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Report/Article Title Agenda, Notes, and Consensus Statement Peer Review Workshop on Dioxins, July 27-29, 1983

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Descriptan 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)

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Special Projects Staff (1020)

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
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6. Firestone
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7. Garattini
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8. Greisemer
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9. Hardell
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39.

Dioxin Document Peer Review
Cincinnati, OH
7/28-29/83

Barnes

7/29 Peer Review
Public Comment
SAB Review
HAD + HEEP — Syracuse Res. Inst
AWQC - 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~~ 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 ~~all~~ 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 CDFs.
Garatfini: 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 ppt in fish. Refer to EPA/UA 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 Ariel Thomas report by Grummett on "criteria" for anal method. Good QA/QC in MO, info on interlab, etc.
Kimbrough: Methods for air+water have not been standardized.

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

Dump.
Schaub-Tsang

Prod + Use

Neuman: Summarize
Tiernan: p4-1 84 lb/yr is probably low.
Thibodeaux: p 4-12 analyses ~~for~~ by WSU + EPA-Houston.
Safe: Best way to make CDDs condense nitro-phenols + chlorophenols. (?)
Rappe: Synthesis by combustion. P.4-12 Rotatory kiln cement kiln 1000°C → detectable CDDs/CDFs
Hawvam (1981) found non 2378
HEER p 1-6 End products are not CDDs, 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.
Bruins: Can't get background info on published lab BCF values.
Kocibu: Several values quoted in the documents.
Isensee, Kenaga, etc. → 5-10,000.
Pocchiari: Half page summary on BCFs.
Stalling: CDFs from combustion.
Lab values probably underestimate BCF.
Bruins: Lab values were not steady state.
Rappe: PCP has TCDDs 1 ppm; 2378-TCDD has not been detected
4-38 Gelatin, yes. ~~TCDF~~ H_xCDDs have been found in fish.
Hay: Cell transformation
~~Stall~~
* Barnes: Schaub/Tsang net
Decomp values diff
Stalling: H_x → O predominate in sediment. Fish show TCDD most. 20 striped bass estuary samples 10-20 ppt.
Peters: Strike 84 lb citation. 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 guidelined at 10ppt
MO has guidelined at 1ppt for fish in Spring River.
Redman (Reg 5): Reg 5 reports are available.
Need to identify species. Table 1 p3C-13.
Completing BCF studies at 28-day studies.
Fitzsimmons: Specify congener + whole/edible portion.
Commercial PCP: 123678 ~½ of total H_xCDD.
123789 contributes less biologically activity. The others are less active.
Tremain: Rinse prime in lab → low CDD/CDF (~ND).
+ HCl → high CDD/CDF.

Env. Pet

Neumann: Summary

Matsumura: Plant pick up. Isensee 1971 → [illegible] beans. Photodegradation does take place on soil surface. $T_{1/2}$ ⇒ 1st order. — data shows that it is not. Microbial in sand ~~[illegible]~~ does not occur (probably). No documentated case of reduction of CDDs 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)

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

Tiernan: Quality vertical movement. Dump sites can.

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

McConnell: Include disposal

Pocchiari: all.

Thibaudeaux: EX PAHS & volatilization from water. Need to quantify.

Vapor within from soil surfaces. Pesticides & similar types ~~etc~~ volatilize.

Garrahan: 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 1983) in Coulston book
Worms BCF = 13x. Moles → ND(?)
Rappe: Sediments are not uniform. Used
Hudson River sediment → 80% recovery on TCDD, HxCDD.
Contain TCDD.
Albert: Need to state whether TCDD is respirable.
Thorman: Yes, published particulate distribution data
Nash: By analogy, very unlikely ~~to~~ for TCDD
to bioaccumulate to plant. Dumpsite volatilization possible
15 year old Nash paper. ⇒ volatilization
Sittingerbl – 5-3 ⇒ photodegradation → lower (?)
Firestone – unpublished data ⇒ 2378 sites are
more susceptible
Wee Hee – 5-3 is wrong. λ_{max} 2378 = 300
~~Tetra~~ 4 → 1 chlorination. (?)
Data very dependent on analytical approach.
McNally – 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/"chloracnogenic" effect.

