

ATTORNEY WORK PRODUCT
ATTORNEY-CLIENT PRIVILEGE

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ANALYTICAL CHRONOLOGY

Prepared by:

Dr. Ralph Munch

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ANALYTICAL CHRONOLOGY

This chronology is a time ordered listing of the long series of advances in analytical science which have cumulatively lead to the development of our present day ability to measure the amounts of many contaminants in environmental samples down to parts per billion, or even less in some cases, and to do this with the certainty that the figure given is real and not an artifact. It is meant to demonstrate the fact that methods now available are the result of the work of many scientists in academic, government, and industrial laboratories in many countries. The best has been sifted from the work of many to give the capabilities we have today. This process has been going on since long before there was a realization that dioxins and other similar materials might become a matter of environmental concern. It will continue in the future as long as new ideas continue to emerge and further need exists. This is the way science progresses. Each generation stands on the shoulders of its predecessors. Also listed are some of the many events leading to the recognition of dioxins as a problem to show the time relationship between analytical capability and the unfolding of the dioxin problem.

1906 Liquid chromatography using solid absorbents was invented by Tswett, a German biochemist. His work on the separation of colored plant compounds gave the name chromatography to all differential migration rate separation methods, even to those where there is no color involved. Tswett - Ber. dtsh. bot. Ges, 1906, 24, 316-384.

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- 1949 Monsanto-Nitro out of control reactor. The existence of TCDD was not even suspected so there was no knowledge of its properties nor any analytical method.
- 1952 Gas-Liquid Chromatography - GLC was developed in England by Martin and James. Biochemical Journal, 1952, 50, 679.
- 1953 The first gas chromatograph in the Western Hemisphere was built in Monsanto's Organic Research Laboratories in St. Louis.
- 1954 The instrument mentioned above was described at the Gordon Research Conference on Instrumentation by a Monsanto chemist.
- 1954- Commercial Gas Chromatograph using thermal conductivity
5 detectors were placed on the market by Perkin Elmer and others as a result of the description given at the Gordon Conference. It is estimated that these instruments could have been measured TCDD to 10ppm. if they had been applied to that problem.
- 1956 The first gas chromatograph at the Nitro Plant was purchased by Warren Wise, now at Akron. It used packed columns and a thermal conductivity detector.
- 1957 An epidemic of chick edema caused by contaminated waste fat used in feed. Nature of the toxic impurity completely unknown. No analytical methods. Firestone et. al, J.A.O.A.C., 1963, 46, 384.

- 1957 2,3,7,8 tetra chlorodibenzo dioxin, TCDD, first synthesized. Chemist made 20 grams of the material, developed chloracne, was taken to a hospital where other cases of this disease were treated. This lead to the final identification of TCDD as the agent causing their problem and to its identification as the most powerful chloracnegen known. Cavallero, et. al, p. 13.
- 1958 Hydrogen flame ionization detectors (FID) were developed for gas chromatography. These detectors are estimated to be capable of 1ppm sensitivity for TCDD analysis Harley, et. al., Nature 1958, 181, 177.
- 1960 Electron Capture detector for GC was developed. EC detector has very high sensitivity for halogen containing compounds. Estimated sensitivity 1ppm for TCDD analysis. Its advantage is that it is much less sensitive to non-halogenated compounds, reducing sensitivity of dioxin analysis to non-halogenated compounds which would interfere with thermal conductivity or flame ionization detectors. Laveloch and Lipsky, J.A.C.S., 1960, 82, 431.
- 1961 A chick bioassay for chick edema factor was proposed. Sensitive to 1ppm. but does not provide any identification of the toxic material. Douglas and Flick, J.A.O.A.C., 1961, 44, 449-56, (Bovcy and Young, p. 276).

