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PRESENTATION ON THE MCA - TOXICOLOGY PROGRAM FOR VINYLIDENE
CHLORIDE TO BE GIVEN AT THE 1975 TAPPI JOINT PVDC/ADHESIVE
LAMINATING SEMINAR, HILTON HEAD INN, HILTON HEAD ISLAND,
SOUTH CAROLINA, 8:45 AM, NOVEMBER 19, 1975.

LADIES AND GENTLEMEN - GOOD MORNING

(Slide 1) I HAVE BEEN INVITED HERE TODAY TO DISCUSS THE
MANUFACTURING CHEMISTS ASSOCIATION PROGRAM FOR THE INVESTI-
GATION OF THE POTENTIAL TOXICOLOGIC EFFECTS AND PHARMACO-
DYNAMICS OF INHALED AND INGESTED VINYLIDENE CHLORIDE (VDC) IN
LABORATORY ANIMALS. THIS PROGRAM WHICH WAS INITIATED EARLY
IN 1974, IS BEING SPONSORED BY THE FOLLOWING FIFTEEN COMPANIES.

(Slide 2) THE STUDIES ARE BEING CONDUCTED IN THE TOXICOLOGY
RESEARCH LABORATORY OF THE DOW CHEMICAL COMPANY IN MIDLAND
MICHIGAN.

(Slide 3) THE VARIOUS STUDIES IN THIS PROGRAM ARE LISTED IN
THE NEXT SLIDE. THE STUDY INCORPORATING VINYLIDENE CHLORIDE
IN THE DRINKING WATER OF RATS FOR 90 DAYS AND THE 90 DAY
VAPOR INHALATION STUDY IN RATS HAVE BEEN COMPLETED. ALL OF
THE OTHER STUDIES HAVE BEEN STARTED. I WILL DISCUSS THE
INTENT OF THE VARIOUS STUDIES, THE RESULTS OF THE TWO COMPLETED
STUDIES AND THE DATA ON THOSE ON-GOING STUDIES WHICH ARE FAR
ENOUGH ADVANCED TO BE REPORTED ON.

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THE DESIGN OF THE 90 DAY AND 2 YEAR STUDIES INCORPORATING VINYLIDENE CHLORIDE IN THE DRINKING WATER OF RATS IS GIVEN ON THE NEXT SLIDES (*Slide 4+4a*). MALE AND FEMALE SPRAGUE-DAWLEY RATS, 6-7 WEEKS OLD, WERE USED IN THESE STUDIES. THE DRINKING WATER, CONTAINING VARIOUS CONCENTRATIONS OF VINYLIDENE CHLORIDE WAS SUPPLIED TO THE ANIMALS FROM 16 OZ BOTTLES WITH PLASTIC SCREW CAPS FITTED WITH A STAINLESS STEEL SIPPER TUBE HAVING A STAINLESS STEEL BALL IN THE TIP OF THE TUBE. USING THIS MODIFIED WATER BOTTLE, THE CONCENTRATION OF THE VINYLIDENE CHLORIDE CAN BE HELD FOR A PERIOD OF 24 HOURS WITHIN AN ACCEPTABLE RANGE (~10%). THE BOTTLES ARE EMPTIED AND RE-FILLED DAILY FROM FRESHLY PREPARED STOCK SOLUTIONS. THE STOCK SOLUTIONS ARE ALSO MADE UP DAILY. STOCK SOLUTIONS AND SOLUTIONS FROM THE WATER BOTTLES ARE ANALYZED FOR VINYLIDENE CHLORIDE THROUGHOUT THE STUDIES.

SIXTY-SIX RATS/SEX/DOSE LEVEL OF VINYLIDENE CHLORIDE AND 98 RATS/SEX AS CONTROLS WERE USED IN THESE STUDIES. THE VARIOUS PARAMETERS MONITORED DURING THE STUDY INCLUDE NON-PROTEIN SULFHYDRYL CONTENT OF THE LIVER AND KIDNEYS OF THE ANIMALS ON THE 90 DAY STUDY. THE PURPOSE OF THESE ANALYSES WAS TO HELP ELUCIDATE THE BIOCHEMICAL EFFECTS AND POSSIBLE MECHANISM OF TOXIC ACTION OF VINYLIDENE CHLORIDE. PARAMETERS ALSO (*Slide 5*) INCLUDED WERE CLINICAL OBSERVATIONS FOR CHANGES IN

