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

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525 Elm Street, Cincinnati, Ohio
(July 27, 28, 29)

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Peer Review
Public Comment
S/A/B Review
HAD + HEEP — Syracuse Res. Inst
AWQC — ECAO Cin
Mukherjee knows all the literature.
OHEA has prepared certain parts.
Post meeting memorandum and/or copy of the draft. By August 5.

Rappaport two general methods
a. The Dow method of getting isomers in individual bottle
   b. Stalling/Rappaport/Busen method having all isomers in one bottle. Have method for
      analyzing all congeners at CDDs + COEs. Possess all isomers at COEs + COEs. Have
      data on penta-CDD in fish.
CDDs are chemically reactive. There are not
chemically reactive under environmental
conditions.

First time POA is developing multi-step HPLC
which will isolate homologous groups. EPA
said to be developing standard method.
Tiarnani: Unlikeh, that a single method
will be useful for all samples/matrices.
Great commonality between methods. I
also have a method for getting all COEs congener
in one bottle.
Pocihari: 3 volumes are not consistent. Decide
on termination date of the references.
Univ. CN - Why were these compounds chosen?

Kimbrough: Goals or limits of detection?

Rappaport: Reference primary sources.

Stalling: We need to include reference to CDF.

Garaffini: p.3-27. Bisacodyl 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 H2O. E.g.,
don't look for H2O when ppt in fish. Refer to EPA/VF/KC note.

Barrow will provide summary.

Rappaport: Guia us accuracy info as well.

Coulston: Need to report whether data has been generated by reliable methods.

Rappaport: State whether or not there is internal standard used and/or % recovery.

Horner: Recent AOAC Vaccine report by Grammett on "criteria" for each method. Good QA/QC in MO, into an interlab, etc.

Kimbrough: Methods for estuarine have not been standardized.

Break

Rappaport: PCE good preservation in Sweden are not working 100%. Problem with long spore.

Boneste: Workers went up back
Newman: Summary

- There are: p<sub>4</sub> 84/6/yr is probably low.
- Threshold: p<sub>4</sub> 4+ analysis at USU.

Safety: Best way to make CO<sub>2</sub> condense not known.

Rappe: Synthesis by combustion, P4+2. Reactors
- Ca+2+SiO<sub>3</sub>->CaSiO<sub>3</sub> + CO<sub>2</sub>/<CO<sub>2</sub>.
- Kucek (1981) found: 2338
- HeP E.p.m. End products are not CO.<sub>2</sub>, the
  only intermediate are:

Nocik: P4+3 Formula

Kociba: Summary, values quoted in the documents.

Bornese, Kenaga, etc. = 5-6,000 ppm.

Rappe: Summary page summary on BCF.

Jellison: CDF from combustion.

Lab values probably underestimate BCF.

Brums: Lab values were not steady state.

Rappe: PCB had TCD <1 ppm; 2338-7200 has not
  been detected

No. Carolina, yes; Hal, CO<sub>2</sub> has been
  found in fish.

Hay: Cell transform formula

Barnes' decay rate calc.

Stellins: H<sub>4</sub> 0 precedent in sediment. Fish shew TCD.

- Most: 20 striped bass estuary sample 1620 ppm.

Peters: Stink 94 lb cattle, too crude.
Kimbrough: FDA uses different method
Makowski: ER notice says we will use it.
Barret: G.5 is freshwater. At mainic
Silverstein: Consider brominated.
Maulathy: Table 4-5 should have MO data.
Makowski: not published.
Barrett: CUDG.5 has not reviewed it yet. Coming.
Stalling: NV has guideline at 100ppm.
MO has guideline for guppies on Spring River.
Redman (RegS): Reg 5 reports are available.
Need to identify species. Table 1 page 13.
Completing BCF studies at 28-day studies.
Estrellita: Specify consumer + whole/edible part/instance.
Commercial BP: 32-67% of total Hg CDD.
Hg32+ seems less biologically active. Others seem less active.
Trenam: Place fish in lab -> low CDD/CDF (-NO3)
+ HCl -> high CDD/CDF.
Neumann: Summary
Mukemura: Plant uptake. I sense 1971 -

Young beans, photodegradation does take
place on soil surface. Ty = 1/2 order.