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- 1962- Agent Orange use period. Candidate Environmental Statement for
1969 Disposal of Agent Orange Herbicide by Incineration, March, 1974.
USAF Health Laboratory. Kelly AFB, Texas, p. 4.
- 1962 Rabbit ear test for chloracnogen. Does not provide any
identification of the toxic material. Sensitive to 4ppm.
Jones - Jour. Investigative Dermatology, 1962, 511-517 (Bovey
and Young, p. 278).
- 1963 Gas chromatography applied to measuring chick edema factor, now
known to be a chlorine compound of unknown structure, using a
coulometric detector sensitive only to chlorine containing
compounds. Sensitivity unknown - nature of compound unknown, no
standard available. Firestone, et. al., J.O.A.C., 1963, 46, 384.
- 1964 Chick embryo bioassay developed sensitivity 0.1ppm.
Sensitive but not specific. Verrett et. al., J.A.O.A.C., 1964,
47, 1003-1006.
- 1965 Combined gas chromatograph - Mass spectrograph first used in
practice. Makes gas chromatography specific. Sensitivity
unknown, was not applied to TCDD analysis at that
time. Watson and Bieman Analytical Chemistry, 1964, 36, 1135-1142.
- 1965 March 17, Dr. R. E. Kelly transmitted Dow method for the

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Determination of 2,3,7,8 Tetrachlorodibenzodioxin (Document 8314455) to John Stevens along with a sample of pure TCDD for use as a standard. Method sensitive to 0.5 to 1 ppm. (Note: The only Dow method now in our files is dated June 22, 1965. We assume this must be a revised method sent by Dow at a later date.)

1965 March 23, the first Monsanto Ag. Lab. notebook record showing duplication of the Dow method. Notebook indicates sensitivity of 1 ppm. Document No. 055377.

1966 July. W. R. Udell sent his gas chromatographic method based on the Dow method but using thermal conductivity detector to Bollinger and Balderson at Nitro. No sensitivity given - estimate 1ppm. Document No. 8315319.

1968 Mass Chromatography developed. Uses computer control and storage of complete mass spectra of components as they exit the gas chromatography column. Sensitivity, estimated 10ppb. Identifies components separated by gas chromatograph unequivocally. Hites and Bieman Anal. Chem., 1968, 39, 1217-21.

1968 Mass fragmentometry developed. Uses computer controlled GC/MS to record a small number of preselected M/e ion currents. Sensitive to 1ppt. Achieves highest sensitivity and retains ability to insure identity by use of selected ion intensity ratios. Hammar et. al., Anal. Biochemistry, 1968, 25, 532-548.

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- 1969 Monsanto Industrial Chemicals Co. acquired Varian-Matt Atlas GC/MS capability. The Matt-Atlas mass spectrometer was a magnetic sector instrument, slow and troublesome to use. Capable of Mass Chromatography only - Sensitivity estimated to be 10ppb.
- 1969 Chemical ionization mass spectroscopy developed. Gives better parent ion peak intensities permitting molecular weight determinations. Aids in identifying material measured. Fales et. al., J.A.C.S., 1969, 91, 3682.
- 1970- Monsanto method for Analysis of Pentachlorophenol for 2,3,7,8-TCDD developed. This method used a Hewlett-Packard gas chromatograph equipped with an electron capture detector and a six foot 6 mm OD column packed with XE-60 or QF-1. ~~The detection limit was given as 0.2 ppm.~~ It was not isomer specific. Mieure and Dietrich Document 7500060.
- 1970 -
- Feb. 7 Dow Biochemical Research Laboratory made their write up of Safe Handling of Tetrachlorodibenzo-p-Dioxin available. This was the first reasonably complete and formal account of precautions necessary for safe laboratory use of TCDD. Document 040807
- 1970 Monsanto GLC flame ionization detector method was written. Sensitivity not stated. Estimated to be in 1ppm. Document No. 001510.

