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Journal/Book Title	
Year	1983
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Descriptor Notes	Workshop organized by the Environmental Criteria and Assessment Office, U. S. Environmental Protection Agency (EPA), Cincinnati, Ohio

AGENDA

Peer Review Workshop on Dioxins

Organized by:

Environmental Criteria & Assessment Office
U.S. Environmental Protection Agency
26 West St. Clair Street
Cincinnati, Ohio 45268

Place: Cincinnati Convention/Exposition Center
525 Elm Street, Cincinnati, Ohio

July 27, 28 and 29, 1983

Documents to be Reviewed

1. Health Assessment Document for Dioxins (HAD)
2. Ambient Water Quality Criteria for 2,3,7,8-TCDD (AWQC)
3. Health and Environmental Effects Profile for Tetra-, Penta- and Hexachlorodibenzo-p-dioxins (HEEP)

July 27, 1983. (Wednesday Morning)

9:00 to 9:20 am — Dr. Jerry F. Stara

- Greetings and Opening Remarks
- Historical Perspectives and Regulatory Impact of Human Health-Risk Assessment Documents
- Development of Documents
- Review Process

9:20 to 9:25 am

- Charge to Reviewers — C. Patrick
- Announcements

9:25 am — Dr. Debdas Mukerjee

- Scientific Review Program

9:25 to 10:15 am — Physical and Chemical Properties/Analytical Methodology — Harless, Rappe

HAD: Pages 3-1 to 3-31
AWQC: Pages A-1 to A-6
HEEP: Pages 1-1 to 1-4; 1-12 to 1-16

10:15 to 10:25 am — Coffee Break

10:25 to 11:10 am — Production, Use, Synthesis, Environmental Sources and Environmental Levels — Nauman, Tiernan

HAD: Pages 4-1 to 4-31
AWQC: Pages C-1 to C-15
HEEP: Pages 1-6 to 1-11; 2-7 to 2-8; 3-1 to 3-3

11:10 am to 12 noon — Environmental Fate and Transport Processes — Nauman, Matsumura

HAD: Pages 5-1 to 5-16
AWQC: Pages A-7 to A-8
HEEP: Pages 2-1 to 2-7

12 noon to 1:00 pm — Lunch Break

July 27, 1983. (Wednesday Afternoon)

1:00 pm — Dr. Jerry F. Stara

Opening of the afternoon session.
Announcements

Scientific Review Session - Dr. Debdas Mukerjee

1:05 to 1:45 pm — Ecological Effects and Aquatic Toxicity

Bruins, Stalling

HAD: Pages 6-1 to 6-16
HEEP: Pages 6-1 to 6-2

1:45 to 2:30 pm — Pharmacokinetics

Mukerjee, Olson

HAD: Pages 7-1 to 7-15
AWQC: Pages C-15 to C-26
HEEP: Pages 4-1 to 4-5

2:30 to 2:40 pm — Coffee Break

2:40 to 4:15 pm — Toxicity (Animal: Acute and Subchronic Exposure)

Mukerjee, Hutzinger

HAD: Pages 8-1 to 8-46
AWQC: Pages C-26 to C-38

4:15 to 5:00 pm — Toxicity (Animal: Chronic Exposure; Human: Acute Exposure)

McConnell, Garattini

HAD: Pages 8-46 to 8-56
AWQC: Pages C-38 to C-39

July 28, 1983. (Thursday Morning)

9:00 to 9:10 am — Dr. Jerry F. Stara
Opening of the Session
Announcements

9:10 am — Dr. Debdas Mukerjee
Scientific Review Session

9:10 to 10:30 am — Toxicity (Human: Chronic Exposure) Summary and Mechanisms of Toxicity
Barnes, Pocchiari

HAD: Pages 8-56 to 8-76
AWQC: Pages C-39 to C-50
HEEP: Pages 5-33 to 5-37

10:30 to 10:40 am — Coffee Break

10:40 to 12 noon — Teratogenicity and Other Reproductive Effects
Courtney, Kimbrough

HAD: Pages 9-1 to 9-35
AWQC: Pages C-53 to C-78
HEEP: Pages 5-12 to 5-33

12 noon to 1:00 pm — Lunch Break

July 28, 1983. (Thursday Afternoon)

1:00 pm — Dr. Jerry F. Stara
Opening of the afternoon session

Dr. Debdas Mukerjee
Scientific Review Session

1:00 to 1:45 pm — Mutagenicity
Rosenthal, Legator

HAD: Pages 10-1 to 10-12
AWQC: Pages C-78 to C-89
HEEP: Pages 5-9 to 5-12

1:45 to 3:00 pm — Carcinogenicity (Including Promotion, Co-Carcinogenic and Anti-carcinogenic Actions)
Hiremath, Mukerjee, Hardell

HAD: Pages 11-1 to 11-17 (Animal Bioassays and Human Epidemiology)
AWQC: Pages C-89 to C-110
HEEP: Pages 5-1 to 5-9

3:00 to 3:15 pm — Coffee Break

3:15 to 4:00 pm — Carcinogenicity (Continued)

4:00 to 4:15 pm — Synergism and/or Antagonism
Mukerjee, Durkin

HAD: Pages 12-1 to 12-2 (Excluding Promotion, Co-Carcinogenic and Anti-Carcinogenic Actions)
AWQC: Pages C-50 to C-52

July 29, 1983. (Friday Morning)

9:00 to 9:05 am — Dr. Jerry F. Stara
Opening of the Session

9:05 — Dr. Debdas Mukerjee
Scientific Review Session

9:05 to 10:30 am — Quantitative Risk Assessment (Air and Water)
Bayard, Schneiderman

HAD: Pages 11-7 to B-14

10:30 to 10:40 — Coffee Break

10:40 to 12:00 am — Major Concern of Human Health Effects - Principal Issues
Albert, Hay

HAD: Pages 14-1 to 14-17

12:00 to 1:00 pm — Lunch Break

July 29, 1983. (Friday Afternoon)

1:00 to 2:00 pm — Press time

2:00 to 4:00 pm — Public Comments

4:45 to 5:00 pm — Dr. Jerry F. Stara
Concluding Remarks

Names of Reviewers for Dioxins Documents

Meeting Room No. 3, Second Floor of the Cincinnati Convention/Exposition Center
525 Elm Street, Cincinnati, Ohio
(July 27, 28, 29)