Tuesday PM
Purpose of HAD
Peters: Is there a problem — quantities, significance?
Purpose of AWQC
Gautomski: Required by CWA.

Ecotoxicity Note: AWQC is responsibility of Duluth. But do include comments on BCF
Brown: Summary.
NOEL not available on fish
Stalling: OK thru 1982. Add Tucker data.
Kimbrough: Add horseraceum data

Pharmacokinetics Mukerjee: Summary.
Olson: Absorption important vehicle. 74% in hamster in olive oil. Sex diff distribution is only slight. Urine + biliary relate to metabolism. No native material in feces. Liver + fat only had native, not metabolism. Bile → glucuronide. Urine → sulfates. Metabolism ⇒ detox. Important in persistence. Fecal in most 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.
Hay: III quoted metabolic pathway by Buser + Rappe.
Induction + toxicity are not necessarily causally related.
Gasiewicz: 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. Extract of liver can block metabolism of prototype enzyme. TCDD is not

Pocchiari: Soil bound TCDD ~~[illegible]~~ was less. ~~[illegible]~~
Being published
p. 7-7 Rewrite
p. 7-13

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

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

Lutkikar: p. 7-10. Really hydroxy compds that go to mutagens.

Mukerjee: Elaborate on DNA binding

Lutkikar: Pollard binding is only sec background ∴ may not be real. Long way from understanding carcinogenic action. Other halogenated HC which do not bind.

Gravatini: 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 CDD, PCB, etc are qualitatively / not quant equivalent when appropriately substituted — binding to receptor as model. Hydroxyl group in lateral position → reduced binding ∴ agree with Porter 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 1/2

McNulty data on persist effect.

Kin: 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 Bunnes question. (p.6)
Never shown the TCDD skin.
Kimbrough: Sebum in chloracne folks → ND.
Silbergeld: include info receptor conc in tissues/species
Stalling: Non-2378 congeners discussion is needed to support our focus on 2378.
Firestone: I will supply some data
Rappe: Yushe data. I will provide.
Albert: Say what we don't know: mechanism, active metabolites.
Kim: CDF-Yushe may be more applicable for dibenzofuran.
Lee Hee: Elimination of CDDs ≠ CDFs.
Rappe: 2378 PCDF congeners are equiv in ~~[illegible]~~ different series.
Kim: Many differences

Break
Silbergeld
Scientific interaction

☆ Sulzbacy citation for risk at MWC is not CEQ

Toxicity (Animal: Acute + Subchronic)
Mukerjee: Summary
Sate: Several additions.
p. 8-64 et al ~~follows~~ overlap this section.
Should order be changed.
☆ not peer reviewed Hay: p. 8-35 Not May; Wardi ↓ Ig D, Ig M ⇒ reduce immune competence
Graveltine: Strain dependent thymic atrophy & ~~[illegible]~~ in docility. ~~Rear~~
Reorder immunological ~~[illegible]~~ section. Cells, systems etc.
8-36 Reggiani: did not consider all parameters — not humoral, the one more likely to show effect.
McNutty: Cite species of monkey
Non-human primate indicates (not conclusive) LD_{50} perhaps as low as 1 μg/kg.
Mention gastric lesion.
McConnell
Nabut Kociba: ~~E-1~~ E-2 LD_{50} as high as 5000 μg/kg
E-34
☆ Barnes: SAP + Rhabit references.
Pocchiari: Table 8-3 add references
Kimbrough: What do we mean about "acute"
8-22 Recent work on lipid peroxidation
-23 No ref on hamster work.
-43 Species variability
Olson - Species variability table
Seefeld + Peterson (Tucker et al) ⇒ ↓ food intake → wt loss.
Silberfeld: How acct for parental doses
Olson: Massive iv doses → liq. storage (possibly)
Matsumura:
Barnes/Hill ⇒ Coulston: Table of species, doses, organs

