CMA - VDC
Comments on HAD

THE CMA-VDC PANEL SUBMITTED COMMENTS ON THE HEALTH ASSESSMENT DOCUMENT ON VDC IN JANUARY, 1984. IN ANTICIPATION OF THIS MEETING, THE PANEL PREPARED A BRIEF POSITION PAPER WITH RECOMMENDATIONS AND SENT COPIES OF THIS POSITION PAPER AND THE JANUARY COMMENTS TO THE SAB.

IN SUMMARY, THESE DOCUMENTS STATE THAT THE HEALTH ASSESSMENT DOCUMENT ON VINYLIDENE CHLORIDE IS BASICALLY AN ACCEPTABLE DOCUMENT REFLECTING THE SCIENTIFIC DATA ON THE CHEMICAL. THERE STILL REMAIN, HOWEVER, TWO ISSUES OF MAJOR CONCERN: THE HYPOTHETICAL UNIT RISK ASSESSMENT AND THE INCLUSION OF VINYLIDENE CHLORIDE IN THE POTENCY INDEXING TABLE. THE PANEL IS CONCERNED WITH THE POSSIBLE MISINTERPRETATION AND MISUSE OF THESE ASSESSMENTS. SPECIFICALLY, THE PANEL NOTES THE INAPPROPRIATENESS OF THE OUTCOME OF THE AGENCY'S POTENCY INDEXING OF VDC. THE SCIENTIFIC DATA CLEARLY DO NOT SUPPORT THE RANKING OF VDC WITH ACRYLONITRILE OR BENZENE, NOR IS IT CORRECT FOR THE AGENCY TO IMPLY OR STATE THAT IT IS "MORE CARCINOGENIC" THAN VINYL CHLORIDE.

BY WAY OF BACKGROUND, THE VDC PANEL WAS FORMED IN 1974 AS A SPECIAL PROJECT WITHIN THE CHEMICAL MANUFACTURERS ASSOCIATION. THE SLIDE NOW BEING SHOWN IS A STATEMENT OF THE PANEL'S PURPOSE.

SLIDE #1

PURPOSE

THE PURPOSE OF THE PROPOSED PROGRAM IS TO CONDUCT RESEARCH AND INVESTIGATIONS TO DEVELOP RELIABLE DATA ON THE CARCINOGENICITY AND OTHER TOXICOLOGICAL PROPERTIES OF VDC, IN ORDER TO ASCERTAIN CONDITIONS NECESSARY TO ASSURE THE SAFETY OF THE WORKERS INVOLVED IN ITS MANUFACTURE, HANDLING, AND USE, AND OF THE COMMUNITIES IN WHICH SUCH PLANTS ARE LOCATED.

AS A PART OF THE PROGRAM PANEL HAS SPONSORED AND CONDUCTED STUDIES LISTED ON THE FOLLOWING SLIDES.

SLIDES #2, AND 3 (ATTACHED)

IN ADDITION, THE PANEL HAS BEEN DILIGENT IN REVIEWING AND EVALUATING THE GLOBAL LITERATURE AS WELL AS THE EPA'S OFFICE OF DRINKING WATER DRAFT CRITERIA DOCUMENT ON THE CHEMICAL AND THE DRAFT HEALTH ASSESSMENT DOCUMENT HERE UNDER DISCUSSION.

RELATING TO THE TWO POINTS OF CONCERN TO THE PANEL, VIZ: THE ASSESSMENTS OF HYPOTHETICAL UNIT RISK AND THE POTENCY INDEX, THE AGENCY HAS RECENTLY SUPPLIED THE SAB WITH ITS RESPONSE TO PUBLIC COMMENTS ON THE DRAFT HAD AND SUGGESTED THAT CHANGES

SHOULD BE MADE IN THE DOCUMENT[1]. THESE CHANGES WOULD DIRECTLY AFFECT THE HYPOTHETICAL UNIT RISK AND POTENCY INDEX.

SPECIFICALLY THE AGENCY STATES THAT IT "HAS RE-EVALUATED THE METABOLISM AND THE RELEVANT KINETIC DATA...AND AGREES THAT ADDITIONAL INFORMATION FROM ACTUAL EXPERIMENTAL DATA CAN FORM THE BASIS OF ANIMAL-TO-MAN EXTRAPOLATION..." (PAGE 2, PARAGRAPH 1). THE AGENCY ALSO STATES THAT IT WILL AMEND THE POTENCY TABLE, "ADDING AT LEAST ONE ADDITIONAL COLUMN TO INDICATE THE WEIGHT OF EVIDENCE FOR A CHEMICAL'S BEING A CARCINOGEN" (PAGE 4, PARAGRAPH 1) AND ALSO THAT" THE CALCULATION OF THE HUMAN EQUIVALENT DOSE... WILL FURTHER AMEND THE POTENCY VALUE..." (PAGE 5, PARAGRAPH 3).