1. Albert
   Dr. Roy Albert
   New York University Medical Center
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   550 First Avenue
   New York, NY 10016

2. Barnes
   Donald Barnes
   U.S. Environmental Protection Agency
   Office of Pesticides and Toxic Substances
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3. Coulston
   Frederick Coulston
   Coulston International Corp.
   1092 Madison Avenue
   Albany, NY 12208

4. Courtney
   K. Diane Courtney
   U.S. Environmental Protection Agency
   Health & Environmental Research Laboratory
   Research Triangle Park, NC 27711

5. Dorough
   H. Wyman Dorough
   Director, Graduate Center for Toxicology
   University of Kentucky
   Lexington, KY 40536

6. Firestone
   Dr. David Firestone
   Bureau of Food, FDA (HFF426)
   200 C Street, SW
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7. Garattini
   Dr. S. Garattini
   Director, Institute di Recerche Farmacologiche "Mario Negri"
   Milan, Italy

8. Greisemer
   Dr. Richard Greisemer
   Biology Division
   Oak Ridge National Laboratory
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9. Hardell
   Dr. Lennart Hardell
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10. Harless
    Robert Harless
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    Atlanta, GA 30333

15. Kociba
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16. Legator
    Dr. Marvin Legator
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17. Lilis
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18. Lotlikar
    Dr. Prab D. Lotlikar
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19. Lowrance
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20. Matsumura
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21. McConnell
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22. McNulty
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23. Miller
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    Dr. James Olson
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26. Pocchiari
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30. Schneiderman
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31. Silbart
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32. Silbergeld
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33. Stalling
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34. Thibodeaux
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38. Mukerjee
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39.

Dioxin Document Peer Review
Cincinnati, OH
7/28-29/93

Barnes

7/29 Peer Review
Public Comment
SAB Review
HAD + HEEP — Syracuse Res. Inst
~~RAWQC~~ - ECAO Cin
Mukerjee knows all the literature
OHEA has prepared certain parts
Post meeting memorandum and/or marked up copy of the draft. By August 5.

P/Chem/Anal ~~P/Chem~~ / Anal
Rappe: Two general methods
a. The Dow method of getting isomers in individual bottle
b. Stalling / Rappe / Buser method having all isomers in one bottom. Have method for analyzing all congeners of CDDs + CDFs. Possess all isomers of CDDs + CDFs. Have data on penta CDD in fish.
CDDs are chemically reactive. There are not chemically reactive under environmental conditions.
Firestone: POA is developing multi-step HPLC which will isolate homologous groups. EPA can take to lead in developing standard method.
Tiernan: Unlikely that a single method ~~for all~~ will be useful for all samples/matrices. Great commonality between methods. I also have a method for getting all congeners in ~~the~~ one bottle.
Pocchiari: 3 volumes are not consistent. Decide on termination date of the references.

Unive Cin – Why were these compds chosen?
Kimbrough: Goals of limit of detection?
Rappe: Reference primary sources.
Stalling: We need to include reference to CDF.
Garrett: p.3-27 Bioassay is not a chemical analysis.
Firestone: Method 613 study has been completed in last week or so. Interested getting AOAC involved.
Stalling: Look at biota, rather than H_2O. E.g. don't look for H_2O when ippt in fish. Refer to EPA/UK KC note.
* Barner will provide summary.
Peters: Give us accuracy info as well as DL
Coulston: Need to report whether data has been generated by reliable methods
Rappe: State whether or not there is internal standard used and/or % recovery.
Tiernan: Recent Appl Chem report by Grummett on "criteria" for anal methods. Good QA/QC in MS, info on interlabs, etc.
Kimbrough: Methods for air+water have not been standardized.

Breaks
Rappe: PCP wood preservation in Sweden are not working 100%. Problems with lung spores. Remediate. Workers want CP back

Drums.
Schaub-Tsang

Product Use

Newman: Summarize
Tsernoua: p4-1 84 lb/yr is probably low.
Thibodeaux: p 4-18 analyses ~~for~~ by WSU & EPA-Houston.
Safe: Best way to make CDDs condense nitro-phenols + chlorophenols. (?)
Rappe: Synthesis by combustion. P.4-12 Rotary kiln cement kiln 1000°C → detectable CDDs/CDFs
Hawkins (1981) found non 2378
HEER p 1-6 End products are not CCDs, the only intermediate are
Pocchiari: p. 4-3 formula
4-5 HEER p. 1-7 2378-TCDD in PCP
4-11 Similar units
BCF needs to be discussed.
Brunius: Can't get background info on published lab BCF values.
Kocibus: Several values quoted in the documents.
Isensee, Konaya, etc. → 5-10,000.
Pocchiari: Have 1 page summary on BCFs.
Stalling: CDFs from combustion.
Lab values probably underestimate BCF.
Brunius: Lab values were not steady state.
Rappe: PCP has TCDDs 1 ppm; 2378-TCDD has not been detected
4-16 Gelatin, yes. ~~Hex~~ Hx CDDs have been found in fish.
Hay: Cell transformation
~~Stalling~~
* Barnes: Schaub/Tsang note Decomp values diff
Stalling: Hx → O predominate in sediment. Fish show TCDD most. 20 striped bass estuary samples 10-20 ppt.
Peterson: Strike 84 lb estimate. Too crude.

Kimbrough: FDA uses different method
Mukerjee: PR notices says we will use it.
Brown: G.S is for freshwater estuarine
Silbergeld: Consider brominated.
McNulty: Table 4-3 should have MO data.
Mule: not published
Barnes: CDW G has not received it yet. Coming.
Stalling: NY has guidelines at copper
MO has guidelines at time for pigs in Spring River.
Redman (Reg 5): Reg 5 reports are available.
Need to identify species. Table 1 p 3C-13.

Completing BCF studies at 28-day studies:

Fiscetta: Specify congener + whole/edible portion.
Commercial PCP: 123678 ~½ of total H_xCDD.
123789 cannot be biologically active. The others are less active.
Tramon: River fauna in lab ⇒ low CDD/CDF (~ND).
+ HCl ⇒ high CDD/CDF.

Env. Pet

Neuman: Summary

Matsumura: Plant pick up. Isensee 1971 → tracing beams. Photodegradation does take place on soil surface. $T_{1/2}$ ⇒ 1st order. — data shows that it is not. Microbial in sand ~~does~~ does not occur (probably). No documented case of reduction of COCs by microbiological. Surface disappearance ≡ vertical movement (possibly lateral movement or volatilization). Bottom feeding fish are most likely to get CDDs/CDFs — selective pick of 2378 documented?

