R.A. Foell / 575 Market:
Attached is cc of the Agenda
and the draft Minutes from the
ICI/Chevron liaison meeting.
DES 12/11

NG, 1985

:novation./BWK

Oregon./BWK

c) Paraquat use on Dormant Bermudagrass./BWK

d) Non-Cotton Harvest Aid uses (also includes Diquat)./BWK

- Small Grains
  Beans/Sunflower
- Potatoes

2. Environmental Fate -

a) Anaerobic Soil Metabolism - more data needed?/All

b) Groundwater Call-In./JA, All

c) Soil studies - general discussion./All

3. Other -

a) Gramocil - Ingredient information on formulations sent to Chevron for testing./Chevron

b) Emergency Test Kits - Discussion of how to distribute to Chevron and ICI personnel./All

c) Other formulations (dyes)./ICI

d) Identification change./ICI

B. DIQUAT:

1. Field Development -

a) Discuss preferential use of Diquat (vs. Paraquat) in trees/vines areas./BWK

b) Wheat Harvest Aid/EDB issue. Review status of petition now at EPA./All

2. Environmental Fate -

a) Anaerobic metabolism study - need for data?/JA, All

AGENDA

CHEVRON/ICI FALL LIAISON MEETING, 1985

TUESDAY, NOVEMBER 5

A. PARAQUAT:

1. Field Development -

   a) Paraquat for Endophyte Fescue Pasture Renovation./BWK

   b) Use of Paraquat for Hay Curing in eastern Oregon./BWK

   c) Paraquat use on Dormant Bermudagrass./BWK

   d) Non-Cotton Harvest Aid uses (also includes Diquat)./BWK

      - Small Grains
        Beans/Sunflower
      - Potatoes

2. Environmental Fate -

   a) Anaerobic Soil Metabolism - more data needed?/All

   b) Groundwater Call-In./JA, All

   c) Soil studies - general discussion./All

3. Other -

   a) Gramocil - Ingredient information on formulations sent to Chevron for testing./Chevron

   b) Emergency Test Kits - Discussion of how to distribute to Chevron and ICI personnel./All

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   b) Wheat Harvest Aid/EDB issue. Review status of petition now at EPA./All

2. Environmental Fate -

   a) Anaerobic metabolism study - need for data?/JA, All

WEDNESDAY, NOVEMBER 6

A. PARAQUAT TOXICOLOGY:

a) Rat study - Discussion of pulmonary lesions and possible response paper/ rebuttal to EPA./JAM

Discuss ocular effects issue - Do we use outside expert?/RDC

b) Review of EPA Data Call-In for mutagenicity - What data are required to fulfill registration requirements?/JAM

c) JMPR review of Paraquat research./JAM

d) Lewis Smith seminar on the biochemical mechanism of action./RDC

e) Human poisonings - Review past cases (according to guidelines discussed at Spring meetings) to evaluate the value of different treatment methods. Determine status of proposed Physicians' Conference in London on treatment of Paraquat poisoning and CEHC's participation./RDC

f) Parkinson's Disease - Discuss Barbeau report and research needs./RDC

g) Skin irritation - Discuss the possible contribution of non-ionic surfactants in Paraquat-induced dermal injury and systemic toxicity./RDC

h) Paraquat on marijuana - Discuss L. Smith's ongoing research and the need for further toxicology testing./ICI, RDC

i) Discuss the potential for chronic Paraquat poisoning in humans and the need for a review article on this subject./RDC, ICI

j) Rat reproduction study - Status of EPA review of our response./ICI

k) 21-day dermal study./ICI

l) Inhalation studies./ICI

m) Use of additives - dye, stench, emetic, bittering agents./ICI

B. DIQUAT TOXICOLOGY:

a) Rat teratology - The rat teratology study (ICI Report HO/EH/P/82B) was conducted by putting Diquat in their diet from Day 1 through 20 of gestation. Current EPA guidelines for conducting teratology studies require administering the test compound by intragastric intubation on Days 6 through 15. Future USA reregistration of Diquat may require a new study to be done./RDC