Data shows that it is not. Microbial in
sand does not occur (probably). No
documented case at reduction of core by
microbiologicals. Surface disappearance =
vertical movement (possibly lateral movement
or volatilization). Bottom feeding fish can not
stick to get core. Core selection prior to
237C documented.

Muir: No proposal on uptake by plants (Salzburg)

I. Tcherniai: No good evidence for 237C degradation.

We have done photodegradation under ideal conditions,
But not on fish.

Tcherniai: Quality vertical movement. Compiles can.

Stullby: Examine biodegradation. Lab & field don't
 correlate well.

McConnell: Include disposal

Pechora: will.

Thibodeaux: EXAMS + volatilization from water.

Need to quantify

Vaporization from soil surfaces. Pavlovskis et

similar types of volatilization.


second, also. Third, more realistic.

Table 5:1. Some initial core and > solubility

Bicarb on worms ≈ 30

So 237C = f(time)

Kinsbrough: MO we don't know much about

fast volatilization possible.
Worms BCF = 1.8. Male -> NO(?)

Papay: Sediments are not an issue. Used.
Anders River sediments -> 80% recovery, TCD, 800.
Cadmium TCD.

Albrecht: Need to state whether TCD is respirable.
Papay: Yes, published data on distribution in data.

Whitlock: By analogy, very unlikely lead for TCD to bromelcates to plant. Dumpsite volatile, issue possible. 15 year old paper = volatile.

Solberg: 5-3, 5-6 photodynamic -> low (?)
Friedman: unpublished data = 2.3 x 2.4, are more conservative.

Whit: Hee = 5-3 is wrong. 1/day, 2250 = 360

Lunch

Kazbok: Recent dissection from Sweden relating TCD toxicity to environmental studies.

Note that animal data = epi Kobe target.
So soft tissue outcome vs. humans are strange.
The hard palate, lungs, etc. seem = local inhalation/particulate/"chloracogenic" effect.
Tuesday AM
Purpose of EPAD
Defects in More of problem - quantitites, significance
Purpose of AWOC
Groundwater Requird by EPA.

Note: AWOC is responsibility of Duluth. But do include comments in BCF

Brain's summary:
NOG not available yet
Kimberly: Add hercules data

Inverness: Summary:
Olson: Absorption important whichever 74% in lungs.
Note: diffusion distributes in only slight.
Urine = Wilkinson role to metabolism. No active
metabolism in urine. Liver to feces feels rotten, no
Metabolism = defect. Important in persistence.
Fecal in all species. Somewhat more via urine
compared. P-450 important induced by TCA

Barrows:
Frechius: McConnell a freshwater data on other cats
in cattle.

McConnell: Need more into an inhalation.
Hays; III quoted earth metabolit pathway by Buser &
Kapra.

Edwards: Toxicity are not necessarily caused by
related.

Gorham: More data for Table 7-1-2. No absorption
study when administered on food.
Extrahepatic circulation is likely; if administer
charcoal days after TCDP.
Microdistribution: initially in nucleus fraction, unlike liver (cannot show uptake) it is in microsomal fraction. Metabolites are "toxic" in sense of lethality. Extract of liver can block metabolism of protein enzyme.

Read the following sentence:

Problems: Said bound TCDD was less being published. P.2.

Keilbaugh: The of McNulty.
McNulty: The 1yr.
Lohle: p.7. Really hydroxy enzyme that go to metabolite.
Makrigiorgis: Elaborate on DNA binding.
Lohle: Potential binding in only one bound. in may not be. Any way from understanding carcinogenic action. Other halogenated HC which do not have bind.
Garrick: Neither does saccharin. But methods may not be sensitive enough to detect binding. 500 molecules per hepatocyte. Could not detect binding of even 1%.