Mukerjee: 2 papers on uptake by plants (Salzburg)

Hutzinger: No good evidence that 2378 degrades. We have done photodegradation under ideal conditions. But not on fly ash

Tiernan: Quality vertical movement. Any sites can.

Stalling: Examine bioavailability. Lab & field don't correlate well.

McConnell: Include disposal

Pocchiari: all.

Thibodeaux: EXAMS + volatilization from water. Need to quantify.

Vapor within from soil surfaces. Pesticides & similar types do volatilize.

Garafinni: pp 5-9 Seveso $T_{1/2}$'s. First, shows movement. Second, also. Third, more realistic.

Table 5-1. Some initial conc are > solubility

Biocon on worms ≈ 30

Sorption = f(time)

Kimbrough: MO ⇒ we don't know much about fate. Volatilization possible.

Pocchiari: Dominici (1982+83) in Coulston book
Worms BCF = 13X. Moles → ND(?)
Rappe: Sediments are not uniform. Used Hudson River sediment → 80% recovery in TCDD, HxCDD. Contain TCDD.
Albert: Need to state whether TCDD is respirable.
Harman: Yes, published particulate distribution data
Nash: By analogy, very unlikely for TCDD to translocate to plant. Dumpsite volatilization possible. 15 year old Nash paper ⇒ volatilization
Silbergeld — 5-3+5-9 photodegradation → lower (?)
Firestone — unpublished data ⇒ 2378 sites are more susceptible
Wee Hee — 5-3 is wrong. λ_{max} 2378 = 310
↑ → ↑ chlorination. (?)
Data very dependent on analytical approach.
McNulty — Solubility in H_2O in lab, not likely to be applicable to environmental situation.
Peters — Should we get both particulate and gaseous samples?

Lunch
Kociba — Recent dissertation from Sweden relating TCDD toxicity to unavailability of vitamin A.
Note that animal data ⇒ epithelial target.
So soft tissue sarcoma in humans are strange.
The hard palate, lung, etc seems ⇒ local inhalation/particulate/"chloracnegenic" effect.

Tuesday pm

Purpose of HAD

Peters: Is there a problem — quantities, significance?

Purpose of AWQC

Gentzkow: Required by CWA.

Bartlett: Note: AWCQ is responsibility of Duluth. But do include comments on BCF

Brown: Summary.

NOEL not available on fish

Stalling: OK through 1982. Add Tucker data.

Kimbrough: Add horseradish data

Pharmacokinetics: Mukerjee: Summary.

Olson: Absorption important for vehicle. 74% in hamster in olive oil. Sex diff distribution is only slight. Urine + biliary relate to metabolism. No native material in feces. Liver to fat only had native, not metabolism. Bile → glucuronide. Urine → sulfates. Metabolism ⇒ detox. Important in persistence. Fecal in all species. Somewhat more via urine in hamster. P-450 important + induced by TCDD.

Barnes:

Firestone: McConnell + Firestone data on other CDDs in cattle.

McConnell: Need more info on inhalation.

Hays: III quoted metabolic pathway by Buser + Rappe.

Induction + toxicity are not necessarily causally related.

Gaylor: More data for Table 7-1 + 2. No absorption study when administered on food.

Enterohepatic circulation is likely; cf administer charcoal days after TCDD.

Microdistribution: initially in nuclear fraction. 2 wks later (when tox shows up) it is in microsomal fraction. Metabolites are "less toxic" in sense of lethality. GI tract of liver can block metabolism of pro-toxic enzymes. TCDD is not

Pachiaroni: Soil bound TCDD ~~was~~ less. ~~less~~
Being published
p. 7-7 Rewrite
p. 7-13

Kimbrough: $T_{1/2}$ of McNulty

McNulty: $T_{1/2}$ ~ 1 yr

Lotlikar: p. 7-10. Really hydroxy compds that go to methoxy.

Mukerjee: Elaborate on DNA binding

Lotlikar: Polland binding is only ex background ∴ may not be real. Long way from understanding carcinogenic action. Other halogenated HC ~~which~~ which do not ~~have~~ bind.

Graveltine: Neither does saccharin. But methods may not be sensitive enough to detect binding. 5000 molecules per hepatocyte. Could not detect binding at even 10^{-7}.

Sato: Substit COD, PCB, etc are qualitatively / not quant equivalent when appropriately substituted — binding to receptor as model. Hydroxyl group in lateral position → reduced binding ∴ agree with Ponzer Weber. Doesn't depend on molecular diameter. 3 properties of substituent

Olson: Used tritiated ^{37}Cl in 1+2 positions. Would like ~~better~~ hot ^{14}C. Weber data is ok, but they looked at final metabolite — maybe intermediates were problem. Persistence — 1st order component for most species (not hamster), with $t_{1/2}$

mcNulty data — persistent effect.

Kim: I don't believe there is binding.

Hay: Asbestos, DES, etal are not mutagenic either.
Albert: Metabolite are electrophilic. May bind with proteins before it gets to nucleus. Target may not be mature hepatocytes. Maybe oval cells from bile duct—not much cytoplasmic protein to "blot up" TCDD.
McKinney: Response to Bowes question. (p.c)
Never shown the TCDD claim.
Kimbrough: Selenium chloroacne folks → ND.
Silbergeld: include info receptor conc in tissues/species
Stalling: Non-2378 congeners discussion is needed to support our decision 2378.
Firestone: I will supply some data
Rappe: Yushe data. I will provide.
Albert: Say what we don't know (e.g. mechanism, active metabolites.
Kimm: CDF-Yushe may be more applicable for different furans.
Dee Hoo: Elimination of $CDD_s \neq CDF_s$.
Rappe: 2378 PCBoners are equiv in ~~toxic~~ detriment series.
Kimm: Many differences

Break
S. Bergeld
Scientific interaction

★ Silbergeld citation for role of MWC & not CEQ

Toxicity (Animal: Acute & Subchronic)

Mukerjee: Summary

Sato: Several additions.

p 8-6 ~~Gaw etal~~ ~~follows~~ overlaps this section.

Should order be changed.

★ not pre-immunotoxicity Hay: p. 8-35 Not Mayi Ward, ↓ IgD, IgM ⇒ reduce immune competence

Gravattini: Strain dependent thymic atrophy & enzyme inducibility. ~~Ke...~~

Reorder immunological section. Cells, systems etc.

