CAS Registry Number: 57-97-6 Toxicity Effects

Selected toxicity information from HSDB, one of the National Library of Medicine's databases. [1]

Names (NTP)

- 7,12-Dimethylbenzanthracene
- DMBA

Human Toxicity Excerpts

- THE POLYCYCLIC AROMATIC HYDROCARBONS, BENZO(A)PYRENE (BP) & THE A-RING REDUCED ANALOGUE OF 7,12-DIMETHYLBENZ(A)ANTHRACENE (DMBA), 1,2,3,4-TETRAHYDRO-7,12-DIMETHYLBENZ(A)ANTHRACENE (TH-DMBA) ARE CARCINOGENIC TO HUMAN CELLS /SRP: IN VITRO/. THE UNSATURATED DMBA EXHIBITS NO CARCINOGENIC ACTIVITY IN HUMAN CELLS AS MEASURED BY GROWTH IN SOFT AGAR.[TEJWANI R ET AL; CANCER LETT 13 (2): 119-27 (1981)] **PEER REVIEWED** PubMed Abstract

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Non-Human Toxicity Excerpts

- OOCYTE & FOLLICULAR DISRUPTION ARE ALSO CAUSED BY EXPOSURE TO DMBA IN VITRO, & OVARIES TREATED IN THIS WAY MAY DEVELOP GRANULOSA-CELL TUMORS AFTER REIMPLANTATION INTO OVARIECTOMIZED MOUSE, OVARIES EXPOSED TO CULTURE MEDIUM ALONE IN VITRO. HOWEVER, DEVELOP NORMALLY WHEN REIMPLANTED INTO OVARIECTOMIZED MICE. IN OVARIAN TUMORS AFTER 7,12-DIMETHYLBENZ(A)ANTHRACENE ... PITUITARY SECRETIONS ARE NECESSARY FOR TUMORS TO ARISE. CONVERSELY, NORMAL OVARIAN TISSUE IS COMPLETELY INHIBITORY TO OVARIAN DEVELOPMENT AFTER EXPOSURE TO 7,12-DIMETHYLBENZ(A)ANTHRACENE ...[Searle, C. E. (ed.). Chemical Carcinogens. ACS Monograph 173. Washington, DC: American Chemical Society, 1976., p. 58] **PEER REVIEWED**
- ... SINGLE DOSE OF 7,12-DIMETHYLBENZ(A)ANTHRACENE (DMBA) /WAS GIVEN/ TO DONOR RAT, & BREAST TISSUE WAS SUBSEQUENTLY TRANSPLANTED TO UNTREATED FEMALE OF SAME STRAIN. CARCINOMAS AROSE ONLY IN TRANSPLANTED BREAST, & THEIR INCIDENCE WAS HIGH EVEN WHEN INTERVAL BETWEEN TREATMENT OF DONOR & TRANSPLANTATION WAS AS LITTLE AS 4 HR.[Searle, C. E. (ed.). Chemical Carcinogens. ACS Monograph 173. Washington, DC: American Chemical Society, 1976., p. 73] **PEER REVIEWED**
- SERUM HAPTOGLOBIN IN MICE TREATED WITH CARCINOGEN 7,12-DIMETHYLBENZ(A)ANTHRACENE WAS DETERMINED. MICE BEARING MAMMARY CARCINOMAS & STOMACH SQUAMOUS CELL CARCINOMAS HAD HIGH HAPTOGLOBIN LEVELS & IN MAJORITY OF MICE WITH MAMMARY CARCINOMAS, THE INITIAL RISE IN SERUM HP COINCIDED WITH 1ST APPEARANCE OF PALPABLE MASSES.[PALMER WG, ULLAND BM; ONCOLOGY (BASEL) 35 (5): 220-3 (1978)] **PEER REVIEWED**
- AFTER 50-DAY-OLD FEMALE SPRAGUE-DAWLEY RATS FED 1 DOSE OF DMBA AT EITHER 112 0R 133 MG/KG BODY WT, PANCYTOPENIA ACCOMPANIED BY SEVERE DEPRESSION OF HEMATOPOIETIC & LYMPHOID PRECURSORS DEVELOPED WITHIN WEEKS.[National Research Council. Drinking Water & Health, Volume 4. Washington, DC: National Academy Press, 1981., p. 261] **PEER REVIEWED**
- FEMALE SPRAGUE-DAWLEY RATS RECEIVING ORAL DOSES OF DMBA AT 300 MG/KG AND MALE RATS RECEIVING IV INJECTIONS OF DMBA AT 50 MG/KG INCURRED INJURY TO INTESTINAL EPITHELIUM, EXTREME ATROPHY OF PORTIONS OF HEMATOPOIETIC SYSTEM, SHRINKAGE OF LYMPHOID ORGANS, AGRANULOCYTOSIS, LYMPHOPENIA, AND PROGRESSIVE ANEMIA. MORTALITY AMONG FEMALE RATS WAS APPROXIMATELY 65%.[National Research Council. Drinking Water & Health, Volume 4. Washington, DC: National Academy Press, 1981., p. 261] **PEER REVIEWED**
- ... 7,12-DIMETHYLBENZ(A)ANTHRACENE ADMIN IN SINGLE IP DOSES OF 80 MG/KG IN CORN OIL DESTROYED PRIMORDIAL OOCYTES IN MOUSE OVARIES.[National Research Council. Drinking Water & Health, Volume 4. Washington, DC: National Academy Press, 1981., p. 263] **PEER REVIEWED**
- ... SIGNIFICANT DOSE-DEPENDENT INCR IN SISTER CHROMATID EXCHANGE FREQUENCY OCCURRED WHEN RAT LIVER CELLS WERE EXPOSED TO 7,12-DIMETHYLBENZ(A)ANTHRACENE.[TONG G ET AL; MUTAT RES 91 (6): 467-73

