Evaluation of the Potential Carcinogenicity of 7,12-Dimethylbenz(a)anthracene (57-97-6)

Syracuse Research Corp., NY

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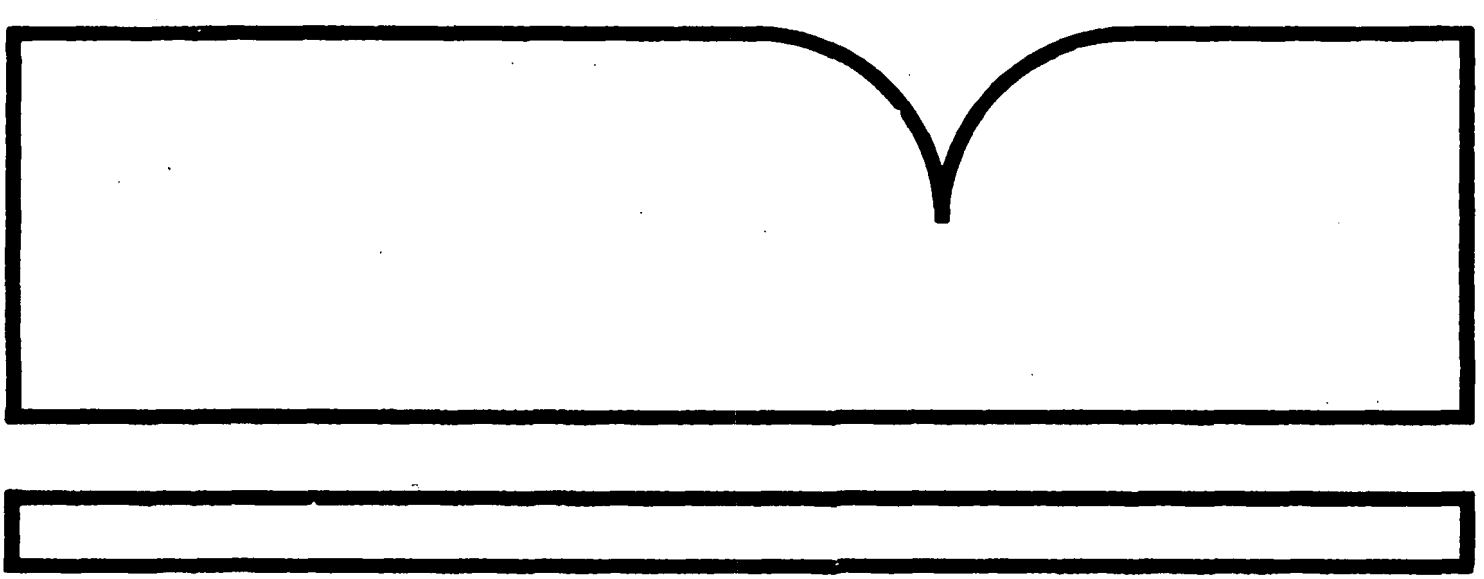

UNITED STATES
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EPA/600/8-91/117
JUNE 1988
FINAL

RESEARCH AND DEVELOPMENT

EVALUATION OF THE POTENTIAL CARCINOGENICITY OF 7,12-DIMETHYLBENZ(A)ANTHRACENE (57-97-6)

IN SUPPORT OF REPORTABLE QUANTITY ADJUSTMENTS PURSUANT TO CERCLA SECTION 102

PREPARED FOR

OFFICE OF EMERGENCY AND REMEDIAL RESPONSE
OFFICE OF SOLID WASTE AND EMERGENCY RESPONSE

PREPARED BY

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OFFICE OF HEALTH AND
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7,12-Dimethylbenz(a)anthracene is a probable human carcinogen, classified as weight-of-evidence Group B2 under the EPA Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1986a). Evidence on potential carcincgenicity from animal studies is "Sufficient," and the evidence from human studies is "No Data."

The potency factor (F) for 7,12-dimethylbenz(a)anthracene is estimated to be 540 $(mg/kg/day)^{-1}$, placing it in potency group 1 according to the CAG's methodology for evaluating potential carcinogens (U.S. EPA, 1986b).

Combining the weight-of-evidence group and the potency group, 7,12-dimethylbenz(a)anthracene is assigned a "HIGH" hazard ranking for the purposes of RQ adjustment.