THE PANEL SEES FAR MORE JUSTIFICATION FOR ITS RECOMMENDATION FOR DELETION OF THE ESTIMATE AND THE RANKING. HOWEVER, IF THE SAB SHOULD FIND THAT THERE MAY BE MERIT IN THE AGENCY'S INTENDED CHANGES, WHICH ARE NOW ONLY CONCEPTUCAL, IT IS THE PANEL'S POSITION THAT THESE CHANGES SHOULD BE DEVELOPED AND MADE SUBJECT TO PUBLIC REVIEW.

NOTWITHSTANDING THE AGENCY'S INTENTION TO REVISE THE HEALTH ASSESSMENT DOCUMENT, THE PANEL HAS CONCERN ABOUT THE SCIENTIFIC BASIS FOR CERTAIN OTHER STATEMENTS MADE BY THE AGENCY IN THIS

---

[1]GRANT, L.D. (1984). EPA, OFFICE OF HEALTH AND ENVIRONMENTAL ASSESSMENT. THE OFFICE OF HEALTH AND ENVIRONMENTAL ASSESSMENT'S POSITION PAPER ON PUBLIC COMMENTS REGARDING THE VINYLIDENE CHLORIDE DOCUMENT. APRIL 13, 1984.

LATEST POSITION PAPER. THE FOLLOWING COMMENTS IN THE AGENCY'S POSITION PAPER ARE OF MAJOR CONCERN TO THE PANEL.

1. PAGE 1, SECTION I, BACKGROUND, PARAGRAPH 3

> "WHILE THE EVIDENCE FOR THE CARCINOGENICITY OF VINYLIDENE CHLORIDE IS LIMITED IN ANIMALS, AND THE COMPOUND CANNOT BE CLASSIFIED AS TO ITS CARCINOGENICITY TO HUMANS, THE KIDNEY ADENOCARCINOMAS IN MALE SWISS MICE (MALTONI ET AL., 1980) DO PROVIDE DATA FOR ESTIMATING AN UPPER LIMIT OF POTENTIAL HUMAN RISK FOR A QUANTITATIVE ASSESSMENT..."

IN MAKING THIS STATEMENT, THE AGENCY HAS ELECTED TO IGNORE THE WEIGHT OF THE EVIDENCE (AS DEFINED IN EPA'S OWN "GUIDELINES FOR PERFORMING REGULATORY IMPACT ANALYSES") AND HAS, INSTEAD, MADE THE TRANSITION FROM ADMITTEDLY LIMITED (POSITIVE) DATA TO A QUANTITATIVE CARCINOGENIC RISK ESTIMATION FOR MAN AND ESTIMATED VDC'S RANKING AMONG CHEMICAL CARCINOGENS.

SPECIFICALLY IN THE HAD-VDC, CAG MAKES THE ASSUMPTION THAT THE PRELIMINARY REPORT OF ONE OF THE EIGHTEEN LONG-TERM TOXICITY/ONCOGENICITY STUDIES CONDUCTED ON THE CHEMICAL, NAMELY, A MOUSE INHALATION STUDY CONDUCTED BY PROF. C. MALTONI (MALTONI, 1980)[2] IS, QUALITATIVELY, SUFFICIENT TO TRIGGER A HYPOTHETICAL

---

[2]MALTONI, C. (1980). TOXICITY AND CARCINOGENICITY BIOASSAYS (FOOTNOTE CONTINUED)

UNIT RISK ASSESSMENT FOR HUMANS. THIS ASSUMPTION CAN BE MISINTERPRETED SINCE IT ALSO ASSUMES THERE IS JUSTIFICATION FOR IGNORING THE RESULTS OF 17 LONG-TERM TOXICITY/ONCOGENICITY STUDIES, AND THE PHARMACOKINETIC/METABOLISM AND MECHANISTIC DATA, PARTICULARLY THOSE DATA THAT LEND PERSPECTIVE TO PROFESSOR MALTONI'S STUDY ON THE SWISS MOUSE.

