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FILE NUMBER : 57
AUTHOR(S) : CONOLLY, R.B.; JAEGER, R.J.
TITLE : ACUTE HEPATOTOXICITY OF VINYL CHLORIDE AND ETHYLENE:
: MODIFICATION BY TRICHLOROPROPENE OXIDE, DIETHYLMALEATE, AND
: CYSTEINE.
PUBLICATION SOURCE : TOXICOL APPL PHARMACOL 50:523-531.1979
LANGUAGE : ENG.
COUNTRY : USA

VC metabolism
Bioassay
Carcinogenicity

**** EXPERIMENTAL DESIGN ****

TRICHLOROPROPENE OXIDE (TCPO) IS AN IN VITRO INHIBITOR OF EPOXIDE HYDRASE AND AN IN VITRO DEPLETOR OF HEPATIC GLUTATHIONE. DIETHYLMALEATE (DEM) IS ALSO AN EFFECTIVE DEPLETOR OF HEPATIC GLUTATHIONE. CYSTEINE IS A RATE-LIMITING GLUTATHIONE PERCURSOR.

MALE HOLTZMAN RATS (WEIGHING 170-150 g) WERE FED AD LIBITUM EXCEPT WHEN FASTED (18 HRS PRIOR TO VC OR ETHYLENE EXPOSURE) OR DURING EXPOSURE AND AFTER EXPOSURE. THE RATS WERE SACRIFICED: 24 HR AFTER THE START OF EXPOSURE (4 HR EXPOSURE) FOR DETERMINATION OF SDH ACTIVITY; 2 OR 4 HR FROM THE START OF A 4 HR INHALATION EXPOSURE FOR GLUTATHIONE (NON PROTEIN SULFHYDRYL CONTENT) DETERMINATIONS. THE RATS WERE PRETREATED WITH ARCOLOR 1254 (PCB) ONCE/DAY FOR 3 DAYS. ON THE 3RD DAY VC OR ETHYLENE EXPOSURE BEGAN AFTER PRETREATMENT. CYSTEINE (0.5 g/kg), DEM (0.5 ml/kg), OR TCPO (0.1 ml/kg) WERE GAVAGED WITHIN 1/2 HR BEFORE THE START OF INHALATION EXPOSURE. TO DETERMINE THE EFFECT OF TCPO ON THE HEPATOTOXICITY OF VC: FASTED RATS INHALED FOR 4 HR EITHER 1000, 4500, OR 8000 ppm; FED RATS INHALED 10000, 25000, OR 40000 ppm. THE EFFECT OF TCPO ON THE ACUTE HEPATOTOXICITY OF ETHYLENE IN PCB-PRETREATED FASTED RATS WAS DETERMINED AFTER THEY INHALED EITHER 6000, 12000, 18000, OR 15000 ppm AND FED RATS INHALED EITHER 10000, 15000, OR 50000 ppm. FOR THE DETERMINATION OF THE EFFECT DEM HAS ON THE ACUTE HEPATOTOXICITY OF VC AND ETHYLENE, IN BOTH FED AND FASTED PCB PRETREATED, RATS INHALED 10000 AND 10000 ppm, RESPECTIVELY. THE EXPOSURES TO VC, IN PCB-PRETREATED FASTED RATS THAT WERE GAVAGED WITH CYSTEINE, WERE EITHER 5000, 8000, 12000, OR 17000 ppm. PCB-PRETREATED RATS GIVEN CYSTEINE WERE EXPOSED TO EITHER 8000, 16000, OR 24000 ppm ETHYLENE. VEHICLE CONTROLS WERE RUN WITH EACH GROUP.

**** KEYWORDS ****

VINYL CHLORIDE; ANIMAL STUDY; RATS; INHALATION; ACUTE HEPATOTOXICITY; ETHYLENE; TRICHLOROPROPENE OXIDE; DIETHYLMALEATE; CYSTEINE; POLYCHLORINATED BIPHENYL; GLUTATHIONE; EPOXIDE HYDRASE; MIXED FUNCTION OXIDASE SYSTEM; NONPROTEIN SULFHYDRYL CONTENT; SERUM SORBITOL DEHYDROGENASE; SDH; LIVER WEIGHT; FASTED RATS; AROCLOR 1254; ELECTROPHILE; METABOLISM; ARYL HYDROCARBON

HYDROXYLASE.

