

SACCHARIN, CYCLAMATE, AND HUMAN BLADDER CANCER: NO EVIDENCE OF AN ASSOCIATION

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PURPOSE: ON THE BASIS OF ANIMAL TESTS, TWO MAJOR NONNUTRITIONAL SWEETENERS (NNS), CYCLAMATE AND SACCHARIN, HAVE BEEN BANNED BY THE US GOVERNMENT AS SUSPECTED HUMAN CARCINOGENS. "THE RELEVANCE OF ANIMAL TESTS TO THE PROBLEM OF HUMAN CANCER ETIOLOGY IS UNCLEAR. SPECIES AND STRAINS WITHIN SPECIES DIFFER WIDELY IN THEIR RESPONSE TO THE SAME ENVIRONMENTAL AGENTS. WHETHER CARCINOGENIC RISKS TO MODERATELY EXPOSED HUMANS CAN BE INFERRED FROM MASSIVELY EXPOSED ANIMALS IS ALSO MOOT. IN ADDITION TO VARIATIONS IN DOSAGE, CONSIDERATION MUST ALSO BE GIVEN TO DURATION OF EXPOSURE, ROUTE OF ADMINISTRATION, AND OTHER DETAILS OF THE EXPERIMENTAL CONDITIONS."

WHILE SEVERAL EPIDEMIOLOGICAL INVESTIGATIONS HAVE FAILED TO REVEAL A SIGNIFICANT NNS-BLADDER CANCER CONNECTION, A LARGE CANADIAN STUDY HAS REPORTED A 60% ELEVATION OF BLADDER CANCER RISK AMONG MALE NNS USERS. THIS PAPER REPORTS ANOTHER LARGE BLADDER CANCER INCIDENCE STUDY CONDUCTED AMONG NNS USERS AND NONUSERS, INCLUDING BOTH SMOKERS AND NONSMOKERS, IN THE BALTIMORE, MARYLAND, AREA. PRELIMINARY FINDINGS OF THIS STUDY HAVE BEEN REPORTED EARLIER (DOCUMENT #51741).

METHODS: NNS USE AS TABLETS, POWDERS, DROPS, DIET FOOD, AND/OR COLAS, AND SMOKING HABITS WERE DETERMINED BY PERSONAL INTERVIEW AND WERE COMPARED BETWEEN 519 SURVIVING MALE AND FEMALE PATIENTS WITH BLADDER CANCER, REPORTED IN THE BALTIMORE AREA FROM 1972 TO 1975, AND 519 AGE-, SEX-, RACE-, AND MARITAL STATUS-MATCHED CANCER-FREE CONTROL PATIENTS WHO HAD BEEN TREATED AT THE SAME HOSPITALS. *Bl*

FINDINGS: THE OVERALL RELATIVE RISK OF BLADDER CANCER AMONG THE NNS USERS (1.11 FOR MALES, 0.80 FOR FEMALES, 1.04 FOR BOTH SEXES) WAS

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NOT SIGNIFICANTLY HIGHER THAN THAT AMONG THE NONUSERS (1.0). THIS FINDING WAS VALID WHEN THE DATA WERE ANALYZED SEPARATELY FOR THE SACCHARIN USERS AND THE CYCLAMATE USERS, WHEN THE NNS DOSE-RELATED ANALYSES WERE DONE, AND WHEN ANALYSES WERE DONE "AFTER SIMULTANEOUS ADJUSTMENT FOR THE EFFECTS OF SMOKING, OCCUPATION, AGE, DIABETES MELLITUS, AND A NUMBER OF OTHER POTENTIALLY CONFOUNDING FACTORS."

THE BLADDER CANCER PATIENTS (NNS USERS AND NONUSERS TOGETHER) WERE SIGNIFICANTLY MORE LIKELY THAN CONTROLS TO USE TOBACCO AND TO SMOKE CIGARETTES. MALE BLADDER CANCER PATIENTS SMOKED CIGARETTES FOR APPROXIMATELY 5 YR LONGER, ON THE AVERAGE, THAN THEIR CONTROLS. RELATIVE RISKS AMONG SMOKERS WERE 1.78 AND 1.57 IN MEN AND WOMEN, RESPECTIVELY.

WHEN NONADJUSTED RELATIVE RISKS OF BLADDER CANCER WERE CALCULATED SEPARATELY FOR SMOKING AND NONSMOKING NNS USERS, THE RISK FOR SMOKERS (0.84) AND NONSMOKERS (1.36) DID NOT DIFFER SIGNIFICANTLY FROM THE RISK AMONG THE SMOKING AND NONSMOKING NONUSERS. HOWEVER, THE RELATIVE RISK OF 2.61, CALCULATED FOR MALE NONSMOKING USERS AFTER ADJUSTMENT FOR POSSIBLE CONFOUNDING FACTORS, WAS SIGNIFICANTLY HIGHER THAN FOR MALE NONSMOKING NONUSERS.