Guerathiri: Guinea pig = non-human primate
Lotlikar: Knutson/Pollard paper have useful table.
Kocitra: Tables in 1982 review
Schwartzman:
Hay: 1982 Cholesterol in Coal tar workers
Kocitra: Cholesterol study in rat
Gressner: Unchlorinated dioxin at 10,000 ppm Non toxic
2,7 DCDD Non toxic
2378 TCDD
67% 70% H_2CDD Dermal .01 mg → liver damage
oral .6 mg/kg LD_{50}

Tissue (with the paper on Tyr?

Tox (Animal: Chronic)

McConnell:
Weight retardation. ~~(Not entirely related to effec~~
Maybe related to reduced intake. (Tucker)
Liver shows morphological changes.
Continuation of subchronic effects.
Include fact that effects are similar to CDFs, PCBs, naphthalenes.

Garatinni:
Prophyria effect should be included.
Immunological response is strain dependent.
Critical review of epidemiology
Immune suppression with TCDD + CDF shows antagonism.

McConnell / Garatinni: no exposures to pure TCDD to humans.

Stara: Dose agreement NOEL?

Kociba: ~~[illegible]~~ Only highest dose showed tox hepatitis.

Garatinni: "NOEL" needs time of dosing since it is cumulative dose. Lag time for 45 days → porphyrin excretion.

Kociba: We did not see porphyrin excretion.

Garatinni: Species dependent. Examine specific porphyrins.

Mukerjee: How sensitive are humans of subhum primates?

Coulston: Species dependent.

Pocchiarri: Can we compare ~~the~~ pure TCDD with env. TCDD. ~~[illegible]~~ Cohort of 2 mo. ft is not enough to see much effects.

Alberts: Mention fat data in humans.

Hardell: Latency 10-20 yrs.

McConnell: Comparative of dose, of lesions.
Chloracne of monkey = chloracne of human. Old world monkeys are good model for clinic pathology. Not necessarily in dose. Also dose + media dependency

Initiative

Kimmel: Only long dermal study.
Silberzweig: Mechanism-of-action
Handell: No chloracne in my cohort. Relative risk
Hay: Holmesburg prison. Applied to 1 m².
Gavatinni: We have no data
8-5: Not likely due to TCDD. Due to acid/alkali
8-6: Beal ~~Platt~~ Lancet 1977 I 748.
Pochiari: Focus on chloracne. Tabulate. Primary source will expand 8-5 Tagoni
Barnes: AMA document as source of chloracne reference?
Smoldermann: Nurse-doctor at Nitro got chloracne. Perhaps suggests a sensitization reaction.

Finger (Reg 4): May short term test for human response?
Kimmel: No. Chromosome test.
Clark (Reg 5): Need to say that Sarna ≠ 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 base study. If not possible, say so.

Kimbrough: What about lab capability? Need to current document

Stalling: Include statement of needs. Ruppel/Bauer with Sum in Anal Chem shows that 2378 congeners can separable

Hutzinger: Brian says

McGinnity: Vapor adsorbed or particulate, etc when air sampling?

The Chemist Mukerjee: Need lab capability standards.

Hanney Barnes: Ret on Neal, PO scattered

Poochikian: 8-62 8-63 ≡ C-48 C-49 5-34

Kimbrough: More studies. Blaboy before Holland.

8-62 Senate fact statement 1st paragraph

Bogan + Stevens articles 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.

Kerr: Need critical review

Cantilow: Answer to Schneidermann

Legator:

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

Gavatin: 8-67 Problems with Stevens. Conjecture 8-67 Binding to DNA discussed yesterday. Intercalation may be a problem.