**** ABSTRACTS ****

AFTER INHALATION OF VC THE TCPO TREATED PCB (ARCOLOR 1254)-PRETREATED FASTED RATS SHOWED SIGNIFICANT ACUTE HEPATOTOXIC EFFECTS, I.E., INCREASES IN LIVER WEIGHT AND SDH ACTIVITY. THE FASTED VEHICLE GROUP EXPOSED TO 4500 ppm HAD MINIMAL INJURY (SDH ACTIVITY 26.8), BUT THE FASTED TCPO GROUP EXPOSED TO THE SAME CONCENTRATION HAD SIGNIFICANT EFFECTS (SDH ACTIVITY 133). HOWEVER, GLUTATHIONE (GSH) CONCENTRATIONS WERE NO DIFFERENT BETWEEN FASTED VEHICLE AND FASTED TCPO GROUPS. THE INCREASED TOXICITY OF VC IN TCPO PRETREATED RATS IS PROBABLY DUE TO INHIBITION OF EPOXIDE HYDRASE. THE IMPORTANCE OF EPOXIDE HYDRASE IS SHOWN WITH THE DEPLETION OF GSH IN BOTH GROUPS OF FASTED RATS.

THE TCPO PRETREATMENT IN FASTED RATS EXPOSED TO 25000 ppm ETHYLENE SHOWED DEPLETED GLUTATHIONE AT 2 HR BUT NOT AT 4 HR, AND WAS FOUND NOT TO BE ASSOCIATED WITH THE HEPATOTOXIC RESPONSE TO ETHYLENE. THE DATA SUGGEST THAT EPOXIDE HYDRASE AND GLUTATHIONE-S-ALKYLEPOXYTRANSFERASE DO NOT ACT ON ETHYLENE OXIDE. HOWEVER, ETHYLENE OXIDE MAY NOT BE A TOXIC METABOLITE OF ETHYLENE.

FASTING NOT DEM TREATMENT SIGNIFICANTLY INCREASED THE TOXICITY OF 10000 ppm VC EXPOSURE IN PCB-PRETREATED RATS. THE FED AND FASTED VEHICLE TREATED GROUPS EXPOSED TO 10000 ppm VC HAD DEPLETED GSH (NO DIFFERENCE BETWEEN THE TWO GROUPS FOUND). IT APPEARS THAT SOME ACTION OF DEM IN ADDITION TO GLUTATHIONE DEPLETION, E.G. INHIBITION OF ARYL HYDROCARBON HYDROXYLASE (CYTOCHSOME P-488), COULD EXPLAIN THE LACK OF POTENTIATION OF VC TOXICITY.

THE DEM TREATED RATS EXPOSED TO 20000 ppm ETHYLENE HAD DEPLETED HEPATIC GSH IN BOTH FED AND FASTED RATS. HOWEVER, THE GSH DEPLETION IN THESE ETHYLENE EXPOSED RATS WAS NOT ASSOCIATED WITH ANY INCREASE IN TOXICITY (SDH ACTIVITY IN ALL ETHYLENE TREATED GROUPS WAS AROUND 300).

CYSTEINE PREVENTED GSH DEPLETION AND THE ACUTE HEPATOTOXIC EFFECTS IN FASTED PCB PRETREATED RATS DURING EXPOSURE TO 8000 ppm VC. THE LIVER WEIGHT AND SDH ACTIVITY WERE SIGNIFICANTLY HIGHER IN VEHICLE TREATED THAN CYSTEINE TREATED. AN EXPOSURE TO 12000 ppm AND ABOVE OF VC, HOWEVER, CAUSED DEVELOPMENT OF HEPATOTOXIC EFFECTS. THEREFORE, CYSTEINE PROTECTION WAS NOT COMPLETE. THE DEVELOPMENT OF LIVER INJURY IN THE CYSTEINE TREATED RATS EXPOSED AT THE HIGHER CONCENTRATIONS OF VC MAY BE DUE TO THE FACT THAT MUCH OF THE -SH WAS PRESENT AS CYSTEINE RATHER THAN GSH.