8-36 Reggiani did not consider all parameters — not humoral, the one more likely to show effect.

McMurthy: Cite species of monkey

Non-human primate indicates (not conclusive) LD_{50} perhaps as low as 1 µg/kg.

Mention gastric lesion.

McConnell

Nisbet Kociba: E-1 C-2 LD_{50} as high as 5000 µg/kg

C-34

★ Barnes: SAP & Rhesus references.

Pochiari: Table 8-3 add references

Kimbrough: What do we mean about "acute"

8-22 Recent work on lipid peroxidation

-23 No ref on hampster work.

-43 Species variability

Olson - Species variability table and Seefeld & Peterson (Tucker et al) ⇒ ↓ food intake → wt loss.

Silbergeld: How acct for parental dose

Olson: Maxim in doses → liq. storage (possibly)

Matsumura:

Barnes/Hill ↔ Coulston: Table of species, doses, organs

Gravatinni: Guinea pig ≈ non-human primate
Lotlikar: Knutson/Polland paper have useful
table.
Kociba: Tables in 1982 review
Schneiderman:
Hay = 8-22 Cholesterol in Coalite workers
Kociba: ~~Ko~~ Cholesterol study in rat
Grossman: Unchlorinated dioxin at 10,000 ppm Non toxic
2,7 DCDD Non toxic
2378 TCDD
H_xCDD .01 mg → liver damage
oral .5 mg/kg LD_{50}

Jensen (attic paper — Tx?

Tox (Abnormal Chronic)
McConnell:
Weight retardation. ~~Not entirely related to effect~~
May be related to reduced intake. (Tucker)
Liver shows morphological change.
Continuation of subchronic effects.
~~Include~~ fact that effects are similar to CDFs, PCBs, naphthalenes.
Garattini:
Porphyria effect should be included.
Immunological response ~~is~~ strain dependent.
Critical review of epidemiology.
~~Immune suppression with TCDD + CDF shows antagonism~~
McConnell/Garattini: no exposure to pure TCDD to humans.
Stara: Do we agree on NOEL?
Kociba: ~~8-50-EC-72~~ Only Highest dose showed tox hepatitis.
Garattini: "NOEL" needs time of dosing since it is cumulative dose. 1µg/kg/d for 45 wks → porphyrin excretion.
Kociba: We did not see porphyrin excretion.
Garattini: Species dependent. Examine specific porphyrins.
Mukerjee: How sensitive are humans cf subhum primates?
Coulston: Species dependent.
Pochiari: Can we compare ~~the~~ pure TCDD with env. TCDD. ~~Will~~ Cohort of Zme A is not enough to see much effects.
Alberts: Mention fat data in humans.
Hardell: Latency 10-20yrs.
McConnell: Comparative of dose, of lesions. Chloracne of monkey = chloracne of humans. Old world monkeys are good model for clinic pathology. Not necessarily in doses. Also dose + media dependency

Hiltmolicu

Kimi: Only Jpng dermal study.
Silbergeld: Mechanism-structure
Handell: No chloracne in my cohorts. Relation not
Hay: Holmesburg prison. Applied to skin.
Gavartinni: We have no data
8-5: Not likely due to TCDD. Due to acid/alkali:
8-6: Beal ~~Nature~~ Lancet 1977 I 748.
Pocchiari: Focus on chloracne. Tabulate. Primary source. Will append 8-7 Tagani
Barnes: AMA document as source of chloracne reference?
Suskind: Nurse + doctor at Nitro got chloracne. Pathology suggests a sensitization reaction.

Fingerhut (Reg 4): Any short term test for human response?
Kimi: No. Chromosome test.
Clark (Reg 5): Need to say that Seveso ≠ no effect
Newell

7/28

Stara: Not enough info for good risk assessment on any chemical. But we can do a reasonable job. Need to include uncertainties.

→ Need NOEL study. Need cancer bone study. If not possible, say so.

Kimbrough: What about lab capability? Need to caveat document

Stalling: Include statement of needs. Ryan/Buser will soon in Anal Chem show that 2378 congeners are separable

Hutzinger: Bioassays

McGinnity: Vapor or particulate, etc when air sampling?

The chemist Mukerjee: Need lab capability standing.

Barnes: Ret on Neal, All section

Poc: E62 E63 = C-42 C-49 5-34

Kimbrough: More studies. Blabung before Poland.

E62 Seventh last sentence 1st paragraph

Bogen & Stevens article are not up to snuff. Stevens should have critical review.

Hay: More industrial work. Martin & Walker. Larger study by Martin underway. May work was biased in that control were sedentary. Czech work should be included. 1963 Holland accident. Monsanto unpublished.

Schneiderman: Anecdotal reports are valid, So are calculations ∴ Don't exclude.

Kim: Need critical review

Coulston: Answer to Schneidermann

Legator:

Kociba: 8-75 NTP lowest dose was NOEL based on NTP report (-42C)

Garatini: 8-67 Problems with Stevens. Conjecture

8-64 Binding to OWA discussed yesterday. Intermediate may be a problem.

Ultramen: Adaptation comes at $> LD_{50}$. ∴ not important
E-66 "Detox via metab" may be too strong.
Edéa: Severe children with chloracne/fem type
study
E-75 no "dose-related" data
Beettee: Do tables with doses + effects
Olson: No sig difference with [Cresyl] in diff organs + species.
Correlation is good only within strains of mice.
Silverfield: Confusion on breast section. "Proximate"
E-67 Norbert tables. Human data (non-clinical)
-69 saturable ⇒ receptor non-saturable ⇒ binding (protein)
-74 liver may not be the most sensitive organ.
NTP data on liver coming
Hay: Loci alterations that are ~~effective~~ affected.
Backstrom: Nuclear binding to receptor
Peters: E-63 Mice reports + editorial
Kimbrough:
Kociba: 5-3+ (WOSW) no chronic data E-75
Beettee: Formats. Reports; late critiques.
Stavers ~~was~~ too simplistic.
Mukherjee: List all references searched and not used.
Hay: Monsanto News & Data accident. External report.
Klein: Take only peer-reviewed à la WHO
Coulston: WHO will take government, industry, etc. documents, if given.
Barry (Mike): Use ~~in~~ peer-reviewed stuff.
Coulston: Don't cut off into from industry
Peters: Put in special section
Barry: SAB will do peer review effectively
Lee: EPA needs policy; accept Mip reports, telephone calls?
Gresener: Unchlorinated CDD → toxic hepatitis. 5000 ppm
Degenerative, inflamatory liver.