Vitamin A depletion comes at >LD50. ∴ not important
8-66 "Detox vs metab" may be too strong.
Edéa: Seveso children with chloracne / fenzyme study
8-75 no "dose-related" data
Beettee: Do tables with doses + effects
Olson: No sig difference with [receptor] in diff organs + species. Correlation is good only within strains of mice.
Silberzeld: Confusion on lineck section. "Proximate"
8-67 Nisbet 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 other than Ah are ~~effective~~ affected.
Backstrom: Nisbet binding to receptor
Peters: 8-63 Mix reports + editorial
Kimbrough:
Kaeiba: 5-34 (OSW) no chronic data 8-75
Beettee: Formats. Reports; late critique.
Stavers ~~[illegible]~~ too simplistic.
Mukerjee: List all references searched and not used.
Hay: Monsanto New S. Wales accident. Internal report.
Kim: Take only peer-reviewed in WHO
Coulston: WHO will take government, industry, etc. documents, if given.
Barry (Mike): Use only peer-reviewed stuff.
Coulston: Don't cut off info from industry
Peters: Put in special section
Barry: SAB will do peer review effectively
Lee: EPA needs policy; accept Mix reports, telephone calls?
Gresemer: Unchlorinated CDD → toxic hepatitis. 5000 ppm
Degenerative, inflamatory liver.

Matsumura: 3MC binds but ~~to~~ tox -: receptor
not whole theory. [receptor]$_{Hump}$ ≠ [ ]$_{sp}$ ∴ [illegible]
- Induction platelets, blood count, [illegible].

Recent ~~the~~ Matz review
McNulty: Don't talk about most sensitive species.
Carlstom: Regulators need guidance for MDI. I say
chloracne
Lotlikar: Should look at induction in skin.
Silbergeld: MC data + Kimbrough/Pollard karatinolic
Safe: Induction ≠ toxicity. Correlation with exposure.
Gavatinni: Hard to classify as ~~[illegible]~~ physiological
or pathological. ex, PH → ~~[illegible]~~ time course
induction ~~and~~ of TCDD → long term
- These are not necessarily the same

Terat. + Repro

Courtney:

Definition: embryo ⇒ ~~embryo~~ of fetus) ends period
term

Terat ⇒ irreversible. (Less distinct distinction)

Repro problem ⇒ reversible. (?!)
not tested

Hamster is sensitive; g.p. not studied.

~~Gp~~ Rabbit " to TCDD, not T

Rats similar

Human spon. ab rate = 45%. Monkeys may about as well.

3-generation study - Nisbet/Paxton

Pratt thinks TCDD bound to receptor in palate ⇒
cleft palate

Male mouse study - Question of using polytrim
animal for these studies. Crossovers could take
place.

Kimbrough: Put in actual dose of TCDD in T studies.
Susceptibility of strains. Discuss immune system
effects. Include criticism of Olson.

Murray: Nesbit/Paxton technique may not be
appropriate. Individual vs. litter mates, family
lines, etc. Need to peer review Nabit/Paxton

Kociba: Two reviews ~~of~~ Murray: ① SAP ② Nesbit/Paxton

Barnes ★ C-67 and 9-17 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: Reference to ~~the~~ estimating

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 Chang 1981
Muscarella on terat (mylky ⇒ terat, terat.

Gavatinni: Interaction of T + TCDD no clear Sys so
9-11 Teratogenic effects on inducibility by strain
9-31 More current info than Fara (1977)
Cunliffe: 9-25
Int. Assoc of Industrial Safety evaluation of Alsea
Monkey (T, .05 ppm). Effects during gestation.
Wilson - 75 pregnant monkeys.
Pochiavi: 9-31 Segi has completed Fara study.
Summary:
Divided into 1km², chloracne, 1st total 1st, 2nd, 3rd, skin lesions, TCDD in soil
High rate of abortion in July 1976. One malformation.
Malignancy & 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 risk
Gee Hee: Other dioxins.
Paper showing higher animals different effects from rodents
Lagator: Need relevance to other chemicals.
Makojne: Get REMB to make a statement.
Kocibe: 9-28 update on McNally
7-35 Not all studies; cf. Cowlin
C-112/113 cf Schantz study, Not discussed earlier.
Pochiavi: C-112 Is .001 NOEL, LOAEL
Hardell: Hexachlorophene nurses in hospitals.
Malformations. New study on neural tube defects.
Clustering around forests. Mothers hexachlorophene exposed;
Some fathers exposed to spray.
Sarnoff contributed (Lawrence/Hunt)
Silberfeld: Other effects
Clark: MI Dept Pub Health. Cleft palate 1971-74.
Townsend study looked at all dioxins.
Hoult said before Congress a cleft palate in
Sub pop at Townsend.