CYSTEINE TREATMENT OF PCB-PRETREATED RATS HAD NO EFFECT ON THE TOXICITY OF ETHYLENE AT THE EXPOSURES TESTED. THEREFORE, GSH DOES NOT PLAY AN IMPORTANT ROLE IN ACUTE ETHYLENE HEPATOTOXICITY.

THE AUTHORS CONCLUDE THAT IN PCB-TREATED RATS , LIVER GSH AND EH INFLUENCE THE ACUTE HEPATOTOXICITY OF VC.

SEP 23, 1980 1192

FILE NUMBER : 226
AUTHOR(S) : LOCKER, G.Y.; DOROSHOW, J.H.; ZWELLING, L.A.; CHABNER, B.A.
TITLE : THE CLINICAL FEATURES OF HEPATIC ANGIOSARCOMA: A REPORT OF FOUR CASES AND A REVIEW OF THE ENGLISH LITERATURE.
PUBLICATION SOURCE : MEDICINE(BALTIMORE) 58(1):48-64,1979.
LANGUAGE : ENG.
COUNTRY : USA

VC. Angiosarcoma Human Occupational Morbidity.

**** EXPERIMENTAL DESIGN ****

THE REVIEW OF THE ENGLISH LITERATURE REVEALED 103 CASES OF HEPATIC ANGIOSARCOMA, WHICH 4 ARE DISCUSSED AS CASE REPORTS. CASE 1: WAS A 42 YEAR OLD WHITE MALE, WHO HAD WORKED IN A VC POLYMERIZATION PLANT FOR 20 YRS. AND HAD A SIGNIFICANT ALCOHOL CONSUMPTION (A PINT OF WHISKEY/DAY). THE SECOND CASE, A 60 YR. OLD WHITE MALE, WAS ALSO EMPLOYED IN VC POLYMERIZATION (FOR 37YRS.). CASE 3 WAS A 23 YR. OLD MALE WELDER WITH NO KNOWN EXPOSURE TO VC, THOROTRACT OR ARSENICALS; HOWEVER, HE HAD A LONG HISTORY OF ALCOHOL AND BARBITURATE ABUSE. THE FOURTH CASE IS A 65 YR. OLD WOMAN, WHO ALSO HAD NO KNOWN HISTORY OF EXPOSURE TO ANGIOSARCOMA LINKED SUBSTANCES NOR ALCOHOL ABUSE. IN THE REVIEW ALL CASES OF JUVENILE HEPATIC HEMANGIOENDOTHELIOMA (ANGIOSARCOMA) ARE EXCLUDED.

**** KEYWORDS ****

HUMAN; CASE REPORTS; HEPATIC ANGIOSARCOMA; VINYL CHLORIDE; PVC WORKERS; OCCUPATIONAL EXPOSURE; THOROTRAST; ARSENICALS; RADIUM; IDIOPATHIC HEMOCHROMATOSIS; NONEPIDEMIOLOGICAL CASES; MEDICAL HISTORY; ALCOHOL; ALKALINE PHOSPHATASE; TOTAL BILIRUBIN; HEPATIC ARTERIOGRAM; HYPERVASCULAR LESION; LAPAROTOMY; NODULAR LIVER; PORTAL FIBROSIS; CIRRHOSIS; LDH; SGOT; ADRIAMYCIN; CYCLOPHOSPHAMIDE; HEMORRHAGE; AUTOPSY; NEOPLASM; METASTASES; REGIONAL LYMPH NODES; LUNG; BONE; SKIN; LIVER SCAN; BIOPSY; HEPATOMEGALY; CARCINOEMBRYONIC ANTIGEN; CEA; ALPHAFETOPROTEIN; AFP; HEMIDIAPHRAGM; BILATERAL FILLING DEFECTS; HEPATOSPLENOMEGALY; ABDOMINAL PAIN; WEAKNESS; FATIGUE; WEIGHT LOSS; ASCITES; JAUNDICE; SPLENOMEGALY; THROMBOCYTOPENIA; PROTHROMBIN TIME; CLINICAL FEATURES; CHEMOTHERAPY; 5 FLOUROURICIL; 5 FU.