b) Skin irritation - CEHC determined a primary skin irritation score for Diquat (2 lb/gal cation) of 0.9/8.0 (SOCAL 1479). This test score is not reflected by the label which says, "Skin contact will cause severe irritation." We would like to discuss ICI's animal testing and human field experience with Diquat formulations to help understand this discrepancy./RDC

c) Mutagenicity - Discuss Central Toxicology Laboratory's test program for Diquat mutagenicity. Also, review mutagenicity data gaps and discuss the possibiity of a Diquat (Mutagenic Effects) Call-In./JAM, RDC

d) Is more work needed on Inhalation?/All

e) Rat study - Is it necessary to ask for historical control data?/ICI

THURSDAY, NOVEMBER 7

1. Items not discussed or items not fully addressed on Tuesday and Wednesday.

2. Summarize action items and assignments.

3. Set tentative dates for next meeting.

DB:pb/Res 21

DRAFT MINUTES

CHEVRON/ICI LIAISON MEETING, FALL 1985

TUESDAY, NOVEMBER 5, 1985

Attending: Chevron: M. W. Testerman, W. D. Sewell, R. B. Huntoon, J. A. Feldman, J. Abell, C. R. Freeman, B. W. Kirby, Jr., T. St. Peter, E. K. Jackson, H. D. Byrne, J. C. White. ICI: T. B. Hart, R. E. Ridsdale, D. Fergusson, J. Glick, B. Johnen.

A. PARAQUAT

1. Field Development

a) B. W. Kirby, Jr., discussed Paraquat's use in renovating fescue pastures infested with an endophytic fungus. Much of the low productive fescue pastures in the South Central part of this country have been infected, causing a reduction in weight among feeding cattle. Seeds produced by infected fescue contain the fungus which is transmitted to other generations. The fungus-free seed sources are quite expensive. In 1985 Ortho conducted a label expansion program in which Paraquat was applied at 0.5 lb active per acre twice to provide control of existing fescue. A petition to the EPA for this label is expected to be submitted within the next few months. Split applications of Paraquat at 0.5 lb active per acre provide about 99% control of existing fescue. Pasture can then be reseeded to fungus-free fescue.

b) Mr. Kirby also discussed Paraquat's use for hay curing in the Western United States, primarily Oregon and Nevada. Samples of treated range grasses are available for analysis. A label submission to EPA is anticipated in early 1986. In this program, split applications of Paraquat at 0.25 lb active per acre are made to range grasses. Proteins are frozen in the plant by these applications and those grasses can be selectively fed to cattle with higher protein levels than untreated grasses. The present Paraquat tolerance for pasture grass is 5 ppm. It is currently believed that a 15 ppm tolerance will be required. If the data prove that a tolerance greater than 5 ppm is necessary, we will wait for the pending 60 ppm tolerance to issue before we submit.

c) This is a Diquat item and is discussed below.

d) Chevron trials show that Paraquat can be used as a small grain harvest aid. Mr. Kirby referred to wheat as a specific example. Residues may be too high to enable us to register. This may be discussed again in May.

2. Environmental Fate

a) Dr. J. Abell led the discussion for Chevron regarding Environmental Fate requirements for Paraquat. Environmental Fate data provided EPA as part of the Paraquat Data Call-In in September were identified. There was a brief discussion regarding the anaerobic metabolism study and whether or not a new study is necessary. Because of Paraquat's characteristics it was decided that such a study would be of little scientific use. Since it is anticipated that the Agency will have reviewed our submissions prior to March 1986, we agreed to wait for the Agency's interpretation on whether the study is still necessary. In the meantime, Dr. Fergusson of ICIA would provide an English translation of the anaerobic study just completed and prepare a rationale for not conducting new studies. This rationale will be provided Chevron by mid February and it will subsequently be submitted to the EPA if a new study is requested.

Action: D. Fergusson

b) Groundwater Call-In. All data and responses have been sent to EPA. The matter of groundwater monitoring was discussed. There was a brief discussion of ICI's groundwater monitoring program in Germany. As far as a U.S. (EPA) groundwater monitoring program, it was suggested that Chevron watch what is happening, offer assistance and advice as needed. There was a discussion of the analytical method and the importance of whether or not filtered or unfiltered water was used to determine the presence of Paraquat. We should determine what the groundwater program involves and is composed of. It was also pointed out that we would more likely find that any Paraquat detected in water would be from surface runoff rather than leaching or underground movement.