(1981)] **PEER REVIEWED** PubMed Abstract

- 7,12-DIMETHYLBENZ(A)ANTHRACENE (DMBA) HAD VARYING DEGREES OF CYTOTOXICITY & PRODUCED MORPHOLOGICAL & MALIGNANTLY TRANSFORMED FOCI WITH DOSE-DEPENDENT FREQUENCY IN A LINE OF CLONED C3H MOUSE EMBRYO CELLS SENSITIVE TO POSTCONFLUENCE INHIBITION OF CELL DIVISION. THREE TYPES OF MORPHOLOGICALLY ALTERED FOCI WERE IDENTIFIED AFTER POLYCYCLIC HYDROCARBON TREATMENT, & FOCI OF EACH TYPE WERE CLONED & INOCULATED INTO IRRADIATED SYNGENEIC MICE. TWO OF THE 3 TYPES PRODUCED FIBROSARCOMAS WHEN INOCULATED AT PASSAGES 2-4 HR AFTER CLONING. THE 3RD TYPE OF FOCUS WAS MORPHOLOGICALLY MINIMALLY ALTERED.[REZNIKOFF CA ET AL; CANCER RES 33 (12): 3229-49 (1973)] **PEER REVIEWED**
- A BROAD SPECTRUM OF TUMORS OF EPIDERMAL ORIGIN COULD BE INDUCED BY TOPICAL INITIATION WITH 7,12-DIMETHYLBENZ(A)ANTHRACENE (DMBA) AND 12-O-TETRADECANOYL-PHORBOL-13-ACETATE (TPA) AS PROMOTOR ON SPRAGUE-DAWLEY RATS. THE TUMORS WERE NOT ONLY LOCALIZED IN INTERFOLLICULAR EPIDERMIS BUT TO A LARGE EXTENT ALSO IN EPIDERMAL APPENDAGES. THE DMBA-TPA TREATMENT LED TO THE DEVELOPMENT OF A VARIETY OF TUMORS OF CONNECTIVE TISSUE & ANGIOFIBROUS MATRIX. THE INCIDENCE OF THESE TUMORS WAS ALMOST COMPARABLE TO THAT FOUND FOR EPIDERMAL TUMORS. IN SOME ANIMALS UP TO 12 HR HISTOLOGICALLY DIFFERENT TUMORS WERE OBSERVED. COMPARED TO MOUSE, THE TUMOR INCIDENCE IN ORGANS OTHER THAN THE SKIN WAS LOWER.[SCHWEIZER J ET AL; CARCINOGENESIS (LOND) 3 (7): 785-90 (1982)] **PEER REVIEWED**
- SIMULTANEOUS SC ADMIN OF 1.0 MG OF 7,12-DIMETHYLBENZ(A)ANTHRACENE (DMBA) TO MICE IMMUNIZED WITH BACTERIAL ALPHA-AMYLASE (0.2 MG, IP) AUGMENTED THE SERUM ANTIBODY RESPONSE, BUT DEPRESSED THE DEVELOPMENT OF IMMUNOLOGICAL MEMORY IN THE SPLEEN.[MATSUOKA Y ET AL; GANN 64 (6): 575-8 (1973)] **PEER REVIEWED** PubMed Abstract
- Viviparous fish (Poeciliopsis lucida) were susceptible to induction of liver tumors by repeated short-term exposures (under 24 hr) to waterborne 7,12-dimethylbenz(a)anthracene (DMBA) at 5 ppm. Exposures to 5 ppm for 24 hr was lethal to fish under 1 mo old and resulted in 60% mortality of adult females 20 to 25 mm in length. Response to 16, 20, and 22 hr exposures of 5 ppm DMBA as measured by mitotic index, was similar in females of two size classes, 20 to 25 mm and 26 to 30 mm. Differences were observed in the onset of mitosis in the liver of fish exposed for 16 hr vs 20 or 22 hr. Hepatocyte proliferation did not begin until 10 to 11 days after the 16-hr exposure and lasted for only 3 days. When exposure was incr to 20 or 22 hr, mitotic activity was observed earlier, 2 days following treatment, and continued for 6 to 8 days. The peak period of cell proliferation also varied, occurring 12 days after a 16 hr exposure, 4 days after a 20 hr exposure, and at least 10 days after a 22 hr exposure. The mitotic index was the highest on the final day specimens of the 22 hr treatment were collected.[Schultz ME et al; Environ Res 48 (2): 248-54 (1989)] **PEER REVIEWED** PubMed Abstract
- Exposure of mouse lymphocytes to 7,12-dimethylbenz(a)anthracene (DMBA) results in significant suppression of a variety of immunological parameters, including the induction of cytotoxic T-lymphocytes. Cytotoxic T-lymphocytes suppression may be reversed in vitro by the addition of exogenous cellular activation products, including IL-2. DMBA-induced cytotoxic T-lymphocyte suppression occurs throughout the induction process with the most pronounced effect occurring within 24 to 48 hr of initiation. Alloantigen-specific cytotoxic T-lymphocyte generated from murine (B6C3F1 mice) thymocytes in the presence of DMBA and T-helper-derived factors (thus circumventing the T-helper) displayed an almost identical degree of cytotoxic T-lymphocyte suppression to that of splenocytes. Antigen nonspecific, polyclonal cytotoxic T-lymphocyte activation by the lectin leucoagglutinin or by IL-2 (LAK cells) was unaffected by chemical exposure. Conversely, polyclonal cytotoxic T-lymphocyte induced with monoclonal antibodies directed against the T-cell receptor-associated subunit CD3, in the presence of conditioned medium, was suppressed in a manner similar to antigen-mediated cytotoxic T-lymphocyte. The CD3 receptor subunit acts as a transmembrane activation signal following binding of antigen to the specific receptor, further implicating dysfunction of antigen recognition or signal processing following DMBA exposure. This was confirmed by the observation that DMBA exposure prevents the anamnestic response of cytotoxic T-lymphocyte memory cells following re-exposure to eliciting tumor antigen.[House RV et al; Int J Immunopharmacol 11 (2): 207-15 (1989)] **PEER REVIEWED** PubMed Abstract
- The Drosophila wing somatic mutation and recombination test was applied to a series of chemicals to determine its suitability in genotoxicity screening. 7,12-Dimethylbenz(a)anthracene was tested at concentrations of 5 to 10 mM in feeding regimes of 24, 72, and 96 hours. The results for the small single spots were positive in all experiments, and those for the large single spot were positive in all experiments except the 5 mM for 72 hour test. The results for twin spots were ambiguous, with both positive and inconclusive effects. The three concentrations tested at 72 hours failed to yield a dose response.[Graf U et al; Mutat Res 222 (4): 359-73 (1989)] **PEER REVIEWED** PubMed Abstract
- 7,12-Dimethylbenz(a)anthracene was assayed for mutagenicity using Salmonella typhimurium strain TA100 in the Ames test, in the presence of hepatic post-mitochondrial preparations (S9 fractions) isolated from the mouse, rat, hamster, pig and man. With the exception of the rat and pig, all animal species activated 7,12-dimethylbenz(a)anthracene (less than 100 ul/plate to mutagens, as evidenced by a doubling of the spontaneous reversion rate.[Phillipson CE, Ioannides C; Mutat Res 211 (2): 147-51 (1989)] **PEER REVIEWED** PubMed Abstract
- The effect of staurosporine on 7,12-dimethylbenz(a)anthracene (DMBA) initiated and 12-O-tetradecanoylphorbol-13-acetate-promoted skin papilloma formation was examined in CD-1 mice. Groups of 20 female DC-1 mice were initiated by applying 200 nmol of DMBA to the dorsal skin. Promotion with 5 nmol of 12-O-tetradecanoylphorbol-13-acetate applied twice weekly was begun 10 days after initiation. A topical application of 0.2, 2, and 20 nmol staurosporine 15 min prior to each 12-O-tetradecanoylphorbol-13-acetate treatment resulted in a dose related inhibition of tumor formation. Treatment with 5 nmol 12-O-tetradecanoylphorbol-13-acetate for 18 wk produced 19 papillomas/mouse on average. Pretreatment with 20 nmoles staurosporine reduced the tumor yield to 26% of the control at 18 wk of promotion. Staurosporine by itself had no tumor producing activity in DMBA initiated mice. Histological studies revealed that staurosporine failed to inhibit 12-O-tetradecanoylphorbol-13-acetate induced inflammation but rather augmented 12-O-tetradecanoylphorbol-13-acetate induced polymorphonuclear leucocyte infiltration. Staurosporine by itself induced a slight polymorphonuclear leucocyte infiltration 1 hr after the drug application but the effect was only transient. Although staurosporine failed to inhibit the 12-O-tetradecanoylphorbol-13-acetate induced epidermal hyperplasia and DNA synthesis significantly, nuclear atypism of the