**** ABSTRACTS ****

OF THE 103 DIAGNOSED HEPATIC ANGIOSARCOMA CASES 42% HAVE AN APPARENT ETIOLOGY: 22 PATIENTS WERE VC WORKERS, 15 PATIENTS RECIEVED THOROTRAST, 2 PATIENTS WERE EXPOSED TO ARSENICALS, 1 PATIENT HAD BEEN EXPOSED TO RADIUM AND 3 HAD UNDERLYING IDIOPATHIC HEMOCHROMATOSIS. HEPATIC ANGIOSARCOMA OCCURS RARELY AND IS ABOUT 1/30TH AS COMMON AS HEPATOCELLULAR CARCINOMA. ANGIOSARCOMA IS MORE COMMON IN MIDDLE AGED MEN. OVERALL THERE IS A 4:1 RATIO, OF MALE TO FEMALE, AND IN THE NONEPIDEMIOLOGIC AND THOROTRAST SUB-

GROUPS THERE IS A 3:1 RATIO OF MALES TO FEMALES. THE MEAN AGE AT PRESENTATION OVERALL IS 53, HOWEVER, THE VC WORKERS HAVE A LOWER MEAN AGE, 50 AT THE TIME OF DIAGNOSIS. THESE DIFFERENCES AND OTHERS BETWEEN THE ETIOLOGICAL SUBGROUP IS PROBABLY DUE TO THE DIFFERENCES IN THE NATURE OF CARCINOGENIC EXPOSURE. THE INCREASE IN ANGIOSARCOMA CASES SINCE 1970 IS NOT ONLY DUE TO MORE SOPHISTICATED PATHOLOGICAL DIAGNOSIS, BUT AN INCREASED INCIDENCE.

THE 15 THOROTRAST TREATED PATIENTS DEVELOPED ANGIOSARCOMA 24 YRS. AFTER INJECTION. THE 2 PATIENTS THAT TOOK ARSENICALS, FOWLER'S SOLUTION (1% ARSENIC) ORALLY, DEVELOPED ANGIOSARCOMA 24 YRS. AFTER THE FIRST INGESTION. THERE IS ONE CASE OF HEPATIC ANGIOSARCOMA CAUSED BY A RADIUM NEEDLE IMPLANT AND THE LATENCY PERIOD WAS ONLY 3 YRS. THE 3 PATIENTS THAT HAD IDIOPATHIC HEMOCHROMATOSIS (IRON DEPOSITION THROUGHOUT THE BODY) DEVELOPED ANGIOSARCOMA AND ALL AT AUTOPSY REVEALED CIRRHOSIS. THE FINDINGS WITH THOROTRAST AND ARSENICALS INDICATE THAT MORE ANGIOSARCOMAS WILL BE DIAGNOSED IN THE FUTURE. THE ASSOCIATION WITH HEMOCHROMATOSIS AND HEPATOMAS IS MUCH HIGHER THAN ANGIOSARCOMA INCIDENCE BUT THE AUTHOR BELIEVES IMPROVED TREATMENT WITH THE DISEASE WILL INCREASE THIS PERCENTAGE.

IN THE 20 PATIENTS THAT WERE EXPOSED TO VC, THEY GENERALLY WERE HEALTHY UNTIL THE TIME OF TUMOR PRESENTATION. THE LATENCY PERIOD RANGED FROM 11 TO 37 YRS. (MEAN WAS 19 YRS.) AND IN HALF THE CASES EXPOSURES WERE CONTINUOUS, IN OTHERS INTERMITTENT. IN CASES 1 AND 2 THE PATIENTS WERE REFERRED, BECAUSE OF SOME ABNORMAL LIVER FUNCTION TESTS IN ROUTINE SURVEILLANCE SCREENING TESTS. CASE 1 WAS ASYMPTOMATIC, BUT CASE 2'S SYMPTOMS WERE WEIGHT LOSS, FATIGUE AND RIGHT UPPER QUADRANT PAIN AND HEPATOMEGALY WAS OBSERVED.