Sato: Substitute COC, PCB, etc are qualitatively not good equivalent when appropriately substituted—binding to receptor as model. Hydroxyl group in lateral position 
reduced binding; agree with Porger Weber. Doesn't depend on molecular diameter. 3 prop aesthetics of substituent.

Olson: Used 3,4,6-tr+1 in 103 positions. Would like better but NC. Weber data's OK, but they looked at final metabolite—maybe intermediate are problem. Persistence-15 order component for most species (not hamster), with 101.

Kim: I don't believe there's binding.
Hey: Are breast, DES, and are not mutagenic either.

Albert: Metabolite in alpha-phire. May bind with protein before it gets to nucleus. Target may not be unique - hormone. Maybe void cells from bile duct - not much cytoplasmic protein to "blot up." ACDD.

MCMB: Response to Barnes question: (pi.)

Never seen the TCD2 shrin.

Krits: Sudden chlorame fols = ND.

Silbergold: Include with receptor one in tissue pumps.

Stalling: Non-2338 consensus document is needed to support our claims 2338.

Fastbec: I'll supply some data.

Reagan: Tsche 1 date. I will provide.

Albert: Say what we don't know. Why mechanism actinic metabolism.

Klein: CPE-Yush after may be more applicable for defense forces.

Reagan: Elimination of CPEs = CPEs.

Reagan: 2325 thermo one quiz五六 different series.

Klein: Many differences.

Break

Silbergold

Scientific initiative
Toxicity (Animals: Acute & Subchronic)

Mechanisms: Summary

Acute: Several additions.
- Polley et al: Those overlap this section.
- Should order be changed?

Hay: p. 8-35, Not May: Ward & IgB & IgM = reduce immune competence

Granuloma: Stem dependent atrophy, area constrictive lesions, etc.
- Record immunological response to section. Cells, systems etc.

E-32 Roggioni: did not consider all parameters - not humoral. He was more likely to show effect.
- McNutt: Cat: Species of making
- Non-human primate indicates (not constrictive) LD... perhaps as low as 1 mg/kg.
- Mention gastrointestinal lesion

Rat: Kociba: Ed. LD... as high as 5000 mg/kg

Bauer: SBR & habit retraining
- Podlachek: Table 8-3, add reference
- Winkler: What does mean about "acute" E-32: Recent work in lipid peroxidation
- E-33: No ref in hamster work.
- E-32: Species variability

Olsen: Species variability table
- Seefeld & Peterson (Tucker et al) = food intake
- Cell loss.

Silberzied: How act for parental dose
- Olsen: Mass in dose = lig. storage (possibly)

Maturumus:
- Brenton: Table of species, doses, organs
Guerrini: Cynocephalus = non-human primate
Lotlikar: Knutson/Powell paper have useful tables.
Kociba: Tables in 1982 review.
Schneiderman:
Hepatitis C: Cholesterol in carcinoembryonic.
Kociba: The cholesterol study in rat.

27 DEC 85

2005 10-05-89

Buni BUN 0.17 0.10-0.30 normal
Calc 10 mg/dl
10 mg/dl normal
The Chronic:
McConnell:
- Weight reduction. Not entirely predictable.
- May be related to reduced intake. (Tidball)
- Liver shows morphological change.
- Continuation of sub-chronic effects.
- Includes fact that effects are similar to CD failure, multiple nephrotoxicants.
Garfimnni:
- Prophyrins effect should be included.
- Immunological response is strain dependent.
- Critical review of epidemiology.
- Disease suppression with TCID + CDL shows antagonism.

