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S. Hearn
G. W. Olsen

cc: Epidemiology Group
V. T. May, 1803
R. L. McCreedy, 2020
W. J. Stearns, 2020
C. E. Nuila, B2234, Freeport
G. G. Bond, 2020
W. C. Hayes, 2020
G. S. Dillon, 2020
J. Y. Domaradzki, 1803

TRIP REPORT - MEETINGS OF CMA VINYL CHLORIDE RESEARCH COORDINATORS

On Thursday and Friday, October 7 and 8, I chaired meetings of the Research Coordinators group of the CMA Vinyl Chloride Panel in Washington, D.C. The primary purposes of the meetings were 1) to meet with interested representatives of the EPA to hear presentations by Drs. Dick Reitz and Jim Swenberg on current mechanistic and biochemical perspectives on vinyl chloride risk characterization, and 2) to discuss the relative merits and costs of the three proposals we have received for the industry-wide mortality study update. My trip expenses were paid for by Environmental Affairs, C&PP.

Dick Reitz's and Jim Swenberg's presentations were very good and seemed to be received with interest by the EPA representatives (about 20 were present, most from the Office of Research and Development). Dick presented his soon-to-be-published PBPK model for extrapolating VCM-associated angiosarcoma risk from animal studies to humans, with which he estimates that the observed numbers of angiosarcoma cases in humans are lower than would be expected. His conclusion is that humans are less sensitive to the carcinogenic effect than rodents at all relevant doses. Dick will submit his manuscript for publication within the next few weeks.

Jim Swenberg presented extremely interesting data, much of which has not been published or presented elsewhere, on the formation and repair of DNA adducts following VCM exposure. He has results which may help to explain

the reportedly greater angiosarcoma risk in animals exposed perinatally to VCM, in terms of lower adduct repair capacity than in adult animals. Moreover, his current work suggests that at very low VCM doses, the adducts observed after cessation of exposure are probably endogenously produced, rather than persistent consequences of exposure. These developments are of great potential importance for understanding the risks associated with low-dose VCM exposure and the effects of exposure to infants and children. The panel agreed to explore the possibility of helping Dr. Swenberg continue his work. For example, he needs a source of ^{13}C-vinyl chloride so that he can quantify and compare the formation of endogenous and exogenous DNA adducts after VCM exposure.

After the meeting I suggested to Dr. Jim Cogliano of the ORD that it might be fruitful at some time to hold a formal interdisciplinary workshop on VCM risk assessment issues (analogous to the meeting held last year on trichloroethylene). He and other EPA folks seemed receptive to this idea, which the VCM panel had also discussed previously. We will look into this again at future panel meetings.

The panel spent most of Friday discussing the proposals we received for the update of the VC/PVC industry-wide cohort mortality study. We received proposals from Drs. Otto Wong of Applied Health Sciences (San Mateo, California), Kenneth Mundt of Applied Epidemiology Inc. (Amherst, Massachusetts), and Roy Shore of New York University (NYC). I had prepared a matrix of evaluative criteria for panel members to use while reading the proposals, so everyone in the group had had the opportunity to look over the proposals in a more or less similar fashion.

The substantial cost differentials among the three proposals were a significant issue for all panel members and constituted the most important evaluative criterion for some. However, questions of scientific merit and technical quality were foremost in the minds of most group members, and I believe that the group made considerable progress in reconciling some competing issues of cost versus quality in the day's discussions. We agreed to obtain more information from one of the potential contractors, meet again in two weeks via conference call, and reach a final decision to award the contract at that time.

Regarding other issues, the group had been made aware that the task force being formed by the Halogenated Solvents Industry Alliance to work on potential HAP test rules for other materials would also like to include ethylene dichloride within their group. The VCM research panel had considered taking on this task for EDC earlier in the summer, but all were quite willing to leave this at HSIA.

With respect to potential test rules for vinyl chloride itself, the group read the September 30th F.R. notice of the proposed test rules and possible ECA's put out by EPA (copy attached). The inclusion of inhalation neurotoxicity on the list for VCM was a surprise for all, since this had not been previously suggested as a priority data need by ATSDR. The group will try to find out the source and implications of this addition. We noted that the agency intends to finalize new testing requirements for reproductive and developmental toxicity, the other two areas of proposed testing for VCM. The group members all agreed on the need for outside counsel in communicating with EPA about these proposed test rules.

Should you wish to discuss any of this material in more detail, please feel free to call me at the number below.

Jonathan M. Ramlow, Ph.D., M.P.H.
Epidemiology, H&ES
Phone (517) 636-1276
FAX (517) 636-1875

Attachment

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assessments by ASTDR. In addition, because of the involvement by other Federal Agencies and EPA offices in reviewing the testing needs identified for these chemicals, this testing program will supply test data which will also meet the needs of other Federal Agencies and EPA programs.