THE 90-DAY STUDIES WERE CONDUCTED FOR EARLY DETECTION OF POSSIBLE TOXIC EFFECTS. INTERIM EVALUATION OF THE VARIOUS TOXICOLOGICAL PARAMETERS MONITORED IN THE 2 YEAR STUDIES, LIKEWISE, GIVE DATA ON THE TOXIC EFFECTS OF THE CHEMICAL. THE MAJOR CONCERN OF THE 2 YEAR STUDIES IS HOWEVER, THE INCIDENCE OF TUMOR FORMATION IN THE TREATED ANIMALS WHEN COMPARED WITH UNTREATED CONTROL ANIMALS. THE 3 GENERATION REPRODUCTION STUDY IS BEING CONDUCTED TO EVALUATE THE POSSIBLE EFFECTS OF VINYLIDENE CHLORIDE ON REPRODUCTIVITY OF THE ANIMALS. THE TERATOLOGY STUDIES ARE DESIGNED TO EVALUATE POSSIBLE EFFECTS ON THE UNBORN BY EXPOSING PREGNANT ANIMALS, BY INGESTION OR BY INHALATION, TO VINYLIDENE CHLORIDE. AND FINALLY, THE PHARMACODYNAMIC STUDIES ARE CONCERNED WITH THE ACTION OF VINYLIDENE CHLORIDE ON THE ANIMAL AND INVOLVE THE DETERMINATION OF THE RATE AT WHICH VINYLIDENE CHLORIDE IS ABSORBED INTO THE ANIMAL'S BODY, THE DISTRIBUTION IN THE BODY AND THE EXCRETION FROM THE BODY, AND BY DETERMINING THE PRODUCTS OF THE METABOLISM OF THE COMPOUND BY THE ANIMAL.

THE VINYLIDENE CHLORIDE USE IN THE VARIOUS TOXICITY STUDIES WAS PRODUCTION MATERIAL FROM THE DOW CHEMICAL COMPANY. THE MATERIAL WAS 99.5% (MINIMUM PURITY).

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APPEARANCE AND Demeanor, BODY WEIGHT, FOOD CONSUMPTION AND WATER CONSUMPTION AND PERIODIC HEMATOLOGY DETERMINATIONS, CLINICAL CHEMISTRIES (LIVER AND KIDNEY ENZYME STUDIES) AND URINALYSES. AT THE TERMINATION OF EACH STUDY, THE WEIGHT OF THE MAJOR ORGANS WERE MEASURED AND COMPLETE GROSS AND MICROSCOPIC EXAMINATION OF ORGANS AND TISSUES WERE MADE. THE HIGHEST CONCENTRATION OF VINYLIDENE CHLORIDE IN THE DRINKING WATER USED IN THESE STUDIES WAS DEPENDENT UPON THE SOLUBILITY OF VINYLIDENE CHLORIDE IN THE WATER. THE CONCENTRATIONS CHOSEN AND THE CALCULATED DOSE IN MG/KG/DAY ARE (Slide 6) GIVEN ON THE NEXT SLIDE. CALCULATIONS ON THE MARGIN OF SAFETY, WHICH THESE DOSE LEVELS WOULD REPRESENT IF THEY WERE "NO-EFFECT LEVELS", ARE GIVEN ON THE NEXT SLIDE (Slide 7). IN CALCULATING THE MARGIN OF SAFETY IT IS ASSUMED (Slide 8) THAT A MAN WEIGHING 75 KG INGESTS 1500 GRAMS OF FOOD PER DAY, AND THAT ALL HIS FOOD IS PACKAGED WITH MATERIAL MADE WITH VINYLIDENE CHLORIDE. THE RATIO OF THE AMOUNT INGESTED BY MAN TO THAT AMOUNT INGESTED BY ANIMALS THAT SHOWED "NO-ADVERSE EFFECT" IN THE TOXICOLOGIC STUDIES GIVES THE MARGIN OF SAFETY.

THE RESULTS OF THE 90 DAY STUDY INCORPORATING VINYLIDENE CHLORIDE IN THE DRINKING WATER OF RATS ARE (Slide 9) GIVEN ON THE NEXT SLIDE. THE AVERAGE DOSAGES IN MG/KG BODY WEIGHT WERE 6, 10 OR 19 FOR MALES AND 8, 13 OR 26 FOR FEMALES. ALL

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OF THE ANIMALS ON THIS STUDY SURVIVED. THERE WAS NO EVIDENCE OF A TOXICOLOGICAL EFFECT ASSOCIATED WITH THE INGESTION OF VINYLIDENE CHLORIDE AS MONITORED BY THE TEST PARAMETERS (refer to Slide 9). (Slide 10) MICROSCOPIC PATHOLOGIC EXAMINATION SHOWED MINIMAL LIVER CHANGES HAD OCCURRED AT THE 200 PPM CONCENTRATION ONLY. THE MICROSCOPIC FINDINGS AT THE TWO LOWER LEVELS WERE COMPARABLE TO THOSE IN THE CONTROL ANIMALS.