THE SYMPTOMS OF HEPATIC ANGIOSARCOMA ARE NON-SPECIFIC AND CONSISTENT WITH MANY DIAGNOSES. THE MOST COMMON COMPLAINTS ARE ABDOMINAL PAIN, WEAKNESS, FATIGUE AND WEIGHT LOSS. MANY PATIENTS ARE SYMPTOMATIC AND A DIAGNOSIS IS GIVEN WHEN ROUTINE SCREENING OR TREATMENT FOR UNRELATED ILLNESSES REQUIRES FURTHER INVESTIGATION. THE VC WORKERS TENDED TO HAVE LESS PROMINENT ABDOMINAL COMPLAINTS. OVERALL, THE HEPATIC ANGIOSARCOMA PATIENTS PRESENT SIGNS OF HEPATOMEGALY, ASCITES AND JAUNDICE, BUT VC WORKES PESENTED THEM LESS COMMONLY AND SPLENOMEGALY WAS MORE PREVALANT. THE BIOCHEMICAL FINDINGS WERE ALSO NON-SPECIFIC, HOWEVER 62 HAD AT LAST ONE ABNORMAL TEST (64 TESTED/103 PATIENTS). THE MOST COMMON ABNORMALITY WAS ELEVATED ALKALINE PHOSPHATASE OR SGOT. THERE WERE COMMON HEMATOLOGICAL FEATURES SEEN: THROMBOCYTOPENIA (54%) AND ELEVATED PROTHROMBIN TIME (76%). THERE WERE NO CASES REPORTED WITH HEPATITIS ASSOCIATED ANTIGEN, CEA OR AFP. THE RADIOLOGICAL EVALUATIONS WERE NON-SPECIFIC TOO, EXCEPT FOR THE ARTERIOGAPHY (14/16 CASES). HEPATIC SCINTIGAPHY WAS ABNORMAL IN ALMOST ALL CASES TESTED (30/31). DISTINCT FILLING DEFECTS WERE FOUND IN 70% OF THE CASES, AND THE OTHERS HAD A NON-SPECIFIC NONHOMOGENEOUS UPTAKE. THEREFORE, THE AUTHORS BELIEVE SCINTIGRAPHY MAY NOT BE A USEFUL SCREENING TEST FOR ANGIOSARCOMA. ARTERIOGRAPHY IS SUGGESTED AS A MORE USEFUL TOOL FOR DIAGNOSIS OF ANGIOSARCOMA AND THE EVALUATION OF RESPONSE TO THERAPY. ANGIOSARCOMA WAS DIAGNOSED IN 65% OF

THE OPEN BIOPSIES COMPARED TO 25% OF THE CLOSED BIOPSIES. 16% OF ALL LIVER BIOPSIES LED TO BLEEDING, HEMMORHAGING, AND LIGATION OF THE HEPATIC BLEEDING AND 3 *PATIENTS DIED*. ABDOMINAL BLEEDING WAS ALSO A PROBLEM ENCOUNTERED WITH THESE PATIENTS (27%). THE HEMORRHAGIC PROBLEMS SEEN MAY BE DUE TO PERIPHERAL DESTRUCTION OF BLOOD ELEMENTS; i.e., INTRAVASCULAR COAGULATION WITH THROMBOCYTOPENIA, HYPOPROTHROMBINEMIA, AND ELEVATED FIBRIN SPLIT PRODUCT (5%); AND PERIPHERAL PLATELET DESTRUCTION (9%). CASE 2 HAD EVIDENCE OF PERIPHERAL PLATELET DESTRUCTION. ANTEMORTEM METASTASES WAS SEEN IN ONLY 7 PATIENTS (INCLUDING CASE 4). THE PATIENTS GENERALLY LIVE FOR A SHORT PERIOD AFTER DIAGNOSIS, THE MEDIAN SURVIVAL WAS 5.5 MONTHS. THE MOST COMMON CLINICAL CAUSES OF DEATH ARE HEPATIC FAILURE AND INTRABDOMINAL HEMORRHAGE. CIRRHOSIS (20%) AND HEPATIC PORTAL FIBOSIS (18%) WAS FOUND ON AUTOPSY. AUTOPSIES ALSO REVEALED METASTASES, IN OVER 60% OF THE PATIENTS, INCLUDING LUNG, SPLEEN, ADRENAL, REGIONAL NODES AND BONE.