Action: J. Feldman

c) Soil Studies. A general discussion was held on methods used to sample and monitor soils for residues of Paraquat. Germany and Holland have begun to focus on Paraquat residues in soils. After a general discussion of the subject area, ICI pointed out that it may reduce application rates of Paraquat applied to soils with less than 5% clay. Chevron's label currently restricts use in soils lacking clay minerals, such as peat, muck, pure sand, and artificial planting media. Even so, Chevron agreed to conduct a monitoring program sampling for Paraquat residues in soils around the U.S.A. in conjunction with ICI America, Chevron, and PPD. Dave Reilly of ICI and Jared Abell of Chevron are to discuss the SAC Bioassay. ICI will forward to H. D. Byrne a protocol and report of the monitoring study by 12/31/85. The goal is to have agreed upon protocol by the next liaison meeting. ICI will forward D. Byrne copies of soil residue reports on potatoes and vines (from Holland?)

Action: H. D. Byrne, J. Abell, D. Reilly, B. Hart

3. Other

a) Gramocil. Robert Ridsdale will provide Chevron with a confidential statement of formula for the Gramocil formulation being produced in Goldsboro, North Carolina. ICIA will also send D. Byrne a label and request to register a Paraquat and Diuron tank mix

Action: R. Ridsdale

b) Emergency Kit. Chevron is to invoice ICIA for 250 kits before the year is over. ICI agreed to provide Chevron with an updated list of people in ICI America who should have emergency kits.

Action: R. Foell, R. Ridsdale

c) Other Formulations

- There was a brief discussion regarding dyes for Paraquat. ICI has used two dyes: (A) 1% Acid Blue 1 and (2) .5% Acid Blue 9. Neither of those dyes is approved by FDA. In addition, there is a stability problem with the .5% Acid Blue 9. ICI America will forward to Chevron formulation information for Acid Blue 3 (also referred to as "FD + C Blue 1"), which is the only one that can be used in the U.S.A.

Action: R. Ridsdale

- Solid Paraquat. W. D. Sewell indicated that formulation work is continuing. Acute tox studies at Chevron Environmental Health Center would begin in December 1985.

d) Identification Change. No discussion.

B. DIQUAT

1. Field Development

a) Diquat may provide effective weed control in trees and vines, Chevron may proceed with trial work.

b) Wheat Harvest Aid. Chevron has withdrawn the temporary tolerance petition (TTP) but not the EUP. It was agreed that Chevron will reinstate the TTP so as to allow the EPA to continue with its risk estimate.

2. Environmental Fate

a). Regarding Diquat, no outstanding Environmental Fate requirements have been identified. It is known that a guidance document is being prepared for Diquat and some environmental studies will likely be required as part of it. It was agreed that we would await the document before beginning any additional environmental studies with Diquat.

WEDNESDAY, NOVEMBER 6, 1985

PRESENT:	Dr. T. B. Hart - Products Medical Advisor	PPD
	Mr. M. H. C. Herlihy - Secretary's Department	
	Dr. S. Jaggers - ICI Central Toxicology Laboratory	CTL
	Dr. L. L. Smith - ICI Central Toxicology Laboratory	
	Dr. D. Fergusson - Directory of Scientific Affairs	ICI Americas
	Dr. R. E. Ridsdale - Director of Regulatory Affairs	
	Dr. J. Glick - Medical Director	
	Mr. W. Hutchinson - Legal Department	
	Mr. H. D. Byrne - Manager, Registration & Regulatory Affairs	CHEVRON
	Mr. R. D. Cavalli - Chevron Environmental Health Center	
	Dr. J. A. MacGregor - Chevron Environmental Health Center	
	Dr. J. H. Carver - Chevron Environmental Health Center	
	Dr. J. E. Ford - Chevron Environmental Health Center	
	Dr. R. D. White - Chevron Environmental Health Center	
	Dr. R. A. Zimmerman - Chevron Environmental Health Center	
	Ms. J. A. Feldman - Coordinator Regulatory Affairs	
	Dr. J. C. White - Coordinator Registration	
	Ms. T. St. Peter - Legal Department	
	Mr. S. H. Roth - Legal Department	
	Mr. M. W. Testerman - Marketing Department	

Note: Agenda was rearranged to meet the schedule of some attendees.