Kaeiba: NOELs on most sensitive species in FDA Asa Tannel sn.
Garattini: Need summary of effects in T.
Lee: Need better summary
Miller: Only 2 teratogens were found first in humans (Thalidomide & Methylmercury).
Neonatal tube defects in Sweden clustering. CDC couldn't find similar situation in Atlanta, Jacksonville, and Ireland.
Graham: Immune effects in rat
Geeke: Multiple exposure problems.

Lunch: Pocchiari fat benign tumors w chloracne
Beck: Metzemann — uptake by grass, photolysis synthesized by chlorophyll, "root uptake"

Mutagenicity
Rosenthal: Results conflicting. Limited TCDD solubility in DMSO is a problem which we should look out for.
Additional studies: + weakly +
Legator: Only few studies, especially in vivo. Rearrange: adducts, in vitro, in vivo. Note key tests done; common ones not done. Table. Additional studies. UDS
Decreased satellites of D group chromosome.
Ecklekar: One dose → ↓survival. May say limited solubility is not the problem.

~~Also~~:
Garatinni: Echo of binding. Put in one place.
Hay: Cell transformation. + [TCDD, DD] → -J. Late passage
Kouba: E-89 say limited recessive test needed. NTP has done it —.
McCormell: TCDD went through the NTP ~~panel~~ battery prior to bioassay
Kaciba: 5-4 How many tests do we need?
Eckter: Clastogenic effect in bone marrow. Not clearly +. Some mutag activity, but not consistent with the highly potent carcinogenicity. May be due to high tox to bacterial systems.
Pocchiari — 10:12

Cancer

Number of IARC

Hiremath: IARC criteria ⇒ sufficient for both TCDD & H_2CDD

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

Hardell: Colon cancer recall bias approach. No relation of colon cancer & exposure to phenoxy.
Studied both Hodgkins & Non H. Note relation to decreased immune response.
H. dioxin in Eng Wood S. for phenoxy 6.5 chlorophenol 13% in quantitative cr 2% exported. ct rats.
Nasal/nasal pharyngeal - Am J. of Ind Med 77 case-control.
Wood dust → cancer. Chlorophenols in sawmill dust 2X increase. No signif xc rt exposed to phenoxy acids.
Nachlaraana people.
~~Summarize. Re and early lymphoma~~

Greiseman: Data are inadequate on 2,4,5-T (one OK(?): lymphoma, included).
Note: Different sites in Kociba vs NTP. Two rat strains; Two routes of exposure.

Kociba: Some fine particulate matter embedded in lung & tracheobronchial area. Squire saw also. Some reviewers saw these as metaplasias, not neoplasias. ~~Always~~ Always saw embedded material, but no tumors. (Hematoxylin & eosin)
Holland study show embedded hair in lung → tumors. & Local chloracne

Mukerjee: Same in plastic shavings.
Kociba: Same thing seen in controls → no carcinomas.
Greiseman: NTP ⇒ female mice s.c.s. Skin painting ⇒ + in female, sugg activ in male.
Kociba: Carcinoma only on skin cutter alteration.
Greiseman: Lots of ulceration experiment ⇒ tumors.
Mukerjee: C-99 Hemangiosarcoma signif?
Greiseman: (Wh?) check.