McConnell/Garfimnni:
- No exposure to pure TCDD to humans.
Storo: Do we agree NOEL?
- Kociuba: 8.5 vs 8.78 mg/kg.
- Highest dose showed no sign of hepatic fibrosis.
Garfimnni: "NOEL" needs time of dying since it is cumulative dose. Inhibitor for 4-6 hrs.
- Porphyrin excretion.
Kociuba: We did not see porphyrin excretion.
Garfimnni: Species dependent. Examine specific porphyrin.
Mukherjei: How sensitive are humans of such humans primates?
Kociuba: Species dependent.
Pochinov: Can we compare pure TCDD with CN, TCDD? Ester Cohen of Zin. It is not enough to see such effects.

Alberto Mention fat data in humans.
Handchild: Eternity 10-20 yrs.
McConnell: Comparative to desire of lesions.
- Eterance. Also close to media dependency.
Karime: Only one delayed study.
Silbergeld: Mechanism of action.
Henry: No changes in my cohort. Melatonin at
Rey: Holmenburg prison. Applied 1-1.3
Barnes: We have no data.
Claire: Not likely due to temp. Due to acid/alkal:
Ross, Real Abnormal (1977-1983).
Pochiars: Focus on choline. Takeda's Primary
source: Willmound 8-7-9 Tegern
Barnes: PMT document as source of choline
reference.
Szaszarmen: Neurondread. Neutra got choline. Pedige
suggests sensitization reaction.

Finger (Reg 4): May start forum test for human response.
Kim: No Chromosome test.
Clark (Reg 5): Need to say that Seros ≠ no effect.
Nowell
Stear : Not enough info for good risk assessment on any chemical. But we can do a reasonable job, need to include uncertainity. 

Need NOEL study. Need cancer bioassay study. It is not possible, says R. 


Stelling: Include statement of needs. Rupp/Bruner will see us next. They show that only cancerous are separable.

Hutkin: Brad says.

McGuinity: Vapor cond for particular, etc., when air sampling?

Pachod: Need lab capability study.

V. Chris, Banker: Act on Neal, all sections.

Pociot: Can one do E.C. bio assay. 5-34.


Ugen & Stearns' articles are not up to snuff. Stearns should have criticial review.

Hay: More an outright crime. Martin & Walker. Larger study by Martin underway. May work was included 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.

Kiner: Need critical review.

Catalon: Review to Schneiderman.

Legater:

Keeshe: 873 NTP lowest dose was NOEL border on no report. (4 x21)

Gavarini: 8-67 problems with Stevens, conjecture 8-67. Binding to DNA discussed yesterday. Information may be the problem.
Uterine A dislocation common at > 40 yrs. not important

"Detect virions" may be too strong.

Edel: Seven children with chloracne, etc.

AlaM: 60% not data-related "deaths"

Recall: The tables with these effects alongside

Olson: No sig difference with [some] vs diff organs + species.

Correlation in go correct, other strains of mice.

Silverblatt: Confusion on brisk section, "proximal"

Flaherty: Confusion on brisk section, "proximal"

-67 c) direct tables. Human data (monochlor)

-64 susceptible = receptor non-susceptible = binding (order)

-74 liver may not be the most sensitive organ.

NF data on liver coming

Hayji: Los other than be were effective affected.

Bacchus: No other linking to receptor

Peters: E-25. Mix reports confounded

Kuwabara:

Kaciba: E-24(03/34) no chemical deaths or 5

Quarles: Formaldehyde section late critique.

Stare - simplistic.

Mike: List all research searched and not used.


Kim: Take the peer-reviewed stuff. WHO

Coulston: WHO will take government, industry, etc.

documents, if given.

Berry (Mike): We no peer-reviewed stuff.

Coulston: Don't cut off info from industry.

Peters: Put in special section

Berry: STS will do peer reviewed effect.

Lee: EPA needs policy; accept trip report, telephone calls.

Greene: Unchlorinated CDD = toxic hepatitis.

Degeneration, inflammatory liver.
Weighmum: SMC birds but tissue: regular
not skeletal type. Injury IC type
Denile platelets, blood count info.

Recent Metz revision

MC: Don't talk about most sensitive species.