superficial layer of the epidermis appeared to be less remarkable in staurosporine pretreated mice.[Yamamoto S et al; Carcinogenesis 10 (7): 1315-22 (1989)] **PEER REVIEWED** PubMed Abstract

- Groups of at least 145 guppies (6 to 11 days old) of the king cobra strain (Poecilia reticulata) were exposed for 6 hr each wk for 4 wk to 7,12-dimethylbenz(a)anthracene (DMBA). Treatment groups included: (1) untreated control; (2) dimethylformamide carrier control; (3) low, water mediated DMBA concn (about 1 to 3 ug/l or ppb DMBA); (4) intermediate, dimethylformamide mediated DMBA concn (about 20 ppb DMBA); and (5) high, dimethylformamide mediated DMBA concn (about 35 ppb DMBA). Hepatic neoplasms developed in guppies exposed to the intermediate and high concn. Both of these exposure media contained the same concn of soluble DMBA. The high exposure medium, however, also contained an insoluble, particulate fraction of DMBA. Hepatic neoplasm incidences in fish exposed to the intermediate concn were 10% (7/71 fish) at 24 wk and 19% (12/62) at 37 wk after initial exposure. In samples from the high concn group, 47% (35/74) had hepatic neoplasms at 24 wk and 46% (23/50) at 37 wk. Histologically, the hepatic lesions were categorized as altered foci, hepatocellular adenomas, and hepatocellular carcinomas. At the high dose, adenomas represented 40% (14/35) of the hepatocellular neoplasms after 24 wk, and 70% (16/23) after 36 wk. Carcinomas, occurring only at the high dose, were found in 9% of the fish (2/23). In addition to liver neoplasms, several other types of lesions developed in DMBA exposed guppies. These included two undifferentiated sarcomas, a rhabdomyosarcoma, a renal adenocarcinoma, and a neurilemmoma. Only one control specimen (representing 0.38% of all controls) had a neoplastic lesion, a small hepatocellular adenoma in a 37 wk specimen.[Hawkins WE et al; Aquat Toxicol 15 (1): 63-82 (1989)] **PEER REVIEWED**
- Among the foreign compounds metabolized by adrenal monooxygenases are the carcinogens, benzo(a)pyrene and 7,12-dimethylbenz(a)anthracene (DMBA). The latter compound causes adrenal necrosis in some species, but the relationship between adrenal DMBA metabolism and the necrosis has yet to be fully resolved.[Thomas, J.A., K.S. Korach, J.A. McLachlan. Endocrine Toxicology. New York, NY: Raven Press, Ltd., 1985., p. 38] **PEER REVIEWED**
- The effect of a single sc administration of 7,12-dimethylbenz(a)anthracene under the skin was studied in the rabbit. Ordered sequental biochemical and cytophotometric changes were induced by the carcinogen. While the biochemical studies comprised of sequental quantitative estimations of DNA, RNA, and protein/mg of skin, the cytophotometric studies consisted of an estimation of the level of macromolecules in a cell/nucleus, in different skin constituents, ie, epidermis, hair follicle shaft region, and hair follicle bulb region. Biochemical results indicate an initial rise in the level of DNA and RNA and reduction of protein up to 20 days. From 40-60 days treatment duration, there was a steady-state showing a consistent level of all the parameters while the highest peak was observed on the 80th day. The cytophotometric study of the site of these biochemical changes among different skin constituents indicates the highest level of nucleic acids in the epidermis region right from the initial stage (ie 10th day) to the 90th day of treatment in comparison to other regions, hair follicle shaft and hair follicle bulb regions. Histological studies, on the other hand, reveal a greatly, though gradual, increased nuclear area and the highest rate of proliferation only in the hair follicle bulb region, thus suggesting a definite role of this region of the skin in the carcinogenesis. Thus, the important event in the initiative phase of 7,12-dimenthylbenz(a)anthracene-mediated carcinogenesis in the rabbit might be associated with the epidermal region but the role of the hair follicle region should also be considered as of an equal significance during the process. A conspicuous difference in the behavior of rabbit skin constituents has been noted when the results of the study are compared with the earlier reports on mice.[Garg A; J Biosci 6 (3): 297-307 (1984)] **PEER REVIEWED**
- The initial and persistent levels of DMBA-DNA adducts in mouse skin, epidermis, and dermis after topical carcinogen application were studied by (32)P-post-labeling assay. In the major experiment, a single dose of 1.2 mumol of the carcinogen was applied to the shaved backs of adult female BALB/cANN mice, and DNA was isolated from the epidermis and dermis, respectively, 24 hr, and 1, 2, 3, 4, 8, 16, 24, 36, and 42 wk later. Total binding at 24 hr was approximately 34 and approximately 28 adducts in 10(+7) normal nucleotides for epidermal and dermal DNA, respectively. (One adduct in 10(+7) nucleotides equals 0.3 fmol adduct/mug DNA). While the initial binding was higher in epidermal DNA, the adducts were approximately 10-fold more persistent in dermal DNA, at 42 wk, total binding levels were approximately 0.17 and approximately 1.7 adducts in 10(+7) nucleotides for epidermis and dermis, respectively. To quantitate low levels of DMBA-DNA adducts, (32)P-post-labeling assays were run in the presence of a limiting amount of carrier-free gamma (32)P ATP; this favored labeling of the adducts, thereby leading to a 20-100-fold enhancement of the method's sensitivity for individual adducts. One of the 3 major DMBA-DNA adducts was more persistent than the others; the level of this adduct remained constant at approximately 60% of the total epidermal and dermal DNA during the last 18 wk of the 42-wk observation period. Since a (3)H thymidine-labeling experiment showed a normal epidermal DNA turnover 40 wk after DMBA treatment, it was concluded that the bulk of the persistent adducts was present in subpopulations of dormant cells. ...[Randerath E et al; Carcinogenesis 6 (8): 1117-26 (1985)] **PEER REVIEWED** PubMed Abstract
- NMRI SWISS MICE EXHIBIT A NATURAL HIGH SENSITIVITY TO THE CARCINOGEN, 7,12-DIMETHYLBENZ(A)ANTHRACENE (DMBA) & THE PRETREATMENT OF MICE WITH BETA-NAPHTHOFLAVONE LEADS TO A LARGE DECR OF FORMATION OF TUMORS. IN CONTRAST, CF SWISS MICE EXHIBIT A VERY LOW SENSITIVITY TO DMBA & A DRAMATIC INCR OF TUMORIGENICITY OCCURS WHEN ANIMALS ARE PRETREATED WITH THIS INDUCER.[LESCA P; CARCINOGENESIS 2 (3): 199-204 (1981)] **PEER REVIEWED** PubMed Abstract
- When anthracene, 8 mg/mouse (strains BALB/C; C3H/A; C57BL x CBA F1 hybrids), was given either sc daily or as a single oral dose during the last week of gestation, greater survival and hyperplastic changes were seen than in untreated controls in explants of embryonic kidney in organ culture. The changes seen were qualitatively similar but less marked than those produced by treatment with 1-8 mg 7,12-dimethylbenz(a)anthracene.[IARC. Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Geneva: World Health Organization, International Agency for Research on Cancer, 1972-PRESENT. (Multivolume work). Available at: http://monographs.iarc.fr/index.php, p. V32 112 (1983)] **PEER REVIEWED**