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- 1971 Field ionization mass spectrometry developed - Gives good parent ion peaks, useful in cases where neither electron ionization or chemical ionization give satisfactory results. Not widely used because of lack of reproducibility.
- 1973 Chlorine 37 isotopically labeled TCDD made available for use as an internal standard in GC/MS analytical methods. Made by Oak Ridge National Laboratories. Use of internal standard minimizes effect of changes in instrumental response and gives better quantitative accuracy. Baughman and Meselson Environmental Health Perspectives, Sept. 1973, p. 31.
- 1973 Round robin test of four analytical methods for TCDD in pentachlorophenol including Monsanto, Dow, FDA and USDA procedures. FDA, sponsor of the test concluded that "the results demonstrate that none of the procedures examined represent a satisfactory method because of loss of chlorodioxin and/or presence of interfering substances and lack of confirmatory techniques such as mass spectrometry." O. Hicks and E.S. Tucker Document 230334
- 1974 Monsanto Research Corporation acquired Hewlett Packard 5982 GC/MS computer controlled instrument combination. High resolution capillary gas chromatography/quadrupole mass spectrometer capable of multiple ion monitoring . Sensitivity 1ppt.

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1977 Monsanto Report - Determination of Trace Amounts of chlorochbinzo-p-Dioxins and Chlordibenzo-furans in Technical Pentachlorophenol. A method developed for routine use by plant control labs using either electron capture, flame ionization or mass spectrometer detection. Sensitivity of 10 ppb with MS. Not highly specific unless mass spectrometer detector is used.

Mieure et al Jour. Chromatographic Science 1977, 15, 275 Document 7500119.

1978 Fused quartz capillary columns for gas chromatography developed. Gave much improved resolving power compared to earlier stainless steel and glass capillary columns. Made possible separation of individual TCDD isomers. Larson et al Fused Silica Capillary Columns for Gas Chromatography - Hewlett-Pachard Journal Dec. 1983 p. 35.

1979 Fully labeled $^{13}\text{C}_{12}$ TCDD became available for use as an internal standard for GC/MS work. Use of an internal standard permits excellent quantitative analyses down to the 1ppt range. Brumley et. al. J. Agric. Food Chem., 1981, 29, 1040-1046.

1979 All 22 tetrachlorodibenzo dioxins reported synthesized, an important milestone because it permitted proof that the present day analytical method - fused quartz capillary column gas chromatography - selected ion mass spectrometry can indeed

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measure the 2,3,7,8 isomer without interference from the others.

This means isomer specific analysis is now possible in environmental samples. Matrix effects are still a problem at low ppt levels.

Nestrick, Anal. Chem., 1979, 51, 2273-81.

- 1980 High Performance Liquid Chromatography, both normal and reverse phase, applied to TCDD analysis. This further improved the ability to eliminate interfering components of samples. Lamparski, Anal. Chem., 1980, 52, 2045-54.
- 1981 Monsanto Report on analysis of still bottoms for chlorinated dibenzo-p-dioxins. Used to analyze still bottoms from pentachlorophenol purification. These contained in the neighborhood of 600 ppb 2,3,7,8 TCDD. The method was a combined capillary column GC/MS method. It could have given sensitivity in the 1ppt range but was used with reduced sample size because the high concentration of TCDD contained in these samples made high sensitivity unnecessary. It was isomer specific. Hileman, MRC Research Report MDA-228 Document 7500338.
- 1981 A six laboratory inter laboratory study showed excellent quantitative agreement and ability to confirm 2,3,7,8 TCDD for three of the seven labs, two more with good quantitative but poor confirmation with the remaining pme unable to analyze the samples. The labs used included Bureau of Foods/Food and Drug Administration, EPA, Fish & Wildlife Services, New York State Department of Health and Dow laboratories. This defined state

of art in 1981 and showed that only the best laboratories were fully capable of both good quantitative results and good confirmation even at that time. Brumley, et. al., Jour. Agric. Food Chem., 1981, 29, 1040-46.

1983 The EPA issued Region VII Dioxin Protocol, Determination of 2,3,7,8 TCDD in Soil and Sediment. The methods contained in this protocol represent the current state of the art for TCDD analysis. They specify methods for ensuring accuracy, minimum detectable limits and freedom from interference by unexpected sample components. They go to great lengths to specify sampling procedure as well as safety precautions to avoid toxicity problems. As of March 1984, there were only 17 laboratories in the U.S. which have passed EPA tests and been certified by EPA as fully capable of satisfactorily making this analyses. MRC Dayton is ^{one}~~are~~ of these.

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