Table 1.--Data Needs and Testing Guidelines

Chemical and CAS No.	Proposed Testing	Guideline (40 CFR)
Vinyl chloride (75-01-4)	Reproductive inhalation	R
	Developmental inhalation	D
	Neurotoxicity inhalation	N
Benzene (71-43-2)	Subchronic oral	798.2650
	Subchronic inhalation	798.2450
	Neurotoxicity inhalation	N
	Functional observational battery	
	Motor activity	
	Neuropathology	
	Reproductive inhalation	R
Trichloroethylene (79-01-6)	Acute oral	798.1175
	Subchronic oral	798.2650
	Immunotoxicity oral	I
Tetrachloroethylene (127-18-4)	Acute inhalation	A
	Reproductive inhalation	R
	Neurotoxicity subchronic inhalation	N
	Functional observational battery	
	Motor activity	
	Neuropathology	
	Developmental inhalation	D
	Immunotoxicity inhalation	I
Hydrogen cyanide (74-90-8)	Acute inhalation	A
	Subchronic inhalation	798.2450

	Developmental inhalation	D
	Neurotoxicity subchronic inhalation	N
	Functional observational battery	
	Motor activity	
	Neuropathology	
Sodium cyanide (143-33-9)	Developmental oral	D
Toluene (108-88-3)	Comparative pharmacokinetic	PK
	Immunotoxicity oral	I
Methylene chloride (75-09-2)	Subchronic oral	798.2650
	Developmental oral	D
	Neurotoxicity subchronic oral	N
	Functional observational battery	
	Motor activity	
	Neuropathology	
	Immunotoxicity oral	I
Chloroethane* (Ethyl chloride) (75-00-3)	Comparative pharmacokinetic	PK
Mercury**(TBD)		
Chromium**(TBD)		
Beryllium**(TBD)		

Notes:

*Note that a soon-to-be-published proposed test rule on hazardous air pollutants (HAPs) will cover chloroethane.

**A workgroup set up by TASARC is in the process of identifying the specific forms of these metals.

TBD -- The Chemical Abstract Service Registry Number(s) for the chemical(s) to be tested is yet to be determined.

R -- Proposed revised EPA guidelines for reproductive toxicity testing are under development and are anticipated to be finalized in the near future. Copies of the latest draft to date are available in the docket established for this action.

D -- Proposed revised EPA guidelines for developmental toxicity testing are under development and are anticipated to be finalized in the near future. Copies of the latest draft to date are available in the docket established for this action.

N -- EPA intends for parties subject to neurotoxicity testing requirements under this rule to follow the 1991 Neurotoxicology Testing Guidelines which

are available in the docket established for this action.

I -- A workgroup established by the Tri-Agency Superfund Applied Research Committee (TASARC) is developing immunotoxicity testing guidelines.

A -- Revised EPA guidelines for acute inhalation testing are under development and will soon be published with a proposed test rule on HAPs. Copies of the latest draft to date are available in the docket established for this action.

PK -- EPA has developed testing guidelines which may be used for conducting comparative pharmokinetic testing. These final guidelines are awaiting publication and are available in the docket established for this action.

II. Procedures for Development of ECAs

EPA will follow the procedures outlined below to develop ECAs for the chemical substances listed in Table 1 above.

1. Submission of testing proposals for ECA negotiations. Following publication of this Notice, manufacturers and processors have 60 days to develop testing proposals for the chemical substances listed in Table 1 above that they wish EPA to consider as candidates for ECA negotiations. EPA may extend the deadline for receipt of testing proposals upon a showing of good faith efforts to develop testing proposals by the initial deadline. The testing proposals should describe the testing to be performed in detail (test guideline or protocol, including route of administration, species, etc.) and explain in detail where there are deviations from tests proposed by EPA in Table 1 above. The Agency suggests as a model the testing proposal submitted on N-methylpyrrolidone (NMP) by the NMP Producers Group on September 11, 1992 found in the docket established for this action. In order for a testing proposal to be eligible for consideration, the proposal should cover all identified data needs of a substance (or multiple substances).

2. Agency selection of most likely candidates for the ECA program. EPA will review the submissions and select the most promising submissions as candidates for negotiation. Submissions which fully address EPA's concerns will have a higher chance of success than those which do not fully address all data needs issues.

3. Formal solicitation of "interested parties" in the Federal Register. If EPA selects a proposal as a candidate for negotiations, such negotiations will be conducted pursuant to procedures described in 40 CFR 790.28. Accordingly, EPA will publish a notice in the Federal Register soliciting persons interested in participating in or monitoring negotiations for the development of an ECA, to so notify the Agency in writing. Those individuals and groups who respond to EPA's notice by the deadline established in the notice will have the status of "interested parties" and will be afforded opportunities to participate in the negotiation process. Designation as an "interested party" will not incur any obligations. Submitters of testing proposals will be considered interested parties with regard to the subject(s) of their proposals and need not respond to the solicitation notice.

4. Negotiation of testing program and development of an ECA. Negotiations will be conducted in meetings open to the public. Notification of meetings will be given only to persons identified as interested parties. The first negotiation meeting will establish the period for negotiation. If agreement is not reached within this prescribed time limit and EPA chooses not to extend the negotiation period, negotiations will be terminated and testing will be required under a rule.

5. Approval of the ECA by interested parties and EPA and publication of a notice in the Federal Register. After EPA and interested parties have agreed in principle on the terms of the ECA, the ECA text will be sent for approval