NINETEEN OF THE 34 PATIENTS THAT WERE DIAGNOSD TO HAVE ANGIOSARCOMA AT BIOPSY WERE TREATED WITH CHEMOTHERAPY. THERAPY WAS CURATIVE IN NO PATIENT, BUT SOME SHOWED CLINICAL RESPONSES WITH IMPROVED STATUS AND TEMPORARY TUMOR REGRESSION. THIS FINDING WAS REPORTED IN THE 4 CASES DISCUSSED; THE INVESTIGATORS TREATED THE PATIENTS WITH ADRIAMYCIN, AND TWO PATIENTS HAD OBJECTIVE ANTITUMOR RESPONSES. TUMOR REGRESSION HAS ALSO BEEN DESCRIBED IN PATIENTS TREATED WITH CYCLOPHOSPHAMIDE OR 5-FLOUROURACIL (5-FU) ALONE OR IN COMBINATION WITH SURGERY OR RADIOTHERAPY.

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FILE NUMBER : 300
AUTHOR(S) : PETO, R.
TITLE : CARCINOGENIC EFFECTS OF CHRONIC EXPOSURE TO VERY LOW LEVELS
: OF TOXIC SUBSTANCES
PUBLICATION SOURCE : ENVIRON HEALTH PERSPECT 22:155-159,1978
LANGUAGE : ENG
COUNTRY : GR BR

Threshold
VC
Extrapolation
model
Statistics

***** EXPERIMENTAL DESIGN *****

THE AUTHOR PRESENTED A DOGMA AND STATISTICAL MODEL TO SUPPORT HIS OPINION. THE PROBABILITY OF GETTING A NEOPLASM OF INTEREST BY A GIVEN CHRONIC EXPOSURE IS GRAPHED P (a, d), WHERE A = THE AGE THAT CANCER INDUCTION IS FOUND AND D = AVERAGE DOSE RATE OF THE CARCINOGENIC AGENT IN UNITS PER DAY. IF IT IS ASSUMED THAT OTHER AGENTS MAY ALSO TRANSFORM THE CELL'S PHENOTYPE FROM NORMAL TO NEOPLASTIC, THE TOTAL EFFECTIVE DOSE CAUSING THIS CHANGE INCLUDES THE DOSE DUE TO BACKGROUND CARCINOGENS, SPONTANEOUS CELLULAR ACCIDENTS, etc. PLUS THE DOSE OF THE CARCINOGEN OF INTEREST. THE AFFECT OF THRESHOLD WAS DISCUSSED, AS WELL AS COUNTER ARGUMENTS TO THE AUTHOR'S DOGMA. THREE MAIN TYPES OF DOSE-RESPONSE RELATIONSHIPS IN ANIMAL EXPERIMENTAL STUDIES, AND THE CONSEQUENTIAL STATISTICAL METHODS ARE PRESENTED.

***** KEYWORDS *****

VINYL CHLORIDE; HUMAN POPULATION; RESIDENTIAL EXPOSURE; DOSE RESPONSE RELATIONSHIP; CARCINOGENS; THRESHOLD; RISK; PROBABILITY; AMBIENT AIR; STATISTICAL MODELS .

***** ABSTRACTS *****

THE AUTHOR PRESENTS HIS DOGMA WITH A HYPOTHETICAL SITUATION, WHERE VC AMBIENT AIR LEVELS AROUND A VC PLANT MIGHT INDUCE CANCERS. AT THESE LOWER DOSE RATES (i.e., SAY CANCERS ARE CAUSED AT 0.01 ppm AND THE AMBIENT CONCENTRATION IS 0.001 ppm) THERE WILL BE FEWER CASES OF CANCERS THAN AT HIGHER DOSE RATES. HOWEVER, THE AGE DISTRIBUTION WILL BE THE SAME, THE CANCERS WILL BE PROPORTIONAL TO THE DOSE, AND NO THRESHOLD IS ANTICIPATED.