SLIDES 4, 5, 6 AND 7 (ATTACHED)

IT SHOULD BE NOTED THAT PROFESSOR MALTONI REPORTED A NON-DOSE RELATED TUMORIGENIC RESPONSE IN THE KIDNEYS OF MALE MICE. THIS RESPONSE OCCURRED: (1) ONLY AT THE VAPOR CONCENTRATION(S) THAT WERE AT OR NEAR THE ACUTELY LETHAL LEVEL FOR THE SWISS MOUSE; (2) AT CONCENTRATION(S) WHICH CAUSED MARKED ACUTE TOXICITY IN THE KIDNEY AND (3) NEAR THE TERMINATION OF THE STUDY, AFTER RECURRENT TISSUE INJURY HAD OCCURRED OVER THE LIFETIME OF THE ANIMALS. PROFESSOR MALTONI HAS EXPRESSED THE OPINION THAT HIS RESULTS FROM THE MOUSE STUDY ARE NOT MEANINGFUL FOR MAN (MALTONI, 1977).[3]

2. <u>PUBLIC COMMENTS, SECTION 2, PAGE 2</u>

THE AGENCY STATES THAT:

(FOOTNOTE CONTINUED)
OF VINYLIDENE CHLORIDE. II. CHRONIC TOXICITY AND CARCINOGENICITY (PRELIMINARY REPORT).

[3]MALTONI, C. (1977). PRESENTATION AT THE TAPPI INTERNATIONAL PVDC SEMINAR, HAMBURG, GERMANY. JANUARY 24-26, 1977.

"THE CAG MAKES A QUALITATIVE WEIGHT-OF-EVIDENCE JUDGMENT CONCERNING THE LIKELIHOOD THAT AN AGENT IS A HUMAN CARCINOGEN AS CALLED FOR IN THE AGENCY CANCER GUIDELINES, ORIGINALLY DEVELOPED IN 1976..."

THE PANEL RESPECTFULLY POINTS OUT THAT THESE INTERIM GUIDELINES WERE A 1976 STATEMENT OF THE AGENCY'S APPROACH TO REGULATORY ACTION AGAINST SUSPECT CARCINOGENS. THE 1984, FINAL GUIDELINES FOR PERFORMING REGULATORY IMPACT ANALYSES UNDER EXECUTIVE ORDER 12291 STATES:

"A DETERMINATION OF THE LIKELIHOOD THAT A SUBSTANCE IS A HUMAN CARCINOGEN SHOULD BE BASED ON A WEIGHT-OF-EVIDENCE JUDGMENT. ALL AVAILABLE INFORMATION FROM HUMAN EPIDEMIOLOGICAL STUDIES AND FROM ANIMAL STUDIES SHOULD BE EVALUATED, ALONG WITH EVIDENCE FROM SHORT-TERM TESTS, STUDIES OF COMPARATIVE METABOLISM, STRUCTURE-ACTIVITY ANALYSIS AND OTHER RELEVANT TOXICOLOGICAL AND BIOLOGICAL ANALYSIS. THE EVALUATION SHOULD CONSIDER THE NUMBER AND KIND OF TUMORIGENIC RESPONSES AND THEIR STATISTICAL SIGNIFICANCE, AS WELL AS THE QUALITY OF THE AVAILABLE STUDIES. PROPERLY EVALUATED ANIMAL DATA MAY BE USED TO PREDICT HUMAN RESPONSE." (EMPHASIS ADDED)

BEFORE CONCLUDING, THE PANEL BELIEVES THE CAG HAS MISUNDERSTOOD A) THE PANEL'S USE OF THE EPA'S TIER APPROACH TO THE INTERPRETATION OF THE MUTAGENICITY DATA AND B) THE PANEL'S COMMENTS ON THE UTILITY OF THE HEALTH STUDY DATA ON WORKERS

OCCUPATIONALLY EXPOSED TO VDC. THESE TWO ISSUES ARE IMPORTANT BECAUSE OF THEIR CONTRIBUTION TO THE WEIGHT OF THE EVIDENCE. IF OUR POINTS ARE STILL UNCLEAR WE ARE PREPARED TO ADDRESS THEM IN FURTHER DETAIL WITH THE AGENCY.

IN SUMMARY, THE PANEL REQUESTS, FOR THE REASONS GIVEN ABOVE, THAT THE VDC HYPOTHETICAL UNIT RISK ESTIMATE AND POTENCY INDEXING BE DELETED FROM THIS OTHERWISE SCIENTIFICALLY ACCEPTABLE DRAFT HEALTH ASSESSMENT DOCUMENT ON VINYLIDENE CHLORIDE.

SLIDE #1

PURPOSE

THE PURPOSE OF THE PROPOSED PROGRAM IS TO CONDUCT RESEARCH AND INVESTIGATIONS TO DEVELOP RELIABLE DATA ON THE CARCINOGENICITY AND OTHER TOXICOLOGICAL PROPERTIES OF VDC, IN ORDER TO ASCERTAIN CONDITIONS NECESSARY TO ASSURE THE SAFETY OF THE WORKERS INVOLVED IN ITS MANUFACTURE, HANDLING, AND USE, AND OF THE COMMUNITIES IN WHICH SUCH PLANTS ARE LOCATED.