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Human Toxicity Values

- None found

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Non-Human Toxicity Values

- None found

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Absorption, Distribution and Excretion

- AFTER IV INJECTION INTO RATS, 7,12-DIMETHYLBENZ(A)ANTHRACENE WAS TAKEN UP RAPIDLY BY THE LIVER, BOUND TO PARTICULAR FRACTIONS, & SUBSEQUENTLY TRANSFORMED INTO POLAR METAB, WHICH HAVE LESS AFFINITY FOR PARTICULATE FRACTIONS THAN THE PARENT HYDROCARBON, & WHICH WERE RECOVERED FROM CELLULAR CYTOSOL. AFTER TRANSFER TO CYTOSOL, METABOLITES WERE SECRETED INTO BILE.[The Chemical Society. Foreign Compound Metabolism in Mammals. Volume 4: A Review of the Literature Published during 1974 and 1975. London: The Chemical Society, 1977., p. 180] **PEER REVIEWED**
- STUDIES IN ANIMALS INDICATE THAT ... 7,12-DIMETHYLBENZ(A)ANTHRACENE ... READILY ABSORBED FROM INTESTINAL TRACT & TENDS TO LOCALIZE PRIMARILY IN BODY FAT & FATTY TISSUES SUCH AS BREAST. ... THE DISTRIBUTION OF RADIOACTIVITY IN RATS AFTER ADMIN OF LABELED ... /CMPD/ BY STOMACH TUBE WAS ... STUDIED. MAJOR ROUTE OF EXCRETION WAS FOUND TO OCCUR VIA THE BILE INTO THE FECES. THERE WAS RATHER PROLONGED RETENTION OF RADIOACTIVITY IN BODY FAT, OVARIES, & ADRENALS.[National Research Council. Drinking Water & Health, Volume 4. Washington, DC: National Academy Press, 1981., p. 257] **PEER REVIEWED**
- 48 HR AFTER ORAL ADMIN, 90% WAS EXCRETED BY MICE. PRETREATMENT OF MICE WITH 3-METHYLCHOLANTHRENE SLIGHTLY INCR INITIAL RATE OF 7,12-DMBA ELIMINATION, BUT AFTER 48 HR AMT OF RESIDUAL 7,12-DMBA WAS THE SAME AS THAT IN THE NONPRETREATED MICE. ETHYL ACETATE EXTRACTABLE POLAR METABOLITES & WATER-SOL METABOLITES WERE MORE ABUNDANT IN URINE & FECES OF PRETREATED MICE THAN IN NONPRETREATED ONES.[GENTIL A ET AL; CR ACAD SCI, SER D, 277 (24): 2849-52 (1973)] **PEER REVIEWED**
- TWO HR AFTER IP INJECTION, 7,12-DIMETHYLBENZ(A)ANTHRACENE (DMBA) WAS PRESENT THROUGHOUT THE BODY OF AMAZON MOLLIES, EXCEPT IN BRAIN & OVARY. THERE WAS AN ENHANCED DEPOSITION AT 4 SITES, IN MACROPHAGES OF ATRIUM OF HEART & PERITONEUM, LIVER, & EXOCRINE PANCREAS. DMBA WAS TAKEN UP BY RETICULOENDOTHELIAL MACROPHAGES FOR 78 HR AFTER INJECTION, THEN IT WAS LOST. ACCUMULATION & DISAPPERANCE OF RADIOACTIVE LABEL SEEN IN LIVER & PANCREATIC CELLS PROBABLY REPRESENTED PATTERN OF METAB OF COMPD. BY 400 HR AFTER INJECTION THERE WAS LITTLE DMBA REMAINING. LABEL ACCUMULATED IN AMELOBLASTS, WHICH SECRETE THE ENAMEL CAPPING OF THE TEETH. NO PREFERENTIAL METAB OF DMBA BY SPLEEN WAS OBSERVED.[WOODHEAD AD, BORNBUSCH A; J FISH BIOL 22 (2): 241-8 (1983)] **PEER REVIEWED**