(Slide 11) ELEVEN MONTHS INTO THE 2 YEAR STUDY THERE WERE NO SIGNS OF TOXICITY AMONG THE ANIMALS. THE FOOD AND WATER CONSUMPTION OF THE ANIMALS ON THE VINYLIDENE CHLORIDE TREATED WATER WERE COMPARABLE TO THE UNTREATED CONTROLS.

AT THIS POINT IN TIME, IT IS CONCLUDED THAT REPEATED INGESTION OF 19-26 MG/KG OF VINYLIDENE CHLORIDE BY RATS RESULTS IN MINIMAL LIVER INJURY. THE AVAILABLE DATA ON THE INTERIM KILL DOES NOT SUGGEST A TUMORIGENIC COMPOUND-RELATED RESPONSE. THE CRITICAL TIME FOR ASSESSMENT FOR TUMORIGENIC POTENTIAL, HOWEVER, HAS NOT AS YET BEEN REACHED IN THIS STUDY SINCE THE DEVELOPMENT OF TUMORIGENIC RESPONSE REQUIRES A LONG LATENCY PERIOD OR A LONGER PERIOD OF TREATMENT.

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(Slide 4+4a) THE REPRODUCTION STUDY WAS STARTED IN A GROUP OF ANIMALS AFTER THEY HAD BEEN ON TEST FOR 90 DAYS. THESE ANIMALS WERE RANDOMLY SELECTED FOR BREEDING AND WERE RETURNED TO THE 2 YEAR STUDY; THE MALES AFTER BREEDING AND THE FEMALES AFTER THE YOUNG HAVE BEEN WEANED. FROM THE YOUNG OF THE FIRST GENERATION, MALES AND FEMALES ARE CHOSEN FOR MATING FOR THE SECOND GENERATION. THE SAME PROCEDURE THEN IS FOLLOWED FOR THE THIRD GENERATION. THE AVAILABLE DATA TO DATE IS ON THE FIRST GENERATION. THE RESULTS ARE GIVEN IN THE NEXT SLIDE. (Slide 12) THERE WERE NO STATISTICALLY SIGNIFICANT DIFFERENCES IN ANY OF THE PARAMETERS MONITORED BETWEEN TEST AND CONTROL ANIMALS. IT IS CONCLUDED THAT AS FAR AS THIS STUDY HAS BEEN ADVANCED, THE INDICATION IS THAT AS HIGH AS 19-26 MG/KG OF VINYLIDENE CHLORIDE HAS NO ADVERSE EFFECT ON THE REPRODUCTIVITY OF THE ANIMALS OR ON THEIR YOUNG.

(Slide 13) THE 90 DAY AND 2 YEAR INHALATION STUDIES ON VINYLIDENE CHLORIDE WERE INITIATED AT THE SAME TIME. TWENTY RATS/SEX/EXPOSURE LEVELS WERE USED FOR THE 90 DAY STUDY AND 100 RATS/SEX/DOSE LEVEL WERE USED FOR THE 2 YEAR STUDY. (Slide 14) THE DESIGN OF THE STUDIES IS GIVEN ON THE NEXT TWO SLIDES. INITIALLY THE EXPOSURE LEVELS USED FOR THESE STUDIES WERE 0, 10 AND 40 PPM WITH THE PROVISION THAT IF NO ADVERSE EFFECTS WERE SEEN AMONG A GROUP OF ANIMAL

SACRIFICED AT 30 DAYS, THE LEVELS WOULD BE INCREASED AT 25 AND 75 PPM, RESPECTIVELY. INTERIM KILLS WERE CONDUCTED AFTER 6 MONTHS AND 12 MONTHS FOR THE EVALUATION OF POSSIBLE PATHOLOGIC COMPOUND-RELATED CHANGES. THE (Slide 15) PARAMETERS MONITORED ARE THE SAME AS IN THE DRINKING WATER STUDY. CYTOGENETIC STUDIES TO EVALUATE THE POSSIBLE MUTAGENIC EFFECT OF VINYLIDENE CHLORIDE ARE INCLUDED IN THE VAPOR INHALATION STUDY. SUCH STUDIES ARE ALSO BEING CONDUCTED ON THE WEANLING RATS IN THE REPRODUCTION STUDY. RESULTS OF THESE STUDIES HAVE NOT AS YET BEEN REPORTED.

