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From: U246074 --S08VRNA Date and time 11/21/95 16:42
To: U077399 --S08VRNA BOND, GREGORY G. / U080899 --S08VRNA DEFORD, CONNIE
U077632 --S08VRNA DILLON JR, GEORGE U076129 --S08VRNA DOMORADZKI, JEANNI
U095202 --S14VM MCLEMORE, MARY K. U303653 --TXDECD NUILA, CARLOS C
U134803 --S08VRNA STEARNS JR, W J. /
cc: U806429 --S08VRNA LEBEAU, JOSEPH J E U084009 --S08VRNA BRESLIN, WILLIAM W
U079317 --S08VRNA HEARN, SUE S

FROM: RAMLOW, JONATHAN M.
SUBJECT: Update On CMA VCM Panel Activity

This week the CMA Vinyl Chloride Panel Health Committee sent out a Request For Proposal to a selected group of laboratories for the combined 2-generation reproductive/developmental toxicity study designed to meet two of ATSDR's Priority Data Needs. The labs to which the RFP was sent included our own here in Midland. Bill Breslin, who wrote the draft protocol which ATSDR accepted, has told me that he will confer with the Inhalation Tox folks here in 1803 to see whether or not it would be possible to schedule this study into 1803 in 1996. After he knows about that he will decide whether or not to submit a proposal to CMA. The Panel has requested that proposals be submitted by December 8.

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Parenthetically, it turns out that one the labs that received the RFP is not actually able to mount the study by itself because it lacks the inhalation facilities. They contacted CIIT to see about subcontracting for the inhalation work. Joe LeBeau called me to bring him up to date about this because of the CIIT connection. Joe, I told you that Dow will be submitting a proposal, but as the first paragraph indicates, this in fact depends on whether or not the lab could schedule the study in 1996. Sorry I spoke too soon.

I hope this brings everyone up to date on what is happening with this study. Should you have any questions, please don't hesitate to call me at 517/636-1276.

Jonathan

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From: U246074 --S08VRNA Date and time 11/01/95 15:05
To: U077399 --S08VRNA BOND, GREGORY G. / U077632 --S08VRNA DILLON JR, GEORGE
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U077494 --S08VRNA BODNER, KENNETH K U287971 --S08VRNA BURNS, CAROL
U063460 --S08VRNA CARTMILL, JANICE J

FROM: RAMLOW, JONATHAN M.
SUBJECT: Vinyl Chloride Health Committee Meeting Report

***** DOW RESTRICTED *****

Yesterday, October 31, I attended a meeting of the CMA Vinyl Chloride Health Committee in Washington. This note is a brief summary of the meeting. I will shortly be sending you a more detailed discussion and copies of meeting handouts related to point number 2.

- 1) University of Louisville brain cancer case-control study (Dr. Carol Tamburro): Has Shah of CMA, Ed Beeler of Geon, and I will be meeting with Dr. Tamburro in Louisville on November 17th. We have asked him to be prepared to respond to a number of questions the committee still has about his proposed brain cancer study, including issues regarding detailed study timelines and budget breakdowns, and also his willingness to work with a co-investigator who is an experienced epidemiologist (such as Dr. Kenneth Mundt of UMass.).
- 2) Applied Epidemiology Inc. industry-wide cohort mortality study update. Dr. Kenneth Mundt of AEI was present at the meeting to explain in detail to the full committee the problems he (and we) have had in trying to obtain and transfer study materials from the previous contractor to AEI. The bottom line is that AEI will be able to complete the mortality update, but the delays caused by shoddy archiving at EHA/ENSR in California will result in additional costs and time required to complete the study. The committee is taking steps that may result in our being able to recover some of the additional cost from ENSR. I will mail you additional detailed information about this particular matter.
- 3) The committee has provided written responses to ATSDR's peer reviewer comments on the protocol (written by Bill Breslin of H&ES) for a combined repro/developmental toxicity study. The committee's counselor advises us that it may be another month before ATSDR is finally prepared to complete a Memorandum of Understanding with us about this testing, even though we are ready to do it now. However, we are going to proceed to ask for study proposals and bids from H&ES and 2-3 other contract laboratories as soon as possible. This was my suggestion since Bill Breslin told me that if H&ES is to be considered as a possible contractor to CMA for this study, the lab needs to start thinking now about how to fit it into the plans for 1996/97.

4) 1996 committee budget: here is how things basically look at this time for 1996 and 1997 the committee will be asking the companies for a total of \$1.44MM to support the following research agenda:

- \$650M - combined repro/developmental toxicity study(1996-97)
- \$350M - neurotoxicity testing: ONLY if required by EPA, which is still not certain(?)
- \$60M - molecular (DNA adduct repair) studies by Dr. J. Swenberg, Univ. of North Carolina ONLY if feasible (?)
- \$150M - Univ. of Louisville brain cancer case-control study (1996,
- \$100M - AEI VCM mortality update study cost over-run (1997)
- \$10M - providing information to EPA for updated and improved VCM risk assessment (1996)
- \$10M - outside legal fees for assistance with ATSDR testing program and figuring out how to get ENSR to make up for their shoddy archiving and foot-dragging (1996)
- \$80M - CMA administrative costs (1996)
- \$30M - contingencies (1996-97)

\$1.44MM

My understanding is that the companies will need to commit to contributing 640M for 1996 in order to make all this possible; if EPA decides to back down on the neurotoxicity testing requirement, that money can be spent on something else, of course, with less money then needed subsequently in 1997. Based on the current allocation formula, Dow's share of the 640M would be 20% or 128M, for which we could be invoiced once or twice.