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Metabolism/Metabolites

- YIELDS 8,9-DIHYDRO-8,9-DIHYDROXY-7,12-DIMETHYLBENZANTHRACENE, 7-HYDROXYMETHYL-12-METHYLBENZANTHRACENE, 12-HYDROXYMETHYL-7-METHYLBENZANTHRACENE IN RAT, GUINEA PIG, PIG & HAMSTER: SIMS P; BIOCHEM PHARMAC 19: 2261 (1970); SIMS P, GROVER PL; BIOCHEM PHARMAC 17: 1751 (1968). /FROM TABLE/[Goodwin, B.L. Handbook of Intermediary Metabolism of Aromatic Compounds. New York: Wiley, 1976., p. D-88] **PEER REVIEWED**
- OXIDN OF /7,12-DIMETHYLBENZANTHRACENE/ ... MOLECULE CAN OCCUR ON EITHER OR BOTH METHYL GROUPS & ON 3,4 & 8,9 BONDS TO YIELD VARIETY OF PRODUCTS. MOST OF PROCESSES INCR IN EXTENT /WITH INCREASING AGE/ HOWEVER, SIGNIFICANT DIFFERENCES EXIST IN SUSCEPTIBILITY OF VARIOUS PATHWAYS TO AGE VARIATION. WHILE OXIDN OF 12-METHYL GROUP & OF 3,4 AROMATIC BOND ARE ONLY SLIGHTLY AFFECTED BY AGE, OXIDN OF 8,9 BOND & TO LESSER EXTENT OF 7-METHYL GROUP ARE MARKEDLY SUSCEPTIBLE TO AGE VARIATIONS.[Testa, B. and P. Jenner. Drug Metabolism: Chemical & Biochemical Aspects. New York: Marcel Dekker, Inc., 1976., p. 407] **PEER REVIEWED**
- FOUR TRANS-3,4-DIHYDRODIOLS WERE IDENTIFIED AS METABOLITES OF 7,12-DIMETHYLBENZ(A)ANTHRACENE. THE TRANS-3,4-DIHYDRODIOLS, 7-HYDROXYMETHYL-12-METHYLBENZ(A)ANTHRACENE ARE FURTHER METABOLIZED TO PRODUCTS WHICH BIND MORE STRONGLY TO DNA IN VITRO. APPARENTLY ONE OR MORE OF THE TRANS-3,4-DIHYDRODIOLS MAY BE THE PROXIMATE CARCINOGENIC & ADRENOCORTICOLYTIC METABOLITE.[CHOU MW, YANK SK; PROC NATL ACAD SCI USA 75 (11): 5466-70 (1978)] **PEER REVIEWED** PubMed Abstract
- (3)H-LABELED 7,12-DIMETHYLBENZ(A)ANTHRACENE WAS METABOLIZED BY LIVER MICROSOMES FROM 3-METHYLCHOLANTHRENE-TREATED RATS TO ITS K-REGION /5,6/ EPOXIDE.[KEYSELL GR ET AL; BIOCHEM PHARMACOL 22 (22): 2853-67 (1973)] **PEER REVIEWED** PubMed Abstract
- A MAJOR CARCINOGENIC HEPATIC METABOLITE OF 7,12-DIMETHYLBENZ(A)ANTHRACENE (DMBA), 7-HYDROXYMETHYL-12-METHYLBENZ(A)ANTHRACENE (7-HMBA) WAS TRANSFORMED BY LIVER CYTOSOLIC SULFOTRANSFERASE TO REACTIVE 7-HMBA SULFATE WHICH IS MUTAGENIC TOWARD SALMONELLA TYPHIMURIUM STRAIN TA98.[WATABE T ET AL; SCIENCE 215 (4531): 403-5 (1982)] **PEER REVIEWED** PubMed Abstract
- METABOLISM OF 7,12-DIMETHYLBENZ(A)ANTHRACENE (DMBA) TO HYDROXYMETHYL DERIV DIFFERS IN HEPATIC

& MAMMARY TISSUE HOMOGENATES. IN THE HEPATIC TISSUE DMBA IS TRANSFORMED INTO 7-HYDROXYMETHYL-12-METHYLBENZ(A)ANTHRACENE (I) 12-HYDROXYMETHYL-7-METHYLBENZ(A)ANTHRACENE (II) & 7,12-DIHYDROXYMETHYLBENZ(A)ANTHRACENE (III) WHEREAS THE MAMMARY GLAND FORMED ONLY THE MONOHYDROXY COMPOUNDS. PRETREATMENT OF RATS WITH 3-METHYLCHOLANTHRENE INDUCES MARKED INCR IN DMBA METABOLIZING ENZYMES IN THE LIVER CAUSING FURTHER CONVERSION OF THE (I), (II), & (III) TO MORE POLAR COMPONENTS.[TAMULSKI TS ET AL; CANCER RES 33 (12): 3117-22 (1973)] **PEER REVIEWED** PubMed Abstract