NO EFFECTS FROM EXPOSURE TO VINYLIDENE CHLORIDE VAPORS WERE SEEN AMONG THE RATS EXPOSED TO 10 OR 40 PPM FOR 30 DAYS. THE ONLY SIGNIFICANT FINDING SEEN IN THE RATS EXPOSED FOR 30 OR 90 DAYS TO 25 OR 75 PPM OF VINYLIDENE CHLORIDE WAS MINIMAL MICROSCOPIC CHANGES IN THE LIVER (CHARACTERIZED BY A MINIMAL INCREASE IN THE DEGREE OF VACUOLATION IN THE CYTOPLASM OF THE HEPATOCYTES). THESE MINIMAL CHANGES WOULD BE REVERSIBLE IF THE ANIMALS WERE PLACED ON UNTREATED WATER. SUBSEQUENT INTERIM KILLS AT 6 AND 12 MONTHS IN THE 2 YEAR STUDY CONTINUED TO SHOW MINIMAL MICROSCOPIC CHANGES IN THE LIVER. THE INCIDENCE OF OCCURRENCE OF THESE CHANGES WAS GREATER IN THE ANIMALS EXPOSED TO 75 PPM VINYLIDENE CHLORIDE AFTER 90 DAYS ON THE STUDY. AN INCREASED INCIDENCE WAS NOT SEEN IN

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THE ANIMALS EXPOSED TO 25 PPM UNTIL THE 12 MONTH INTERIM KILL. I SHOULD EMPHASIZE HERE THE INTENT OF THE 2 YEAR STUDY IS TO EVALUATE THE POSSIBLY TUMORIGENIC EFFECT OF VINYLIDENE CHLORIDE. AT THIS POINT IN TIME, THE CONCLUSION THAT CAN BE DRAWN IS THAT REPEATED EXPOSURE OF RATS TO 25 OR 75 PPM OF VINYLIDENE CHLORIDE VAPORS RESULTS IN MINIMAL LIVER INJURY. THE AVAILABLE DATA ON THE ANIMALS AT THE INTERIM KILLS DOES NOT SUGGEST A TUMORIGENIC EXPOSURE-RELATED RESPONSE. HOWEVER, IT MUST BE POINTED OUT THAT THE NUMBER OF ANIMALS EXAMINED SO FAR IS LIMITED AND THE CRITICAL TIME FOR TUMOR OCCURRENCE HAS NOT BEEN REACHED. THIS WILL HAVE TO WAIT UNTIL THE 2 YEAR STUDY IS TERMINATED.

THE OTHER STUDY WHICH IS FAR ENOUGH ALONG TO REPORT ON, IS THE 90 DAY TOXICITY STUDY IN DOGS. (Slide 16) THIS STUDY IS BEING CONDUCTED TO ASSESS THE EFFECTS OF INGESTED VINYLIDENE CHLORIDE IN A NONRODENT SPECIES. MALE AND FEMALE BEAGLE DOGS ARE BEING GIVEN GELATIN CAPSULES CONTAINING VINYLIDENE CHLORIDE CONTAINING VINYLIDENE CHLORIDE IN PEANUT OIL ONCE DAILY. THE DOSE LEVELS ARE APPROXIMATELY 6, 12 AND 25 MG/KG/DAY. CONTROL DOGS ARE GIVEN CAPSULES CONTAINING ONLY THE PEANUT OIL. THIRTY DAYS INTO THIS STUDY, NO ADVERSE SIGNS HAVE BEEN OBSERVED IN ANY OF THE DOGS.

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TO SUMMARIZE - NO ADVERSE EFFECTS OTHER THAN SOME MINIMAL LIVER CHANGES IN RATS AT THE TOP DOSE LEVEL AT THE 90 DAY ORAL STUDY AND MINIMAL LIVER CHANGES AT 25 AND 75 PPM VAPOR CONCENTRATIONS IN RATS EXPOSED DURING THE FIRST YEAR OF A 2 YEAR STUDY. AS THIS POINT IN TIME, THERE IS NO EVIDENCE OF A TUMORIGENIC EFFECT TO INHALED OR INGESTED VINYLIDENE CHLORIDE.

ALL STUDIES IN THIS PROGRAM SHOULD BE COMPLETED DURING 1976. ALLOWING FOR SUFFICIENT TIME TO ANALYZE THE DATA FROM THE ON-GOING STUDIES, I BELIEVE THAT THE FULL REPORT ON THE TOXICITY OF VINYLIDENE CHLORIDE WILL BE READY EARLY IN 1977.

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