If you have any questions regarding these matters, and I expect that you will, please feel free to call me at any time. Also, I would very much appreciate hearing whether anyone needs to be added to or removed from my VCM PROFS distribution list in view of the many recent changes in the organization. Thanks very much in advance.

Best regards,

Jonathan

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cc: U079317 --S08VRNA HEARN, SUE S

FROM: RAMLOW, JONATHAN M.
SUBJECT: CMA Vinyl Chloride Health Committee Update

DOW RESTRICTED

We have just received comments from ATSDR's peer reviewers on the CMA proposed protocol for a combined reproductive/developmental toxicity test. The protocol was originally drafted by Bill Breslin of H&ES, as you may recall.

The peer reviewers were Ronald D. Hood, PhD, Barbara F. Hales, PhD, and Mildred S. Christian, PhD, ATS. I am not familiar with these scientists, but perhaps Bill is. Their comments were quite favorable overall and seem to call only for some "fine-tuning" of the proposed protocol. I will share the comments with Bill Breslin and go from there. We have three weeks to submit our responses to ATSDR. Given the favorable response from the peer reviewers and what I heard in a conversation I had with Chris DeRosa and Bill Cibulas of ATSDR, I think there is no question that the study will be approved and ATSDR and CMA can develop and MOU for this testing.

Please let me know where the business is in the budgeting cycle so that I can work with Has Shah at CMA on planning for the funding of this study. We have been working with a ball-park estimate of \$500,000 for the study up to now, but I will also talk with Bill about fine-tuning that estimate as well.

Please feel free to call should you have questions about this matter.

Jonathan

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FROM: RAMLOW, JONATHAN M.
SUBJECT: "Vinyl Chloride/Early Life Exposure"

The May 3 issue of Pesticide and Toxic Chemical News carried an item describing a presentation by James Coglianò of the EPA at a conference on risk assessment for sensitive populations. He apparently discussed vinyl chloride in terms of increased cancer risk associated with exposure of very young animals, in which the risk is expressed in adult life. One of the statements attributed to him was that "brief exposure" in early life "can induce unseen tumors and higher incidence of apparent tumors following long-term exposure later in life."

The story did not indicate the basis for Coglianò's remarks, but he must have been referring at least to the following: Maltoni et al., Env. Health Perspect 1981;41:3-29; Drew et al., Toxicol Appl Pharmacol 1983;68:120-30; and Maltoni & Cotti, Ann NY Acad Sci 1988;534:145-59. All of these papers report results of carcinogenicity assays in animals exposed prenatally or in early life.

I've asked Has Shah at CMA to communicate with Coglianò and find out more about the context in which he spoke and the data he was referring to. We may want to review the available data ourselves and then offer comments to EPA if and when appropriate.

Finally, this issue may make it advisable to consider again the proposal we received from Dr. James Swenberg to conduct some experimental work looking at the efficiency of DNA repair mechanisms in young and old animals. His thinking has been that if young animals are more susceptible to VC carcinogenic effects than older animals, it will be because their DNA repair mechanisms do not work as well as in the adults. Currently this proposal has been tabled by the VC Panel Health Committee. If we can find out more about where EPA may be going with this issue, I will ask for your input again about Swenberg's proposal.

Please write or call if you have any questions about this matter.

Jonathan Ramlow

cc: U079317 --S21VM HEARN, SUE S

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FROM: RAMLOW, JONATHAN M.
SUBJECT: VC Epidemiology Study

This is a brief update on the status of the industry-wide vinyl chloride mortality study being conducted by Applied Epidemiology, Inc., sponsored by the CMA Vinyl Chloride Panel member companies.

Currently, we are in the process of transferring previous study materials from ENSR Health Sciences in California to AEI in Amherst, MA. AEI has received most of the hard-copy employee records and a line listing of the cohort as it existed at the time of the previous update. AEI also received several boxes of material totally unrelated to the vinyl chloride study. This has turned out to be a harbinger of confusion.

Unfortunately, ENSR has apparently lost track of about half of the death certificates used in the previous update. In going through the existing inventory of VC-related materials at ENSR, Don Whorton has found quite a number of mislabeled boxes and has been unable to track down the missing death certificates. It may be necessary for Don and the ENSR people to go through everything that they put in storage since last November, a process likely to take some time. Thus, even though we have gotten permission from virtually all states to transfer death certificates from ENSR to AEI, this will not happen as quickly as we had hoped.

Meanwhile, Don Whorton has arranged for the study computer tapes to be copied and sent to AEI, so AEI will be able to get to work on the study. We have also initiated the application process with the National Death Index so that AEI can begin follow-up vital status checking on the cohort when they receive and process the study tape. Thus, the confusion at ENSR, while annoying, should not delay the progress of the current study too much.

I would say that this development confirms yet again my belief that we made the correct decision in deciding to transfer the study from Otto Wong/ ENSR to AEI. I will keep you posted as we learn more about what is going on out there.

Jonathan Ramlow

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