical Collaborators

A meeting of the analytical collaborators (Dow Chemical, Harvard University, and Wright State University) was held on June 15, 1976, to discuss the results obtained to date. As a result of this meeting the following statement was issued by the analytical collaborators.

1. Of the beef fat famples (85) analyzed, one shows a positive TCDD level at 60 ppt; two samples appear to have TCDD levels at 20 ppt; five may have TCDD levels which range from 5-10 ppt. While several laboratories detected levels (5-10 ppt) in this range, the values reported were very near the sample limits of detection. There exist a great deal of uncertainty of the procedure below 10 ppt.

2. The analytical method is not valid below 10 ppt

3. An introduction to a neutral extraction technique shows promise of the capability of detecting levels below 10 ppt. This was demonstrated by comparative data at the lower parts per trillion range (5-10 ppt). However, this method has been demonstrated by only one laboratory at this time and has not been validated below 10 ppt by another competent analytical facility.

4. The samples analyzed were peritoneal fat and kidney fat taken from cattle which had grazed on rangelands of known treatment with 2,4,5,-T. Controls were the same sample type taken from cattle from non-treated areas within the same state.

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5. Of the liver samples (43) analyzed, only one sample suggest any TCDD residue, but the residue observed was to close to the sensitivity of the sample detection limits for quantitation. The fat sample analyzed from the same animal showed no TCDD residue. Three liver samples (for which fat samples were analyzed and showed positive data) showed no TCDD residues.

6. None of the collaborators reported TCDD in samples of beef fat taken from cattle in non-treated areas (at the sensitivity of the analytical method). Three of the laboratories receiving liver samples from cattle in non-treated areas observed no TCDD in the samples.

Due to the improvement and agreement among the anlytical collaborators with the analytical data, the above data supercedes the EPA beef fat monitoring data released in memoranda dated August 5, 1975 and December 19, 1975.

B. Phase II Experimental Design

The design phase II calls for preparation of two "pools" of control beef fat (say, Pool F and Pool G) and two pools of control beef liver (Pool L and Pool M) from which all spiked samples are to be constructed. The fat pools are constructed from equal amounts of fat from each control animal selected, using a separate set of animals for each pool. Liver pools are constructed in a similar manner. (Necessary pool sizes are to be determined by Dr. Aubry Dupuy after study of the design).

Eleven samples each are prepared from fat pool F and liver pool L. The samples from each pool are spiked individually at levels between 0 and 100 ppt of 35 Cl-TCDD. Samples are then extracted, and the extract is divided into three equal aliquots for shipment to the analytical labs, (the spiking levels are systematically spaced). The spiking system allows close spacing at lower levls and moderate increases in spacing at higher levels).

Next, five samples each are prepared from fat pool G and liver pool M. The samples from each of these pools are spiked individually at levels between 0 and 100 ppt of TCDD. These samples are extracted and divided into three equal aliquots for shipment as above.

It is necessary that each laboratory receive enough extract from sets G and M and from the comparably-spiked samples of sets F and L to allow duplicate measurements of each sample. For other samples, labs need receive only enough extract for a single measurement.

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A single series of standards, prepared as set S and set T, will serve for comparison both with fat and liver samples. Set S will comprise eleven aliquots spiked at levels, comparable to fat set F and liver set L.

Standard set T will contain 5 aliquots spiked at levels comparable to fat set G and liver set M. Again labs must receive enough standard from set T and corresponding levels of set S to permit duplicate measurement of each standard.

Thus, a total of 48 samples -- 16 standards, 16 fat and 16 liver -- are needed; these will require a total of 78 measurements by each laboratory, counting duplicate measurements of specified samples. A diagram of the design is attached.

All samples -- fat, liver and standards -- are to be prepared and shipped in random order, except that aliquots from a given sample wil be shipped to the three labs simultaneously. Laboratories are to analyze the samples in the order in which they are received. Labs are to perform blind analyses, i.e., they are not to know either the origin of the material or the level of TCDD in any sample. A sample numbering system should be used that provides no clue to sample identity.

All data will be used to develop recovery curves. Data from duplicate analyses of replicated samples will be used to measure extraction and GC-MS precision. Data evaluation will be by analysis of variance and regression methods.

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TCDD Level (ppt)	Standard Measurements			Beef Fat Measurements			Beef Liver Measurements		
Pool Code	Lab. A	Lab. B	Lab. C	Pool Code	Lab. A	Lab. B	Lab. C	Pool Code	Lab. A	Lab. B	Lab. C
A S	2	2	2	F	2	2	2	L	2	2	2
A T	2	2	2	G	2	2	2	M	2	2	2
B S	1	1	1	F	1	1	1	L	1	1	1
C S	1	1	1	F	1	1	1	L	1	1	1
D S	1	1	1	F	1	1	1	L	1	1	1
E S	2	2	2	F	2	2	2	L	2	2	2
E T	2	2	2	G	2	2	2	M	2	2	2
F S	1	1	1	F	1	1	1	L	1	1	1
G S	2	2	2	F	2	2	2	L	2	2	2
G T	2	2	2	G	2	2	2	M	2	2	2
H S	1	1	1	F	1	1	1	L	1	1	1
I S	2	2	2	F	2	2	2	L	2	2	2
I T	2	2	2	G	2	2	2	M	2	2	2
J S	1	1	1	F	1	1	1	L	1	1	1
K S	2	2	2	F	2	2	2	L	2	2	2
K T	2	2	2	G	2	2	2	M	2	2	2
Tot. Pools	16			16				16			
Tot.	26	26	26	26	26	26		26	26	26	

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