USING THE STATISTICAL MODEL PRESENTED BY THE AUTHOR THE GRAPH OF P (a,d) AGAINST D HAS A POSITIVE SLOPE. THIS SUPPORTS THE AUTHOR'S DOGMA SINCE, AT LOW DOSE RATES: (1) THE AGE DISTRIBUTION OF EXTRA TUMORS IS INDEPENDENT OF THE DOSE RATE AND THAT EXPECTED NUMBER OF EXTRA TUMORS IS SIMPLY PROPORTIONAL TO THE DOSE. THE PATHOLOGICAL CHANGES IN MAN CAUSED BY CARCINOGENS MAY BE FOUND EVEN WITH AGENTS CONSIDEED TO HAVE THRESHOLD TYPE ACTION, SINCE MAN IS SO HETEROGENEOUS. THEREFORE, THE AUTHOR BELIEVES HIS DOGMA SHOULD BE THE FOUNDATION OF REGULATORY ACTION.

THERE ARE TWO COUNTER ARGUMENTS PRESENTED: (1) THE LEVEL WHEN A THRESHOLD IS OBSERVED AND (2) THAT AT LOW ENOUGH DOSE LEVELS ALMOST ALL TUMORS WOULD OCCUR LONG AFTER AGE 100 AND SO WOULD BE IRRELEVANT TO THE HUMAN CONDITION. THE AUTHOR INDICATES THE FIRST COUNTER ARGUMENT DOES NOT TAKE INTO CONSIDERATION BACKGROUND CARCINOGENS AND DEPENDS ON A SAFE RISK RATHER THAN A ZERO RISK. THE SECOND COUNTER ARGUMENT IS BASED ON STUDIES WHERE HIGH LEVELS OF CARCINOGENIC AGENTS WERE GIVEN REPEATEDLY TO EXPERIMENTAL ANIMALS.

THIS COUNTER ARGUMENT IS CONSIDERED BY THE AUTHOR TO BE BASED ON TOO HIGH DOSE LEVELS GIVEN TO EXPERIMENTAL ANIMALS AND ONLY THE FIRST OF SEVERAL TUMORS THAT THE ANIMAL DEVELOPS WOULD BE OBSERVED.

THE EXPEIMENTALLY OBSERVABLE RANGE AT WHICH ATTRIBUTABLE RISK CAN BE CHARACTERIZED IS 10% AND UPWARDS. MATHMATICAL MODELS ATTEMPT TO USE THESE EXPERIMENTAL RESULTS TO ESTIMATE THE DOSE RESPONSE DATA TO ESTIMATE THE DOSE RESPONSE RELATIONSHIP IN THE UNOBSERVABLE RANGE (1% AND DOWNWARDS) WHICH MAY BE VALID AS A BASIS FOR LEGISLATION. THE AUTHOR PRESENTS 3 CASE GRAPHS SHOWING: (1) DOSE LINEAR GRAPH THROUGH ZERO WITH THE UPPER AND LOWER CONFIDENCE LIMITS ON THE RISK AT LOW DOSES, WHICH GENERALLY DIFFER FROM EACH OTHER BY LESS THAN A FACTOR A 2; (2) NO SIGNIFICANT EFFECT AT ANY OF THE DOSE LEVELS WITH A LOWER CONFIDENCE LIMIT OF ZERO AND THE UPPER CONFIDENCE LIMIT A STRAIGHT LINE THROUGH ZERO, THEREFORE THIS SUBSTANCE SHOWS NO CARCINOGENICITY; (3) AN UPWARD CURVATURE OF THE DOSE RESPONSE IN THE OBSERVABLE RANGE TO SUGGEST EITHER THAT A THRESHOLD EXISTS, OR THAT THE RISK AT THE LOWEST DOSE MAY BE MUCH LESS THAN 0.1 OR 0.01 TIMES THE EFFECT AT THAT DOSE LEVEL. CASES 1 AND 3 ARE CONSIDERED SUFFICIENTLY ACCURATE TO ASSIST IN RATIONAL LEGISLATION.

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