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PREFACE

This report summarizes and evaluates information on the potential carcinogenicity of a substance designated as hazardous under Section 101 (14) of the Comprenensive Environmental Response, Compensation and Liability Act of 1980 (CERCLA). Pertinent epidemiologic and toxicologic data were obtained through on-line searches and from hard-copy sources. On-line searches were extended as far back as the data bases would allow. Retrieval of historical data was accomplished through searches of hard-copy sources and bibliographies of relevant publications. Every attempt has been made to rely upon primary publications as opposed to data summaries or abstracts contained in secondary sources such as monographs, surveys, review articles, criteria documents, etc. The on-line data bases that were searched included CHEMLINE (National Library of Medicine [NLM]), RTECS (NLM), Toxicology Data Bank (NLM), TOXLINE (NLM), CANCERLINE (NLM), and Chemical Abstracts (DIALOG Information Services). Unpublished data were not used in this evaluation.

The Agency's Methodology for obtaining, evaluating, and ranking CERCLA potential carcinogens is described in the Technical Background Document to Support Rulemaking Pursuant to CERCLA Section 102, Volume 3, April 26, 1988 (EPA/600/8-99/053). This document revises the previous methodology document of 1986 according to the public comments received on the March 16, 1987 Notice of Proposed Rulemaking (52 FR 8140). The Methodology for Adjusting reportable quantities is described in the Technical Background Document to Support Rulemaking Pursuant to CERCLA Section 102, Volume 1, March, 1985, and is also summarized in Volume 2, August, 1986, and Volume 3, December, 1986. The EPA's Office of Emergency and Remedial Response (OERR) has considered this evaluation in adjusting reportable quantities pursuant to CERCLA Section 102. This report is consistent with the revised methodology. It draws largely on information supplied by the Syracuse Research Corporation in 1984 under EPA Contract No. 68-03-3112. Due to the amount of time elapsed between the original work performed by Syracuse Research Corporation and the present

effort to produce this document, Environmental Monitoring & Services, Inc., under EPA Contract No. 68-03-3182, has been involved in an extensive review of all the Syracuse documents. In some cases, this review involved updating the information provided but it was primarily a quality assurance effort. The present document is a result of this effort.

ABSTRACT

7,12-Dimethylbenz(a)anthracene is a probable human carcinogen, classified as weight-of-evidence Group B2 under the EPA Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1986a). Evidence on potential carcinogenicity from animal studies is "Sufficient," and the evidence from human studies is "No Data."

The potency factor (F) for 7,12-dimethylbenz(a)anthracene is estimated to be 540 $(mg/kg/day)^{-1}$, placing it in potency group 1 according to the CAG's methodology for evaluating potential carcinogens (U.S. EPA, 1986b).

Combining the weight-of-evidence group and the potency group, 7,12-dimethylbenz(a)anthracene is assigned a "HIGH" hazard ranking for the purposes of RQ adjustment.

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1.1 ANIMAL STUDIES

The carcinogenic activity of 7,12-dimethylbenz(a)anthracene (DMBA) in animals has been very well documented. 7,12-Dimethylbenz(a)anthracene produces tumors in multiple target organs in several animal species when administered by various routes. When applied to the skin of mice, 7,12-dimethylbenz(a)anthracene can act as both a complete carcinogen and as a tumor initiator (Grube et al., 1975; Law, 1941; Roe, 1956; Terracini et al., 1960; Klein, 1956; Howell, 1962; Slaga et al., 1974). Skin application of 7,12-dimethylbenz(a)anthracene also produces tumors in guinea pigs (Pawlowski et al., 1976; Berenblum, 1949; Edgecomb and Mitchelich, 1962) and rats (Albert et al., 1978). Sarcomas developing at the site of injection are frequently observed with 7,12-dimethylbenz(a)anthracene administered to rats and mice (Flesher et al., 1976; Buu-hoi, 1964). Intratracheal instillation or implantation of 7,12-dimethylbenz(a)anthracene has produced lung tumors in dogs (Paladugu et al., 1980; Staub et al., 1965; Beattie et al., 1961) and hamsters (Della Porta et al., 1958).

Mammary cancer induced in rodents by 7,12-dimethylbenz(a)anthracene has become an important model system for the study of human breast cancer (Griswold et al., 1966; Pearson, 1973; Dao, 1964). Huggins et al. (1962) demonstrated that a single intragastric feeding of 20 mg 7,12-dimethylbenz(a)anthracene to Sprague-Dawley rats resulted in the production of mammary cancer or fibroadenomas in 100% of the treated animals. Huggins (1965) later reported that intragastric feeding of 7,12-dimethylbenz(a)anthracene to Sprague-Dawley rats could be substituted with a single intravenous injection of 5 mg 7,12-dimethylbenz(a)anthracene for the purpose of inducing mammary cancer. By this technique, Huggins successfully produced mammary carcinomas in all of 1500 Sprague-Dawley rats treated at age 50 days. Tumors were detected by palpation as early as 20 days after 7,12-dimethylbenz(a)anthracene injection. Medina et al. (1980) showed a 50% tumor incidence reached after 34 weeks, with 70% of the tumors being adenocarcinomas, in female C57BL/6x, DBA/2fF1 mice when given