Caudino: Regulation need guidance for ADI. I say chloroform

Lakner: Should look at induction in skin.

Silberzahn: TK data + Kummer/Weihl Heartmate


Geochemistry: Hard to classify as physiological or pathological. e.g., TK elains tissue injury

Other chemicals of TCA longer time.

These are not necessarily the same.
Terato Rogen

Contrary:

Definition: embryo = germinal period
time

Tert = irreversible. (Loss distinct distinction)
Repro problem = irreparable. (??)
Hypotilious sensitive; g.p. not studied
Rabbit: to T000, not T

References
Human sperm: rate = 35%. Monkeys may not do as well.
3-generation study - Nisbet/Paton
Blatt thinks T000 bound to replete w/palate -
ectopic palate
Male mouse study - Qaudri et al, post/necropsy
animal. For these studies, control group could be
place.

Kume: Put in actual dose of T000 in T studies.
Susceptibility of strains. Discuss immune system
effects. Include criticism of Gilman.

Murray: Nisbet/Paton technique may not be
appropriate. Individual vs. interm, factors,
individual. Need to peer review Nisbet/Paton

Kescha: Two reviews of Murray: @ Sher D/Paton
1-17 and 4-17 should have 5000
There are NBLS for tert

Schradermann: Who did study for Sher?

Courtney: Dams may have depleted by feeding. 50%.
Get to zero, then only uptake 70% by term of 50%.

Silberndol: Refer to McShane & others, but not.
Fuel: Have not found animal effects in humans.
Birth weight would be a good measure. Chem therapy
+ decreased birth weight.

Olson, 9-9 Chung 871.

Muscarella: in tert, male > female, female.
Garabito: Development T 77607 no clear. Sys 01 7-11 Terat effects - inconclusivity by strain.

9-31 More current data from Terra (1977)

Conclusion: 9-25

Inkling: need to retest. Evaluation of Mena Monday.. 2 weeks during gestation.

Wilson - 75 pregnant animals.

Debates: 9-27. Segi has completed Terra study.

Summary:


High rate of abortion in July 1976. One malformed.

Wilson - chlorenes.

Albert: Document is not too clear, capacitor? water analysis.

- Is it a hazard? If so, how big is it?

Need a bottom line.

No quantitative assessment of pyro.

Are Hexes: Other diines.

Piperonyl bromide higher animal deficient effects from psych.

Logan: Need reprints of other chemicals.

Makrui: Got REPs to grade a statement.

Koskin: 9-25 update on Mena lathy.

7-35 Not all studies, ch. Cabelin

C-112, 13, cf Schmida study, not discussed earlier.

Poeperovici: c-112, Is, 001 NO 6Z, LAGEL

Handels: Hexachlorphene on human capital.

Malformations. New study on neural tube defects.

Clarke, around farms. Hexachlorphene exposed.

Some further exposed to sprays.

Silbergeld: Other effects


Torrance study 994 looked at all drums.

Heick said before Goyno a cluster plate on sub pop of Torrance.
K rode: NOEL in most sensitive species in FDA format on.
Gordon: Need summary of effects in T.
Koo: Need better summary.
Miller: Shh, I thawed my own Gerbils in human
(Percutaneous + Inhalation).
Mitchell tube defected in Sweden chicken. CDC
cooled but found similar situation in Atlanta, Jacksonville,
and Idaho.
Graham: Immune effects in torso.
Cee Kee: Multiple exposure problem.
Mutagenicity

Relevant: Results conflicting. Limited TCDD solubility in blood is a problem which we should look out for.

Addendum: Studies are still weak;

Legators: Only few studies, especially in vivo. Relevance:

Add: Results in vivo. Note key facts: dose; common are not done. Table. Additional studies, UBS done.

Deceased satellites, 3 groups chromosome.

But before: One dose -> unsurvival. May say solubility is not the problem.

Anomalous: Echo of binding. Put in one place.