DISCUSSION: "OUR FINDINGS SUGGEST THAT INGESTION OF NNS, AT LEAST AT THE MODERATE DIETARY LEVELS REPORTED BY THE PATIENT SAMPLE, IS NOT ASSOCIATED WITH AN INCREASED RISK OF BLADDER CANCER... HOWEVER, CYCLAMATES WERE INTRODUCED TOO RECENTLY TO PERMIT THE DETECTION OF CARCINOGENIC EFFECTS APPEARING MORE THAN TEN OR 15 YEARS AFTER INITIAL EXPOSURE..."

"[T]HERE WAS A TENDENCY OF RELATIVE RISKS IN MALE (BUT NOT FEMALE) NNS USERS TO EXCEED 1.00, THOUGH INSIGNIFICANTLY. SECOND, THERE WAS AN INCREASED RELATIVE RISK IN MALE (BUT NOT FEMALE) NONSMOKING NNS USERS." SINCE A DIVERGENCE IN RELATIVE RISK BETWEEN MEN AND WOMEN "WOULD BE EXTRAORDINARY FOR A HUMAN CARCINOGEN," THE FOLLOWING EXPLANATION OF THESE FINDINGS IS OFFERED. "[T]HE MEN DRANK

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SIGNIFICANTLY MORE CUPS OF COFFEE PER DAY THAN THEIR CONTROLS, WHILE THERE WERE NO SUCH DIFFERENCES AMONG WOMEN. COFFEE IS OFTEN SWEETENED WITH NNS AND HAS BEEN SUGGESTED AS A BLADDER CARCINOGEN. THUS, THE SEX DIFFERENCE IN ODDS RATIOS COULD, AT LEAST IN PART, REFLECT DIFFERENCES IN COFFEE HABIT RATHER THAN NNS EXPOSURE PER SE....

"[T]HE FINDING [OF A SIGNIFICANT INCREASE IN BLADDER CANCER RISK] AMONG MALE NONSMOKERS [WHO USED NNS] MAY...BE ARTIFACTUAL. MALE NONSMOKERS WERE SIGNIFICANTLY OLDER AND MORE LIKELY TO HAVE MEMORY PROBLEMS AT INTERVIEW THAN THEIR CONTROLS.... IN ANY EVENT, THE FINDINGS DO NOT SUGGEST AN INTERACTION BETWEEN SMOKING AND NNS THAT INCREASES BLADDER CANCER RISK."

(SEE ALSO DOCUMENT NO. 51741.)

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EPIDEMIOLOGICAL STUDY, RETROSPECTIVE STUDY, DIETARY STUDY, MALE FEMALE DATA, TEN THOUSAND, BLADDER CANCER SACCHARIN NONASSOC, BLADDER CANCER CYCLAMATES NONASSOC, BLADDER CANCER SMOKING ASSOC, ARTIFICIAL SWEETENER, DIETARY SACCHARIN, CIGARETTE SMOKING, TOBACCO USE, NONSMOKERS, BLADDER CANCER RISK FACTORS, BLADDER CANCER RISK, BLADDER CANCER DIETARY FACTORS NONASSOC, DIETARY CARCINOGENS, BLADDER CANCER SMOKING DURATION ASSOC, BLADDER CARCINOGENS, SACCHARIN NONCARCINOGENICITY, FOOD ADDITIVES NONCARCINOGENICITY, FOOD SWEETENER, RELATIVE RISK, RISK ESTIMATION/  
BLADDER CANCER SACCHARIN CAUSATION 2, BLADDER CANCER CYCLAMATES CAUSATION 2, BLADDER CANCER SMOKING CAUSATION 1, MULTIPLE FACTORS INTERACTION, INTERPRETATION VALIDITY CONCESSION, BLADDER CANCER LATENT PERIOD, BLADDER CANCER COFFEE CAUSATION 2, COFFEE INGESTION, DATA VALIDITY CONCESSION, INTERVIEWS CONCESSION, DOSE RESPONSE,