A. PARAQUAT TOXICOLOGY

1. Review of Human Poisonings to Evaluate Value of Treatment Methods:

   R. White and L. Smith presented data on treatment and recovery rates. Chevron will reevaluate its treatment book in light of data shared at meeting. Further discussion of treatment methods will be held at May 1986 Liaison meeting.

   Action: R. D. Cavalli

2. Physicians' Conference in London:

   B. Hart will present paper on safety and use of Paraquat. His talk will be written up in Human Toxicology. This journal article will satisfy need for review article on chronic poisonings. R. D. Cavalli will tell ICI by 30 November the name of Chevron person who will attend conference.

   Action: B. Hart/R. D. Cavalli

3. Rat Chronic Study, Response to EPA:

A meeting will be held 3 December 1985 at EPA with Chevron and ICI toxicologists to discuss historical control data and to respond to EPA questions about the lung lesions and squamous cell carcinomas in the head region.

It was agreed that some action ought to be taken to shore up the scientific review of the study. Thus, J. MacGregor and L. Smith will meet in U.K. to brainstorm low risk options. In preparation for this meeting, J. MacGregor will seek opinions from other scientists (i.e., Dr. Squires).

ICI Americas and Chevron regulatory people will attempt to clarify possible regulatory actions, i.e., will EPA initiate a special review which would put the issue before the Science Advisory Panel?

ICI is doing a one hit and a multi stage risk assessment (diet, dermal, applicator exposure). To assist in calculating dietary exposure, Chevron will send ICI residue data from our market basket survey, corrected for percent of crop treated (do by 20 November 1985).

When completed, ICI will send Chevron the risk assessment.

Action: J. MacGregor/L. Smith/B. Hart/D. Byrne

4. Ocular Effects:

At the May liaison meeting, a question arose as to the need for outside experts to review this issue (NOEL in rat study). However, EPA has not raised it and, since we believe we do have a NOEL, we will do nothing at this time.

5. Mutagenicity:

Studies have been submitted to EPA in every category. However, J. Carver pointed out that the mouse lymphoma may be rejected because an atypical technique was used. L. Smith reported that mouse lymphomas using the well technique have never been submitted to EPA. It was agreed that since there is no history of its acceptance at EPA and no data base to support its use, we can expect EPA to reject it. Thus, each company's toxicologists will think about alternatives to the mouse lymphoma in well to fill the EPA guidelines, but no action will be taken until EPA responds to the study submitted. J. Carver will attempt to learn more from EPA as to what studies will fill the Category I requirement.

Discussed strategy to rebut the in vitro positive data. Agreed J. MacGregor and L. Smith will explore the options, i.e., a micro nucleus at high doses, and compare notes.

ICI is currently preparing a protocol for an in vivo cytogenetics study. It will meet EPA guidelines.

Action: J. MacGregor, L. Smith

6. JMPR:

B. Hart reported that the complete review will be deferred until 1986.

7. Parkinson's Disease:

B. Hart and L. Smith met with Dr. Barbeau and described the survey he did in Quebec Province. ICI will identify the major Paraquat sales and use areas in Quebec to see if any connection can be made with overlapping incidences of Parkinson's. This information will be given to Dr. Barbeau.

ICI's white paper on the Paraquat/Parkinson's issue (previously sent to R. Cavalli) is being revised. When completed, it will be sent to Chevron for review.

Action: B. Hart/R. Cavalli

8. Skin Irritation:

Chevron will prepare a wish list of items to send to ICI which ICI will incorporate in their debate on the issue.

Action: J. Ford

9. Rat Reproduction Study:

EPA's review classified the study core supplementary. Chevron's response to EPA's review seeks an upgrade to core minimum status. At the time of the meeting, EPA had not responded.

10. 21-Day Dermal:

Chevron repeated this study in order to respond to the Data Call-In. A preliminary report was submitted to the EPA. The final report awaits completion of the histopathology data. It is hoped that the histopathology data will provide indication of an MTD. If not, additional action will be required. Whatever additional research is needed to establish an MTD will be decided upon without waiting to hear back from EPA.