- ... 7,12-DIMETHYLBENZ(A)ANTHRACENE IS METABOLIZED INTO /SRP: 7,12-PEROXIDE/, WHICH MAY THEN BE FURTHER REDUCED TO CIS-7,12-DIHYDROXY-7,12-DIMETHYL(A)ANTHRACENE BY RAT-LIVER MICROSOMES. OXIDATION REACTION REQUIRED NADPH & WAS INHIBITED BY ... METYRAPONE & CARBON MONOXIDE ... INHIBITORS OF THE CYTOCHROME P450 MONOOXYGENASE SYSTEM.[The Chemical Society. Foreign Compound Metabolism in Mammals. Volume 5: A Review of the Literature Published during 1976 and 1977. London: The Chemical Society, 1979., p. 103] **PEER REVIEWED**
- MAMMARY TUMORIGENESIS BY 7,12-DIMETHYLBENZ(A)ANTHRACENE (DMBA) WAS TESTED IN 2 RAT STOCKS & 2 RAT STRAINS: OUTBRED SPRAGUE-DAWLEY & LONG-EVANS & INBRED WISTAR/FURTH (WF) & FISCHER F344 (F344) RATS. BOTH SPRAGUE-DAWLEY & WF RATS SHOWED COMPARABLY HIGH SUSCEPTIBILITY TO TUMORIGENESIS, WHEREAS LONG-EVANS & F344 RATS PROVED RELATIVELY RESISTANT. MAMMARY STROMAL & PARENCHYMAL CELL POPULATIONS FROM THESE 4 TYPES OF RATS WERE STUDIED IN A CELL-MEDIATED MUTAGENESIS ASSAY, & ALL PRODUCED COMPARABLE LEVELS OF MUTAGENIC METABOLITES OF DMBA. STROMAL CELLS METABOLIZED CARCINOGEN AT FASTER RATE THAN EPITHELIAL CELLS. EPITHELIAL CELLS GENERALLY MAINTAINED HIGHER INTRACELLULAR CONCN OF CARCINOGEN COMPARED TO THOSE OF STROMAL CELLS. DATA DEMONSTRATE THAT THE RAT TYPE-SPECIFIC SUSCEPTIBILITY TO POLYCYCLIC AROMATIC HYDROCARBON-INDUCED TUMORIGENESIS DOES NOT RESIDE IN THE ABILITY OF MAMMARY CELLS TO METABOLICALLY ACTIVATE THESE CARCINOGENS.[MOORE CH ET AL; J NATL CANCER INST 70 (4): 777-84 (1983)] **PEER REVIEWED** PubMed Abstract
- BIOTRANSFORMATION OF 7,12-DIMETHYLBENZ(A)ANTHRACENE (DMBA) WAS STUDIED IN UNINDUCED & INDUCED 10,000G ORGAN SUPERNATANTS DERIVED FROM FEMALE SPRAGUE-DAWLEY (SD) & LONG-EVANS (LE) RATS WHICH ARE RESPECTIVELY SENSITIVE & RESISTANT TO DMBA-INDUCED CARCINOGENESIS. QUALITATIVE & QUANTITATIVE DIFFERENCES IN METAB OF DMBA ARE SUMMARIZED AS FUNCTION OF ORGAN (LIVER, LUNG, KIDNEY, & MAMMARY) & STRAIN & OXIDATIVE ENZYME INDUCTION PROTOCOL UTILIZED & ATTRIBUTED TO DIFFERENTIAL INDUCTION OF CYTOCHROME P450. PERCENT PRODN OF 7,12-DMBA-3,4-DIHYDRODIOL & PHENOL METABOLITES IN 10,000G ORGAN SUPERNATANTS FROM BETA-NAPHTHOFLAVONE INDUCED ANIMALS CORRELATED WITH ORGAN SUSCEPTIBILITY TO DMBA-INDUCED CARCINOGENESIS IN SD & LE RAT STRAINS. A NEGATIVE CORRELATION WAS OBSERVED BETWEEN 8,9-DIHYDRODIOL PRODN & REPORTED SENSITIVITY TO SPECIFIC ORGAN TUMORIGENESIS, BUT NO OTHER RELATIONSHIP WAS OBSERVED WITH OTHER METABOLITES.[SHEIKH YM ET AL; DRUG METAB DISPOS 11 (2): 158-63 (1983)] **PEER REVIEWED** PubMed Abstract
- THE 1- & 2-POSITION OF 7,12-DIMETHYLBENZ(A)ANTHRACENE (DMBA) WERE THOUGHT NOT TO BE INVOLVED IN BIOTRANSFORMATION TO 1,2-EPOXIDE & 1,2-DIHYDRODIOL BECAUSE OF STERIC HINDRANCE FROM THE 12-METHYL GROUP. FOUR 2-PHENOLS WERE IDENTIFIED AS RAT LIVER MICROSOMAL METABOLITES OF DMBA & ITS METHYL-HYDROXYLATED METABOLITES, 7-HYDROXYMETHYL-12-METHYLBENZ(A)ANTHRACENE, 7-METHYL-12-HYDROXYMETHYLBENZ(A)ANTHRACENE, & 7-12-DIHYDROXYMETHYLBENZ(A)ANTHRACENE. NEITHER THE 12-METHYL GROUP NOR THE 12-HYDROXYMETHYL GROUP BLOCKS THE MICROSOMAL OXYGENATIONS OF THE 1,2-POSITIONS OF DMBA OR ITS METHYL-HYDROXYLATED DERIVATIVES. THE 2-PHENOLS MAY BE FORMED AS NONENZYMATIC REARRANGEMENT PRODUCTS OF THE 1,2-EPOXIDE INTERMEDIATES, ALTHOUGH THEIR FORMATIONS BY DIRECT HYDROXYLATION MECHANISM CANNOT BE RULED OUT.[CHOU MW ET AL; BIOCHEM BIOPHYS RES COMMUN 88 (3): 1085-91 (1979)] **PEER REVIEWED** PubMed Abstract
- METABOLISM OF 7,12-DIMETHYLBENZ(A)ANTHRACENE (DMBA) IN RAT LIVER 10,000G SUPERNATANT FRACTION WAS EXAM BY FRAGMENTOGRAPHY FOLLOWING HPLC SEPARATION OF INCUBATION MIXT. IN ADDN TO MONO-, DI-, & TRIHYDROXYLATED OXIDATIVE METABOLITES USUALLY ASSOC WITH BIOTRANSFORMATION OF POLYCYCLIC AROMATIC HYDROCARBONS, A METHANOLYSIS PRODUCT WAS FORMED FROM THE K-REGION EPOXIDE INT DURING THE WORKUP PROCEDURE. IDENTIFICATION OF THIS COMPD PROVIDES DIRECT EVIDENCE FOR THE PRESENCE OF K-REGION EPOXIDE IN METAB MIXT, & IT SERVES AS A CONVENIENT MEANS TO ASSAY FOR THIS METABOLITE. THE METHANOLYSIS DERIV WAS DETECTED ONLY FROM K-REGION EPOXIDE. THIS FINDING SUGGESTS THAT THE NON-K-REGION EPOXIDES UNDERGO FACILE ENZYMATIC & NONENZYMATIC HYDROLYSIS &/OR REARRANGEMENT REACTIONS AS SOON AS THEY ARE PRODUCED. THE K-REGION EPOXIDE POSSESSES GREATER STABILITY. IT CAN REMAIN LONGER IN METAB MIXT & SUBSEQUENTLY REACT WITH METHANOL.[WONG LK ET AL; DRUG METAB DISPOS 8 (1): 28-33 (1980)] **PEER REVIEWED** PubMed Abstract
- BIOTRANSFORMATION OF 7,12-DIMETHYLBENZ(A)ANTHRACENE (DMBA) IN VARIOUS INDUCED & UNINDUCED S-10 FRACTIONS FROM RAT LIVERS IN PRESENCE & ABSENCE OF HEPATIC MIXED FUNCTION OXIDASE INHIBITORS (ALPHA-NAPHTHOFLAVONE, METYRAPONE, SKF-525A & CARBON DISULFIDE) IS DESCRIBED. PARTICULAR ATTENTION IS PAID TO PRODN OF DIHYDRODIOLS & DMBA-7- & 12-METHYL HYDROXYLATED METABOLITES. RESULTS SUGGEST THAT HYDROXYLATION PROCEEDS BY DIFFERENT ENZYME ACTIVITIES.[SHEIKH YM ET AL; BIOCHEM BIOPHYS RES COMMUN 93 (3): 782-91 (1980)] **PEER REVIEWED** PubMed Abstract
- Seven different forms of cytochrome p450 were purified from rat liver microsomes. The major 3-methylcholanthrene (MC)-inducible p450 (form c) exhibited the greatest activity toward both benzo(a)pyrene (BP) (58 min-1) and 7,12-dimethylbenz(a)anthracene (DMBA) (29 min-1) and formed substantially high-spin, high-affinity complexes (Kd=10 nM) with both hydrocarbons. /The cytochrome/ p450d, a minor MC-inducible form, had far lower activity for metabolism of both polycyclic aromatic hydrocarbons (PAH), yet also formed high-affinity complexes (Kd approximately 100 nM) with both PAH, retaining the full high-spin state of the free cytochrome. Although two phenobarbital (PB)-induced forms (b and e) differed by