SL 063307

STUDIES CONDUCTED BY VINYLIDENE CHLORIDE PROGRAM PANEL

A 90-DAY STUDY INCORPORATING VDC IN THE DRINKING WATER OF RATS

A TWO-YEAR TOXICITY AND ONCOGENICITY STUDY WITH VDC INCORPORATED IN THE DRINKING WATER OF RATS

- A MULTIPLE GENERATION REPRODUCTION STUDY IN RATS MAINTAINED ON DRINKING WATER CONTAINING VDC

RESULTS OF A 97-DAY TOXICITY STUDY IN MALE AND FEMALE BEAGLE DOGS ORALLY ADMINISTERED VDC IN PEANUT OIL VIA GELATIN CAPSULES

90-DAY REPEATED INHALATION TOXICITY STUDY OF VINYLIDENE CHLORIDE IN RATS

2-YR VAPOR INHALATION STUDIES ON VDC IN RATS

STUDIES CONDUCTED BY VINYLIDENE CHLORIDE PROGRAM PANEL(CONTINUED)

THE EFFECTS OF MATERNALLY INHALED OR INGESTED VDC ON RAT AND RABBIT EMBRYONAL AND FETAL DEVELOPMENT

THE PHARMACOKINETICS OF ^{14}C IN RATS FOLLOWING INHALATION EXPOSURE

METABOLISM AND PHARMACOKINETICS PROFILE OF VDC IN RATS FOLLOWING ORAL ADMINISTRATION

EFFECTS OF VINYLIDENE CHLORIDE ON DNA SYNTHESIS AND DNA REPAIR IN THE RAT AND MOUSE: A COMPARATIVE STUDY WITH DIMETHYLNITROSAMINE

A COMPARISON OF FOUR MOUSE STRAINS EXPOSED TO SUBCHRONICALLY INHALED VDC

RESULTS OF CARCINOGENICITY BIOASSAYS OF VINYLIDENE CHLORIDE

- Inhalation -

Species	Dose	Total duration of observation	Findings
Sprague-Dawley rats	10, 25, 50, 100, 150 ppm 4 to 5 days/week for 12 months	137 weeks	Statistically significant increase in total mammary tumors, but not carcinomas alone, only at 10 and 100 ppm, no dose response
Swiss mice	10, 25 ppm 4 to 5 days/week for 12 months	121 weeks	Kidney carcinomas at 25 ppm in males
Chinese hamsters	25 ppm 4 to 5 days/week for 12 months	157 weeks	No statistically significant increase
Wistar rats	200 ppm for 6 months, followed by 100 ppm for 6 months, 5 days/week	Lifetime	No statistically significant increase
Sprague-Dawley rats	100, 75 ppm 5 days/week for 12 months	Lifetime	No statistically significant increase

RESULTS OF CARCINOGENICITY BIOASSAYS OF VINYLIDENE CHLORIDE

- Inhalation -

Species	Dose	Total duration of observation	Findings
CD-1 mice	55 ppm 5 days/week	12 months	No statistically significant increase
CD rats	55 ppm 5 days/week for 12 months	12 months	No statistically significant increase
Sprague-Dawley rats	25, 75 ppm for 24 months	104 weeks	No statistically significant increase
CD-1 mice	55 ppm, 5 days/week 1, 3, or 6 months	13, 15, or 18 months	No statistically significant increase
CD rats	55 ppm, 5 days/week 1, 3, 6, or 10 months	13, 15, 18, or 22 months	No statistically significant increase
Sprague-Dawley rats	10, 25, 50, 100, 150 ppm	52 weeks	No brain tumors

RESULTS OF CARCINOGENICITY BIOASSAYS OF VINYLIDENE CHLORIDE

- Ingestion -

Species	Dose	Total duration of observation	Findings
Sprague-Dawley rats	0.5, 5, 10, 20 mg/kg for 12 months	147 weeks	No statistically significant increase
Sprague-Dawley rats	50, 100, 200 ppm in drinking water	104 weeks	No statistically significant increase
Fischer 344 rats	5 ml/kg of a 1000 or 200 ppm solution	103 weeks	No statistically significant increase
B6C3F1 mice	10 ml/kg of a 1000 or 200 ppm solution	103 weeks	No statistically significant increase
Sprague-Dawley rats	0.5, 5, 10, 20 mg/kg/day	52-59 weeks	No brain tumors

SL 063312

RESULTS OF CARCINOGENICITY BIOASSAYS OF VINYLIDENE CHLORIDE

- Other -

Species	Dose	Total duration of observation	Findings
Ha:ICR Swiss mouse	121 mg/mouse skin application 3 times/week	Lifetime	No tumors
Ha:ICR Swiss mouse	2 mg/mouse subcutaneous injection once/week	Lifetime	No tumors at site of injection or in other organs
3 strains*	unknown	unknown	Negative

*Maltoni (cited in ICAIR, 1981).