Action: D. Byrne/J. MacGregor

11. Inhalation Studies:

ICI did a fine and a coarse study. Both were submitted to EPA.

12. Use of Additives:

a. Stench. D. Fergusson will send Chevron studies Union Carbide has conducted on valeric acid.

Action: D. Fergusson

b. Emetic. ICI is examining issue of optimum dose of the emetic to cause earliest possible vomiting. B. Hart will report results to Chevron.

Action: B. Hart

c. Bittering agents. ICI has concluded a bittering agent is not useful in accidental or suicide poisonings. but they are considering its value in homicide cases. ICI will run a taste test in Japan and report results at May 1986 liaison meeting.

J. Ford will contact the supplier of denatorium saccharide to obtain their human taste threshold study for ICI.

Action: D. Fergusson/B. Hart/J. Ford

13. Gramocil:

ICI has no toxicology data on Gramocil ~~native~~ alone, although it and CEHC has Paraquat and Diuron data which presents a likely toxicological profile of Gramocil.

14. Dr. Smuckler, Chief of Pathology at UCSF Medical Center, has requested slides of lung sections so he can compare pathology among lung lesions in humans. Both companies agreed to cooperate. J. Ford will draw up a list of the slides Chevron has and send them in to ICI which will then supply the slides needed to fill in the gaps in our data.

Also, J. Ford will talk to Dr. Smuckler about an idiopathic lung fibrosis Paraquat lesion protocol. Is Smuckler the one to do this or someone else? Chevron will report back to ICI

Action: J. Ford/D. Byrne

B. DIQUAT TOXICOLOGY

1. Mutagenicity:

By the end of 1986, ICI will have completed all mutagenicity studies required for EPA reregistration. All studies will be done using Diquat technical.

2. Rat Chronic Study:

L. Smith gave Chevron historical data which Chevron will give to EPA.

3. Rat Teratology:

The study was conducted by putting Diquat in the diet from Day 1 through 20 of gestation. Current EPA guidelines for conducting teratology studies require administering the test compound by intragastric intubation on Days 6 through 15. EPA has not issued a review of the study. However, if it is classified core supplementary, ICI agreed to redo the study.

Action: B. Hart

4. Skin Irritation:

CEHC determined a primary skin irritation score for Diquat (2lb/gal cation) of 0.9/8.0 (SOCAL 1479). This test score is not reflected by the label which says, "Skin contact will cause severe irritation" (which is too strong a statement if we were to use the results of animal studies alone). Discussion on how the label recommendation is based on a conservative reading of human field experience, and not on animal tests. L. Smith agreed to review ICI's test results and report back to Chevron.

Action: L. Smith

5. Inhalation Data:

Chevron has almost completed an acute study. The report will be ready by February 1986.

Medical Conference in the U.S. on Paraquat

ICI Americas has raised the question of holding such a conference. D. Byrne and B. Hart will discuss internally and share conclusions at May liaison meeting.

Action: D. Byrne/B. Hart

THURSDAY, NOVEMBER 7, 1985

1. Study Costs:

B. Hart wrote to L. Stelzer (June/July 1985?), after May meeting regarding cost of inhalation study, £ 8480.00. No response yet.

Action: D. Byrne

2. Mutagencity Studies/Paraquat:

ICI will write to Byrne with summary of costs.

Action: B. Hart

3. Captafol:

United Kingdom has requested all available toxicology data from ICI. A "white paper" is being prepared by ICI which will be sent to D. Byrne before going to Government.

Action: B. Hart

4. Paraquat/Corn Harvest Aid - Byrne will send Hart the data package submitted to EPA. Any other data in Chevron files on this usage will also be included.

Action: D. Byrne

5. Communication:

B. Hart and D. Byrne are principal liaisons and should be copied on all correspondence and transcripts of telephone conversations between CEHC and ICI. All other communications should be directly between Hart and Byrne who will see that appropriate people are copied.

6. Next Meeting:

May 19, 20, 21 1986 in England

DESMOND BYRNE

DB:cw/JCW P-1