Matsumura: 3MC binds but no tox. ∴ receptor not whole theory. $[receptor]_{Hamp} \neq [\;]_{gp}$ ∴ thrombocytopenia
" " " – Diminished platelets, blood count, ratio.

Recent ~~the~~ Matz review

McNulty: Don't talk about most sensitive species.
Carlston: Regulators need guidance for ADI. I say chloracne
Lotlikar: Should look at induction in skin.
Silbergeld: NK data + Knutson/Polland keratinization
Safe: Induction ≠ toxicity. Correlation with exposure.
Gasiewicz: Hard to classify as ~~[illegible]~~ ~~[illegible]~~ physiological or pathological. eg, PH → ~~[illegible]~~ short time enzyme induction ~~[illegible]~~ of TCDD → long time
∴ These are not necessarily the same

Terat. + Repro
Courtney:
Definition: embryo → ~~embryo~~ organogenesis period
fetus
Terat → irreversible. (Less distinct distinction)
Repro problem → reversible. (?!)
Hamster is sensitive; g.p. not studied. (immature)
~~G.P.~~ Rabbit " to TCDD, not T
Rats & mice
Human spon. ab. rate = 45%. Monkeys may abort as well.
3-generation study - Nisbet/Paxton
Pratt thinks TCDD bound to receptor in palate → cleft palate
Male mouse study - Question of using polytocous animal for these studies (resorptions could take place)
Kimbr: Put in actual dose of TCDD in T studies.
Susceptibility of strains. Discuss immune system effects. Include criticism of Olsen.
Murray: Nesbit/Paxton technique may not be appropriate. Individual vs. littermates, family links, etc. Need to peer review Nisbet/Paxton
Kociba: Two reviews of Murray: ① SAP ② Nesbit/Paxton
Barnes ★ C-67 and 4-17 should have SAP
There are NOELs for terat
Barnes ★ Schneidermann: Who did stats for SAP?
Courtney: Dams may have depleted by feeding F₁A.
If to zero, then only up to 70% by time of F₁B.
Silbergeld: Reluctance to underestimating
Miller: Have not found animal effects in humans. But not expected.
Birth weight would be a good measure. Chemotherapy → decreased birth weight.
Olson: 9-9 Cheng 1981
Muscarella on terat (roughly → terat, terat.

Gavatinni: Interaction of T + TCDD no clear. Sy 50
9-11 Terat effects & inducibility by strain
9-31 More current info than Fara (1977)
Coulston: 9-25
Interim Head of Dikrund Safety evaluation of Also
Monkey (T, .05 ppm) Bleeding during gestation.
Wilson - 75 pregnant monkeys.
Dominicis: 9-31 Segi has completed Fara study.
Summary:
Divide into 1 km², chloracne, skin lesions, TCDD in soil
High rate of abortion in July 1976. One malformation.
Marijuana & chloracne.
Albert: Document is not to be encyclopedic; rather answer
"Is it a hazard? If so, how big is it?"
Need a bottom line.
No quantitative assessment of repro
Que Hee: Other dioxins
Paper showing higher animals different effects from rodents
Legator: Need relevance to other chemicals.
Makojue: Get REMs to make a statement.
Kociba: 9-24 update on McNulty
9-35 Not all studies; cf. Coulston
C-112/113 Cf Schantz study, Not discussed earlier.
Pochiari: C-112 Is .001 NOEL, LOEL
Hardell: Hexachlorophene nurses in hospitals.
Malformations. New study on neural tube defects.
Clustering around forests. Mothers hexachlorophene exposed;
Some fathers exposed to spray.

Severely criticized (Lawrence/Hoyt)

Silbergeld: Other effects
Clark: MI Dept Pub Health. Cleft palate 1971-74.
Townsend study looked at all dioxins.
Houk said before Congress a cleft palate is subpop of Townsend.

Kaczka: NOELs in most sensitive species in FDA Assessment.
Gaylor: Need summary of effects in T.
Lee: Need better summary
Miller: Shh, a teratogen was found first in humans (Cleft lip + Holoprosencephaly).
Need to be careful in Swedish clustering. CDC could not find similar situation in Atlanta, Jacksonville, and Iceland.
Graham: Immune effects in rats
Gee Hee: Multiple exposure problems.

Lucier - Pocchiari - fat benign tumors w chloracne
Brookes: Matsumura - uptake by grass, photolysis synthesized by chlorophyll, "root uptake"

Mutagenicity
Rosenthal: Results conflicting. Limited TCDD solubility in H₂O is a problem which we should look out for. —
Additional studies: + and weakly +
Legator: Only few studies, especially in vivo. Rearrange: adduct, in vitro, in vivo. Note key tests done; common ones not done. Table. Additional studies. UDS
Decreased satellites of D group chromosomes.
Kotliker: Our doses → ↓ survival. May say limited solubility is not the problem.

~~Also~~
Gamatinni: Echo of binding. Put in one place.
Hay: Cell transformation. + [T]CDD, ■DD, → -S. Late passage
Kaufman: E-say sex linked recessive test needed. NTP has done it —.
McConnell: TCDD went through the NTP ~~[illegible]~~ battery prior to bioassay
Kociba: 5-7 How many tests do we need?
Legator: Clastogenic effect in bone marrow. Not clearly +. Some mutagenic activity, but not consistent with the highly potent carcinogenicity. May be due to high tox ~~to~~ bacterial systems.
Pocchiari - 101B

(21)

Cancer

Hiremath: IARC criteria ⇒ sufficient for both TCDD & H_xCDD

No member of IARC

Baylies: Epi → IARC 2A (when in combination with phenoxy)

Harrdell: Colon cancer recall bias approach, No relation of colon cancer & exposure to phenoxy.
Studied both Hodgkins & NonH. Note relation to decreased immune response.
Hodgkins in Eng Med 5. for phenoxy 6.5 chlorophenol.
13% in gastrointestinal cf 2% expected. cf rats.
Nasal/nasal phargeal - Am J. of Ind. Med. 77 case-case control.
Wood dust → cancer. Chlorophenols in sawmill dust 7X increase. No signif xs of exposed to phenoxy acids.
No chloracne people.
~~Summaries. Recall verify lymphoma~~

Greisemer: Data are inadequate on ? TCP (me OK(?):
lymphoma, included).
Note: Different sites in Kociba vs NTP. Two rat strains; two route of exposure.