Key: Cell transformation. TCDD, 300, -> J. Late

Process.

Kuehn: Early selected resources that needed. NTP have done it.

McConnell: TCDD needs through the NTP good backing prior to breaking.

Kuehn: 5-9. How many tests do we need?

Legators: Chromatic effect in bone marrow. Not clearly +.

Some acute activity, but not consistent with the highly potent carcinogenicity. May be due to high tox.

Pashian: 10-12.
Cancer

Hirschaut: IRAC criteria = sufficient for
both TCDD & H-CCD

Biogics: Epi → IRAC 2.4 (when in contact with planar)

Handley: Colon cancer recall biopsy approach, No
relation of colon cancer + exposure to planar.

Studies: Both Hodgkin + Malta, Not related to increased
common response.

Kocher: Long term 5 for planar, 6.5 chlorophanid
13% in qualitative vs 2% expected, 2 rats.

H-CCD recall planar = 5 in 8 of 50 dose, with 72 cancer cases control.

Kocher data = cancer, Chlorophanid vs same size detergent
in mice. No sign of increased exposure.

Nachmanova people...

Greisemer: Data are inadquate on TCP (n=52):

Hepatoma, included.

Note: Different site in Kocber vs NTP! Two rat
strains, same side of exposure.

Kocber: Same particular route, embedded in lung or skin
rate. Slight variation. Same results same time
no metastases, not nephrosis. Always saw
embedded meatal, but no tumors.

Holland study show embedded hair in lung =
tumors. Elevated chlorella.

Mukarzer: Same in plastic shavings.

Kocber: Same thing seen as control = no carcinoma.

Greisemer: NTP = female mice s.t.s. Skin pox - human →

t = female, supratome males

Kocber: Carcinoma only on skin after alteration.

Greisemer: Lot of alteration experiment = tumors.

Mukarzer: C-99 Hemangiosarcoma sign if?

Greisemer: Will check.
Discussion on site of application

Caution: When wouldn't accept

Exposition: Sub & data correlated with EMPR: Toronto

Unsoap: 28 reps per group 27,500, 10,000, et al. Hutt (7)

Caution at spikes of exposure

Caution Combined exposure at CODE plus

From: Kneale: Mitrofan Study, Smith Study, PMR

Hardell: Cannot

Estimation: Combined apprs to assign results

Makushin: Abnormal voltage 1952. Conclude evidence is

strong

Break

March: Caution has due to physiology. Potency would
be higher. Stratification. Bricker data
reanalyses may = 

Backstrom: US cohort had CC exposure, not radiation

= 1.20 vs common

Exposure vs 2.4 - 0 contərmation between dos.

Kneale: 1/92 cc 5 vs 2B (inadequate)

Jurgenssen 4 (1972)

Albert: We must be independent.

Makushin: Gyspore not metastatic

Randlund limited cohort

[Need comment on Randlund]
Miller: Classification of site: Can key be evidenced by one agent? Don't think so. Most chemicals are synergistic, not additive. But can't link them together easily.

Soft tissue: Anyhow, between burs and skin of a limb, particularly lymph nodes.

Emerson: I pass.

McConnel: WIP wouldn't allow one to group Rem. Study at point is in line with suggested common.

Emerson: Shouldn't group.

Keith: NCI/NIOSH and WIP are doing a review.

Handel: Some chemicals (activator) can do more harm. Interactions groups (1972). Grouping:

Handel: There are a number of possible common themes, namely smaller groups of tumors. Still = 54 risk.

McMillan: You have some tissue tumors from same scheme.

Emerson: 

Handel: No.

Albert: Radiation more than tumor types.

Handel: Broad range of different.

Emerson: Yes.

Albert: Some suggest walking away.

Emerson: This. Not sure when out of airplane.

Lotlikin: Table 11-3. Scratch von Miller.


Case control study to be done.

Koch: 11-5

Albert: Bottom line? P. 11-106

Rappe: HECOD in chlorophyll should be cut.