an intragastric feeding of 7,12-dimethylbenz(a)anthracene of 1.0 mg once/week. In another study (Yoshida and Fukunishi, 1977), mammary adenocarcinomas and leukemia developed in male Sprague-Dawley rats treated intragastrically with 7,12-dimethylbenz(a)anthracene. It is now known that 7,12-dimethylbenz(a)-anthracene can also produce tumors in the mammary gland, ovaries, and pancreas of rats by direct local application to the target organ (Sinha and Dao, 1974; Kato et al., 1975; Satake et al., 1975). By direct application, mammary adenocarcinomas could be produced with single doses of 7,12-dimethylbenz-(a)anthracene as low as 300 ug (Sinha and Dao, 1974).

1.2 HUMAN STUDIES

Pertinent data regarding the effects of human exposure to 7,12-dimethylbenz(a)-anthracene were not located in the available literature.

1.3 WEIGHT-OF-EVIDENCE ASSESSMENT

Studies with experimental animals of several species exposed to 7,12-dimethyl-benz(a)anthracene by various routes provide unequivocal evidence that the substance is an animal carcinogen. Single doses of 7,12-dimethylbenz(a)anthra-cene, often in microgram quantities, are generally sufficient to induce tumor formation. 7,12-Dimethylbenz(a)anthracene is most often used for the induction of experimental tumors and as a model compound for studying the mechanism of action of carcinogens. Because of its high carcinogenic potency in animals, chronic exposures are not necessary to demonstrate the tumorigenic activity; thus, published studies involving long-term exposure to 7,12-dimethylbenz(a)-anthracene are not available. This situation complicates any attempt to calculate a carcinogenic potency factor (F) for 7,12-dimethylbenz(a)anthracene. A human population has not been identified which is exposed to 7,12-dimethyl-benz(a)anthracene in either the community or the workplace. Thus, using the EPA Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1986a) for evaluating the overall weight of evidence to humans, 7,12-dimethylbenz(a)anthracene is most appropriately classified as a Group B2 chemical. The appendix contains summaries of the significant human and/or animal studies cited in this review.

2.0 POTENCY

The potency factor (F) for 7,12-dimethylbenz(a)anthracene is estimated to be 540 $(mg/kg/day)^{-1}$, placing it in potency group 1 under the CAG's methodology for evaluating potential carcinogens (U.S. EPA, 1986b). Table 2-1 contains data from the selected study used to derive the potency factor (F) for 7,12-dimethylbenz(a)anthracene.

Table 2-1. Derivation of Potency Factor(F) Agent: 7,12-Dimethylbenz[a]anthracene

REFERENCE:	Medina et al., 1980	
EXPOSURE ROUTE:	intragastric	
SPECIES:	mice	
STRAIN:	BD2F1	
SEX:	F	
VEHICLE OR PHYSICAL STATE:	cottonseed oil	
BODY WEIGHT:[a]	0.03 kg	
DURATION OF TREATMENT:	6 weeks (42 days)	
DURATION OF STUDY:	730 days	
LIFESPAN OF ANIMAL:[a]	730 days	
TARGET ORGAN:	breast	
TUMOR TYPE:	adenocarcinoma/adenocanthoma	
EXPERIMENTAL DOSES/ EXPOSURE:	1.0 mg	0.0 mg
TRANSFORMED DOSES:[b] (mg/kg/day)	0.27	0.0
TUMOR INCIDENCE:	24/35	0/43
ANIMAL POTENCY: $(mg/kg/day)^{-1}$	40.69	
HUMAN POTENCY:[c] $(mg/kg/day)^{-1}$	540	

[a] Estimated

[b] To derive the transformed dose from the experimental dose data: experimental dose (mg)/ animal's weight (kg) x 1 (treatment day/week)/ 7 (days/week) x duration of treatment (days)/duration of study (days).

[c] Human potency = animal potency x (70kg/0.03kg)

3.0 HAZARD RANKING

Based on the weight-of-evidence Group B2 for 7,12-Dimethylbenz(a)anthrene and the potency factor (F) of 540 (mg/kg/day), 7,12-dimethylbenz(a)anthrene receives a hazard ranking of "HIGH."