Kociba: Same particulate matter food embedded in lung & tongue base. Squire same also. Some reviewers saw these as metaplasias, not neoplasias. ~~Also~~ Always saw embedded material, but no tumors. Kimbrough agrees
Holland study show embedded hair in lung → tumors. ∑ Local chloracne

Mukerjee: Same in plastic shavings.

Kociba: Same thing seen in controls → no carcinomas.

Greisemer: NTP ⇒ female mice s.t.s. Skin painting ⇒ + in female, suggestive male.

Kociba: carcinoma only on skin after ulceration.

Greisemer: Lots of ulceration experiment ⇒ tumors.

Mukerjee: C-99 Hemangiosarcoma signif?

Greisemer: Will check.

Discussion on site of angiosarcoma [?]
Coulston: WHO wouldn't accept
Greenwood [?]: Sub data correlate with IARC: Tomatis.
Unsubst- 80 ... [illegible] TCDD 10,000, etc. Huff (?)
Question of spikes of exposure,
Coulston: Combined exposure of CDDs plus..
~~Kou~~ Kouten [?]: Milham study. Smith study. PMR
Hardell: Counter
Lotbiker [?]: Combined expos → dioxin results
Mukerjee: Aitken Nature 1982. Conclusive evidence is ~~not~~ strong

Break
Albert: Could be due to phenoxys. Potency would be high [?]. Stratification. Eriksson data reanalysis may → ~~TCDD~~ TCDD ↑

Backstrom: US cohort had PCP exposure, not phenoxy
∴ ~TCDD in common
Inconsistency in 2,4-D contamination between doc.
~~[illegible]~~
Kouten [?]: IARC sts → 2B (inadequate)
Supplement 4 (1982)
Albert: We must do independent.
~~Albert~~
Hardell: Glyoma not metastatic
Ranch Hand limited cohort

[Need comment on Ranch Hand]

ArB
MW call
[illegible]

(23)

Miller: Classification of sts? Can they be induced by one agent? Don't think so. Most chemicals → one type, e.g. fibrohystiosarcoma. But can't link them together easily.
Soft tissue: anything between bone & skin of a limb, excepting lymph nodes
Greiseimer: ~~agree~~ pass.
McConnell: NTP wouldn't allow me to group them. Burden of proof is on those who suggest common
Kociba: shouldn't group
Kimb: NIOSH + AFIP are doing a review.
Hardell: Some chemicals (asbestos) can do more than one. International group (1977) ~~[illegible]~~ working on grouping. Agreed based on histopath. Possible common stem cell. Use smaller groups of tumors. Still → sig risk
McClintly: Some hard tissue tumors from same stem cell. Ever examined?
Hardell: No
Albert: Radiation → many tumor types.
Silbergeld: Broad range of the effect.
Lotlikar: ?
Albert: No one suggests walking away.
Coulston: Dilute when out of airplane.
Lotlikar: Table 1 11-3. Scratch van Miller
Clark: May 83. MI sts
Case control study to be done.
Kociba: 11-5
Albert: Bottom line? P. 11-106
Rappe: HxCDD in chlorophenols should be 2B.
Coulston:

Greiseimer: Predict a TCDD would be 3 — TCDD alone - animal + no human
~~[illegible]~~ TCDD + phenoxy " 2B — TCDD in mixt. - limited evidence.
Vote: Don't use IARC scheme.

7/29 Qualitative Summary

2378 : prob. carc in hum on basis of animal

Epi of workers [illegible] of 245-T 245-TP in [illegible]

[illegible] and → site & site

Because 2378 is in [illegible] . [illegible]

1. Hx in comb with Hx prob in hum on basis

Limited that suggest exp to mix

Syn. Effects

Mukerjee:

Dickin: Pull in summaries from other chapters.

Senatumi: Gregg used doses > LD_{50} ∴ don't use.

Say it is an inducer ∴ predict interaction.

Therapeutic with C. [illegible]

Paper showing antagonism of TCDF with TCDD in immune response

Silbergeld: Also talk about competition for receptor.

Kim. TCDD ⇒ less effect when Fe deficient.

~~Greene~~ Lotlikar.

Matsumura: Poland/Pitot data ⇒ TCDD 500x more potent than TPA.

Legator: Lack of binding ⇒ not initiator.

Lotlikar: Agree. Don't believe that covalent binding is needed for initiation.

Mukerjee: Lots of toxic, non-carcinogenic chemicals → DNA binding.

Multiple Models? 11-90
Grouping of tumors?
cf. Canadian Analysis? FDA: approx

Quant.

Bayard: Summary
Schneidermann: CAG has done good work.
Appropriate model when we have "different type" substance. Reasonable to use Multi-stage.
Why not Day-Brown and others? ~~If TCDD was~~
Would children expect to have fewer cancers (eg. antagonistic)? Would we expect sudden increase later in life (eg. late stage promoter)? Need to rationalize model. No use of ... or pharmacokinetics, etc.
Additional exposures needed?
How react to actual vs. perceived doses? Tissue dose.
Rigid use of model.
Formaldehyde is sharply curvalinear. Yet we force q_1. Actually $\to q_3 > 0$.
Abbot's correction needed for maximal limit.
Stara: Schn. do you agree with oral for inhalation, etc.
Shoe: No sensitivity analysis.
Albert: Inhalation → tumors from food. Not sufficient data.
Legator: No data to show that it is not complete carcin.
∴ Use MS (multi-stage)
Schneid: Try analysis of Crump assuming late stage carcin.
Pocchiari: B-7-9 ≡ Weibull model used in Italy ... Seveso.
Other data show differences in different experiments.
Add bioblend
Garattini: pp A-102
Low dose death wk 17
Low dose is so low you don't ... ...
Bacteria could metabolize, etc.
Below measurable levels
Too clear to make practical calculation.

)

Albert: Ballpark. <. Reservations are justified, however... Limited practical use

Stara:

Barnes: Multiple models — Data conveying

Grouping of tumors?

Safe: PCBs, etc are also unknown mechanistically.

McConnell: Potency table. Not good correlation with human experience. Need discussion, disclaimer.

Buckstram: MS may not be the most conservative

Pochiarri: Yes, with Kociba MS. is not " "

Kimb: CDC sees it as a promoter + maybe weak initiator.