Grossman: Predict T30D would be 5.

T30D has not been.

Vote: Don't use LARC scheme.
Qualitative Summary

[Text obscured]

Symptoms

[Text obscured]

[Text obscured]

[Text obscured]
Multiple Models? 11-20
Grouping of tumors? 11-20
Canadian Analysis? 11-20

Quart.

Bayard: Summary
Schneidermann: CHG has done good work
IPM was a model when we have different types of substance. Reasonable to use Multistage
Why not, any Brown and others? 11-20
Would children expect to have fewer cancers (e.g. contaminated)? Would we expect sudden increase later in life (e.g. late stage prostate)? Need to rationalize model. No one studies on carcinogenic, etc.
Additional points needed?
How past to actual vs. perceived dose? Tissue dose. Forget use of model.
Forward hybrid: is almost curvilinear. Yet we face q, actually q = 1
Robert's discussion needed for maximal input.
Starr: Some, do you agree with test for induction, etc.
Same as sensitivity analysis.
Albert: Inhalation = tumors from food. Not sufficient data.

Legator: No data to show that it is not complete carcinin.

Schwald: Try analysis of group assuming late stage carcinin
Pocchiari: B-7-9 = Weibull model used in Ithkenen's work
Other data show differences in different organisms. Add biobehavior.

Carcinin, p. 11-20
Low dose death 17
Low dose is no low dose carcinin, non-carcinin
Bacteria could metabolize, etc.
Below measurable levels
Too clear to make practical calculation.
Albert: Bullpen - C. Reservoir are justified. However, limited practical use.

Steadman:

Barrow: Multiple models - Data coming. Grouping of tumors?

Safer, Perl, etc. are also unknown mechanistically.

McConnell: Delaney Table. Not good correlation with human experience, need discussion, disclaimer.

Dedrickson: MS may not be the most conservative.

Pachmarhi: Yes, with Kociba. MS, i.e. not.

Kinsel: CDC sees it as a promoter, maybe coinitiator.

Grouping tumors: Need discussion.

Agreement with Pachmarhi on death in Kociba. Need time adjustment.

Albert: Agree with Kociba. Will not do it in future. Drift into these cannot mean death to lung tumor. Maybe to discriminate for lung.

My criteria to show it is only a promoter or initiator.

Kociba: Survival, FETT analyzed it differently.

Grosemai: Would have appreciated a more structured discussion.

Would have looked at same of death survival curve, competing risks, etc.

Early death seen in other studies also. DDE 90 days death, DD 35%, with 100.

Quoting all the denominators.

Adjusted human tumor would be smaller.

Are these rare tumors? E.g. cutaneous. Female lung, they are common.

Selson: Worries about use of Table 28.

Try promutagen analysis.

Albert: Masteral + DDE was done this way for promoters.

(assume: we should do it as...
Exposure is important.

Diseased Don't use data from different kinds of
agents (bacteria, viruses, etc.)

Albert: Wide range of differences would be swamped

Scheftmann: Exposure is important.

Dietzel et al.: ANOVA in each death,
John Grant

Albert: Table 28 shows error range.

Determines: Ordens et al.

Barnes: FDR/Correlal/CDC

Albert: Recommended method for using these figures.

Dietzel et al.: Line went up?

Albert: Program of his problems.

Albert: Read.

Colburn: Basically OK. Strike stomach cancer.
Hartung: Summary

Did not do ADI's for liver damage, etc.
Courtney: Use biomometric data.
Sillbergfeld: Not convinced that we have looked at
cell organe, Reproduction table.
Hartung: Carefully state limitation of table.
Kearns: As thoroughly
Puchner: ANEL. BCF = 3000. [Kb] < DL.
Stora: Schneidermann will look at study (Nov 85, 86).
Kanda: Nitrate level of corn not ADI.
Sillbergfeld: ADI is correct to cancerogem.
Kleba: Cordta paper (41) should be included.
Schneidermann: Unjust
Kearns: Fish is the problem.
Budin: FDA did cancer assessment. Congressional
statement
Mottly: NEC like in toxins.
Fish is the problem.
Stalling: Calculation to show BCF dependency.
BCF = 100,000. Reason needed.
Hartung: Note BCF is almost an artifact. S/B going
to do electron fish in the field.