only 13 amino acids, they exhibited significant differences in the metabolism of PAH and in complex formation. Whereas p450 form b was only active in the metabolism of (DMBA 9.8 min vs 1.9 min for BP), p450 form e had low activity for both substrates (3.3 and 1.2 min). Nevertheless, p450 form e formed a high-affinity complex (Kd approximately 100 nM) with both PAH that enhanced the proportion of the high-spin state (from 30-70%). Failure to displace n-octylamine suggested binding that is removed from heme. Form b remained low spin in the presence of PAH and again n-octylamine was not displaced. In addition, the two forms can be distinguished by their regioselectivities for both PAH. /The cytochrome/ p450 a,h, and pregnenolone-16alpha-carbonitrile (PCN) exhibited little activity toward BP or DMBA, but p450 PCN did form a low-spin complex with BP (not DMBA). Regioselectivity in the metabolism of DMBA by PB-induced microsomes did not agree with that of the major constituent forms. Only the minor, less active purified forms (e and a) mediate substantial 12-hydroxylation and 3,4-epoxidation of DMBA. Thus, additional factors in microsomal reactions must contribute to these differences.[Wilson NM et al; Carcinogenesis 5 (11): 1475-83 (1984)] **PEER REVIEWED** PubMed Abstract

- DNA containing bound radioactive 7,12-dimethylbenz(a)anthracene was isolated from mouse fetal cell cultures exposed to this carcinogen. The carcinogen-deoxyriboside adducts within the DNA were found to be sensitive to acid-catalyzed hydrolysis. Adducts derived from reaction of a syn-dihydrodiol epoxide with deoxyadenosine residues in DNA were the most sensitive to acid and were hydrolyzed to yield a 1,2,3,4-tetrahydrotetraol of 7,12-dimethylbenz(a)anthracene under mild conditions. The structure of this tetraol was established by synthesis and mass spectrometry.[Dipple A et al; Biochem 24 (9): 2291-98 (1985)] **PEER REVIEWED**
- The enantiomers of DMBA 5,6-epoxide (I) were directly resolved by normal-phase HPLC with an ionically bonded chiral stationary phase. The absolute configurations of the resolved enantiomers were detected by comparison of CD spectra of the methanolysis products formed from (I) enantiomers with DMBA trans-5,6-dihydrodiol enantiomer of known absolute stereochemistry. DMBA 5R,6S-epoxide was hydrolyzed by rat liver microsomal epoxide hydrolase predominantly (95%) to a 5S,6S-dihydrodiol. The 5S,6S-dihydrodiol formed from the metabolism of DMBA by microsomes prepared from the livers of 3-methylcholanthrene-treated rats was predominantly derived from a 5R,6S-epoxide intermediate.[Mushtag M et al; Biochem Biophys Res Commun 125 (2): 539-45 (1984)] **PEER REVIEWED** PubMed Abstract
- 7-Hydroxymethyl-12-methylbenz(a)anthracene (7-HMBA) and 12-hydroxymethyl-7-methylbenz(a)anthracene (12-HMBA), carcinogenic major metabolites of 7,12-dimethylbenz(a)anthracene (DMBA) in untreated rat liver, showed high mutagenic activities toward Salmonella typhimurium TA98 after preincubation with a sulfotransferase-PAPS system consisting of ATP, sodium sulfate, and a post-mitochondrial fraction (S-9) or a soluble supernatant fraction (S-105) from untreated rat liver. The 7- and 12-HMBAs themselves induced His + mutation in TA98 only slightly after preincubation with S-9 in the presence of a NADPH-generating system. Mutagenicity of DMBA toward TA98 after preincubation with S-9 in the presence of the NADPH-generating system was remarkably enhanced by the addition of ATP and sodium sulfate. The active metabolites, 7-HMBA sulfate and 12-HMBA sulfate, were isolated from these preincubation systems and identified by comparison with the corresponding synthetic specimens. The sulfuric acid ester conjugates were potent mutagens toward TA98 in the absence of rat liver subcellular fractions. The conjugates bound covalently at significant rates to calf-thymus DNA as well as to S-105 proteins at 37 deg /C/ and pH 7.4 through the 7- or 12-methylene carbon with concomitant loss of their sulfate group. In the presence of S-105, glutathione inhibited the mutagenicity of the metabolically formed or exogenously added 7- and 12-HMBA sulfates. The non-mutagenic glutathione conjugates were isolated from the incubation mixtures and identified as S-(12-methylbenz(a)anthracen-7-yl)methylglutathione from 7-HMBA or its sulfate and S-(7-methylbenz(a)anthracene-12-yl)methylglutathione from 12-HMBA or its sulfate.[Watabe T et al; Jpn J Cancer Res 76 (8): 684-98 (1985)] **PEER REVIEWED** PubMed Abstract