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APPENDIX

SUMMARY OF SIGNIFICANT HUMAN AND/OR ANIMAL STUDIES

Table A. Animal

Agent: 7,12-Dimethylbenz[a]anthracene

Reference: Grube et al., 1975

Exposure Route	Species/ Strain	Sex	Dose or Exposure	Duration of Treatment	Duration of Study	Purity of Compound	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence (P value)
d	mice/ HSR/J	F	100 ug once/week	12 weeks	40 weeks	NR	acetone (0.1 ml)	skin	papilloma/ sarcoma/ carcinoma	28/29[a,b]
d	mice/ HSR/J	F	250 ug once/week	12 weeks	40 weeks	NR	acetone (0.1 ml)	skin	papilloma/ sarcoma/ carcinoma	30/30[a,c]
NA	mice/ HSR/J	F	untreated	NA	life	NA	NA	skin	papilloma/ fibrosarcoma	2/76

A-2

QUALITY OF EVIDENCE

Strengths of Study: Relatively extended duration of exposure; histopathology performed on some animals; good reporting of data.

Weaknesses of Study: Route of exposure may be considered environmentally irrelevant.

Overall Adequacy: Adequate

[a] Animals were 10-12 weeks of age at start of study and were fed 30% casein pelleted diet throughout the experiment.
[b] Total number of carcinomas was 15; final incidence was 13%.
[c] All animals have multiple papillomas and lesions that appeared to be malignant by the 15th week and the experiments were terminated. No histopathologic examination was carried out.
NA = Not applicable; NR = Not reported

Table A. Animal

Agent: 7,12-Dimethylbenz[a]anthracene

Reference: Medina et al., 1980

Exposure Route	Species/ Strain	Sex	Dose or Exposure	Duration of Treatment	Duration of Study	Purity of Compound	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence (P value)
ig	mice/ C57BL/6x DBA/2fF1	F	1.0 mg once/week beginning at 8 weeks of age	6 weeks	lifetime	NR	1.0 mg dissolved in 0.2 ml cottonseed oil	breast	adenocarcinoma adenocanthoma	24/35[a,b]
ig	mice/ C57BL/6x DBA/2fF1	F	untreated	NA	lifetime	NA	NA	breast	NA	0/43

A-3

QUALITY OF EVIDENCE

Strengths of Study: Excellent reporting of data; histopathologic examinations conducted; animals observed for life.

Weaknesses of Study: Limited duration of exposure; tumor incidence data reported only for breast.

Overall Adequacy: Adequate

[a] 50% tumor incidence was reached at 34 weeks. Mean age of mice dying without tumors was 43 weeks.

[b] 70% of tumors were adenocarcinomas.

NA = Not applicable; NR = Not reported

Table A. Animal

Agent: 7,12-Dimethylbenz[a]anthracene

Reference: Staub et al., 1965

Exposure Route	Species/ Strain	Sex	Dose or Exposure	Duration of Treatment	Duration of Study	Purity of Compound	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence (P value)
it	dog/ mongrel	M,F	2 mg once/week	up to 63 weeks	19-32 months	NR	1% in gelatin suspension	lung	carcinoma	3/14[a]
NA	dog/ NR	NR	untreated	NA	NR	NR	NA	lung	carcinoma	15/9282[b]

QUALITY OF EVIDENCE

A-4

Strengths of Study: Repeated exposure regimen; good reporting of data; histopathologic examinations performed.

Weaknesses of Study: Early death among several animals; no concurrent control group.

Overall Adequacy: Adequate

[a] Carcinoma developed in animals treated for 53-58 weeks with DMBA. Ten of the 14 dogs died with an ulcerative tracheobronchopneumonia; 8 of the dogs survived for ≥1 year.

[b] Historical necropsy data cited by the authors.

NA = Not applicable; NR = Not reported

Table A. Animal

Agent: 7,12-Dimethylbenz(a)anthracene

Reference: Yoshida and Fukunishi, 1977

Exposure Route	Species/ Strain	Sex	Dose or Exposure	Duration of Treatment	Duration of Study	Purity of Compound	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence (P value)
ig	rat/ Sprague-Dawley	M	8 doses of 10 mg each at biweekly intervals (total dose= 80 mg)	16 weeks	200 days	NR	0.5% in sesame oil	mammary gland,	adenocarcinoma	85/164[a]
								hematopoietic system	leukemia	31/164[a]

QUALITY OF EVIDENCE

Strengths of Study: Large number of animals, multiple doses administered, histopathologic examinations performed.

Weaknesses of Study: No control group

Overall Adequacy: Limited

A-5

[a] 147 of the 311 rats died during the treatment period and were eliminated from the study.

NR = Not reported

END