Discussion on site of application
Coulston: WHO wouldn't accept
Grossman: Sub-Q data correlate with IARC: Tomatis.
Unsubst. 88 in 10,000 ≥ 700 in 10,000, etc. Huff (?)
Question of spikes of exposure.
Coulston: Combined exposures of CODs plus.
Kouba: Milham study. Smith study. PMR
Hardell: Counter
Eriksson: Combined expos → dioxin results
Mukherjee: Nature 1982. Conclusion evidence is strong

Breslin
Albert: Could be due to phenoxys. Potency would be highest. Stratification. Eriksson data remarkable wrong → TCDD ↑

Backstrom: US cohort had FCP exposure, not phenoxy
in TCDD in common
Inconsistency in 2,4-D contamination between doc.

Kouba: IARC sts → 2B (inadequate)
Supplement 4 (1982)
Albert: We must do independent.
Hardell: Gly soma not metastatic
Randt Hand limited cohort

[Need comment on Randt Hand]

Dr B
MM cell
Contin

Miller: Classification of sts? Can they be induced by one agent? Don't think so. Most chemicals → one type; e.g. fibrohistiocytoma. But can't link them together easily.
Soft tissue: anything between bone + skin at a limb, excepting lymph nodes
Greenemer: ~~agree~~ pass.
McConnell: NTP wouldn't allow me to group them. Burden of proof is on those who suggest common
Kaczka: should not group
Lewis: NIOSH + NFIP are doing a review.
Hardell: Some chemicals (actinomycin) can do more than one.
International group (1977) ~~[illegible]~~ working grouping.
Based bone on histo path. Possible common stem cell.
Like smaller groups of tumors. Still → sig risk
McMintly: Some hard tissue tumors from same stem cell. Ever examined?
Hardell: No
Albert: Radiation → Many tumor types.
Silberzeldt: Broad range of the effect.
Lathlean: To
Albert: No one suggests walking away.
Coulston: Dilute when out of airplane.
Lathlean: Table 1 11-3. Scratch van Miller
Clark: May 83. MT sts
Case control study to be done.
Kaczka: 11-5
Albert: Bottom line? p. 11-106
Rappe: HxCDD in chlorophenols should be 2B.
Coulston:

Greiemer: Predict: TCDD would be 3 — TCDD alone - carcinogenic to human
~~[illegible]~~ TCDD + phenoxy " 2B — TCDD in cont - clinical evidence
Vote: Don't use IARC scheme.

7/29

Qualitative Summary

2378 prob. cause in hum or bum of cancer

Expt of workers contam eg WYS-5 WYS-TUB

is consistent

Rodent cancer → sta & stan

Human 2378 is in consistent . impossible

1. H_x in cont with H_m prob in hum or bum

Limited that suggest exp to mix

Syn. Effects

Mukerjee:

Dickins: Pull in summaries from other chapters

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

Say it is an inducer: predict interactions.

Therapeutic with Cisplatin.

Paper showing antagonism of TCDF with TCDD in immune response

Silbergeld: Also talk about competition for receptor.

Kim. TCDD less effect when Fe deficient.

~~Lottikar~~

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

Legator: Lack of binding ⇒ not initiator.

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

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

Multiple Models? 1-90
Grouping of tumors?
cf. Canadian Analysis? FDA: Cypress

Quant.

Bayard: Summary
Schneiderman: CAG has done good work.
Inappropriate model when we have "different type" substance. Reasonable to use Multistage.
Why not Day-Brown and others? ~~If FDA was~~
Would children expect to have fewer cancers (e.g. contraceptives)? Would we expect sudden increase later in life (e.g. late stage promoter)? Need to rationalize model. No use of info on pharmacokinetics, etc.
Additional exposures needed?
How relate to actual vs. perceived doses? Tissue dose.
Rigid use of model.
Formaldehyde is sharply curvilinear. Yet we force q_1. Virtually $q_3 > 0$.
Albert's correction needed for maximum limit.
Stara: Schn. do you agree with Crd for inhalation, etc
Schn: 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 [illegible]
Other data show differences in different experiments.
Add bioassays
Garatinni: pp A-102
Low dose death wk 17
Low dose is so low we can't [illegible] mutagenesis.
Bacteria could metabolize, etc.
Below measurable levels
Too clear to make practical calculation.