- The effects of induction by either phenobarbital (PB) or 3-methylcholanthrene (MC) on the kinetics of both primary and secondary metabolism of DMBA (I) were studied. Both PB and MC induction stimulate the initial rate of total DMBA metabolism 4- and 8-fold, respectively. Individual metabolites exhibited distinct time courses dependent on the inducer. With both induced and uninduced microsomes, formation of DMBA 5,6-dihydrodiol exhibited 2-5 min time lag before 7-hydroxymethyl-12-methylbenz(a)anthracene (7HOMMBA) declined substantially from linearity at a very early point in the reaction. This was most apparent after 2 min and total levels decreased after 5 min. Regioselectivity for both DMBA and 7HOMMBA were measured based on the initial rates of mono-oxygenation derived from these kinetics. In each set of microsomes, prior 7-hydroxylation redirected metabolism towards DMBA 3,4-dihydrodiol formation and away from 5,6-dihydrodiol. Large differences were noted for the effectiveness and regioselectivity of secondary metabolism via 7HOMMBA. MC-induced liver microsomes exhibited a stronger preference for secondary metabolism of 7HOMMBA than PB-induced and control microsomes. In all cases, 7HOMMBA dihydrodiols, formed from DMBA, appeared in the same ratio as when they formed directly from 7HOMMBA rather than from 7-hydroxylation of primary dihydrodiols. The extent of secondary metabolism of primary products was calculated as the difference between the calculated formation (determined from the appropriate regioselectivity and DMBA disappearance) and the quantitated level at a particular reaction time. However, for MC-induced microsomes, quantitation of 7HOMMBA mono-oxygenated metabolites accounted for <50% of the calculated 7HOMMBA secondary metabolism. This discrepancy results from selective further oxidation of 7HOMMBA phenols. For control and PB-induced liver microsomes, quantitation of identifiable 7HOMMBA mono-oxygenated metabolites agreed well with the calculated secondary 7HOMMBA metabolism. Based on these results, factors that favor hydroxylation of polycyclic aromatic hydrocarbons prior to bay-region diol-epoxide formation are discussed.[Christou M et al; Carcinogenesis 5 (10): 1239-47 (1984)] **PEER REVIEWED** PubMed Abstract
- The metabolism of 7,12-dimethylbenz(a)anthracene in primary cultures of Rhesus monkey ovarian cells was investigated with special reference to the consequences of unilateral intraovarian injection of pregnant mare serum gonadotropin (PMSG). Two sexually mature rhesus monkeys received intraovaria injections of 200 IU pregnant mare serum gonadotropin in 0.3 ml saline unilaterally and an equal vol of saline in the other ovar under anesthesia 48 hr prior to ovariectomy. Cells isolated from the untreated monkey ovaries did not metabolize DMBA to any significant degree. In both monkeys cells from the gonadotropin-treated ovaries demonstrated a capacity to metabolize DMBA. The bulk of this activity was exhibited by those cells recovered at the interphase between 30 and 50% Percoll.[Bengtsson M, Mattison DR; Biochem Pharmacol 38 (11): 1869-72 (1989)] **PEER REVIEWED** PubMed Abstract

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- Dimethylbenz(a)anthracene (CAS # 57-97-6) was evaluated for mutagenicity among polycyclic aromatic hydrocarbon components of kerosene soot. Exposed exponentially-growing cultures of Salmonella typhimurium strain TM677 were observed for expression of mutagenicity in treatment-induced resistance to 8-azaguanine, a purine analog. Simultaneous exposure to 25% (w/v) postmitochondrial supernatant from the liver of aroclor-induced rats potentiated metabolism of any promutagens to their active forms in treated bacterial cultures. Following 2-hour incubation, the treated colonies were resuspended in phosphate-buffered saline and plated either with or without 50 ug/ml 8-azaguanine for selective and non-selective determination of mutagenicity. A mutant fraction was quantitatively defined as the number of treated colonies of a selective culture relative to number of colonies of the permissive culture, adjusted for dissimilar dilutions in respective assays. Exposure to a concentration of 25 uM 7,12-dimethylbenz(a)anthracene for 2 hours was associated with significantly induced mutant fraction resistance to 8-azaguanine (0.44 relative mutagenic activity relative to that of benzo(a)pyrene, the positive control). Further details of study methodology, statistical criterion for significance and data/assay were not provided.[PHILLIPS PETROLEUM CO; Mutagenicity of Kerosene Soot and Associated Polycyclic Aromatic Hydrocarbons to Salmonella Typhimurium; 12/09/78; EPA Doc No. 88-920009009; Fiche No. OTS0555325] **UNREVIEWED**
- Summary information indicates that 7,12-dimethylbenzanthracene (CAS # 57-97-6) was evaluated for carcinogenicity in a group of 32 female Swiss CD-1 albino mice by application of a single dose of the test substance (in 100 uL of acetone) followed by tri-weekly dosing with the promoter phorbul myristate acetate (in 100 uL of acetone). Treatment with the promoter began 2 weeks following application of the test substance and continued for 180 days. Tumors were found in 29 of 32 of the mice. There was a total of >350 tumors in the group. The first observable tumor was seen at 45 days.[Haskell Laboratory; Two Stage (Initiation Promotion) Skin Tumorigenicity Testing on Mice, (1978), EPA Doc. No. 86-870001032, Fiche No. OTS0514934] **UNREVIEWED**

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Footnotes

[1] Source: the National Library of Medicine's Hazardous Substance Database, 11/28/2012.

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