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GOVERNMENT REGULATIONS HI, CARCINOGENICITY TESTING A HI, SPECIES  
SUSCEPTIBILITY A HI, STRAIN SUSCEPTIBILITY A HI, CARCINOGENS  
SUSCEPTIBILITY A HI, CARCINOGENS DOSE A HI, CARCINOGENS EXPOSURE  
DURATION A HI, CARCINOGENS ADMINISTRATION ROUTE A HI, CARCINOGENS  
DOSE HI, ANIMAL MODEL EXTRAPOLATION HI, ETIOLOGICAL CRITERIA HI,  
EPIDEMIOLOGICAL STUDY HI, STATISTICAL ASSOC HI, DATA VALIDITY HI,  
DEATH CERTIFICATES ACCURACY, SACCHARIN CARCINOGENICITY A, BLADDER CANCER  
MORTALITY CHANGES, MORTALITY STATISTICS HI, QUESTIONNAIRE VALIDITY,  
POPULATION SAMPLE SIZE VALIDITY, EPIDEMIOLOGICAL STUDY VALIDITY,  
SACCHARIN CARCINOGENICITY, BLADDER CANCER SEX FACTORS CAUSATION 2,  
METHODOLOGY VALIDITY, POPULATION SAMPLE VALIDITY, DATA COMPARABILITY,  
BLADDER CANCER RISK DECREASE, BLADDER CANCER DIETARY FACTORS  
CAUSATION 2, COFFEE CARCINOGENICITY, FOOD CARCINOGENICITY, ARTIFICIAL  
SWEETENER A, FOOD ADDITIVES CARCINOGENICITY A, FOOD ADDITIVES  
CARCINOGENICITY, CYCLAMATES CARCINOGENICITY, COLA DRINKS, CYCLAMATES  
CARCINOGENICITY A, CARCINOGENS LEGISLATION, GOVERNMENT LEGISLATION,  
METHODOLOGY A HI, EXPERIMENTAL METHODS A HI, METHODOLOGY VALIDITY A,  
DIETARY CARCINOGENS A, COLA INGESTION, BLADDER CANCER SURVIVAL,  
BLADDER CANCER SEX FACTORS ASSOC, BLADDER CANCER SACCHARIN ASSOC,  
BLADDER CANCER CYCLAMATES ASSOC, BLADDER CANCER DIETARY FACTORS ASSOC,  
BLADDER CANCER RISK INCREASE, INTERPRETATION VARIABILITY, SMOKING AGE  
FACTORS CAUSATION 2, MENTAL FUNCTION DECREASE SMOKING CAUSATION 2,  
MEMORY RETENTION DECREASE, STATISTICAL ANALYSIS VALIDITY, DEMOGRAPHIC  
FACTORS, CARCINOGENS ADMINISTRATION ROUTE A HI, CARCINOGENS DOSE HI/  
BLADDER CANCER OCCUPATIONAL FACTORS CAUSATION 2, DIABETES,  
STATISTICAL SIGNIFICANCE, STATISTICAL ANALYSIS, INTERVIEWS,  
CARBONATED BEVERAGES, SOFT DRINKS, BACON, HAM, CANDY, ICE CREAM,  
PASTRIES, CHEWING GUM, GELATIN, BLADDER CANCER AGE FACTORS CAUSATION 2,  
BLADDER CANCER RACE FACTORS CAUSATION 2, EDUCATIONAL FACTORS, TEA  
INGESTION, BODY HEIGHT, BODY WEIGHT CONTROL, MEDICAL HISTORY,  
OCCUPATIONAL HISTORY, BLADDER CANCER SACCHARIN CAUSATION 1, BLADDER  
CANCER MARITAL STATUS CAUSATION 1, BLADDER CANCER DIETARY FACTORS  
CAUSATION 1, RELIGIOUS FACTORS, METABOLIC FACTORS, GLYCOSURIA,  
OBESITY/

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ENGLISH LANGUAGE, BALTIMORE MD RESIDENCE, USA RESIDENCE, GRANTOR  
USPHS NATL CANCER INST, GRANTOR AMER CANCER SOC, BLADDER CANCER  
PATIENTS, BALTIMORE MD, HOSPITAL PATIENTS, ~~CANADA, CANADIANS,~~ US DEPT  
HEW, US FOOD AND DRUG ADMIN, CATHOLICS, JEWS, CAUCASIANS, USA,  
BALTIMORE CITY HOSP, BON SECOURS HOSP, CHURCH HOME HOSP, FORT HOWARD VA  
HOSP, FRANKLIN SQUARE HOSP, JOHNS HOPKINS HOSP, LUTHERAN HOSP,  
MARYLAND GEN HOSP, MERCY HOSP, NORTH CHARLES GEN HOSP, ST AGNES HOSP,  
ST JOSEPH HOSP, SOUTH BALTIMORE GEN HOSP, UNION MEMORIAL HOSP, UNIV  
MARYLAND HOSP