Albert: Ballpark. <. Reservations are justifiable, however... Limited practical use.
Stara:
Bauer: Multiple models — Data convincing
Grouping of tumors?
Sofo: PBBs, etc are also unknown mechanistically.
McConnell: Potency table. Not good correlation with human experience. Need discussion, disclaimer.
Buchtrom: MS may not be the most conservative
Pocchiarri: Yes, with Kociba. MS is not " "
Kimbo: CDC sees it as a promoter + may be weak initiator.
Grouping tumors: Hoel doesn't agree.
Agree with Gavatirini 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. Easy 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.
Greesemer: Would have appreciated a more structured discussion.
Would have looked at causes of death, survival curves, competing risks, etc.
Early death seen in other studies also. DDDD early death. DD female 35% wk 12-20. female mouse
Quotient all the denominators.
Adjusted numerator would be smaller
Are these rare tumors? ⇒ Initiator. Except for female lung, they are common.
Silberzeld: Worried about use of Table 28.
Try pooling analysis
Albert: Mestenol + DDT was done this way for promoter.
Consensus: We should do it here

Gavatin: Exposure is important.
Greiseman: Don't use data from different kinds of experiments (route of exposure, species, etc)
Albert: Wide range ⇒ differences would be swamped out
Greiseman: Approach ~~[illegible]~~ negative data.
Scheuplein: Exposure is important.
Pitot et al. IARC } cancer death / cause of death
John Gart
Qualtiere: 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.

~~[illegible]~~
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 ~~organs~~ table.
Hartung: Carefully state limitation of table.
Kocibe: Ats thoroughly
Pochiari: NOEL. BCF ≅ 3000. [H_2O] << DL
Stara: Schneiderman will look at stats (Nesbit/Pontius)
Kimbo: Apple level st. conc not ADI.
Silbert: ADI is counter to carcinogen.
Kocibe: Cradle paper (1981) should be included.
Schneidermann: Cannot
Kocibe: Fish is the problem.
Bunnes: FDA did cancer assessment. Congressional statement.
McNally: Criterion too low.
Fish is the problem.
Stalling: Calculation to show BCF dependence.
BCF ≅ 100,000. Research need.
Hartung: Low BCF is almost an artifact. SPB going to direction of fish in the field.

Press Conference

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

Lindsay: Vulcan Chemical
Reevaluation of H_2CO_3 slide - Squire re-read.
4/27/88 "Equivocal evidence, weak carcinogen
Gilbert "Wood Preservation Workers" sp.
"No xs morbid/mortal attributable to wood

prematurity 88 cohort.

Clemmer - 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 - Cancer chapter

Murray - review with statistician and reproductive biologist.

Pocharski - No correlation between chloracne in children & enzyme problems.

Coulston - Children in MO over have chloracne

Clemmer - Nothing evident.

Stalling - Canadian fat ≈ 10 ppt.

~~Human Health Effects~~ Research

Rappaport: The penta is found in assembled samples - not in commercial chemicals

Pocharski: Rescanal

BCF

Were cancer animals

Fate in field

Isomer tax

Long term on agent:

Coulston: Monkey comparative toxicity

Reproductive studies

Albert: Inhalation experiment
Dose-response of promoter
Harting: Bioavailability
McMullin: Analytical capability.
Stalling: Furan. Sts and PCBs. Carcinogenicity.
Rappe: 2378 T < 1% of total TCDD in fly ash
12378 T < 1
In fly ash, the toxic furans predominate.
Nonexcess incin → larger conc of high tox.
Queltee: 2378 TCDF in lieu of Yusho Taiwan

Human Health Effects
Hay: Summary
Mukerjee: Has anyone died of exposure to 2378-TCDD
Albert: Yes
Burnes: No. Can't show cancer effect
Pochiari: No one died in Seveso. Abortions increased but not spont abortion.

[Comment] Statement that cancer effect unknown

Write to Stan re 2378 HxCDD

Barnes

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	TCDD(ppb) in the liver $\bar{x} \pm \sigma$	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