Grouping tumors: Hoel doesn't agree.

Agree with Gerstiunni on death in Kociba. Need time adjustment

Albert: Agree with Hoel. Will not do it in future. Drifted into this. Cannot assign doses to lung tumors. Messy to dice out the dose for lung.

No criteria to show it is only a promoter or initiator.

Lung cancer not typical promoter.

Kociba: Survival. FDA analyzed it differently.

Greaseman: Would have appreciated a more structured discussion.

Would have looked at cause of death, survival curves, competing risks, etc.

Early death seen in other studies also. DDD early death. DD female 35% wk 12-30.

Question all the denominators.

Adjusted numerator would be smaller

Are there rare tumors? ⇒ Initiator. Except it female lung, they are common.

Silbergeld: Worried about use of Table 281

Try promotion analysis

Albert: Mestranol + DDT was done this way for promoter.

Consensus: We should do it by a

Garatini: Exposure is important.
Greisemer: Don't use data from different kinds of experiments (route of exposure, species, etc.)
Albert: Wide range ⇒ differences would be swamped out
Greisemer: Approach ~~~~ results negative data.
Scheidermantle: Exposure is important.
Pitot et al. IARC } early death / cause of death
John Gart
Oeattee: Table 28 Show error ranges.
Ligator: Order of magnitude
Barnes: FDA/Canada/CDC
Peters: Recommend method for using these figures.
1. Appropriate to use unit risk?
2. Over what range?
Albert: Program office problems.

~~Summary~~
Summary Albert: Read.
Coulston: Basically OK. Strike stomach cancer

Uncertainty

WQC

Hartung: Summary
Did not do ADIs for liver damage, etc.
Courtney: Use megamouse data.
Silbergeld: Not convinced that we have looked at all organs. Remove ~~organ~~ tables.
Hartung: Carefully state limitations of tables.
Kociba: Rats thoroughly
Pochran: NOEL. BCF ≅ 3000. [H_2O] << DL
Stara: Schneiderman will look at stats (Weisburger/Pantani)
Kimbo: Apple level of concern not ADI.
Silbert: PNE is counter to carcinogen.
Kociba: Cordle paper (1991) should be included.
Schneidermann: Comment
Kociba: Fish is the problem.
Bunnell: FDA did cancer assessment. Congressional statement.
McNulty: RfD criterion too low
Fish is the problem.
Stalling: Calculation to show BCF dependence.
BCF ≅ 100,000. Research need.
Hartung: Lotk BCF is almost an artifact. SAB going to direct attention at fish in the field.

Press Conference

Public Comment
Eggelmeier - Counted lots of possible objections to the evidence.

Lindsay: Vulcan Chemical
Reevaluation of H_2CO slide - Squire re-read.
4/27/88 "Equivocal evidence, weak carcinogen
Gilbert "Wood Preservation Workers" ep.
"No xs morbid/mortal attributable to wood

premature" & cohort.

Clearwater - MO

Concerns:
① Young - Background data on human fat. So What?
② Little info from MO in report
- Not in accuracy/precision
③ Young showed Seveso data that children most susceptible to chloracne

Proc. Vietnam Vets - Circum chapter

Murray - review with statistician and reproductive biologist.

Pocharski - No correlation between chloracne in children & enzyme problems.
Coulston - Children in MO can have chloracne
Clearwater - Nothing evident.
Stalling - Canadian fat ≈ 10 ppt.

~~Human Health Effects~~
Research

Rappe: The penta is found in ~~arrested~~ samples - not in commercial chemicals
Pocharski: Research
BCF
Were cancers animals
Fate in field
Isomer tox
Long term or acquat.:
Coulston: Monkey comparative toxicity
Reproductive studies

Albert: Inhalation experiment
Dose-response of promoter
Harting: Bioavailability
McNulty: Analytical capability.
Stalling: Furans. Sts and PCBs. Carcinogenicity.
Rappe: 2378 T < 1% of total TCDD in fly ash
12378 T < 1 " "
In fly ash, the toxic furans predominate.
Norwegian incin → large conc of high ~~[illegible]~~ tox.
Quettee: 2378 TCDF in liver of Yusho Taiwan
[redacted]
Human Health Effects
Hay: Summary
Mukerjee: Has anyone died of exposure to 2378-TCDD
Albert: Yes
[comment] Statement that [illegible] unknown
Burns: No Can't show cancer effect
Pocchiari: No one died in Seveso. Abortion increased but not spont abortion.

7/29/83

PEER REVIEW SCIENTIFIC PANEL ON DIOXINS

CONSENSUS STATEMENT

2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) is probably carcinogenic for humans on the basis of animal carcinogenicity studies which were positive in multiple species and organs. Epidemiological studies of workers exposed to chemicals contaminated with TCDD such as 2,4,5-Trichlorophenoxyacetic acid and 2,4,5-Trichlorophenol are consistent with the position that TCDD is probably carcinogenic for humans; the available evidence indicates an excess incidence of soft tissue sarcomas. Because TCDD is almost always found in association with other materials (e.g., chlorophenols, combustion products, etc.), it may never be possible to evaluate the carcinogenicity of TCDD by itself in humans.

1,2,3,6,7,8-Hexachlorodibenzo-p-dioxin (HCDD) and 1,2,3,7,8,9-HCDD in combination with each other is probably carcinogenic for humans on the basis of animal bioassay studies which showed an excess incidence of hepatocellular tumors in rats and mice. There are limited data in humans that suggest a link between exposure to mixtures of chemicals which include these two HCDDs and soft tissue sarcomas.

Note: This statement is from a workshop of outside experts in the field held by the U.S. Environmental Protection Agency (EPA) to evaluate all health related findings on dioxins in order to eventually reach a decision on how to regulate these chemicals.

Archives of Toxicology, in press

THE INFLUENCE OF SOIL PARTICLE ADSORPTION ON TCDD BIOLOGICAL UPTAKE IN THE RABBIT

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Abstract. A comparative study on the biological uptake in the rabbit of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) in different formulations, including accident-contaminated Seveso soil, was attempted. On the whole, our results indicated that soil-borne TCDD had a bioavailability lower than that of free (solvent-borne) TCDD.

Key words: 2,3,7,8-TCDD uptake; bioavailability; Seveso soil; ICMESA accident; environmental TCDD.