Press Conference

Public Comment

Eggerson: Counted 10 or possible objections to
the evidence.

Lindsay: Vulcan Chemical
Revaluation of H2COD study - Squime re-read.
63/70 "Equivalent evidence, weak carcinogen"
Calbert: "Wood Preservation Workers" 83.
No xs morbid/mortal attributable to wood
preservation & cohort

Chloracne - 1970
Concerns:
1. Young background data unknown. So what?
2. Little info from 1970 in report
   - Put on accurate/poor
3. Young showed some data that children most susceptible to chloracne

Pres. Vietnam Vets - Cincinnati chapter

Murray - foreground statistics and reproductive biologist.

Pacheco - No correlation between chloracne in children & semen problem.
Coalton - Children in 1970 were home chloracne.
Clearwater - Nothing evident.
Stalling - Canadian fat = 10 ppt.

Research

Reggie: The pentachlorophenol in armament / not in commercial chains.

Pacheco: Research

BCF
Were cancer animals.
Fate in food.
Tissue tax
Long term no adverse.
Coalton: Making comparison / not.
Reproductive studies.
Albert: Dehydration expansion
Dose response of promoter
Herding: Bioavailability
Mortality: Analytical capability
Staining: Furans, Sts and PCBs, Concerning safety
Rapp: 2378 T < 1% of total Tab: T < 1%

In fish, the tris furans predominate.
Norwegian rain = larger case of high 1970
Weather: 2378 TCD in line of X-187 February

House Effect

Hagi: Summary
Makaroff: How many died of exposure to 2378-1970
Abbeq: Yes
Burns: Not a slow cancer effect
Rochman: No one died of Burns. No certain discussion that not enough toxicity.
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.
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., 1980a), 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 (~2g) 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.
Acknowledgements. The Authors wish to express their appreciation to the Regione Lombardia, Ufficio Speciale di Seveso, for providing financial support for this research project.

REFERENCES


TABLE I - Recoveries of analytical procedures

<table>
<thead>
<tr>
<th>Item</th>
<th>No. of data</th>
<th>Recovery %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multilayer column</td>
<td>67</td>
<td>96 ± 10</td>
</tr>
<tr>
<td>Alumina column</td>
<td>22</td>
<td>94 ± 5</td>
</tr>
<tr>
<td>TCDD-added soil</td>
<td>19</td>
<td>94 ± 14</td>
</tr>
<tr>
<td>TCDD-added soil (aged)</td>
<td>16</td>
<td>92 ± 8</td>
</tr>
<tr>
<td>TCDD(Cl_{37}^3), added to soil</td>
<td>28</td>
<td>94 ± 6</td>
</tr>
<tr>
<td>TCDD(Cl_{37}^3), added to liver</td>
<td>57</td>
<td>80 ± 10</td>
</tr>
</tbody>
</table>

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

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

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

<table>
<thead>
<tr>
<th>TCDD ng/die</th>
<th>Item</th>
<th>Group difference meaningfulness</th>
<th>Relative decrease, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>Lab-contaminated soil</td>
<td>Not significant</td>
<td></td>
</tr>
<tr>
<td>40</td>
<td>Lab-contaminated soil</td>
<td>p &lt; .01</td>
<td>5.0 - 53</td>
</tr>
<tr>
<td>80</td>
<td>Lab-contaminated soil</td>
<td>p &lt; .01</td>
<td>19 - 68</td>
</tr>
<tr>
<td>80</td>
<td>Seveso soil</td>
<td>p &lt; .01</td>
<td>40 - 95</td>
</tr>
</tbody>
</table>