Introduction. TCDD (2,3,7,8-tetrachlorodibenzo-p-dioxin) is the most toxic of the polychlorodibenzodioxins and is generally an unwanted trace contaminant of the widely-produced 2,4,5-trichlorophenol. TCDD has also been formed in relatively high amounts in a number of industrial accidents of which the one that occurred at the ICMESA chemical plant at Seveso (Milan), in July 1976, is an example. This event yielded a widespread TCDD contamination of the environment and its extreme seriousness could still be appreciated over 5 years later as was sustained by Pocchiari et al. (1981).

The literature offers many instances of toxicological studies on isolated TCDD normally aimed at evaluating its toxicity rather than its absorption (Poiger and Schlatter, 1980). However, contact with TCDD in the environment most often involves the compound in a form bound to environmental substrata rather than as a pure chemical. Therefore, it was thought of interest

to assess the effects of using different formulations of TCDD on its absorption in the rabbit. As the liver was known to be the main target organ for TCDD in such species (Fanelli et al., 1980 a), TCDD concentration in the liver was taken as a measure of uptake. TCDD was administered via gavage with different solvents and soils. Maximum uptake was assumed to be associated with solvent-administered TCDD and was taken as a reference to evaluate the relative bioavailability of soil-borne TCDD. Bioavailability may have a bearing on the assessment of toxicological risk.

Analytical methods. Determination of TCDD levels in soil was carried out by adapting a previously described GC-MS method (di Domenico et al., 1980) to small samples (~2 g) and using the following steps: Soxhlet extraction, and multilayer and alumina column chromatography. Determination of TCDD levels in the liver was carried out by applying a GC-MS method reported in the literature (Fanelli et al., 1980 b) and using the following steps: alkaline digestion, extraction, and Kieselguhr and alumina column chromatography. Recoveries of analytical procedures are summarized in Table I. The identity of TCDD in some respectively pooled soil and liver samples was ascertained by hrGC-MS (Buser and Rappe, 1978). Purity of chemicals used as per referenced papers.

Treatments and results. (a) Soil was taken from a highly TCDD-contaminated area at Seveso, allowed to dry, and sieved to obtain a powder (200-400 mesh) which exhibited a mean TCDD content of 81 ± 8 ppb. (b) TCDD-free soil (200-400 mesh) was contaminated at 10- and 40-ppb TCDD levels by adding the toxicant in acetone which was allowed to evaporate prior to use. In some cases, contaminated soil samples were allowed to age for 30 days before use. (c) Solutions of TCDD in acetone-vegetal oil (1:6) and alcohol-water (1:1) had a title of 20 and 40 ppb.

Albino male rabbits (2.6 ± 0.3 kg at sacrifice) were kept in individual cages for the entire period of the experiment. TCDD

was administered by gavage every day for 7 days in any one of the formulations mentioned above. Soil (1-2 g) was given suspended with 10-ml water. Rabbits were sacrificed at the eighth day and their livers assayed. Treatment results are shown in Table II (all figures rounded to two digits). It can be pointed out that at 40 and 80 ng/die, data from administration-homogeneous groups (i.e. alcohol or acetone-oil, soil, and again soil) were pooled to evaluate the final statistical figures shown in the table.

Conclusions. Table III summarizes the statistical appraisal (ANOVA and Duncan test) of TCDD bioavailability as estimated from Table II data, as follows:

a) No difference is observed between uptakes at the lowest administration level (20 ng/die) with either solvent or soil vehicles.
b) Uptake of soil-borne TCDD appears to be an average of 29 and 44% lower than that of solvent-borne TCDD at 40 and 80 ng/die, respectively. However, the lower confidence limits ($p < .01$) of such means appear at 5 and 19% only.
c) Uptake of Seveso soil-borne TCDD may be seen to be an average 68% lower than solvent-borne TCDD. Here again however, the lower confidence limit ($p < .01$) of the mean is at 40% only.
d) Statistical analysis of individual groups at the 40-ng/die administration level (unreported in this text) shows that no significant difference exists between data obtained with non-aged lab-contaminated soil and TCDD given in two solvent media out of three.
e) Two highly significant linear regressions can be determined on solvent-borne TCDD and lab-contaminated soil treatment data sets, respectively. These regressions enable extrapolated TCDD levels in liver to be estimated at 160 ng/die doses. Unlike the case for lab-contaminated soil, the value obtained for the solvent-borne TCDD set appears to be significantly higher than the Seveso soil value.

In summarizing, it may be said that, in the rabbit, uptake of soil-borne TCDD appears to be lower than that of solvent-borne TCDD. Differences in uptake are more evident at higher doses of TCDD.

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TABLE I - Recoveries of analytical procedures

Item	No. of data	Recovery %
Multilayer column	67	96 ± 10
Alumina column	22	94 ± 5
TCDD-added soil	19	94 ± 14
TCDD-added soil (aged)	16	92 ± 8
TCDD(Cl^{37}), added to soil	28	94 ± 6
TCDD(Cl^{37}), added to liver	57	80 ± 10

TABLE II - TCDD levels in rabbit liver after 7-day treatment

TCDD ng/die	Vehicle	No. of rabbits	$\bar{x} \pm \sigma$ TCDD(ppb) in the liver	Conf.int.(99%)
20	Acetone-oil	5	0.26 ± 0.07	0.12 – 0.40
	Lab-contaminated soil	7	0.26 ± 0.08	0.15 – 0.37
40	Alcohol or acetone-oil	16	1.1 ± 0.3	0.94 – 1.3
	Lab-contaminated soil	13	0.81 ± 0.31	0.54 – 1.1
80	Alcohol	5	2.7 ± 0.5	1.7 – 3.8
	Lab-contaminated soil	10	1.5 ± 0.2	1.3 – 1.8
	Seveso soil	7	0.88 ± 0.28	0.48 – 1.3
160	Seveso soil	7	2.2 ± 1.0	0.84 – 3.5

TABLE III - Statistical evaluation of the bioavailability of soil-borne TCDD versus TCDD in solution (bioavailability: 100%)

TCDD ng/die	Item	Group difference meaningfulness	Relative decrease, % $\bar{x}$	Conf.int.(99%)
20	Lab-contaminated soil	Not significant		
40	Lab-contaminated soil	$p < .01$	29	5.0 – 53
80	Lab-contaminated soil	$p < .01$	44	19 – 68
80	Seveso soil	$p < .01$	68	40 – 95